Notice of Award

PRIMATE RESEARCH CENTER GRANT **Issue Date:** 08/13/2014

Department of Health and Human Services
National Institutes of Health
OFFICE OF THE DIRECTOR, NATIONAL INSTITUTES OF HEALTH

Grant Number: 2P51OD011092-55
FAIN: P51OD011092

Principal Investigator(s):
JOSEPH E ROBERTSON, MD

Project Title: SUPPORT FOR NATIONAL PRIMATE RESEARCH CENTER

JASON JAWORSKI
GRANTS & CONTRACTS ADMIN
3181 SW SAM JACKSON PK RD
L106RGC
PORTLAND, OR 972393098

Award e-mailed to: orserv@ohsu.edu

Budget Period: 08/15/2014 – 04/30/2015
Project Period: 05/01/1997 – 04/30/2019

Dear Business Official:

The National Institutes of Health hereby awards a grant in the amount of $12,651,521 (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to OREGON HEALTH & SCIENCE UNIVERSITY in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award including the "Terms and Conditions" is acknowledged by the grantee when funds are drawn down or otherwise obtained from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the Office Of The Director, National Institutes Of Health of the National Institutes of Health under Award Number P51OD011092. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please contact the individual(s) referenced in Section IV.

Sincerely yours,

Dawn Walker
Grants Management Officer
OFFICE OF THE DIRECTOR, NATIONAL INSTITUTES OF HEALTH

Additional information follows

SECTION I – AWARD DATA – 2P51OD011092-55

Award Calculation (U.S. Dollars)

Salaries and Wages	$5,079,594
Fringe Benefits	$1,646,298
Personnel Costs (Subtotal)	$6,725,892
Consultant Services	$32,827
Equipment	$494,522
Supplies	$1,273,675
Travel Costs	$61,130
Alterations and Renovations	$8,382
Other Costs	$1,397,583
Federal Direct Costs	$9,994,011
Federal F&A Costs	$2,657,510
Approved Budget	$12,651,521
Federal Share	$12,651,521
TOTAL FEDERAL AWARD AMOUNT	$12,651,521
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$12,651,521

SUMMARY TOTALS FOR ALL YEARS		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
55	$12,651,521	$12,651,521
56	$12,651,521	$12,651,521
57	$12,651,521	$12,651,521
58	$12,651,521	$12,651,521
59	$12,651,521	$12,651,521

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

Fiscal Information:

CFDA Number:	93.351
EIN:	1931176109A1
Document Number:	POD011092J
PMS Account Type:	P (Subaccount)
Fiscal Year:	2014

IC	CAN	2014	2015	2016	2017	2018
OD	8014499	$12,651,521	$12,651,521	$12,651,521	$12,651,521	$12,651,521

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

NIH Administrative Data:
PCC: CMP01 / **OC**: 414B / **Released**: eRA Commons User Name 08/07/2014
Award Processed: 05/08/2014 01:52:21 PM

SECTION II – PAYMENT/HOTLINE INFORMATION – 2P51OD011092-55

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – TERMS AND CONDITIONS – 2P51OD011092-55

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 74 or 45 CFR Part 92 as applicable.
d. The NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget period.
e. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

This institution is a signatory to the Federal Demonstration Partnership (FDP) Phase V Agreement which requires active institutional participation in new or ongoing FDP demonstrations and pilots.

Carry over of an unobligated balance into the next budget period requires Grants Management Officer prior approval.

This award is subject to the requirements of 2 CFR Part 25 for institutions to receive a Dun & Bradstreet Universal Numbering System (DUNS) number and maintain an active registration in the Central Contractor Registration. Should a consortium/subaward be issued under this award, a DUNS requirement must be included. See http://grants.nih.gov/grants/policy/awardconditions.htm for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) P51OD011092. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see http://grants.nih.gov/grants/policy/awardconditions.htm for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

Treatment of Program Income:
Additional Costs

SECTION IV – OD Special Terms and Conditions – 2P51OD011092-55

SUBJECT FOA
This award is subject to the conditions set forth in PAR-11-136, "Limited Competition: National Primate Research Centers (P51)," which are hereby incorporated by reference as special terms and conditions of this award. Copies of this Funding Opportunity Announcement can be found at the following link: http://grants.nih.gov/grants/guide/pa-files/PAR-11-136.html

ORIP FUNDING PLAN FOR FY2014
This competing award reflects the NIH Fiscal Policy for Grant Awards for FY2014 (see NIH Guide Notice NOT-OD-14-055) and the implementation of the ORIP FY2014 grants funding policy: http://dpcpsi.nih.gov/orip/rf/fyg_fp2014.aspx

TOTAL COSTS

This award is funded at a total cost ceiling of $12,651,521. Funds may be re-budgeted as necessary between direct and facilities and administrative costs consistent with policy and institutional requirements for prior approval; however, no additional funds will be provided.

DIRECT CHARGES OF F&A-TYPE COSTS:
Funds requested for office and administrative supplies, administrative coordinators/assistants, custodians, computers, laptops, maintenance & repairs, telecommunications are included in the awarded budget. The allowability of charges to this project for this purpose is predicated on the grantee's compliance with the applicable cost principles.

FUTURE YEAR SUPPORT ADJUSTMENT
Escalation on recurring costs has been removed. Future years have been flatlined.

MEALS
The charging of meal costs directly to a grant is an exceptional activity and contingent upon the following: the grantee institution having a written policy in place ensuring consistent treatment of charging meal costs. This policy must define what constitutes a meeting for the dissemination of technical information when meals are allowable for such meetings, and must define the limitations and other controls on these recurring costs. This policy must be consistently applied regardless of whether the meeting is related to or funded by the Federal government or another source. These costs must also be reasonable.

KEY PERSONNEL
In addition to the PI, the following individuals are named as key personnel (individuals who have effort that ORIP staff is tracking):

Excluded by Requester

Written prior approval is required if any of the individuals named above withdraws from the project entirely, is absent from the project during any continuous period of 3 months or more, or reduces time devoted to the project by 25 percent or more from the level that was approved at the time of award.

PRIOR APPROVAL REQUEST
Any prior approval request (e.g., changes to key personnel as noted on the award, changes in human and animal subjects requiring prior approval, carryover requests) must be submitted to the assigned Grants Management Specialist and Programmatic Official. Please refer to the NIH Grants Policy Statement for the activities and/or expenditures that require NIH approval at http://grants.nih.gov/grants/policy/nihgps_2013/nihgps_ch8.htm#prior_approval_requirements.

RECYCLING FUTURE BUDGET PERIOD START DATES
In order to redistribute awards more evenly throughout the fiscal year, this grant has been issued with a 8.5-month initial budget period with 12 months of monetary support. The continuation award for this grant will cycle each year on May 1st. The non-competing continuation application must be submitted two months (non-SNAP) prior to the anticipated start date of the award. Information for where to submit reports may be found at: http://grants.nih.gov/grants/submitapplication.htm.

NON-COMPETING RENEWAL
Future year non-competing progress reports and other documents applicable to this grant should be submitted by March 1, 2014, two months prior to the anticipated start date of the award. NIH will require the use of the Research Performance Progress Report (RPPR) module to submit non-competing progress reports submitted on or after October 17, 2014. Additional information can be found here: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-092.html

COMMUNICATIONS/PRESS RELEASE
If the grantee plans to issue a press release concerning the outcome of ORIP grant-supported research, it should notify Ms. Patricia Newman, ORIP Communications at 301-435-0744, in advance to allow for coordination.

The ORIP WWW home page is at http://dpcpsi.nih.gov/orip/

STAFF CONTACTS

The Grants Management Specialist is responsible for the negotiation, award and administration of this project and for interpretation of Grants Administration policies and provisions. The Program Official is responsible for the scientific, programmatic and technical aspects of this project. These individuals work together in overall project administration. Prior approval requests (signed by an Authorized Organizational Representative) should be submitted in writing to the Grants Management Specialist. Requests may be made via e-mail.

Grants Management Specialist: Amy R Bartosch
Email: mcguirear@mail.nih.gov **Phone**: 301-435-0853 **Fax**: 301-480-3777

Program Official: John D. Harding
Email: hardingj@mail.nih.gov **Phone**: 301-435-0776 **Fax**: 30- 480-3819

SPREADSHEET SUMMARY
GRANT NUMBER: 2P51OD011092-55

INSTITUTION: OREGON HEALTH & SCIENCE UNIVERSITY

Budget	Year 55	Year 56	Year 57	Year 58	Year 59
Salaries and Wages	$5,079,594	$5,079,594	$5,079,594	$5,079,594	$5,079,594
Fringe Benefits	$1,646,298	$1,646,298	$1,646,298	$1,646,298	$1,646,298
Personnel Costs (Subtotal)	$6,725,892	$6,725,892	$6,725,892	$6,725,892	$6,725,892
Consultant Services	$32,827	$32,827	$32,827	$32,827	$32,827
Equipment	$494,522	$332,755	$280,788	$354,547	$302,245
Supplies	$1,273,675	$1,273,675	$1,273,675	$1,273,675	$1,273,675
Travel Costs	$61,130	$61,130	$61,130	$61,130	$61,130
Alterations and Renovations	$8,382	$170,149	$222,116	$148,357	$200,659
Other Costs	$1,397,583	$1,397,583	$1,397,583	$1,397,583	$1,397,583
TOTAL FEDERAL DC	$9,994,011	$9,994,011	$9,994,011	$9,994,011	$9,994,011
TOTAL FEDERAL F&A	$2,657,510	$2,657,510	$2,657,510	$2,657,510	$2,657,510
TOTAL COST	$12,651,521	$12,651,521	$12,651,521	$12,651,521	$12,651,521

Facilities and Administrative Costs	Year 55	Year 56	Year 57	Year 58	Year 59
F&A Cost Rate 1	28%	28%	28%	28%	28%
F&A Cost Base 1	$9,491,107	$9,491,107	$9,491,107	$9,491,107	$9,491,107
F&A Costs 1	$2,657,510	$2,657,510	$2,657,510	$2,657,510	$2,657,510

PRIMATE RESEARCH CENTER GRANT **Issue Date:** 09/03/2014
Department of Health and Human Services
National Institutes of Health
OFFICE OF THE DIRECTOR, NATIONAL INSTITUTES OF HEALTH

Grant Number: 2P51OD011092-55 REVISED
FAIN: P51OD011092

Principal Investigator(s):
JOSEPH E ROBERTSON, MD

Project Title: SUPPORT FOR NATIONAL PRIMATE RESEARCH CENTER

JASON JAWORSKI
GRANTS & CONTRACTS ADMIN
3181 SW SAM JACKSON PK RD
L106RGC
PORTLAND, OR 972393098

Award e-mailed to: orserv@ohsu.edu

Budget Period: 08/15/2014 – 04/30/2015
Project Period: 05/01/1997 – 04/30/2019

Dear Business Official:

The National Institutes of Health hereby revises this award to reflect an increase in the amount of $85,114 (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to OREGON HEALTH & SCIENCE UNIVERSITY in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award including the "Terms and Conditions" is acknowledged by the grantee when funds are drawn down or otherwise obtained from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the Office Of The Director, National Institutes Of Health of the National Institutes of Health under Award Number P51OD011092. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please contact the individual(s) referenced in Section IV.

Sincerely yours,

Dawn Walker
Grants Management Officer
OFFICE OF THE DIRECTOR, NATIONAL INSTITUTES OF HEALTH

Additional information follows

SECTION I – AWARD DATA – 2P51OD011092-55 REVISED

Award Calculation (U.S. Dollars)

Salaries and Wages	$5,113,775
Fringe Benefits	$1,657,368
Personnel Costs (Subtotal)	$6,771,143
Consultant Services	$33,047
Equipment	$497,849
Supplies	$1,282,242
Travel Costs	$61,538
Alterations and Renovations	$8,438
Other Costs	$1,406,989
Federal Direct Costs	$10,061,246
Federal F&A Costs	$2,675,389
Approved Budget	$12,736,635
Federal Share	$12,736,635
TOTAL FEDERAL AWARD AMOUNT	$12,736,635

AMOUNT OF THIS ACTION (FEDERAL SHARE) $85,114

SUMMARY TOTALS FOR ALL YEARS		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
55	$12,736,635	$12,736,635
56	$12,736,636	$12,736,636
57	$12,736,635	$12,736,635
58	$12,736,636	$12,736,636
59	$12,736,636	$12,736,636

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

Fiscal Information:

CFDA Number: 93.351
EIN: 1931176109A1
Document Number: POD011092J

PMS Account Type: P (Subaccount)
Fiscal Year: 2014

IC	CAN	2014	2015	2016	2017	2018
OD	8014499	$12,386,903	$12,386,904	$12,386,903	$12,386,904	$12,386,904
AG	8470701	$349,732	$349,732	$349,732	$349,732	$349,732

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

NIH Administrative Data:
PCC: CMP01 / **OC**: 414B / **Released**: eRA Commons User Name 09/02/2014
Award Processed: 05/08/2014 01:52:21 PM

SECTION II – PAYMENT/HOTLINE INFORMATION – 2P51OD011092-55 REVISED

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – TERMS AND CONDITIONS – 2P51OD011092-55 REVISED

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 74 or 45 CFR Part 92 as applicable.
d. The NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget period.
e. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

This institution is a signatory to the Federal Demonstration Partnership (FDP) Phase V Agreement which requires active institutional participation in new or ongoing FDP demonstrations and pilots.

Carry over of an unobligated balance into the next budget period requires Grants Management Officer prior approval.

This award is subject to the requirements of 2 CFR Part 25 for institutions to receive a Dun & Bradstreet Universal Numbering System (DUNS) number and maintain an active registration in the Central Contractor Registration. Should a consortium/subaward be issued under this award, a DUNS requirement must be included. See http://grants.nih.gov/grants/policy/awardconditions.htm for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) P51OD011092. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see http://grants.nih.gov/grants/policy/awardconditions.htm for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

This award is funded by the following list of institutes. Any papers published under the auspices of this award must cite the funding support of all institutes.

Office Of The Director, National Institutes Of Health (OD) National Institute On Aging (NIA)

Treatment of Program Income:
Additional Costs

SECTION IV – OD Special Terms and Conditions – 2P51OD011092-55 REVISED

REVISION #1

CO-FUNDING

This award reflects support from the National Institute of Aging in the amount of $349,732 total costs.

All previous terms and conditions remain in effect.

PREVIOUS TERMS & CONDITIONS

SUBJECT FOA
This award is subject to the conditions set forth in PAR-11-136, "Limited Competition: National Primate Research Centers (P51)," which are hereby incorporated by reference as special terms and conditions of this award. Copies of this Funding Opportunity Announcement can be found at the following link: http://grants.nih.gov/grants/guide/pa-files/PAR-11-136.html

ORIP FUNDING PLAN FOR FY2014
This competing award reflects the NIH Fiscal Policy for Grant Awards for FY2014 (see NIH Guide Notice NOT-OD-14-055) and the implementation of the ORIP FY2014 grants funding policy: http://dpcpsi.nih.gov/orip/rf/fyg_fp2014.aspx

TOTAL COSTS
This award is funded at a total cost ceiling of $12,651,521. Funds may be re-budgeted as necessary between direct and facilities and administrative costs consistent with policy and institutional requirements for prior approval; however, no additional funds will be provided.

DIRECT CHARGES OF F&A-TYPE COSTS:
Funds requested for office and administrative supplies, administrative coordinators/assistants, custodians, computers, laptops, maintenance & repairs, telecommunications are included in the awarded budget. The allowability of charges to this project for this purpose is predicated on the grantee's compliance with the applicable cost principles.

FUTURE YEAR SUPPORT ADJUSTMENT
Escalation on recurring costs has been removed. Future years have been flatlined.

MEALS
The charging of meal costs directly to a grant is an exceptional activity and contingent upon the following: the grantee institution having a written policy in place ensuring consistent treatment of charging meal costs. This policy must define what constitutes a meeting for the dissemination of technical information when meals are allowable for such meetings, and must define the limitations and other controls on these recurring costs. This policy must be consistently applied regardless of whether the meeting is related to or funded by the Federal government or another source. These costs must also be reasonable.

KEY PERSONNEL
In addition to the PI, the following individuals are named as key personnel (individuals who have effort that ORIP staff is tracking):

Excluded by Requester

Written prior approval is required if any of the individuals named above withdraws from the project entirely, is absent from the project during any continuous period of 3 months or more, or reduces time devoted to the project by 25 percent or more from the level that was approved at the time of award.

PRIOR APPROVAL REQUEST
Any prior approval request (e.g., changes to key personnel as noted on the award, changes in human and animal subjects requiring prior approval, carryover requests) must be submitted to the assigned Grants Management Specialist and Programmatic Official. Please refer to the NIH Grants Policy Statement for the activities and/or expenditures that require NIH approval at http://grants.nih.gov/grants/policy/nihgps_2013/nihgps_ch8.htm#prior_approval_requirements.

RECYCLING FUTURE BUDGET PERIOD START DATES
In order to redistribute awards more evenly throughout the fiscal year, this grant has been issued with a 8.5-month initial budget period with 12 months of monetary support. The continuation award for this grant will cycle each year on May 1st. The non-competing continuation application must be submitted two months (non-SNAP) prior to the anticipated start date of the award.

Information for where to submit reports may be found at:
http://grants.nih.gov/grants/submitapplication.htm.

NON-COMPETING RENEWAL
Future year non-competing progress reports and other documents applicable to this grant should be submitted by March 1, 2014, two months prior to the anticipated start date of the award. NIH will require the use of the Research Performance Progress Report (RPPR) module to submit non-competing progress reports submitted on or after October 17, 2014. Additional information can be found here: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-092.html

COMMUNICATIONS/PRESS RELEASE
If the grantee plans to issue a press release concerning the outcome of ORIP grant-supported research, it should notify Ms. Patricia Newman, ORIP Communications at 301-435-0744, in advance to allow for coordination.

The ORIP WWW home page is at http://dpcpsi.nih.gov/orip/

STAFF CONTACTS

The Grants Management Specialist is responsible for the negotiation, award and administration of this project and for interpretation of Grants Administration policies and provisions. The Program Official is responsible for the scientific, programmatic and technical aspects of this project. These individuals work together in overall project administration. Prior approval requests (signed by an Authorized Organizational Representative) should be submitted in writing to the Grants Management Specialist. Requests may be made via e-mail.

Grants Management Specialist: Amy R Bartosch
Email: mcguirear@mail.nih.gov **Phone**: 301-435-0853 **Fax**: 301-480-3777

Program Official: John D. Harding
Email: hardingj@mail.nih.gov **Phone**: 301-435-0776 **Fax**: 30- 480-3819

SPREADSHEET SUMMARY
GRANT NUMBER: 2P51OD011092-55 REVISED

INSTITUTION: OREGON HEALTH & SCIENCE UNIVERSITY

Budget	Year 55	Year 56	Year 57	Year 58	Year 59
Salaries and Wages	$5,113,775	$5,113,775	$5,113,775	$5,113,775	$5,113,775
Fringe Benefits	$1,657,368	$1,657,368	$1,657,368	$1,657,368	$1,657,368
Personnel Costs (Subtotal)	$6,771,143	$6,771,143	$6,771,143	$6,771,143	$6,771,143
Consultant Services	$33,047	$33,047	$33,047	$33,047	$33,047
Equipment	$497,849	$334,994	$282,677	$356,933	$304,279
Supplies	$1,282,242	$1,282,242	$1,282,242	$1,282,242	$1,282,242
Travel Costs	$61,538	$61,538	$61,538	$61,538	$61,538
Alterations and Renovations	$8,438	$171,294	$223,610	$149,355	$202,009
Other Costs	$1,406,989	$1,406,989	$1,406,989	$1,406,989	$1,406,989
TOTAL FEDERAL DC	$10,061,246	$10,061,247	$10,061,246	$10,061,247	$10,061,247
TOTAL FEDERAL F&A	$2,675,389	$2,675,389	$2,675,389	$2,675,389	$2,675,389
TOTAL COST	$12,736,635	$12,736,636	$12,736,635	$12,736,636	$12,736,636

Facilities and Administrative Costs	Year 55	Year 56	Year 57	Year 58	Year 59
F&A Cost Rate 1	28%	28%	28%	28%	28%

F&A Cost Base 1	$9,554,959	$9,554,959	$9,554,959	$9,554,959	$9,554,959
F&A Costs 1	$2,675,389	$2,675,389	$2,675,389	$2,675,389	$2,675,389

Form Approved Through 6/30/2012

12168200

Health and Human Services
c Health Services

Grant Application FEB 25 2013

Do not exceed character length restrictions indicated.

PI: ROBERTSON, JOSEPH E
1 P51 OD017953-01
Dual: RI
IRG: ZOD1 SRC(99)

Council: 08/2013
Received: 02/25/2013

1. TITLE OF PROJECT *(Do not exceed 81 characters, including spaces and punctuation.)*
SUPPORT FOR NATIONAL PRIMATE RESEARCH CENTER

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT OR SOLICITATION ☐ NO ☒ YES
(If "Yes," state number and title)
Number: PAR-11-136 Title: LIMITED COMPETITION: NATIONAL PRIMATE RESEARCH CENTERS (P51)

3. PROGRAM DIRECTOR/PRINCIPAL INVESTIGATOR

3a. NAME (Last, first, middle)	3b. DEGREE(S)	3h. eRA Commons User Name
ROBERTSON, JOSEPH E.	PhD MD	eRA Commons User Name

3c. POSITION TITLE	3d. MAILING ADDRESS *(Street, city, state, zip code)*
PI, PRESIDENT	OREGON HEALTH & SCIENCES UNIVERSITY 3181 S.W. SAM JACKSON PARK ROAD PORTLAND, OR 97201
3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT PRESIDENT'S OFFICE	
3f. MAJOR SUBDIVISION OREGON NATIONAL PRIMATE RESEARCH CENTER	
3g. TELEPHONE AND FAX *(Area code, number and extension)* TEL: 503-494-7789 FAX: 503-494-7787	E-MAIL ADDRESS: orserv@ohsu.edu

4. HUMAN SUBJECTS RESEARCH	4a. Research Exempt	If "Yes," Exemption No.
☒ No ☐ Yes	☐ No ☐ Yes	

4b. Federal-Wide Assurance No.	4c. Clinical Trial	4d. NIH-defined Phase III Clinical Trial
	☐ No ☐ Yes	☐ No ☐ Yes

5. VERTEBRATE ANIMALS ☐ No ☒ Yes	5a. Animal Welfare Assurance No. A3304-01

6. DATES OF PROPOSED PERIOD OF SUPPORT *(month, day, year—MM/DD/YY)*		7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD		8. COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT	
From	Through	7a. Direct Costs ($)	7b. Total Costs ($)	8a. Direct Costs ($)	8b. Total Costs ($)
05/01/2014	4/30/2019	$11,923,552	$15,094,147	$63,386,581	$80,294,823

9. APPLICANT ORGANIZATION	10. TYPE OF ORGANIZATION
Name OREGON HEALTH & SCIENCES UNIVERSITY Address 3181 SW SAM JACKSON PARK ROAD PORTLAND, OREGON 97239	Public: → ☐ Federal ☒ State ☐ Local Private: → ☐ Private Nonprofit For-profit: → ☐ General ☐ Small Business ☐ Woman-owned ☐ Socially and Economically Disadvantaged
	11. ENTITY IDENTIFICATION NUMBER 1931176109A1 DUNS NO. 09-699-7515 Cong. District OR-001

12. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE	13. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION
Name JASON JAWORSKI Title GRANTS & CONTRACTS ADMINISTRATOR Address 3181 SW SAM JACKSON PARK RD., L106RGC PORTLAND, OR 97239-3098 Tel: 503-494-7784 FAX: 503-494-7787 E-Mail: orserv@ohsu.edu	Name DEBORAH GOLDEN-EPPELEIN Title DIRECTOR, GRANTS & CONTRACTS Address 3181 SW SAM JACKSON PARK RD., L106RGC PORTLAND, OR 97239-3098 Tel: 503-494-7784 FAX: 503-494-7787 E-Mail: orserv@ohsu.edu

14. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.	SIGNATURE OF OFFICIAL NAMED IN 13. *(In ink. "Per" signature not acceptable.)* Deborah Golden-Eppelein	DATE 2/19/13

PROJECT SUMMARY (See instructions):

The 5-year renewal for Grant P51OD011092 requests funding for programs at the ONPRC that support biomedical research. The application reflects a strategic focus on interdisciplinary research to optimize the use and development of nonhuman primate (NHP) models. The aims of this application are to: 1) Conduct state-of-the-art research for which NHPs are uniquely suited for solutions to human health problems 2) Provide a regional and national resource for the conduct of interdisciplinary biomedical research, especially as it relates to NHPs. 3) Pursue the highest standards of humane and responsible animal care. 4) Provide research training and experience for those preparing to enter research and biological teaching careers. To accomplish these aims, support is requested in eight broad areas.

1) Administration provides the administrative and service support required for all aspects of the ONPRC. Units include: the Director's Office; Administrative Services; Business Services; Facilities; Information Systems; Research Library; and Research Safety. 2) Animal Services. Units include: Resources, Facilities, and Operations; Pathology Services; the Tissue Distribution Program; Surgical Services; Behavioral Services; Research, Education and Training; Clinical Medicine; NHP Resources (Obese, Primate Aging, Infectious Disease, Time-mated Breeding, and Japanese macaque). 3) Core Science Services. Units include: Assisted Reproductive Technology, Endocrine Technology, Flow Cytometry, Imaging & Morphology, Molecular & Cellular Biology, Molecular Virology, Magnetic Resonance Imaging, and Primate Genetics. 4) Scientific Components include support for Scientific Divisions (Neuroscience, Pathobiology & Immunology, Reproductive & Developmental Sciences and Diabetes, Obesity & Metabolism) and the Interdisciplinary Research Programs (Biology of Aging, Early Childhood Health & Development, Primate Genetics Research). 5) Pilot Project Program. 6) Improvement & Modernization. 7) Outreach and Community Engagement. 8) NPRC Consortium-Based Activities.

RELEVANCE (See instructions):

The funds requested will provide support for the research infrastructure required to conduct the most advanced biomedical research using NHPs as models of human health and disease, and to meet the needs of new emerging areas of research in which the NHP model is critical, including increased biodefense and HIV vaccine research, as well as translational research initiatives that are highly interdisciplinary in nature.

PROJECT/PERFORMANCE SITE(S) (if additional space is needed, use Project/Performance Site Format Page)

Project/Performance Site Primary Location			
Organizational Name: Oregon Health & Science University / Oregon National Primate Research Center			
DUNS: 09-699-7515			
Street 1: 505 NW 185th Avenue		Street 2:	
City: Beaverton	County: Washington		State: OR
Province:	Country: USA		Zip/Postal Code: 97006
Project/Performance Site Congressional Districts: 01			
Additional Project/Performance Site Location			
Organizational Name:			
DUNS:			
Street 1:		Street 2:	
City:	County:		State:
Province:	Country:		Zip/Postal Code:
Project/Performance Site Congressional Districts:			

SENIOR/KEY PERSONNEL. See instructions. *Use continuation pages as needed* to provide the required information in the format shown below. Start with Program Director(s)/Principal Investigator(s). List all other senior/key personnel in alphabetical order, last name first.

Name	eRA Commons User Name	Organization	Role on Project
Robertson, Joseph E. Excluded by Requester	eRA Commons User Name	OHSU ONPRC	Principal Investigator Center Director

OTHER SIGNIFICANT CONTRIBUTORS

Name	Organization	Role on Project

Human Embryonic Stem Cells ☒ No ☐ Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://stemcells.nih.gov/research/registry/eligibilityCriteria.asp. *Use continuation pages as needed.*

If a specific line cannot be referenced at this time, include a statement that one from the Registry will be used.

Cell Line

TABLE OF CONTENTS

Program Director/Principal Investigator (Last, First, Middle): Robertson, Joseph E./Haigwood, Nancy L.

COMPOSITE BUDGET DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Robertson, Joseph E.	Principal Invest.	EFFORT				0	0	0
See Detailed Budget								
SUBTOTALS →						6,060,326	1,964,134	8,024,460

CONSULTANT COSTS See Detailed Budget	39,164
EQUIPMENT *(Itemize)* See Detailed Budget	590,000
SUPPLIES *(Itemize by category)* See Detailed Budget	1,519,582
TRAVEL See Detailed Budget	72,930
INPATIENT CARE COSTS	0
OUTPATIENT CARE COSTS	0
ALTERATIONS AND RENOVATIONS (Itemize by category) See Detailed Budget	10,000
OTHER EXPENSES *(Itemize by category)* See Detailed Budget	1,667,416

CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 11,923,552
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 11,923,552

PHS 398 (Rev. 6/09) **Form Page 4**

JUSTIFICATION

Personnel

See detail budgets for complete justification

Consultant Costs

See detail budgets for complete justification

Equipment

See Improvements and Modernization for complete justification

Supplies

See detail budgets for complete justification

Travel

See detail budgets for complete justification

Alterations and Renovations

See Improvements and Modernization for complete justification

Other

See detail budgets for complete justification

ONPRC RESOURCES

OVERVIEW:

The ONPRC began in 1962 as an independent research institute, administered by the Medical Research Foundation of Oregon. It was established as one of eight federally-sponsored national primate centers as a major scientific resource for the breeding, maintenance, and study of non-human primates, particularly as essential for basic and applied research towards solving human health problems and diseases. In 1998, the ONPRC was merged into the Oregon Health & Science University (OHSU) as a free-standing institute. As a result of the merger, the land that housed the Center (about 250 acres) along with the Oregon Graduate Institute (OGI - 50 acres located adjacent to ONPRC) were renamed as the OHSU West Campus. In recent years the portion belonging to the OGI and a small portion of land to the east of the ONPRC were sold by the University. The ONPRC portion of this campus (165 acres) is also home to the Vaccine and Gene Therapy Institute which houses the ONPRC Division of Pathobiology and Immunology. Most services provided by OHSU to the West Campus are provided from its downtown locations with the exception of the Small Lab Animal Unit, Research Safety (previously Environmental Health and Radiation Safety), Shipping and Receiving, and Central Stores.

The ONPRC is organized into five divisions: Administration, Division of Comparative Medicine, Division of Neuroscience, Division of Reproductive & Developmental Sciences, Division of Pathobiology and Immunology, and the Division of Diabetes, Obesity, & Metabolism. These divisions employ 361 people, 79 of whom are doctoral-level scientists or DVM's.

The ONPRC is fully accredited by the American Association for the Accreditation of Laboratory Animal Care, its animal census includes about 4,729 nonhuman primates composed of 4221 Rhesus macaques, 350 Japanese macaques, 148 Cynomolgus macaques, and 10 baboons.

Resources housed at the Center that are critical to its mission include:

- Research laboratories that house 38 independently funded investigators. These include 30 Core Scientists and 8 Affiliate Scientists.
- Laboratory and support space for eight research support cores, including
    1. an Assisted Reproductive Technologies (ART) – Embryonic Stem Cell (ESC) Support Core that provides NHP gametes, embryos, and relevant technologies critical for the development of research models for human diseases;
    2. an Endocrine Support Core with regional and national stature in steroid and protein hormone analyses in non-human primate studies;
    3. a Flow Cytometry Core with four multi-parameter flow cytometric analyzers and a 14-parameter high speed flow cell sorter;
    4. an Imaging and Morphology Support Core that provides advanced microscopy techniques, including confocal and wide field fluorescence with deconvolution, stereology and image analysis, and laser capture microdissection;
    5. a Molecular and Cell Biology Support Core that provides customized support for conventional and Next-Generation sequencing, qPCR, genotyping, nucleic acid preps, lentiviral vectors, cell culture and provides automation for higher throughput applications;
    6. a Molecular Virology Support (MVSC) that provides essential virology services, reagents, specialized expertise and training to advance a wide array of non-human primate research, including viral biology, pathogenesis, immunology, viral vaccines, gene transfer, and gene therapy;
    7. an MRI Support Core, located within 100 feet of the ONPRC surgical suite, equipped with a Siemens 3 Tesla Tim Trio MRI system that is optimized for studies of sedated nonhuman primate research subjects; and
    8. a Primate Genetics Services Support Core that uses state-of-the-art technology for the genetic characterization of NHPs, supporting both colony management and scientific research goals.

- ONPRC scientists have access to proteomics and microarray gene-profiling through the OHSU Proteomics and Genomics Shared Resources, both located on the main campus.
- A Research Library that functions in cooperation with the main campus library and contains an extensive database relating to articles on primates, various scientific journals and electronic access to a variety of libraries and online subscriptions
- A Bioengineering Service that supplies specialized technological expertise to solve problems with complex equipment on the ONPRC campus.
- Animal housing and support space for approximately 4.500 to 5,000 NHPs, housed in a variety of indoor and outdoor facilities. Over 84% of the NHPs are socially housed in groups.
- An expanded Animal Services Building Specific Animal Location containing a BSL-2+ containment area for animals in the AIDS research program, and new laboratory and behavioral testing space.
- An NHP ABSL3 facility composed of two ABSL3 suites each capable of housing up to 36 animals and approved by the CDC for select agent work.
- Sheltered outdoor group housing that employed a novel design. Twelve duplexes and two quads containing 32 units, each holding 30 to 60 specific pathogen free (SPF) animals in environmentally protected space.
- A P51 colony of 3,560 SPF Indian-derived rhesus macaques, valuable for being an important model for infectious disease and vaccine development, as well as for their genetic characterization.
- Development of the ONPRC AIDS Research Expanded SPF Rhesus Macaque Breeding Colony to provide genetically characterized Indian-origin rhesus macaques free of a broad number of enzootic and zoonotic agents to enhance the usefulness of the resource for cutting edge opportunistic agent and vaccine research. The goal is to maintain a production group of 100 adult breeder females capable of producing 35 surplus animals annually for research use.
- Development of specialized NHP resources including an aging colony of 100 animals, an obese colony of 168 animals, a National AIDS Macaque Resource of 60 animals and a Japanese Macaque colony of 350 animals.
- A computerized animal records system (currently Integrated Records Information System, IRIS, but will be transitioning to PRIMe) that tracks all animal records, including the documentation of their psychological well being, specific pathogen free status, pedigree analysis, and also is used to charge service fees to projects.
- The coming PRIMe system will provide data storage capabilities for Research Support Cores and laboratories.
- A tissue distribution program that every year distributes about 1,589 tissue samples, including about 512 to investigators from outside the Center.

FACILITIES

The ONPRC consists of an administration building, three major research buildings, eight main facilities for indoor animal housing, and a number of structures dedicated to service functions (see ONPRC Campus Map on the next page). The following facilities statistics include the VGTI/ONPRC building which contains the Vaccine Gene Therapy Institute and the ONPRC Divisions of Pathobiology and the Division of Reproductive and Developmental Sciences along with the OHSU Small Animal Lab Unit. These facilities contain Specific Animal Location of indoor area: Specific Animal Location is dedicated to laboratory use; Specific Animal sq. ft. is dedicated to indoor animal housing; Specific Animal Location is dedicated to support space for both laboratories and indoor animal housing; and Specific Animal is assigned to office space. The remaining space contains service areas, mechanical rooms, hallways, restrooms, etc. In addition, there is a total of Specific Animal of outdoor animal space composed primarily of 32 shelter housing units providing Specific Animal Location of animal housing and eight outdoor primate corrals, covering a total of Specific Animal Location

As noted above, the Pathobiology Department core scientists and staff and the Division of Reproductive and Developmental Sciences are located in the VGTI/ONPRC Building located on the ONPRC campus. This building provides Specific Animal laboratory and laboratory support space including BSL3 labs, Specific Animal Location of office space, and Specific Animal Location of small animal housing space that is

available to ONPRC researchers for small animal research work.

Descriptions of major facilities and a summary of statistics on all facilities follow. Detailed descriptions of facilities constructed or renovated during the last five years may be found in "Progress during the Past 5 Years" in the Facilities and Properties section.

Building Number	Building Name
Facility Security	Administration Building
	Research Building
	Physical Plant
	Colony Building
	Colony Annex
	Equipment Shed
	Physical Plant Shops
	Storage Shed
	Diet Kitchen
	Sheltered Group Housing
	Generator & Liquid Nitrogen Freezer
	Colony Generator Shed
	Corral #8
	Higgins Building
	Trash Holding Shed
	Central Stores
	Research Annex
	Kroc Building
	Corral #1
	Corral #2
	Corral #3
	Corral #4
	Corral #5
	Corral #6
	Cammack Building
	Montagna Auditorium
	Cage Wash Building
	Staff Support Building
	Cooley Cellular & Molecular Biology Building
	Harem
	ASB I
	ASB II
	Vaccine & Gene Therapy Institute
	ASB III
	Animal Support/ABSL3 (ASA) Building
	PENS
	Data Center
	MRI Building
	Guard House
	Corral #7

Facility Security **Administration Building.** Constructed in 1962, with a major renovation completed in 2010 that seismically retrofit the building. The Administration Building contains administration offices, two conference rooms, large meeting hall, kitchen facilities, library, and information technology support space, an IS training room, and offices. The Division of Comparative Medicine Administrative offices were moved to this building in 2012.

Facility Security;Specific Animal Location Constructed in 1962, with a major renovation in 2012 that seismically retrofit the building. The Facility Security Building contains research laboratories primarily occupied by the Division of Diabetes, Obesity & Metabolism; the Endocrine Support Core; the Molecular Virology Support Cores; the Division of Comparative Medicine administration; offices; two conference rooms; conventional primate caged housing; and rooms for animal procedures and radiographic procedures.

Facility Security **Physical Plant.** Constructed in 1965 with minor renovations since then. It houses the main chillers for campus cooling. During the last P51 core grant period the boilers were removed, and the boiler located at the VGTI/ONPRC Building is used to provide heating for the campus.

Facility Security Constructed in 1961 and partially renovated in 1973, 1979, 1985, 1999 and 2002. This facility contains Division of Animal Resources veterinary staff offices, clinical pathology laboratory, main feed storage area, clinical space used for examination and small procedures, eight rooms for NHPs in conventional cages, four large indoor-outdoor runs for group housed NHPs, and 22 smaller group pens for NHPs.

Facility Security;Specific Animal Location Constructed in 1962 and 1963, and partially renovated in 1986 and 1987; contains three NHP animal rooms, four indoor/outdoor runs for group housed primates, and quarantine facilities containing three animal rooms. The building also has a cage wash facility, a radiology room, a procedure room, and a central diet preparation room. Final NIH approval is expected early in 2013 for a major remodel to add socially housed behavioral observation suites and upgrade the HVAC system.

Facility Security **Physical Plant Shops.** Constructed in 1965 and provides support space for facilities technicians and their equipment, a carpenter shop, paint shop, metal shop, and a plumbing and HVAC shop.

Facility Security **Colony Diet Kitchen.** Constructed in 1968 and totally renovated in 1986; contains kitchen for experimental and clinical special diet preparation, walk-in refrigerator, and freezer.

Facility Security;Specific Animal Location Constructed in 2001, 2005, and 2008, 32 units house groups of 30 to 60 SPF rhesus monkeys in 14 environmentally protected greenhouse style buildings.

Facility Security;Specific Animal Location One one-acre corral houses the Japanese macaque troop with an associated covered and heated feed pen. This was previously a two-acre corral that was divided to create an additional rhesus corral.

Facility Security **Higgins Building.** Constructed in 1967; remodeled in 2010 to contain locker rooms and a bathroom for DCM.

Facility Security **Central Stores.** Constructed in 1972; this building houses OHSU supplied research stores and shipping/receiving services. It also houses the Facilities Custodial Team and biomedical engineering services.

Facility Security **Research Annex Building.** Constructed in 1974 and partially renovated In 1991, the south Research Annex includes research laboratories, a virology laboratory, and a biosafety level-3 room. The north Research Annex has a laboratory and Division of Comparative Medicine offices along with a conference room, a training room and a small kitchen.

Facility Security;Specific Animal Location Constructed in 1974 and renovated in 1982, 2003, and 2007, this facility provides cage wash, autoclave, procedure room, food preparation room, and three NHP containment animal rooms.

Facility Security;Specific Animal Location house rhesus in the SPF production group. Each has an associated covered and heated feed pen.

Facility Security **Cammack Building.** Constructed in 1977; renovated in 2007 to provide office space for DAR technicians.

Facility Security **Montagna Auditorium/illustrations Building.** Constructed in 1979; remodeled in 2012 to add an education lab. It also contains Radiation Safety offices and an auditorium.

Facility Security **Cage Wash Building** Constructed in 1975; contains a tunnel cash washer and an associated boiler.

Facility Security **Staff Support Building** Constructed in 1984 and renovated in 2007; contains employee break/lunch room and training area, locker rooms and shower facilities.

Facilit **Cellular and Molecular Biology Building.** Constructed in 1988 to accommodate the research methods and tools of cell and molecular biology. This building hosts the Neuroscience Division the Molecular & Cell Biology Support core, the Primate Genetics Services Support Core, and contains research laboratories, a cell culture facility, offices, and a conference room.

Facility Security;Specific Animal Location Constructed in 1990; houses primates in harem groups in ten indoor/outdoor runs, with associated support space, feed preparation, and procedure areas.

Facility Security;Specific Animal Location Constructed in 1992; contains surgery and necropsy suites, special containment biosafety level-2+ and conventional biosafety level-2 animal housing, multiple cage rack sterilizing and washing units, and offices for surgical, veterinary, and Division of Animal Resources staff. Additions to the original building were constructed in 1998, 2000, 2004, and 2010 with the building being recorded in three distinct phases on the university records and containing a nonhuman primate nursery, two major and two minor surgical suites, necropsy suite, 91 animal rooms, behavioral and observation rooms, research laboratories, animal procedure space, clinical support, feed prep rooms and animal care staff offices, locker rooms and a state-of-the-art barrier-housing facility for the U24 supported expanded SPF colony.

Facility Security Constructed in 1999-2000, as part of OHSU's expansion on the West Campus; the East wing of the building contains research laboratories, 4 biosafety level-3 rooms, research support space for virology, the Flow Cytometry Support Core, hybridoma/monoclonal antibodies, proteomics, and DNA microarray, offices and a conference room. The ONPRC Pathobiology Division is located in VGTI space. The West wing houses VGTI/Pathobiology laboratories on the third floor and the Division of Reproductive and Developmental Sciences on the first and second floor. This building hosts the Assisted Reproductive Technology (ART) –Embryonic Stem Cell Support Core and the Imaging and Morphology Support Core. Currently the ONPRC Director has her lab on the third floor of this building and OHSU provides a small lab animal housing unit in the basement that includes 1,620 square feet of conventional rodent space and 800 square feet of rodent ABSL3 space. This building also contains a modem boiler with sufficient capacity to heat the entire ONPRC campus.

Facility Security;Specific Animal Location Constructed in 2009, the Facility Security Building provides two NHP ABSL3 suites that hold up to 36 animals each and are CDC certified for select agent work. The suites are state-of-the-art with biometric entry control and each contain a procedure room. The building also houses a cage wash, cage storage, kitchen facilities, food storage facilities including refrigeration and freezer areas, five conventional housing animal rooms, and a third procedure room in the conventional housing

area.

Facility Security;Specific

under construction). This is a group housing primate facility based on a corn crib design with 12 indoor/outdoor runs that have heated floors. Each run will accommodate 10 to 15 primates. It also includes a service building that provides an office for DCM staff, food preparation facilities, and animal support space for temporary housing and clinical care of up to 56 NHPs.

Facility Security

Data Center (planning phase). This data center is being built by the university to supply redundancy for their main data center that provides support for the entire campus. It will house ONPRC data. The Data Center

Facility Security

Facility Security

MRI Building. The MRI Building is a modular building that was moved from the main OHSU campus in 2008 and hosts the MRI Support Core. The MRI Building has offices, an animal preparation room, wet lab space, and a 3 Tesla magnet for use on live nonhuman primates.

Facility Security

AERIAL PHOTO OF THE ONPRC

Facility Security

OVERVIEW

Background and mission of the ONPRC

The mission of the Oregon National Primate Research Center (ONPRC) is to promote scientific discovery, particularly in nonhuman primate (NHP) models, to accelerate progress in understanding human diseases, leading to better health. The availability of information about human genetics, coupled with the similarity of the NHP genome to that of humans, provides the opportunity for NHP models to make significant contributions to the discoveries of new cures and therapies. In the last five years, the NIH Office of Research Infrastructure Programs (ORIP, formerly NCRR) re-emphasized its mandate to foster collaborative and translational research, and has formed the "Ninth Primate Research Center" as a consortium of the eight National Primate Research Centers (NPRC Consortium). The ONPRC had previously developed four goals directed toward meeting the objectives of this important ORIP-sponsored program. All four of these goals are supported by the funds from the P51 Core grant to various degrees. Furthermore, all of the research programs have leveraged P51 funding by successfully bringing in external funding for scientific studies and training opportunities for fellows, students, interns, and visiting and collaborating scientists. Our original 2008 goals for the past funding period were:

1. **Conduct state-of-the-art research for which NHPs are uniquely suited for solutions to human health problems.** The primary goals of the Center during the past several years have been to develop the most advanced molecular, cellular, and imaging techniques and provide them as core services to the Center scientists, while at the same time providing Center resources to support the development of new NHP models for the study of human health and disease. AIDS vaccine and pathogenesis models, along with NIH investments in biodefense-related agents, have continued to be one of the major thrusts of the portfolio, the biodefense research having been made possible with the opening of the ABSL-3 space for NHP research in 2010. The availability of molecular and cellular techniques has been a critical component in new programmatic development in molecular genetics and genomics. The ability to perform genetics studies, afforded by our large specific-pathogen-free (SPF) rhesus breeding colony, creates a unique opportunity to use genetic approaches to elucidate the specific functions of genes, diagnose diseases, and search for means to cure or treat diseases. Since 2009, a number of new areas of NHP model-based research have developed at the Center. These are summarized in the Progress Report and in detail in the **SCIENTIFIC COMPONENTS** section, in the **Scientific Divisions** and **Interdisciplinary Research Programs** (IDRPs). These programs focus on current and future cross-disciplinary opportunities in Primate Genetics, Biology of Aging, and Early Childhood Health & Disease. Metabolic disease research, defined as a Working Group in the last P51 grant submission, was expanded in 2012 to create the newest Research Division, in Diabetes, Obesity and Metabolism.

2. **Provide a regional and national resource for the conduct of interdisciplinary biomedical research, especially as it relates to NHPs.** The Center supports research programs using NHPs for investigators housed at the Center, at the host institution, and from other parts of the country. The management of these projects is dependent on an experienced and skilled staff to help design and execute a wide range of research protocols. From 2009-2012 (FY2010, FY2011, and FY2012), external scientists who served as collaborators to ONPRC scientists and whose research programs benefit from services provided by the Center increased each year, resulting in the largest number yet of multiple-PI grants, program project grants, cooperative agreements, and collaborative and directly subcontracted work. The interdisciplinary nature of much of this research was, in fact, the impetus for the establishment of the IDRPs. The Center also supports an active Tissue Distribution Program, which provides samples to both Center and outside scientists, as well as the Primate Pathology Imaging Database (PPID), a collaborative program within the NPRC Consortium that provides data sharing across the nation amongst pathologists and other investigators. Other Center resources include the primate Reference Library and access to Center Research Support Cores. These cores provide services, on a fee-for-service basis, and also serve as training centers for students or faculty who want to learn a particular technique. The SPF rhesus macaque breeding program insures a supply of NHPs for the Center's research programs, and, in its proposed expanded capacity, will continue to provide SPF NHPs for investigators collaborating with the Center. To better address availability and access for outside investigators,

our Collaborative Research Unit (CRU) coordinates these research requests within and outside our scientific divisions. Finally, through Center publications (external web site, intranet, electronic newsletters, and dissemination of scientific discoveries in the press), information about research programs and support services is made available to the public. Participation in the NPRC Consortium Working Groups has grown significantly, as noted in the Progress Report for the **NPRC CONSORTIUM-BASED ACTIVITIES**.

3. **Pursue the highest standards of humane and responsible animal care.** The Center's Division of Comparative Medicine (previously the Division of Animal Resources) directs and provides complete oversight of the entire animal care and use program. The Center has been continuously AAALAC-accredited for over 40 years, and once again received Continued Full Accreditation in 2010. The quality of animal care is first served by having adequate staffing with the requisite NHP training and expertise to ensure appropriate husbandry, clinical care, and behavioral assessment. The Division significantly increased the size and composition of the veterinary staff and has revised the organizational structure to better facilitate research support as necessitated by a substantial increase in NHP research and breeding populations over the last 5 years. The recruitment of Excluded by Requester, the Associate Director and Division Chief and a Diplomate of the American College of Laboratory Animal Medicine (DACLAM), along with several newly appointed veterinarians, have strengthened the repertoire of clinical care and management oversight capabilities. Animal care is also enhanced by the modernization and expansion of animal facilities that has been a hallmark of infrastructure improvements over the last several years. Utilizing multiple C06 and G20 grants from NCRR and ORIP, we were able to renovate old facilities, build new facilities, and purchase cages for paired housing. Collectively, these activities allowed us to greatly increase the number of NHPs living in paired-housing conditions. Following completion of the new addition to the Animal Services Building (ASB) and expanded indoor-outdoor housing in early 2013, there will be an even greater increase in social housing. Expansion of the Behavioral Services Unit has enabled the Center to utilize group housing more effectively, which has benefits for breeding, overall colony health, and psychological wellbeing. These are summarized in the Progress Report and in detail in the **ANIMAL SERVICES** section.

4. **Provide research training and experience for those preparing to enter research and biological teaching careers.** The Center participates in a number of educational programs that target elementary school students and teachers through postdoctoral fellows, and, in the last funding period, we have added the elderly as a new outreach population. Members of the faculty participate in numerous doctoral-level training grants. Four Core Scientists, Drs. Excluded by Requester are PIs on four training grants funded by NIAID, NIA, NICHD, and the Fogarty International Center (NIH), respectively. The Center has greatly expanded the number of trainees who are working in ONPRC scientists' laboratories, having trained 107 graduate students and postdoctoral fellows during the last year alone. Of particular relevance to the Center's role in translational research, more than ten clinical fellows (from the OHSU Departments of Pediatrics, Ob-Gyn, and Medicine, including its Division of Infectious Disease) received research training at the Center in the use of NHP models for human disease. Additionally, the Center provided NHP training for 34 veterinary externs (2009-12), sponsored three veterinary residents using an R25 Nonhuman Primate Veterinary Clinical Education Program completed in 2012, and, together with OSU and OHSU, established an ACLAM approved Oregon LAM Residency Consortium; the first 3 veterinary residents entered this 3-year program in 2012. We also have an active summer program for high school students and science teachers, who receive support from a number of NIH and foundation sources. To provide science education to the general public and to create an awareness of the need for animal research, the Center conducts numerous tours. Since 2009, an average of 3,000 visitors per year have toured the Center, featuring on overview of research and tours of the primate breeding enclosures, and have gained a greater appreciation of the important role of an NPRC.

Overview of the relationship of the NPRC to the grantee institution

Oregon Health & Science University (OHSU) is the host institution for the ONPRC, and OHSU President Joseph Robertson, M.D., is the Principal Investigator to whom the Center Director, Excluded by Requester is responsible. From its founding in the 1960s through 1998, the ONPRC was an independent research institution and was responsible for providing all of its administrative and operations services. In July 1998, the ONPRC formally merged with OHSU, and in December 2003, the fiscal and business/grants management

systems were incorporated into OHSU Central Services. The purpose of these central services is to provide a basic business and compliance-assurance structure, within which the three-fold mission of clinical care, teaching, and research can function effectively. Some areas, such as legal, banking, technology transfer, and environmental health and radiation safety, are handled entirely by OHSU, while most administrative functions are handled cooperatively between resources at the University and at the institute/department level. Central Services provides essential operational support and continuity when addressing emergency management and incident response capability. This approach requires significant expertise and staffing for administrative and business services offices at ONPRC. Similarly, because of the physical distance and unique nature of primate center facilities, the Facilities & Property staff and its operation were retained by ONPRC in agreement with OHSU and ORIP. This approach has been a significant advantage to ONPRC by enabling the Center to retain decades of experience in a responsive and dedicated local staff, and centralizing and harmonizing key functions while tailoring non-duplicative services to meet unique needs that arise for an NPRC. Importantly, OHSU provides shared governance, oversight, and resources from the Office of the Senior Vice President for Research, including support in Finance, Research Grants & Contracts, Sponsored Projects, Human Resources, and overall leadership. Additional shared governance and oversight stem from the Office of Research Integrity, via a West Campus Integrity Officer appointed in 2010 and via shared oversight and coordination of the Main Campus and West Campus IACUCs; in Environmental Health & Radiation Safety within a local group that oversees Research Safety; in the Office of Research Advocacy, which was established in 2008; and in Public Safety and Emergency Management. Details of these organizational relationships are described in the **ADMINISTRATION** section and **Administration Overview**.

All ONPRC Core Scientists have academic appointments as faculty in appropriate departments at OHSU and are subject to the same promotion guidelines for their academic rank. The OHSU merger played an important role in the increased number of graduate students at the Center, as Core Scientists joined several NIH T32 training grants as mentors. Several of our new recruits, such as Drs. Excluded by Requester in the Division of Neuroscience, have shared-FTE faculty appointments with the Department of Behavioral Neuroscience at OHSU. Similarly, Dr. Excluded by Requester in the Division of Pathobiology & Immunology is jointly appointed in the VGTI and the ONPRC, and Dr. Excluded by Requester in the Division of Diabetes, Obesity & Metabolism has a joint appointment with Ob/Gyn. Two other new recruits have been welcomed as adjunct faculty members in the appropriate basic science or clinical departments, Dr. Excluded by Requester in Neurology and Dr. Excluded by Requester in Pediatrics and Ob/Gyn. These types of co-recruitment and shared support underscores the intent of enhancing ties between the OHSU basic science and clinical departments and the ONPRC, particularly in areas where research is more translational in nature.

Most of the members of the Division of Pathobiology & Immunology at ONPRC have appointments in the Vaccine and Gene Therapy Institute (VGTI). Leadership at the VGTI includes the Director Dr. Excluded by Requester and Associate Director Dr. Excluded by Requester served as Head of the Pathobiology & Immunology Division at ONPRC until the fall of 2012. The VGTI has laboratories on the OHSU West Campus, co-located and highly integrated into the ONPRC in terms of research facilities, scientific activities, cores, and research interests. All of the buildings on the West Campus are managed by the ONPRC Facilities group, with oversight from OHSU.

Overview of the organization and administration of the ONPRC

An organizational chart is shown depicting the relationship of the PI, Dr. Joseph Robertson, president of OHSU and the ONPRC Center Director, Dr. Excluded by Requester As reflected by this chart, the Center is organized as a fairly flat organization, with Associate Directors, Scientific Division Chiefs, and the Public Information Office reporting to the Director. Dr. Excluded by Requester reports to the OHSU Senior Vice President for Research, Excluded by Requester who reports to the PI of the grant, Dr. Robertson. Key external and internal committees essential for decision-making also report to the Director, including the External Scientific Advisory Board. Integral to the support of research programs are well-defined service units, which manage the infrastructure of the Center. This structure was put into place with the prior renewal and has been maintained and enhanced by the addition of key staff members to accomplish new objectives defined below in the strategic planning process. The Director serves as the formal liaison to OHSU and in practice all of the senior leaders work closely with committees, divisions, departments, and initiatives at OHSU.

Qualifications of the Senior Leadership

Excluded by Requester Director

Excluded by Requester was appointed fifth Director of the ONPRC and a Senior Scientist in the Division of Pathobiology & Immunology in October 2007. She holds an appointment as Adjunct Professor of Molecular Microbiology & Immunology at OHSU in the School of Medicine. Dr. Excluded by Requester is a leading investigator in HIV vaccine and antibody research, with a focus on work in NHP models for AIDS. Her work, published in 2010 in Nature Medicine, was the first to show that neutralizing antibodies can modulate infection and AIDS in newborn macaques. She was recruited to the Center from Seattle Biomed, where she was founding Director of the Viral Vaccines Program and Professor of Pathobiology in the School of Public Health and Community Medicine, and jointly in Microbiology in the School of Medicine at the University of Washington (1997-2007). Prior to joining the nonprofit and university sector, Dr. Excluded by Requester was a Research Director at Chiron Corporation in Emeryville, CA (1983-1992), where she led the preclinical development of one of the first HIV vaccines, to the Envelope subunit protein gp120. She was a Senior Principal Scientist at the Bristol-Myers Squibb Pharmaceutical Research Institute in Seattle from 1992-97. She served as the first Scientific Ombudsperson at the Fred Hutchinson Cancer Research Center from 2004-2006. Thus, she has brought significant scientific leadership, negotiation, and managerial experience to the Center. She has served as a regular member on NIH Advisory Panels, NIH Study sections, and journal editorial boards and presently serves on the Board of Scientific Counselors at the Vaccine Research Center at NIH. In the summer of 2011, Dr. Excluded by Requester was asked to co-author an article for the Institute of Medicine that was published as part of the IOM report "Chimpanzees in Biomedical and Behavioral Research: Assessing the Necessity." Dr. Excluded by Requester served as the Chair of the AIDS Vaccine Research Subcommittee at NIH from 2009-2012 and she was just appointed to serve on the Council of Councils at NIH. She has maintained continuous NIH funding since 1988, is currently the PI of one NIH R01 grant, the PI for several subcontracts for external investigators performing NHP research at ONPRC, plus the PI and Project and Core Leader of an NIH P01 grant. She has published over 100 journal articles and book chapters, as well as numerous scholarly commentaries, and has trained 6 Ph.D. students, 3 M.S. students, and 15 postdoctoral fellows. She serves as primary liaison to the office of the Senior Vice President for Research and other OHSU senior leadership committees to represent the interests of the ONPRC and the NPRC program.

Excluded by Requester Associate Director for Research

Excluded by Requester was appointed Associate Director for Translational Research at ONPRC in May 2007 and Associate Director for Research in 2009, and is also Senior Scientist in the Divisions of Diabetes, Obesity & Metabolism and Reproductive and Developmental Sciences. He previously served as Professor and Associate Chair for Research in the Department of Pediatrics and Doernbecher Children's Hospital at OHSU from 1994-2007, and retains joint appointments as Professor of Medicine, Pediatrics, and Cell and Developmental Biology at OHSU. Dr. Excluded by Requester is also Director of the OHSU Center for Diabetes and Obesity Research. Dr. Excluded by Requester was Senior Investigator at the Diabetes Branch in NIDDK's intramural research program from 1984-1994 and Assistant Professor of Biological Sciences at the University of California, Santa Barbara, from 1978-1984. Dr. Excluded by Requester is an expert in the molecular endocrinology of growth factor action, and has focused on insulin and insulin-like growth factor research for the last 29 years. Since his recruitment to the Center, he has developed new approaches for the analysis of islet and adipose function in NHP models. Dr. Excluded by Requester has had continual extramural or intramural NIH research funding for over 35 years, as well as significant funding from the DOD-managed prostate cancer research program, the Private Source and various pharmaceutical companies. He has served on numerous review panels for NIH and DOD research programs, the editorial boards of Endocrinology and the Journal of Biological Chemistry as well as an ad hoc reviewer for >50 other professional journals, various national society committees and external advisory boards. He has authored over 180 primary research articles and more than 60 reviews, and is the inventor on issued patents in both diagnostics and therapeutics. Dr. Excluded by Requester tenure at the main OHSU campus and his established links with basic and clinical departments and the OHSU Foundation and Office of Technology Transfer and Business Development contribute to the strong linkages between the Center and the host institution.

Excluded by Requester Associate Director for Comparative Medicine

Excluded by Requester was appointed Associate Director for Comparative Medicine (formerly Animal Resources) in May 2012, succeeding Dr. Excluded by Requester (2008-2012), who left to pursue a position at the University of Arizona that facilitated her professional interest in hands-on animal care and teaching. Excluded by Requester is a Diplomate of the American College of Laboratory Animal Medicine and a senior leader with broad experience in the support and oversight of laboratory animal care and use programs using multiple NHP species in the commercial, academic and government sectors. Excluded by Requester plays a vital part in the overall supervision of every aspect of the animal care program, including: management of all breeding colonies; successful preservation of SPF rhesus macaque colonies; management and allocation of special subsets of NHP resource populations dedicated to obesity, aging, and infectious disease research; subsequent animal allocation to research programs; and the successful provision of animal-related research support services. Excluded by Requester practical knowledge and familiarity with staffing management supporting the development and refinement of animal research models to meet scientific objectives has allowed him to successfully maintain the ONPRC colonies at optimum target populations, to provide the requisite number of animals for AIDS research, to genetically characterize the colonies, and to ensure SPF colony status for future requirements. His background includes experience as an Assistant Vice President for Research (Kansas State University, 2008-2009), AAALAC ad-hoc consultant (2000-present), IACUC Chair, Senior Director, Senior Scientist, and Attending Veterinarian; on-site clinical veterinarian for ABSL-2/3/4 biocontainment studies using rhesus, cynomolgus, and pigtail macaques for infectious disease research, including HIV and Select Agents; corporate oversight of the Alamogordo Primate Facility housing 200+ chimpanzees and an NIAID free-ranging rhesus breeding colony of over 4,000 rhesus macaques; and the managerial oversight for staff and resource utilization as Deputy Director of the NIH Office of Animal Care and Use (1998-2001), and as Senior Director for Charles River Laboratories (2001-2008). Dr. Excluded by is an experienced veterinary professional, well-seasoned in assisting science and program professionals set priorities and fund projects in chemical and biological diagnostics, vaccines, and therapeutics. He continues to be actively engaged as a Subject Matter Expert for the enhancement of new and existing technologies for NHP animal model development.

Excluded by Requester Interim Associate Director for Administration

Ms. Excluded by is the Director of Finance under the Senior Vice President for Research, Excluded by Requester Ph.D. She has held this role since 2004, overseeing critical financial programs for the university, including the F&A rate negotiation. Prior to coming to OHSU, she spent five years as an auditor for Arthur Andersen and KPMG, specializing in healthcare and not-for-profit organizations. Ms. Excluded by has been instrumental in developing a number of important infrastructure programs at OHSU, including establishing the University Shared Resources program (with an annual budget of $1 million) and the Emerging Technology Fund (with an annual budget of between $500,000 and $1 million). She oversees the finances of all of OHSU's research administration, with an annual budget of approximately $16 million, including the pre- and post-award offices, the research integrity office, the department of comparative medicine, and the vice president for research office. She also oversees the finances for the office of Technology Transfer and Business Development. She is responsible for the finances and budgets for the institutes and centers that report to the Senior Vice President for Research. These include the Vollum Institute, the Oregon Clinical and Translational Research Institute, the Advanced Imaging Center, the Center for Regenerative Medicine, the Center for Environmental Toxicology, and ONPRC. Together, these institutes and centers comprise budgets of $132 million dollars. She established the financial infrastructure for new OHSU research centers such as the Center for Regenerative Medicine, and she has ongoing roles in the financial management of this and other centers and institutes. She also plays a key leadership role in the finances of the university as a whole; she has a dual report to Lawrence Furhnstahl, the Chief Financial Officer of the institution, to establish budget priorities and implement strategic goals established by the university President, Joe Robertson, M.D. She has provided institutional leadership for the restructuring and growth of research associated with two philanthropic gifts totaling $225 million, as well with the new Collaborative Life Sciences Building currently under construction. Finally, she provides on-going financial management of high-level faculty and director recruitments, including start-up packages, scientific infrastructure, and other components.

Excluded by Requester Chief, Division of Neuroscience

Following a national search, Excluded by Requester was recruited in December 2011, to succeed Excluded by Requester who served in this capacity since 1987. Excluded by Requester is a recognized leader in the field of alcohol research and has focused for over 25 years on the development of NHP models of alcohol addiction. Her work has established the only animal model (NHP or other) of alcoholism that captures the phenotype of voluntarily drinking to physical dependence, opening up wide avenues of novel research for discoveries in prevention and treatment of alcoholic drinking. Excluded by was recruited to the ONPRC and OHSU in 2005 from Wake Forest University School of Medicine in the Department of Physiology & Pharmacology rising from Assistant Professor (1991) to Full Professor (1998) and served as Director of the Center for Neurobiological Studies on Alcohol (P50). Dr. Excluded by is the founding and current director of the NIAAA consortium (U24) "Integrative Neuroscience Initiative on Alcoholism" consisting of 9 Principal Investigators (each a U01) from national and foreign universities. Dr. Excluded by has also established a NIH-funded Monkey Alcohol Tissue Research Resource that has been utilized by dozens of laboratories resulting in over 40 NHP publications. The unique aspect of this tissue resource is the creation of a bioinformatics-interactive website where users have advanced statistical and graphical tools for data exploration. Excluded by Requester is closely connected with the OHSU campus, retaining a cross-appointment in the Department of Behavioral Neurosciences, where she is a tenured professor and a PI in the OHSU-based P60 Portland Alcohol Research Center. Excluded by Requester has been continually funded by the NIH for 28 years and has over 140 peer-reviewed publications. Excluded by has served on 5 editorial boards of leading pharmacology journals, is the recipient of numerous research awards from scientific organizations, and is active in scientific societies, including serving as President of the Research Society on Alcoholism (2006-2007). Excluded by Requester is actively involved in graduate and post-doctoral training, including serving as the PI of a T32 training grant from NIAAA (2002-2005).

Excluded by Requester Interim Chief, Division of Diabetes, Obesity & Metabolism

Excluded by Requester was appointed the Interim Chief of this new division in August 2012, which was established in response to the successful development and maturation of the Metabolic Disease Working Group. Dr. Excluded by joined ONPRC in 1996 as a staff scientist, following a postdoctoral fellowship at the Institute of Clinical Research of Montreal, Canada. Excluded by Requester became a Core Assistant Scientist in the Division of Neuroscience in 2003 after he developed an independently funded research program. He was subsequently promoted to Associate (Feb. 2007) and Senior (Sept. 2010) Scientist within that Division. Excluded by Requester research focuses on two main areas; (1) developmental programming of metabolic systems, which uses a powerful NHP model to investigate the relative impact of poor maternal health and diet on the development of metabolic and psychological diseases in the offspring; and (2) pathophysiology and therapeutics for adult-onset obesity, diabetes, and cardiovascular diseases. For the latter program Excluded by Requester developed a NHP model of diet-induced obesity/diabetes. Excluded by Requester is a co-Principal Investigator on multi-center research consortium grants supporting both of these programs, as well as having several independently funded programs. He also serves as the Program Manager of the Obese NHP Resource that provides accessibility of these research models to programs throughout the US. Furthermore, he and his NHP research program were highlighted in OHSU philanthropic projects that have resulted in a $25 million contribution for the development of the Moore Center for Health and Nutrition and a $125 million contribution for the development of the Private Source Cardiovascular Institute. Excluded by is a four-time recipient (2008-2011) of a Technology Innovation Award from OHSU, and the 2012 recipient of the Outstanding Leadership in Research Award. Since 2009, he has had more than 30 invited presentations, and published eight review articles and 29 peer-reviewed research articles.

Excluded by Requester Chief, Division of Reproductive and Developmental Sciences

Excluded by Requester became division chief in 1996, eleven years after leaving the Department of Physiology, University of Arizona to join the division as a senior scientist. He also is active in OHSU programs as Professor in the Departments of Ob-Gyn and Physiology & Pharmacology, and as ambassador in the Center for Women's Health. His research effort, funded continuously by the NIH and supplemented with nonfederal projects, emphasizes basic and translational research on the follicle and corpus luteum in the NHP ovary, as related to treating infertility and improving contraception for women. He is currently promoting research interactions between basic and clinical scientists at OHSU and other universities through leadership roles in a NICHD-funded Specialized Cooperative Center Program in Infertility and Reproductive Research (SCCPIR; 2004-2011, Pending Support a Contraceptive Development and Research Center (CDRC, 2007-2016), and an NIH Director's Roadmap Initiative (Oncofertility Consortium, 2007-2013). Excluded by Requester has also provided

leadership at the national level, serving on the Board of Directors and as President-Elect and President of the Society for the Study of Reproduction (SSR, 1990-1996), and the Board of Directors for the Ovarian Workshop. He has served on many NIH advisory groups, including member (1991-1995, 1999) and chair (2000-2002) of the Reproductive Endocrinology Study Section. He has served as Associate Editor (e.g., Molecular Human Reproduction, 2000-2004) and on editorial boards (e.g., Biol Reprod, 1999-2007) of major journals in reproductive sciences. To date, Excluded by Requester has published 194 peer-reviewed research articles and 52 reviews/chapters. He received awards for his research accomplishments (2007 SSR Research Award, 2010 Distinguished Researcher Award from the American Society for Reproductive Medicine) and his mentoring (University of Arizona, Excellence in Teaching 1985; OHSU Faculty Research and Mentoring Award, 2001). Excluded by Requester has trained 12 graduate students, 30 postdoctoral fellows, as well as numerous summer interns (high school and undergraduate students, high school teachers). His combination of whole animal, cellular, and molecular studies on folliculogenesis, ovulation, and luteal structure-function continue to advance our knowledge of primate ovarian function, with recent applications to understanding the causes of polycystic ovarian syndrome, to restoring fertility in cancer patients after gametotoxic therapy, and to developing ovary-based, nonhormonal contraceptives.

Excluded by Requester Interim Chief, Division of Pathology & Immunology

Excluded by Requester succeeded Excluded by Requester as Division Chief in September 2012, when Excluded by Requester elected to expand his leadership role at the VGTI after serving in this capacity for 12 years. Excluded by Requester joined the ONPRC in 1991 following a postdoctoral fellowship at Harvard Medical School. He has joint appointments with the Vaccine and Gene Therapy Institute and the Department of Molecular Microbiology and Immunology, where he is a Senior Scientist and Professor, respectively. Prior to his appointment as Interim Division Chief, Excluded by Requester was Chair of the West Campus Institutional Animal Care and Use Committee (IACUC) and Chair of OHSU Institutional Biosafety Committee. His research, funded continuously by the NIH and nonfederal institutions for 20 years, emphasizes NHP virology, with a specific focus on viral pathogenesis. His work elucidated the role of rhesus macaque rhadinovirus (RRV), a gamma-2 herpesvirus that is closely related to Kaposi sarcoma-associated herpesvirus (KSHV), in viral-associated lymphoproliferative disorder in AIDS-associated malignancies in simian immunodeficiency virus (SIV)-infected rhesus macaques. He developed the NHP model of rhadinovirus-associated AIDS-related malignancies and is identifying viral determinants of pathogenesis in an effort to develop novel vaccine strategies to prevent the onset of disease in susceptible animals. Excluded by Requester also has extensive experience with other NHP models of viral pathogenesis including, monkeypox virus, West Nile virus and simian hemorrhagic fever virus. Excluded by Requester has served on several NIH review panels (e.g., AIDSRC Study Section, 1998-2002; AOIC Study Section, 2001-2005; VirB, 2010-present, and other NIH Training Grant and Special Emphasis Panels), and other regional review panels (California University-wide AIDS Research Program, 2005-2000). He is on the Editorial Board for the Journal of Virology. Excluded by Requester has also chaired International Meetings/Workshops, and served on Scientific Program Committees for several International meetings.

Excluded by Requester Director of the Office of Research Advocacy

Excluded by Requester was recruited to ONPRC in 1994, where he served as Associate Director for Research until 2009. In that year, OHSU developed a new Office of Research Advocacy, whose focus is to provide information and insights into the landscape of animal extremist movement with the goal of decreasing the risk to researchers and to the Institution and increasing public awareness of this problem. Prior to his appointment at OHSU, Dr. Excluded by was Head of the Department of Pharmacology at the University of Iowa College of Medicine for 11 years. He has published over 335 articles and nearly 200 authored or edited books, including texts in endocrinology, molecular and cell biology, and pharmacology. He published op-eds in the *LA Times*, *Wall Street Journal*, *Washington Post*, and scientific publications on the value of animal research. The research of his laboratory, continuously funded by the NIH for over 35 years, was recognized with a MERIT award from the NIH, the J.J. Abel Award of the American Society for Pharmacology and Experimental Therapeutics, the Weitzman, Oppenheimer, and Ingbar Awards of the Endocrine Society, the National Science Medal of Mexico (the Miguel Aleman Prize), the Stevenson Award of Canada, the Oregon State Award for Discovery and the Distinguish Alumnus Award of Baylor College of Medicine. He founded Star Park, a consortium of local Universities and private enterprise, which led to the formation of the West Campus of OHSU. Excluded by Requester served on the National Board of Medical Examiners, including two years as chairman of the reproduction and endocrinology

committee. He is a previous member of Council for the American Society for Cell Biology, FASEB and the Endocrine Society and a prior President of the Endocrine Society, during which time he founded the Hormone Foundation. He is an elected member of the Mexican Institute of Medicine and a fellow of the American Association for the Advancement of Science. Recently, he led an effort by FASEB to create an international meeting on animal extremism.

Governance

Director. Governance of the center is accomplished through **Integrated Leadership** led by the Director's office via weekly meetings of the leadership team that includes the Director and Associate Directors for Administration, Research, and Comparative Medicine, termed the Executive Leadership Committee (ELC). These senior leaders represent the ONPRC at the NPRC National Directors' Meetings held twice yearly and serve as an oversight group for interactions with the NPRC Consortium. On alternate weeks, the ELC is joined by the Scientific Leadership group (the four Scientific Division Chiefs), a group termed the Expanded Executive Leadership Committee (EELC). Minutes are recorded and maintained on SharePoint for both of these meetings to assure transparency and to record decisions and action items. To assure linkages with the broader scientific programs, there are Quarterly EELC Meetings that include leaders from the Interdisciplinary Research Programs, the NHP Special Resource Programs, and Research Support Cores, as well as leaders from all of the key administrative areas such as Research Advocacy, Research Safety, and Research Integrity. The Director meets monthly with [Excluded by Requester] Vice President for Research, and also attends key leadership meetings at OHSU within the School of Medicine to assure strong linkages between ONPRC and other key groups at OHSU, including the Vaccine & Gene Therapy Institute. She represents the ONPRC at the President's Council, which meets monthly. During the last funding period, she and Associate Director Dr. Roberts actively participated in the School of Medicine Strategic Planning Process (termed the Roadmap), and they continue to implement the initiatives that stemmed from this cooperative and collaborative planning effort. The Director's Office is responsible for all ONPRC communications to NIH and ORIP, to the NSAB, to OHSU, and within the community. The Director participates regularly in teleconferences with the other NPRC Directors and NIH staff to assure effective communication and follow-up on strategic goals and action items identified by ORIP and at the biannual NPRC Directors' meetings. The Director and Associate Director for Research jointly oversee and meet regularly with Interdisciplinary Research Program managers, the Outreach group, the West Campus Integrity Officer (who has a dual report to the OHSU Office of Research Integrity), the West Campus Safety group (part of OHSU's Environmental Health & Research Safety).

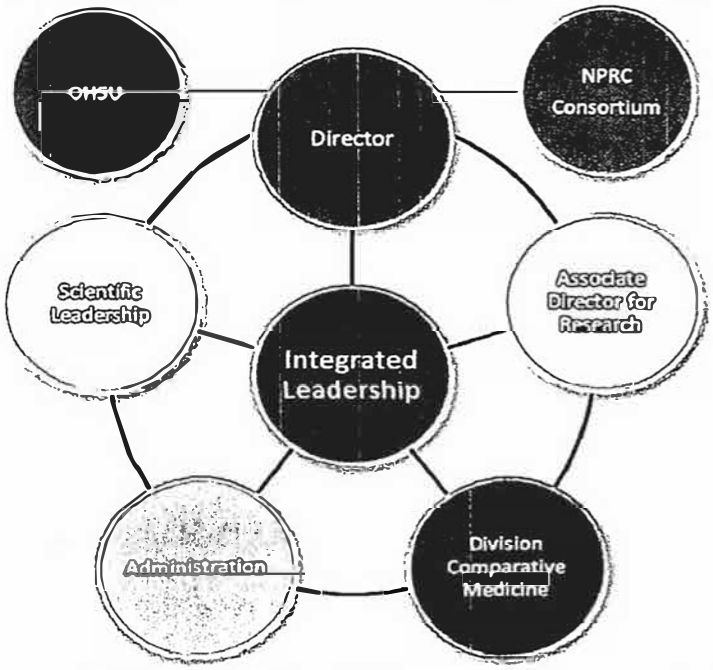


Figure 1. The Integrated Leadership Model is shown in this diagram to indicate the relationship between the Director and Associate Directors, the host institution OHSU and the other NPRCs and NIH (NPRC Consortium).

The Associate Director for Research serves as Chair of the Research Advisory Committee, and is also responsible for management of the Pilot Project Program as well as the Collaborative Research Unit (CRU). The CRU component assures that all inquiries from external sources are directed to the appropriate internal collaborator, and that external research projects are run smoothly and are provided with scientific leadership and expertise, as well as administrative support. The Associate Director for Research also serves as a major liaison between the Center and the OHSU Foundation and the OHSU Office of Technology Transfer and Business Development, particularly to promote and manage research interactions with industry and public-private partnerships. He also oversees the management of the Research Support Cores; these cores are essential components in establishing new technologies that have played such an important role in

the growth in external grant funding. These services have been improved through purchase of new equipment and the establishment of new techniques. Each of the eight Research Support Cores (Assisted Reproductive Technology, Endocrine Technologies, Imaging and Morphology, Flow Cytometry, Magnetic Resonance Imaging, Molecular & Cellular Biology, Primate Genetics, and Molecular Virology) has a senior staff member as a Core Manager and an oversight committee that determines the services to be offered and the charge-back fees associated with each service.

The Associate Director for Administration is responsible for the business services, including grants and contracts, internal NHP-related rate setting and indirect cost proposal development, procurement, human resources (in partnership with OHSU Human Resources), internal and external billing, and development and maintenance of databases related to these activities. Financial oversight is provided via the Office of the Senior Vice President for Research. Grants administration is linked to the OHSU Research Grants and Contracts and the Sponsored Research Agreements groups. The Associate Director for Administration also oversees Facilities and Property, which has close linkages with and oversight by the OHSU Design and Construction group for all construction projects, and Information Systems. The unit of Information Systems works closely with the OHSU central Information Technology Group to coordinate information services on the OHSU West Campus. Specific activities managed by the ONPRC include the computer-based animal records system (IRIS and its replacement, LabKey, renamed PRIMe at ONRPC) the telephone system, and bioengineering services. The Associate Director also oversees the Research Library.

The Associate Director for Comparative Medicine and Division Chief provides NHPs and critical expertise to the scientific aims of all Divisions and Programs. This Division has been reorganized, in keeping with the ever expanding NHP population and increased number of funded research projects using NHPs; the construction of new and renovation of existing animal facilities; and the increasingly complex nature of managing multiple disease models, unique NHP resource populations, various housing modalities, increasingly important genetic characterization of every animal, and the demand for maximizing social housing. The Division maintains excellent communications with the Department of Comparative Medicine on the OHSU main campus and the Associate Director serves as West Campus Attending Veterinarian and has a dual reporting relationship to the Institutional Official, Excluded by Requester

The four research divisions (Diabetes, Obesity, & Metabolism; Neuroscience; Pathobiology & Immunology; and Reproductive & Developmental Sciences) continue to represent the major research areas of the Center. Division Chiefs are responsible for mentoring and promoting the careers of the scientists within the division, appointing Affiliates, and managing and apportioning divisional research space. The Division of Diabetes, Obesity, & Metabolism was established in 2012 in recognition of the growing importance of the need for NHP-based biomedical research that can support the development of treatments and prevention for diabetes and obesity and their sequelae. The Division of Pathobiology & Immunology is the focus for all AIDS-related research conducted at the Center, as well as a focus for Infectious diseases and biodefense initiatives. The Division of Neuroscience addresses fundamental questions of primate neurobiology in the areas of neuroendocrinology, neurodevelopment, neurodegeneration, addiction, aging, and primate genetics. The former Division of Reproductive Sciences changed its name to include developmental sciences, to broaden awareness of its activities in primate development and stem cell biology. The research divisions are essential in that they provide the scientific resources that enable the Center to develop its research programs. The research divisions also enhance the research environment of the scientists by bringing together a critical mass of scientists with similar interests. The research divisions are critical for developing collaborative research efforts with scientists outside of the Center. Having well-defined research divisions has been important in our very successful efforts to increase the number of graduate students performing their dissertation research under the direction of Center scientists.

One of the major thrusts of the last funding period was the expansion of collaborative, interdivisional, and interdisciplinary research. To this end, we established Working Groups in 2008 as a means of to develop **Interdisciplinary Research Programs (IDRPs).** The three original Working Groups (Biology of Aging, Metabolic Disease, and Stem Cells & Developmental Biology) have continued to develop since 2009, with presentations and evaluations at regular Scientific Retreats. With the change in focus of the Division of

Reproductive Sciences to include Developmental Sciences, the Stem Cell Working Group efforts found a natural home for future development within this division. With the recruitment of Excluded by Requester as Chief of the Division of Neuroscience, a strong interdisciplinary group in Addiction was established within that division, and in the Divisions of Reproductive & Developmental Biology and Pathobiology & Immunology. As noted above, we created a new Scientific Division in recognition of the success of the Metabolic Disease Working Group. As a result of these discussions and recommendations from the Expanded Executive Leadership Committee and the P51 NSAB, we have designated three IDRPs as the major emphasis areas outside the scientific divisions for the next funding period (Primate Genetics, Biology of Aging, and Early Childhood Health & Disease). Interdisciplinary Research Programs are responsible for the development of extra-divisional scientific symposia and funding opportunities. These IDRPs are placed on the ONPRC Overall Organizational chart connecting the Scientific and Comparative Medicine Divisions to emphasize the connectivity and interdisciplinary nature of this endeavor.

The **NHP Resources Program** (termed Special NHP Resources in the last submission), which was added in recent years, continues to evolve in response to scientific directions and the need for new NHP models. Currently, four NHP Resource Programs (**Aging Nonhuman Primates, Obese Nonhuman Primates, the Infectious Disease Resource, and the Japanese Macaque Resource**) have developed to manage and support the various NHP resources at the Center. The Managers of these Programs are scientists who work closely with the Director and the Associate Director for Comparative Medicine, since their resources require coordination with NHP planning and breeding and are utilized by members of multiple divisions. Maintenance of special NHP Resources assures oversight and prioritization of these resources, subject to standard Animal Allocation Policies. The Infectious Disease Resource group works closely with investigators in the Division of Pathobiology & Immunology and the Vaccine & Gene Therapy Institute. The Aging Resource and Japanese Macaque Resources work with multiple divisions to provide appropriately aged and characterized NHP for key studies. These Resource Programs also take advantage of their respective user groups and Center oversight committees to ensure that their special animal resources serve the at times competing scientific needs of the research programs and are managed in a cost-effective manner, as these programs play a key role in enabling research for the Interdisciplinary Research Programs.

Overview of the animal colonies

The Division of Comparative Medicine maintains a healthy, specific pathogen-free (SPF) and robust NHP population to expressly support the ONPRC biomedical research mission. Collectively, the population exceeded 5,000 animals in May 2012, and we anticipate remaining consistently at or above this number of NHPs for the foreseeable future. The NHP population consists primarily of three macaque species divided into two larger breeding colonies and two small nonbreeding research-only populations, of which approximately 2,000 are currently housed indoors: *Macaca mulatta* (4,681; principally of Indian-origin only for the SPF breeding colony, with some imported and SPF Chinese-origin rhesus macaques for research purposes); *Macaca fuscata* (Japanese macaque breeding colony of 356 animals), *Macaca fascicularis* (115 cynomolgus macaques for research purposes); plus a small number of *Papio anubis* (13 baboons used for research only). The facilities for NHP housing and research are located in eight buildings, eight outdoor one-acre corrals, and thirty-two Sheltered Group Housing Units and associated catch areas, as well as indoor facilities in seven buildings on the 166 acre ONPRC campus. To provide additional animals and research space, continued construction will bring an additional Specific Animal Location of group and indoor housing on line in the spring of 2013, and an expansion project in the design phase will add Specific Animal Location and six additional ABSL-2+ animal holding rooms when completed in the fall of 2013.

Research support cores

The Support Cores at ONPRC are summarized in the Table on the following page and are described in greater detail in the **CORE SCIENCE SERVICES** section.

Core name	Division in which this Core resides	Other groups that utilize the core

Assisted Reproductive Technologies	Reproductive and Developmental Sciences	Neuroscience
Endocrine Technologies	Reproductive and Developmental Sciences	Neuroscience; Diabetes, Obesity, & Metabolism
Flow Cytometry	Pathobiology and Immunology	All Divisions
Imaging and Morphology	Neuroscience	All Divisions
Magnetic Resonance Imaging	Neuroscience	All Divisions
Molecular Virology	Pathobiology and Immunology	Neuroscience; Reproductive and Developmental Sciences; Diabetes, Obesity & Metabolism
Molecular and Cellular Biology	Neuroscience	All Divisions
Primate Genetics	Neuroscience	All Divisions

Overview of training and outreach

As described in the review of our goal #4 for the previous funding period, the ONPRC hosts a wide spectrum of trainees, including graduate, postdoctoral and clinical fellows, and veterinarians, in many cases through the participation of Core Scientists in NIH-funded training grants. In addition, internal training is provided for all ONPRC employees as appropriate with respect to laboratory safety, research compliance, animal research, etc., through on-site training offered by Research Safety personnel and through the OHSU "Big Brain" portal for online education. The ONPRC's **OUTREACH AND COMMUNITY ENGAGEMENT PROGRAM** hosts thousands of visitors a year, from elementary through high school students and high-school teachers as well as the general public. Many Outreach Program activities are also training opportunities by virtue of providing hands-on experience in laboratory research.

Description of the oversight committees, including functions and composition

Each of the Oversight Committees is described with full memberships and academic titles of members in the **ADMINISTRATION OVERVIEW** section on Committees. The role of each committee and its function and composition is summarized in the Table below.

Oversight Committee	**Function**	**Composition of membership**
Executive Leadership Committee	Oversight to the entire center, advice to the Director, budgetary oversight, strategic direction, resource management	Director and Associate Directors
Expanded Executive Leadership Committee	Scientific input into leadership decisions, recommendations for scientific areas and recruitment, solving of interdivisional issues, advice to the Director, resource recommendations	Director, Associate Directors, and Division Chiefs
National Scientific Advisory Board (NSAB, external)	Provides advice and guidance to the Principal Investigator and Center Director on planning and strategic initiatives.	Internationally recognized experts in disciplines relevant to ONPRC scientific initiatives
Research Advisory Committee (internal)	Reviews scientific merit and advisability of initiation of research projects lacking peer review, including ONPRC pilot projects, relevance of the study to the mission of the Center, justification for use of NHPs in the study, and research support required.	Division Chiefs, Research Advocacy Director, Associate Director for Research, OHSU main campus representative

Animal Utilization Advisory Committee (AUAC)	Meets quarterly to address policies and procedures for determining long-range and short-term plans and needs for NHPs/animals and to resolve issues related to all aspects of NHP/animal use in research programs. It also serves to educate about policy decisions related to use of NHPs in research protocols.	Director; Associate Directors for Research, Comparative Medicine, and Administration; Division Chiefs, Colony Manager
Animal Utilization Subcommittee (AUS)	Provides a smaller working group to review animal requests in order to optimize the use of NHP/animal resources, to determine the feasibility of studies prior to submission, to track pending and awarded grants, and to recommend NHP allocation according to guidelines; meets quarterly with the Animal Utilization Advisory Committee.	Colony Manager and Staff, in addition to group above for AUAC
Policy Group	Reviews and develops Center policies; provides updates on issues regarding scientific program planning, facilities/property, primate/animal resources, information technology, environmental health and safety, administrative services and public relations/information.	Director, Associate Directors, Division Chiefs and Unit Representatives
Institutional Animal Care and Use Committee	Reviews and approves all animal protocols for OHSU West Campus. This committee has cross-memberships of the Attending Veterinarians with the IACUC on the OHSU Main Campus.	Per policy, see details in Administration
ABSL-3 Oversight Committee	Reviews and recommends priorities and procedures for initiating NHP experiments in the ABLS-3 containment building, the ASA Building in an effort to coordinate smoothly and to maximize usage of the facility for appropriate research.	Comparative Medicine Chief, Research Safety Manager, Infectious Disease Resource Manger, Scientific leadership from Pathobiology & Immunology
West Campus Radiation Safety Committee	Integrates West Campus radiation use in research; i.e., ONPRC/OHSU, VGTI, and OGI.	Per policy, see details in Administration
Research Support Core Oversight Committees	Periodically assesses Core operations, procedures, and recommendations for new services and equipment, plus fees for services.	Users and representatives from each Scientific Division and Core Directors
Campus Safety Committee	Evaluates incidents, summarizes information and makes recommendations for corrective action. It is responsible for overseeing the adherence to local, state and federal workplace health and safety guidelines in conjunction with the Environmental Health & Research Safety Office (EH&RS).	Per policy, see details in Administration
Library Committee	Oversees the acquisitions of the library and reviews its use of resources by Center scientists, support staff, affiliated and visiting scientists, and graduate students.	Per policy, see details in Administration
Promotions Committee	Evaluates candidates, including core and affiliate scientific staff and veterinary staff, for promotion according to procedures described in the Promotions Policy.	Representative faculty from each Scientific Division, plus OHSU main campus
Information Technology Advisory Group	Provides oversight and guidance to the continued development and deployment of information technologies and establishes new goals and priorities for additions to the system.	IS Manager, DCM and scientific and administrative representatives

reviewers' comments

reviewers' comments

reviewers' comments

reviewers' comments

reviewers' comments

Progress Report. A brief summary of accomplishments, significance, and publications (where appropriate) is described below in each of the major areas of emphasis in the P51 FOA outline.

Within the mission of the ONPRC, there were four major goals that were articulated in the prior submission for this funding period: (1) Provide the infrastructure support for advanced biomedical research; (2) Increase the availability of defined NHPs for biomedical research; (3) Expand the research programs; and (4) Enhance the Center's resources. However, as noted and endorsed in the Summary Statement, we considered it very important for the ONPRC that we undertake formal strategic planning. An overarching theme to this plan was vetted and enhanced through a formal Strategic Planning Process that was initiated in 2008 and completed in 2010. This process is described in greater detail in the ADMINISTRATION/Director's Office section. As a result of this work, we have reshaped and refined our strategic goals, resulting in six major goals and serves as a framework by which to address what we perceive are the key opportunities and challenges that face us as a Center. The aims are integral to ONPRC's mission as an NPRC and will remain at the center of any Strategic Plan.

- **Provide leadership and infrastructure effective in setting and achieving scientific and strategic priorities.**
- **Foster innovative, effective scientific divisions, interdisciplinary programs, and support cores.**
- **Integrate scientific priorities with Division of Comparative Medicine (previously Animal Resources).**
- **Foster and enhance interactions within our campus, community, host institution, and other NPRCs.**
- **Enhance the Center's resources to assure stable, diverse funding.**

- **Develop effective, community-oriented outreach programs by which to educate the public about science.**

In our strategic planning, we focused on how individual units within the Center connect with the overall Scientific Strategic Plan, to ensure that divisional goals are integrated. Major progress during the last funding period is noted below in each of the six areas listed above.

1. Provide leadership and infrastructure effective in setting and achieving scientific and strategic priorities. This goal focuses on the integrated leadership of the ONPRC to provide a mechanism to assure that our NPRC addresses important problems in biomedical research and that we collectively define the most effective administrative support to achieve this end. In addition, there is a continuing need to communicate these goals and plans clearly throughout all of the divisions and units. Key mechanisms used to this achieve this goal include: (a) Regular Leadership Meetings with clearly articulated goals and outcomes; (b) Quarterly in-person updates and electronic reports that communicate the outcomes of strategic planning and ensuing decisions across the Center; (c) Yearly scientific retreats and targeted symposia to enhance scientific interactions; (d) Yearly review by the National Scientific Advisory Board (NSAB); (e) Monthly meetings with key OHSU leadership and stakeholders; and (f) Biannual NPRC Directors' conferences.

Strategic planning. In 2009, the ONPRC began formal efforts in strategic planning. The Center contracted an expert in Lean and *Hoshin Kanri* methodologies to guide the process. The ELC and the EELC worked together to develop strategic plans that encompassed the activities of all of the units, all of which were guided by an overall Scientific Strategic Plan for the Center. These working documents have regularly updated goals and milestones following Scientific Retreats and meetings with the NSAB. These have served to prioritize scientific initiatives and recruitment at the Center. As part of the Strategic Plan, the Organizational Chart was revised to better reflect the current alignments and organizations of the units overseen by the EELC.

Leadership training. In 2012, the ONPRC EELC team undertook leadership training using the system designed by Tom Rath in his book "Strengths Finder 2.0." The training was led by our senior Human Resources Director from the Office of the Vice President for Research at OHSU. The exercises revealed diversity amongst the senior leaders, and the training resulted in a better understanding of how we can communicate within the team and with colleagues throughout our scientific and administrative groups. Subsequently the Division of Comparative Medicine undertook the same training for the senior veterinary faculty.

Project management. In 2011, the Director's Office began using a project manager and project management techniques to manage and coordinate projects in the Director's Office. The project manager, Excluded by Requester is responsible for; (a) Strategic planning, which includes educating leadership and units about the methodology, then working with teams to develop plans; (b) Working as a team within the Director's Office to manage the operations and reporting of the RAC; (c) Production and submission of the P51 Annual Progress Report, including review and refinement of efficiency of the report and process; (d) Senior leadership searches; (e) SharePoint implementation and education; (f) Site development (see Communication, below); and (g) Special Projects of the Director that are in response to Task Force recommendations. Excluded by Requester regularly networks with other local Project Managers in the greater Portland area via a formal program that meets monthly.

Recommendations from leadership meetings. Our most pressing need at ONPRC for infrastructure changes was in the area of Information Technology and Electronic Medical Records (EMR). During the last 3.5 years, we met several times with the West Coast Centers to share best practices within the IT departments and to explore alternatives for new EMR software. The ONPRC set up an IT Advisory Committee to (1) Determine the most effective management structure for the West Campus Information Sciences group; (2) Make recommendations to the Director and the ELC about leadership, resulting in the hiring of a Manager for the group, Excluded by Requester and (3) Manage an external review of the EMR system in use with the acronym "IRIS" together with a review of the overall IT infrastructure. This review resulted in a recommendation to the

Director for purchase of a new system, LabKey, here called PRIMe, and is described in detail in the **ADMINISTRATION** section.

Linkages to OHSU. Our National Scientific Advisory Board (NSAB) has met each year and reviewed the progress and plans of the ONPRC with Drs. [Excluded] and Robertson, who attended the meetings and special debriefing sessions. Drs. Robertson and [Excluded by] continue to reiterate the value of our Center, and twice the OHSU Board of Directors met at ONPRC and was briefed by Director Haigwood on the state of the Center. Prior to these visits, the OHSU Board had not visited the ONPRC and was not as well informed about the important linkage that Center research provides in the "bench-to-bedside" translational pipeline. OHSU has been very generous in funding the recruitment of six new Core Scientists, four of whom were co-recruited with other departments or institutes. The ONPRC was thus able to greatly enhance its genetics component by co-recruitment with Molecular & Medical Genetics, Behavioral Neuroscience, the Advanced Imaging Center and the Vaccine & Gene Therapy Institute.

Improvements to streamlining grant submissions. We have developed an integrated process to assist investigators in the efficient development of research budgets, coordination with animal assignments, and administrative management and approval to streamline grant submissions through the ONPRC units involved. There is a diagram of this process in the **ADMINISTRATION** section in the Administration Overview. Each investigator is assigned to work with an individual Financial Analyst, who then becomes familiar with the types and scope of applications and subcontracts. This has led to better coordination with the Administrative staff and Principal Investigators and a better on-time submission rate with the OHSU Research Grants and Contracts Department.

Communication. Since our last submission, the ONPRC has worked to improve its e-based communication through the widespread implementation of SharePoint. In 2011, the ONPRC began implementing SharePoint technology to improve Center operations. SharePoint is a Microsoft platform technology implemented over the internet to facilitate collaboration and efficiency. This technology created a dynamic, collaborative intranet within the ONPRC community has increased communication, streamlined announcements, provided a place for feedback and access to forums, allowed for automatic archiving of press releases, newsletters and other communications, and allowed more transparency and consistency of information. Users of SharePoint have access to subsites that allow them to update information and communicate with other staff and users. Core Service and Comparative Medicine Rates are posted in one location, increasing effectiveness in consistency in pricing information. Grant preparation, including the P51 integrated effort, is now more efficient and transparent.

Infrastructure upgrades and changes. At the time of our last competitive renewal, we were faced with the need to [Facility Security] and the requirement to upgrade two aging buildings that lacked seismic strengthening due to changes in building codes in the last 50 years. We also had very limited options for expansion of laboratory space. In the intervening 3.5 years, we have remodeled space in the former Neurological Sciences Institute (NSI) to create state-of-the-art laboratory infrastructure. OHSU sold a portion of the land on the West Campus, necessitating an upgrade to perimeter security that was completed in 2012 and which underscored the decision on the part of our host institution to keep the ONPRC on the West Campus as its permanent home. The resulting electric fence serves as secondary containment should a problem occur with one of our outdoor corrals, and the new secure gatehouse has modern amenities and computer monitoring systems that will ultimately serve as the visitor entry badge area. Moving research activities to the former NSI building has provided access to state-of-the-art research facilities for the Divisions of Reproductive & Developmental Sciences and Pathobiology & Immunology as well as expansion of certain core research activities. Finally, the OHSU Foundation has committed to raising funds to remodel our original "Research Building" to a state-of-the-art research and office building. Seismic upgrades were completed to "Re-Life" the Administration and Research buildings, retaining the 1960s-era look and feel of these buildings on the exterior while completing or planning state-of-the-art upgrades to these buildings. Concomitant with seismic upgrades, we improved our kitchen and lunchroom/conference rooms in these buildings. The redesign of the Administration Building created more functional space for the Director's and Associate Director's Offices and associated support space, the business office, and Information Systems staff members in Administration, a

consolidated and better designed the library, and a classroom for online training on the West Campus. In the Research Building, upgrades provided some new research laboratories and additional office space for the Division of Comparative Medicine, including the Chief and the Operations Staff adjacent to the Pathology Unit veterinarians.

2. Foster innovative, effective scientific divisions, interdisciplinary programs, and support cores. This goal is driven by the desire to assure that scientific initiatives are supported by recruitment, that sufficient support exists for appropriate service cores to advance this research, and that initiatives are identified to further integrate research programs utilizing NHPs in stem cell biology, aging, obesity, genetics, infectious diseases, vaccine development, neuroscience, and women's health. As part of this goal, we identified key areas of research and administration that would benefit from better efficiencies, including grants submission and information technology.

Leadership and organizational changes. In each of the four Scientific Divisions, there are world-class research programs that address high-priority biomedical needs that are expected to increase in importance and funding over the coming decades. In addition to very strong disciplinary research, there is an emphasis on interdisciplinary and translational research that exploits the particular combination of resources, expertise, and unique capabilities at the ONPRC. Since 2009, a number of new leadership appointments were made. In 2011, Excluded by Requester Personal Info his long-term leadership of the Division of Neuroscience, and we opened a national search for the new leader. We chose Excluded by Requester who was at OHSU in the Department of Behavioral Neuroscience, and is a national leader in animal models of addiction. In 2012, Dr. Excluded by Requester elected to step down as Pathobiology & Immunology Division Chief in order to focus his efforts more on his own internationally recognized research program in HIV vaccine development. Excluded by Requester is serving as Interim Division Chief and a search for a permanent faculty member to serve as Chief is being opened. Finally, we appointed Excluded by Requester as founding and Interim Division Chief for the newly formed Division of Diabetes, Obesity & Metabolism. A search for a permanent leader will be initiated later in 2013.

With the recruitment of the new Director in 2007, OHSU pledged recruitment funds for six new investigators. Thus, identifying the best areas in which to recruit was an important part of our strategic planning. The Director and Executive Team then prioritized recommendations for the recruitments based on the needs of the Scientific Divisions and the Center as a whole, following Strategic Planning Exercises. All but one of these recruitments is now complete, and these recruitments have resulted in dual appointments and shared appointments with academic departments at OHSU.

Interdivisional communication and scientific exchange. ONPRC has a number of programs that enhance scientific exchange within and between Divisions. One of the advances in the last funding period was to confer cross-appointments for Core and Affiliate Scientists who work in areas that are outside their primary divisional appointments. Opportunities for interaction include divisional seminars, Scientific Retreats, monthly Work-in-Progress seminars for Center scientists and all staff, the VGTI Seminar Series, and the Distinguished Scientist Seminar Series. The latter two series invite external scientists to visit and speak with Center and OHSU researchers and staff.

Research portfolio funding. Each of the Scientific Divisions has experienced overall stable funding, despite the challenges at NIH. At the height of ARRA funding in FY2010, the ONPRC had a total of $54.29 million in direct costs for research; this amount dropped to $46.96 million in FY2011 and is $46.94 million for FY2012. The scientific programs have greatly expanded and have leveraged funding via divisional efforts and the Interdisciplinary Research Programs, an outgrowth of the Working Groups that were established in the last funding period. The sections below highlight scientific discoveries and accomplishments by Division. As described in detail in the Research Plans, we established a Collaborative Research Unit (CRU) in the previous funding period to facilitate collaborative research between ONPRC scientists and the external scientific community in both the academic and private sectors, and to maximize the effective use of our NHP models and resources. The CRU functions as a portal for collaborative work, evaluates potential collaborations, and manages and tracks approved projects. The CRU is directed by Excluded by Requester ONPRC Associate Director for Research.

Key scientific advances by division.

Division of Diabetes, Obesity & Metabolism:
This new Division was established in August 2012 in response to the success of the Metabolic Disease Working Group. The Division currently comprises three Senior Scientists and two Assistant Scientists as well as a number of affiliates. This group is very productive and well supported by several national consortium grants as well as significant independent funding. The Division will be strengthened over the next several years through the recruitment of new Associate and Assistant-level scientists, including the recruitment of a new investigator focused on cardiovascular diseases, who will be recruited in conjunction with the establishment of the new $125 million Private Cardiovascular Institute at OHSU. Furthermore, the expansion of the non-invasive imaging capabilities here at ONPRC as part of the Private Source Cardiovascular Institute, such as CT and PET imaging, will greatly increase our capabilities, allow for quicker translation of our research, and make our investigators more competitive for diversified funding.

One of the strongest programs in the Division are studies using the Japanese macaque, investigating the impact of poor maternal metabolic health and diet on the development of metabolic and psychiatric diseases in the offspring. These studies involve 4 investigators at ONPRC, 2 at OHSU, and 4 at outside institutions. This consortium has published 13 manuscripts in the past 2 years on this project, with several of the studies accompanied by editorials and commentaries as well as being highlighted in the lay press. For example, a study led by Excluded by Requester (ONPRC Assistant Scientist with a joint appointment in the Dept. of Ob/Gyn, OHSU) was the first to demonstrate that chronic consumption of a diet high in fats and calories, mimicking the Western-style diet, during pregnancy can cause placental insufficiency and inflammation that leads to pregnancy complications and developmental abnormalities that lead to an increased risk of cardiovascular disease for the offspring. Importantly, these studies have demonstrated that these effects are independent of the mother being obese or insulin-resistant, and that they can be reversed by consumption of a healthy diet, even in very obese animals. With a funding from a new NIH grant, Excluded by Requester is developing new noninvasive imaging techniques that can be used clinically to diagnosis early complications in placental function.

Using this same model, another young investigator, Excluded by Requester has found a link between consumption of a Western-style diet during pregnancy, as well as maternal obesity, with a broad range of behavioral disorders in the offspring. This includes an increase in anxiety, aggressiveness, and anti-social behaviors that are consistent with an autism-spectrum disorder. These findings have led to a new collaboration with investigators in the Dept. of Pediatric Psychiatry at OHSU, as well as the development of a new clinical study

Pending Support

Division of Neuroscience:
All of the Scientists in the Division have advanced our knowledge of kev normal and diseased states of the nervous system. This section highlights new recruits and programs. Excluded by Requester was recruited in 2010 on a P30 mechanism to increase our expertise in primate genetics. Gibbons are lesser apes that have accumulated chromosomal rearrangements at a much higher rate than other primates and therefore they serve as excellent models for studying mechanisms underlying genome instability, a phenomenon frequently observed in cancer. In fall 2011, Excluded by Requester has been asked to lead the efforts to analyze and annotate the gibbon draft genome, which is an exceptional circumstance as these types of large projects are usually assigned to scientists associated with one of the genome centers. This is a wonderful testament to how Dr. Excluded by Requester is viewed by her peers and her excellent track record. She formed an international consortium of about 50 members leading experts in the genomic field and the project started in January 2012 with the goal of completing the annotation of the gibbon draft genome and obtaining a publication in a high-profile journal (i.e., Nature or Science). In the first year of the project, Excluded by Requester has already showed exceptional organizational and leadership skills as proved by the fact that most of the analyses have been completed.

Excluded by Requester was also recruited in 2010 to increase our expertise in NHP neurodegeneration models, and to help establish gene therapeutic approaches. In a remarkably short period of time, she has successfully developed an innovative use of MRI imaging to guide surgical placement of the viral vector-based RNAi into

the striatum of a NHP, published in the journal Molecular Therapeutics in 2012. This was as a critical step in gene delivery to treat Huntington's disease and with this preclinical information the approach is now moving into phase 1 clinical trial in humans.

The newly established Addictions Program addresses alcohol and nicotine addiction, two of the three leading causes of preventable death in the USA, with the possibility of expanding to cannabinoids in the near future. The program utilizes the propensity of NHPs to self-administer psychoactive substances in a repeated manner that recapitulates addictive disorders in humans. In the next 5 years this program will: (1) identify key neuroendocrine aspects of the risk for heavy alcohol drinking, particularly as related to HPA-axis response, menstrual cycle quality and immune system regulation of inflammatory cytokines and chemokines; (2) explore a genetic basis of nicotine and alcohol co-morbidity by focusing on nicotinic receptor SNPs specific to risk for smoking in humans that also occurs in cynomolgus monkeys; (3) quantify the effects of *in utero* exposure to alcohol, nicotine and alcohol-nicotine co-morbidity on fetal brain growth with *in vivo* MRI imaging; (4) identify the neural circuitry changes associated with the transition from low and moderate use of a psychoactive substance (alcohol nicotine, cannabinoids) to the development of dependence and (5) test pharmacotherapeutic interventions to decrease addictive alcohol drinking and alcohol/nicotine co-morbidity in partnership with clinical partners at OHSU.

Division of Pathobiology & Immunology:

For the most part, host-pathogen interactions are kept in balance enabling the host to function normally. Unfortunately, there are instances when this balance can be tipped in the pathogen's favor and lead to pathogen-associated disease. Identifying and defining the components associated with the host or pathogen that is intricately involved with this balance is the goal of scientists within the Division. Some of the highlights from Division scientists are summarized here, and include animal model development to investigate human disease or insights into host determinants associated with protection. Excluded by Requester who was recruited in 2008, reported the development of a simian varicella virus (SVV)-infection model of rhesus macaques (RM) that closely resembles varicella zoster virus (VZV)-associated chicken pox in humans. This is an important animal model that will allow scientists to improve their understanding of the immune response to VZV and to develop and test better vaccines to reduce the incidence of shingles and its attendant neurological complications. Subsequently, her laboratory found that CD4+ T cells are critical for the control of SVV infection, which identifies the arm of the immune system that must be stimulated to protect from reactivation. Excluded by Requester who was recruited in 2010, has reported that endogenous retrotransposable elements associated with cancer and HIV infection are safe, which opens the door to new vaccination strategies to protect against AIDS-associated malignancies. His novel approach has led to funding support from the Private Source Private Source to expand these studies further. Excluded by Requester reported that Japanese macaques (JM) housed at the ONPRC have developed a spontaneous demyelinating disease, referred to as Japanese macaque encephalomyelitis (JME), which possesses clinical and histopathological similarities to multiple sclerosis (MS). This finding represents the first natural occurring NHP model of MS and, interestingly, preliminary studies indicate the virus, which is a novel simian herpesvirus may be associated with disease. If true, the investigators could develop an inducible model of MS-like disease.

Significant advances were also reported in the Division's efforts to create an AIDS vaccine. Here, Excluded by Requester Excluded by Requester laboratory reported that rhesus cytomegalovirus (rhCMV) vectors encoding SIV antigens can elicit high frequency, persistent and mucosal-oriented CD4+ and CD8+ effector memory T cell responses to SIV proteins, and these TEM cell responses in the mucosa of RM were protective against pathogenic SIV disease in ~50% of animals. Utilizing this model, Excluded by Requester reported that, for CMV to successfully re-infect a CMV-positive host, the newly infectious virus must evade the host's CD8+ T cells. This study helps define how CMV vectors must be constructed to enable the virus to serve as a vaccine vector in previously CMV-exposed hosts. Additionally, Excluded by Requester and colleagues reported that infusion of neutralizing antibodies at levels incapable of blocking infection before oral challenge was effective in inducing a rapid B cell response in the animals, which substantially reduced plasma viremia. This important study revealed the importance of maternal neutralizing antibodies to control HIV infection in newborns.

Division of Reproductive and Developmental Sciences:

NHP gamete and embryo biology, particularly in the applied area of assisted reproductive technologies (ARTs) is a unique, innovative feature in DRDS. Excluded by Requester and colleagues validated a new technique called "spindle transfer", whereby the condensed chromosomes/spindle complex in a mature, metaphase II oocyte is isolated by micromanipulation and introduced into an enucleated egg from another monkey. The newly constructed oocyte, containing the nuclear genome from one female and the cytoplasmic components (including mitochondria and their DNA) of another, is capable of fertilization, embryonic development and ultimately yielding a healthy offspring Excluded by Requester Translational studies on human oocytes at OHSU Riverfront Campus (in collaboration with clinical scientists in Ob-Gyn) support this technique as therapy to prevent transfer of mitochondrial gene defects from the mother to her child while retaining the mother's genomic contribution.

To strengthen its research program in maternal-fetal medicine and pregnancy disorders, the Division added Dr. Excluded by Requester to its faculty. A recipient of a K99/R00 career development grant from NICHD, Excluded by Requester competed successfully for her first R01 grant, which is based on her landmark research establishing that maternal antibiotic therapy for intrauterine infection (IUI) delays preterm delivery and reduces fetal lung injury in the macaque model Excluded by Requester Dr. Excluded by Requester is establishing collaborations with clinical scientists in Pediatrics and Ob-Gyn to examine the effects of IUI and its treatment on the mother, fetus and newborn.

Development of the next generation of contraceptives for women, notably nonhormonal approaches, is the focus of the NICHD-funded Contraceptive Center co-directed by Excluded by Requester Basic mechanistic research can be followed by testing promising agents in the NHP Contraceptive Core comprised of groups of 10 adult female cynomolgus monkeys and one male. Excluded by Requester in collaboration with scientists at Bayer Health Care (Berlin, Germany), recently reported that exposure to an antagonist of the PGE receptor 2, markedly reduced fertility during five months of treatment, which was reversed within two months of stopping the drug. Other approaches are in development and will receive similar testing as the center was recently renewed for five years.

Interdisciplinary Research Programs and Working Groups. These groups have grown from scientific review as previously described Working Groups have matured and details of the new programs can be found in the **SCIENTIFIC COMPONENTS – IDRP** section. The Stem Cell and Developmental Biology Working Group was reinvigorated as a major thrust of the new Reproductive and Developmental Sciences Division, and the many scientific breakthroughs of this group are noted above. The Healthy Aging Working Group attracted and developed a consortium of investigators invested in aging research and hosted the *Healthy Aging Alliance* here in Portland. This group, now an IDRP, has been extremely successful in obtaining funding for interdisciplinary aging research and continues under the able leadership of Excluded by Requester The Obesity and Metabolism Working group has become the newest division. The Primate Genetics IDRP was identified following the successful building of the genetics program here at ONPRC via strategic recruitment and the building of a strong grant portfolio in primate genetics. Finally, the Early Childhood Health & Development IDRP was constituted in 2012 to bring together efforts spanning *in utero* development through early infant, spanning developmental biology including neurological development, infectious disease susceptibility and prevention, and early childhood immunity.

Support Cores (SERVICE CORES). Major changes to the Research Support Cores included: (a) Transfer of the ART/ESC Core leadership from Excluded by Requester along with a move to newly renovated facilities; (b) Elimination of the monoclonal antibody and Luminex components originally proposed for the Immunology core, based upon the critiques and a lack of projected use, plus transfer of Cellular Immunology Unit to the new Infectious Disease Resource, described in ANIMAL SERVICES; (c) Reinstatement of the Flow Cytometry Unit to its previous status as an independent Core; (d) Recruitment of a new head of the Molecular Virology Core in 2011; and (e) Transfer of serology operations to the Division of Comparative Medicine. These changes, along with the other actions described in the individual Core descriptions, illustrate the continuing improvement in Core operations and capabilities, documented in those sections.

3. Integrate scientific priorities with Division of Comparative Medicine (previously Animal Resources).

Our mandate as a Center is to provide NHP resources for the important, innovative scientific programs. Since May 2009, the ONPRC has experienced consistent growth from increasing external grant funding, which has placed increasing demands on our infrastructure, research, and husbandry space during a time of essentially flat NIH funding. Our goal is to increase the availability of defined NHPs for biomedical research through expansion of the existing SPF Indian-origin rhesus macaque breeding program, thereby ensuring an adequate pipeline of viral-free animals with defined parentage and genotype. The NHP population is at an all-time high, as is the percentage of animals assigned to studies and the number of models in various stages of development and use. As NHPs are at the heart of our research enterprise, an effective strategy for optimal supply to meet increasing research demands is a key objective to our strategic planning. As described in several sections below (ANIMAL SERVICES Progress Report), this strategy will facilitate better management of NHPs and support services.

Leadership and organizational changes. The Center recruited Excluded by Requester to replace Excluded by Requester Excluded by Requester, when she left to take a faculty position at the University of Arizona. Excluded by Requester had already right-sized our veterinarian and support staff to care for the NHP population, based on time-in-motion analyses that she completed in 2010 and 2011. Excluded by Requester has refined the organizational chart to optimally align staff functions for increased efficiencies, and to institute a new focus on research model refinement and professional staff development. Capitalizing on this approach, a Research, Education, and Training Unit was established. Headed by Excluded by Requester this unit will oversee the education and training of veterinarians and veterinary students in laboratory animal medicine and research through residencies and externships and to support and optimize research support services, scientific discovery, and animal health and well-being through structured programs of continuing education, training, and informational resources for technical and professional staff.

Animal allocation. Another important advance has been the streamlining and communication of the Animal Allocation Process. All forms are submitted electronically by investigators to delineate the numbers/types of animals needed for a proposed project, and reviewed online at the monthly meeting for animal planning (prior to grant submission), animal allocation (once a grant is funded) and animal assignment (when a funded project is ready to begin). Future capabilities to improve *Tracking and Forecasting* (see section below) will allow greater accuracy to this process. These steps of planning and allocation fit into the overall Research Funding Process flowchart that is shown in the ADMINISTRATION Overview section below.

Special Resource Programs. These programs were carefully evaluated and, in several cases, modified to become more cost-effective and to better align with our strategic objectives and areas of scientific focus. Examples include the Obese NHP Resource to support expanding research in the new Division of Diabetes, Obesity & Metabolism and the Japanese Macaque Resource to support the initiatives to develop models for macular degeneration and multiple sclerosis.

Integrating Division of Comparative Medicine veterinarians as members of project teams. A commitment to development and refinement of NHP models by partnering with ONPRC scientists is a priority for the Center. Through continuing provision of superior surgical services, expansion of behavioral assessments, strengthening of pathology services and staff, and stabilizing clinical veterinary partnerships with the Scientific Divisions, the Division builds strong and experienced team members for the Center research enterprise. The integration of veterinarians with investigator protocols is promoting NHP model refinement and optimal management of NHP resources through the special expertise they bring to the project. Veterinary clinicians provide collaborative project support for the investigators, as well as clinical service and management for the NHPs on study. In concert with the scientific aims of the approved projects, strategic decisions addressing the prioritization of longitudinal phenotypic parameters will maximize research utility, clinical prognostication and colony management. Such collaborative efforts are expected to continue to yield numerous advances and insights into NHP model characterization. This process has been formalized in the standard ONPRC project development process through the requirement of a planning meeting involving the project PI and their team with the Scientific Division-affiliated veterinarian prior to filing of a request for animal assignment.

Tracking and forecasting. As part of our IT initiatives, we are now able to monitor the locations of all animals on campus by species, age, gender, housing, and SPF status. We have made progress in implementing bar coding; impeded in part by concrete buildings that do not transmit signal well. Ongoing efforts to characterize and then improve the wireless envelope will permit real-time data capture and assessment to better manage both equipment and animal assets. A more unique project, with potentially greater impact on the successful oversight of NHP movement and utilization forecasting, is the systems management effort we have undertaken. Specifically, we have partnered with local experts from the Computer Sciences Department of Portland State University to model and forecast the supply and demand of NHPs. We expect to simulate scenarios of resource utilization to effectively forecast NHP availability, growth of special populations and genetic diversity, all within our limited infrastructure. Because our breeding and research needs form a highly complex interplay of moving targets, effective management must balance research needs with the health and breeding capacity of the colony as a whole. Variables include concerns of genetic diversity, disease management, and behavioral issues that arise when large populations of NHPs are kept in confined areas. Initial efforts confirmed that development of a computer simulation tool can be used to identify bottlenecks, leverage points, and animal resource dynamics that could managed to improve the performance of the breeding program, with respect to both research and resource objectives. We anticipate that by simulating resource management *in silico*, animal resource managers and research investigators will have the opportunity to predict the expected consequences of proposed changes with a degree of formalism that cannot be obtained without careful consideration of whole-system dynamics.

Primate genetics and pedigrees. Recruitment of key faculty members who have active research programs in NHP genetics has provided a significant enhancement to our ability to evaluate and plan our for colony maintenance. To assess the standing genetic diversity in the current ONPRC P51 breeding colony, we estimate observed and expected heterozygosity, and allelic diversity from 14 genetic markers in male and female breeding-age animals. These data indicate that the ONPRC breeding colony continues to display a substantial degree of genetic diversity. We will continue to employ strategies designed to reduce colony mean kinship and coancestry by making it a top priority to reduce relatedness among males, and between males and females within new breeding groups. New breeding groups are formed by selecting breeders according to lowest mean kinship in relation to the rest of the breeding colony, and by removing from consideration males that are related to each other, or to proposed group females at the level of 2nd cousin or greater. Additionally, males or females with >5 living offspring within the breeding colony are removed from consideration. Although genotype data at microsatellite markers has been used for many years to establish the parentage of offspring born into the breeding colony, we are transitioning over the next 1-2 years to using a panel of 96 single nucleotide polymorphism (SNP) markers developed for parentage analysis by the OD/ORIP-supported Genetics and Genomics Working Group. Unlike microsatellite markers, SNP markers are found in much larger numbers in the genome, and genotyping is easily automated, thus reducing the relatively high error rate found in microsatellite genotyping. This 96-SNP parentage array has equal or greater power to assign parentage, compared to the more limited set of microsatellite markers we have used in the past, and will work in conjunction with a web-based parentage analysis pipeline that is centrally accessible at the Non-Human Primate Research Center (NHPRC) Consortium web portal.

Improved colony management and project management. Both the U24 and U42 NHP resource grants were competitively reviewed and funded over the last year, and these resources are critically important in augmenting our P51 colony for provision of SPF and expanded-SPF rhesus macaques for AIDS research and for related infectious disease research. Based on an external review of the Breeding colony by NHP scientific and veterinary experts [Excluded by Requester] from NIAID at NIH, [Excluded by Requester] from the Tulane NPRC, and [Excluded by Requester] from the Washington NPRC) held in the fall of 2011, we adopted some suggested changes for best practices in managing these resources. We are hopeful that the e-SPF breeding will be more successful when moved to the PENS enclosures upon their completion in the spring of 2013, adopting a model that Tulane has used successfully for many years.

West Campus Occupational Health Nurse. Identification and evaluation of potential hazards inherent or intrinsic to the use of animals, including animal bites and scratches, sharps, pressure vessels, electrical hazards, UV radiation, ionizing radiation, ergonomics, noise, hazardous chemicals, allergens and zoonoses, is

performed by the Department of Environmental Health & Radiation Safety (EHRS) and/or the ONPRC Occupational Health Nurse (OHN) in cooperation with veterinary, animal husbandry, research and facilities management. Potential infection of NHPs with disease organisms that are communicable to humans is evaluated during regular health checks. If infection with zoonotic agents is suspected, hazard reductions strategies are developed by EHRS/OHN in cooperation with DCM. Intentional introduction of hazardous biological agents, including bacteria, viruses, protozoa, fungi, and biological toxins are reviewed and approved by the Institutional Biosafety Committee, which determines policies and requirements for containment of biological hazards. EHRS staff reviews the use of hazardous chemical agents or physical agents, and recommendations are made for safe use and compliance with state and federal exposure and disposal regulations. The use of ionizing and nonionizing radiation in animals is reviewed by the Radiation Safety Committee and the Radiation Safety Officer. All areas where radioactive materials are used are monitored monthly and inspected annually to maintain ALARA practices and compliance with state and federal regulations. All personnel who have access to animal housing areas are required to participate in the Occupational Health Program, including research staff, animal care staff, students, facilities staff, and vendors/contractors.

Improvements to the NHP resource over the past grant cycle included the following: The ONPRC added several new animal buildings for NHP housing to keep pace with the expanding research program, including four sheltered group housing units [Specific Animal Location] and a biocontainment building [Specific Animal Location] of caged housing, including [Specific Animal Location] of conventional ABSL-2 housing and 4,000 sq ft of ABSL-3 space). Corral populations of rhesus macaques were maximized to free up research space, and the segregation of the U42 and P51 colonies was discontinued, thus promoting genetic diversity and production. Ongoing discussions between the scientific Divisions, the Division of Comparative Medicine, and the ONPRC business office resulted in purchase of small numbers of cynomolgus macaques readily available for research assignment for use with funded grants. Purchase is driven by specific needs of funded projects with approved IACUC protocols, where the need cannot be met by the breeding colony. We have also worked to clarify the goals and management of the NHP Japanese Macaque, Aging Macaque, and Obese Macaque Resource Programs to maximize their scientific value as shared resources.

4. Foster and enhance interactions within our campus, community, host institution, and other NPRCs. Participation of senior ONPRC leadership in strategic planning, joint recruitment, and the NPRC consortium.

Integrate OHSU strategic planning and outcomes with ONPRC. As part of the overall OHSU strategic planning process, initial evaluations done internally and by outside consultants (The McKinsey Group), recognized the Center as one of the key assets of the host institution. This position has been emphasized and strengthened by the active participation of Director [Excluded by Requester] and Associate Director [Excluded by Requester] in the OHSU School of Medicine's Research Roadmap process. In parallel, a recent major philanthropic gift for the establishment of an OHSU Cardiovascular Institute has enabled the planning for set up of a major imaging facility at the Center. This initiative will also include space renovation, additional animal housing and research space, and new faculty recruitment linked to the new Division of Diabetes, Obesity & Metabolism.

Leveraged work with existing centers, NPRCs, shared resources. In the previous funding period, the Center established strong links with the OHSU Clinical and Translational Science Award (CTSA)-funded Oregon Clinical and Translational Research Institute (OCTRI). In addition to sharing review panel members between the two entities, a four-year joint pilot grant program was initiated in 2011 to encourage collaboration between translational investigators at OCTRI and OCTRI. Additionally, research support cores at each site are made available to each other's researchers.

NPRC Consortium Activities. Support NPRC Consortium work and share best practices. We have participated in each of the NPRC Working groups and several leaders of these groups are from ONPRC, as described in the **NPRC CONSORTIUM-BASED ACTIVITIES** section of this P51 application.

Emergency planning and security. In the last three years, we have had the opportunity to train all of the ONPRC leadership (to the level of department managers) in the standard emergency training programs in

Incident Command Structure (ICS). Our local law enforcement and safety groups (fire, police, FBI, etc.) have heartily endorsed the new perimeter fence and gatehouse. They work closely with the Department of Public Safety at OHSU and the Office of Research Advocacy to communicate potential security threats and to communicate with faculty to mitigate home demonstrations.

Office of Research Integrity. This office was established several years ago to provide better linkage of the ever-growing Research Integrity requirements to the needs of investigators to perform research efficiently and correctly. Excluded by Requester serves in this capacity and has a dual report to the OHSU Research Integrity Office (ORIO). Some of the gains in efficiency have been a move to an all electronic IACUC, a gain in support for IACUC submissions with a full-time IACUC Analyst on the West Campus, and the development of a post-approval monitoring program.

Office of Research Advocacy. Excluded by Requester continues to do an outstanding job advising the ONPRC locally, working with OHSU Public Safety and Strategic Communications. Excluded by Requester also is a frequent and eloquent speaker at national and international forums, as well as an effective and prolific writer as detailed in the Director's Office section of **ADMINISTRATION**.

Long-range planning. The interface of our administrative functions between ONPRC and OHSU has been enhanced by regular meetings with Design & Construction to oversee the building and remodeling of campus buildings. In the coming several years, the OHSU Planning Department will be working with the city of Hillsboro to develop a new Master Plan for the West Campus that is in synchrony with the long-range plans of the Hillsboro community.

5. Enhance the Center's resources to assure stable, diverse funding. The goal of this emphasis area is to enhance the scientific expertise, laboratories, support facilities, animal services, research support cores, and equipment, so as to serve as a regional, national, and international resource. Not only is there innovative research within the Center, but interactions with the outside research community have increased significantly, involving other NPRCs as well as other institutions, to fulfill the mission/mandate of the primate centers and NCRR.

Defining areas of scientific excellence for ONPRC. As an integral member of the OHSU research community, the ONPRC participates in the use of yearly capital expenditures from OHSU and receives support for essentially all of its capital projects to complement CO6 and G20 grants. The Center also participates through the office of the Senior Vice President for Research Excluded by Requester in helping to choose the areas of investment of OHSU, termed Centers for Scientific Excellence. A recent gift to OHSU in the area of Cardiology was made with investments at the ONPRC in mind, to enhance imaging.

Partner with the OHSU Foundation and the OHSU Business Development groups to align strategic funding initiatives with opportunities in the donor and Pharma communities. Based on recommendations from our host institution as well as our NSAB, we have made it a major priority to diversify our funding sources for research, increasing funds from foundations and industry, and we have begun a highly productive partnership with the OHSU Foundation to raise unrestricted funds for the Center to complement its NIH portfolio.

6. Develop effective, community-oriented outreach programs by which to educate the public about science.

Leadership and Organizational changes. The progress and future plans for this important goal are summarized in the section OUTREACH and COMMUNITY EDUCATION. During the last 3.5 years, the center has averaged 3,000 visitors per year, including school classes, teachers, interns, visiting scientists, and the general public. The goal of these visits is education about the research performed at ONPRC and how scientific advances support the development of new cures, vaccines, and therapies to improve human health. During the last funding period, ONPRC received a generous foundation grant to build and support a teaching laboratory, the Private Source Teaching Laboratory. The Center now provides opportunities for hands-on science exercises for visitors to experience the joys of discovery.

OHSU maintains an outstanding office of Strategic Communications that interfaces with ONPRC and OHSU to promote the unique nature of the Primate Center within the University and the community. The ONPRC enjoys a regrettably high degree of exposure to animal extremist groups, and has been targeted frequently in the last several years. The OHSU/ONPRC partnership has been crucial to assure that the security is provided and that public information was accurate, and rapidly posted on the OHSU website. Our efforts at Public education have also been substantial and critical to our stature in the community, in order to reach students and teachers. A full accounting of the progress and plans for these activities is in the Program Directions section. We added a Scientific Advisor, Excluded by Requester to help promote the outreach programs on campus. Excluded by Requester has been a frequent participant in community outreach and will bring his knowledge of neuroscience and stem cell biology. Early discussions with leaders from the Portland Zoo have indicated interest in helping us, and as members of the Westside Economic Alliance, we will be talking with business leaders to determine potential board members.

Changes in key personnel since the last review are noted in the Appended Report. There are no changes to the Official Key Personnel for the P51, as both Drs. Robertson and Excluded by Requester have the same roles. However, there are some important changes to leadership. These include the departure of Excluded by Requester from the Division of Comparative Medicine (2012) and Excluded by Requester from Administration (2013), who have taken positions at other universities, and the recruitment of Excluded by Requester to DCM in 2012. As noted above, Excluded by Requester is serving as Interim Associate Director for Administration.

SUMMARY OF CHALLENGES, PLANS, AND OPPORTUNITIES FOR THE REQUESTED PERIOD OF SUPPORT

We face the next five years with a strong base of knowledge, scientific expertise, and integrated NHP models, and a fiscally sound Center that is well supported by its host institution OHSU. We are fortunate to have a strong slate of National Scientific Advisors, many of whom were advisors during the last funding period and who wanted to continue to provide us with advice and support.

Challenges.

1. Attracting and maintaining the very best faculty to lead independent and interrelated research programs is our first goal, and the potential loss of successful faculty is something we have experienced during the last funding period Excluded by Requester were recruited away by other top universities). Our long-term faculty support is based on the P51, and as the research enterprise comes to grip with funding models at Academic Medical Centers, we may find ourselves at a disadvantage in recruitment. We have been successful on the whole, but the future is unclear.
2. Funding for research and need for diversified funding in an uncertain economy remains an external threat to our research enterprise. It goes without saying that all NPRCs are endeavoring to "do more with less" and to deal with flat budgets. We have chosen to continuously leverage and to partner with multiple investigators, departments, and external institutions so that we can maximize our opportunities to compete effectively for interdisciplinary and program project funding opportunities. We must continue to be aggressive in seeking these opportunities.
3. Increased funding needed for baseline operations and to address increasing regulatory requirements. As we continue to develop new models and new breeding and research facilities such as the PENS and ABSL-3 building, as well as additional regulatory requirements, we have recognized that we must increase our veterinary and animal care staff and their training to adhere to CDC and USDA regulatory guidelines. We have enhanced our efficiencies and are continuing to evaluate how we may further increase these by testing for example dry bedding in lieu of daily hosing for enclosures, as an effort to save time and utility costs. Nonetheless there are limits to efficiencies and we may need to devote a higher proportion of the P51 funding to animal care and oversight in future years to meet these critical needs.
4. Future funding sources for space for laboratory research and for NHP research are unclear at this time. It is encouraging that ORIP has received approval for a C06 grant for 2013. However, basing long-range plans for capital building project on NIH funding makes for a very challenging environment. We find

ourselves increasingly dependent upon OHSU for the funding of capital projects, and we recognize the challenge that this presents to the OHSU leadership team, which must balance many competing priorities and interests in a time of economic uncertainty and changing healthcare practices.

5. Capital investment for aging buildings and research expansion are needed in an environment where capital is available in an unpredictable timeframe. OHSU has been an extremely valuable and supportive partner in capital projects. As we work to develop a master plan, part of the equation that will need to be addressed more adequately will be how to fund our buildings for research and animal housing.
6. Facility Security
7. Right-sizing the NHP breeding colony to meet the complex demands of scientific research, while balancing infrastructure limitations is a tightrope that we walk continuously. During the last funding period, we expanded our NHP colony and we also greatly expanded the number and complexity of NHP models for research. Fortunately, we were also able to take advantage of C06 and G20 (and OHSU) funding to provide additional research space and through painstaking management to more efficiently utilize the space that we have. In the next funding period, we will not be able to expand without relief to infrastructure needs and we will need to be working to manage and to share our NHP resources even more effectively.
8. Optimal restructuring and streamlining of administrative leadership and support while retaining functionality and job satisfaction remains a challenge. The move of Excluded by Requester to the California NPRC allows him to remain a partner and consultant to us in the NPRC Consortium. As a result of his departure we are doing some realignments of administrative functions to better link ONPRC and OHSU functions. With significant changes in how we perform business compared to 50 or even 10 years ago, it will be important to assess needs accurately and to determine how we can more effectively perform our business.

Future Plans and Opportunities. These plans are based on the current strategic goals of the ONPRC. Details of these plans can be found in the sections of the P51 that follow, as noted below. We anticipate that these goals may change somewhat in our strategic planning process in response to scientific or programmatic needs, but we expect them to be similar.

1. **Continue to develop Integrated Leadership to provide optimal communication and enhanced infrastructure for the future (ADMINSTRATION; IMPROVEMENT AND MODERNIZATION).**
   a. Hold another formal Strategic Planning exercise to update the ONPRC Plan, following review of the P51 renewal.
   b. Maintain and enhance leadership training and communication of decisions throughout the campus to assure transparency.
   c. Complete the installation and development of LabKey (PRIMe); IT and electronic medical records (EMR) to integrate with billing, business, training records, bar-coding
   d. Finish conversion to eIACUC to enhance simplicity and compliance for all research projects, in collaboration with the OHSU Research Integrity Office.
   e. Complete construction of the OHSU Data Center on the West Campus; placing the OHSU Data Center on campus will benefit speed of data transfer, security, and longevity of the ONPRC at its present locale, in collaboration with OHSU Information Technology and Design & Construction.
   f. Streamline administrative functions in response to institutional initiatives
   g. Complete new version of West Campus Master Plan update, needed by 2018, coordinated with OHSU Planning, NIH ORIP, and the City of Hillsboro
   h. Continue energy and cost-savings initiatives such as the dry-bedding initiative.
   i. Obtain capital funding to renovate the Research Building into a state-of-the-art facility (with #5)

2. **Support the continued development of strong, innovative scientific divisions, support cores, and interdisciplinary programs (ADMINISTRATION/Director's Office; PILOT RESEARCH PROGRAM; CORE SCIENCE SERVICES; SCIENTIFIC COMPONENTS).**

a. Complete recruitment of permanent chief for Pathobiology & Immunology Division (2013) and continue to enhance communication and shared resources with the Vaccine & Gene Therapy Institute.
b. Support the further development of new Division of Diabetes, Obesity, and Metabolism by:
    i. Division chief recruitment at an appropriate time within the next year or two;
    ii. Joint faculty recruitment and infrastructure expansion through OHSU Cardiovascular Institute; and
    iii. Enhanced relationship with University of Washington Diabetes Research Center.
c. Complete succession planning for the next Chief, Division of Reproductive & Developmental Sciences
d. Support the Division of Neurosciences initiative to hire an Assistant Scientist in the area of functional neurocircuitry to compliment the already strong molecular, cellular and behavioral research efforts.
e. Continue the development of LabKey (PRIMe) for laboratory databases and related uses, as is currently done at many internationally recognized research centers such as the Fred Hutchinson Cancer Research Center.
f. Support the bioinformatics initiative at OHSU and determine the best fit for research and shared faculty at the ONPRC, including the recruitment of a new core scientist in bioinformatics.
g. Encourage development of IDRPs with symposia and shared faculty recruitment.
h. Evaluate and modify (as needed) the Service Cores to best serve the scientific needs of the ONPRC and its collaborating scientists.

3. **Develop and refine modeling methods to optimize genetically diverse NHP colonies, animal care, and research models (ANIMAL SERVICES; ADMINISTRATION/Information Systems; PILOT RESEARCH PROGRAM; SCIENTIFIC COMPONENTS).**
    a. Develop improved strategies for the socialization of NHPs
    b. Train the next generation of veterinarians dedicated to the advances in the understanding and improvement of NHP models
    c. Provide a reliable number of healthy and defined pathogen-free source of NHPs:
        - Develop and utilize long-range modeling methods to refine estimates of NHP supply and demand to support scientific research.
        - Work closely with Genetics group to define and maintain genetic health of the colony
        - Take advantage of opportunities of downsizing or change in NHP demographics at other NPRCs or institutions to enhance certain NHP colonies
    d. Complete rollout of PRIMe, including bar coding to maximize efficiencies in EMR and personnel
    e. Develop new NHP space
        - Populate new PENS modules (2013)
        - Modify the way that U24 Expanded SPF breeding is accomplished in PENS (2013-2014)
        - Modify group housing space for cynomolgus macaques for research in diabetes and cardiovascular research
    f. Continue to expand the involvement of veterinarians in scientific research

4. **Foster and enhance interactions within our campus, community, host institution, and other NPRCs (OUTREACH & COMMUNITY ENGAGEMENT; NPRC CONSORTIUM-BASED ACTIVITIES).**
    a. Expand emergency management resources and capabilities through training and joint exercises.
    b. Continue leadership and integration of NPRC-based Consortium efforts.
    c. Actively participate with OHSU School of Medicine Research Roadmap (strategic planning implementation) process and related initiatives (TTBD planning, commercialization committees, etc.)
    d. Continue director's participation in OHSU leadership through President's Council, Basic Science Chair's Committee, OCTRI, and other opportunities to develop tighter linkages to the other mission areas of OHSU (education and clinical care).
    e. Participate in the planning for the new School of Public Health (partnership with Portland State and Oregon State University) and as part of that "Global OHSU" Task Force.

5. **Enhance the Center's resources to assure stable, diverse funding (ADMINISTRATION; SCIENTIFIC COMPONENTS).**

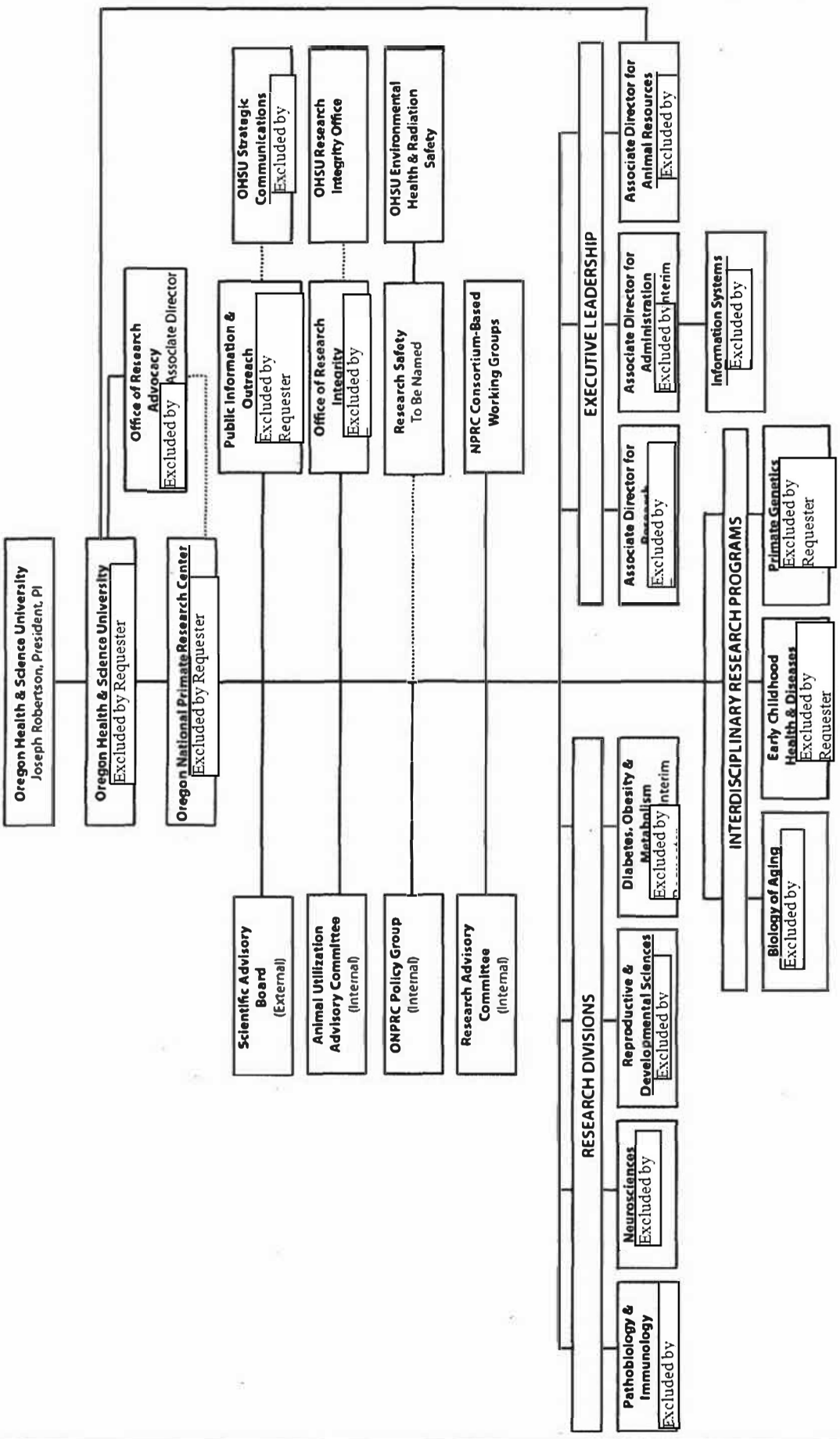
a. Continue engagement with OHSU and Doernbecher Foundations to achieve a more balanced, diversified funding portfolio and stable funding for faculty support.
b. Develop plans with OHSU Foundation around key science initiatives, in collaboration with Division Chiefs and Interdisciplinary Research Program Manager.
    - Build on the success of recent OHSUF and DCHF board meetings at ONPRC.
    - Hold regular meetings with ONPRC liaisons at the Foundation.
    - Continue the education of Foundation staff about disease-related research mission of ONPRC pertinent to philanthropy.
c. Work to seek funds for endowed chairs and recruitment dollars.
d. Obtain capital funding to complete the Research Building to a state-of-the-art facility.
e. Carefully manage development of public-private partnerships.
    - Maintain strong linkage with OHSU TTBD for exposure to industry.
    - Diversification of funding stream through appropriate industry collaborations.
    - Encouragement of investigator-initiated industry-supported research opportunities.

6. Develop effective, community-oriented outreach programs by which to educate the public about science (OUTREACH AND COMMUNITY ENGAGEMENT).

a. Expand funding and programs to support education and educational outreach.
b. Develop programs to educate the community, working closely with the NPRC Consortium to adopt programs that have been successful at other NPRC institutions
c. Continue to support outreach via speaking engagements arranged by NWABR and local science organizations.
d. Develop new laboratory-based learning activities for students for use in the Silver Learning Laboratory, working with Core Scientists who have this interest in teaching about their research.
e. Develop a Community Advisory Board to provide advice on public science programs.

Oregon National Primate Research Center

Organizational Chart



Pages 53-375 (Biographical Sketches) Removed – Excluded by Requester

ACRONYM GLOSSARY

- **ABSL-3**: Animal Biosafety Level 3
- **ACLAM**: American College of Laboratory Medicine
- **AIDS:** Acquired Immune Deficiency Syndrome
- **BSU**: Behavioral Services Unit
- **CMMS:** Computerized Maintenance Management System
- **CMU**: Clinical Medicine Unit
- **CMV:** Cytomegalovirus
- **CRU:** Collaborative Research Unit
- **DCM**: Division of Comparative Medicine
- **DOM:** Division of Diabetes, Obesity and Metabolism
- **DPI:** Division of Pathobiology & Immunology
- **DRDS:** Division of Reproductive & Developmental Sciences
- **EHRS:** Environmental Health & Radiation Safety
- **ELC, EELC**: Executive Leadership Committee, Expanded ELC
- **EMR:** Electronic Medical Record
- **eSPF:** Expanded Specific Pathogen Free
- **HIV:** Human Immunodeficiency Virus
- **IACUC:** Institutional Animal Care and Use Committee
- **ICS:** Incident Command System
- **IFMA:** International Facility Management Association
- **IRIS:** Integrated Research Information System
- **IS:** Information Systems
- **ITG:** Information Technology Group
- **NHP:** Nonhuman primate
- **NIH:** National Institutes of Health

- **NCRR:** National Center for Research Resources
- **NPRC:** National Primate Research Center
- **NSAB:** National Scientific Advisory Board
- **OCT:** Optimal Cutting Temperature
- **OHSU**: Oregon Health & Science University
- **ONPRC**: Oregon National Primate Research Center
- **ORIP**: Office of Research Infrastructure Programs
- **PPID:** Primate Pathology Image Database
- **PRIMe**: Primate Records and Information Management
- **QA:** Quality Assurance
- **QMP:** Quality Management Program
- **RAC:** Research Advisory Committee
- **RCE:** Regional Center(s) of Excellence
- **RET**: Research, Education, and Training
- **RFO**: Resources, Facilities, and Operations
- **SIB**: Self-injurious behavior
- **SIV:** Simian Immunodeficiency Virus
- **SNP:** Single Nucleotide Polymorphism
- **SOP:** Standard Operating Procedure
- **SPF:** Specific Pathogen Free
- **SSU**: Surgical Services Unit
- **TDP:** Tissue Distribution Program
- **TMB:** Time Mated Breeding
- **VGTI**: Vaccine & Gene Therapy Institute
- **WaNPRC**: Washington National Primate Research Center

TITLE: ADMINISTRATION

CORE-SUPPORTED PERSONNEL:

Director's Office

Excluded by Requester	Director
	Associate Director for Research/CRU
	Director, Office of Research Advocacy
	IACUC Chair/CRU
	Research Integrity Officer
	Administrative Coordinator
	Administrative Coordinator
	Research Subject Protection Analyst
	Project Manager, Director's Office

Administrative Services

Excluded by Requester	Interim Associate Director, Administration
	Financial Analyst
	Manager, Human Resources
	Human Resource Coordinator
	Executive Specialist
TBN	Associate Director, Administration
TBN	Assistant Director, Administration
TBN	Cost Accountant

Business Services

Excluded by Requester	Manager, Business Services
	Administrative Coordinator
	Financial Analyst
	Office Specialist
	Financial Analyst-Lead
	Financial Analyst
	Financial Analyst
TBN	Accounting Specialist
TBN	Student Worker

Facilities

Excluded by Requester	Manager, Facilities & Properties
	Supervisor, Custodial Support
	Administrative Coordinator
	Facilities Building Coordinator
	Custodian
	Facilities Technician 3
	Biomed Equip Technician 2

Excluded by Requester	Laborer 1
	Facilities Technician 3
	Laborer 1
	Assistant Facilities Technician
	Assistant Facilities Technician
	Custodian
	Facilities Technician 3
	Landscape/Groundskeeper
	Sustainability Manager
	Stationary Engineer 1
	Administrative Assistant
	HVAC Engineer 1
	Plumber
	Custodian
	Manager, Facilities Operations
	Assistant Facilities Technician
	Stationary Engineer 1
TBN	Custodian
TBN	Assistant Facilities Technician
TBN	Summer Help
TBN	Overtime
TBN	On-call

Information Systems

Excluded by Requester	Manager, Information Systems
	Senior Research Informatics Engineer
	Programmer/Analyst
	Application Developer Supervisor
	Multimedia Specialist
	Business Data Analyst

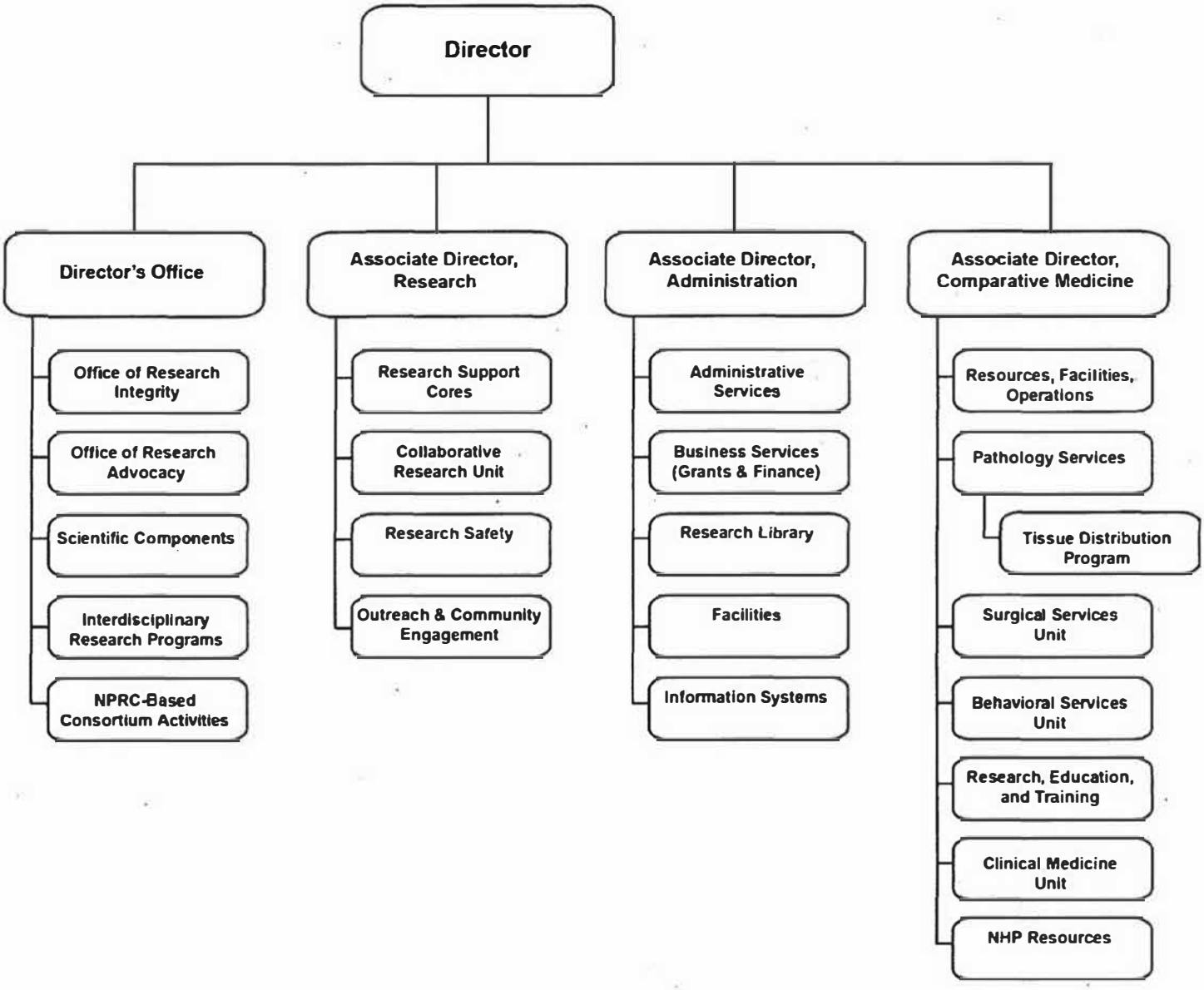
Research Library

Excluded by Requester	Research Librarian
TBN	Student Worker

Research Safety

Excluded by Requester	Occupational Health Nurse
TBN	Occupational Health Nurse

ADMINISTRATION
Organizational Chart



ADMINISTRATION: PERSONNEL AFFILIATION AND ROLE

Core Scientists:

Excluded by Requester	Center Director, Senior Scientist Associate Director for Research/CRU, Senior Scientist Director, Office of Research Advocacy, Senior Scientist

Staff Scientist

Excluded by Requester	IACUC Chair/CRU, Staff Scientist 3

Research Support

Excluded by Requester	Research Integrity Officer

Affiliates

Excluded by Requester	Environmental Health & Radiation Safety, OHSU Environmental Health & Radiation Safety, OHSU

ADMINISTRATION

DESCRIPTION:

The Administration of the Oregon National Primate Research Center (ONPRC) is responsible for the leadership, management, communication, and financial and personnel administration of the organization within the host institution, Oregon Health & Science University (OHSU), and all of its administrative, financial, and regulatory units.

The Administration serves the Mission of the ONPRC and the Office of Research Infrastructure Programs (ORIP) at NIH by providing the highest quality planning, service, oversight to achieve the strategic goals of the P51 and the NPRC program. As described in the Overview and detailed in the Components sections, the ADMINISTRATION section of the P51 describes:

- The organizational structure of OHSU as it relates to the ONPRC, including the institutional chain of professional and administrative responsibilities;
- The structure of the ONPRC administration and its relationship to and interaction with OHSU;
- The administrative relationships between the Principal Investigator, the Director, and other senior leaders and their responsibilities, the National Scientific Advisory board and other advisory groups, and a listing of the committees;
- The members, functions, record keeping, and composition of all committees with advisory roles on specific aspects of the ONPRC's research projects; and
- The process outline for review and approval of research proposal.

Through its individual and combined units, it coordinates and facilitates the research enterprise and access to nonhuman primate (NHP) resources for research. The units of ADMINISTRATION at the ONPRC include:

- Director's Office
- Administrative Services
- Business Services
- Research Safety Program/Environmental Health & Radiation Safety
- Facilities & Property
- Information Systems
- Library

A Research Strategy is provided for each of these components following the Administration Overview.

RESOURCES

Follow the 398 application instructions in Part I, 4.7 Resources.

Director's Office:

Computer:
Seven desktop workstations and one laptop that are linked to the local network and to OHSU. The Director's desktop workstation has video and telephone conferencing capability. Software includes: Adobe Creative Suite, Endnote, Microsoft Office Suite.

Office:
The Director's Office Suite occupies 828 sq. ft. The Director, Associate Directors for Research and Associate Director for Administration have individual offices in the Administration Building. The Associate Director for Comparative Medicine keeps main office in the Division of Comparative Medicine. The Project Manager and Administrative Coordinator have work areas in the Director's Office suite.

Administrative Services:

Computer:
Seven Dell desktop and two laptop computers are linked to the local network and to OHSU. Software: Microsoft Suite and Adobe Professional. OHSU provided Oracle Accounting (OGA); Discoverer (query tool); KRONOS (time Entry); Monarch; Shared Network Drives.

Office:
Administrative Services and Business Services share 1,727 square feet of office space.

Business Services:

Computer:
OHSU-provided Oracle financials which includes: Oracle Grants Accounting (OGA); Discoverer Query Tool; Time Entry; KRONOS; Info-Ed; OHSU network access; Shared network drives. Seven workstations with Dell computers.

Office:
Business Services and Administrative Services share 1,727 square feet of office space, shared access to 337 square feet of storage space, and a 181 square foot reception/mailroom area.

Facilities:

Computer:
Desktop computers are available in all of the office spaces (Physical Plant, Bio-Med shop, custodial office, equipment shed, and general shop). These computers are networked to the OHSU/ONPRC main system which enables the exchange of information and files through electronic mailings and document transfers. The Facilities department uses a Computerized Maintenance Management System (MP2) to track equipment information and the generation of preventive maintenance work orders. Facilities staff has access to the Diamond II software package for generating badges. Facilities staff utilize a Facility Commander software package to monitor and maintain the security cameras in select agent areas, BSL3 laboratories, and for gate access and perimeter fence monitoring.

Office:
Facilities office space consists of a Physical Plant office (2,980 square feet), a Bio-Med shop (382 square feet), a custodial office (98 square feet), an equipment shed (2,629 square feet) and a general shop area (4,501 square feet). The office uses the MP2, Diamond II, and Facility Commander software packages for maintenance, badge generation/control and security cameras, as well as handling all of the purchasing, accounts receivables, accounts payables, timesheets, estimating, budgeting, and general accounting/data entry activities.

Other:
The Physical Plant staff maintains a complete set of tools for operating and maintaining the campus, including hand tools for all disciplines of trade's workers (mechanical, plumbing, carpentry and sheet metal), cutting and welding equipment, jacks, dollys, refrigeration equipment, stainless steel cage repair equipment and HVAC components. Testing and cleaning equipment is also available for plugged drains, infrared testing of electrical panels, HVAC balancing, HVAC controls, and underwater cameras. Konica-Minolta shared networked MFP (multi-function printer, fax, scanner and copier).

Major Equipment:
28 Vehicles, including vans, pick-up trucks, and a flatbed truck ranging in age from 1985 to 2002
1 tractor with a front end loader, sweeper, grader and brush hog attachments
1 (ea) John Deere and Toro riding lawn mowers
1 walk behind snow blower
2 fork lifts

Information Systems:

Computer:
All IS staff use developer class laptop or desktop PCs running Windows 7 or Apple OS. There are 3 Windows 7 laptops available as loaners via online reservation, for remote access, and for presentations and 2 MacBook Pro laptops also for the same purposes. IS staff also have access to a 3-node VMWare vsphere virtualized cluster environment with multi-terabyte iSCSI storage, hosted at the Academic Computing Center (ACC), for business application hosting servers and for software development resources.

Office:
IS Manager/conference room: 202 sq. ft.; office for business analyst, programmer-analyst and systems analyst: 241 sq. ft.; Research Informatics Engineer: 159 sq. ft.; Development supervisor office: 146 sq. ft.; and staff-contractor workrooms: 176 sq. ft. All IS personnel are physically located together in the same building.

Other:
Media Room and Audio Visual office: 619 sq. ft. Contains secure storage for loaner computer and audio-visual equipment such as spare projectors, media converters, microphones. Used for computer based training, webinars, general conference room uses, and for alternate Emergency Operations Center (EOC) purposes

Research Library:

Computer:
The Library has six Dell personal computers. Four are designated as public computers and two are staff computers.

Office:
The Library occupies 1,921 square feet in the ONPRC administration building with an additional 172 square feet of storage space.

Major Equipment:
The Library has a networked HP Color Laser (4525DN) printer and a networked HP 8650 scanner with automatic document feeder. There is also a Minolta microfilm/fiche reader and printer, and a Konica Minolta bizhub 323 (combined photocopier, fax, scanner and b&w printer).

Research Safety:

EHRS

Laboratory:
Montagna 116 is a small laboratory space with a ventilated hood located within the EHRS office that is used for sample analysis and instrument and supply storage. It is available 100% for EHRS use.

Computer:
Two Dell Optiplex GX780 desktop computers, 1 Optiplex GX620, 2 Dell Latitude E6420 laptop computers with docking stations (typically used as desktop computers), 1 Dell Latitude E6410 laptop computer with docking stations, 1 Dell Latitude E6400 laptop computers with docking station, Toshiba Satellite laptop computer.

Office:
Montagna 115 is common office space containing 5 cubicles that are used 100% by EHRS staff. Montagna 113 is an private office used 100% by the EHRS manager.

Other:
Montagna 114 is a small conference room with a capacity of 12 people. It is controlled 100% by EHRS, but is made available to others at ONPRC when available. One small cinderblock buildings on the ONPRC campus is used by EHRS for hazardous waste storage and processing. It is located equidistant between the Research Building, Central Stores and the Cooley Building, and is approximately 150 yards from the EHRS office. This building is used to store hazardous chemical waste prior to disposal. A steel storage container is located between the Colony Building and the Colony Annex, approximately 0.25 mile from the EHRS office, and is used for long-term storage of radioactive waste. Both are available 100% for EHRS use, and are accessible only to EHRS personnel. A cargo container leased by EHRS for the storage and processing of biohazard waste is located between Central Stores and the Cooley Building. This space is approximately 150 yards from the EHRS office and is also available 100% for EHRS use.

Major Equipment:
Montagna 116: 3M Qualititave Fit Test apparatus for required testing of N-95 respirators, Bicron RSO50E Dose Rate Meter for measuring radiation fields, BW Technologies 5 Gas Detector for air monitoring, Delmhorst BD-2100 Moisture Meter for humidity measurements, 4 Ludlum 3 Radiation Survey Meters with β and γ probes for radiation detection, Ludlum 14C Radiation Survey Meter with γ probe for radiation detection, Ludlum Model 500 Pulser for calibration of radiation survey meters, Ludlum Model 2200 Scalar Ratemeter with γ probe for bioassays, Quest Electronics M-27 Noise Logging Dosimeter for noise monitoring, tif VelociCalc Air Velocity Meter for chemical hood testing. Montagna 115: Konica bizhub 283 photocopier, HP LaserJet P3005n B&W printer, HP Color LaserJet 3800n printer, HP 1040 Fax machine, Fujitsi Scansnap 1500 scanner, Fellowes PS70-2 Document Shredder, Dymo Label Manager 150, GBC Heat Seal H400 laminator. Montagna 114: , In –Focus IN 122 Digital Projector for training presentations, ,Nikon Coolpix Digital Camera for documentation and training images, 6 Day Wireless Systems ICOM walkie talkies for Emergency Response communications. Hazardous waste storage areas: Peristaltic pump with timer for sewer sample collection, Ludlum Model 3 Radiation Survey Meter with γ probe for detection of radioactivity, Packmaster Air Pneumatic Drum Barrel compressor for waste compaction. Central Stores: Bicron RSO50E Dose Rate Meter for measuring radiation fields, 2 Ludlum Model 3 Radiation Survey Meters with β and γ probes for detection of radioactivity.

Occupational Health Nurse

Laboratory:
Occupational Health Nurse office is about 215 sq. ft. in room 000 and 000A in the Research building and designated to provide employee services such as N95 fit testing, immunizations, TB testing/screening, injury and exposure care & referral.

Computer:
Dell OptiPlex 780 Desktop computer and a Dell laptop with docking station

Office:
HP Photosmart C5250 printer

Other:
ICOM BC 160 hand held pack set.

ADMINISTRATION OVERVIEW - SPECIFIC AIMS

The ONPRC Administration provides leadership and integration of administrative functions, working closely with the host institution, Oregon Health & Science University (OHSU utilizes a strategic planning process to develop strategies and tactics for the Director's office that are aligned with overall ONPRC strategic goals:

Specific Aim 1. Manage an efficient and effective Director's Office with the following sub-aims: (1) Coordinate the activities of the Director and Associate Directors in leading the ONPRC and in setting scientific and strategic priorities; (2) Promote and assure fair external and internal access to nonhuman primates and support cores for research; (3) Assure stable funding for the Center; (4) Provide effective communication within ONPRC and with OHSU, NIH, and the broader scientific and lay communities; and (5) Provide oversight and linkage to key regulatory functions that are integral to interactions with OHSU and state and local governments.

Specific Aim 2. Provide Administrative Services with the following sub-aims: (1) Ensure the continued provision of physical and personnel resources to provide an appropriate environment for the safe and effective conduct of animal care and research; (2) Strengthen work and financing relationships at OHSU to ensure infrastructure development in a timely manner; (3) Work with the OHSU and local governments to establish a long-range master plan for the next ten years; and (4) Engage with Administrative leaders in the NPRC Consortium to continue to define and document best practices that can be used throughout the NPRC system.

Specific Aim 3. Provide Business Services with the following sub-aims. (1) Provide appropriate levels of support and staffing to provide for the efficient, effective, and compliant conduct of the P51 award; (2) Provide excellent customer service to ONPRC Divisions while maintaining productive relationships with OHSU Business and Grants Management Departments; (3) Fully implement and utilize an RFID inventory system to track ONPRC fixed assets; and (4) Explore and implement a new system for budget development for the competing and non-competing P51 award.

Specific Aim 4. Provide a Research Safety office for the West Campus to coordinate regulatory oversight and compliance with OHSU Environmental Health & Radiation Safety with the following sub-aims: (1) Monitor and evaluate the efficiency and effectiveness of the new RSP/EHRS organizational structure with respect to ONPRC operations; (2) Improve laboratory safety awareness and compliance; (3) Continue to strengthen the Occupational Health and Safety Program; (4) Continue to strengthen training and injury prevention strategies; and (5) Continue to strengthen security and biosecurity at the ONPRC.

Specific Aim 5. Provide an outstanding Facilities and Property group with the following sub-aims: (1) Ensure the continued safe, efficient, productive and sustainable operations at the ONPRC, complying will all regulations; (2) Work cooperatively with the Administrative, Research, and DCM staffs to identify campus upgrades and renovations necessary to support the ongoing research goals; and (3) Work with the OHSU Design & Construction Department and Space Planning Group to assure timely identification and funding of future projects in support the ONPRC research and animal care mission.

Specific Aim 6. Provide state-of-the-art, integrated Information Systems with the following sub-aims: (1) Continue the development of technologies to serve the needs of the research, finance, and colony management groups; (2) Provide support and expertise leadership for research and colony management informatics internally and at the national NHPRC level;(3) Continue progress in adoption of operational and industry best practices to deliver higher quantity and quality of service delivery to ONPRC and other stakeholders; and (4) Foster effective communications and collaboration internally and externally.

Specific Aim 7. Provide an efficient and useful Research Library with the following sub-aims: (1) Maximize resources available for the needs of NHP researchers, veterinarians and support staff; (2) Provide assistance and support to Comparative Medicine for their expanded educational and research role in primatology; (3) Preserve the unique NHP historical resources of ONPRC while making them more available to researchers and the wider community; (4) Help ensure compliance with NIH public access policy in a timely manner; and (5) Develop novel training methods and continue to leverage resources with OHSU main library.

ADMINISTRATION OVERVIEW

Administration at the Oregon National Primate Research Center (ONPRC) includes the following units:

- The Director's Office, including the Public Information Officer
- Administrative Services
- Business Services
- Facilities & Property
- Research Safety (part of Environmental Health & Radiation Safety)
- Information Systems
- Research Library

ORGANIZATIONAL FRAMEWORK

Oregon Health & Science University (OHSU) is the host institution for the ONPRC, and OHSU President Joseph Robertson, M.D., is the Principal Investigator of the P51. The ONPRC Director, [Excluded by Requester] Ph.D., reports to [Excluded by Requester], who is the Senior Vice President for Research at OHSU. The ONPRC is located on the West Campus of OHSU, 12 miles west of the main campus and hospital and teaching facilities. From its founding in the 1960s through 1998, the ONPRC was an independent research institution. ONPRC formally merged with OHSU in 1998 and in December 2003, the fiscal and business/grants management systems were incorporated into OHSU central services. These central services provide a basic business and compliance-assurance structure, within which diverse units such as hospital, research, and educational units can function effectively. Some areas such as legal, banking, business development, technology transfer, public safety, and health and safety are handled entirely by OHSU, but most administrative functions are handled cooperatively between resources at the University and at the institute/department level. This approach requires significant expertise and staffing for administrative and business services offices at ONPRC. Similarly, because of the physical distance and unique nature of primate center facilities, the Physical Plant staff and its operation were retained by ONPRC in agreement with OHSU and the NIH Office of Research Infrastructure Programs (ORIP). This approach has been a significant advantage to ONPRC by enabling the Center to centralize and harmonize key functions while tailoring non-duplicative services to meet unique needs that arise for an NPRC. Importantly, OHSU provides shared governance, oversight, and resources from the Office of the Vice President for Research in Finance, Research Grants & Contracts, Sponsored Projects, Human Resources, and overall leadership. Additional shared governance and oversight stems from the Office of Research Integrity, including coordination of the Main Campus and West Campus IACUCs; Environmental Health & Radiation Safety within a local group that oversees West Campus Research Safety; the Office of Research Advocacy; Information Technology & Engineering; Planning, Design and Construction; Public Safety; and Emergency Management.

There are three Associate Directors: Administration [Excluded by Requester] Interim, replacing [Excluded by Requester] who directs finance and administrative units; Research [Excluded by Requester] Ph.D.); and Comparative Medicine [Excluded by Requester] DACLAM). The Director and Associate Directors form the Executive Leadership Committee, and with the Scientific Division Chiefs, the Expanded Executive Leadership Committee (described below). The National Scientific Advisory Board (NSAB, membership listed in the Committees section following) serves in an advisory capacity. Administrative support is provided to each of the Associate Directors and to the Director. There is a new position in the Director's Office, a Project Manager.

The Vaccine and Gene Therapy Institute (VGTI) is a research institute within OHSU that is highly integrated within the ONPRC and co-located on the West Campus, sharing many administrative functions, scientific resources, and collegial activities. Members of the ONPRC Pathobiology & Immunology Division are members of the VGTI, which is led by [Excluded by Requester] (Director) and [Excluded by Requester] (Associate Director). It is the stated goal of both directors [Excluded by Requester] to seek further collaborative alignments. An example of this is the current co-recruitment of a Senior Scientist to lead the Division and who will have a joint appointment in Pathobiology & Immunology at the ONPRC and in the VGTI. These relationships are diagrammed on the Organizational Chart for ADMINISTRATION. Detailed Organizational Charts are provided for each of the

subsections in ADMINISTRATION. The overall Organizational Chart for the ONPRC as a whole can be found in the OVERVIEW.

OVERALL INTERACTIONS AND RESPONSIBILITIES BETWEEN ONPRC AND OHSU

Responsibilities of Center Director and Associate Directors:
Director. The Director provides overall leadership for the Center, setting scientific and managerial priorities that are congruent with the mission of the Center and of OHSU. Excluded by Requester is responsible for oversight of all of the activities of the Center, including management of the core grant, strategic planning, communication, development of new research programs, and development of new revenue sources to fund an expansion of research facilities and animal housing, as well as liaison with OHSU and ORIP and other NPRCs. Governance of the center is accomplished through **Integrated Leadership** led by the Director's office via weekly meetings of the leadership team including the Director and Associate Directors for Administration, Research, and Comparative Medicine, termed the Executive Leadership Committee (ELC). These senior leaders represent the ONPRC at the NPRC National Directors' Meetings held twice yearly and serve as an oversight group for interactions with the NPRC Consortium. The Expanded Executive Leadership Committee (EELC) meets bimonthly and includes the Scientific Division Chiefs. To assure linkages with the broader scientific programs, there are Quarterly EELC Meetings that include leaders from the Interdisciplinary Research Programs, the NHP Resource Programs, and Research Support Cores, as well as leaders from Research Advocacy, Research Safety, and Research Integrity. The Director meets monthly with Excluded by Requester Senior Vice President for Research, and also attends key leadership meetings at OHSU within the School of Medicine to assure strong linkages between ONPRC and other key groups at OHSU, including the Vaccine & Gene Therapy Institute. She represents the ONPRC at the President's Council, which meets monthly. During the last funding period, she and Associate Director Excluded by Requester actively participate in the School of Medicine Strategic Planning Process, and they continue to implement the initiatives that stemmed from this cooperative and collaborative planning effort. The Director's Office is responsible for all ONPRC communications, via the Public Information Officer to NIH, to the NSAB, to OHSU, within the community and nationally, via OHSU Strategic Communications. The Director participates regularly in teleconferences with the other NPRC Directors and NIH staff to assure effective communication and follow-up on strategic goals and action items identified by ORIP and at the biannual NPRC Directors' meetings. In addition to the Division Chiefs, the Director meets regularly with Interdisciplinary Research Program managers and hosts or facilitates conferences and symposia. She and the Associate Director for Research oversee the Outreach Program.

The Associate Director for Research The Associate Director, Excluded by Requester has primary responsibilities for internal research support, compliance, training, and outreach. He was appointed Associate Director for Translational Research in April 2007 and was appointed as Associate Director for Research in 2008 when Dr. Excluded by took on his current role as Director of Research Advocacy. He serves as Chair of the Research Advisory Committee, and is also responsible for management of the Pilot Project Program as well as the management of the Collaborative Research Unit (CRU) to assure access to NHP resources by external investigators with NIH funding. The CRU component assures that all inquiries from external sources are directed to the appropriate internal collaborator, and that external research projects are run smoothly and are provided with scientific leadership and expertise, as well as administrative support. OHSU's Clinical and Translational Science Award (CTSA) is called the Oregon Clinical and Translational Research Institute (OCTRI). OCTRI has committed funds to supplement the ONPRC pilot grant program to support collaborative projects involving ONPRC and OHSU/OCTRI co-investigators. The Associate Director for Research also serves as a major liaison between the Center and the OHSU Foundation and the OHSU Office of Technology Transfer and Business Development, particularly to promote and manage research interactions with industry and public-private partnerships. He also oversees the management of the Research Support Cores; these cores are essential components in establishing new technologies that have played such an important role in the growth in external grant funding. These services have been improved through purchase of new equipment and the establishment of new techniques. Each of the eight Research Support Cores (Assisted Reproductive Technology, Endocrine Technologies, Imaging and Morphology, Flow Cytometry, Magnetic Resonance Imaging, Molecular & Cellular Biology, Primate Genetics, and Molecular Virology) has a senior staff member as a Core Manager and an oversight committee that determines the services to be offered and the charge-back

fees associated with each service. The Associate Director works with the Office of Research Integrity via the newly created (during the last funding period) West Campus Research Integrity Officer and with the Office of Environmental Health & Radiation Safety via the West Campus Research Biosafety Officer and the Occupational Health Nurse. Excluded by Requester provides local compliance oversight (with further veterinary compliance coming from the Attending Veterinarian Excluded by Requester with the IACUC and research training modules. Excluded by Requester is the primary resource for regulatory compliance with agencies overseeing importation/exportation, scheduled and non-scheduled drug acquisition, shipping compliance, etc., including NIH, USDA, FAA, CITES, and DEA.

The Associate Director for Administration is responsible for the operations, finances, grants management, human resources, facilities, information systems (IS) and the research library for the Center. In addition, the Associate Director plays a key role in the short and long-range financial modeling that supports the scientific direction set by the ELC. The Associate Director for Administration develops policies and procedures affecting a wide range of administrative activities, and reviews and disseminates University policy and procedure governing these activities. This person also assures that the financial activity at ONPRC is in compliance with various regulatory agencies. With the role of overseeing facilities and IS at the Center, the Associate Director for Administration works closely with the University's central units, specifically Design & Construction and the Information Technology Group (ITG) for construction projects and coordination of information and telephone systems. This position also participates in the following University wide committees: Internal Audit Committee, OHSU Policy Advisory Committee and the Administrative Information Systems Steering Committee. Mr. Excluded by Requester served in this capacity from 2006 through the submission of this application in 2013. His long-term experience at the ONPRC in Administration and Finance (more than 25 years) has provided an excellent foundation upon which to build the next several years. With his planned departure, the Center has engaged the able leadership of Excluded by Requester Director of Finance for the Office of the Vice President for Research. Excluded by Requester will serve as the Interim Associate Director for Administration, until a suitable replacement is recruited for both the Associate Director and the Assistant Associate Director, Excluded by Requester who retired in December 2011.

The Associate Director for Comparative Medicine (DCM) provides oversight of all NHP-related activities and brings critical veterinary and regulatory expertise to the scientific aims of all Divisions and Programs. The DCM has been reorganized, in keeping with the ever expanding NHP population and increased number of funded research projects using NHPs; the construction of new and renovation of existing animal facilities; and the increasingly complex nature of managing multiple disease models, unique NHP resource populations, various housing modalities, increasingly important genetic characterization of every animal, and the demand for maximizing social housing. The Division maintains excellent communications with the Department of Comparative Medicine on the OHSU main campus and the West Campus Attending Veterinarian has a dual reporting relationship to the ONPRC Director and to the Institutional Official. Excluded by Requester was appointed as Chief of this Division in May 2011, succeeding Excluded by Requester who served in this capacity from 2008-11. The Division of Comparative Medicine has expanded significantly, in keeping with the increase in the NHP population, in funded research projects using NHPs, and the development of new animal facilities. The Head of DCM serves as the Attending Veterinarian for the West Campus and in this capacity reports to the Institutional Official, Excluded by Requester He is responsible for all of the DCM staff and the overall management of the animal colony. The Division maintains excellent communications with the Department of Comparative Medicine on the OHSU main campus, and the Associate Director serves as liaison to this group.

Description of the oversight committees, including functions and composition.
Each of the Committees listed in the Organizational Framework section are noted below with full memberships and academic titles of members. The role of each committee and its reporting relationship, frequency of meeting, and term of membership are indicated below.

NATIONAL SCIENTIFIC ADVISORY BOARD (NSAB, external)
The NSAB provides advice and guidance to the Principal Investigator and Center Director on planning and strategic initiatives. This board meets yearly in Oregon to advise Drs. Robertson, Excluded by Requester concerning plans for the Core grant submission and scientific strategic initiatives. This group has provided a

yearly written assessment of their observations and recommendations, and this information is shared widely with all scientific leadership and summarized for the entire ONPRC; reports are maintained in the Director's Office. During 2009-2012 Excluded by Requester served as advisors to the Reproductive Sciences Division. Excluded by Requester provided guidance to the Neuroscience Division. Dr. Excluded by served a dual role as an advisor to the Division of Animal Resources, while also providing expertise in HIV vaccine design and lentiviral pathogenesis. She was joined by Excluded by Requester as advisors to the Pathobiology & Immunology Division. Many of these members were re-appointed in October 2012 to serve for the next funding period, with the addition of new members to support new interdisciplinary Research Programs in Genetics and Aging and the new Division of Diabetes, Obesity, and Metabolism. Current members are noted in **bold** type. Term of membership is 5 years, with reappointment possible.

Member and degrees	Title	Department/Institution	Advisor for Division or Program	Appointment
Excluded by Requester	**Professor and Chair**	**Veterinary Medicine, Tulane National Primate Research Center, Tulane University**	**Comparative Medicine**	**2012-present**
	Director & Professor	**Reproductive Medicine, University of California, San Diego**	**Reproductive & Developmental Sciences**	**2007-present**
	Professor	Molecular Physiology & Biophysics, University of Iowa	Neuroscience	2007-2012
	Professor	**Psychiatry and Biobehavioral Sciences, University of California at Los Angeles**	**Genetics**	**2012-present**
	Senior Investigator	National Institute of Allergy & Infectious Diseases/NIH	Pathobiology & Immunology	2007-2012
	Professor	**Pennington Biomedical Research Center**	**Aging**	**2012-present**
	Professor	Neurobiology & Physiology, Northwestern University	Neuroscience	2007-2010
	Program Director	**National Cancer Institute-Frederick**	**Pathobiology & Immunology**	**2007-present**
	Director & Professor	**Pharmacology,** Private Source	**Neuroscience**	**2007-present**
	Professor	Molecular Genetics & Microbiology, University of Florida	Pathobiology & Immunology	2007-2012
	Director & Professor	**Obstetrics & Gynecology,** Private Source **University**	**Reproductive & Developmental Sciences**	**2007-present**
	Professor	**Fred Hutchinson Cancer Research Center**	**Pathobiology & Immunology**	**2007-present**
	Chief, Program Director & Senior Investigator	National Institute of Child Health & Human Development, NIH	Reproductive & Developmental Sciences	2007-2012
	Professor and Director	**Cincinnati Diabetes and Obesity Center, University of Cincinnati**	**Diabetes, Obesity, and Metabolism**	**2012-present**
	Professor	**Psychiatry & Behavioral Sciences,** Private Source	**Imaging**	**2012-present**

EXECUTIVE LEADERHIP COMMITTEE (internal)

Center leaders meet weekly in the Director's office to review and address strategic, organizational and administrative goals and issues. The minutes are edited and posted on SharePoint for this group to utilize and to track Action Items. Appointment is by position and continues as long as that person is in that role.

Member	Title	Department/Division
Excluded by Requester	Director and Senior Scientist	Director's Office/Administration and Pathobiology & Immunology
	Associate Director for Research & Senior Scientist	Director's Office, Diabetes, Obesity, & Metabolism, and Reproductive & Developmental Sciences
	Associate Director	Comparative Medicine
	Interim Associate Director	Administration

EXPANDED EXECUTIVE LEADERHIP COMMITTEE (internal)

Center leaders and Division Chiefs meet bimonthly in the Director's office to review and address strategic, organizational and administrative goals and issues and to review any key Action items and decisions requiring the input from this larger group. The minutes are edited and posted on SharePoint for this group to utilize and to track Action Items. Appointment is by position and continues as long as that person is in that role.

Member	Title	Department/Division
Excluded by Requester	Director and Senior	Director's Office/Administration
	Associate Director and Division Chief	Comparative Medicine
	Associate Director for Research	Director's Office/Administration
	Interim Associate Director	Administration
	Interim Division Chief & Senior Scientist	Pathobiology & Immunology
	Division Chief & Senior Scientist	Neuroscience
	Division Chief & Senior Scientist	Reproductive & Developmental Sciences
	Interim Division Chief & Senior Scientist	Diabetes, Obesity, & Metabolism

RESEARCH ADVISORY COMMITTEE (internal)

Scientists representing the scientific disciplines within the Center meet to scientifically review projects unless the protocol has been previously reviewed and approved by a federal peer-reviewed body (NIH, NSF). The committee reviews scientific merit and advisability of initiation of the proposal, relevance of the study to the mission of the Center, justification for use of NHPs in the study, and research support required. The committee meets monthly or as needed. Records are kept for all of the applications and outcomes and recommendations in the Director's Office. Excluded by Requester Administrative Coordinator, staffs this committee. Appointments are reviewed yearly and typically have a three-year duration. This group reviews Pilot Research Program applications and when these are reviewed, members of the NSAB are included in the reviews.

Member	Title	Department/Division
Excluded by Requester	Associate Director for Research & Senior Scientist	Director's Office, Diabetes, Obesity, & Metabolism, and Reproductive & Developmental Sciences
	Director and Senior Scientist	Director's Office/Administration and Pathobiology & Immunology
	Director for Research Advocacy & Senior Scientist	Director's Office, Neuroscience and Reproductive & Developmental Sciences
	Professor	OHSU Pediatric Endocrinology (external)
	Interim Division Chief & Senior Scientist	Pathobiology & Immunology
	Division Chief & Senior Scientist	Neuroscience
	Division Chief & Senior Scientist	Reproductive & Developmental Sciences
	Interim Division Chief & Senior Scientist	Diabetes, Obesity, & Metabolism
NSAB members as needed	Ad hoc reviewers to provide external expertise	Most relevant to applications

ONPRC POLICY GROUP

All division and unit heads meet monthly to discuss, review and develop Center policies; issues regarding scientific program planning, facilities/property, primate/animal resources, information technology, environmental health and safety, administrative services and public relations/information are addressed. Minutes of meetings are available to Center staff. Excluded by Requester Administrative Coordinator, staffs this committee and records minutes, which are distributed monthly. Appointment is by position and continues as long as that person is in that role.

Member	Title	Department/Division
Excluded by Requester	Director	Director's Office/Administration
	Project Manager and Public Information Officer	Director's Office/Administration
	Interim Associate Director	Administration
	Director	Office of Research Advocacy
	Associate Director for Research	Director's Office/Administration
	Associate Director	Comparative Medicine

Excluded by Requester	Manager	Fiscal Services/Administration
	Manager	Information Science/Administration
	Manager	Facilities & Property/Administration
	Main Campus Biosafety Officer	OHSU Environmental Health & Radiation Safety
	West Campus Biosafety Officer	Environmental Health & Radiation Safety
	Interim Division Chief	Pathobiology & Immunology
	Interim Division Chief	Diabetes, Obesity, & Metabolism
	Division Chief	Neuroscience
	Associate Director	OHSU Strategic Communications
	Division Head	Reproductive & Developmental Sciences
	Outreach Manager	Outreach/Administration
	West Campus Integrity Officer	Director's Office and OHSU Research Integrity

INSTITUTIONAL ANIMAL CARE & USE COMMITTEE

This committee meets monthly to review all animal protocols for the West Campus. Minutes are kept and decisions are communicated formally to investigators and to the OHSU Office of Research Integrity. Appointments are three years and are approved by the Vice President for Research, Excluded by Requester

Member	Title	Department/Division
Excluded by Requester	Staff Scientist, IACUC Chair	Neuroscience, CRU
	Research Integrity Officer	Director's Office and OHSU Research Integrity
	Associate Director, Attending Veterinarian	Comparative Medicine
	Affiliated, Non-Scientific Member	
	West Campus Biosafety Officer	EH&RS
	Surgical Services	Comparative Medicine
	Assistant Scientist	Pathobiology & Immunology
	Senior Scientist	Diabetes, Obesity & Metabolism
	Associate Scientist	Reproductive & Developmental Sciences
	Senior Scientist	Neuroscience
	Scientist, Non-human Primate Behaviorist	Reproductive & Developmental Sciences and Comparative Medicine
	Non-Affiliated Member	
	Affiliated, Non-Scientific Member	Administration (Information Science)
	Research Integrity Officer	OHSU
	IACUC Liaison	OHSU

ANIMAL UTILIZATION ADVISORY COMMITTEE

This committee meets quarterly to address policies and procedures for determining long-range and short-term plans and needs for NHPs/animals and to resolve issues related to all aspects of NHP/animal use in research programs. It also serves to educate about policy decisions related to use of NHPs in research protocols. The committee is broad-based and has representation from the following areas: scientists in all research divisions, the veterinarians, lab animal medicine staff and administrative staff. Appointment is by position and continues as long as that person is in that role.

Member	Title	Department/Division
Excluded by Requester	Director, ONPRC, & Senior Scientist	Director's Office, and Pathobiology & Immunology
	Associate Director Research & Senior Scientist	Director's Office, Diabetes, Obesity, & Metabolism and Reproductive & Developmental Sciences
	Division Chief and Associate Director	Comparative Medicine
	Associate Veterinarian and Head	NHP Resources Unit, Comparative Medicine
	Interim Associate Director	Administration
	West Campus Research Integrity Officer	Administration and Research Integrity
	Operations Manager	Comparative Medicine

Excluded by Requester	Associate Scientist and Resource Manager	Pathobiology & Immunology and Infectious Disease NHP Resource
	Resource Manager and Staff Scientist	NHP Aging Resource & Neuroscience
	Program Manager	NHP Genetics Resource and Japanese Macaque Resource
	Division Chief	Neuroscience
	Interim Division Chief	Pathobiology & Immunology
	Interim Division Chief	Diabetes, Obesity, & Metabolism
	Division Chief	Reproductive & Developmental Sciences
	Senior Scientist	Neuroscience

ANIMAL USAGE SUBCOMMITTEE

The Committee meets monthly and provides a smaller working group to review issues in order to optimize the use of NHP/animal resources and meets quarterly with the Animal Utilization Advisory Committee to address policies and procedures for determining needs for and use of NHPs/animals and to resolve issues related to all aspects of NHP/animal use in research programs. Appointment is by position and continues as long as that person is in that role.

Member	Title	Department/Division
Excluded by Requester	Director	Director's Office/Administration
	Associate Veterinarian and Head	NHP Resources Unit/Comparative Medicine
	Associate Director	Comparative Medicine
	Program Manager	NHP Genetics and Japanese Macaque Resources/Comparative Medicine
	Division Chief	Neuroscience
	Interim Division Chief	Pathobiology & Immunology
	Interim Division Chief	Diabetes, Obesity, & Metabolism
	Associate Director for Research	Director's Office/Administration
	Division Chief	Reproductive & Developmental Sciences

ABSL3 OVERSIGHT COMMITTEE

This committee meets monthly to approve, schedule, monitor, and review projects utilizing the ABSL3 facility, providing advice, counsel and feedback to researchers. Furthermore, the AOC provides guidance for facility staffing, health and safety, maintenance, and compliance with all regulations. The AOC works collaboratively with the director's office to ensure adherence to organizational concepts, standards and procedures. Records of minues are kept in the Research Safety office.

Member	Title	Department/Division
Excluded by Requester	Senior Scientist	Pathobiology & Immunology
	Associate Veterinarian and Head	NHP Resources Unit/Comparative Medicine
	Associate Scientist	Pathobiology & Immunology
	Main Campus Biosafety Officer	OHSU Environmental Health & Radiation Safety
	Program Technician II	OHSU Environmental Health & Radiation Safety
	Assistant Associate Director	Comparative Medicine
	Supervisor, Small Laboratory Animal	Comparative Medicine
	Manager	Facilities & Property/Administration
	West Campus Biosafety Officer	Environmental Health & Radiation Safety
	Assistant Veterinarian	Comparative Medicine
	Associate Director & Division Chief	Comparative Medicine
	Interim Division Chief	Pathobiology & Immunology
	Assistant Veterinarian	Comparative Medicine

PROMOTIONS COMMITTEE

The Promotions Committee evaluates candidates, including Core Scientists and Veterinary staff, for promotion according to procedures described in the Promotions Policy. Appointments are for three years.

Member	Title	Department/Division

Excluded by Requester	Senior Scientist	Neuroscience and Reproductive & Developmental Sciences
	Senior Scientist	Reproductive & Developmental Sciences
	Senior Scientist	Pathobiology & Immunology
	Senior Scientist	Neuroscience
	Associate Director	Comparative Medicine

CAMPUS SAFETY COMMITTEE

This Committee educates and trains to protect the safety and health of employees. The goal is to reduce potential for injuries and illnesses due to hazards in the workplace. The Committee evaluates incidents, summarizes information and makes recommendations for corrective action and is responsible for overseeing the adherence to local, state and federal workplace health and safety guidelines. More specifically, the Committee defines actual or potential occupational risk, promotes accident prevention, helps identify and define employee safety training needs and utilizes accident investigation resources in the event of an incident.

Member	Title	Department/Division
Excluded by Requester	Safety Specialist	Research Safety Program – Environmental Health & Radiation Safety
	Administrative Assistant	Research Safety Program – Environmental Health & Radiation Safety
	Admin. Coordinator	Vaccine and Gene Therapy Institute
	Program Administrator	Vaccine and Gene Therapy Institute
	Financial Analyst 1	Business Services/Administration
	Occupational Health Nurse	Environmental Health & Radiation Safety
	Zone Leader	OHSU Facilities
	Research Tech. 2	Pathology/Comparative Medicine
	Research Tech. 2	BSU/ Comparative Medicine
	Investigations Sergeant	Public Safety
	Manager, Workman's Comp	Risk Management
	Assist. Vet.	Comparative Medicine
	Facilities tech. Senior	ONPRC Facilities
	Manager	Human Resources/Administration
	OGI Real Estate Manager	OGI
	Facilities Tech.	OGI
	Human Resources Coordinator	Human Resources/Administration
	Senior Res. Assist.	OGI
	Community Service Officer	Public Safety
	Building Systems Control	Facilities
	ONPRC Research Librarian	Library/Administration
	Manager	OHSU Pharmacy Services
	Finance Manager	OGI

OHSU INSTITUTIONAL BIOSAFETY COMMITTEE

This Committee evaluates all research that is conducted with recombinant DNA (rDNA), regardless of funding, to ensure compliance with NIH Guidelines. The Committee routinely reviews and makes recommendations for all research projects performed at the ONPRC, VGTI, and NSI.

Member	Title	Department/Division
Excluded by Requester	Associate Scientist	Vaccine & Gene Therapy Institute
	Research Assistant Professor	Vaccine & Gene Therapy Institute
	Assistant Professor	OHSU Infectious Disease
	Main Campus Biosafety Officer	OHSU Environmental Health & Radiation Safety
	Assistant Professor	OHSU Molecular Microbiology & Immunology
	Associate Professor	OHSU Molecular & Medical Genetics
	Assistant Professor	Hematology & Oncology
	West Campus Biosafety Officer	Environmental Health & Radiation Safety
	Sr. Research Associate	Vaccine & Gene Therapy Institute
	Associate Director	OHSU Research Integrity Office
	Director	OHSU Comparative Medicine
	Associate Scientist	Pathobiology & Immunology

Excluded by Requester	Community Member	N/A
	Community Member	N/A
	Research Assistant Professor	Vaccine & Gene Therapy Institute
	Department Head, Pathology	Pathology
	Biosafety Specialist	OHSU Environmental Health & Radiation Safety
	Community Member	N/A
	Assistant Professor	OHSU Molecular Microbiology & Immunology
	Staff Scientist 3	Neuroscience
	West Campus Biosafety Officer	Environmental Health & Radiation Safety
	Community Member	N/A
	Assistant Scientist	Vaccine & Gene Therapy Institute
	Community Member	N/A
	NHP Resource Veterinarian	Comparative Medicine
	Associate Professor	OHSU Comparative Medicine
	Associate Professor, Ad hoc consultant	Clinical Infection Control Expert
	Assistant Professor	OHSU Infectious Disease Division

WEST CAMPUS RADIATION SAFETY COMMITTEE

The new Committee, established in 2001, integrates the West Campus—ONPRC/OHSU, VGTI and OGI. The ONPRC license will change from a Broad Scope B Radioactive Materials License from the State of Oregon to a Broad Scope A License to include all institutions on campus. New radiation policies and procedures were developed in the fall of 2001 and are updated as needed.

Member	Title	Department/Division
Excluded by Requester	Research Radiation Safety Officer	OHSU Environmental Health & Radiation Safety
	Interim Associate Director	Administration
	Professor	Environmental & Biomolecular Systems
	Associate Scientist	Pathobiology & Immunology
	Industrial Hygienist	Environmental Health & Radiation Safety
	Associate Scientist	Reproductive & Developmental Sciences
	Staff Scientist 2	Neuroscience

INFORMATION TECHNOLOGY ADVISORY GROUP (ITAG)

The IT Advisory Oversight Committee, heavily customer focused, provides guidance for the continued development and deployment of information systems, helps the IS Manager establish new development and operational goals and priorities, and helps to evaluate how the new research informatics system that is being implemented, PRIMe (LabKey), can introduce new efficiencies into our animal care program and research initiatives. Appointments are for three years.

Member	Title	Department/Division
Excluded by Requester	West Campus Integrity Officer	
	Manager, Information Science	Information Science/Administration
	Interim Associate Director	Administration
	Manager	Field Services/OHSU ITG

Excluded by Requester		Associate Scientist	Neuroscience
		Senior Staff Scientist	Molecular Virology Core/Research Cores
		Senior Scientist	Molecular & Cellular Biology Core/ Research Cores
		Assistant Scientist	Pathobiology & Immunology
		Senior Scientist	Neuroscience; Reproductive & Developmental Sciences
		Assistant Associate Director	Comparative Medicine
		Associate Veterinarian	Comparative Medicine
Vacancy			Comparative Medicine
Vacancy			Diabetes, Obesity, and Metabolism

LIBRARY COMMITTEE

This Committee oversees the acquisitions of the library and reviews its use of resources. The Research Library provides an essential service to Center scientists, support staff, affiliated and visiting scientists, and graduate students. Appointments are for three years.

Member		Title	Department/Division
Excluded by Requester		Associate Scientist	Reproductive & Developmental Sciences
		Senior Veterinary Pathologist	Comparative Medicine/Pathology Services
		Associate Scientist	Vaccine & Gene Therapy Institute
		Associate Scientist	Neuroscience
		Senior Scientist	Pathobiology & Immunology

MAJOR PROGRESS DURING THE PAST 5 YEARS FOR OVERALL ADMINISTRATION

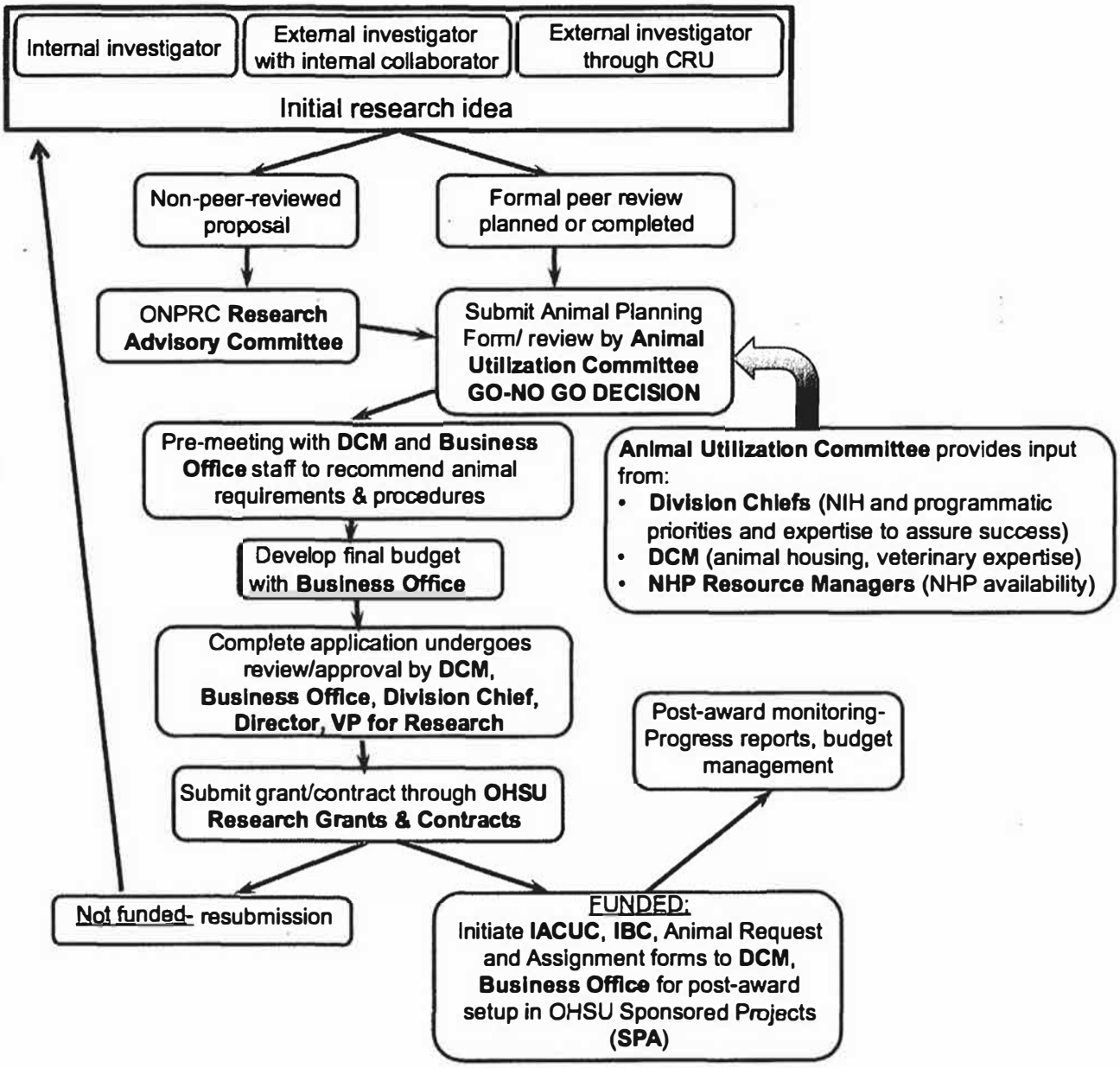
Overall key objectives and milestones that were met in the last 3.5 years include:

1. Completion of a formal Strategic Planning Process that was initiated in 2008 and completed in 2009. This plan has increased transparent decision-making and collaborative planning. The role of the ONPRC Administration in contributing to the success of the research, animal services, outreach, and consortium activities is to ensure that there is outstanding administrative and fiscal support for the facilities, information systems, and grant submission and management post-award. Effective linkage of these elements via strategic goal setting has been vital to the success of the enterprise.
2. Successful recruitment of strong Divisional leaders in two divisions and new junior faculty in all of the Scientific Divisions. We collectively identified and recruited two internationally recognized and highly talented leaders to the ONPRC to lead Neuroscience and Comparative Medicine and brought in four new Assistant Core Scientists.
3. Replacement of the outdated IRIS computerized EMR and billing system, a major concern at the last P51 review. This process has resulted in the selection and partial installation of a new database system for the management of its electronic medical and fiscal, billing, and regulatory records to replace the old and outdated IRIS system. The new system is based on LabKey, developed at the University of Wisconsin and adopted by the Wisconsin NPRC, is called PRIMe at the ONPRC. Its first phase of installation is complete, and we anticipate full functionality in 2013.
4. Enhanced research infrastructure to provide state-of-the-art laboratories and office facilities. Successful remodel of research space in the VGTI/ONPRC building for the Divisions of Neuroscience and Pathobiology & Immunology; successful seismic upgrades to the two oldest buildings, Administration, and the Research Building; plans for "Re-Life" of the Research Building in four phases and completion of Phase I. These efforts were enabled by OHSU investments that allow growth of the research enterprise.
5. Better integration of research and colony management. Multiple strategies were used to enhance the partnership with the Division of Comparative Medicine to predict and manage the needs for NHP resources for research while maintaining healthy breeding programs for key NHP populations and disease models.
6. Facility Security

7. Solving of major areas of concern in the last submission in the areas of Environmental Health & Radiation Safety to provide a West Campus Biosafety Office that is both enlarged and highly integrated with staff from the OHSU main campus. In addition, the ONPRC has added an Occupational Health Nurse to address any potential NHP exposures and to monitor health of employees on site.

MAJOR PLANS FOR THE NEXT 5 YEARS: DISCUSSED IN EACH SECTION

PROCESS OUTLINE FOR RESEARCH PROPOSALS AT THE ONPRC



The overarching principle for research proposals at the ONPRC is for Administration to provide fair, open access to all NIH-funded investigators who seek to perform NHP research at our facility. Investigators requesting access are given the following flow chart to help to facilitate the rapid, accurate, and appropriately prioritized submission of grants and contracts, as well as to assure that NHP assignment follows the guidelines from ORIP. There are a number of steps for review and approval of submitted research projects at the planning, submission, and award stages, as noted above. If the recommendation at the Animal Utilization Committee is that the ONPRC does not have or is unlikely to obtain the NHP resources for the proposal, every effort is made to recommend other NPRCs for the proposed research.

DIRECTOR'S OFFICE - SPECIFIC AIMS

The Director's Office provides leadership and oversight to the overall management of the ONPRC. Both the Director and the Associate Director for Research contribute to the overall liaison with the various units of the Center and units of the host institution (Oregon Health & Science University; OHSU) that affect research. The office serves as a centralized nexus for communication within ONPRC as well as OHSU, NIH, and the scientific and lay communities. As noted in the Overview, the ONPRC utilizes a strategic planning process to develop strategies and tactics for the Director's office that are aligned with overall ONPRC strategic goals:

Specific Aim 1. Provide leadership in setting scientific and strategic priorities by leading the strategic planning process and its integration across the Center. Efforts will continue to integrate the next five year plan of the Center with those of the OHSU's strategic planning and outcomes, linked through the Office of the Vice President for Research. Integrated leadership across the Center will be accomplished by scheduled and agenda-driven weekly meetings of the Director and Associate Directors, bimonthly meetings with the Division Chiefs, quarterly meetings with an expanded group of leaders, and regular monthly meetings of key committees to accomplish animal allocation, policy setting, and goals as noted in the Administrative Overview. Finally, the Director's office will continue to plan, coordinate, and sponsor scientific retreats and symposia in collaboration with the Division Chiefs and Interdisciplinary Research Program managers to identify shape opportunities for joint scientific ventures, joint recruitment, and new research initiatives.

Specific Aim 2. Promote and assure fair external and internal access to nonhuman primates and support cores for research. This aim is accomplished via the linked operations of the Research Advisory Committee (RAC), the Collaborative Research Unit (CRU), the Pilot Project Program, and the ONPRC animal allocation process and the Comparative Medicine Division, as well as through linkage with the NPRC Consortium. The CRU will continue to assure that all inquiries from external sources are directed to the appropriate internal collaborator for scientific leadership and expertise. Both the CRU and the Pilot Program have the goal of increased collaboration with outside investigators. The Associate Director for Research will continue to oversee the operation of the Research Support Cores, including procedures for access.

Specific Aim 3. Assure stable funding for the Center. This aim will be accomplished primarily via administration, oversight, and management of the submission of the P51 grant and its yearly progress reports. The office will continue to serve as the communication point for the National Scientific Advisory Board (NSAB) and arranges all meetings and reviews by this group for the purposes of advancing the P51 aims and goals. In addition, the Associate Director for Research will serve as the major liaison with the OHSU Foundation and the OHSU Office of Technology Transfer and Business Development, to align strategic funding initiatives and to promote and manage research interactions with industry and public-private partnerships.

Specific Aim 4. Provide effective communication within ONPRC and with OHSU, NIH, and the broader scientific and lay communities. The Office will continue to maintains minutes for all meetings on SharePoint, to publish the electronic newsletter, and to hold quarterly All-Campus meetings to inform employees of ongoing activities and initiatives. This Public Information Officer communicates scientific advances and administrative matters with the Office of Research Infrastructure Programs (ORIP) in DPCPSI at NIH. The Office will continue to work closely with OHSU's Strategic Communications office to publicize scientific breakthroughs. The Director will hold monthly meetings with the Vice President for Research and biannual meetings with the other NPRC Directors and senior staff and NIH staff. The Director's office oversees the ONPRC Outreach program, which is directed to scientists of all ages.

Specific Aim 5. Provide oversight and linkage to key regulatory functions that are integral to interactions with OHSU and state and local governments. The Director's Office will continue to provide a liaison with the Offices of Research Integrity, Research Safety, and Research Advocacy. The Office coordinates Emergency Response Planning in close collaboration with the Departments of Public Safety and Emergency Planning, working with local law enforcement and public safety groups. This office serves as the contact for the OHSU Government Relations office, which represents the ONPRC in state, local, and national meetings with elected officials.

DIRECTOR'S OFFICE - RESEARCH STRATEGY

SIGNIFICANCE

One of the most important requirements for the continued success of the P51 grant and the National Primate Research Center (NPRC) program is strong, effective, and integrated leadership. This is critical in assuring that the ONPRC can maintain and enhance its position as a leading scientific research organization that provides expertise on nonhuman primate (NHP) models, and access to these models for researchers. The Director provides overall leadership for the Center, setting scientific and managerial priorities that are congruent with the missions of the Office of Research Infrastructure Program's (ORIP's) NPRC program, the Center, and of the host institution, Oregon Health & Science University (OHSU). The Director is aided in this responsibility by the senior leadership of the Center, including the Associate Director for Research, the Associate Director for Administration & Finance, the Associate Director for Comparative Medicine, and the Chiefs of the four Research Divisions, all of whom report to the Director. This organization ensures that the activities of the Center are coordinated to provide maximum support for the Center's scientific programs. The Director's Office serves as the nexus for communication and planning and as liaison to the host institution, as well as to NIH and to the NPRC Consortium. The Director reports to the OHSU Vice President for Research and to OHSU's President, who is the Principal Investigator of the P51. As one of the most successful research units at OHSU, the ONPRC is a leader in a number of key scientific areas of importance to OHSU, and was recently identified as one of OHSU's "key strengths" in the strategic visioning process of the School of Medicine (SoM). Through regular meetings with OHSU leaders, standing committees, and councils, and via the Departments and Divisions of the SoM, there are regular, targeted efforts to assure and enhance collaborative and translational science and to discuss potential faculty co-recruitment. One of the principal goals of the NPRC Consortium is to serve as a national resource to support meritorious research using nonhuman primate models. The role of the ONPRC as a national resource includes facilitating access to NHP research by external investigators as appropriate. The ONPRC Collaborative Research Unit (CRU) serves as the primary interface between outside investigators and the resources and scientific expertise at the Center. The Director is responsible, through the Associate Director for Administration, for the efficient and financially responsible administration of the ONPRC, as well as, through the Associate Director for Comparative Medicine, the maintenance of a healthy breeding and research colony that has the appropriate composition of NHP populations and models for current, pending, and planned research. It is vital that these activities are coordinated and managed in an effective and transparent system that is consistent with strategic goals.

INNOVATION

Based on the ONPRC's Strategic Planning Process, the Director's Office made a number of changes to facilitate improved and transparent communication of management progress and decisions. The first of these was to create a Project Manager position in the Director's Office to manage and to coordinate multiple ongoing initiatives. This position was instrumental in the adoption and development of SharePoint as the ONPRC intranet. All minutes from committee meetings are posted, and projects such as the Annual Progress Report and P51 competitive renewal are managed using this flexible and useful software tool. The Director and Associate Directors have also utilized specific Task Forces to provide feedback on ad hoc projects related to ONPRC functions; these have included important issues such as communication, etc. The Director and Associate Director for Research have also merged and coordinated administrative management of all their activities in the Director's Office to facilitate integrated leadership and direction oft he ONPRC scientific enterprise.

The ONPRC Research Integrity Office, headed by Excluded by Requester was established in the past funding period and has developed strong working relationships with investigators through an innovative approach to minimize paperwork involved in IACUC submissions through an electronic IACUC system and direct assistance in the preparation of IACUC protocols. The revised eIACUC system being developed will provide even more innovation to the IACUC process, and the Research Integrity Officer has been a major player in establishing the format and flow of the process. The Research Integrity Officer has established direct communication with the OHSU Office of Research Integrity and is an integral part in policy development and leadership decisions that affect the operation of ONPRC. The Research Integrity Officer established the NPRC Integrity/Compliance Consortium, which brings together all NPRCs to discuss and formulate policies, and is

working on a Post-Approval Monitoring program that will bring together the needs and objectives of all the NPRCs.

To leverage the unique and clinically relevant nature of the research at ONPRC, the Director's Office has esteblished liaisons with the OHSU office of Technology Transfer and Business Development (TTBD) and the OHSU and Doernbecher Children's Hospital Foundations (OHSUF and DCHF) to explore additional opportunities for development of public-private partnerships and philantropy. This represents an important and novel extension of traditional sources of support through standard NIH and other fereral research grants.

Finally, the engagement of systems science experts through a collaboration with Portland State University has the potential to revolutionize the mechanics of colony management and resource allocation in an era of tightened budgets and increased demand.

APPROACH

reviewers' comments

reviewers' comments

B4:reviewers' comments

reviewers' comments

Progress Report

Specific accomplishments in the previous funding period are described below in relation to the areas defined by the specific aims.

Center leadership, oversight, and strategic planning.

Executive leadership. The Director provides overall leadership for the Center, setting scientific and managerial priorities that are congruent with the mission of the Center and of OHSU. The Director is aided in this responsibility by the senior leadership of the Center, including the Associate Directors for Research, Administration, and Comparative Medicine, and the Chiefs of the four Research Divisions, all of whom report to the Director. This organization ensures that the activities of the Center are coordinated to provide maximum support for the scientific programs of the Center. Weekly meetings with the Director and Associate Directors (Executive Leadership Committee), bimonthly meetings with the Division Chiefs (Expanded Executive Leadership Committee), quarterly meetings with an expanded group of leaders, and regular monthly meetings of key committees to accomplish animal allocation, policy setting, and goals as noted in the Overview. During the past funding period, we have kept and distributed minutes of these meetings for purposes of tracking key discussions, action items, and decisions.

Oversight of the Scientific Divisions and the Division of Comparative Medicine. The four research divisions, Diabetes, Obesity, & Metabolism, Neuroscience, Pathobiology & Immunology, and Reproductive &

Developmental Sciences, represent the major scientific disciplines of the Center, and are each led by leaders in their respective fields. The Division of Pathobiology & Immunology is the focus for all AIDS-related research conducted at the Center, and will provide a similar focus for new biodefense initiatives. The Division of Comparative Medicine (previously called Animal Resources) provides health and well being for nonhuman primates and veterinary and procedural expertise to research projects in all divisions. The Director oversees the three Interdisciplinary Research Programs (see next section) and coordinates with the Associate Director for Comparative Medicine the NHP Resource Programs that are designed to assure that appropriate NHP resources are maintained/expanded to meet the needs of these new focus areas. Each of the NHP Resource Programs also has an oversight committee/user's group to ensure that the NHP resources serve the scientific needs of the research programs and are managed in a cost-effective manner. Based on the strategic plan, and in partnership with the Division Chiefs and the OHSU Vice President for Research, the Director advocates for and allocates recruitment funds for new Core Scientists. A discussion of recruitment during the past 5 years and future recruitment can be found in the OVERVIEW and SCIENTIFIC COMPONENTS sections.

Strategic planning for resource enhancement and fostering of new scientific areas. The ONPRC strategic planning was led by an expert consultant, Excluded by Requester, using the ***Hoshin Kanri*** methodology. This type of strategic plan was developed in Japan, utilized at Intel, and emphasizes a dynamic plan that is continuously updated. The planning was initiated in 2008 and completed in 2009. The Director plans and holds regular strategic planning meetings to update plans, with an eye toward enhancing scientific interactions and supporting new initiatives. One of the major changes that resulted from ongoing strategic leadership review and planning was the transition of the Metabolic Disease Working Group into the new Division of Diabetes, Obesity, & Metabolism. As part of the other changes, we identified two enhanced areas of emphasis within the Scientific Divisions: Stem Cell research in Reproductive & Developmental Science and Addiction research in Neuroscience. The Pathobiology & Immunology Division strategic planning dovetails with that of the Vaccine & Gene Therapy Institute, resulting in the establishment of tuberculosis research as well as a new model for multiple sclerosis, in collaboration with the Neuroscience Division.

Committee leadership. The Associate Director for Research chairs the Research Advisory committee, while the Director chairs the Animal Utilization Advisory Committee, and the Policy Group Committee, and oversees the appointments of and communication with the External Scientific Advisory Board.

NSAB meetings, retreats, and symposia. Finally, the Director's office plans, coordinates, and sponsors NSAB meetings, scientific retreats and symposia in collaboration with the Division Chiefs and Interdisciplinary Research Program managers to identify shape opportunities for joint scientific ventures, joint recruitment, and new research initiatives. During the last funding period, the ONPRC has held annual meetings of the NSAB, one scientific retreat, two major symposia, and has helped to facilitate the planning for several topical workshops in interdisciplinary research with the Working Groups and more recently with the Interdisciplinary Research Program Managers. As the communication point for the National Scientific Advisory Board (NSAB) and arranges all meetings and reviews by this group for the purposes of advancing the P51 aims and goals. During the last funding period, we hosted on site meetings of our NSAB to review our programs in 2009, 2010, and 2011. Appointment and approval of modified slate of NSAB members was accomplished in the fall of 2012 to better align our advisors with our current and projected scientific initiatives. Many of the SAB members are continuing in their roles, and we greatly appreciate their commitment and dedication to our Center.

ONPRC 50th Anniversary Celebration- Scientific Symposium - October 2, 2009			
Speaker	**Affiliation**	**Title**	**Division Representation**
Excluded by Requester	Chief, Laboratory of Comparative Ethology NICHD, National Institutes of Health	Risk, Resilience and Gene X Environment Interactions in Primates	Plenary Speaker
	Yerkes National Primate Research Center Emory University	Monkey Model of Huntington's Disease: Animal vs Pluripotent Stem Cell	Reproductive & Developmental Sciences
	Oregon National Primate Research Center Oregon Health & Science University	Nonhuman Primate Models for Stem Cell and Gene Therapies	Reproductive & Developmental Sciences
	Departments of Psychiatry	Injury of the Developing Primate Brain by Anesthetic	Neuroscience

Excluded by Requester	and Neuropathology Washington University School of Medicine	Drugs	
	Oregon National Primate Research Center Oregon Health & Science University	Novel Strategies for the Reversal of Neurodegeneration: From Multiple Sclerosis to Healthy Aging	Neuroscience
	Head, Retroviral Pathogenesis Laboratory NCI, National Institutes of Health	Insights into the Pathogenesis, Treatment and Prevention of AIDS from Nonhuman Primate Models	Pathobiology & Immunology
	Oregon National Primate Research Center Oregon Health & Science University	Progress in HIV/AIDS Vaccine Development	Pathobiology & Immunology

Scientific Symposium- Involvement of Inflammation in Physiological Processes- April 15, 2011

Speaker	Affiliation	Title
Excluded by Requester	Chair, Reproduction and Development Research Group, University of Wisconsin-Madison	Immunodepletion and passive immunization paradigms in nonhuman primates for interrogating the maternal-fetal immune interface
	Assistant Professor, Departments of Physical Therapy & Rehabilitation Science and Neurological Surgery University of California, San Francisco	Neuroinflammation and gene expression involved in synaptic plasticity and memory
	Director, Alcohol Research Program and Member, Immunology & Aging Program Private Source Health System	Advanced age, inflammation, and innate immunity
	Division of Endocrinology and Metabolism University of California, San Diego School of Medicine	GPR120 is an omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin sensitizing effects
	George A. Zimmermann Professor of Neurology and Neurological Sciences, Pediatrics and Genetics Chair, interdepartmental Program in Immunology Private Source	Predictive biomarkers for response to therapy in multiple sclerosis

Management of access to Center resources.

The role of the Center as a national resource is addressed via the linked operations of the Collaborative Research Unit (CRU), the Pilot Project Program, and the ONPRC animal allocation process, as well as through linkage with the NPRC Consortium. The CRU assures that all inquiries from external sources are directed to the appropriate internal collaborator to provide scientific leadership and expertise. Both the CRU and the Pilot Program contribute to increased collaboration with outside investigators. The CRU has three primary responsibilities:

1. Serve as a portal for enquiries from external investigators requesting access to NHP resources. The Associate Director for Research office receives enquiries from the ONPRC Website, direct communication from outside individuals, or through referrals from Center investigators or other NPRCs. If initial evaluation per the CRU SOP determines that a collaborative project is appropriate, an ONPRC PI will be recruited if possible. Potential internal PI's include center/staff scientists in any of the three research divisions, as well as qualified DCM veterinary personnel. If a project is deemed to not be appropriate for the ONPRC due to the particular scientific or technical expertise or animal characteristics required, the CRU determines if another NPRC can support the request. If so, the request for collaboration will be directed to the appropriate NPRC. All collaborative work proposed for the CRU requires ultimate approval by the RAC and will also include the Technology Transfer and Business Development (TTBD) Office concerning potential intellectual property and commercialization issues, including work done by the CRU service center. This allows for the practical and scientific evaluation of proposed collaborative projects based on the initial information gathered per the CRU SOP. All proposed work is also subject to assessment by DCM management to assure that required animals and cage space are available for the duration of the proposed work, and that animal resources committed are consistent with the overall ONPRC colony management plan. Efforts are made to utilize existing Support Cores as appropriate. CRU access to Center resources follows ONPRC guidelines; i.e., first priority is internal

investigators doing federally funded research (these projects can be collaborative), followed by other internal research projects, external research proposals without an internal sponsor (in which case the CRU would provide the PI), and service-type work. In light of current limitations on animal and housing availability, commitments for either academic collaborative or service work will require that both animal and physical resources exist and that the RAC deems the work to be an appropriate use of ONPRC resources.

2. Direct management of research projects that are not transferred to on-site investigators. If a project is appropriate for ONPRC resources, but no internal PI is recruited, the CRU will provide the PI function and research effort. This support is provided by Excluded by Requester CRU Staff Scientist, who will be responsible for direct project management and efficient use of animal resources, and, as appropriate, research support cores.

3. Maintain up-to-date and accurate records of external requests and outcomes. The CRU manages the budgetary and regulatory functions for the proposed work, in conjunction with the ONPRC Business Office. Pricing of CRU projects follows standard ONPRC pricing procedures and is done in coordination with DCM or the support core being utilized. The CRU maintains records of completed, ongoing, and pending projects and the cost recovery and scientific benefits accrued from these activities. This includes peer-reviewed and RAC-approved projects; however, CRU tracking of these projects is limited to maintaining records of overall collaborative work for Center Grant progress reports and renewals.

The original proposal for the CRU included personnel comprised of a staff scientist and technician assigned to each of the three research divisions. Based upon the critique and projected demand, the staff was reduced to one FTE. This has proven to be sufficient during the past funding period. Even with this reduced staff, the CRU has managed a significant volume of requests and projects. Table 1 illustrates the number of inquiries received by the CRU (through the CRU portal on the ONPRC website or through referral by other investigators) during the previous grant period, as well as their disposition. The CRU has also directly managed 12 projects (principally NIH-supported studies with external PIs) totaling $2.3 million in total costs.

Table 1. Requests for collaborative research triaged by the CRU, 2009-2012.

	2012- Year 53	2011- Year 52	2010- Year 51	2009- Year 50
# of inquiries	16	13	21	23
# of inquiries referred to internal PIs, no immediate collaborations	2	3	5	10
# of inquiries that resulted in a project or grant submission	5	3	2	9
# of inquiries where information provided and no follow-up from requestor	5	0	7	2
# of inquiries referred to other NPRCs or facilities	2	4	2	1
# of inquiries model not available/ not practical	1	3	5	1

The Associate Director for Research also oversees the operation of the Research Support Cores, including procedures for access. He assures regular meetings of the Oversight Committees for each of the Cores and recommends changes to the Executive Leadership Committee. To enhance ONPRC's utility as a research resource, the ONPRC web page disseminates information about what resources and services are available at the ONPRC, including detailed descriptions of the Research Support Cores.

The Director (or the Associate Director for Research in her absence) chairs the Animal Utilization Committee, which is staffed by the Colony Management Group from the Division of Comparative Medicine. An important advance during the last funding period was to clarify the roles and responsibilities of the Division Chiefs in reviewing and prioritizing Animal Allocation Requests so that every investigator in the divisions could have access to optimal NHP animals in a timely manner, while supplying the needs of all requestors without extended wait times. Improvements to the Animal Allocation Process have included electronic, web-based online planning and allocation forms. This process is outlined in the ADMINISTRATION OVERVIEW.

Initiatives to ensure stable funding for Center research and operations.

In the areas of administration, oversight, and management of the submission of the P51 grant and its yearly progress reports, one of the key advances that we made was to bring in a Project Manager into the Director's Office.

Fiscal and administrative oversight. The Director works in partnership with the Associate Director for Administration & Finance to assure best business practices for all employees and grants administration. Other interactions with central administration regarding the fiscal and physical resources of the Center are also handled through the Director's office. As part of this, Information Technology and Engineering works closely

with all aspects of the center to deliver computer, telephone, and videoconferencing support as well as supporting the computer system for our animal medical records and for the IACUC.

Leveraged funding. As the major liaison with the OHSU Foundation and the OHSU Office of Technology Transfer and Business Development, Excluded by Requester had regular meetings with individuals and groups with the goal of aligning strategic funding initiatives and promoting research interactions with industry and public-private partnerships. Senior officers from the OHSU Foundation including President Excluded by Personal Info attended and made presentations at the Scientific Retreat held in October 2011. Tragically, Personal Info but his legacy at the Foundation continues, and plans have been developed in a series of workshops and meetings. These have included hosting the annual Doernbecher Children's Hospital Board meeting at ONPRC, which involved presentations of joint research between ONPRC investigators and Department of Pediatrics physician-scientists, as well as regular meetings with OHSU Foundation and Doernbecher Foundation staff in specific areas represented by ONPRC research, such as infectious disease, obesity/diabetes, maternal-fetal health, neuroscience, and others. This has resulted in recent philanthropic support for pilot funding in pediatric research from a member of the Doernbecher Foundation Board. Through Excluded by Requester Director of Business Development, OHSU Office of Technology Transfer and Business Development, multiple presentations to pharmaceutical and biotechnology representatives have been made to showcase ONPRC research strengths and capabilities. These efforts have already resulted in significant sponsored research agreements between ONPRC investigators and major pharma entities such as Private Source and Private Source We will continue to develop opportunities for appropriate public-private partnerships to diversify the sources of funding for ONPRC research.

Increased communication within ONPRC and with external entities (OHSU, NIH, and the broader scientific and lay communities).

One of the key advances in assuring transparent communication has been the adoption and implementation of SharePoint to serve as the ONPRC Intranet as a means of sharing documents within various leadership subgroups and with the campus as a whole. The Office maintains minutes for all meetings on SharePoint, edits and publishes an electronic newsletter quarterly, and holds quarterly All-Campus meetings to inform employees of ongoing activities and initiatives. This office communicates scientific advances and administrative matters with ORIP at NIH.

Linkages to OHSU. To integrate the plans of the Center with those of the OHSU's strategic planning and outcomes, the Director meets monthly with both the Office of the Vice President for Research and with the Director of Finance in that office. The Public Information Officer (PIO Excluded by Requester works closely with OHSU's Strategic Communications office to publicize scientific breakthroughs. One of the tactics that we have employed during the last 15 months has been the adoption of a more "layperson" approach to our monthly Work-In-Progress seminar series by the ONPRC Core Scientists and key Affiliate Scientists.

Liaison with other institutes. The Director meets regularly with Excluded by Requester Director of the Vaccine and Gene Therapy Institute (VGTI), and Excluded by Requester OHSU Vice President for Research, to manage issues that are pertinent to both the VGTI and the Center. She and Excluded by Requester represent ONPRC's interests in discussions with the OHSU SoM and other key scientific and business initiatives at OHSU, as well as efforts directed toward fundraising.

Educational outreach. The Director and Associate Director for Research oversee the Outreach and Community Engagement Program, which sponsors a number of outstanding outreach programs to middle school, high school, college and university students, and teachers, and most recently "Road Scholars."

Communication and links with OHSU central administration and West Campus administration. The Director is responsible for communicating progress and issues with Excluded by Requester and with the President of OHSU (Dr. Joseph Robertson, the Principal Investigator of the core grant) through regularly scheduled monthly meetings and frequent e-mail and telephone contact. In addition, there are numerous issues related to services on the OHSU West Campus that are discussed in meetings with all West Campus units (ONPRC and VGTI).

Linkages with NCRR and other NPRCs. The Director is the key contact to participate in regular telephone and videoconferences, semiannual conferences, and special meetings with all of the other NPRCs and the NIH staff working with the Centers. The NCRR is working to encourage interactions and shared resources among the eight NPRCs and Excluded by Requester and Roberts share this responsibility.

Education and outreach, including interactions with OHSU and state and local governments.

The Director's office oversees the ONPRC Outreach program, which is directed to scientists of all ages. Details of this unit are in a separate section (OUTREACH & COMMUNITY ENGAGEMENT). It also provides a liaison with the Offices of Research Integrity, Research Safety, and Research Advocacy. The Office coordinates Emergency Response Planning in close collaboration with the Departments of Public Safety and Emergency Planning, working with local law enforcement and public safety groups. This office serves as the contact for the OHSU Government Relations office, which represents the ONPRC in state, local, and national meetings with elected officials. Key progress in three of these areas is summarized below.

Research Integrity. During the last 3.5 years, we created the ONPRC Research Integrity Office, consisting of the Research Integrity Officer (RIO) and an IACUC Analyst. The RIO oversees the administration of the Institutional Animal Care and Use Committee (IACUC) and shares responsibility with the IACUC Analyst for review of the 160 IACUC protocols, including three-year renewals, annual reviews and modifications. The Analyst organizes and creates an agenda, attends and minutes for the monthly IACUC meeting and for designated member reviews outside of the regular meetings. Both the RIO and the IACUC Analyst consult with investigators to assure timely submission of documents and to answer questions. The IACUC Analyst is responsible for the organization of review of all current and new IACUC policies. The RIO is a member of the West Campus (WC) and the Central /Waterfront Campus (CWC) IACUCs and serves on the IACUC Leadership Team, the OHSU IACUC Advisory Council, the Integrity Leadership Group and work on IACUC Policy Development and elACUC revisions with the CWC Research Integrity Officer. The RIO meets monthly with the ONPRC Director, the West Campus Attending Veterinarian, and the Associate Director for Administration and serves on the ONPRC Policy Group. With the Attending Veterinarian and the IACUC Chair, the RIO is responsible for reviewing all incidents that might be reportable to OLAW and USDA and reporting to the IACUC, preparing reports to institutional, local and federal officials. The RIO provides an ongoing educational program for members of the IACUC and ONPRC community, presenting webinars and training programs prepared by the Office of Laboratory Animal Welfare (OLAW), Public Responsibility in Medicine and Research (PRIM&R), Northwest Association for Biomedical Research (NWABR), Massachusetts Society for Medical Research (MSMR), National Association for Biomedical Research (NABR) and Laboratory Animal Welfare and Training Exchange (LAWTE). The RIO originated and is the head of the NPRC Integrity-Compliance Consortium, whose purpose is to cultivate open discussions and critical thinking about issues related to compliance with federal regulations and NIH guidelines at the NPRCs. Furthermore, the RIO has developed, with the assistance of the IT group, eTools, designed to assist investigators in complying with regulations and providing easy access to training records. These eTools are being evaluated by other NPRCs for potential use.

Public Safety, ICS Training, Emergency Response Planning. During this funding period, OHSU has enhanced its emergency preparedness for all sites. All ONPRC senior leaders and managers have been trained in Incident Command (ICS) to the ICS100, 200, and 700 levels, and we have a plan for 25 people to take ICS300 in March 2013. Through the use of Table Top exercises/drills held at the ONPRC (4 in the last 3.5 years), there were multiple opportunities for training on two-way radios, improving communication, and increasing familiarity with responses to different possible scenarios. We have documented emergency plans for all parts of the organization, with emergency food, water, and emergency generator fuel for human and nonhuman primate needs onsite or in development.

Office of Research Advocacy. The ORA is headed by Excluded by Requester, who has long-term experience and expertise in the animal rights field and its potential impact on the conduct of biomedical research, in addition to his ongoing role as a Senior Scientist in the Division of Neuroscience. The ORA has primary responsibility for monitoring the activities of animal rights groups that may affect ONPRC operations, educating ONPRC staff on security issues, and educating the academic community and the general public about the importance of animal research and the dangers of animal extremism. Specific accomplishments of the ORA in the previous funding period include:

- Education and training on the Animal Enterprise Terrorism Act (AETA) was organized for local police jurisdictions in two sessions two years apart, with a total of 221 on site attendees. Lectures were given by representatives of the FBI and by the US Attorney for the District of Oregon. One of these sessions was broadcast to 4 other institutions live. Excluded by Requester participated in an Amicus brief in support of the AETA (http://www.nabr.org/uploadedFiles/[illegible]ontent/Hosted_Files/Scientists_AETA_Amicus_Brief.pdf).
- Excluded by Requester created venues for education of researchers on the tools available for their personal protection and the protection of the ONPRC.

- Excluded by Requester created a (voluntary) listing of personal contact information on our staff that is shared with police and federal law enforcement, so that home addresses are flagged.
- Excluded by Requester lectures to our NIH Training Grant lecture program on Ethics in Research, to our tour docents (from the public), to the local academic community (and internationally) on the use of the AETA for their protection, how to deal with bomb threats and crank and harassing calls, and how "social engineering" is used by animal extremists to gain entry, computer passwords and other secure information. He hosted a training session by Foundation for Biomedical Research executive Excluded by Requester and served as a scientific reader for Excluded by Requester two books. ORA works closely with OHSU Media Relations to provide information and advance notice of relevant events. Excluded by Requester offers one-on-one discussions with 'at-risk staff to assist them in preventing problems related to their own security.
- In June 2011, Excluded by Requester organized and hosted, working through FASEB, an International Meeting on Animal Extremism. He also worked with FASEB's animal committee, the National Association for Biomedical Research, and the Society for Neuroscience to create a document circumscribing the best practices for responding to FOIA requests. Excluded by Requester serves on the FASEB animal committee and has assisted in preparing educational information for congress.
- Processes were put in place to redact researchers' driver's license information and to alert investigators and OHSU administration to changes in local law related to identity protection and how personal information is obtained for the purpose of harassment. Information was disseminated on the means by which grant proposal keywords are used by extremists.
- Facility Security
- We maintain an intranet website and a bulletin board on our activities.
- ORA sponsored an advanced IACUC conference of The Scientists Center for Animal Welfare (SCAW) at ONPRC/OHSU on September 11, 2009. Topics presented at this workshop are designed to fulfill the responsibility of USDA/APHIS/AC Policy 15 requirements.
- Communication with the public and the scientific community. A number of presentations in national public, scientific media and at Institutions were made, as noted in the References section.

In the next funding period, ORA will continue these activities to ensure that ONPRC is kept informed of all pertinent animal rights issues that may arise as well as continuing efforts to enhance protection of personnel, facilities, and sensitive files.

Future Plans

Specific Aim 1. Provide leadership in setting scientific and strategic priorities by leading the strategic planning process and its integration across the Center. Efforts will continue to integrate the next five-year plan of the Center with those of the OHSU's strategic planning and outcomes, linked through the Office of the Vice President for Research. Integrated leadership across the Center will be accomplished by scheduled and agenda-driven weekly meetings of the Director and Associate Directors, bimonthly meetings with the Division Chiefs, quarterly meetings with an expanded group of leaders, and regular monthly meetings of key committees to accomplish animal allocation, policy setting, and goals as noted in the Administrative Overview. Finally, the Director's office will continue to plan, coordinate, and sponsor scientific retreats and symposia in collaboration with the Division Chiefs and Interdisciplinary Research Program managers to identify and shape opportunities for joint scientific ventures, joint recruitment, and new research initiatives.

The recruitment of key leaders will be a critical task in the next funding period, since it will include the recruitment of two to three new leaders for the Scientific Divisions. These will be phased in over the next several years, with the first focus on Pathobiology & Immunology, following in the footsteps of Excluded by Requester strong and effective leadership of that division. Excluded by Requester is planning to hand over the reins of Reproductive & Developmental Science in a few years, and we will open a national search for the permanent Chief of the Division of Diabetes, Obesity & Metabolism. With the planned vacancies in the Associate Director and the Assistant Associate Director for Administration, we have an opportunity to shape the administration and finance in directions that can be potentially more in alignment with the goals of OHSU. We are in the process of evaluating the best structures and composition for the open administrative leadership positions and we will be widely advertising for all of these leaders.

Specific Aim 2. Promote and assure fair external and internal access to nonhuman primates and support cores for research. This aim is accomplished via the linked operations of the Research Advisory Committee (RAC), the Collaborative Research Unit (CRU), the Pilot Project Program, and the ONPRC animal allocation process and the Comparative Medicine Division, as well as through linkage with the NPRC Consortium. The CRU will continue to assure that all inquiries from external sources are directed to the appropriate internal collaborator for scientific leadership and expertise. Both the CRU and the Pilot Program have the goal of increased collaboration with outside investigators. The Associate Director for Research will continue to oversee the operation of the Research Support Cores, including procedures for access.

Specific Aim 3. Assure stable funding for the Center. This aim will be accomplished primarily via administration, oversight, and management of the submission of the P51 grant and its yearly progress reports. The office will continue to serve as the communication point for the National Scientific Advisory Board (NSAB) and arranges all meetings and reviews by this group for the purposes of advancing the P51 aims and goals. In addition, the Associate Director for Research will serve as the major liaison with the OHSU Foundation and the OHSU Office of Technology Transfer and Business Development, to align strategic funding initiatives and to promote and manage research interactions with industry and public-private partnerships.

Specific Aim 4. Provide effective communication within ONPRC and with OHSU, NIH, and the broader scientific and lay communities. The Office will continue to maintain minutes for all meetings on SharePoint, to publish the electronic newsletter, and to hold quarterly All-Campus meetings to inform employees of ongoing activities and initiatives. This Public Information Officer communicates scientific advances and administrative matters with the Office of Research Infrastructure Programs (ORIP) in DPCPSI at NIH. The Office will continue to work closely with OHSU's Strategic Communications office to publicize scientific breakthroughs. The Director will hold monthly meetings with the Vice President for Research and biannual meetings with the other NPRC Directors and senior staff and NIH staff. The Director's office oversees the ONPRC Outreach program, which is directed to scientists of all ages.

It is apparent from the recent Institute of Medicine Report, and the subsequent adoption of the recommendations from the NIH Working Group, that chimpanzee research is not just on the wane, but nearly extinct. The NPRC program is critically important to NIH and to biomedical research, and we plan to work with our local communities, NIH, Congressional delegates, and the NPRC Consortium to find better ways to share this message.

Specific Aim 5. Provide oversight and linkage to key regulatory functions that are integral to interactions with OHSU and state and local governments. The Director's Office will continue to provide a liaison with the Offices of Research Integrity, Research Safety, and Research Advocacy. The Office coordinates Emergency Response Planning in close collaboration with the Departments of Public Safety and Emergency Planning, working with local law enforcement and public safety groups. This office serves as the contact for the OHSU Government Relations office, which represents the ONPRC in state, local, and national meetings with elected officials.

REFERENCES

Excluded by Requester

Excluded by Requester

Program Director/Principal Investigator (Last, First, Middle): Robertson, Joseph E./Haigwood, Nancy L.

ADMINISTRATION - DIRECTOR's OFFICE DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Excluded by Requester	Director	% Effort			Institutional Base Salary	134,775	33,694	168,469
	Assoc Dir-Res/CRU					13,478	3,369	16,847
	Dir of Res Advocacy					2,696	674	3,369
	Admin Coordinator					2,759	966	3,725
	IACUC Chair/CRU					4,837	1,499	6,336
	Admin Coordinator					8,036	2,813	10,849
	Res Integrity Officer					14,849	4,603	19,453
	Res Subject Protection A					10,246	3,176	13,422
	Project Manager					10,756	3,334	14,091
	SUBTOTALS →					202,432	54,133	256,561

CONSULTANT COSTS		
Scientific Advisory Board	1,500	
		1,500
EQUIPMENT *(Itemize)*		
None Requested	0	0
SUPPLIES *(Itemize by category)*		
Office & Admin Supplies	2,144	
		2,144
TRAVEL		
Domestic	8,767	8,767
INPATIENT CARE COSTS		0
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		
None Requested	0	0
OTHER EXPENSES *(Itemize by category)*		
Conference Registration	75	
Seminar Speakers	1,049	
Miscellaneous Rental	111	
Hosting Groups & Guests	1,533	
Printing & Publishing	159	
Telecommunications	1,105	
Membership in Profesnl Org	105	
Registration/Training	1,986	
INA Fees	600	6,723
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 275,695
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 275,695

ADMINISTRATION - DIRECTOR's OFFICE
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	256,561	264,258	272,185	280,351	288,761
CONSULTANT COSTS	1,500	1,545	1,591	1,639	1,688
EQUIPMENT	0	0	0	0	0
SUPPLIES	2,144	2,209	2,275	2,343	2,414
TRAVEL	8,767	9,030	9,300	9,579	9,867
INPATIENTS CARE COSTS	0	0	0	0	0
OUTPATIENTS CARE COSTS	0	0	0	0	0
ALTERATIONS AND RENOVATIONS	0	0	0	0	0
OTHER EXPENSES	6,722	6,924	7,132	7,346	7,566
DIRECT CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	275,694	283,965	292,484	301,258	310,296
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	275,694	283,965	292,484	301,258	310,296
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					1,463,698

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

PERSONNEL

Director – Excluded by Requester (% Effort Responsible for the oversight of all ONPRC activities; provides scientific leadership and administrative oversight of ONPRC's resources, scientific programs and institutional and regional functions; works closely with the OHSU President, Principal Investigator on the ORIP-supported core grant, as well as the Senior Vice President for Research; facilitates interaction between research divisions as well as the service units; coordinates strategic planning; provides oversight for land and space management. The Director serves as a liaison to key regulatory and oversight leadership, including the Office of Research Integrity, Emergency Planning, Environmental Health & Radiation Safety, Strategic Communications, the OHSU Foundation, the Office of the Dean of the School of Medicine, serves on the President's Council and oversees the ONPRC's Outreach Programs.

Associate Director for Research/Collaborative Research Unit (CRU) – Excluded by Requester % Effort % Effort Responsible for the oversight of key research functions which includes Research Support Cores and the CRU. Oversees working committees at the Director's discretion, to enhance efficiency of service and research units; serves as chair of the Research Advisory Committee (RAC) and manages the Pilot Research Program. Responsible for coordinating internal and external requests for use of ONPRC resources; operating a centralized process for managing CRU, so that requests and inquiries are processed consistently through standard procedures; encouraging new potential collaborators, and enhancing the capability to serve as a national resource for NHP research; overseeing a unit that will serve as a portal for collaborative work, providing accurate and helpful information to potential collaborators, managing a range of projects including those without a vested internal scientist and representing a concrete demonstration of ONPRC's commitment to serve as a local and national resource.

Director of Office of Research Advocacy – Excluded by Requester % Effort % Effort Responsible to the Director and Senior Vice President for Research. Serves as an OHSU-wide resource to faculty, staff, and administration to provide access to current information on animal extremism. Provides an educational resource by collecting and sharing information on animal extremism and on the experiences of other Institutions, and also acts as a faculty resource for consultation on issues of animal extremism and measures to assure personal and institutional safety.

Administrative Coordinator – Excluded by Requester % Effort Income). Responsible to the Director of Office of Research Advocacy. Coordinates travel, meeting scheduling and general correspondence; provides administrative services by coordinating and tracking projects as requested.

IACUC Chair/CRU – Excluded by Requester % Effort Responsible for chairing a committee that approves use of animals for conducting research at ONPRC.

Administrative Coordinator – Excluded by Requester % Effort Income).. Coordinates travel, meeting scheduling and general correspondence; provides administrative services to support the Director's Office by coordinating and tracking projects as requested; assists in the coordination of the Annual Progress Report (APR) and five-year core grant competitive renewal for the Director and Associate Directors; provides support to the Associate Director of Research/CRU; answers to and provides back up support to the Project Manager.

Research Integrity Officer – Excluded by Requester % Effort Income). Responsible for oversight of all regulatory matters including all aspects of laboratory animal welfare, employee training, identifying areas needing policies and preparing policies for approval by appropriate leadership staff, design and implement electronic system for IACUC, preparing reports to government agencies, assuring compliance with all governmental regulations and assuring that all records are maintained according to regulations and policy, interacting with the OHSU Integrity Office personnel and the ONPRC Leadership to assure communication and collaboration on university wide programs.

Research Subject Protection Analyst – Excluded by Requester % Effort
Income). Provides support to the Research Integrity Office by performing analytical work on IACUC protocols.

Project Manager – Excluded by Requester % Effort
Responsible for project management including strategic planning and process improvement projects as assigned; provides support for Incident Command System (ICS); provides support for correspondence, scheduling of appointments, coordinates the APR and the 5-year ORIP-supported core grant competitive renewal to ORIP, Division of Comparative Medicine (DCM); arranges the annual visitation of the National Scientific Advisory Board (SAB); arranges campus-wide staff meetings and e-messages.

CONSULTANT COSTS
Funds are requested to cover expenses incurred with the annual review of the research programs by the SAB and for external consulting for strategic planning.

SUPPLIES
Office & Admin Supplies.. Funds are requested for:
- Letterhead, paper, envelopes, filing, pens, pencils,
- Upgrades of systems and software such as Adobe Acrobat, Adobe Creative Suite, and EndNote.
- Toner cartridges, computer supplies, notepads
- Printers, fax machines, monitors, etc

Funds requested include the Offices of Director, Research Integrity and Research Advocacy.

TRAVEL
Funds are requested for:
- Administrative travel by the Director, such as the NPRC directors meetings, as well as scientific travel when it is determined that the ONPRC should be represented
- Administrative travel by Associate Director of Administration, Associate Director of Research/CRU, and the Associate Director of Comparative Medicine, when deemed appropriate by the Director
- Travel to attend training seminars for scientific and professional staff when it is determined that the ONPRC will benefit
- Travel for SAB
- Travel for the Offices of Research Integrity and Research Advocacy to support efforts on behalf of ONPRC
- To support a seminar speaker program, which includes travel for speakers
- Travel to support recruitment and relocation activities as deemed appropriate by the Director
- Local mileage for travel, i.e., local meetings, training seminars, etc., as deemed appropriate by the Director.

OTHER EXPENSES
Conference Registrations: Funds are requested to support continuing education in compliance areas such as for the IACUC chair or integrity officer for coursework pertaining to NHP research.

Speaking Fees: Funds are requested for invited speakers, as a part of the seminar speaker program.

Miscellaneous Rentals: Funds are requested for rentals related to the SAB meeting

Hosting Groups & Guests: Funds are requested for retiring employees, employee recognition; annual scientific staff retreat held locally, off site, where core scientists, affiliate scientists, staff scientists and collaborative scientist meet to share ideas, developments and plans; staff and guest events with seminar speakers; staff and working meetings to address scientific and operational needs, as deemed appropriate by the Director.

Printing & Publishing: Funds are requested for printing and publishing such as the ONPRC Center Page.

Telecommunications: Funds are requested for long distance telephone charges, long distance FAX, pagers and cell phones for the Offices of the Director, Research Integrity and Research Advocacy.

Registration & Training: Funds are requested for the Office of Research Integrity, providing IACUC and other regulatory training to staff.

INA Fees (Office of Research Advocacy): Funds are requested for a service providing daily updates regarding animal activist activity.

ADMINISTRATION: Director's Office Income Table

Last Funded Year (53)

Source	Funding (direct costs)
P51 base grant support	$168,792.55
Program income derived from P51 base grant	791,323.13
Other Sources	87,233.01
Total	$1,047,348.69

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$275,695.16
Program income derived from P51 base grant	656,877.31
Other Sources	89,850.00
Total	$1,022,422.47

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

The Director's Office receives salary support and support for other expenditures from program income, and salary support from other sources.

ADMINISTRATIVE SERVICES SPECIFIC AIMS

The Associate Director for Administration is responsible for the overall infrastructure and financing of the ONPRC. He and his team provide comprehensive support for a safe, productive, and environmentally sound infrastructure to support the administrative and facility related needs of ONPRC research and NHP animal care staff. This includes the oversight and management of Center budgeting and financial planning and implementation, Business Services, Information Technology, Human Resources, Facilities, Construction, Campus Planning, and Library Services. The Associate Director and his team work with their University counterparts in participatory teamwork that facilitates the infrastructure support and financing of the ONPRC in areas such as grants management, design and construction, purchasing, logistics, budgeting, financial services, F&A rate proposal development and negotiation, security, emergency response, and library services. The ONPRC Administrative team also works with NIH, local governments, and utilities to provide comprehensive infrastructure support.

Through these functions and support team the Associate Director for Administration:

- Safeguards the resources of the ONPRC in association with OHSU central services.
- Ensures planning, management, and financing for the infrastructure resources that support NHP animal colonies and research.
- Ensures ONPRC services to facilitate the day to day business operation of the center in coordination with central university services.
- Ensures core and ancillary grant compliance in association with central Research Grant and Contracts.
- Ensure Information Systems resources appropriate to the NHP research mission.
- Ensures infrastructure construction and renovation projects are appropriately managed meeting the goals and aims of these projects and that their continued use is consistent with funding sources.
- Ensures compliance with local governments and regulatory agencies in relationship to the physical land and buildings.
- Ensures the security of the physical facilities.
- Ensures that appropriate, specialized NHP Library services are provided.
- Ensures financing and managerial support for sustainability related programs/projects.
- Provides essential support for emergency and Incident Command response.

Specific Aim 1: Ensure the continued provision of the effective and efficient operation of the ONPRC infrastructure resources, both physical and personnel resources, to provide an appropriate environment for the safe and effective conduct of animal care and research at the ONRPC.

Specific Aim 2: Work with the University to strengthen work and financing relationships and make timely and accurate resource requests to ensure that the additional expertise and funding necessary to support infrastructure development appropriate to the ONPRC NHP research endeavor are provided in a timely manner.

Specific Aim 3: Work with the University and local governments to establish a realistic and therefore fundable long-range master plan to provide a growth roadmap for the next ten years for the ONPRC.

Specific Aim 4: Increase engagement with other Administrative Directors in the NPRC consortium to continue work on defining and documenting best practices that can be used within the varied institutional environments throughout the NPRC system.

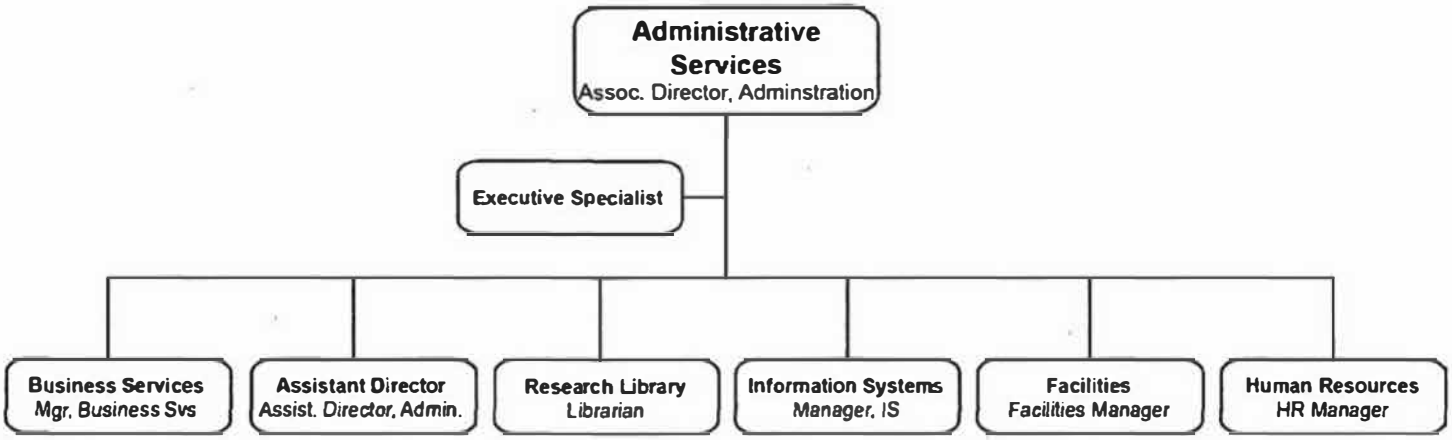
ADMINISTRATION: ADMINISTRATIVE SERVICES RESEARCH STRATEGY

SIGNIFICANCE

The P51 base grant provides funding mechanisms for an infrastructure sufficient to make facilities and resources available for NHP research as a distinct, structural component affiliated with a major research institution. A significant part of this infrastructure is provided through Administrative Services which, in coordination with OHSU main campus, has managerial responsibility for the ONPRC land, buildings, new construction, renovations, overall budget development and management, grants management, equipment purchases and fixed asset tracking, information services, human resources, library services and the strategic planning related to these areas.

The successful conduct of Administrative Services requires multiple teams to provide these services, as reflected in the following organizational chart.

ORGANIZATIONAL CHART



This provision of services also requires partnerships with multiple entities inside and outside of OHSU as reflected in the following matrix table, Table 1.

Table 1. Partnership between ONPRC and the host institution, OHSU

ONPRC Manager	Primary Report	Primary OHSU Areas worked with	Primary External Contacts worked with
Associate Director for Administration	Director, ONPRC	• Sr. VP of Research Office • Legal • Campus Planning • Technology Transfer & Business Development • OHSU Risk Management • Research Grants and Contracts • Sponsored Projects Administration • Design and Construction	• NIH - ORIP • City of Hillsboro Planning Department
Assistant Director for Administration	Associate Director for Administration	• Research Grants and Contracts (P51 related) • Sponsored Projects Administration (P51 related) • Sr. VP for Research Office	
Manager, Business Services	Associate Director for Administration	• Central Financial Services	
Librarian	Associate Director for Administration	• OHSU Main Library	

Facilities Manager	Associate Director for Administration	• Design and Construction • OHSU Facilities	• City of Hillsboro Planning Department • Clean Water Services • Portland General Electric • Northwest Natural Gas • Tualatin Valley Water District
Human Resources Manager	Associate Director for Administration	• OHSU Human Resources	

Through these teams and relationships, Administrative Services:

- Provides for the daily financial administration of the P51 award and collaborates in its long-range planning.
- Safeguards the resources of the ONPRC in association with OHSU central services.
- Ensures planning, management, and financing for the infrastructure resources that support NHP animal colonies and research.
- Ensures services to facilitate the day-to-day business operation of the center in coordination with central university services.
- Ensures core and ancillary grant compliance in association with central Research Grant & Contracts and Sponsored Projects Administration.
- Ensure information systems resources appropriate to the NHP research mission.
- Ensures infrastructure construction and renovation projects meet the goals and aims of the project.
- Ensures compliance with local governments and regulatory agencies in relationship to the physical land and buildings.
- Ensures resources for the security of the physical facilities.
- Ensures that appropriate, specialized NHP Library services are provided.
- Ensures financing and managerial support for sustainability related programs/projects.
- Provides essential support for emergency and incident command response.
- Works to bring industry best practices into administrative services, facilities operations, and construction and renovation projects.
- Meet regularly with counterparts at other seven NPRCs to share information, practices and collaborate on finding ways to improve the physical and process infrastructures of our respective organizations.

Financially, the ONPRC functions largely as a self-sustaining unit within OHSU that has oversight from the Office of the Senior Vice President for Research. The ONPRC receives 100% of the F&A recovery (B & C rates) generated, to be used according to the program guidelines, as is the intent of additive program income. The ONPRC does receive capital funding from the main university for building, renovation, and software systems upgrades on campus, thus has been a major financial partner for the ONPRC.

In terms of daily operation, with the main exception of the telephone system and Facilities & Property, ONPRC Administrative Services is organized like other center, institutes and schools of the university. Major functions exist centrally, with supporting roles at the center, institute, school level. The following, while not exhaustive, describes the current financial and administrative relationship with the OHSU. Functions provided entirely by OHSU include:

- Legal
- Banking
- Research Safety (includes Institutional Biosafety)
- Shipping & Receiving
- Central Stores
- Technology Transfer and Business Development
- Contracts
- Fundraising

- Functions with a supporting role to the central service provided include:
  - Human resources
  - Payroll
  - Accounts payable
  - Purchasing/requisitioning
  - Information systems
  - Financial administration
  - Internal billing
  - Accounts receivable
  - Pre and Post award
  - Fixed asset inventory
  - Miscellaneous logistical functions
  - IACUC (West Campus has a separate IACUC but some functions are cooperative)
  - Research integrity
  - Land management (ONPRC land is federally controlled)
  - Construction planning and management oversight
  - Reporting/forecasting
  - Systems maintenance
  - Security/Monitoring
  - Occupational health

- ONPRC has its own telephone system (entirely updated in 2003). This system has been retained due to significant cost savings.

- The ONPRC is different from all other units at OHSU in that it has its own facilities operation. The facilities operation began in the 1960's and was maintained after the merger. Because of the unique NHP resource this continues as the most effective and efficient means to support the vital physical resources at ONPRC.

To the extent the above items are provided by ONPRC, the costs are included in the B- and C-rate. Services provided by central OHSU are included in the A-rate. The center receives 100% of the A-rate recovery to offset the overhead cost allocation that is charged to the ONPRC for these services..

Current ONPRC and OHSU rates are as follows:

ONPRC A-rate – 28%
ONPRC B-rate – 47%
Total ONPRC rate for federal grants - 75%

ONPRC C-rate – 16%
Total ONPRC rate for industry contracts – 91%

OHSU Main Campus Rate 54%

The ABC structure is unique to primate centers and these rates are explained in the seventh edition of the National Primate Research Centers Program Guidelines as published January 26th, 2010, pg. 35.

Budgeting

The Associate Director for Administration is the chief budgeting officer for the ONPRC and is therefore responsible for the budget development of the P51 award application. The budget process begins with budget managers estimating future staffing needs and non-payroll expenses to make a budgetary request. This initial request normally has an upper limit increase over the previous year requiring managers to make budgetary choices. The responses to this initial request are totaled and compared to expected funding levels. Normally this is an iterative process in which budgets are returned to managers with cost cutting goals.

At the same time the Executive Leadership Committee (ELC, see **Administraton-Director's Office**) is meeting and discussing budgetary needs to coordinate with the goals of the ONPRC strategic plan. Major adjustments in budgets, such as was made in the ART Core in year 53, reflect the leadership's decisions to change how our units do their work. Unit elimination or addition is normally the result of a strategic change, either as a direct result of the strategic planning process, or as an adaptation of that process to budgetary needs by the ELC.

Program income provides more than 50% of the total P51 award program funding and therefore forms a significant component for budgeting. The budget managers request a total funding number, and the Associate Director for Administration develops the methodology for splitting costs between ORIP and program income. This methodology recognizes that program income is returned to the award and is not the possession of individual units within the award. In general the following budgeting percentage splits were followed in this current application.

Administrative areas -15% ORIP, 85% program income
DCM - 50% ORIP, 50% program income
Research Support Cores – 55% ORIP, 45% program income
Divisions – Core scientists budgets calculated based on their contribution to the core program, other expenses split 15% ORIP, 85% program income.
I&M – 100% ORIP
Consortium – 100% ORIP

Within each area there may be exceptions based on specific reasons. For example within the Administrative areas the Director is funded at [% Effort] on ORIP, which is allowed by the guidelines.

INNOVATION

At the center of excellence in administrative services is a collaborative approach that brings the appropriate expertise and service levels to bear on the challenges and day-to-day work of our research enterprise. It is important for any unit to recognize it is not, nor is it intended, to be a self-sufficient unit, but rather as a unit it facilitates the application of expertise and service processes to the unit's work and problem resolution.

We continue to focus on innovation in two areas to continually strengthen and create new opportunities for Administrative Services at the ONPRC. The first is discovering, establishing, and maintaining connections with the appropriate groups that have expertise and influence in areas that partnerships are necessary. An example of this is our relationship to the City of Hillsboro. The City of Hillsboro is the oversight-governing agency for all of our construction, renovation, and improvements on campus. Administrative Services has worked to maintain a close working relationship with the City and with other key OHSU units involved, including Planning and Design & Construction. This working relationship will be especially important as the campus master plan expires and will be renewed during the core grant period of this application.

Although a comprehensive approach was attempted and the resulting master plan is a very valuable document, certain omissions in the planning process have become obvious. The education of the City of Hillsboro regarding the federal interest in the land and buildings and the implications of that interest is not represented in the current master plan and has been the subject of ongoing education as issues have arisen. In other areas clarity needs to be increased. Although the document states clearly that the campus is a closed campus and public access is not allowed, at times the development standards are interpreted as if the campus were a public campus. This resulted in small projects in a forested area being initially required to plant landscaping as if it were in a public area of Hillsboro. Although our close working relationship has allowed us to come to reasonable compromises in areas such as these, these projects underscore the importance of working closely with OHSU and Hillsboro to assure that communication lines are open for future projects.

OHSU has been an invaluable resource in this master planning process and will be the primary lead. This is an example where the University, the ONPRC, the NIH, and the City of Hillsboro will need their interests and concepts clearly and properly represented in the new master plan.

This same concept of continual work to make sure that the right people are around the planning and implementation tables permeates all that Administrative Services does. We continue to refine administrative related project planning process, reviewing whether the right parties and appropriate interests are represented in our planning groups, whether it is a software development process like the LabKey implementation or the planning of a new building project. We take the same approach to our external partnerships with utilities such as Portland General Electric and the Tualatin Valley Water District.

One area of continued growth and success in this concept has been the very significant accomplishments in the area of sustainability. Partnering with Oregon resources such as the Oregon Energy Trust, Environmental Protection Agency (building challenge to reduce energy usage), Portland General Electric, Northwest Earth Institute, and the City of Hillsboro Recycle at Work Program have provided valuable partnerships. Work at partnering with TerraCycle and implementing Labs 21 best practices are current new focuses of our sustainability effort.

This first area of innovation has been and will be a focus of Administrative Services to encourage all of our areas; Business Services, Library, Facilities, Human Resources, and Information Systems; to identify and establish working relationships with appropriate partners to provide the expertise and resources necessary for our provision of excellent services to the ONPRC program.

The second area of innovation is the provision of technologies that encourage and facilitate the cooperative work between parties that benefit from working together. LabKey and SharePoint are two technologies that have been recently embraced and are being developed to facilitate this kind of cooperation.

SharePoint provides a dynamic work environment and platform that is accessible via intranet technology. Our IS Unit is leading the campus into developing and using this platform for processes using electronic workflow, electronic support for project management, committee work, enhanced communication, and secure and directed work collaboration beyond the borders of the ONPRC/OHSU.

PRIMe (based on LabKey) is another example of a choice of platform that emulates Administrative Services value of bringing in technologies that foster collaboration. It was strongly felt that the upgrade of our Animal Health Records system needed to not only solve the issues of animal care but needed to provide a more comprehensive solution to all areas of our research campus. This value of information sharing and collaboration is at the heart of PRIMe's design and we are working through the implementation process to help our research community embrace these values in more practical and easy to use ways. PRIMe provides a critical technology allowing us to advance in this area.

Administrative Services through the excellent services and talent of our Information Services employees is leapfrogging from dated technology to making full use of some of the latest technologies and aims to continue to be an example and maintain a position of leadership within the NPRC consortium.

APPROACH

reviewers' comments

reviewers' comments

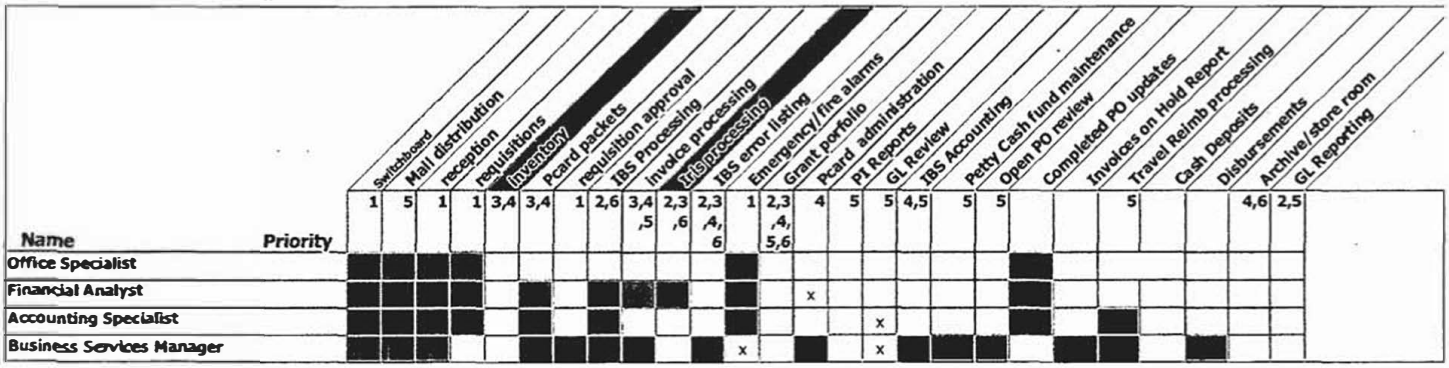
Progress

Because the Associate Director for Administration is responsible for a number of the key elements within this section, this progress report indicates some of the key accomplishment for these units.

a. Business Services and Administrative Services. The Associate Director led Business Services and subsequently the other units he manages through an exercise utilizing a tool to evaluate their workforce for the following. More details can be found in the **Administration – Business Services** section.

- What are the knowledge/skill domains that need to be understood and trained for?
- How many workers are needed for each knowledge/skill domain?
- What is the current strength of the workforce in these knowledge/skill domains?
- What is the risk that there will be insufficient expertise in these knowledge/skill domains in the future?

The basic tool for this evaluation picture below as applied to Business Services for non-sponsored project activity, comes from The Steve Trautman Company (www.stevetrautman.com). The basic tool is called a Knowledge Silo Matrix (KSM) and is very effective in visually pointing out weaknesses in a department's current structure and identifying potential areas of weakness in the future.



Name / Priority	Switchboard	Mail distribution	reception	requisitions	Inventory	Pcard packets	requisition approval	IBS Processing	invoice processing	Trip processing	IBS error listing	Emergency/fire alarms	Grant portfolio	Pcard administration	PI Reports	GL Review	IBS Accounting	Petty Cash fund maintenance	Open PO review	Completed PO updates	Invoices on Hold Report	Travel Reimb processing	Cash Deposits	Disbursements	Archive/store room	GL Reporting
	1	5	1	1	3,4	3,4	1	2,6	3,4 ,5	2,3 ,6	2,3 ,4, 6	1	2,3 ,4, 5,6	4	5	5	4,5	5	5			5			4,6	2,5	
Office Specialist	■	■	■	■								■								■							
Financial Analyst	■	■	■	■		■		■	■	■		■		x						■							
Accounting Specialist	■	■	■	■		■		■				■			x					■			■				
Business Services Manager	■	■	■			■	■	■			■	x		■		x	■	■	■	■	■	■			■		

Even a brief review of this completed tool will provide great information to anyone reviewing it. Along the top are the names of the major processes in a unit. Each process is given a priority (1 to 6). The colors code for the following characteristics: purple indicates a mentor, green indicates full competency, yellow indicates an active apprentice, blue indicates a person capable of back up in emergency, and an x indicates a potential trainee. Red indicates an area at risk. No entry indicates an individual is not involved with that process.

This tool was piloted in Business Services allowing an effective evaluation of their workforce and led to a series of adjustments to strengthen the mentoring and depth in knowledge/skill silos. This tool was then applied to all the other units in Administrative Services and provides a regular means of review and analysis of the relative workforce strength in each area.

Another aspect of workforce strengthening that was a subject of review and reorganization, was the on-boarding process that Human Resources provides to all employees and volunteers coming into the ONPRC workforce, and the training resources provided to managers and supervisors.

Excluded by Requester the Human Resources Manager, continued to refine and improve the ONPRC on-boarding process for new employees. On-boarding now follows a regular schedule for all aspects of new employee training and includes a module in the Director's Office to gain an overview of the entire Center. The process for onboarding volunteers at the ONPRC has been identified at the University as unique due to worker's compensation issues for volunteers working at a primate center. This has allowed our HR and the university to cooperatively set up a more effective program for volunteers at our Center. Excluded by has also lead a significant effort in bringing training to the ONPRC having to deal with improving managerial and supervisory skill sets, communications, and conflict resolution. This is strengthening a proactive approach to workforce management

resulting in improved workplace performance, improved attitudes, and more effective means of providing workplace compliance with applicable rules and regulations through better trained work teams. This effort is providing a workplace culture shift that requires less disciplinary action through proactive mentoring and training.

Committee work and service has also been a means to provide the necessary connections between Administrative Services and areas of the ONPRC and main campus. Committee service by the Associate Director for Administration is as follows:

- OHSU Audit and Advisory Services Committee member (standing)
- OHSU Policy Advisory Committee member (standing)
- OHSU Administrative Information Systems Steering Committee member (standing)
- ONPRC Executive Leadership Committee member (standing)
- ONPRC Policy Subcommittee Chair (standing)
- ONPRC Information Technology Advisory Group Chair (standing)
- ONPRC Steering Committee member (standing committee on construction)
- ONPRC Improvements & Modernization committee (Ad hoc)

Although the ONPRC has a Policy Committee, the committee often lacked the time to work on and review policy to the appropriate detail needed. At the suggestion of the Associate Director for Administration an ONPRC Policy Subcommittee was established to focus on the discovery of needed policy at ONPRC, review of and assistance in policy writing, and presentation of policy to the ONPRC Policy Committee for discussion and approval. OHSU's provision is that Centers, Institutes and Schools may create policy specific to that unit's need as long as it is consistent with and at least as restrictive as OHSU policy.

b. Research Safety and Occupational Health. During the past three and a half years, Administrative Services played a major role in the creation of startup of Occupational Health Services. This effort has been coordinated and in part lead by Excluded by Requester the former head of Research Safety. Excluded by Requester was recruited and hired by the Associate Director for Administration, and regular meetings were established with Research Safety to hand over their historical supervision of this area to the new Occupational Health Office.

Excluded by Requester was recruited from the OHSU main campus Occupational Health Department and had received certification in 2005 as an Occupational Health Nurse Specialist COHN-S. Since the ONPRC did not have specific expertise in Occupational Health, the recruitment of a nurse having both experience within the OHSU Occupational Health System and certification as an Occupational Health Nurse Specialist was key to ensuring we would have the expertise for the new implementation of a successful program. The details of this current program, its progress, and its role within Research Safety is included in the **Administration - Research Safety** section.

c. Facilities & Property. There were a number of construction and renovation projects completed during the last 3.5 years. Two significant accomplishments during this period were the seismic retrofit of the Administration and Research Building, two of the oldest buildings on campus. A series of studies funded by Improvements and Modernization were completed between 2007 and 2009 providing a seismic evaluation of the buildings on the ONPRC campus. The Research Building and Administration Building are multi-floor buildings, were constructed in the 1960's and were least prepared to survive a seismic event. One goal of the seismic remodels, which has been realized, was to preserve the historic character of these buildings.

The Administration Building was seismically retrofit to life safety standards in 2010 funded by ONPRC reserves. A proposal was made in 2011 to OHSU to provide substantial funding toward the $2.2 million dollar remodel of the Research Building. The main campus provided $1.7 million and ONPRC reserves provided $500,000 to fund the project. This retrofit was completed in August 2012 and substantially completes the seismic retrofit of ONPRC campus buildings, providing environments upgraded to seismic life safety standards in which ONPRC employees conduct their work.

Other significant construction and alteration and renovation projects (described in the **Administration – Facilities & Property** section) completed were:

- Completion of the Excluded by Requester; Specific Animal Location Building in 2009.
- Completion of the addition of two procedure and two animal rooms to the Specific Animal in 2010.
- Facility Security
- Completion of the design phase and commencement of construction for the PENS in 2012.

Sustainability became a primary focus of the ONPRC Administrative Services effort. The Associate Director worked with Facilities & Property to apply for Oregon Energy Trust funds and designate them to a sustainability fund. This fund was used to hire a full-time sustainability manager, Excluded by Requester in May 2011. As detailed in the Facilities section, Excluded by Requester has been instrumental in many sustainability initiatives and studies.

d. Information Systems. As noted above another area of major change during the past three and a half years has been the reorganization of Information Services. At the time of the past site visit, the group was referred to as Information Technology and Engineering and included the following major functions: 1) IRIS support, 2) Technical equipment support, and 3) Phone system support. The OHSU main campus Information Technology Group provided management of these functions.

The IT Advisory Ad Hoc Committee provided broad-based review, input, perspective, and support to the Associate Director for Administration in identifying the Information Technology needs of the ONPRC program and recommending changes to the ONPRC Director. The changes recommended by the committee focused on two structural changes: 1) Establishment of a full-time Manager, Information Systems position at ONPRC reporting to the Associate Director for Administration; and 2) Establishment of a permanent Information Technology Advisory Group composed of members from across the ONPRC program and the OHSU main campus to provide continuing input to the Manager, Information Systems. These two changes have provided the basis for many improvements in the Information Systems function at ONPRC. These improvements are detailed in the **Administration - Information Systems** section but highlights are as follows:

- Adoption of PRIMe to replace IRIS as the Electronic Health Records (HER) system for the ONPRC.
- Use of PRIMe as an information system for lab and service center data. The Executive Leadership group determined that it is critical to provide a tool that had capabilities to serve the entire NHP research effort at the ONPRC. While PRIMe provides excellent EHR, it also provides native capability to serve Lab and Research Support Core electronic information needs.
- Adoption of MS SharePoint as a Business facilitation tool. Supporting MS SharePoint through our information services is providing key business solution technologies such as the electronic routing and approval of Research Support Core rates, or an on-line work order system for Facilities.
- Remodel of office space for Information Services allowing the entire team to be located together in appropriate space.

e. Research Library. During this period the Library was remodeled and changes were made allowing a reduction of floor space occupied through Spacesaver moveable shelving and purging of books and journals that were no longer needed. The Librarian also was successful in applying for and receiving a grant award through the Private Source to digitalize rare NHP books in the library collection and make them available over the internet. This project is substantially complete, entering a promotion phase in 2013, as detailed in the **Administration – Research Library** section.

Effective progress has been made in many areas of the ONPRC during the past award period. This progress lays the foundation for further progress to be made in the coming award period along the lines of the specific aims outlined in the Specific Aims section of this document.

Future Plans

Specific Aim 1 – Ensure the continued provision of the effective and efficient operation of the ONPRC infrastructure resources, both physical and personnel resources, to provide an appropriate environment for the safe and effective conduct of animal care and research at the ONRPC. The ONPRC infrastructure resources include the land, physical buildings, and central equipment. The effective operation of these physical resources depends on the teams of employees that provide expertise in infrastructure areas such as Administration, Facilities, Business Services, Information Systems, Library, Occupational Health and Research Safety, Emergency Operations, Research Support Cores, and DCM. The Associate Director for Administration provides support either by direct management of these programs or by providing financial/business/grant expertise to support the success of these areas.

As noted above in the progress report, the KSM has been an effective tool for the evaluation of how well a department is prepared to do its work today and into the future. This tool provides information that allows the restructuring of a workforce to better accomplish its tasks. It has been applied effectively within Administrative Services to aid in the evaluation of the workforce that supplies infrastructure support services through Facilities, Information Services, Business Services, Human Resources, Occupational Health, and the Library.

This tool will be able to be effectively applied in other infrastructure support areas in the future such as Emergency Operations, DCM, and the Research Support Cores. The Associate Director will continue work within Administrative Services to evaluate and improve the workforce through this tool, but will offer to provide expertise in use of the KSM to other infrastructure units within the ONPRC.

Another way this support is provided is by ensuring that appropriate relationships are identified, maintained, and appropriately used. An example of this is the work with Facilities and with the OHSU Design & Construction Department to identify relationships within the City of Hillsboro, utility companies, the OHSU main campus, and specialized expertise providers. The Associate Director works closely with the Facilities Manager to determine the identity and status of these relationships. Although this is a formal effort within all areas of Administrative Services, no tool has been applied to date to characterize and document these relationships.

In order to formalize this work, the Associate Director for Administration will adapt the KSM to list and evaluate these relationships. Taking advantage of the KSM to identify all of the important areas of work performed in a department, we can ask the question, "What external relationships are required or helpful in the performance of this area?" Although it is known at an organization that external relationships are often critical to success, little is done to formalize the identification of those relationships and their management.

By listing down the spreadsheet the external agencies, companies, and individuals that we work with, and through a similar color coding scheme, this tool will give a clear, graphical representation of the status of our external partnerships. This comprehensive evaluation then allows the discussion of these relationships, the prioritization of effort needed based on current status, and the determination of steps to be taken to increase the effectiveness of these relationships. Effective external relationships provide a necessary addition to effective internal operations in ensuring the continued success of the infrastructure operations at the ONPRC.

To ensure effective and efficient operations, it will be critically important to recruit the very best talent to fill the open positions of Associate and Assistant Directors for Administration in the next three to six months. Under the leadership of Interim Associate Director for Administration, Excluded by Requester the ONPRC can be assured of a smooth transition and preparation for the site visit. Indeed, Excluded by Requester has been an important partner during the preparation of the P51 for submission over the last six months. She and the Director Excluded by Requester will be working closely in the next few months to choose outstanding permanent leadership.

Specific Aim 2 – Work with the University to strengthen work and financing relationships and make timely and accurate resource requests to ensure that the additional expertise and funding necessary to support infrastructure development appropriate to the ONPRC NHP research endeavor are provided in a timely manner. Administrative Services plays a central role in the planning and implementation of infrastructure modernization through sources such as Improvement & Modernization (I&M) funding, requests

into the capital process at OHSU, grant writing and submission for funding sources such as G20 and C06 grants, and the effective management of other sources of funding to create savings allowing the funding of infrastructure resources.

The Associate Director for Administration will provide cost projections and analysis for both deferred maintenance and for proposed infrastructure expansion plans. Essential to predicting deferred maintenance are the Facilities systems that track the age and expected replacement/upgrade of existing components such as roofs, HVAC, water heaters, etc. These comprehensive records are used when planning the coming five-year renewal. Facilities submits comprehensive requirements for campus upkeep and renewal and participates with the I&M Committee in prioritizing the individual items.

These priorities are then further reviewed at the ELC level and decisions regarding priority and funding approaches are approved. This process is then repeated annually to ensure that plans are up to date and appropriate for the opportunities and challenges the Center is facing.

For specialized projects, such as the "Re-Lifing" of the Research Building or the addition of a NHP Catheterization Laboratory, we work closely with OHSU's Design and Construction Department. This group provided project management oversight and coordinated work the external architectural and design firms. At time we also utilize specialized architectural and engineering resources, such as SRG or The Estime Group, which have extensive knowledge of the ONPRC campus and the requirements of facilities supporting NHP husbandry and research. These resources are engaged as appropriate to provide accurate cost estimates for projects.

Annually, beginning in January each year, the Associate Director works with the Director to submit requests to the Vice President for Research for funding in the coming fiscal year. The University utilizes a space committee to review all requests being made throughout the university, prioritizes those requests, and makes allocations appropriate to the funding available. Most recently the seismic renovation of the Research Building and the installation of LabKey as the electronic health records system are examples of the University funding process providing funds to supplement key infrastructure needs of the ONPRC.

Specific Aim 3 – Work with the University and local governments to establish a realistic and therefore fundable long-range master plan to provide a growth roadmap for the next ten years for the ONPRC. The current master plan for the OHSU West Campus expires in 2018. The last plan was created in 1998 and updated in 2004. While this plan was visionary in creating sufficient growth capacity for the future, it did not predict well the particular path an NHP research campus would take. It currently does not include future outdoor housing, which should be considered in the expansion of NHP breeding facilities for animal welfare purposes. There are many advantages in trying to reproduce aspects of natural habitats in NHP housing.

It is the intent of the Associate Director and Director to assure that the committee working on the next master plan has appropriate information, representation as needed, and expertise from the NHP perspective. This work should begin planning in 2015 and will include communication with representatives in the NIH Office of the Director regarding the provisions in the new master plan.

Specific Aim 4 – Increase engagement with other Administrative Directors in the NPRC consortium to continue work on defining and documenting best practices that can be used within the varied institutional environments throughout the NPRC system. The challenges facing the ONPRC and its host institution are not unique. Similar challenges are being faced by the other NPRC's. It has been extremely useful in the past to share information on rates, practices, policies, procedures and benchmarks to provide input regarding particular situations and the related decisions that need to be made at Oregon.

During the past five-year period, the NCRR guidelines for NPRCs were updated. The ability to share practices and host institutions perspectives on program income, allowed the Associate or Assistant Directors over infrastructure resources to work together and craft a statement on program income and the ABC F&A rate methodology that has helped create a more uniform and appropriate treatment of program income at the

various primate centers. The Associate Director at Oregon was able to create draft language that was adjusted, reviewed and approved at other centers and then included in the 2010 guidelines.

This type of effort needs to be increasingly formalized through a cooperative effort by these Directors. In 2012 at the Fall Director's meeting, the Associate/Assistant Directors schedule a half-day meeting with an agenda related to a number of issues that NPRCs face. These issues included competitive applications, funding, IDC negotiations and rates, rate setting, organizational structure, and personnel. This face to face meeting then contributed to many email and phone interactions on these subjects in the subsequent months.

It is the intent of the Associate Director for Administration to make this type of interaction a priority in the coming renewal period. Although this is not an activity that can be dictated as it relies on the cooperation of all the Administrative Directors, it can be encouraged, and working to establish an appropriate meeting mechanism to directly deal with issues facing NPRC Associate/Assistant Directors will provide great help within the NPRC system. Note that in 2012 and 2013, approximately 50% of the Administrative Director type of positions turned over. It is critical to the financial and operational health of the centers that knowledge be shared and questions be answered to support incoming Administrative Directors in the accomplishment of their job duties.

As there are only eight National Primate Research Centers, the role of the Associate/Assistant Directors as a group in interpreting and applying the provisions of the P51 infrastructure award to their operations and institutions cannot be overemphasized. While it may not be as obviously important as the NHP research work, that work cannot be properly conducted without a sufficient and effective infrastructure.

Program Director/Principal Investigator (Last, First, Middle): Robertson, Joseph E./Haigwood, Nancy L.

ADMINISTRATION - ADMINISTRATION DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
To Be Named	Assoc Dir - Admin	1.80			Institutional Base Salary	24,436	6,109	30,545
Excluded by Requester	Financial Analyst	% Effort				12,068	3,741	15,809
	HR Manager					10,174	3,154	13,327
	HR Coordinator					5,290	1,851	7,141
	Exec Specialist					8,698	2,696	11,394
To Be Named	Asst Director for Admin	1.80				16,322	4,081	20,403
To Be Named	Cost Accountant	1.80				11,925	3,697	15,622
	→							
	SUBTOTALS					88,913	25,329	114,242

CONSULTANT COSTS		
Consulting	1,269	
		1,269
EQUIPMENT *(Itemize)*		
None Requested	0	0
SUPPLIES *(Itemize by category)*		
Office & Admin Supplies	75	
Minor Equipment	231	306
TRAVEL		
Domestic	750	750
INPATIENT CARE COSTS		0
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		
None Requested	0	0
OTHER EXPENSES *(Itemize by category)*		
Conference Registration & Course Fees	255	255

CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 116,822
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 116,822

PHS 398 (Rev. 06/09) Form Page 4

ADMINISTRATION - ADMINISTRATION
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	114,242	117,669	121,199	124,835	128,580
CONSULTANT COSTS	1,269	1,307	1,346	1,387	1,428
EQUIPMENT	0	0	0	0	0
SUPPLIES	306	315	325	334	344
TRAVEL	750	772	796	820	844
INPATIENTS CARE COSTS	0	0	0	0	0
OUTPATIENTS CARE COSTS	0	0	0	0	0
ALTERATIONS AND RENOVATIONS	0	0	0	0	0
OTHER EXPENSES	255	263	271	279	287
DIRECT CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	116,822	120,326	123,936	127,654	131,484
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	116,822	120,326	123,936	127,654	131,484
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					620,222

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

PERSONNEL

Associate Director for Administration – To be named, recruitment in process. (12 calendar months, 1.8 ORIP and 10.2 Program Income). Responsible for directing the operational, financial, grants management, human resources, facilities, information services and the research library at ONPRC. Plays a key role in the short and long range program planning and systematically monitors and prioritizes goals to achieve the ONPRC's mission and vision and assure research activities are compliant with various regulatory agencies. In addition, develops policies and procedures affecting a wide range of administrative activities; review and disseminate OHSU policy and procedure governing these activities. Coordinates the budgetary process for the five-year ORIP-supported core grant application and annual progress reports. Direct responsibility for the following units: Business Services, Human Resources (HR), Facilities, Information Systems (IS) and the Research Library.

Financial Analyst – Excluded by Requester % Effort. Responsible for ORIP-supported core grant activity including day-to-day accounting and reporting from initial proposal to close out; day-to-day accounting and reporting of the program income as it relates to the grant; annual budget proposal, data entry for the five-year competitive renewal; approving grant-related purchases; providing miscellaneous monthly detailed reports including projections of both income and expenditures; tracking of improvement and modernization program; establishing budgets in the accounting system.

Human Resources (HR) Manager – Excluded by Requester % Effort
Responsible for day-to-day HR activities at ONPRC in coordination with the OHSU HR Director for Research. Provides services ranging from on-boarding, effort certification, and arranging education programs, to assistance with personnel, benefit, and payroll matters and end of work services. Provides complete HR services to personnel and develops those services as necessary for effective and efficient personnel operations.

Human Resources Coordinator – Excluded by Requester % Effort
Responsible for entering labor distribution changes; completing paperwork involved in hiring and termination processes; coordinating termination checkout process; distributing payroll, both paper checks and automatic deposit information; distributing timekeeping records for input and maintaining timekeeping records; generating management and staff reports, as requested; coordinating the distribution and return of effort certification statements, providing back up to the HR Manager.

Executive Specialist – Excluded by Requester % Effort
Responsible for providing administrative support to the Associate Director for Administration, the Assistant Director for Administration, and the Business Services Manager. Provides external invoice billing and collection services for the for the Research Support Cores and DCM sales..

Assistant Director for Administration – To be named, recruitment in process. (12 calendar months, 1.8 ORIP and 10.2 Program Income). Responsible for the day-to-day operational administration of the ORIP-supported core grant, budget development, budget proposal development and submission for the competitive and non-competitive cycle in cooperation with budget managers; for cost accounting function and ensures that appropriate rate studies and schedules are in place; for overall reporting to assure that reporting and informational needs of senior management and budget managers are met; ensures that policies and procedure are followed.

Cost Accountant – To be named, recruitment in process. (12 calendar months, 1.8 ORIP and 10.2 Program Income). Responsible for collecting, analyzing, summarizing and evaluating various alternative courses of action for ONPRC. Will be focused on cost centers such as DCM and the Research Support Cores. Develops rates and rates schedules in coordination with unit managers Provides support to ORIP-supported core grant cost centers, helping with budget management and development.

CONSULTANT COSTS

Consulting services are requested to provide assistance with the transition of the ONPRC Administrative Services Administration to new personnel. Key aspects will be the implementation of the new ORIP-supported core grant budget and assistance in the development of the next master plan for the ONPRC campus (2016 – 2018).

SUPPLIES

Office & Admin Supplies: Funds are requested for general office supplies including filing supplies, copy paper, pens, pencils, toner cartridges, staplers and staples, sticky notes, tape, notepaper, writing tablets, binding supplies, file folders, calendars, paperclips, etc. for a staff of 7 permanent employees. Supplies are also requested for upgrades of systems and software such as Monarch, Datapump, Microsoft Office, etc., for 7 workstations.

Minor Equipment: Funds are requested to replace the seven employee workstations over the five year award period.

TRAVEL

Funds are requested to support the Associate Director for Administration in travel to other Primate Centers for best practices sharing, and to provide training at conferences to upgrade staff skills as appropriate in Administrative Services.

As senior personnel will be new, it is important over the next five-year period to provide opportunity to visit other NPRCs, as appropriate, to gain first hand information regarding primate center administration. It is anticipated that ORIP and program income sources will be used for an average of four trips per year (2 Associate Director, 1 Assistant Director, 1 HR Manager) and for local training opportunities for staff.

OTHER EXPENSES

Funds are requested for registration and course fees for conference/training for new staff, as needed, and with the approval of the Director.

ADMINISTRATION: Administrative Services Income Table

Last Funded Year (53)

Source	Funding (direct costs)
P51 base grant support	$93,587.03
Program income derived from P51 base grant	530,326.47
Other Sources	28,395.91
Total	$652,309.41

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$116,821.72
Program income derived from P51 base grant	663,071.71
Other Sources	29,247.79
Total	$809,141.22

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

Administration receives salary support and support for other expenditures from program income.

BUSINESS SERVICES SPECIFIC AIMS

Business Services at the ONPRC provides services and resources to assist faculty and administration in the development and management of grants and other financial resources that fund the accomplishment of the strategic research mission of the ONPRC. The business functions are in accordance with OHSU policy and procedures, and NIH rules and regulations. The business service staff provides support for ONPRC ancillary proposals and awards. This includes from initial planning stages, to mid-project financial management and budget tracking, to close-out and final reporting of all non P51 projects. Business Services provides a single-point-of-contact for ONPRC staff to accomplish all business process tasks, accounts payable, requisitioning, fixed assets inventory, purchase orders and travel reimbursements. This facilitation of these processes helps free ONPRC staff to concentrate on their areas of expertise in research, support cores and other areas, and reduce the distraction that can result from the increased administrative burden in the conduct of research.

Through these functions, Business Services provide:

- Accountability and guidance in coordination with central University resources to internal and external funding guidelines, rules, and regulations, and budgetary and schedule commitments.
- Comprehensive support for all human resources and related systems processes at the university including hiring, on-boarding, union matters, labor distribution, etc.
- Provide single-point-of-contact efficiency for ONPRC staff in performing business processes such as ordering research supplies, obtaining purchase cards, submitting travel claims, processing internal billing charges, tracking fixed assets, submitting accounting adjustment forms, and many other business related processes.
- Budgetary development assistance for ancillary proposals and non-human primate costs.
- Consultation services for financial aspects of project planning.
- Education regarding university and federal systems; and requirements for the conduct of research projects with OHSU Rearch Grants and Contracts, Sponsored Projects Administration and Central Financial Services.
- Review and evaluation of financial progress and assistance in research project resource management.
- Research Award compliance and close-out in coordination with central University resources.
- Reporting and accounting expertise to provide information for individual projects as well as overall ONPRC financing and future projections.

Specific Aim 1: To provide appropriate levels of support and staffing to provide for the efficient, effective, and compliat conduct of the P51 award. This involved the facilitation of all business processes at the university in behalf of the core award and its budget managers from budget planning and submission to Federal Financial Report (FFR) calculation and providing assistance in progress report writing and submission.

Specific Aim 2: To provide excellent customer service to our ONPRC Divisions while maintaining productive relationships with OHSU Business and Grants Management Departments. Standard Operating procedures are being updated and created to clearly define roles and responsibilities. This will clarify and provide efficiencies in the day to day operations.

Specific Aim 3: Fully implement and utilize an radio-frequency indentification (RFID) inventory system to track ONPRC fixed assets and include maintenance agreements and service dates on equipment. This will greatly reduce the time and effort involved in equipment inventory tracking and reduce the burden on lab personnel.

Specicific Aim 4: Explore and implement a new system for budget development for the competing and non-competing P51 award. The current system is built on multiple Excel spreadsheets with extensive links. Aterations to the award require extensive manual changes throughout multiple spreadsheets and is error prone. The selection and implementation of a system better suited to the P51 award and the requirements of electronic submission will be necessary in the coming competitive period.

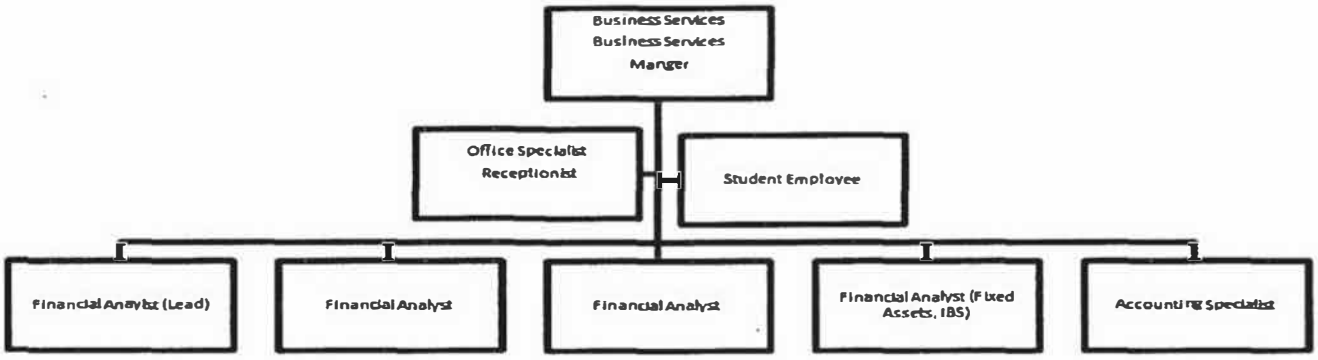
BUSINESS SERVICES - RESEARCH STRATEGY

SIGNIFICANCE

Business Services at the ONPRC provides quality services and resources that assist faculty and administration in the development and management of grant and other financial resources that fund the accomplishment of the strategic research mission of the ONPRC. At the center of this mission are the processes related to the P51 core grant. Business Services provides the expertise and staffing for the set-up, monitoring, reporting, and close-out of the P51 award in accordance with OHSU policy and procedure and NIH rules and regulations. Additionally this office provides support for all phases of all projects and all resources used to fund work at the ONPRC from initial planning stages, to mid-project financial management and budget tracking, to close-out and final reporting. Business Services provides a single-point-of-contact for ONPRC staff to accomplish all business process related tasks at the university. This facilitation of these processes help free ONPRC staff to concentrate on their areas of expertise in research, husbandry and other areas, and reduce the distraction that can result from the increased administrative burden in the conduct of research.

The successful conduct of the business processes at the ONPRC requires skilled and dedicated staff members to provide these services, as reflected in the following organizational chart.

ORGANIZATION CHART



The Business Services team is organized through the Business Services Manager, Excluded by Requester in providing distinct but complementary services under the direction of the Associate Director for Administration. Excluded by E was recruited to this position during the last funding period. The day-to-day tasks of budgeting, budget monitoring, expenditure approval, reporting, analyzing, and creation of adjusting entries is performed primarily by the Financial Analysts. The Assistant Associate Director for Administration is the primary representative for the Associate Director for Administration when he is absent, with the Business Services Manager providing this role if both are absent.

The Business Services manager is responsible for providing all business services through a staff of seven. These staff are responsible for reception and switchboard operation, 911 emergency communications, mail room operations, grants management for all grants and contracts ancillary to the P51 award, primary requisitioning support, purchasing cards, internal billing, adjustments, fixed assets, and all other aspects of business services as delegated by the University to Departments and Institutes. Table 1 below shows the positions in Business Services and their primary areas of responsibility and relationships.

Table 1. Business Services, Primary areas of Responsibility and Relationships

Staff Member	Primary Report	Primary OHSU-ONPRC Areas	Primary External Contacts
Business Services Manager	Associate Director for Administration	Research Grants and Contracts (RGC), Sponsored Projects Administration(SPA), Accounts Payable, Central Finance Services, IBS, Logistics, Stores, Fixed Assets Administration, Space Administration, Information Technology, West Campus Cashier, Technology Transfer and Business Development (TTBD), Bursar, Wireless & Telecommunications, Purchasing card Administration, Accounts Receivable, Public Safety	Vendors, NIH, Other Universities (sub contracts)
Financial Analysts (3)	Business Services Manager	RGC, SPA, Logistics, OHSU Research Departments	NIH, Other Universities (sub contracts)
Financial Analyst	Business Services Manager	RGC, SPA, Logistics, OHSU Research Departments, Central Financial Services, Fixed Asset Administration	NIH, Other Universities (sub contracts), Vendors
Accounting Specialist	Business Services Manager	Accounts Payable, Central Financial Services, Logistics	Vendors, Public, Other Universities (services/payments)
Office Specialist	Business Services Manager	OHSU Public Safety, 911 service, Logistics, Information Technology	Public, Vendors, Visitors
Student Worker	Business Services Manager	Logistics, West Campus Store	Public, Visitors, Vendors

The OHSU model is to provide a comprehensive business service through central resources and responsibilities at the main campus and distributed resources and responsibilities at the Institute level. The Functions provided cooperatively are as follows (various levels of functions exist both centrally and at the institute/department level)

- Effort Certification
- Accounts Payable
- Purchasing/Requisitioning
- Financial Administration
- Internal and External Billing
- Accounts Receivable
- Sponsored Projects Administration
- Grant/Project Accounting
- General Ledger Accounting
- Fixed Asset Inventory
- Reporting/Forecasting
- Switchboard Operations
- Mailroom Operations
- Space Allocations
- Miscellaneous Logistical Functions

Each of these areas can then be described as to the main campus and the institute cooperative responsibilities. Fixed assets provides a relatively simple and good example. The main campus provides the fixed asset tracking module through the Oracle system which provides the university record of assets, calculates depreciation, uses this information for financial statements and F&A proposal preparation, and allows the main campus a high level of overall review. The institutes are responsible to code equipment

purchases correctly, tag equipment, inventory equipment at least every two years, release equipment and arrange for its removal, provide a granular level of review and resolve most errors found in the system.

It is key then to the effective functioning of the system that strong relationships exist and are maintained between Business Services and Central Financial Services, Research Grants and Contracts, Logistics, and Technology Transfer and Business Development. Through the Business Services personnel and these relationships, Business Services provides the following:

- Accountability and guidance in coordination with central University resources to internal and external funding guidelines, rules, and regulations, and budgetary and schedule commitments.
- Provide single-point-of-contact efficiency for ONPRC staff in performing business processes such as ordering research supplies, obtaining purchase cards, submitting travel claims, processing internal billing charges, tracking fixed assets, submitting accounting adjustment forms, and many other business related processes.
- Budgetary development assistance.
- Consultation services for financial aspects of project planning.
- Education regarding university and federal systems and requirements for the conduct of projects.
- Review and evaluation of financial progress and assistance in project resource management.
- Project compliance and close-out in coordination with central University resources.
- Reporting and accounting expertise to provide information for individual projects as well as overall ONPRC financing and future projections.

INNOVATION

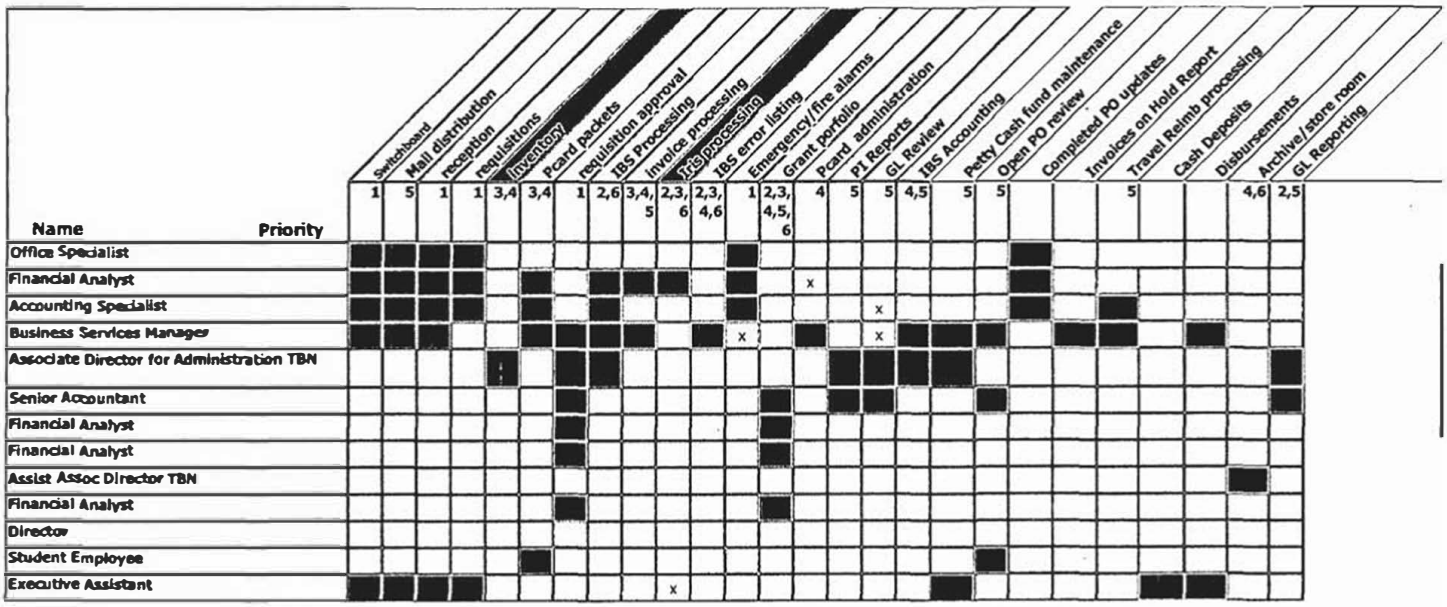
The effective and efficient use of staff in task accomplishment, mentoring, and the appropriate distribution of duties requires a manager to characterize his/her workforce with accuracy. This characterization must evaluate their level of skill, recognize the ability of team members to provide backup, access the mentoring that is taking place within the work unit, and recognize weaknesses that need to be addressed. The Associate Director of Administration introduced a fairly simple but surprising effective tool for evaluation of the workforce and providing for a continuing evaluation of how well the Business Services team is prepared to accomplish its required work.

The tool is a simple excel spreadsheet. Along the rows on the left hand side are listed all the workers in a unit. Across the top in each column are the work requirements/products of the unit. Each cell in this table represents an intersection of a worker and a requirement or product. The cell is then color coded to evaluate that worker for that particular aspect. The color codes are as follows:

Green – Can independently do the job
Purple – Chosen to mentor
Yellow - Actively learning/apprentice
Blue – not a current job duty but can provide backup
Blank – not using this skill
Red – At risk

Each task is also rated using the following scale
1 – mission critical, must be accomplished within 24 – 48 hours
2 – mission critical, time period not as critical
3 – Important, mandated by compliance
4 – Important, mandated by policy, practice, or management
5 – Important, routine
6 – Needed for ongoing business, if not done multiple times there will be an effect
7 – Not sure why we do this

The resulting table appears as follows:



Name	Priority	Switchboard	Mail distribution	reception	requisitions	Inventory	Pcard packets	requisition approval	IBS Processing	invoice processing	Trip processing	IBS error listing	Emergency/fire alarms	Grant portfolio	Pcard administration	PI Reports	GL Review	IBS Accounting	Petty Cash fund maintenance	Open PO review	Completed PO updates	Invoices on Hold Report	Travel Reimb processing	Cash Deposits	Disbursements	Archive/store room	GL Reporting
		1	5	1	1	3,4	3,4	1	2,6	3,4, 5	2,3, 6	2,3, 4,6	1	2,3, 4,5, 6	4	5	5	4,5	5	5			5			4,6	2,5
Office Specialist		■	■	■	■								■								■							
Financial Analyst		■	■	■	■		■		■	■	■		■		x						■							
Accounting Specialist		■	■	■	■		■		■				■			x					■			■				
Business Services Manager		■	■	■			■	■	■	■		■	x		■		x	■	■	■		■	■		■				
Associate Director for Administration TBN						■		■	■							■	■	■	■									■
Senior Accountant								■						■		■	■			■								■
Financial Analyst								■						■														
Financial Analyst								■						■														
Assist Assoc Director TBN																										■		
Financial Analyst								■						■														
Director																												
Student Employee						■													■									
Executive Assistant		■	■	■	■						x							■						■	■			

The color patterns allow an immediate evaluation. This reveals if someone if expected to be an apprentice in too many areas, or if someone is required to be a mentor in too many areas. It also shows where task areas are not appropriately covered by staff. It show what will be lost if someone leaves or retires. The visual aspect of this tool allows it to be used both in managerial and employee discussions. It is an easy way to represent where the work force is today and what changes we need to work on if the team is to be healthy. The tool provides flexibility in that particular task areas can be broken down into smaller segments and evaluated in the same manner.

Through the use of this tool and meetings with the Associate Director for Administration, an effort has been engaged for the continuing evaluation of the workforce through the next grant cycle. As we enter the era when more and more members of the workforce are expected to retire, this will provide an evaluation of our ability to handle those changes and a map for working on task areas that are not appropriately provided for.

APPROACH

reviewers' comments

reviewers' comments

Progress Report. Accomplishments during the past 3.5 years include the following:

- Hiring of a new Business Manager, Excluded by Requester
- An in-depth evaluation of the positions and the position assignments to reorganize the office's task completion and service provision in more efficient and effective ways.
- Completion of the fixed asset inventory with planning underway to evaluate the possibility of an RFID system to reduce time and effort in the process.
- Completion of major cost accounting/rate setting studies for our Division of Comparative Medicine (previously termed Division of Animal Resources)..
- Regular attendance by staff at other Scientific Divisions and departmental meetings to provide regular education and question and answer opportunities.
- Increased efforts and regular meeting leadership to help other campus units organize their administrative help in more effective and efficient ways.
- Unique aspects of on boarding for volunteers with Human Resources were identified and the process as adjusted in cooperation with the main campus to establish a more effective system for volunteers.
- Piloting paperless systems for the main campus. An example was the adoption of a paperless system for handling purchasing card documentation submission to the university. This system was then adopted university wide. Other areas that have moved to at least partially paperless are Accounts Payable, disbursements, and travel reimbursements.
- Facilitation of a university internal audit of the ONPRC Research Support Cores (CORE SCIENCE SERVICES). The audit's conclusion was that the ONPRC Cores following sound accounting and division of duty practices. Suggestions were made to improve documentation, provide consistency in oversight meetings, and provide better use of the main campus provided systems such as IBS (Internal Billing System).
- During this time the seismic upgrade of the Administration Building took place, requiring staff to vacate their offices and move to temporary quarters in the Research Building. The upgrade took about five months, and staff members were able to return to a safer environment. We also took this opportunity to

reorganize and to redesign the cubicles and dividers to allow for more sound privacy while still allowing maximum access to natural lighting.

- Changes were made to the Electronic System IRIS and IBS to improve the accuracy and timeliness of our internal billing processes.
- The Business Services staff successfully handled an increase volume and requirements of ARRA awards, in cooperation with the main campus during this time period, with no corresponding increase in staff.

Continued progress in Business Services will require continued support of assuring that staff members are adequately trained and tasks appropriately assigned. Participation in the strategic planning process provides the opportunity for Business Services to set goals and outline the resources and path necessary to reach those goals. The strategic aims for the next five years will support the continued success of Business Services in the following ways.

Future Plans

Specific Aim 1 – Provide appropriate levels of support and staffing to provide for the efficient, effective, and compliant conduct of the P51 award. This involves the facilitation of all business processes at the university in behalf of the core award and its budget managers from budget planning and submission to FFR calculation and providing assistance in progress report writing and submission.

Business services will work with OHSU Research Grants and Contracts and ONPRC managers in providing information, training and updates in managing the P51 award. This will include regular budget review, future plans and FFR reporting requirements. The financial analysts work with the Researchers and Administrative staff with the proposal application and submission. OHSU provides workshops and trainings for the Financial Analysts and Administrative staff, keep ONPRC up to date with process changes and information. The ONPRC has also had the long-standing practice to support staff in their pursuit of certifications in grants management. This support has helped raise the level of expertise within the office for grants administration.

Specific Aim 2 – Provide excellent customer service to ONPRC Divisions while maintaining productive relationships with OHSU Business and Grants Management Departments. Standard Operating procedures are being updated and created to clearly define roles and responsibilities. This will clarify and provide efficiencies in the day-to-day operations.

Business services are reviewing, updating, and documenting as needed standard operating procedures for the functions provided by business services. This is to provide written documentation and consistency with the Financial Analysts in their day to day monitoring of the federal awards. Excellent customer service is to be helpful and productive at all times. Consistency among the Financial Analysts will ensure that the information is available to assist the various ONPRC Divisional staff at all times. OHSU Research Grants and Contracts and Sponsored Project Administration attend the ONPRC Grant Management Team meetings monthly. This attendance has provided a close working relationship and provides appropriate central OHSU support when working on grant related issues. ONPRC staffs attend OHSU p-card administration meetings, meet with accounts payable staff and other Central Financial Service departments regularly.

Specific Aim 3 – Fully implement and utilize an RFID inventory system to track ONPRC fixed assets and include maintenance agreements and service dates on equipment. This will greatly reduce the time and effort involved in equipment inventory tracking and will reduce the burden on laboratory personnel.

An RFID system was recently purchased that will allow the identification of tags in a much more effective and efficient manner. Although inventory taking will still require getting close to equipment, it will no longer be a matter of finding a tag. There has always been an attempt to consistently tag equipment in similar places, but the design of some equipment makes this impossible. Variations in tag location will no longer present the challenge it has in the past.

The increase in effectiveness and efficiency of taking inventory will allow inventory to be updated more often. Plans are being implemented to walk the campus every six months, taking inventory by RFID, and then using that information to update records and resolve issues. This will also allow much more efficient and effective inventory tracking for individual PIs when they move equipment or change labs.

The RFID inventory system is being implemented in each lab. The PI is given a list of assigned assets, and the RFID tag is placed on the item, in addition to the OHSU ID tag. The information is then entered into the RedBeam software system for tracking. This system will allow the inventory tags to be read by the RFID reader for accuracy. The Financial Analyst will maintain the inventory by PI and location, thus readily provide accurate information for equipment inventory.

Specific Aim 4 – Explore and implement a new system for budget development for the competing and non-competing P51 award. The current system is built on multiple Excel spreadsheets with extensive links. Alterations to the award require extensive manual changes throughout multiple spreadsheets and the process is error-prone. The selection and implementation of a system better suited to the P51 award and the requirements of electronic submission will be necessary in the coming competitive period.

A small team will investigate current budget software tools, to evaluate if they allow for the complexity of the P51. The ONPRC P51 award covers several departments and programs. A new system would allow for continuity from the lower division level budgeting needs to the high level reporting required by NIH and OHSU. The system would allow for the budget adjustment and reallocations as needed during the award to be in compliance with ONPRC, OHSU and NIH reporting structure. One aspect of this program is that it must facilitate budget creation for both the submission of the P51 budget and the creation of a day-to-day management budget. Although these budgets are often the same, sometimes budgets are further broken down to multiple budget managers for their day-to-day administration and activity tracking.

A team will be selected to evaluate, test and make the recommendation to ONPRC Director and OHSU Research Administration for final approval. An implantation plan will be developed to include adequate testing and review. This will need to happen in the early years of the renewal as it makes sense to develop this new budget tool on the annual budgets, before it is used to develop a five-year submission budget.

Through these specific aims and the capabilities of the staff within the Business Services office, excellent service will be provided to the staff of the ONPRC to help facilitate research in NHPs.

Program Director/Principal Investigator (Last, First, Middle): Robertson, Joseph E./Haigwood, Nancy L.

ADMINISTRATION - BUSINESS SERVICES DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*

Use Cal, Acad, or Summer to Enter Months Devoted to Project·
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Excluded by Requester	Mgr. Business Svcs	% Effort			Institutional Base Salary	13,964	4,329	18,292
	Admin Coordinator					2,207	773	2,980
	Financial Analyst					7,693	2,692	10,385
	Office Specialist					5,950	2,082	8,032
	Financial Analyst - Lead					10,199	3,162	13,361
	Financial Analyst					9,091	2,818	11,910
	Financial Analyst					8,470	2,964	11,434
To Be Named	Student Worker	1.80				1,478	148	1,625
To Be Named	Accounting Specialist	1.80				7,517	2,631	10,148
	SUBTOTALS					66,568	21,599	88,168

CONSULTANT COSTS		
None Requested	0	0
EQUIPMENT *(Itemize)*		
None Requested	0	0
SUPPLIES *(Itemize by category)*		
Office & Admin Supplies	2,719	
Minor equipment	409	
Dry Ice/Liquid Nitrogen	18,285	21,413
TRAVEL		
Domestic	477	477
INPATIENT CARE COSTS		0
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		
None Requested	0	0
OTHER EXPENSES *(Itemize by category)*		
Hosting Groups & Guest	159	
Conference/Registration Fee	477	
Membership in Profesnl Org	44	
Maintenance & Repairs	82	
Parking	477	
Postage	48	
Printing & Publishing	80	
Shipping	32	
Books, Periodicals, Subscriptions	40	
Training/Registration	80	
Telecommunications	604	
Misc Purchased Serv	8,864	
Miscellaneous Other	2,703	
		13,688
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 123,746
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 123,746

ADMINISTRATION - BUSINESS SERVICES
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	88,168	90,813	93,537	96,343	99,234
CONSULTANT COSTS	0	0	0	0	0
EQUIPMENT	0	0	0	0	0
SUPPLIES	21,413	22,056	22,717	23,399	24,101
TRAVEL	477	491	506	521	537
INPATIENTS CARE COSTS	0	0	0	0	0
OUTPATIENTS CARE COSTS	0	0	0	0	0
ALTERATIONS AND RENOVATIONS	0	0	0	0	0
OTHER EXPENSES	13,688	14,099	14,522	14,958	15,406
DIRECT CONSORTIUM/CONTRACTUAL COSTS					
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	123,746	127,459	131,282	135,221	139,278
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	123,746	127,459	131,282	135,221	139,278
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					656,986

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

PERSONNEL

Manager. Business Services – Excluded by Requester % Effort
Responsible for day-to-day activities of information processing, problem solving, accounting, requisitioning and related purchasing issues, internal billing, travel and relocation processing, mailroom and reception area, overseeing reports production; developing, implementing, and managing processes and procedures to maintain an efficient and effective business/grants management operation; implementing and maintaining policies and procedures in compliance with applicable regulations such as OMB Circulars A21 and A110, and OHSU policies.

Administrative Coordinator – Excluded by Requester % Effort
Provides miscellaneous administrative assistance to the Manager, Business Services which may include word processing, assisting with p-card processing, administrative services for the research building such as ordering office supplies, etc. for the common work room.

Financial Analyst – Excluded by Requester % Effort . Responsible for analyzing and processing Integrated Research Information System (IRIS) charges generated on a twice monthly basis into an Internal Billing System (IBS) and charged to research projects; error correction, as needed to IRIS and IBS (review of up to 30,000 entries on a monthly basis, lease, per diem, and surgery), . Responsible for a portfolio of scientists through the Collaborative Research Unit (CRU), including the review of proposed projects and budgets. Responsible for maintaining the fixed equipment Inventory to ensure compliance and accuracy.

Accounting Specialist- TBN (12 calendar months effort: 1.8 ORIP, 10.2 Program Income). Responsible for the processing of travel expense claims; providing back up for the Office Specialist; processing of requisitions and resolution of requisitions into the purchasing system, transferring requisitions electronically to an approved status; processing P-card applications and reconciliations; orders office supplies through the OHSU Eway contract, processing month end entries into IBS, as well as problem resolution for up to 20,000 entries for research support core charge backs (virology, etc.). Processing all invoices to accounts payable; reviewing purchase orders to ensure accurate reports; resolves invoice holds as needed.

Office Specialist – Excluded by Requester % Effort Responsible for day-to-day operation of a multi-line switchboard and reception area; greeting and registering visitors; receiving all incoming calls to main switchboard; monitoring of emergency telephone equipment located in the reception area; paging, using the central public address system; sorting and stamping outgoing mail; sorting and distributing all incoming mail; scheduling use of multipurpose conference rooms; Copy/FAX/Scan machine in the switchboard area; distribution of internal telephone billings; distribution of P- card statements; create purchasing requisitions , maintain a requisition-to-purchase order log which is used to advise users of the acceptance of purchase orders through the logistics.

Financial Analyst, Lead - Excluded by Requester % Effort Serves as lead financial analyst, in a group of four financial analysts responsible for all research grants from proposal through closeout. In addition to serving as lead analyst, this position has a portfolio of scientists assigned and is responsible for review of proposed projects and existing funded projects to insure compliance with rules and regulations of awarding agencies. Additionally, routine analysis of expenditures for appropriateness, projection of expenses to the end of the budget period., corrections and information and problem resolution assistance is a responsibility of this position; assists scientists in development of proposed budgets; assists in providing reports to management regarding active and/or pending grants; provides data analyses specific to management requests; reviews effort certification reports for accuracy prior to researchers validation. In addition, provides support for approximately 10 PIs.

Financial Analyst – Excluded by Requester % Effort With a portfolio of scientists, responsible for review of proposed projects and existing funded projects to ensure compliance with the rules and regulations of the awarding agency, which includes routine analysis of

expenditures for appropriateness, projection of expenses to the end of the budget period to ensure sufficient funds, requests corrections and provides information and problem resolution assistance for grants and contracts, as needed; assists scientists in development of proposed budgets; assists management by providing reports regarding active and/or pending grants; reviewing effort certification reports for accuracy prior to scientists validation. Provides support for 12 PIs and construction grants.

Financial Analyst – Excluded by Requester % Effort
With a portfolio of scientists, responsible for review of proposed projects and existing funded projects to ensure compliance with the rules and regulations of the awarding agency, which includes routine analysis of expenditures for appropriateness, projection of expenses to the end of the budget period to ensure sufficient funds, requests corrections and provides information and problem resolution assistance for grants and contracts, as needed; assists scientists in development of proposed budgets; assists management by providing reports regarding active and/or pending grants; reviewing effort certification reports for accuracy prior to scientists validation. Provides support for 12 PIs.

Student Worker – Excluded by Requester % Effort Student Worker – % Effort;Excluded by Requester
Duties are assigned to assist Business Service staff with mail distribution, opening mail, scanning pcard packets, assists with HR tasks as assigned by the ONPRC HR Manager. Duties include miscellaneous projects as assigned by Business Services Manager.

SUPPLIES

Office & Admin Supplies includes

- Filing supplies, pens, pencils, toner cartridges, staplers and staples, sticky notes, tape, writing tablets, etc. for 7 permanent employees.as well as systems and software such as Monarch, Bluebeam, Redbeam, Microsoft Office, etc. for 7 workstations. Duplicating and printer supplies for Business Services.
- Minor equipment includes desktop computers, calculators and printers for replacement as need to support the business services work stations.
- Dry Ice and liquid nitrogen is provided for the labs for support of research

TRAVEL

Travel funds are requested for:

- Financial Analysts for ongoing staff training, allowing continuing education and professional development opportunities, including attending NIH Regional Conferences.
- Business Services Manager to attend a national meeting, as appropriate.
- Mileage and parking for locally held seminars and trainings are also requested

OTHER EXPENSES

Funds are requested for:

- Hosting Groups and Guests for training and grant information sharing with non OHSU personnel
- Conference/Registration fees for conference
- Memberships in professional organizations such as Guide for Managing Grants and Contracts for Colleges and Universities
- Maintenance and repairs for minor office equipment
- Parking Pass for meetings at OHSU main campus
- Postage and express deliver, shipping – for US mail, FedEx, etc. as needed
- Printing/publishing – print/binding for reports
- Shipping costs associated with delivery of minor equipment
- Books, Periodicals, Subscriptions for current information on grants, accounting and business operations.
- Training registration for continuing education registration fees for Business Services Manager and Financial Analysts,

- Telecommunications -Long distance telephone charges, cell phones
- Miscellaneous Purchased Services -Temporary employment for special projects and/or to cover staffing needs during unplanned, extended leaves
- Miscellaneous – expenses that may occur throughout the year but were not t previously identified.

ADMINISTRATION: Business Services Income Table

Last Funded Year (53)

Source	Funding (direct costs)
P51 base grant support	$131,651.68
Program income derived from P51 base grant	804,453.52
Other Sources	45,536.83
Total	$981,642.03

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$123,746.32
Program income derived from P51 base grant	699,987.46
Other Sources	46,902.94
Total	$870,636.72

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

Business Services receives salary support and support for other expenditures from program income.

SPECIFIC AIMS

In support of the Associate Director for Administration, the Facilities and Property (F&P) Manager is responsible for the safe, efficient, sustainable and cost-effective management of ongoing operations, maintenance, upgrades, and security associated with the ONPRC campus buildings, grounds and infrastructure. On a daily basis, the F&P team works directly with the Division of Comparative Medicine (DCM) staff to assure that all animal housing and holding areas are in compliance with the applicable regulatory codes and standards for the proper care and use of laboratory animals. Additionally, the F&P staff provides support to all research laboratories and administrative areas to assure all of these spaces are kept clean, safe, and environmentally controlled, thereby allowing for a comfortable and productive work environment. With the relatively recent addition of a Sustainability Manager to the F&P, all operational approaches to maintaining the campus are being reviewed to incorporate the latest innovations in energy savings measures. The F&P Manager works closely with the University's Design and Construction department to plan, fund, design and construct major buildings on the campus in accordance with the rules for project management and financial accountability. As part of this responsibility, the F&P Manager also works directly with the City of Hillsboro and the city's regulatory agencies to assure that all construction and major renovations on the campus are in compliance with the ONPRC's Master Plan on file with the City of Hillsboro, and associated building codes and standards, including the proper care and treatment of storm water runoff, wetland maintenance, and protection of natural resources on the campus. As part of the campus security program, the F&P Manager works with the University's Public Safety Office and the local police and fire departments to assure that the campus is secure and safe at all times.

- Through these functions, the F&P Manager: Coordinates, with the F&P Operations Manager, to assure that all Heating, Ventilating and Air Conditioning (HVAC) equipment is operational and set to the proper temperature ranges at all times.
- Monitors and tracks necessary building repairs to assure the structural integrity and well-maintained appearance of all campus structures.
- Oversees the care and maintenance of all campus grounds, walkways, paths and roads to assure that the work performed to keep the property fully accessible and in good condition is being performed in a sustainable and cost effective manner.
- Ensures that future construction and tenant improvement projects and those working on those projects are fully versed in applicable standards, such as University, NIH, City (JHAs) and State standards.
- Coordinates with the ONPRC Business Office the University Central Financial Services and Design and Construction departments to assure proper funding exists for all new work on the campus
- Oversees campus security and programs for badging and key control access on campus.
- Coordinates with the Sustainability Manager to develop and implement best practices and energy management strategies for the campus

Specific Aim 1 – Ensure the continued safe, efficient, productive and sustainable operations at the ONPRC, complying will all local, state and federal regulations governing the administrative office spaces, research laboratories, and in particular, areas related to the care and welfare of the research animals.

Specific Aim 2 – Work cooperatively with the Administrative, Research, and DCM staffs to identify campus upgrades and renovations necessary to support the ongoing research goals of the University and ONPRC. This should include infrastructure upgrades to support anticipated changes in research methodology or desired animal housing refinements. Incorporate information into a comprehensive Campus Master Plan that will not only support the future needs of biomedical research but will also meet the requirements of the City of Hillsboro.

Specific Aim 3 – Working with the University's Design and Construction Department and Space Planning Group develop a clear understanding of the capital project planning process to assure timely identification and funding of future projects to support the ONPRC research and animal care mission.

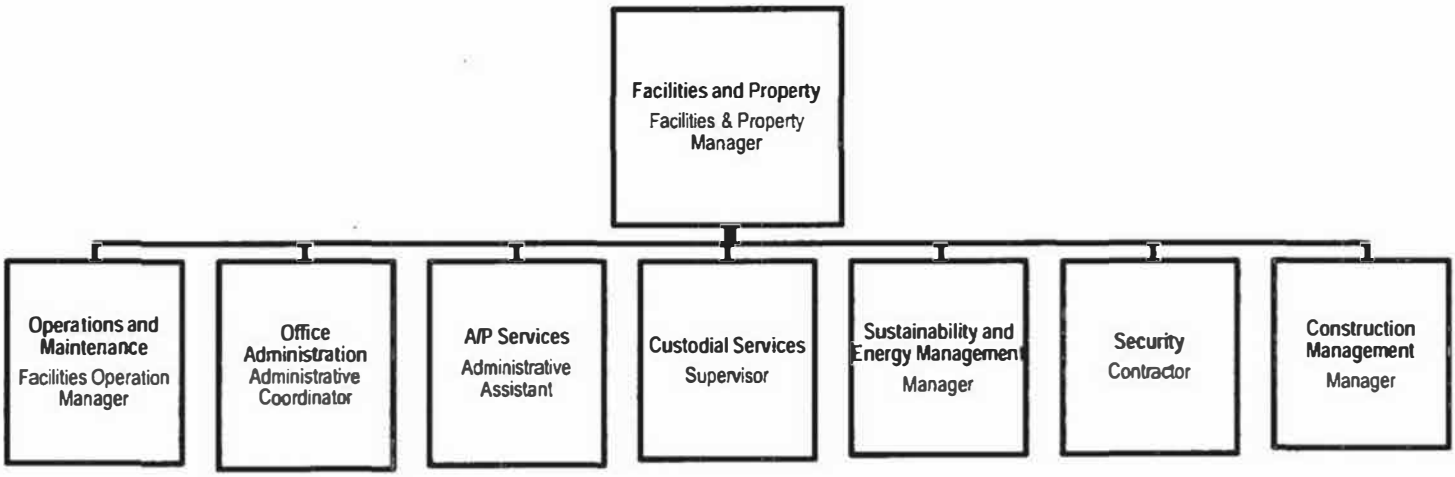
FACILITIES & PROPERTY - RESEARCH STRATEGY

SIGNIFICANCE

The Facilities & Property (F&P) Department operates and maintains the ONPRC campus infrastructure, buildings, and grounds to assure a safe, secure, productive and environmentally sound atmosphere for the conduct of critical biomedical research and the housing of valuable research animals. This mission includes construction and renovation of new space needed for state-of-the-art research and indoor and outdoor animal housing areas.

The F&P staff has extensive in-house expertise in the area of operations and maintenance, with some of the employees having over 25 years of experience with the ONPRC campus. The staff of Stationary Engineers are constantly re-evaluating and upgrading the HVAC systems to assure they are meeting the needs of the researchers and complying with the federal regulations for research animal care. In doing this they are also creating ways to conserve energy through various sustainability initiatives which have resulted in reduced costs of electricity, gas, hot water and chilled water.

The staff also has extensive experience in the management of new building construction and alteration renovation projects, with the larger projects being performed by outside contractors. The ONPRC has also developed beneficial relationships with numerous outside firms that can perform maintenance and construction activities in support of the ONPRC staff and campus needs. This includes laboratory renovations and alterations as new grants are obtained for specific research activities or when new research staff is recruited. All of the animal housing areas are also maintained by the F&P staff through direct on-site contact with the researchers and animal care staff.



PARTNERSHIPS

In certain areas of maintenance, the Facilities staff has determined that the use of our own personnel is not cost effective, so certain activities have been subcontracted out to firms with the appropriate expertise, such as private security contractors, linen laundering, grounds maintenance, roof repairs/replacements, chiller maintenance, electrical installation and repairs, design services and construction management firms. These companies are used whenever specialized expertise is needed or when it is more cost effective and does not require us to invest in large pieces of specialized equipment.

As a result of the merger with OHSU in 1998, Facilities has several changes in our practices in planning and execution of capital construction projects, security procedures and day-to-day facilities management functions.

Facility Security

OHSU has also assisted us in the planning and development of major projects as evidenced by their collaboration with the ONPRC on the Research Building Seismic Renovation project, the Cooley Building Freezer Farm project, the PENS (Primate Enclosures in a Natural Setting) project, the Colony Annex Renovation and the ASB I Expansion project.

In addition to the OHSU partnerships mentioned above, the F&P Department works closely with other entities outside of OHSU as defined in the Primary External Contacts portion of the following table.

Manager	Primary Report	Primary OHSU Areas worked with	Primary External Contacts worked with
Facilities & Property Manager	Associate Director for Administration	- Design and Construction - Facilities - Public Safety - Contracting - ITG, Network Engineering, Telecom - Risk Management - Facilities & Real Estate	- City of Hillsboro Planning Dept - City of Hillsboro Engineering Dept. - Clean Water Services - Portland General Electric - Northwest Natural Gas - Tualatin Valley Water District - NIH - Architectural Design Firms - Construction Management Firms
Facilities Operations Manager	Facilities & Property Manager	- Facilities Operations - Heating Plant - Chiller Plant - Controls Group - Standby Generator Group	- State Boiler Inspector - State Elevator Inspector - City of Hillsboro Electrical Inspectors - City of Hillsboro Building Inspectors - DEQ/EPA
Office Administration	Facilities & Property Manager	- Facilities - Public Safety - Central Financial Services - Logistics - IT/Wireless Services - Planning and Real Estate	- Oregon DEQ - Oregon Building Codes - Oregon Dept of Consumer & Business Services
A/P Services	Facilities & Property Manager	- A/P - Parking and Transportation - Locksmith - Public Safety	- Electrical Services for maintenance and upgrades to such programs as Facility Commander for card readers and security cameras
Sustainability Manager	Facilities & Property Manager	- Sustainability Manager - Custodial & Recycling Services	- Energy Trust of Oregon - Aloha Garbage - City of Hillsboro–Recycle at Work Program - Oregon Metro - Garment Recovery Systems - EPA Energy Star Program & Building Challenge - Labs21

SERVICES WE PROVIDE, REGULATIONS WITH WHICH WE ARE IN COMPLIANCE

Working with these teams and relationships the F&P Department provides the following services to the ONPRC campus and its staff:

- Day-to-day operations and maintenance of all mechanical, electrical, plumbing and HVAC equipment on the campus, all in conformance with the applicable codes and standards such as ASHRAE, NEC, NFPA and OHSA

- Compliance with all ADA access regulations, fire codes, and general safety requirements for the campus
- Control and coordination of all personal and vehicular access to the campus, including the maintenance of an electronic keycard access program and the key control program for all research laboratories and select agent areas
- The monitoring of all temperature control, fire, burglar and equipment alarms and for developing the proper response and corrective action plan
- Operation of all boilers, pressure vessels and heating equipment in conformance with the Oregon State Boiler Code
- Construction and renovation of all new facilities in conformance with the local building codes, including the most recent Unified Building Code and those associated with the City of Hillsboro, Washington County and other Jurisdictions Having Authority (JHA's) over work performed on the ONPRC campus
- Construction, operation and maintenance of all equipment and facilities associated with animal housing and Vivarium space in conformance with the NIH Design Requirements Manual, the Guide for the Care and Use of Laboratory Animals, the USDA rules and regulations for animal research facilities, and the CDC BMBL guide for ABSL 2 and 3 laboratories and select agent areas
- The performance of corrective actions related to inspections by NIH, AAALAC, USDA and the OHSU IACUC committee
- Maintenance of agreements with companies providing water, sewer, power, garbage and gas services to the campus and the upkeep of all internal utility systems
- Maintenance of all campus natural resources including timber management in accordance with State of Oregon Forestry regulations, stream and water quality management in accordance with the requirements of the Army Corps of Engineers, Oregon Fish & Wildlife, and the local JHA, and Clean Water Services, including the management of several designated wetland areas on the ONPRC campus
- Additionally, the F&P Department actively participates in many committees and oversight groups who monitor and review the functions performed by groups outside of Facilities, such as:
  - The ABSL-3 Oversight Committee who reviews and approves planned experiments, projects and uses of the CDC approved Select Agent areas
  - The AAALAC survey pre-review program which inspects animal holding areas on a regular basis prior to the official inspection.
  - The ONPRC Steering Committee who reviews and directs the Capital Construction process for the Center
  - The ONPRC Policy Group who is responsible for approving all policies for the Center
  - The IACUC review team who inspects and provides direction on ongoing animal housing and husbandry issues, as well as approve all research projects utilizing NHP's.

INNOVATION

In order for the F&P Department to continue with development of the campus and its infrastructure we have had to reinforce and, in some cases, create new professional relationships with the internal and external organizations that directly influence how work is approved, funded, permitted, performed and completed in accordance with our long range plans. This has included learning the University's electronic tracking system (eBuilder) for defining, funding, documenting and tracking projects from the conceptual design and planning phase through to project completion. Additionally, we will be working very closely with the University Planning and Design and Construction teams to develop the next Campus Master Plan which is due to be submitted to the City of Hillsboro in the 2015-2016 time frame.

Utilizing this same collaborative approach we are redefining our relationship with the City of Hillsboro and their Planning, Engineering and Inspection departments to assure that our plans are in conformance with the current Master Plan and all applicable code (City and State) requirements. The development of the new Master Plan will allow us to strengthen our relationship with the City while at the same time solidifying our relationship with the University as described above.

To better respond to our customers' needs and requests we are also working with the ONPRC Business Services office and internal IS Department to develop a more comprehensive electronic tool that will allow us to receive, record, track, and close out work orders in a more timely and documented fashion. The ONPRC IS Department is working with our Administrative staff to model the work tracking system used in the Facilities Department of the University, SharePoint. One of our largest areas of work is the response to the day-to-day requests from the DCM Animal Care Staff for repairs to the support systems for the animals, i.e. caging, water supply and drainage, structural problems and environmental controls. Using the new SharePoint system we will be able to track what requests come in, their progress, and closeout, which in turn will be available to DCM on a real-time basis so that they can not only track our progress but also eliminate the duplication of requests. Working closely with DCM we have also developed a priority system which allows DCM to indicate how serious the problem is, which in turn allows F&P to respond accordingly. This priority list includes immediate response for personnel or animal life safety, one hour response, one day response, one week response and a last category for scheduling long term purchases, projects and/or repairs. This information will also be used to track the necessary Facilities staffing requirements to support DCM and identification of problems that may require a more comprehensive fix rather than an immediate repair that reappears time after time.

APPROACH

The F&P department performs the following functions at the ONPRC:

- Facilities & Property management, in collaboration with OHSU Public Safety and local law enforcement agencies, is responsible for security services on campus and for implementing emergency response plans

Facility Security

- Facility Security: Specific Animal Location

- The Custodial Department performs a variety of custodial services to the interiors of buildings on a daily basis, final cleanup at the end of large remodel projects, and performs scheduled preventive maintenance activities related to floor coatings and sealing. This department also assists the Center staff during office relocations and/or moving of furniture and equipment, meetings setup, delivery of scrubs and gowns, and operation of the Center shuttle.

- F&P also manages all maintenance and construction requests in close consultation with the Design & Construction team at OHUS. These requests are classified as emergency requests (evaluation and repair of temperature problems, unplugging of floor drains, etc.), routine maintenance requests (repair of light fixtures, drinking fountains, etc.); preventive maintenance (replacement of air filters, cleaning of gutters, etc.); major maintenance (resurfacing of roads, exterior and interior painting of buildings, etc.); minor improvements (projects funded by other departments, such as office remodels); and construction management services which includes all construction and remodel and/or major maintenance projects performed by outside contractors. This department has been involved in the preliminary design, as well as construction document preparation, negotiation of contracts with the architectural and construction firms, and has supervised as an owner's representative various maintenance and construction projects. Based on the workload and/or the nature of work involved, some functions of the maintenance department are contracted out. All outsourced/contracted projects are performed under the supervision of F&P staff. The maintenance crew is often involved in these projects by providing technical support, inspections, quality control and coordination of utility shutdowns.

- In 2011 the Facilities Department made two major changes in the way business was performed. At the beginning of the year campus custodial activities that were subcontracted out in prior years were brought in-house with the hiring of a Custodial Supervisor and several new janitorial staff members. By bringing this function in-house and recruiting direct employees, we have been able to improve service and provide new and expanded services which better support the research and administrative staff at a reduced cost.

- In an even more significant move, the Facilities Department adopted a more sustainable approach to facilities operation and maintenance activities and recruited a full time Sustainability Manager to identify these opportunities. The position is being funded by reduced energy costs and rebates from the Energy Trust of Oregon (ETO) based on project energy savings. All existing maintenance programs are now being evaluated for potential energy savings and an advanced project for monitoring ongoing electricity, gas and water usage is being implemented. Studies are also being performed to identify cost savings through recycling programs, energy reduction strategies and the potential use of composting for the generation of electrical energy. Many of the current buildings and their associated HVAC systems/components are over fifty years old and functioning with outdated and energy intense components which are being evaluated for progressive upgrade over the coming years. Working directly with the ETO, the Sustainability Manager in conjunction with the F&P HVAC and Control Technicians, has engaged contractors to perform building energy audits which have identified several building tune-up programs that can substantially reduce the overall energy consumption of the building through building set back programs or adjustment of the building HVAC system operational parameters.

Progress Report

reviewers' comments

reviewers' comments

SIGNIFICANT ACCOMPLISHMENTS

Major Building Upgrades and Renovations - 2009

- In late 2009, construction work on the Specific Animal Location **Building** was completed and initial testing, certification and operational shake down of the ABSL-3 suites was begun. This building is approximately Specific Animal total, and consists of four conventional animal holding rooms, a cage washer, diet kitchen, freezer, cold storage, loading/receiving dock, and two ABSL-3 laboratory suites for select agent studies, each with two animal holding rooms, necropsy suites, autoclave sterilizers, bio-safety cabinets, changing/shower rooms for the staff, and an effluent decontamination floor drain system. This project was funded by Grants 1-C06-RR020178-01 and 3-P51-RR00163-48S2, and institutional funding from both the ONPRC and OHSU. Testing and certification of the air handling system for the ABSL-3 suites was completed in late 2009 and was recertified in December of 2010, along with the autoclave sterilizers and effluent decontamination system. Successful testing of the room decontamination system (ClorDiSys) was also completed this year, and all of the standard operating procedures have been reviewed and approved by the Certification Agent. All of this data was submitted to the CDC in preparation for certifying these spaces in March 2011 and was subsequently approved for use with select agents.
- As an administrative supplement to the ONPRC Core Grant (P51 RR000163), authorization and funding was obtained to design and build an extension to the Specific Animal Location

Area. This project consists of a building addition of approximately [Specific Animal] to accommodate two minor procedure rooms, two animal holding rooms and the associated support spaces in an interstitial attic above the new rooms. The construction budget initially established for this project was $1.8M; however, through the use of the existing mechanical, electrical, and HVAC systems, and the use of a very competitive bidding process, the estimated price was reduced to $1.5M which included fixed equipment cost. Schematic design drawings were completed in January 2009, and detailed construction drawings were ready for subcontractor bidding in May. Actual construction started in July and was completed the end of April 2010.

- In September 2010 OHSU received funding to upgrade the **MRI** magnet on the ONPRC campus. As part of that project, the ONPRC F&P department was asked to install a new 175 amp power supply service to the magnet, and add a new access door to the building for moving the upgraded magnet parts into the area. Since the MRI would be shut down for several months, it was decided to initiate several other building improvements and upgrades including a major revision to the heat pump system for cooling the magnet, the addition of floor drains in the main console room, and the installation of an anesthesia vent system. All of this work was completed in November 2010.
- In July 2009 the ONPRC took control of a major research building constructed on campus by OHSU in 2000, known as the [Specific Animal Location] This [Specific Animal] sq ft building housed ONPRC animal research facilities and an ABSL-3 suite in the basement, with the remainder of the building being used by the OHSU divisions of Neurological Science Institute (NSI) and Vaccine and Gene Therapy (VGTI). In July 2009 NSI was largely absorbed into other existing divisions of OHSU and moved to the Marquam Hill campus, while VGTI became a major independent part of the ONPRC. Throughout the remainder of 2009 the old NSI side of the building was re-fitted to absorb the Reproductive Sciences Division of ONPRC as those personnel were moved out of the existing Research Building.
- In October 2009 the ONPRC was informed that a previously submitted grant request (Grant No. C06 RR022120-01, **PENS (Primate Enclosures in a Natural Setting)** was being funded as one of the American Resource and Recovery Act (ARRA) projects. This facility consists of a [Specific Animal Location] central services building with mechanical and electrical infrastructure, food storage, animal management housing, and a minor procedure room. The service building is designed and built to support five [Specific Animal] sqft independent "crib buildings" consisting of 12 new "corn crib" breeding pens with indoor and outdoor runs capable of housing 12-15 NHPs each. Design of the PENS project continued throughout the remainder of 2009 and 2010. Competitive bidding of the project construction is expected to be done in 2011 with actual construction scheduled for 2012.
- In 2008 a Federal Grant (RR024793-01) was issued for renovation of Run 5 at the Colony Building group housing area. After careful consideration of the animal housing needs at the ONPRC, it was decided that a better use of these funds would be to renovate and upgrade space in the [Specific Animal Location] **Building** which had previously been used for rodent housing. In 2009 NCRR approved this change and along with funding from a supplement to the ONPRC Core Grant (3P51RR00163-51S4), $958,362 was made available to design and build new research and animal holding space for the NHP's. The existing [Specific Animal Location] Building is [Specific Animal Location] of which [Specific Animal Location] would be renovated with funding from these two grants. Renovations would provide NHP animal holding facilities with procedure and group housing observation space, a kitchen, staff work room and supply and equipment storage. This project will update the HVAC system and provide for the renovation of currently unneeded rodent space into specialized primate group housing space for several highly anticipated studies of obesity.

Improvements and Modernizations - 2009

- Purchased and installed individual temperature and humidity monitoring equipment for use in various animal holding areas
- Installed new door handles and associated locking hardware on exterior doors to the north and south exterior doors of the Colony Building
- Constructed a new outdoor storage building for PPE at the Sheltered Group Housing area
- Constructed new secondary containment man-ways on each of the 10 com crib cages at the [Specific Animal] Building
- Installed new misters in the outdoor corrals for animal cooling during the summer months

- Converted the existing Higgins building from research and rodent space to a locker and storage room for the DCM animal care staff
- Extended secondary containment fencing at the Kroc Building to include the entrance to the cage washing area
- Installed new step off pads at the entrances to each of the Sheltered Group Housing units
- Installed several new 208v outlets in numerous buildings for new minus 80 freezers
- Installed suspended antennas for a new research project in the Animal Services Building
- Conducted a solar energy study of the campus to locate potential sites and uses. Incorporated this study in the conceptual plans for the new PENS project mentioned above
- Cleaned up and modified the existing VGTI parking lot to add an additional 24 spaces
- Renovated five rooms in the Cooley Building to create a new Electrophysiology lab and a dark room
- Replaced the roof and installed a new heating and cooling system on the Physical Plant
- Replaced the existing siding and painted the Cooley Building

Major Building Upgrades and Renovations – 2010

- Continued the design effort on the **PENS project** as well as Request for Qualifications (RFQ) and request for Proposal (RFP) documentation packages for the competitive bidding of the General Contactor responsibilities in accordance with the AARA funding requirements. The General Contractor is expected to be selected in 2011.
- In 2010 the ONPRC elected to seismically upgrade the **Administration Building**. This building is considered a historic design and houses the ONPRC Director's Office, the Business Services Division, and the Library, along with the Cafeteria and the primary Network and ITG Services Group for the campus. The upgrade assured a safer working environment for the staff and allows for continued use of the building for many more years, thus eliminating the need to construct new and obviously more expensive office space. The campus cafeteria and ITG space remained operational throughout this project with only very short periods of downtime. All of the upgrades were completed in May 2010 and the building was reoccupied in June.
- The **Sheltered Group Housing** area of the campus has Specific Animal Location indoor/outdoor group housing pens that require daily high pressure/hot water cleaning. Because of reduced water pressure currently being supplied to the campus by the local public water utility, increases in the number of animal husbandry staff, and the regulatory requirements for daily cleaning of these areas, the current pumping system for this cleaning water was inadequate. In late 2009 the ONPRC entered into an agreement with one of our local engineering consultants to evaluate the existing pumping system and develop a more powerful and dependable system which would consistently deliver the needed pressurized water. The new design consisted of two independent pumping systems with one extra pump for backup in case of a system failure. The installation and testing of this system was completed in July 2010.
- Facility Security

Improvements and Modernizations – 2010

- Rebuilt the ESPF group housing cage drains and ceilings in the Specific Animal Location to improve sanitary conditions and cleaning capabilities.
- Replaced doors and frames with new stainless steel framed FRP doors at Facility Security
- Added a new observation tower and a new concrete feed pen pad to outdoor Specific Animal Location
- Upgraded the Facility Security generator to correct a new electrical code requirement and allow for tie-in of the new PENS project power supply and emergency diesel generator system.
- Constructed a new section of asphalt road to the corrals replacing an aging gravel roadway.

- Commissioned an independent engineering study of the Research Building to determine the feasibility and costs associated with "re-lifing" the building through a process of seismic upgrades, new ventilation systems, and a complete rebuild of the existing laboratory space. The local engineering firm of SRG Partnership provided this study at no cost to the ONPRC.
- Completed installation of a new hot water boiler in the VGTI Building.
- Installed a new 650 ton cooling tower at the Physical Plant.
- Replaced the siding and repainted the Montagna Auditorium.
- Reinforced the ceiling panels at the Sheltered Housing quads.
- Improved the west campus emergency service entrance and exit including resurfacing the bridge over Bronson Creek and Facility Security
- Rerouted the VGTI basement ground/storm water drain line system to feed in to the campus collection pond rather than emptying into unused forest areas.
- Installation of drains and electrical outlets in Specific Animal Location Excluded by Requester Lab) to accommodate a new lab and an animal observation room
- Renovated six rooms in the Research Building for use as new lab and research space for the Exclu ded lab.
- Renovation of NSI rooms Facility Security which had originally been used as darkrooms for film processing. Work included replacement of doors, electrical retrofit and repainting.

Major Building Upgrades and Renovations – 2011

- Over recent years the Facilities and DCM departments have been investigating various methods of sealing floors in the outdoor animal housing areas. The industry standard for these types of areas has been epoxy coatings, which will break down when exposed to high pressure hot water wash-downs and UV rays on a day after day basis. These breakdowns of the floor coating requires relocation of the animals while the epoxy is reapplied, which is both time consuming and costly. This year the F&P department located a source for grinding and polishing of these surfaces so that a simple reapplication of a sealing compound is the only thing necessary to keep these areas properly maintained. This has resulted in reduced maintenance costs and less stress on the animals as they do not need to be totally relocated and can simply be moved between segmented areas in the existing shelters units. This process has been discussed with the Facilities department at the Oregon Zoo for potential use in their NHP animal holding areas.
- Renovation of 14 spaces in the Facility Security to accommodate offices and labs of the Excluded by Requester lab. These repairs included patching and painting of wall, stripping and waxing of floors, re-carpeting or replacement of vinyl flooring in some rooms, replacement or resurfacing of countertops, new lighting, updating of data cables and ports, etc.
- Renovations of six offices and labs in the Facility Security Excluded by Requester Excluded by Requester which included repairs to ceilings, patching and repainting of walls, updating of voice and data ports, new cabinetry and carpeting, etc.
- Facility Security

Improvements and Modernizations – 2011

- Fabrication and installation of a new tunnel from Specific Animal Location one of the Sheltered Group Housing units to facilitate bi-yearly processing of animals in that corral. This project included the tunnel, concrete pads, stairs and landing with new transfer doors.
- Renovation to the Exclude d ab and office which included replacement of the carpet in office, stripping and waxing of the lab floors, patching and repainting of walls, replacement of cabinetry, reinstallation of two bio-safety cabinets and installation of ductwork, and installation of a new wall to create a separate tissue culture lab within the larger lab.

- Renovation of a lab in the [Facility Security] to accommodate the Roberts lab including removal of a fume hood, installation of a new exhaust fan , installation of ductwork for hood and associated electrical work, updating of electrical outlets for freezers, new telecom cabling, patching of walls and repainting, changes to lighting fixtures, etc.
- Renovation of two labs and offices spaces in the old [Facility Security] to accommodate the [Excluded by Requester] lab, another part of the Reproductive Sciences Unit that moved over from the Research Building
- Construction of a new feed pen at the west end of [Specific Animal] which consisted of a concrete foundation with floor drains, three new animal access doors through the existing corral wall, one man-door through the corral wall, remotely operated access control slides and a welded metal enclosure with a roof and lights installed on the outside of the corral.
- Fabrication and installation of a small accessory building to cover an existing well and pump used for emergency water supply for the ONPRC campus. Work included the pump house, concrete slab and miscellaneous electrical work including plugs and lighting.

Major Building Upgrades and Renovations – 2012

- Work commenced on the **Research Building Seismic Renovation** in early 2012. This was the last major renovation specified by the seismic evaluation funded through the P51 grant in the previous five year funding cycle. Total cost of this seismic and laboratory upgrade phase of construction was $2.3 million including a schematic design package which allowed for the planning of all future remodeling phases in such a way that the completed remodeling efforts will result in a state-of-the-art laboratory facility capable of significant flexibility and improved energy efficiencies. Included in these renovations was the creation of a new research laboratory for the [Excluded by] lab and included a new office and two research labs with new benches, three new bio-safety cabinets and a new fume hood. Additionally the DCM administrative staff was relocated to this new area from Research Annex and included new office space and a state-of-the-art media/conference room
- As part of the Research Building seismic renovation, a significant number of freezers containing valuable research samples were moved from this building to allow for construction of the seismic bracing and future renovation of the laboratories. Because of this need and the large number of freezers already being stored in various locations around the campus, the F&P department elected to reclaim unused space in the basement of Cooley Building through the creation of the **Cooley Building Freezer Farm** where a large number of freezers could be grouped together and properly monitored. The cost for this project was $130K and work was completed in June 2012.
- The [Specific Animal Location] **Containment Expansion Part 2** design is currently underway to add seven animal rooms and a food dispensing kitchen to our ASB1 containment area, expanding capacity by 96 animals for AIDS related studies. The project is being funded by Grant C06RR032703-1 and in currently in the Design Development phase and is expected to start construction by December 2012 with a substantial completion date of July 2013. Approximate cost: $1.5 million.
- Oregon Health & Science University has obtained approval from NIH to locate a back-up **Data Center** on the ONPRC campus. This data center would provide redundancy and back up for the entire University data collection and distribution system. Construction on the Center property will provide an opportunity for needed infrastructure improvements on the ONPRC campus such as a secondary source for water supply and a new primary electrical feed from the utility service off campus. Both of these improvements will allow the Center to create redundant sources of water and electricity for emergency situations. The proposed project is in the conceptual design stage and will be submitted to the City of Hillsboro for Design Development Review sometime in November 2012. Final costs for the project have not yet been established.
- NIH gave final approval for construction of the **PENS project** and groundbreaking for the 12 initial corn crib type housing units along with a service building began in June 2012. This facility will house approximately 180 animals in 12 breeding groups and be supported through a new service building. Approximate total cost for this project is $4.8 million. As mentioned above the total build out plan for this project provides for five crib buildings which will be completed as funding is made available.

Improvements and Modernizations – 2012

- Replaced the outside sump pump at the VGTI Building
- Built a water quality swale for filtering runoff water from the campus pond
- Replaced 42 control valves in ASB I
- Installed a new mesh network in the Sheltered Group Housing area to allow the use of wireless computers for the DCM animal care staff
- Upgraded network cabling to Cat6 in the [Excluded] Lab in the Research Building
- Upgraded [Specific Animal] to include wall repairs, additional flashing to close lower wall gap, added concrete pads, added rock around walls and built new play structures for the animals.
- [Facility Security]
- Created a new lab for the ART Core in VGTI room 2114

Future Plans

Specific Aim 1 – Ensure the continued safe, efficient, productive and sustainable operations at the ONPRC, complying will all local, state and federal regulations governing the administrative office spaces, research laboratories, and in particular, areas related to the care and welfare of the research animals. The F&P Department has established several processes and programs to assure that buildings, systems and components are monitored and properly maintained in accordance with applicable codes and regulations. A computerized maintenance management system has been established to issue and track preventative maintenance (PM) requests allowing for the pre-assignment of all PM tasks to the technicians on a bi-weekly basis. These tasks are designed to assure continued operation of the equipment in a safe and efficient manner, including recommendations on replacement of the equipment when that becomes necessary. Additionally, there is a Building Automation System (BAS), the Siemens Apogee system, connected to all critical equipment in the Facility which is used for monitoring of the systems on a 24x7 basis. This system automatically alarms and notifies the on-call Facilities Manager and the applicable technician(s) whenever a piece of equipment, or an entire system, begins to function outside of its pre-established parameters. As an example of this, animal room temperatures are monitored at all times to assure that their environmental conditions (temperature, air changes per hour, etc.) are in accordance with the Guide for the Care and Use of Laboratory Animals in Research and the associated USDA requirements. When any one of several parameters is found to be out of design specification a technician is immediately notified and the problem is corrected. This same process is set up for laboratory and administrative space as well.

With the relatively recent addition of a Sustainability Manager to the F&P staff (2010) the department has been able to evaluate how and when systems are used in an effort to increase efficiency and reduce overall energy use. As part of this the Sustainability Manager has been able to establish numerous working relationships with agencies such as the Energy Trust of Oregon (ETO) to evaluate building functions and determine how to operate them more effectively and efficiently. Working with the ETO the department has performed several Building Tune-up exercises which have identified ways to lower our energy consumption through operational temperature, air flow and lighting set back times.

This process of monitoring and maintaining the equipment and systems at the ONPRC will be an ongoing effort to refine the efficiencies and operating parameters of our existing building and campus infrastructure to assure cutting edge technology and sustainable measures are implemented whenever and wherever applicable. The attached Improvements and Modernization chart shows several projects related to infrastructure upgrades planned as part of our effort to continuously improve operations at the Center

Specific Aim 2 - Work cooperatively with the Administrative, Research, and DCM staffs to identify campus upgrades and renovations necessary to support the ongoing research goals of the University. This should include infrastructure upgrades to support anticipated changes in research methodology or desired animal housing refinements. Incorporate this information into a comprehensive Campus Master Plan that will not only support the future needs of biomedical research but will also meet the requirements of the City of Hillsboro.

The existing Campus Master Plan will expire in 2018 and plans are currently underway to begin a revision of this plan to take the Center into the year 2038 (next 20 years). This new plan is scheduled to be available for review by the City of Hillsboro in 2017. As part of the new plan the Center will be required to identify how the campus will look over the next twenty years, including planned growth in the way of new buildings, major renovations, locations and/or relocations of animal housing, and the plans for continued use of the corrals and indoor/outdoor housing for animals. All of this will be predicated on the plans for ongoing and future types of research, and the types of animal housing needed to support this research, including breeding quarters, investigative and project space, and the necessary upgrades to the campus infrastructure to support these needs. The F&P staff has been working with numerous architects and general contractors over the past five years to assure that any campus infrastructure upgrades or improvements driven by the addition of new builds retains the ability to continue expansion into the future. This approach allows for the identification of additional underground components such as cut-off valves and space on new switchgear to retain the ability to expand again as new projects are developed. As shown in the Improvements and Modernization chart mentioned above, the F&P Department has already identified some major components of the infrastructure that will require replacement equipment and/or upgrades to the systems to support the future growth of the campus. Working with the Research Staff and DCM to create a comprehensive Master Plan revision will all the refinement of this list and identification of other necessary upgrades.

Throughout the previous Core Grant period the F&P Department, and our associated contacts at the City of Hillsboro Planning and Engineering Departments, have (and continue to) develop a clearer understanding of the existing Campus Master Plan requirements established through the City approval process back in 1998. As part of that understanding the subjects of project definition, required plan development reviews, engineering review requirements, permitting cost definitions, Federal Government funding cycles, and the process for assuring that all City and State reviews are completed and documented prior to starting development projects have been clarified and refined by both the City and the ONPRC.

Specific Aim 3 – Working with the University's Design & Construction Department and Space Planning Group develop a clear understanding of the capital project planning process to assure timely identification and funding of future projects in support the ONPRC research and animal care mission. With the University becoming more involved with the capital construction needs of the ONPRC it has become necessary for the F&P Department to more thoroughly understand how projects of this nature are initially defined, how the associated funding is requested and accounted for in the overall University budget, and how these projects are approved and tracked through to completion with the University's Design and Construction Department. The differences between the way NIH provides funding to the ONPRC and the way that the University defines and assigns budget dollars to capital projects is very different and the F&P Department, in conjunction with the ONPRC Business Office, will need to more thoroughly understand these processes, and identify needed projects and infrastructure improvements, not necessarily out of the NIH sequence, but in a more timely and upfront way so that the capital budgets can be set at the University level thereby assuring that these activities can be performed when scheduled and needed without going back through the internal approval process with the University.

Over the past year (2012) the Business Office and the F&P Department have established an improved working relationship with the University's Design & Construction Department and their Space Planning Committee through monthly OHSU/ONPRC Steering Committee meetings with senior management from both organizations. These meetings were highly successful in completing the Research Building Seismic Upgrade project earlier this year (2012) as this project involved funding from the University and the ONPRC to complete the seismic upgrade as well as new laboratory space and a relocation of the DCM senior management team. All of this happened within budget and on schedule, and resulted in not only a significant enhancement to one of the older buildings on campus, but also in eliminating the last structural seismic integrity issue on the campus. Additionally, and in some ways more important to future project activities on the campus, these discussions and decisions made by the Steering Committee proved that the two organizations could work together as a cohesive team to complete a major project and remain in compliance with the University's funding and design program. This approach will be used on all future major capital projects and will become more refined and streamlined over the coming years.

ADMINISTRATION - FACILITIES
DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY

FROM 5/1/14 THROUGH 4/30/15 GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*

Use Cal, Acad, or Summer to Enter Months Devoted to Project

Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Excluded by Requester	Mgr. Facilities & Property	% Effort			Institutional Base Salary	13,131	3,283	16,414
	Custodial Support Spvr					6,360	2,226	8,586
	Admin Coordinator					6,622	2,318	8,940
	Facilities Building Coord					8,623	2,673	11,295
	Custodian					3,416	1,366	4,782
	Facilities Tech 3					6,860	2,127	8,987
	Biomed Equip Tech 2					8,194	2,540	10,734
	Laborer 1					3,400	1,360	4,760
	Facilities Tech 3					7,064	2,190	9,254
	Laborer 1					3,133	1,410	4,543
	Asst Facilities Technician					3,723	1,489	5,212
	Asst Facilities Technician					3,723	1,489	5,212
	Custodian					3,266	1,470	4,735
	Facilities Tech 3					6,860	2,127	8,987
	Landscape/Grds Keeper					6,657	2,330	8,986
	Sustainability Mgr					7,250	2,248	9,498
	Stationary Engineer 1					7,173	2,224	9,396
	Admin Asst					5,157	1,805	6,961
	HVAC Engineer 1					7,966	2,470	10,436
	Plumber					8,493	2,633	11,126
	Custodian					5,129	2,052	7,181
	Mgr. Facilities Operations					10,017	3,105	13,122
	Asst Facilities Technician					4,720	1,652	6,372
	Stationary Eng 1					7,173	2,224	9,396
To Be Named	Custodian	1.44				3,127	1,407	4,535
To Be Named	Asst FacilitiesTech	1.44				3,723	1,489	5,212
Temp/Summer help	0	1.44				2,622	262	2,884
Overtime	0	1.44				5,477	1,917	7,395
On-call pay	0	1.44				4,930	1,725	6,655
	→							
	SUBTOTALS					173,988	57,609	231,597

CONSULTANT COSTS		
Engineering Services	795	795
EQUIPMENT *(Itemize)*		
None Requested	0	0
SUPPLIES *(Itemize by category)*		
Office & Admin Supplies	795	
Cleaning Supplies	2,387	
Physical Plant Supplies	15,105	
Gasoline	5,400	
Security Operation Supplies	80	
Landscaping Supplies	795	
Operating Supplies	5,565	
Minor Office Equipment	239	
		30,365
TRAVEL		
Domestic	1,125	1,125
INPATIENT CARE COSTS		0
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		
None Requested		0

ADMINISTRATION - FACILITIES DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55
OTHER EXPENSES *(Itemize by category)*			
Expense Credit Labor			(6,750)
Material for Re-issue			(4,770)
Security Service			20,615
Buildings Maint & Repair			41,437
Electricity			173,325
Natural gas			92,411
Water/Sewer			28,103
Garbage			10,462
Conference/Registration Fee			675
Equipment Maint & Repair			35,781
Taxes & Licenses/Permits			300
Ground Contract Maintenance			6,098
Contract Maintenance(Bldgs/Equip)			1,590
Laundry Service			6,360
Maintenance/Repairs-Security			3,000
Maintenance/Repairs - Vehicles			1,725
Telecommunications			2,417
Maintenance/Repairs - Grounds & Roads			3,366
Hazardous Waste Disposal			3,737
Membership in Profesnl Org			86
Misc Maintenance & Repair			7,950
Equipment Maint Contract			4,120
Maintenance - Equipment			11,925
Maintenance - Building			1,590
Syst Development - Tualatin Valley Water District			7,258
Shipping Charges			318
Testing & Certification			176
			453,305

CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 717,187
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 717,187

ADMINISTRATION - FACILITIES
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	231,597	238,545	245,701	253,072	260,665
CONSULTANT COSTS	795	819	843	869	895
EQUIPMENT	0	0	0	0	0
SUPPLIES	30,365	31,276	32,214	33,180	34,176
TRAVEL	1,125	1,159	1,194	1,229	1,266
INPATIENTS CARE COSTS	0	0	0	0	0
OUTPATIENTS CARE COSTS	0	0	0	0	0
ALTERATIONS AND RENOVATIONS	0	0	0	0	0
OTHER EXPENSES	453,305	466,904	480,911	495,339	510,199
DIRECT CONSORTIUM/CONTRACTUAL COSTS					
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	717,187	738,703	760,864	783,689	807,200
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	717,187	738,703	760,864	783,689	807,200
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					3,807,643

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

JUSTIFICATION

PERSONNEL

Manager, Facilities & Property - Excluded by Requester % Effort
Responsible for management of facility budgets, programs and personnel; provides construction management services in the preparation of schematic design, design development and construction documents on animal housing and research space renovations and construction projects, in order to comply with the requirements of NIH guidelines and local governing jurisdictions; oversees all aspects of day-to-day maintenance activities; acts as liaison between Public Information and Public Safety, Hillsboro Police and Fire Department and other enforcement agencies to monitor the activities of animal right groups and to take proper measures to assure safety and security to staff and facilities.

Custodial Support Supervisor - Excluded by Requester % Effort
Income) Supervisory oversight of three Custodians and two Laborers. Responsibilities include supervising work activities and performance, making staff changes due to vacation or sick leave absences, developing schedules and assigning non-routine duties, and assisting with custodial duties, as needed. Responsible for keeping the MSDS sheets current in multiple locations throughout campus. Monitors and places orders for janitorial supplies and schedules outside contractors for large-scale floor and carpet cleaning projects. Works with the Sustainability Manager to broaden the scope of the recycling services provided on the campus.

Administrative Coordinator - Excluded by Requester % Effort
Responsible for tracking facility budget as well as other major project expenses; scheduling/calendar coordination for Manager, Facilities & Property; dispatching of facilities staff to handle routine maintenance repairs and emergencies in animal areas, including problems with animal water lines, cage doors, animal room doors and clogged drains; issuing work orders, managing costs and closing out work orders; providing data collection and narrative for grant applications; preparing purchase requisitions for capital construction projects, processing invoices for payment on projects, monitoring construction reports and inserting data into eBuilder construction management software. Coordinates (and is the primary contact point within the Facilities office) responses to security issues and ERT mobilization, interfacing with Public Safety regarding animal rights issues, and onsite security officers regarding card reader and burglar alarms.

Facilities Building Coordinator - Excluded by Requester % Effort
Income) Coordinates small and large facilities projects performed by outside contractors; arranges for contractor access, utility tie-ins, system outages, material delivery, and oversees the completion of work in a timely and cost-effective manner. Coordinates renovations in NHP housing areas for drain replacement, roof replacement, cage support hardware and modifications by outside contractors. Works with the Operations Manager in maintaining construction files and prints, etc.

Custodian - Excluded by Requester and a To be Named. % Effort
% Effort
Income for each position) Responsible for janitorial services on the campus including vacuuming, mopping, waxing, cleaning of lavatories, stocking paper products, changing light bulbs, dusting, dumping of trash cans, collection of recyclables, and other general janitorial tasks. Assists in setup for special functions and events and insures a clean and safe environment for staff and visitors to the campus.

Facilities Technician 3 - Excluded by Requester % Effort
% Effort
for each position) Responsible for general maintenance activities including cage repairs, office renovations and moves, vehicle and generator maintenance, doors and locks, painting projects throughout campus and general service requests. Supports the NHP program with stainless steel repair and welding work on cages and animal housing areas; responsible for locks and building hardware and supervises the emergency generator maintenance program with an outside contractor; maintains the surface maintenance and painting program for all animal rooms, including walls, floors and ceilings, regularly touring

with DCM staff to inspect building conditions throughout animal housing areas and documents items that require repair; maintains the Integrated Pest Management Program for NHP areas.

Biomed Equipment Technician 2 - Excluded by Requester % Effort
Income) In addition to the laboratory equipment, autoclaves and -80 freezers, Excluded by is responsible for the operation of all cage washers and sterilizers in the NHP areas on campus Excluded by also assists the Building Controls Technician and the Plumber with the maintenance of the effluent decontamination unit for the ABSL-3 building.

Laborer 1 - Excluded by Requester % Effort
Program Income for each position) Responsible for transporting passengers between the MAX Light Rail station and campus. In addition responsible for storing and distributing scrubs, gowns, uniforms, and other linen supplies to Facilities, DCM and researchers to meet required needs for PPE. Also assists Facilities staff with furniture relocation, hanging pictures, box moves, moving cabinetry and other related tasks.

Assistant Facilities Technician - Excluded by Requester and a To be Named
% Effort for each position) Assist Stationary Engineers and Senior Facilities Technicians in performance of assigned duties Assists with roof repairs, light fixture maintenance and hardware repairs in all NHP locations; work together under the leadership of the Plumber and two Stationary Engineers with the HVAC and plumbing systems throughout the NHP quarters and help maintain the systems.

Landscaper/Groundskeeper Excluded by Requester % Effort
Responsible for maintenance of the grounds, fertilizing and mowing of lawns, pruning shrubs, treatment of weeds along roadways, cleaning of drainage systems, maintaining fence lines (for security reasons), maintaining perimeter fire roads and gravel roads around corrals, removing dead and diseased trees, removing snow and ice from walkways, etc. Oversees the contracted landscape company who is responsible for routine maintenance of the large, general campus and the areas around outdoor animal housing and corrals.

Stationary Engineers - 2, Excluded by Requester % Effort
Program Income for each position) Responsible for maintenance of heating, ventilating and air conditioning systems, minor design and engineering functions on area remodels, and monitoring renovation work performed by subcontractors; responsible for all boilers providing steam and hot water for heating, cage washers and autoclaves; monitors chillers and cooling towers and coordinates with contractors for annual shutdown for more extensive cooling systems maintenance; responsible for all HVAC systems (fans, chillers, motors, etc.) related to the heating and cooling of laboratories, offices and animal holding areas; maintains the HVAC filters and belts, including the 2 ABSL-3 suites and 2 BSL-3 suites, and monitors room temperatures in all NHP areas throughout campus.

Administrative Assistant - Excluded by Requester % Effort
Responsible for providing administrative support for daily functions of Facilities, including timekeeping, preparation of purchase orders for maintenance and repairs to campus infrastructure and processing of invoices related to Facilities activities; dispatching facilities staff to handle routine maintenance repairs and emergencies in animal areas. This position serves as the central point of contact for security equipment issues including maintenance and monitoring of an electronic keycard access program and the key control program for all research laboratories and select agent areas.

HVAC Engineer 1 - Excluded by Requester % Effort Maintains all building and equipment controls for the campus and is assisted by the Stationary Engineers to make sure all NHP rooms, research labs and office areas are set and remain at the correct temperature. In cooperation with the Plumber and Biomed Equipment Technician 2; monitors and maintains the effluent decontamination equipment for the ABSL-3 building.

Plumber - Excluded by Requester % Effort Responsible for maintenance of plumbing systems, minor design and engineering functions on area remodels, and monitoring renovation work performed by subcontractors. With the aid of two Assistant Facilities Technicians; maintains the drains throughout campus and, in particular, clears plugged drains in all NHP rooms. Coordinates with the Building Controls Technician and Biomed Equipment Technician in the maintenance of the effluent decontamination equipment for the ABSL-3 building.

Facilities Operations Manager - Excluded by Requester % Effort)
Responsible for day-to-day activities which include scheduling the work of facilities technicians, preparing and tracking major maintenance and preventive maintenance projects. With the assistance of the Facilities Building Coordinator, monitors the work of subcontractors in completion of minor renovations for office, laboratory and NHP areas and larger construction projects, providing guidance concerning utility connections and maintaining construction files and prints, etc. In addition, he coordinates, with the Sustainability Manager, on innovations to enhance the efficiencies of the facility operations as well as areas to be investigated for further energy savings.

Sustainability Manager - Excluded by Requester % Effort
Responsible for the environmental management of operations, including tracking, maintaining, and analyzing energy, water, waste, and carbon footprint statistics for laboratory, office, and animal areas. Identifies and documents operational efficiencies for maintenance of all facilities, including animal housing areas, taking into account appropriate requirements and all animal care standards. Collaborates with other departments to identify potential energy and resource savings projects. Develops programs to drive down consumption while maintaining or improving existing laboratory practices and animal care standards. Involved in emergency response and disaster recovery to evaluate and promote sustainable practices in these situations.

Temporary/Summer Help. (9.60 calendar months effort: 1.44 ORIP, 8.16 Program Income, equivalent of one full time position) Responsible for a variety of duties including assisting Landscaper/Groundskeeper in maintenance of yards, gardens, and flower beds, and assisting Senior Facilities Technicians with painting and repair projects in laboratories, offices and indoor/outdoor animal housing areas.

Overtime: (9.60 calendar months effort: 1.44 ORIP, 8.16 Program Income, equivalent of one full time position) Facilities is a single shift, six-day per week operation. However, there are maintenance emergencies and scheduled maintenance tasks which must be performed after normal working hours in order to ensure the health and safety of the animals and the uninterrupted operation of the scientific research. Staff is also scheduled to be on call after normal work hours, on weekends and on holidays to handle maintenance emergencies which requires overtime pay differential.

On-Call Pay (9.60 calendar months effort: 1.44 ORIP, 8.16 Program Income, equivalent of one full time position) Facilities is a single shift, six-day per week operation, and as such, assigns one rotating technician to respond to maintenance emergencies after normal work hours, on weekends and holidays. While on this assignment the technician receives an "on-call" pay differential.

CONSULTANT COSTS

Funds are requested for engineering and architectural services to assist with the maintenance, upgrades and functionality of the facilities supporting research and the care of the animals, which may include line drawings, design calculations, and blue print development, advice on problem solving issues involving long term care and upkeep of buildings and properties. Consultants will be used to evaluate and recommend corrections or upgrades to HVAC systems, control systems, security systems, etc. in both research, administrative, and animal housing and support space. Funds are also requested for geo-technical studies, construction inspection and testing agencies, and air balancing of the mechanical systems.

SUPPLIES

Funds are requested for the following:

- Office and Admin Supplies: include forms, software, toner, copy and printer paper, batteries, business cards, stationery, envelopes, media storage, filing supplies and other routinely-used office items.

- Cleaning Supplies: Custodial operation supplies include paper products, light bulbs, mops, brooms, dusting supplies, cleaning supplies, trash can liners, gloves, liquid hand soaps, etc

- Physical Plant Supplies: include paint, HVAC filters, belts, lumber, metals, tiles, plumbing parts, electrical parts, building hardware, water filters, safety apparel (PPE), drill bits, gloves, shop towels, refrigerants, plastics, flooring, welding parts, and water treatment chemicals.

- Gasoline: is needed for all campus vehicles. With a fleet of 28 vehicles, two cage crew flatbed trucks, two forklifts and a tractor, fuel needs have grown over the years; diesel is needed for campus back-up generators. Funds requested have tripled in the last two years due to the substantial increase in fuel prices.

- Security Operation Supplies: include building key blanks, access badges, clips for badges, lanyards, padlocks, safety cones, access tape, and signage.

- Landscaping Supplies: include bark dust, sand, gravel, seed, fertilizers, herbicides and pesticides, all of which are necessary to maintain the areas immediately adjacent to the buildings, animal housing area and road ways

- .Operating Supplies: includes paint, lumber, metals, tiles, plumbing parts, electrical parts, building hardware and water filters

- Minor office equipment, which may include calculators, printers, monitors, etc.

TRAVEL

Funds are requested to cover costs of local mileage, travel to vendor-sponsored meetings, travel for training events on facility technology, travel to technical conferences and additional on-going training for continually upgraded regulatory maintenance and animal housing requirements.

The following is a breakdown of the anticipated travel activities:

- Facilities and Property Manager; two trips/year to attend technical conferences @ $1,500
- Operations Manager; one trip/year to attend conferences and training events @$1,500
- Sustainability Manager; one trip/year to attend conferences and training events @ $1,500
- Technicians; 4 trips/year to attend specialized two day training events (some training is local) @ $500
- Local mileage charges for attending meetings and localized training events, for pick up of supplies from local vendors, and for "on call' drive-ins (1,800 miles a year x prevailing federal mileage rate)

OTHER EXPENSES

Funds are requested for:

- Expense Credit Labor: represents funds coming back to Facilities for jobs performed for a specific protocol, such as a research program requiring certain building modifications that are above and beyond normal maintenance activities (e.g. adding electrical outlets for freezers, building bottled gas storage stands, modifying HVAC systems, etc.).

- Material for Re-issue: represents funds coming back to Facilities for the materials used in jobs performed for a specific protocol, such as a research program requiring certain building modifications that are above and beyond normal maintenance activities (e.g. adding electrical outlets for freezers, building bottled gas storage stands, modifying HVAC systems, etc.).

- Security Services: to provide on-site officers who perform entry gate staffing to monitor closed campus access, hourly security patrols during off shifts, fire watch, and equipment operations patrols in all mechanical and electrical spaces for the entire campus.

- Buildings Maintenance & Repair: work such as minor painting projects, caulking, floor covering, light fixtures, door and window sealing, pressure washing, concrete sealing, duct sealing, moss treatment and roof replacements within office, laboratories and animal areas. See I&M section for major repairs/renovations.

- Utilities costs for electricity, natural gas (the primary fuel source for hot water heating and steam generation), water/sewer and garbage.

- Conference/Registration Fees: for training courses on equipment and repair, and other relevant subjects.

- Equipment Maint & Repair: of generators, walk-in coolers, heating and cooling units, water heaters, and other fixed and general purpose equipment within offices, laboratories and animal areas throughout campus. The I&M section addresses repairs above and beyond the day-to-day maintenance/repair activities described here.

- Taxes & Licenses/Permits: to cover plumbing and electrical work; local permits for vehicles, elevators, pressure vessels, steam generators, and equipment installations; building permits, soil erosion control permits, and Design Development Review fees.

- Ground Contract Maintenance: for the campus landscaping around buildings and animal housing areas.

- Contract Maintenance (Blds/Equipt): for inspection, maintenance and repair of elevators, chillers, boilers, central heating, ventilation, and air conditioning systems and generators within offices, laboratories and animal areas. Rentals of earth moving and trenching equipment for maintaining and installing underground utilities. Contracted services for support of in-house custodial activities such as window washing, major periodic floor waxing projects, major carpet cleaning, etc

- Laundry Service: which provides campus wide service for cleaning of laboratory coats, surgical clothing, uniforms, scrubs, etc.

- Maintenance/Repair Security: including key blanks, access passes with photo identification and re-keying services.

- Maintenance/Repair – Vehicles: including DCM vehicles and equipment. Facilities personnel maintain a fleet of 28 vehicles, two cage crew flatbed trucks, two forklifts, and a tractor. Also covered in this category are vehicle maintenance items such as tires, and tire chains.

- Telecommunication: includes cell phones for security services personnel and facilities staff that work in areas where no other effective means of communications exist (e.g. electrical vaults, roofs, basements, etc.), and for emergency communications after hours; for administrative personnel who receive calls related to temperature monitoring equipment and after hours emergency communications related to security issues; hand-held radios and repeaters for daily dispatch of maintenance personnel, and for emergency communications and support of the Incident Command Structure

- Maintenance/Repairs - Grounds &Roads: including repairs to concrete pads, gates and fences, and cleaning and maintaining drainage systems. The I&M section addresses repairs above and beyond the day-to-day maintenance/repair activities described here.

- Hazardous Waste Disposal: Funds would be used to pay for disposal of biological and chemical waste generated by the division laboratories that cannot be practically attributed to specific grants. Charges are per the standard OHSU Radiation Safety schedule.

- Membership in Profesnl Org: includes International Facilities Management Association (IFMA) and other related organizations.

- Miscellaneous Maintenance & Repair: includes routine maintenance, including repairs of all outdoor corrals.

- Equipment Maintenance Contract: requests funds maintenance of autoclaves, incubators and research equipment (Steris), for control systems (Siemens), and for maintenance and repair of security access equipment, including electronic door locks, cameras, sensing equipment (Convergint).

- Maintenance – Equipment: for maintenance and repair of generators, walk-in coolers, heating and cooling units, water heaters and other fixed equipment throughout campus.

- Maintenance – Building: for minor painting projects, caulking, floor covering, light fixtures, door and window sealing, pressure washing, concrete sealing, duct sealing, moss treatment and roof replacements.

- System Development - Tualatin Valley Water District: for upgrades and improvements to the distribution system based on contracted water use for the ONPRC.

- Shipping Charges: to cover costs of receipt of goods.

- Testing & Certification: Boiler certifications required annually for campus heating.

ADMINISTRATION: Facilities Income Table

Last Funded Year (53)

Source	Funding (direct costs)
P51 base grant support	$861,025.42
Program income derived from P51 base grant	3,405,942.80
Other Sources	50,950.73
Total	$4,317,918.95

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$717,186.80
Program income derived from P51 base grant	3,774,665.74
Other Sources	52,479.25
Total	$4,544,331.79

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

Facilities receives salary support and support for other expenditures from program income and salary support from other sources.

INFORMATION SYSTEMS SPECIFIC AIMS

The Information Systems (IS) Manager is responsible for the IS service program at the ONPRC. The IS Program comprises IS staff directly reporting to the IS Manager, and the OHSU Information Technology Group (ITG) staff dedicated to the ONPRC but reporting to ITG Management. IS services include but are not strictly limited to: software applications, computational and database services, intranet websites, and multimedia support for all ONPRC seminars, videoconferences or symposia. ITG provides network and telecommunications infrastructure, workstation support, enterprise-wide core applications, resource hosting-management and customer support for the OHSU enterprise network.

Together, the IS Program is a comprehensive technical resource providing people, processes, and technology with a mission in support of ONPRC scientific, clinical and research programs; maintenance of animal resources; development of business applications; and technical integration with OHSU and other institutions. IS' vision is to achieve the most productive synergy between people and computing technologies.

IS specifically focuses on core strategic responsibilities and functions that provide key capabilities to the ONPRC research endeavor and leverage the OHSU IT infrastructure:

Software application support and development in line of business applications such as the integrated research and clinical information LabKey system platform called PRIMe; for office productivity workflows using Microsoft SharePoint; Research laboratory support in areas such as server/system configuration and hosting consultation; and Lab Information System (LIMS) or lab instrumentation interface development and integration

- Business process analysis to achieve improved informational and computational workflows
- Database administration; database and report design, consultation and migration
- Security and privacy of data along with business continuity, disaster recovery and capacity planning
- Service, quality and project management
- Audio-visual, conferencing and training content development support for local and offsite meetings
- NHP Consortium Participation including ONPRC representation for the Data Access Guidelines Group (DAGG) working group

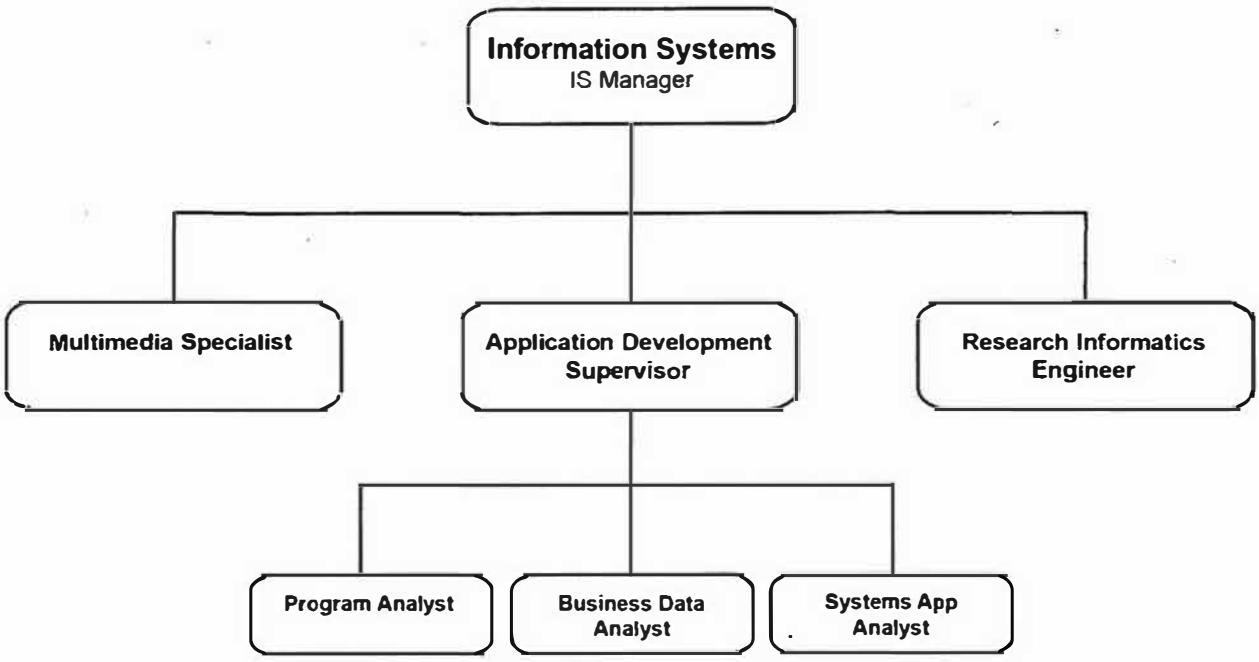
Specific Aim 1. Continue progress in adoption of operational and industry best practices to deliver higher quantity and quality of service delivery to ONPRC and other stakeholders. Focusing on quality improves output. Becoming more efficient helps to lower or create more sustainable operating costs. Systems engineering and technology is getting more complex, not less, requiring prioritizing the highest value efforts.

Specific Aim 2. Leverage and exploit existing technology resources while adding technologies only as strategically needed. This will maximize the return on investments in technology resources, reduce risk in areas such as staffing, and to create a synergistic effect between systems resulting in more agile and scalable technical infrastructure, and ultimately more effective and efficient research, clinical and administrative operations that lead to better research.

Specific Aim 3. Provide support and expertise leadership for research and colony management informatics internally and at the national NHPRC level. Efforts such as creating interfaces to instrumentation allow for the streamlined and automatic capture of data. Facilitating the development of simulations and modeling, for example, help colony managers optimize a limited resource.

Specific Aim 4. Foster effective communications and collaboration internally and externally to, among other things, make it easier for stakeholders to find and use the right quality data in innovative ways. The future success of the NPRCs as a consortium will be increasingly based on collaborative work supported by Information Systems technologies.

INFORMATION SYSTEMS - RESEARCH STRATEGY



SIGNIFICANCE

Information Systems Engineering (IS), part of ONPRC Administration, primarily provides programming and systems analysis services to ONPRC stakeholders for Departmental applications and systems such as IRIS, Intranet and PRIMe. Other Technology Services applications such as email or time keeping are provided for the broader OHSU community by the University. While the latter set is provided and supported by the OHSU Information Technology Group (ITG), IS is the only resource supporting the ONPRC resources. Consequently, IS performs roles in varying levels of degree for systems and database administration, helpdesk, printing, storage, data mining, workstation-server equipment consulting, and trainings. The IS Manager and team is charged with helping lead campus Research Informatics efforts. Therefore, IS is "information and systems engineering" focused over a technology and operations emphasis.

The successful conduct of IS requires skilled and dedicated staff members to provide these services, as reflected in the organizational chart. The IS team consists of 7 FTE: 3.5 programmer-analysts; a business analyst with strong SSRS Reporting and SharePoint skills; a multimedia specialist that provides a vast range of audio-visual-conferencing services; a supervisor with MS-SQL Database Administration skills and a deep understanding of Division of Comparative Medicine (DCM) and Business Services operations; a newly hired Research Informatics Engineer, holding a PH.D in Cellular & Molecular Biology, with application development experience in the LabKey platform technologies; and a veteran IS Manager with security and networking certifications. The team composition is constantly under assessment with plans for skill development in selected areas to ensure as much support as possible to the ONPRC staff. The Research Informatics Engineer position provides a much needed team member to assess and address some the needs of ONPRC Researchers to include Informatics support and leadership. With this position, IS can self-develop future PRIMe Electronic Health Record (EHR) features or research modules. Fully staffed, IS now envisions supporting all aspects of ONPRC. This provision of services also requires partnerships with multiple entities inside and outside of ONPRC to appropriately leverage the tremendous resources of the OHSU main campus as reflected in the following table.

Table 1. ONPRC Information Science Engineering Key Leaders and Responsibilities

Staff Member	Primary Report	Dotted line Report	Primary OHSU-ONPRC Areas	Primary External Contacts

IS Manager	Associate Director for Administration	OHSU ITG Manager	- OHSU ACC - OHSU ITG Staff & Managers - ONPRC ELC/EELC - Any ONPRC employee	- Excluded by NPRC Consortium Manager - Excluded by IS Manager Wisconsin NPRC - HW-SW Vendors as needed
Application Development Supervisor	IS Manager		- OHSU ITG Database Administrators - OHSU Advanced Computing Center	LIMS and Barcode system vendors
Research Informatics Engineer	IS Manager		- Scientific (focus) staff at ONPRC or OHSU - Any ONPRC employee engaged with PRIMe	- NHPRC Consortium - Any NHPRC looking at or engaged with the LabKey platform
Multimedia Specialist	IS Manager		- OHSU EdComm - Any user requesting service	A/V vendors Other NHPRCs
IS Development staff	Applications Development Supervisor		Any and all ONPRC employees	Vendors as needed

OHSU Information Technology consists of a Chief Information Officer (CIO) reporting directly to the OHSU Chief Financial Officer (CFO). Reporting to the CIO are several managers, including the manager of Technology Services. Technology Services, generically referred to as ITG, provides enterprise application, telecommunication and networking infrastructure functions. The ONPRC IS Manager meets bi-weekly with the ITG Field Services Manager for Academic and Research, who has West Campus employees providing helpdesk and workstation support to ONPRC. The ONPRC IS Manager also meets with the ITG Manager Infrastructure Design & Operations at least annually as staff from this function provide support to ONPRC telecommunications, cabling, networking and the fire system. The Academic Computing Center (ACC) reports to the manager of Technology Services. ACC acts as an internal managed service provider frequently used by Research units throughout OHSU, including the ONPRC, as well as anyone with unique computing needs that are not offered by centralized ITG. ACC runs a remote data center to provide hosting, storage, security, and consulting services.

IS has stronger relationships with the broader OHSU ITG and with ACC by being actively engaged in relationship building, supporting OHSU policies, strategies and standards. The IS Manager has assisted in the development of new and improved support and pricing models with ACC as an example of such engagement and cooperation. ONPRC's IS Program has defined responsibilities and the following table reflects the essential scope of them.

Table 2. Responsibilities and Scope by Owner

TASK	IS	ITG	ACC	Data Owner
Provide help and other software support services for ONPRC business applications (e.g. EHR)	A/R			
Prepare IS proposals, feasibility studies, compare technology solutions for ONPRC	A/R	r	r	S
Perform requirements gathering, analysis, design, development, testing, training	R	S	S	
Create ad-hoc reports	r	r		A/R
Create and modify databases	A/R	r		
Prepare technology purchase orders	r	r	r	A/R
Review and approve technology purchase orders	A/R		S	I
Resolve IS task and service requests	A/R	R	R	
Develop and manage internet and intranet postings	S			A/R
Share data sets with outside entities	S		r	A/R
Design and execute data extracts	R	r	S	
Provide help and other desktop support services	S	A/R		

Develop and maintain information services policies, standards, and practices for University	S	A/R	r	
Manage user accounts and their rights	r	A/R	r	
Provide training on in-house developed systems to users	R			r
Enhance systems to increase functionality	A/R	r	r	
Modify ONPRC systems to comply with law, policy, and business changes or to fix defects	A/R	r	r	
Upgrade systems to run on current version of software	R	r	r	
Apply third-party security and maintenance patches to software infrastructure--operating systems, web servers, databases, development tools for ONPRC	r	A	R	
Perform security audits	S	A/R	r	
Protect systems via daily back-ups	S	A/R	r	
Service and maintain IT equipment		A/R	r	
Replace old workstation and server hardware with newer hardware	r	A/R		I
Process telecommunications and network cabling requests	I/S	A/R	r	

A=accountable R=responsible S=support C=consulted
I=Informed a=secondary accountability r=secondary responsibility s=secondary support

Through this team, assigned responsibilities, and relationships, the IS Program:

- Provide EHR technology and support, facilitating care of animals and DCM in the support of research projects
- Assist in the safeguarding of information assets/resources of the ONPRC, in association with the University Central Information Technology Group Security Engineering staff
- Ensure information and technology policy compliance in association with OHSU ITG
- Strive to apply industry best practices to improve operational efficiency throughout ONPRC
- Assists to ensure human and animal safety compliance
- Ensures planning, management and budgeting for technological infrastructure resources to support research and the day-to-day operations of the Center
- Meets with counterparts at the other eight NPRC's to share information, practices, and collaborate on finding ways to improve the technical infrastructures of our respective organizations. Meets regularly with other NPRCs that have adopted LabKey for collaborating on LabKey development or enhancements.
- Ensures audio-visual, physical and web meeting conferencing needs are met

INNOVATION

The IS Program's central and most significant challenge has been tackling how to maintain IRIS (Integrated Research Information System) as a state-of-the-art EHR system. Other challenges include how to ensure data quality and help customers with compliance or how to be more productive developing software all while providing even higher quality customer service. Several new approaches to ONPRC have been employed to tackle these challenges including a much greater strategic focus and deploying proven industry best practices. A strategic project management tool called the LogFrame helps address key project questions before the project actually begins. Some beginning stages of governance have been employed to ensure ONPRC is making the right investments into Information Systems. IS has begun using Scrum and Agile methodologies to manage software development efforts at the tactical or operational levels.

IS is facilitating a significant cultural change that helps to increase the technical capacity of ONPRC. IS is working to streamline workflows and gain efficiencies at every opportunity. Effort includes teaching staff how to use Excel Power Pivot for improved data analysis or developing an application with SharePoint such as the Facilities Maintenance Request system where an electronic system did not before. It also includes, through the implementation of PRIMe (Primate Records and Information Management), built upon the LabKey platform, the push of data entry out to its source in real time. This is a huge paradigm shift for many operations at the ONPRC. The use of PRIMe vastly improves compliance fundamentally via the enhanced, built in data input validation checks and notification alerts.

LabKey was explicitly chosen as the web-based platform due to its capability to provide a data management platform for scientific staff involved in NHP research while also addressing some compliance issues. LabKey started as a lab management system and enhanced, among other things, with an Animal Electronic Health Records (EHR) module. PRIMe provides the granular security and expandable functionality for scientific data to interoperate if researchers agree to host and share their data via PRIMe. PRIMe will also play the prominent role in capturing a more complete animal record by providing an easy to use, reliable, and extensible research informatics and electronic health record platform at the lowest capital and operational cost.

Data accuracy in the PRIMe EHR is essential both for ONPRC's daily operations, and to ensure the colony data is a useful resource for research. The EHR has several layers designed to promote accurate entry and capture errors if they occur. Where possible, the system is designed to capture clinical data in real time, and at the point of acquisition. Entry is browser-based, using interactive web forms. In the data entry pages, multiple approaches are used. A very simple strategy involves using auto-completion and restricting entry to allowable values (i.e. drop-down menus), where appropriate. In addition, the EHR application includes a data validation layer for all incoming information. In this layer, a large number of programmatic validations are performed on all imported records. The data checks range from validation of the animal identification, verifying that an animal is actively assigned to a given IACUC protocol, etc. In addition to validations that completely reject erroneous entries, this same layer is used to raise real-time warnings of suspicious values. An example of the latter is entering an animal weight that +/-10% changed compared to the previous weight. This is a plausible event, but much of the time it represents user error. If this occurs, the user is given immediate warning, but the submission is allowed to occur. The goal is to provide feedback at a time when they are most able to review and correct a problem.

In addition to point-of-entry, the EHR contains a system for automated data validation. A number of checks run against the database at pre-determined intervals. These checks facilitate both data accuracy and clinical care. Examples of these checks are: animals listed as being housing simultaneously in two locations, animals with significant weight loss, and incomplete or suspicious medication entries. If problems are detected, emails are sent to the appropriate users. There are automatic alerts tailored toward veterinarians and clinical staff, the colony management team and database administrators. These checks run at intervals ranging from nightly to hourly.

The LabKey EHR module is designed to be modular, allowing multiple Centers to share a core EHR module, yet permitting individual Centers to augment or modify core features through additional modules. The design is important in order to allow Centers to realize the benefits of a shared system (distributed cost for development and maintenance), while mitigating many problems associated with attempting to build a one-size-fits-all solution. WNPRC initially developed the EHR module as part of an AARA grant. ONPRC is the second adopter of the EHR, and is funding a significant amount of core feature development. While some of this work will create features that primarily benefit ONPRC, the Center is actively communicating with WNPRC staff, and will add many features into the core that will benefit all Centers. In order to facilitate the communication, there is a bi-weekly meeting between WNPRC and ONPRC IT staff where members discuss the state of the EHR, problems, and potential enhancements. The general purpose features ONPRC will add to the EHR fall into (3) main categories:

- There will be a sizable amount of minor improvements spread throughout the EHR, focused on improving performance and overall user experience.
- In addition to these, ONPRC will introduce several major additions. ONPRC will augment the service request system, which allows end-users to request services such as blood draws, procedures and laboratory tests through a web-based portal. This system will help streamline many workflows for center staff, and should improve the interaction between the center and external users.
- The next major improvement involves hooks to financial systems. While there are no plans to develop the EHR into a true financial system, the animal record is the source of most of the data required to center billing. ONPRC will introduce a system to better capture charge and accounting information when the clinical data is entered, and the EHR will provide automated reports or exports for external finance systems. The system will also maintain a list of all changed items for audit purposes.

Another big advantage of the LabKey platform is the flexibility it provides to potentially subsume, enhance or integrate with a Consortium-led application such as the Pathology Imaging Database (PPID) or other applications running on the BIRN platform. While there are no specific ONPRC IS projects, strategies or tactics to enhance the BIRN platform, IS will provide as much technical and systems support as necessary to the consortium working groups who are chartered to develop and support such applications. The PPID is a good example of the improved collaboration or enhancement capabilities of LabKey. BIRN has announced they will cease support of the curation component of this application. The NHPRC consortium staff led by John Nylander has stated they will support certain elements of the PPID. LabKey may be enhanced to provide the curation function all while it continues integrating with the federated BIRN platform that shares the PPID data with other NPRCs.

A master "product backlog" of requested features and functionality for the PRIMe application has been created. The specific timing of implementation over the next five years is not known, but we do know which features are scheduled for inclusion in the ONPRC v1.0 release and which features will come in subsequent releases. ONPRC is planning on following LabKey Software's release cycle of 3 times per year for moderate and major versions. ONPRC may release minor updates out of cycle to accommodate urgent enhancements and fixes. ONPRC plans to build as many interfaces to equipment for processing assays as resources will allow. There is grant information to capture in terms of submission data for researchers which will allow time to be spent doing analysis rather than preparing data for that analysis.

ONPRC is seriously looking at RFID for data capture and over the next 5 years the price of improved technology will continue to allow the implementation of such technology to become more feasible. PRIMe will be engineered to use the data generated from RFID.

The implementation of an enterprise class virtualized environment and storage area network dedicated to ONPRC, hosted at the ACC, provides a great deal of flexibility, scalability, performance, and improved fault tolerance. Virtualized servers are hosted in an N+1 VMware cluster using hardware with redundant components. Multiple networking paths exist for data access including an isolated iSCSI network segment for good security. Database and other virtual servers reside on either a mirrored pair of storage arrays, each using RAID 6 to survive a two drive failure or on a single storage array also using RAID 6 and redundant components. Physical access to all resources is tightly controlled in an isolated data center with very limited staff access. All resources are protected by a dedicated firewall at the ACC. All systems are patched regularly. Critical data is backed up with standard tape backup rotation schemes (e.g. daily incremental, weekly full backups, tape retention for up to 1 year). Storage volumes are snapshotted twice daily. Virtual servers are both snapshotted regularly and have an emergency offline copy. PRIMe can run in a major disaster on a physical server located on ONPRC premises with copies of backups from the primary production systems. New servers can be provisioned on the fly. IS can facilitate moving data stored by PIs on inappropriate locations onto the new equipment which drastically reduces risk of intellectual property loss due to accident or intent.

APPROACH

reviewers' comments

Pages 482-485 (Reviewer's Comments) Removed

reviewers' comments

Future Plans

Future progress in the upcoming P51 grant proposal requires strategic thinking and planning. IS has identified some strategic outcomes affiliated with the following specific aims, and employable strategies to help achieve those outcomes:

Specific Aim 1 – Continue the installation, testing, and development of PRIMe, SharePoint, and other technologies to serve the needs of the research, finance, and colony management groups. Leverage and exploit existing technology resources while adding technologies only as strategically needed.

Strategic Outcome: Maximized grant funded technological efforts

This aim is obtainable by such efforts as: a) developing SharePoint-Intranet based applications with in house expertise to improve administrative type workflows or others such as for animal use planning. SharePoint is provided free of charge by OHSU site license agreement(s) with Microsoft; b) develop simulation-computational modeling within or integrated to PRIMe such as an NHP population simulator (PRIMe incorporates the R reporting language-tool which is open source. Developing a simulator with this tool or running it within the PRIMe resource makes great use of an existing investment) and c) develop mobile applications for real time data entry and streamlined workflows (take advantage of strategically planned ubiquitous wireless networking infrastructure).

Specific Aim 2 – Provide support and expertise leadership for research and colony management informatics internally and at the national NHPRC level.

Strategic Outcome: Research and Colony Management Informatics Leadership

Efforts to implement enhance and promote LabKey in general, or specifically creating interfaces between PRIMe and instrumentation, allow for the streamlined, automatic capture of data. Facilitating the development of simulations and modeling will help colony managers optimize a limited resource. Developing new assays within PRIMe to support Research Cores, such as the Endocrine Core, eliminates a lot of manual effort and provides the robust database of mineable data. All such efforts require coordination between ONPRC and other NPRCs that are using LabKey for Lab and Clinical purposes to reduce or eliminate duplication of efforts but also to gather specifications that result in a better end product. Post release v1.0 go-live will result in some extra personnel capacity to focus on supporting LabKey externally. There has already been a discussion with the NPRC Consortium regarding the possibility of using LabKey to take on the component of the Pathology Imaging database system that BIRN will stop supporting. ONPRC wants to promote LabKey to the point which future development budget from others result in benefits to the ONPRC such as having additional instrument types defined for assays.

ONPRC has a bi-weekly conference call with WNPRC to discuss progress and issues. A responsibilities document established by ONPRC is used to communicate and track specific enhancements and who is responsible for completing or funding the enhancements. The document is also used during bi-weekly meetings between ONPRC and LabKey Software to help manage the contract and specific project schedules.

Specific Aim 3 – Continue progress in adoption of operational and industry best practices to deliver higher quantity and quality of service delivery to ONPRC and other stakeholders.

Strategic Outcome: Improved service delivery

ONPRC IS will achieve the above by: a) developing competency (maturing) in Scrum-Agile SW development and other strategic project management frameworks; b) implement advanced features of common, well

supported, existing systems such as MS-SQL Server SSIS-SSAS-SSRS components; c) foster and strengthen partnerships (internal & external); and d) ensure adequate networking infrastructure exists (pervasive wireless in all animal areas and gigabit wired Ethernet at strategic locations of big data usage)

Specific Aim 4 – Foster effective communications and collaboration internally and externally.
Strategic Outcome: Improved communication, collaboration and data sharing

This Aim is met by nearly all of the aforementioned strategies working together beyond the confines of the IS Program, to the entire ONPRC, and hopefully the NPRC consortium. Principles of transparency, building trust, proper stewardship of resources entrusted to IS care, changing culture while helping people cope with change. One tactic has been the creating of a "reporting" group as part of the Scrum approach to PRIMe system development. This group comprises a cross section of ONPRC staff chartered to ensure there are no information silos while ensuring the most valuable reports are addressed first. This is synonymous with the aims of typical IT Governance and Portfolio management. The most significant effort in this aim is the implementation and continued enhancement of the Intranet based on SharePoint technology. Additional applications, such as the Facilities Work Order system, have automated a long standing and inefficient manual or semi-automated process. The old system posed a communication challenge between animal care staff and facilities staff charged with preventative maintenance and break-fix items especially critical to human and NHP safety-wellbeing. IS, at every opportunity, looks to remove data silos by providing education and training, shared file and print resources, and conversion of local databases or Excel based stores of information. The latter often is implemented with MS Access instead of in an enterprise class database such as MS-SQL. During that conversion, the database can be optimized and combined with other pieces of data much more easily. Perhaps most importantly, the amount of data duplication is reduced.

Program Director/Principal Investigator (Last, First, Middle): Robertson, Joseph E./Haigwood, Nancy L.

ADMINISTRATION - INFORMATION SYSTEMS DETAILED BUDGET FOR INITIAL BUDGET PERIOD DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT P51 OD011092-55

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Excluded by Requester	Mgr, IS	% Effort			Institutional Base Salary	17,490	4,373	21,863
	Sr. Res Informatics Engir					17,252	4,313	21,564
	Programmer/Analyst					11,202	3,472	14,674
	Application Dev Spvr					13,038	4,042	17,080
	Mutlimedia Specialist					9,280	2,877	12,157
	Business Data Analyst 3					10,500	3,255	13,755
	System/Application Analy					13,536	4,196	17,733
	SUBTOTALS					92,298	26,527	118,826

CONSULTANT COSTS		
None Requested	0	0
EQUIPMENT *(Itemize)*		
None Requested	0	0
SUPPLIES *(Itemize by category)*		
Office & Admin Supplies	450	
Telephone System Supplies	525	
Audio/Visual Supplies	150	
Software Licenses/Upgrades	450	
		1,575
TRAVEL		
Domestic	720	720
INPATIENT CARE COSTS		0
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		
None Requested	0	0
OTHER EXPENSES *(Itemize by category)*		
Equipment Maint & Repair	675	
Conference & Registration Fee	675	
Dues & Registration Fees	75	
Duplicating & Copying	225	
Maintenance & Repair	300	
ACC Service	4,875	
Equipment Lease-Rent	3,750	
Shipping	75	
Cell Phones	375	
Telecommunications	3,750	
Sharepoint - Other Business Apps	6,300	
Training & Instructional	1,500	
Labkey Software Maint & Support	3,000	25,575

CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 146,696
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 146,696

ADMINISTRATION - INFORMATION SYSTEMS
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	118,826	122,390	126,062	129,844	133,739
CONSULTANT COSTS	0	0	0	0	0
EQUIPMENT	0	0	0	0	0
SUPPLIES	1,575	1,622	1,671	1,721	1,773
TRAVEL	720	742	764	787	810
INPATIENTS CARE COSTS	0	0	0	0	0
OUTPATIENTS CARE COSTS	0	0	0	0	0
ALTERATIONS AND RENOVATIONS	0	0	0	0	0
OTHER EXPENSES	25,575	26,342	27,133	27,946	28,785
DIRECT CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	146,696	151,096	155,629	160,298	165,107
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	146,696	151,096	155,629	160,298	165,107
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					778,827

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

PERSONNEL

Manager, Information Systems (IS), Excluded by Requester % Effort Program Income). Responsible for oversight of IS which includes providing programming, network engineering, staffing of help desk, strategic planning, project management and overseeing of a five-person staff. Responsible for overseeing the development and implementation of LabKey, an evolving integrated research informatics systems platform to include an electronic animal records system. Serves as a primary point of contact for consortium activities, including the DAGG working group representative for ONPRC. Responsible for SharePointas the general system administrator

Sr. Research Informatics Engineer, Excluded by Requester % Effort Program Income). Primary responsibility is to oversee the successful architecture and implementation of an evolving integrated research informatics systems platform to include an electronic animal records system, while ensuring streamlined access to data and computational Development and implementation of PRIMe will result in streamlining workflows, providing more capabilities in recordkeeping and reporting, enabling more efficient processing of charges of service units included in the database. Provides tier 2 or senior level support of PRIMe (vendor provides tier 3), Java/JavaScript programmer support, and support for consortium based technological activities.

Programmer-Analyst, Excluded by Requester % Effort Provides primary tier 1 IRIS and PRIMe help desk support as well as reporting expertise, provides system administration and support to miscellaneous EHR/clinical systems like the Merge LIS that interfaces with IRIS & LabKey. Other primary responsibilities include analysis, design, programming and maintenance of primary business applications such as PRIMe built on the LabKey platform.

Application Development Supervisor, Excluded by Requester % Effort Income). Responsible for providing a vital role in the implementation and development of PRIMe built upon LabKey, supervising of three direct reports, providing primary, tier 1 support for all MS SQL Databases and the MS SQL technology which includes analysis, reporting and integration services. Also shares a general system administrator role with the IS Manager to include database maintenance, operating system patches (as needed), barcoding and other third party equipment.

Multimedia Specialist, Excluded by Requester % Effort Responsible for audio-visual-conferencing support to research and administrative staff, provides videotaping of events and symposia for on-demand playback and reference.

Business Systems Analyst, Excluded by Requester % Effort Provides analytical and customer liaison across campus, serves as primary SharePoint application developer while sharing responsibility for SharePoint system administration and support, facilitates the adoption of Scrum and Agile with IS customers, provides expertise to product owners on the IRIS to PRIMe system conversion, provides training/education as it relates to the use of technology and systems.

Systems Application Analyst, Excluded by Requester % Effort Responsible for providing , Visual Basic, C, C++, JAVA and JavaScript expertise, as needed, as a senior software developer, shares Tier 1 IRIS and PRIMe Help Desk responsibilities, shares in the development of the LabKey platform which is built upon programming technologies, primary support for the GRIP and SNP application databases, implementation the IRIS Small Lab Animal module within PRIMe.

SUPPLIES

Office & Admin Supplies: Funds are requested for standard office supplies (paper, pens, folders, toner cartridges, desk utensils, small furniture and ergonomic enhancements) for IS activities.

Telephone System Supplies: Funds are requested for new and replacement telephone handsets for the 800+ lines in use at ONPRC, small repair parts, line cards, cabling and other parts related costs for the ONPRC owned telephone system.

Audio/Visual Supplies: Funds are requested for minor and miscellaneous parts to maintain all audio-visual-conference services such as replacement projector bulbs, cables-cords, infrared remotes, speakers.

Software Licenses/Upgrade: Funds are requested for software to address specific needs (e.g. system monitoring and alerting software; Visio professional for system documentation, video editing-conversion).

TRAVEL

Domestic travel is requested for up to (4) staff members to conferences noted below and includes travel related expenses up to $1200 each trip: One such annual trip for (1) staff member is to the Annual Symposium on NHP Models for AIDS. Another is to the annual LabKey User Conference for up to (2) staff members. The remaining 1-2 trips will be distributed among staff fairly.

OTHER EXPENSES

Equipment Maint & Repair: Funds are requested for equipment repairs that are not covered by warranty or maintenance plan, repairs for privately- owned telephone system. As many pieces of equipment are old but serviceable, anticipated costs of operating such systems are expected to increase.

Conference & Registration Fee: Funds are requested for up to (3) conference registration fees. The actual cost of registration fees may allow a 4th conference. One such conference is the Annual Symposium on NHP Models for AIDS and another the LabKey user conference. Others could typically include a conference on Sharepoint/SQL technologies which play a vital role at the ONPRC.

Dues & Registration Fees: Funds are requested for IT professional association annual membership dues and local professional association chapter memberships and functions, which includes continuing education for certification upkeep.

Duplicating & Copying: Funds requested includes costs for the per-copy charges of one multi-function device supporting the Reproductive and Developmental Sciences Division.

Maintenance & Repair: Funds requested coverer the labor and material expense of installing new, or troubleshooting existing, network cabling.

ACC Service: Funds are requested for server & storage hosting, maintenance and service.

Equipment Lease-Rent: Funds requested cover the annual lease fees for up to ten multi-function copy/print/fax/scan network-based devices distributed across campus.

Shipping: Funds are requested for costs from FedEx, UPS, etc., for shipping supplies and minor equipment such as computers and computer parts.

Cell Phones: Funds are requested for costs associated with cell phones and cellular charges on tablet devices for IS staff in order to provide routine support and coverage during emergencies.

Telecommunications: Funds are requested for telephone services such as trunk line, long distance and usage feature fees.

SharePoint - Other Business Apps: Funds requested are to be used to "right size" specific projects on a case by case basis. Since SharePoint is but one of two main strategic environments for developing applications, LabKey (PRIMe) being the other, it is envisioned existing IS staff will be supplemented with outside professionals to assist with a specific need when the existing resources are unavailable or inadequate. SharePoint is currently employed to improve document management and general communication and collaboration, automate facilities service and support requests, and to help automate the workflow of grant applications. All such efforts help to improve the efficiencies or effectiveness of many ONPRC work units and individuals.

Training & Instruction: Funds are requested provides for up to (4) typically local, week long classes as opportunities to enhance IS staff skills when technology advances. Examples include anticipated need to support the upgrades to MS SQL Server 2012 and MS SharePoint 2013. Or a custom on site class teaching advanced Java programming techniques to software developers.

LabKey Software Maint & Support: The primary strategic environment for developing or enhancing applications devoted to an evolving integrated research informatics systems platform for laboratory data management as well as an electronic health record for NHPs (Clinical). While internal staff will do most of the enhancement, a time and materials contract with Labkey Software is vital for issues staff cannot resolve, and to ensure receipt of the latest in updates programmed by LabKey, and other NHP centers using the software.

ADMINISTRATION: Information Systems Income Table

Last Funded Year (53)

Source	Funding (direct costs)
P51 base grant support	$134,036.11
Program income derived from P51 base grant	757,637.95
Other Sources	357,709.77
Total	$1,249,383.83

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$146,695.56
Program income derived from P51 base grant	840,774.86
Other Sources	368,441.06
Total	$1,355,911.48

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

The Information Systems receives salary support and support for other expenditures from program income.

ADMINISTRATION: LIBRARY SPECIFIC AIMS

The ONPRC library provides all library services for ONPRC researchers, veterinarians, behavioral services team and staff with the major emphasis on NHP literature. Services include document delivery and interlibrary loan (ILL) of books and articles and reference services including in depth research projects; active assistance, information and advice ensure compliance with NIH public access policy. The librarian is also responsible for collection development and maintenance of the library's holdings of books and journals. The ONPRC library is closely associated with the OHSU main library to ensure that the needs of ONPRC and its NHP research mission are considered regarding access to e-journals and databases.

Through these functions the library:

- Ensures the ONPRC library collection meets the changing needs of ONPRC patrons and maintains its focus on NHP literature.
- Obtains requested articles and books that are not within the collection.
- Assists researchers and veterinarians in their mission of performing research on and maintaining the health and well being of NHPs by performing in depth literature searches.
- Assists ONPRC authors to comply with NIH Public Access policy.
- Preserves the areas of the collection of historical significance to the center and unique NHP materials.
- Provides books and articles from its specialized collection of NHP literature to other primate centers, public, government and academic libraries, hospitals and research institutions in Oregon, throughout North America and even worldwide.

Specific Aim 1: Ensure the continued provision of efficient and effective services and maximize resources available for the needs of NHP researchers, veterinarians and support staff.

Specific Aim 2: Work closely with ONPRC Division of Comparative Medicine to provide assistance and support for their expanded educational and research role in Primatology.

Specific Aim 3: Preserve the unique NHP historical resources of ONPRC whilst making them more available to researchers and the wider community.

Specific Aim 4: Help ensure ONPRC authors comply with NIH public access policy in a timely manner.

Specific Aim 5: Develop training methods and techniques using new technologies and resources to effectively meet the needs of the ONPRC community and continue leveraging resources and connections with OHSU main library to ensure that ONPRC has access to any additional resources it needs to efficiently perform its mission of NHP research.

ADMINISTRATION: LIBRARY RESEARCH STRATEGY

SIGNIFICANCE.

The ONPRC Library staffed by a research librarian provides all library services for ONPRC researchers, veterinarians, behavioral services team and staff. The Library has 65 subscriptions to print and online journals, a print collection of approximately 14,000 journal volumes and newsletters and 4,000 books with a strong emphasis on NHP literature. Services include high-volume document delivery and interlibrary loan (ILL) of books and articles to assist the ONPRC community obtain speedy access to information necessary for performance of their work. The librarian performs specialized in depth literature research projects on NHP related topics for researchers and veterinarians enabling them to efficiently design projects and benefit from pre-existing knowledge. Other duties of the librarian include assistance with NIH public access policy compliance, collection development and maintenance of the library's holdings of books and journals. The librarian works closely with the OHSU main library to ensure the specialized needs of ONPRC are considered regarding access to e-journals and databases.

Through these functions the librarian:

- Ensures the ONPRC Library collection meets the changing needs of ONPRC patrons.
- Obtains items requested that are not within the specialized collection.
- Assists researchers and veterinarians in their mission of performing research on and maintaining the health and well being of NHPs by performing in depth literature searches.
- Assists researchers to comply with NIH Public Access policy.
- Preserves the areas of the collection of historical significance to the center and conserves its unique NHP materials.
- Provides books and articles from its specialized collection of NHP literature to other primate centers, public, government and academic libraries, hospitals and research institutions in Oregon, throughout North America and even worldwide. The ONPRC Library is a valued resource for NHP literature and is on the ILL routing tables of over 1300 libraries.

The library has an oversight committee consisting of Excluded by Requester (chair), Excluded by Requester Excluded by Requester The committees receive reports on and are consulted before major changes to library policy or operations.

INNOVATION.

- The ONPRC Library has been invited to participate in OHSU's eagle-i Network, a NIH funded research bioinformatics project designed to help researchers connect, collaborate and share resources. Eagle-i is a free, web-based application that makes it easy to discover over 50,000 resources and more than 400 different core laboratories available at 25 different institutions. ONPRC Library's participation will help increase the number and variety of resources in OHSU's repository. There are currently 36 core laboratories listed in the Network, and the ONPRC Library will be added to the growing list of resources.
- Changes have been made in the Library delivery system to meet the needs of patrons and outside libraries. In the last year almost all article requests from outside libraries have been filled through an electronic document delivery system. By utilizing a virtual printer and links from emails to articles hosted on a server, this system allows requests to be filled from online journals while still complying with publishers licensing agreements. This process has drastically reduced processing time for requests; in one case the library fulfilled an urgent medical request within 15 minutes. The Library will continue to make the fullest use of improved technology to increase speed and efficiency.
- New photocopier scanners allow the direct scanning of print journals to email (although this was theoretically possible with the previous scanner, practically it made more sense to photocopy and then scan).The scanner copier has dramatically decreased paper use. Unless requested by the patron all article requests, including those originating in print, are now delivered in the form of PDFs. An additional bonus of this system is that it makes it easier for patrons to import articles into programs such as Endnote.

- It is proposed to set up a special workstation in the Library and purchase software such as Prism, Photoshop and EndNote in order to provide access to patrons who need occasional use of these programs.
- The librarian has attended several training courses including an OHSU course on Expert Searching and a NIH NLM course on PubMed for trainers which have honed the librarians own skills and has also introduced new training ideas. The librarian also plans to make use of survey tools now available to determine changes in needs.

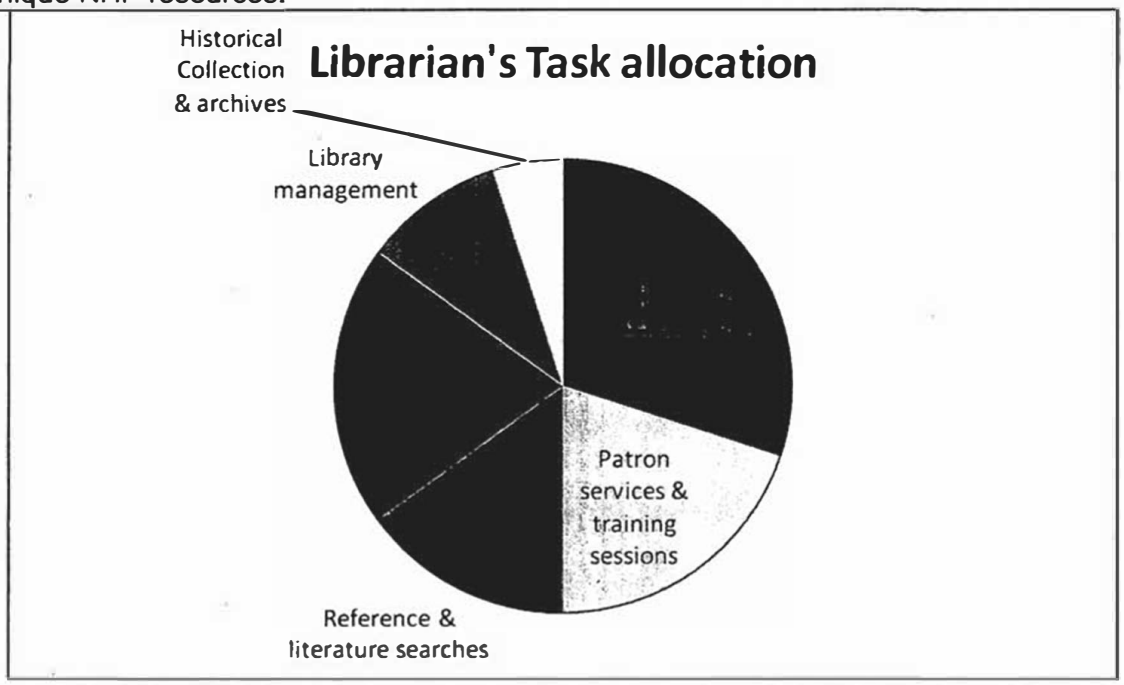
APPROACH

reviewers' comments

Progress Report.

- The past three and a half years have brought many changes to the ONPRC Library. The Library has been extensively remodeled initially as part of the seismic upgrade project and then to meet needs for additional office space in the Administration Building. As a result of these renovations the Library had reduced its footprint but actually feels more open, brighter and modernized while maintaining the warm character and user-friendliness of the old library.
- The Library has 65 subscriptions to print and online journals, a print collection of approximately 14,000 journal volumes and newsletters and 4,000 books in the collection with a strong emphasis on NHP literature.
- The Library has continued to transition to mainly online journals with print subscriptions being maintained for a few core titles. Exceptions are cases where archival electronic access is not secure; or if cancelling print would not secure any cost saving (in some cases changing long term agreements would result in price increases). Reduction in current print subscriptions has decreased processing time and cut the binding budget, although maintaining access to online journals still requires regular checking and problem solving by the librarian.
- The librarian continues to review the collection remove duplicate holdings with the OHSU main library, journals that are either underused, not needed for archival purposes, or do not fit with ONPRC's NHP research needs. Purchase of online back file collections, including the Endocrine Society archives and Neuroscience and Nature archives (to which ONPRC contributed), has fulfilled patron demands by making journals more easily accessible and reduced space needs and preservation costs. The review and removal process has freed up much of the library storage room and has provided space for expanding needs for other Administrative Services. Space formerly occupied by the library now encompasses a media room for computer and other classes and two offices for expanded Information Systems Services. The Library maintains sufficient storage space for its needs and has been able to house the poster printer formerly used by Medical Illustrations
- Use of sophisticated management and document delivery software and streamlining of the Library procedures have continued to allow the Library to function efficiently with only 1 FTE and the addition of student worker assistance for special projects including weeding and a complete move of the collection during various renovations. Approximately 30% of the Librarian's time is used for ILL and Document Delivery Services, 20% for training sessions and other patron interactions, 15% for responding to reference questions and performing literature searches, 20% for collection activities including: accessions, processing, claiming, maintaining, analysis and weeding. Historical collections and archives projects take roughly 5% of the time. The remaining 10% is used for daily library functions such as dealing with mail and email, equipment maintenance, ordering of supplies, payment of invoices and budget management, as well as for participation in the OHSU Collection Development Committee, West Campus Safety Committee and professional training workshops and meetings. The Librarian currently participates in the OHSU Collection

Development Committee, West Campus Safety Committee and professional training workshops and meetings. The OHSU library has undergone budget cuts; however, the Librarian's service on the Collection Development committee and an independent library budget has given the Library leverage to ensure decisions favorable to ONPRC patrons. The Librarian has been invited to join the OHSU Digital Conservation Committee and will be able to use this opportunity to increase awareness of ONPRC Library's unique NHP resources.



- Along with training a number of backup employees and volunteers to perform some of the functions of the Library the Librarian has developed a procedures manual that includes step by step instructions for many of the routine tasks such as ordering articles and books through interlibrary loan and filling ILL requests from other libraries. The manual with the assistance of temporary staffing enables a single-person library to continue to provide basic services during short absences of the Librarian
- Currently the Library has approximately 95 registered Loansome Doc patrons (patrons registered with the NLM's PubMed service) other researchers and staff use either paper or email to order articles and books. Efficient use of resources has led to improvement of previously high service standards; the Library service goal is that all requests will either be filled from library resources or entered into the ILL system within four hours. By use of routing tables, the requests are sent primarily to libraries offering fast service so 99% of requests are filled within 24 hours. The Library's fill rate for articles requested by patrons is extremely effective, in the past year only two requests have not been filled: one for a Japanese trade organization publication (although we were able to obtain a summary) and the other where the cost was prohibitive (over $120 for a short article).
- The ONPRC Library collection holds the only copy in Oregon and the Northwest of many older and rare primatology books and journals, which are often requested by other libraries through interlibrary loan and Summit. With a unique collection of primate books and holdings of a number of specialized and less common journals, the Library is a valuable resource for researchers and students throughout Oregon and the Northwest that perform primatology research. Through ILL, the Library provides materials to other Primate Centers, research centers and hospitals throughout the USA and other countries; ONPRC Library is on the ILL routing tables for over 1300 libraries. ONPRC Library does not charge for these services which make it a valuable resource for underfunded libraries; however this also benefits ONPRC because reciprocal agreements allow the Library to obtain the majority of ILL articles free of charge. The trend in the last 18 months has been for the number of requests from other libraries to decrease slightly, and the majority of requests are now for items from the specialized NHP collection. This altered request profile is probably the result of discarding titles which can readily be obtained from other libraries. The majority of requests are filled the day of receipt and none more than

24 hours later and all articles are delivered by web PDF unless specifically prohibited by the borrowing library.

Table 1. ILL statistics May 2009 –December 1, 2012

	FILLED IN LIBRARY	FILLED BY ILL	NOT FILLED	TOTAL FILLED
Loansome Doc Patrons	1046	1495	3	2541
Other ONPRC patrons	4393	2452	7	6845
External requests	3371			3371
TOTALS	8810	3947	10	12757

- The ONPRC Library affiliation with the OHSU Library system enables the Library to make joint collection development decisions, participate in cost-sharing for electronic resources and eliminate duplicate subscriptions for lesser-used print journals. As a result of the collaboration, Library users now have access to over 13,000 full-text electronic journals, 16,000 e-books and over 100 purchased databases. Remote (off-campus) access to these resources is available with a Library barcode, allowing around-the-clock access to many Library resources.
- To make the best use of limited financial resources the Library has essentially moved to a purchase on demand program where, with the exception of core NHP texts, books are only purchased if requested and justified by patrons. In addition, the Library book collection has been supplemented without additional expense by the ability to request books online from other OHSU libraries and from 38 academic libraries in Oregon and Washington through Summit. This collaborative venture has a courier service which ensures a three to five-day delivery from any member library. A load balancing program ensures the Library receives requests mainly for its unique collection, in order that borrowing and lending remain fairly even.
- Reference questions and literature searches are an essential service to all ONPRC departments. Answering reference queries can take less than an hour, for example if identifying the best resource for illustrations of the vasculature of the NHP uterus or up to six hours or more for queries as complex as a background literature search on blood values and sampling frequency in obese NHPs. The Librarian examines hundreds of citations each month in order to refine results in answer to patron queries. Depending on the requirements of the requestor, search results are delivered either in the form of PDFs of relevant articles, list of references or a mixture of both. Using the Librarian's professional expert searching skills for these searches and queries ensures not only that the coverage of the retrieved results is more comprehensive but the time involved in searching is less than that of a non-professional and allows researchers and veterinarians to focus on their main duties.
- The Library owns a number of books that are possessed by few other libraries in the USA or worldwide, in 2012 the Librarian obtained a Library Services and Technology Act (LSTA) grant to digitize some of the rare NHP books in the ONPRC Library collection. On completion, these books will be available online for the benefit of the researchers and members of the public, both locally and worldwide. This project has wide appeal with letters of support for the grant written by local school teachers, medical illustrators, and the directors of the Wisconsin National Primate Research Center Library and the Texas Biomedical Research Institute Library. On completion of the project eleven rare historical NHP books from the collection will be available on the internet including a link from Wisconsin's Primate Information Network. A special exhibition is being planned with OHSU Historical Collections and Archives staff to display the digitized books in the OHSU main library coinciding with their availability in the digital form.
- The Library has taken an active role in submission of articles to PMC (formerly PubMed Central) in order to conform to NIH Public access policy. The Librarian has contributed in a variety of ways: directly submitting article for PIs who have sent files to the Librarian, training sessions at their desk tops for PIs who wanted to learn how to submit articles themselves, training sessions for administrative assistants so they can submit articles for the PIs they support, and serving as an information resource/problem solver for those with questions or problem with the process. In all cases, rather than using a theoretical approach, the sessions involved submission of actual articles which was sometimes more challenging for the instructor but prepared the "students" for real life situations. Typical questions posed and

problems solved included situations such as an article which the publisher had agreed to submit within 6 months but was not in compliance 18 months later, or co-authors not submitting articles. The Librarian has written several articles for the ONPRC newsletter the CenterPage reminding PI's of the basic requirements of the NIH Public Access policy and their obligations, to comply with the policy. After each article there was an increase in queries and requests for assistance. The Librarian will continue this outreach and education service to accommodate new employees and evolving policy.

Specific Aim 1: Ensure the continued provision of efficient and effective services and maximize resources available for the needs of NHP researchers, veterinarians and support staff. The Library will continue to maintain the current high standards of fast and efficient ILL and document delivery services with priority given to ONPRC patron requests but also providing fast, free services to outside libraries requesting items from the NHP centered collection. Literature on library services is given to new employees and most employees perform required new employee online orientation in the Library. This is an excellent opportunity for them to be introduced to the Library and library services but it is planned to make more use of an outreach program to new employees and offer more library orientation and training sessions. New developments in technology and resources will be adopted in order to continue to provide effective services and adapt to changes in patron needs. Use of the ONPRC intranet will help to make library information on services and news updates on resources more accessible to patrons. It is intended to pursue further opportunities to develop and to evaluate user needs in the future by using available survey tools. The practices that the ONPRC Library has made part of its methodology since its inception and that have been increasingly focused on are now recognized as essential to usefulness and relevance of a successful library. Current library professional journals place a great deal of emphasis on User Experience which can be defined as the many different ways a user interacts with the services and resources provided and also the placement of computer workstations to fit observed patterns of use. Essentially this means being responsive to the needs and wants of patrons rather than providing services based on the library centric work practices and resources and organizing the library space according to user needs. Provision of reference services including complex literature searches will continue to be a valuable service to veterinarians, researchers and graduate students.

Specific Aim 2: Work closely with Division of Comparative Medicine (DCM) to provide assistance and support for their expanded educational and research role in Primatology. Increased training sessions will help scientists and DCM staff to effectively make use of the available NHP resources and increase awareness of potentially useful databases and tools. Finding NHP specific material can be challenging, so extra assistance from the Librarian in the form of training in database use and provision of reference services and literature searches is invaluable both in terms of time and the skill set. Literature searches on specialized topics such as diarrhea, uterine rupture, tourniquet use and blood sampling on obese subjects have provided invaluable information to veterinary staff. Three and a half years ago only about 30% of literature searches were requested by DCM, but currently approximately 60% of literature and reference services are performed for DCM, and it is envisaged that this will increase with DCM's focus on research. Use of a trained expert searcher allows a more efficient use of time and ensures more comprehensive retrieval of information.

Specific Aim 3: Safeguard the unique NHP historical resources of ONPRC whilst making them more available to researchers and the wider community. The recent Personal Info Excluded by Requester the ONPRC medical illustrator for over 45 years, has brought into the library a treasure trove of NHP artwork that is of value to ONPRC community and has recognized artistic merit in the world at large (in the 1980's some of Ito's artwork was selected to be part of a Smithsonian traveling exhibit). Cataloging the Excluded by art collection will continue and the librarian will attempt to obtain grant funding in order to digitize the collection in order to preserve it and also make it available to a wider community. In addition there is also an important legacy of documents and photographs, film and 1" video of the Center and its NHPs which needs to be to be preserved both from a historic point of view but also to ensure preservation of valuable knowledge which is part of ONPRC's legacy. In collaboration with the ONPRC audio visual technician the librarian has begun screening of uncatalogued, and in many cases cryptically labeled collections of 16mm films and 1" video tapes and selecting valuable items for transfer to digital media. Although in its early stages this project has already identified some items for discard, but more interestingly has also found early footage of the corrals and a study of Japanese macaque behavior. The project will continue as the librarian's other duties allow. Volunteers have begun sorting a huge

collection of mostly unlabeled ONPRC photographs and photographic slides; including many of NHPs dating from the early 1960's through the 1980's. It is anticipated that volunteers (under the supervision of the librarian) will continue with this project. Once the scope of this project is established, it may be feasible to recruit a library school intern to complete the project as part of their thesis requirements.

Specific Aim 4: Help ensure ONPRC authors comply with NIH public access policy in a timely manner. The Library plans to be more proactive in ensuring that ONPRC authors' of research papers comply with the NIH Public Access Policy and preempting problems regarding including articles in progress reports and grant submissions. The Librarian will continue to answer questions and provide information on the requirements, submit manuscripts on the behalf of researchers if requested and train administrative assistants and researchers in the NIH manuscript submission process. Although there are a number of online resources available through the NIH, the Library has produced a number of short guides and FAQs which give an overview and quick guide to the NIH policy. To further disseminate information the Librarian will place articles in the CenterPage newsletter and have links and documents on the library's intranet page. It is also planned to offer a new service to researchers to assist in tracking their publications progress through PMC.

Specific Aim 5: Develop training methods and techniques using new technologies and resources to effectively meet the needs of the ONPRC community and to continue leveraging resources and connections with OHSU main library to ensure that ONPRC has access to any additional resources it needs to efficiently perform its mission of NHP research. Mobile librarian sessions offering at-your-desk training will be developed. Informal trials have shown that although these sessions are challenging for the Librarian, it is an extremely effective training method and feedback has been very positive. The value of this style of teaching is that the balance shifts from what librarians want to teach to what researchers want or need to know. One of the growing trends in librarianship is to closely involve librarians in the researchers' environment as this has proved highly beneficial and increased the relevance of the library to the community. At ONPRC the Librarian has strong working relationships with the community and uses this to promote relevant library services and collections. The volume of information is expanding and so the task of keeping up with the latest developments is increasingly difficult. The Library plans to help the process by offering short training sessions and increasing awareness of services such as My NCBI. Many investigators are not aware that if they open a NCBI account they can save frequently performed searches in PubMed and have the searches run automatically at a frequency of daily, weekly, monthly, etc. and then have results emailed directly to the investigator, saving time and reducing duplication of effort. In addition, the volume of information makes it increasingly difficult for investigators to keep track of articles they have received electronically. Commercial products such as RefWorks and EndNote make it easier to manage the volume of information but often can't be made full use of without training, which currently the Librarian is able to provide.

Program Director/Principal Investigator (Last, First, Middle): Robertson, Joseph E./Haigwood, Nancy L.

ADMINISTRATION - RESEARCH LIBRARY DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Excluded by Requester	Research Librarian	% Effort			Institutional Base Salary	8,438	2,953	11,392
To Be Named	Student Worker	0.18				312	31	343
	SUBTOTALS	→				8,750	2,985	11,735

CONSULTANT COSTS		
None Requested		0
EQUIPMENT *(Itemize)*		
None Requested		0
SUPPLIES EXPENSES *(Itemize by category)*		
Office & Admin Supplies	119	
Operating Supplies	135	
		254
TRAVEL		
Domestic		225
INPATIENT CARE COSTS		
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		
None Requested		0
OTHER EXPENSES *(Itemize by category)*		
Books & Periodicals	18,000	
Interlibrary Loans/OCLC Catalogin	716	
Conference/Registration Fee	98	
		18,813
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 31,027
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 31,027

ADMINISTRATION- RESEARCH LIBRARY
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	11,735	12,087	12,450	12,823	13,208
CONSULTANT COSTS	0	0	0	0	0
EQUIPMENT	0	0	0	0	0
SUPPLIES	254	262	270	278	286
TRAVEL	225	232	239	246	253
INPATIENTS CARE COSTS	0	0	0	0	0
OUTPATIENTS CARE COSTS	0	0	0	0	0
ALTERATIONS AND RENOVATIONS	0	0	0	0	0
OTHER EXPENSES	18,813	19,377	19,959	20,557	21,174
DIRECT CONSORTIUM/CONTRACTUAL COSTS					
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	31,027	31,958	32,917	33,904	34,921
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	31,027	31,958	32,917	33,904	34,921
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					164,727

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

PERSONNEL

Research Librarian - Excluded by Requester % Effort
Income). Responsible for all operations of the ONPRC research library which includes Interlibrary Loans and document delivery services, acquisitions and serials management, on line searching, training in the use of NHP databases; managing the library's unique NHP resources and fulfilling the specialized information needs of the ONPRC community. The librarian is also responsible for budget management; coordinating all library functions and services.

Student worker: To Be Named. (1.2 calendar months effort: 0.18 ORIP, 1.02 Program Income). Assist librarian on major projects such as inventory, perform routine task such as scanning, shelving books and journals and in the absence of the librarian fill routine requests for NHP articles and books.

SUPPLIES

Office & Admin Supplies: Funds are requested for standard office supplies (paper, pens, notebooks, printer cartridges).

Operating Supplies: Funds are requested for software (Endnote, Adobe Photoshop, Prism) or other statistical software, archival supplies, etc. The software will be installed on one library workstation to be made available as a communal resource reducing the need for multiple purchases by researchers needing only occasional use. Archival supplies are needed to help preserve the unique NHP resources.

TRAVEL

Funds are requested annually to attend a local library conference such as the Northwest Interlibrary loan conference to learn of new and improved methodologies and network with local librarians helping to improve library services and contacts. Alternatively funds may be used to attend training sessions or workshops to improve the librarian's ability to meet the needs of the ONPRC community. Attendance at a national conference every other year will allow the librarian to gain knowledge of new techniques, systems and products that will improve services and make the best use of available resources.

OTHER EXPENSES

Books & Periodicals: Funds requested are part of the ONPRC specialized NHP resources and include current subscriptions and the support of cooperative agreements with the OHSU library system on specific projects which include collection development and resource sharing. Publishers increase Journal subscriptions on average 8% per annum.

Interlibrary Loans/OCLC Cataloging: Funds are requested for material borrowed, photocopied and/or purchased for researchers and veterinarians.

Conference/Registration Fees: Funds are requested to attend a library conference or training course to enhance the Librarian's ability to perform and provide continuing service improvements.

ADMINISTRATION: Research Library Income Table

Last Funded Year (53)

Source	Funding (direct costs)
P51 base grant support	$26,781.32
Program income derived from P51 base grant	151,760.83
Other Sources	0
Total	$178,542.15

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$31,027.15
Program income derived from P51 base grant	178,020.50
Other Sources	0
Total	$209.047.64

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

The Research Library receives salary support and support for other expenditures from program income.

SPECIFIC AIMS

A new organizational structure has been proposed for the Research Safety Program (RSP), which is part of the OHSU Environmental Health and Radiation Safety (EHRS) department and provides a broad spectrum of services to all ONPRC and other personnel. The RSP department formed in 2011 as a distinct program within EHRS, but reporting to the OHSU Research Integrity Office, with a direct reporting line to the Vice President for Research (VPR). This change was made in order to provide the organizational accountability for research safety by moving program authority to the VPR. This change in organization addresses comments made in the prior critique. The RSP/EHRS departments oversee programs and policies addressing biosafety, chemical safety, radioisotopes, medical waste, hazardous waste, worker safety, ergonomics, emergency response and occupational health programs are developed, administered and periodically updated. During program development, emphasis is placed on program functionality, cost control, and compliance with all federal, state, and local regulations. Training for ONPRC personnel is conducted as required by regulations and/or ONPRC Administration. RSP/EHRS personnel receive training needed to perform their assigned duties and maintain a network of contacts within the regulatory community. Requested funding is needed to maintain the ONPRC as an environmentally responsible member of the community and as a safe and healthy workplace.

The RSP/EHRS program consists of the Research Safety Manager/Biosafety Officer, Assistant Biosafety Officer, two Biosafety Specialists, Industrial Hygienist/Radiation Safety Officer, Industrial Hygienist/Safety Specialist, and an Administrative Assistant. To be hired is a new position that will serve as the Chemical Hygiene Officer for the OHSU campuses and that will report to the Research Safety Manager.

Specific Aim 1. Monitor and evaluate the efficiency and effectiveness of the new RSP/EHRS organizational structure with respect to ONPRC operations. As the proposed personnel arrangement represents a number of changes in the structure operating in the previous funding period, which itself was organized to address aspects of the previous critique, it will be important to continue assessment of the proposed new structure to ensure optimal levels of research safety.

Specific Aim 2. Improve laboratory safety awareness and compliance. In light of recent high-profile laboratory accidents and the resultant increased oversight of laboratory safety practices, it is essential to ensure that the ONPRC and its investigators and research staff are adequately protected from accidental injury and personal and institutional liability. The RSP/ERHS has begun to expand and improve laboratory safety monitoring and consulting by developing a laboratory safety audit program consistent with that developed by the University of California Center for Laboratory Safety. The goal of this program is to ensure that investigators are adequately informed about safety practices specific to the type of research being performed, and to assist them in maintaining compliance with all applicable federal, state, and local health and safety regulations.

Specific Aim 3. Continue to Strengthen the Occupational Health and Safety Program. The OHN has established working relationships with RSP/EHRS staff, Department of Comparative Medicine (DCM) staff, Risk Management, and the OHSU Employee Health department since she was hired in 2010.

Specific Aim 4. Continue to strengthen training and injury prevention strategies. The Research Safety Manager represents the ONPRC with the Occupational Health and Safety (OHS) Working Group. The stated goals of the OHS working group are to meet annually to share information critical to protection of personnel working with nonhuman primates. Preliminary efforts are expected to be completed by early 2014.

Specific Aim 5. Continue to strengthen Security and Biosecurity at the ONPRC. The RSP/EHRS works with the Oregon Health & Science University (OHSU) Department of Public Safety (DPS), DCM staff, facilities, local law enforcement, and first responders to improve Security/Biosecurity at ONPRC.

RESEARCH SAFETY PROGRAM/ENVIRONMENTAL HEALTH AND RADIATION SAFETY RESEARCH STRATEGY

SIGNIFICANCE.

The Research Safety Program/Environmental Health and Radiation Safety (RSP/EHRS) is essential to the safety of the personnel at ONPRC and those who visit the campus. RSP/EHRS advises and assists researchers and support personnel in doing research safely and in compliance with local, state, and federal regulations. RSP/EHRS personnel provide training to all affected personnel, including visiting scientists, volunteers, animal support personnel, facility workers, and contract workers. RSP/EHRS assists in developing and maintaining biosecurity of the research for protection of the environment and the community. RSP/EHRS is involved in review and post-approval monitoring of Institutional Care and Use Committee (IACUC) and Institutional Biosafety Committee (IBC) protocols, assuring compliance with regulations using safe working conditions.

INNOVATION.

RSP/EHRS is exploring using online tools such as Sharepoint to produce databases for tracking information on processes such as laboratory inspections (biological, chemical, and physical), chemical fume hood certification, etc., that save time during the inspection, in follow-up, and data handling for metrics. Sharepoint is also being used to produce a RSP/EHRS website that is easily accessible and updateable for users. RSP/EHRS is using and exploring different training methods to meet the needs and learning methods of users such as on-line (OHSU produced), on-line (vendor produced), in-person trainings, Safety Fairs, Work Shops, competency assurances and safety signage.

APPROACH.

reviewers' comments

reviewers' comments

reviewers' comments

Evaluative Info

Evaluative Info

The reporting structure of the Environmental Health and Safety Program (now Research Safety Program) has changed significantly since the time of the last site visit. Evaluative Info an

indirect reporting relationship was established between the EHRS Manager and the Center Director's office. Since then, the RSP/EHRS Manager has met with the Director or Associate Director on a monthly basis, and informally as needed. In 2011, administration of the Research Safety component of EHRS was transferred to the OHSU Research Integrity Office, with a direct reporting line to the Vice President for Research. This change has resulted in greater responsiveness for funding of research safety programs, and has led to the addition of an Assistant Biosafety Officer to the West Campus RSP staff. The addition of the Assistant Biosafety Officer, OHN, and the shared Biosafety Specialist has greatly added to the strength of the RSP/EHRS program and the safety of the West Campus. The addition of the OHN, in particular, has addressed many of the critiques concerning employee accidents, how these accidents are addressed, employment screenings, and occupational health of small contractors. Regular meetings with the Director and Associate Director of the ONPRC greatly improved communication and understanding of the needs of the ONPRC personnel and programs and how RSP/EHRS can have positive involvement, increased safety awareness, and regulatory compliance.

Since the 2007 inspection, the EHRS/RSP has grown and reorganized to serve all of the OHSU campuses, with special emphasis to the West Campus for Biosafety. In September, 2012, Excluded by Requester WC Research Safety Manager (OHSU Research Safety Manger until July 2011), left OHSU for a biosafety management position at the University of Oregon. A review of RSP/EHRS at this time resulted in a reorganization of the staffing of the program. Excluded by Requester CBSP, joined the OHSU RSP/EHRS team in 2006 as a Biosafety Officer/Laboratory Safety Advisor with more than 20 years of experience in research and brings a wealth of knowledge and experience (much gained working directly with Excluded by to the position of OHSU Research Safety Manager/Biosafety Officer/Responsible Official. Excluded by Requester who was hired as the Assistant Biosafety Officer/Alternate Responsible Official in 2012, has been promoted to West Campus Biosafety Officer/Alternate Responsible Official. Additionally, Excluded by Requester Central Campus Biosafety Officer assists as an Alternate Responsible Official and Biosafety/General Safety Advisor as needed for the West Campus. In addition to the listed Biosafety professionals, the current team located at the West Campus includes Excluded by Requester Excluded by Biosafety specialist (ABSL3 specialist), Excluded by Requester Safety Specialist, and Excluded by Requester Industrial Hygienist. A Chemical Hygiene Officer/Lab Safety Advisor is being recruited for the EHRS/RSP OHSU team to provide an additional safety professional to the team overseeing research on all the OHSU campuses.

The OHN came to ONPRC in February 2010 and works as a partner with the RSP/EHRS, Risk Management, and the OHSU Employee Health department to provide a safe and healthy work site. The goal is to provide efficient services and referrals as needed for injuries, non-human primate exposures, human bloodborne pathogen exposures, communicable disease exposures, required immunizations and screenings, tuberculosis program management, medical certification for respirator use, N95 respirator fit testing, and health assessment associated with the Occupational Health and Safety Program. The OHN provides any immunization or services based on risks associated with work assignment and as recommended by APIC Immunization standard, CDC, OLAW, Oregon Administrative Rules, or OHSU policy for the following:

1. Tuberculosis screening. Required within 2 weeks of hire, and annually thereafter, for employees who enter non-human primate areas. Semi-annual testing is required for personnel involved in Mycobacterium tuberculosis research.
2. Hepatitis B vaccination. Required for employees with potential workplace contact to human blood or body fluids, or primary human tissue cultures.
3. Tetanus/Diphtheria (Td or Tdap) vaccination. Strongly recommended to all employees every 10 years.
4. Influenza vaccination. Strongly recommended each fall season for all employees with the goal to immunize all staff or have a declination form signed and on file.
5. Required or recommended vaccinations. May include Vaccinia, Yellow Fever, or MMR based on work assignment.
6. Work related health evaluation. Includes medical certification for respirator use and Occupational Health and Safety Program enrollment.
7. Blood titers. Provided for Hepatitis B, and post-exposure for HIV, Hepatitis C, Herpes B, SIV, and SHIV as indicated.

8. First aid. Triage, risk assessment, referral, and follow up of communicable disease exposures, occupational injuries, occupational acquired allergies, and potential blood and or body fluid exposure or exposure to Herpes B, SIV, SHIV, Hepatitis B, Hepatitis C, and HIV.
9. Medical Surveillance. Provided for staff that works with or around research animals or human pathogens. Employees with any allergies or immune compromising conditions are seen by the Occupational Health physician. Anyone who develops allergies or any immune comprising condition is also referred to the MD for guidance.

All services are provided under the direction of Excluded by Requester the Occupational Health medical director. Exposures to Herpes B virus/SIV/SHIV are evaluated by Providence St. Vincent's Medical Center Infectious Disease physicians. All injuries or exposures are reported within 24 hours to OHSU Risk Management via direct online reporting.

Employee compliance is closely monitored for TB, Measles, Mumps, Rubella, Tetanus, Hepatitis B, and also for the Occupational Health Program. TB testing and immunizations are provided for docents and volunteers and are tracked by the volunteer office. Contractors are required to provide TB testing information for access into or near any animal areas.

Compliance statistics as of 10/18/2012
TB- 99% compliant
Hepatitis B- 100% compliant
Measles, Mumps, and Rubella- 100% compliant
N95 respirator fit testing- 99% compliant

Non-Exposure Work-Related Injury Statistics:
2010 (Aug.-Dec.)- 18 injuries
2011- 47 injuries
2012 (Jan.-July)- 28 injuries

Potential B Virus Exposure Statistics
2010- 62 exposures
2011- 47 exposures
2012 (Jan.-July)- 42 exposures

Specific Aims/Plans for next grant period

Specific Aim 1. Monitor and evaluate the efficiency and effectiveness of the new RSP/EHRS organizational structure with respect to ONPRC operations. The RSP/EHRS will maintain and evolve staffing type and number to continue to serve the safety needs of the ONPRC. Regular reviews of work metrics, program and regulatory changes, inspection results, performance reviews, and discussions with ONPRC administration and staff will be the driving force to maintain the RSP/EHRS at the highest service levels possible. Our goal is to always maintain flexibility for temporary needs (including drawing on Central Campus personnel to fill temporary gaps or special consultants) and extended/growing needs (adding personnel or reorganizing roles to fit needs) to maintain a safe environment for personnel and animals under our care.

Specific Aim 2. Improve laboratory safety awareness and compliance. In light of recent high-profile laboratory accidents, and increased oversight of laboratory safety practices, it is essential to ensure that ONPRC, and its investigators and research staff is adequately protected from accidental injury and personal and institutional liability. The RSP/EHRS has begun to expand and improve laboratory safety monitoring and consulting by developing a laboratory safety audit program consistent with that developed by the University of California Center for Laboratory Safety. The major plans to accomplish this are as follows:

- The formation of a new Research Safety Committee has been proposed, with both senior faculty and senior technician representatives, and laboratory safety staff participating. This committee will be established and functioning in 2013. The committee would develop safety policies, review safety programs, and recommend improvements to the RSP/EHRS safety programs.
- A standardized Laboratory Safety Audit form has been drafted. Once the form is finalized, a program will be established for ensuring that all laboratories at ONPRC receive a safety audit annually, which may include either a self-audit or a site visit by RSP/EHRS staff.
- Establishment of an easily accessible and searchable Sharepoint Website for RSP/EHRS providing information on policies, work practices, and training.
- Review available trainings and work with DCM, Facilities, and Research personnel to improve and develop additional needed trainings.

The goal of the RSP/EHRS program is to ensure that investigators are adequately informed about safety practices specific to the type of research being performed, and to assist them in maintaining compliance with all applicable federal, state, and local health and safety regulations.

Specific Aim 3. Continue to Strengthen the Occupational Health and Safety Program. The OHN has established working relationships with RSP/EHRS staff, Department of Comparative Medicine (DCM) staff, Risk Management, and the OHSU Employee Health department since she was hired in 2010. Additionally:

- All personnel will receive wallet cards that include emergency contact information as well as information regarding signs and symptoms of B virus infection and for work/exposure to experimental pathogens.
- IACUC semi-annual program review of the Occupational Health Program will provide recommendations for process and program improvement.
- Relationships will be strengthened by regular interactions/meetings with DCM, Facilities and ONPRC researchers by RSP/EHRS and the OHN.

Specific Aim 4. Continue to strengthen training and injury prevention strategies. The Research Safety Manager represents the ONPRC with the Occupational Health and Safety (OHS) Working Group. The stated goals of the OHS working group are to meet annually to share information critical to protection of personnel working with nonhuman primates and to provide a mechanism for:

- Sharing of injury and exposure data across centers.
- Identify trends.
- Improve training and injury prevention strategies.
- Reduce injuries/exposures and related costs.
- Provide a means for measuring success.

Preliminary efforts are expected to be completed by early 2014.

Specific Aim 5. Continue to strengthen security and biosecurity at the ONPRC. The RSP/EHRS works with Department of Public Safety (DPS), DCM staff, facilities, local law enforcement and first responders to improve Security/Biosecurity at ONPRC, focusing on:

- Increasing urbanization of the areas around the ONPRC and working with DPS to develop plans to address security/biosafety issues.
- Training of ONPRC personnel for Security/Biosecurity awareness.
- Live drills used to develop/improve working relationships with local first responders and DPS.

Program Director/Principal Investigator (Last, First, Middle): Robertson, Joseph E./Haigwood, Nancy L.

ADMINISTRATION - RESEARCH SAFETY DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Excluded by Reviewer	Occupational Health Nurse	% Effort			Institutional Base Salary	14,287	3,572	17,859
To Be Named	Occupational Health Nurse	0.48				4,233	1,058	5,292
	SUBTOTALS	→				18,520	4,630	23,151

CONSULTANT COSTS		
None Requested		0
EQUIPMENT *(Itemize)*		
None Requested		0
SUPPLIES EXPENSES *(Itemize by category)*		
Office & Admin Supplies	80	
Med Care Matls & Supplies	636	
		716
TRAVEL		
None Requested		0
INPATIENT CARE COSTS		
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		
None Requested		0
OTHER EXPENSES *(Itemize by category)*		
Employee Health Service	3,762	
Telecommunications	215	
Radioactive Materials Licenses	834	
		4,811
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 28,677
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 28,677

ADMINISTRATION - RESEARCH SAFETY
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	23,150	23,845	24,560	25,297	26,056
CONSULTANT COSTS	0	0	0	0	0
EQUIPMENT	0	0	0	0	0
SUPPLIES	716	737	759	782	805
TRAVEL	0	0	0	0	0
INPATIENTS CARE COSTS	0	0	0	0	0
OUTPATIENTS CARE COSTS	0	0	0	0	0
ALTERATIONS AND RENOVATIONS	0	0	0	0	0
OTHER EXPENSES	4,811	4,955	5,104	5,257	5,414
DIRECT CONSORTIUM/CONTRACTUAL COSTS					
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	28,677	29,537	30,423	31,336	32,276
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	28,677	29,537	30,423	31,336	32,276
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					152,248

JUSTIFICATION. *Follow the budget justification instructions exactly. Use continuation pages as needed.*

PERSONNEL

Occupational Health Nurse (OHN) – Excluded by Requester % Effort Income). Provides Occupational Health Services to employees and volunteers such as immunizations, vaccinations, TB testing/screening, medical certification and N95 mask fit testing. Also, provides counseling, care, and referral for occupational injuries or exposures.

Occupational Health Nurse (OHN) – To be named (3 calendar months effort: 0.48 ORIP, 2.52 Program Income). This position will provide part-time coverage to bring OHN staffing to full-time and to provide backup for primary OHN.

The total of % Effort months effort between the two OHN positions is to account for vacation coverage as well as simultaneous work time necessary for consultation on current employee heath situations.

SUPPLIES

Office & Admin Supplies: Funds requested include items such as paper, tape, staples, pen's, file folders, post it notes, postcards, and business cards.

Med Care Matls & Supplies: Funds requested include items such as needles, syringes, dressing, tape, gloves, blood collection supplies, sharps disposal containers, N95 masks and hood for testing, AED equipment, oxygen tank and mask/cannulas, vaccines and TB testing supplies, emergency medications, first aid and disaster preparedness supplies, blood pressure monitoring, CPR training manuals & supplies.

OTHER EXPENSES

Employee Health Service: Funds requested include cost for herpes B virus testing and shipment.

Telecommunications: Funds are requested for a shared cell phone for the OHN and OHN backup.

Radioactive Materials Licenses: Funds requested are coordinated through EH&RS.

ADMINISTRATION: Research Safety Income Table

Last Funded Year (53)

Source	Funding (direct costs)
P51 base grant support	$27,956.35
Program income derived from P51 base grant	158,419.29
Other Sources	385,169.51
Total	$571,545.15

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$28,676.55
Program income derived from P51 base grant	160,295.65
Other Sources	396,724.60
Total	$585,696.80

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

Research Safety receives salary support and support for other expenditures from program income.

TITLE: **DIVISION OF COMPARATIVE MEDICINE**

CORE-SUPPORTED PERSONNEL:
(See Biographical Sketches for Veterinarians, listed alphabetically in the Overview of the ONPRC)

Division of Comparative Medicine (DCM)

Excluded by Requester

TBN

Director, DCM/Associate Director
Administrative Coordinator
Quality Assurance Specialist

Resources, Facilities, and Operations (RFO)

Excluded by Requester

Associate Veterinarian
Manager, Operations
Lab Animal Tech 2
Research Analyst 2
Lab Animal Tech 2
Laboratory Animal Technician 3
Veterinary Research Health Technician 1
Veterinary Research Health Technician 1
Veterinary Research Health Technician 2/ABSL3
Lab Animal Technician 1
Lab Animal Technician 1
Veterinary Research Health Technician 1
Veterinary Research Health Technician 1
Lab Animal Technician 1
Lab Animal Technician 1
Veterinary Research Health Technician 1
Lab Animal Technician 1
Lab Animal Technician 1
Lab Animal Technician 1
Research Assistant 2
Lab Animal Technician 1
Lab Animal Technician 1
Lab Animal Technician 2
Lab Animal Technician 1
Veterinary Research Health Technician 1
Veterinary Research Health Technician 3/ABSL3
Lab Animal Technician 1
Veterinary Research Health Technican 3
Lab Animal Tech 1
Laboratory Animal Technician 3
Research Support Supervisor
Lab Animal Technician 1
Lab Animal Technician 1
Research Assistant I
Lab Animal Technician 2
Lab Animal Technician 1
Lab Animal Technician 1
Manager, Small Laboratory Animals Unit
Manager, Research and Support
Veterinary Research Health Technician 2
Lab Animal Technician 1

Excluded by Requester	Veterinary Research Health Technician 1
	Manager, Research and Support
	Lab Animal Technician 1
	Lab Animal Tech 2
	Veterinary Research Health Technician 2
	Senior Research Assistant
	Lab Animal Technician 1
	Veterinary Research Health Technician 1
	Head, Colony Hospital, Associate Veterinarian
	Lab Animal Techncian 2
	Laboratory Animal Technician 3
	Lab Animal Technician 2
	Lab Animal Technician 1
	Lab Animal Technician 1
	Veterinary Research Health Technician 3
	Veterinary Research Health Technician 2
	Veterinary Research Health Technician 1
	Veterinary Research Health Technician 3-Lead
	Lab Animal Technician 1
	Lab Animal Technician1
	Lab Animal Technician 2
	Veterinary Research Health Technician 1
	Administrative Coordinator
	Lab Animal Technician 2
	Lab Animal Technician 2
	Veterinary Research Health Technician 2
	Office Administrator
	Lab Animal Technician 1
	Veterinary Research Health Technician 2
	Lab Animal Technician 2
	Research Support Supervisor
	Veterinary Research Health Technician 2
TBN	Assistant Operations Manager
TBN (10)	Lab Animal Technician 1
TBN (2)	Lab Animal Technician 3
TBN (2)	Veterinary Research Health Technician 2
TBN (3)	Veterinary Research Health Technician 3
TBN	Research Support Manager
TBN	Manager, NHP Resources

Pathology Services

Excluded by Requester	Senior Veterinarian, Head Pathology Services
	Research Assistant 2
	Associate Veterinarian
	Research Assistant 2
	Postdoctoral Trainee
	Associate Veterinarian
	Medical Lab Technician 2
	Manager, Clinical Pathology Laboratory
	Senior Research Assistant
	Research Assistant 2
	Research Associate
	Office Specialist
	Research Assistant 2

Excluded by Requester

TBN — Manager, Pathology Services
TBN — Research Assistant 2

Surgical Services Unit

Excluded by Requester

Head, Surgical Services/Senior Veterinarian
Manager, Surgical Services Unit
Veterinary Surgical Technician 3
Senior Research Assistant
Assistant Veterinarian
Senior Research Assistant
Veterinary Surgical Technician 3
Veterinary Surgical Technician 3
Senior Research Assistant

Behavioral Services Unit

Excluded by Requester

Staff Scientist 3
Senior Research Assistant
Postdoctoral Fellow
Senior Research Assistant
Research Assistant 2
Manager, Behavioral Services
Program Technician 1
Research Assistant 2
TBN — Socialization Specialist
TBN — Research Assistant 2

Research, Education, and Training

Excluded by Requester

Assistant Associate Director
Laboratory Animal Medicine Resident
Training Program Coordinator
Training Lead/VRHT 3
TBN — Laboratory Animal Medicine Resident

Clinical Medicine Unit

Excluded by Requester

Associate Veterinarian/Head-Clinical Medicine
Clinical Vet Technician 2
Clinical Vet Technician 2
Clinical Vet Technician 2
Clinical Vet Technician 3
Clinical Vet Technician 2
Assistant Veterinarian
Clinical Vet Technician 2
Clinical Vet Technician 2
Manager, Clinical Medicine
Clinical Vet Technician 2
Clinical Vet Technician 2
Assistant Veterinarian
Clinical Vet Technician 3
Clinical Vet Technician 1
Clinical Vet Technician 2

Excluded by Requester	Assistant Veterinarian
TBN	Assistant Veterinarian
TBN	Lab Aide
TBN	Clinical Vet Technician 2/PENS

Obese NHP Resource

Excluded by Requester	Senior Scientist
	Research Associate
	Research Assistant 1
	Staff Scientist 3
	Research Assistant 1
	Staff Scientist 2

Primate Aging Resource

Excluded by Requester	Senior Research Assistant
	Senior Staff Scientist
	Research Assistant 2

Infectious Disease Resource

Excluded by Requester	Associate Scientist/Head
	Research Assistant 2
	Research Associate
	Project Manager
	Staff Scientist 3
TBN	Staff Scientist

Japanese Macaque Resource

Excluded by Requester	Associate Scientist
	Senior Research Associate

Animal Resources\Division of Comparative Medicine
Organizational Chart

DIVISION OF COMPARATIVE RESOURCES PERSONNEL AFFILIATION AND ROLE

Core Scientists:

Excluded by Requester	Associate Director, ONPRC Director, Division of Comparative Medicine Head, Resources, Facilities, and Operations Unit, Associate Veterinarian Head, Colony Hospital, Associate Veterinarian Head, Pathology Services Unit, Senior Veterinarian Head, Clinical Pathology Laboratory, Associate Veterinarian Veterinary Pathologist, Associate Veterinarian Head, Surgical Services Unit, Senior Veterinarian Head, Small Laboratory Animal Unit, Assistant Veterinarian Head, Behavioral Services Unit, Staff Scientist 3 Head, Research, Education, and Training Unit Head, Clinical Medicine Unit, Associate Veterinarian Assistant Veterinarian Assistant Veterinarian Assistant Veterinarian

DIVISION OF COMPARATIVE MEDICINE (DCM)

DESCRIPTION:

The Associate Director for the Division of Comparative Medicine (DCM) provides the animal and personnel resources to support nonhuman primate (NHP) research at the Oregon National Primate Research Center (ONPRC). The facilities for NHP housing and research include Specific Animal Location facilities, and indoor facilities in Specific Animal Location campus in Hillsboro, Oregon. The DCM staff provides for the health and well-being of all NHPs 24/7, 365 days per year, and provides personnel to perform research procedures and manage the service component for research protocols. As evident by the many inspections from regulatory agencies, the ONPRC has consistently demonstrated an excellent animal care and use program.

In the previous grant renewal, the DCM (formerly DAR) was comprised of eight separate components. The current Division has been reorganized and integrated into seven units to reduce business redundancy and increase operational efficiency based upon functionally oriented utility. The Business & Research section was assimilated into the ONPRC Business Office; NHP Operations and Resource Management was combined into one Resources-Operations-Facilities unit, which also includes the colony hospital; a new Research-Education-Training centralizes all training and education efforts, as well as forging a new focus on research integration; and all pathology functions are now organized as a single unit. The improved interoperability and mutual cross-unit support provides far greater flexibility for managing animal resources, diagnostic services, and research protocol support.

The ONPRC possesses one of the largest captive breeding colony of *Macaca mulatta* in the United States. Approximately 1050 of these animals are in the Specific Pathogen Free breeding program, supported by both U-42 and U-24 grants from the National Institutes of Health. In addition, the DCM manages the only breeding colony of *Macaca fuscata*, and the Center possesses several other unique NHP Resources: obesity, aging, and infectious disease colonies. The majority of the investigations at ONPRC use *M. mulatta* models, but *M. fascicularis* are a popular choice for reproductive science, and *P. Anubis* have become very useful for cardiovascular work.

Of special note are two electronic management efforts currently underway. The present electronic animal records systems will be replaced by a new NHP electronic medical record and research data management system, PRIMe. DCM clinical veterinarians were front-loaded in this highly iterative process to allow DCM to leverage decisions regarding animal movements, procurement planning, breeding programs, preventive medicine, psychological well-being strategies, evaluation and documentation of animal histories, facilities planning, and general administrative oversight of colony operations. Additionally, development of a systems management simulation tool is being developed to identify bottlenecks, leverage points, and potential animal resource management changes that would then improve the performance of the breeding program, with respect to both research and resource objectives. We anticipate that by simulating various resource management approaches *in silico*, animal resource managers and research investigators will be able to forecast expected consequences.

The DCM strives to support the mission and core values of the ONPRC (see OVERVIEW OF THE ONPRC), and has complied with the reviewers' comments reviewers' comments The Division is committed to ensuring that high quality services are provided to support all investigative groups at the ONPRC, the Oregon Health Science University, and other outside institutions. Many DCM personnel are nationally and internationally recognized experts in the field of NHP management, production, care, behavioral management, regulatory compliance, and research support. These individuals provide valuable consultative services to the NIH and other national and international research communities regarding all aspects of NHP care and use. The DCM provides support to all core, affiliate, and outside investigators by assisting the investigators with regulatory interpretation and research compliance as they pursue their use of animals in biomedical research with the resources available at the ONPRC. This comprehensive infrastructure support network allows the ONPRC to serve as a regional, national, and international resource for NHP-based biomedical research.

Pages 523-526 (Publications) Removed – Excluded by Requester

Vertebrate Animals Section

The Division of Comparative Medicine (DCM) maintains a large nonhuman primate (NHP) colony in excess of 4,700 animals in support of the research mission at the Oregon National Primate Research Center (ONPRC). Animals species used include: *Macaca mulatta* (Indian and Chinese origin rhesus macaques); *Macaca fascicularis* (cynomolgus macaques); *Macaca fuscata* (Japanese macaques); and *Papio hamadryas & anubis* (baboons). The number of NHPs used in research at the ONPRC has steadily increased since completion of the last core grant cycle, and the breeding colony has correspondingly expanded to meet research program needs. DCM also oversees a small animal vivarium used as a centralized resource for the university.

Nonhuman primates continue to be a unique and valuable resource in biomedical research because of their close genetic relationship with humans. Studies in NHPs are well positioned for translation to human clinical trials, since NHP models permit the study of human conditions in a physiologically and anatomically analogous species. With restrictions on exportation from many countries of origin and the high cost associated with importation and quarantine of NHPs, the need for well-structured, rigorously maintained, federally funded breeding colonies is necessary to secure the future of NHP research programs.

The Division of Comparative Medicine provides oversight for all animal care activities with a staff of 150 professional, technical and husbandry personnel, including a board certified laboratory animal veterinarian as Chief of the Division, six clinical veterinarians, certified veterinary and surgical technicians and over 100 full-time animal care staff. A PhD level behaviorist manages the Psychological Well-being program, and board certified veterinary pathologists direct the diagnostic services and clinical pathology laboratory. Clinical, surgical and pathology services are available 24/7, 365 days a years, including afterhours, weekend and holiday coverage provided by on-call personnel. Animal care staff provides routine husbandry support and perform daily observations on all animals. Animal health concerns are reported immediately to the veterinary staff for evaluation. The veterinary staff performs daily rounds on all open clinical and surgical cases and assesses newly reported abnormalities. Sick or injured NHPs housed in outdoor social groups identified through daily observation are transferred to the colony hospital for clinical evaluation and care. The veterinary staff has access to a full pharmacy as well as multiple diagnostic modalities including, but not limited to, radiography, ultrasound, MicroCT, MRI and endoscopy. Veterinary staff also utilizes an onsite diagnostic clinical pathology laboratory for timely processing and reporting of blood, urine and culture results. The animal care program is accredited by and maintains emeritus status with the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC International). ONPRC is a Category I facility with an approved Assurance (#A3304-01) on file with the Office for Laboratory Animal Welfare (OLAW) and is registered with the USDA (#92-R-001).

Every effort is made by both veterinary and research staff to minimize pain and distress in NHPs. The veterinary staff provides appropriate clinical care including provision of sedation, general anesthesia, analgesics, antibiotics, supportive fluid and nutritional therapy and other pharmaceuticals as indicated on a case-by-case basis. Humane endpoints are collaboratively established by both veterinary and scientific staff based on the condition of the animal, chronicity of disease, ability to therapeutically relieve pain and distress and the prognosis associated with the disease process. Animals are trained and conditioned for blood sample collection or for the use of restraining devices such as jackets and chairs. Time in such restraining devices is minimized. Animals are sedated and/or placed under general anesthesia for any procedures that may cause pain and/or distress. Surgical procedures are refined to minimize invasiveness whenever possible. Multimodal analgesia regimes are preferred and practiced over single drug pain management unless research restrictions or medical contraindications are present. All NHPs are housed in social situations unless otherwise exempted for research or veterinary-related purposes. The veterinary staff has authority to euthanize any animal based on animal welfare concerns at any time.

All methods of euthanasia utilized at the ONPRC are consistent with AVMA Guidelines on Euthanasia (2007). NHPs are euthanized via exsanguination after deep anesthesia induced by intravenous pentobarbital (50mg/kg). NHPs may be euthanized by the veterinary staff outside of the necropsy suite by intravenous administration of an appropriate dose of Beuthanasia-D.

RESOURCES

Follow the 398 application instructions in Part I, 4.7 Resources.

Division of Comparative Medicine (DCM):

Computer:
The Division Chief and Administrative Coordinator have a laptop and desktop computers respectively, attached to individual color laser printers. There is a networked color laser printer for larger printing jobs located in an adjacent small closet, which is also used for supply storage and as a mailroom.

Office:
There are two large Administrative offices for DCM located in the Research Building, one for the Division Chief and the other for the Administrative Coordinator. An adjacent large Research Building conference room with complete audiovisual and teleconferencing equipment is used for DCM meetings and training. The offices and conference room have both telephone and Internet connections.

Other:
The Division of Comparative Medicine maintains 1 industrial shredder used for document control.

Resources, Facilities, and Operations (RFO):

Laboratory:
Located in the Facility Security building, the SPF Surveillance Serology Lab is a BSL-2 bench-top laboratory providing testing and expertise for both colony maintenance and research needs. This lab uses a screening and diagnostic program with multiple diagnostic tools for tuberculosis surveillance, including serial TST with clinical examinations, serological assays, and molecular diagnostic tests run in parallel.

Clinical:
Facility Security is a dedicated treatment area for SPF breeding colony animals and contains four treatment stations. Two stations have fixed treatment tables and surgical lights, one station has a fixed surgical light and two mobile treatment tables, and the fourth station includes a warm water wash table. Each station has cabinets and drawers for medical supplies and bandage materials, and an IV fluid pump. Additional equipment, including 2 CRI pumps, 2 iSTAT chemistry analyzers, warm water blankets, warm air blankets, surgical instruments, portable ultrasound, two handheld ophthalmic/otoscopes, 6 infant incubators, a suction unit, a vacuum, scales for weighing animals and measuring pharmaceuticals, and a portable anesthesia unit are shared between the four stations. Injectable drugs and IV fluids are stored in dedicated cabinets in the main treatment area. All other pharmaceuticals are stored in the dedicated pharmacy section of the adjacent diet kitchen. Controlled substances are stored in two wall-mounted narcotics cabinets.

Complex surgical procedures, including orthopedic repairs and emergency C-sections are performed in the Specific Animal suites. Routine dental care and oral surgery is performed in a dedicated dental suite. Dental equipment includes a dental unit with high and low speed hand pieces, ultrasonic scaler, heated procedure table, warm air blanket, warm water blanket, anesthetic machine, and dental radiography unit. Digital radiography, CT, and MRI are also available on campus, and utilized as needed for diagnosis and monitoring.

Animal:
Corrals Specific Animal Location
There a corrals; seven of the corrals contain breeding SPF Indian rhesus, approximately 230 animals each. The eighth corral contains Japanese macaques with approximately 215 animals. Each corral is open topped with 11.5' corrugated sheet metal with 15 degree inward angel. Each corral has an associated covered feed heated pen, 200 – 600 sq. feet.

Catch Areas (three total)
These are considered temporary (thirty days or less) housing. These are designed to house large groups of animals from shelters and corrals during group animal processing and/or new group formation. The caging is mostly hanging caging Specific Animal Location The design is cement floor with insulated sheet metal walls and overhead heating.
Specific Animal Location can house up to 120 cages. Specific Animal Location holds up to 96 cages. Specific Animal Location holds up to 150 hanging and mobile cages.

Shelter Group Housing (32 total)
There are thirty-two shelter group housing units. Each unit contains thirty to sixty Indian SPF rhesus, the majority of which are breeding groups. There are associated food preparation and feed storage rooms to the shelter group housing complex.

Specific Animal Location (conventional housing)
There are Specific Animal Location animal holding rooms containing up to 4, two over two mobile racks. There are three associated blind sample/procedure rooms and one minor procedure room. Additionally there is a Lynx LX 450 rack washer, it can hold four two over two racks at one time. There is centralized imaging room for radiographs and ultrasounds. There is an associated feed prep and food storage room. There is a small PPE don/doff/storage room. Additionally, there is a large cage storage room (300 sq feet) between ASB1 and ASB2.

Specific Animal Location (containment ABSL2+)
There are Specific Animal Location animal holding rooms containing 8, one over one mobile racks. There is a pass through cage feed preparation and food storage rooms.

Specific Animal Location
There are Specific Animal Location animal holding rooms containing up to 4, two over two mobile racks. Additionally, there are animal holding rooms, containing 8, two over two mobile racks. There are two associated feed preparation and food storage rooms. There are two smaller minor procedure rooms. Moreover, there is a centralized laundry room. This area houses our nursery. There are four PI controlled behavior testing suites.

Specific Animal Location (non SPF and SPF areas)
There are Specific Animal Location animal holding rooms, containing 4, two over two mobile racks. There are Specific Animal animal holding rooms each holding up to 8, two over two racks. Each of these rooms has one small group housing space. There are two smaller minor procedure rooms. There are three associated feed preparation and food storage rooms. Additionally there is a rack Lynx LX 430 rack washer; it can hold two, two over two racks at one time. There is one blind sample room. There are eight behavior testing suites. There is associated office and break room/conference room space. There are also two locker rooms for husbandry staff.

Specific Animal Location (ESPF area)
There are three, Specific Animal animal holding rooms, containing 8, one over one mobile racks. Many of these cages can be opened to allow for group animal socialization. There are two Specific Animal Location animal holding rooms each holding up to 16, one over one racks. Each of these rooms has one small group housing space. There are eight large group housing breeding runs/pens, holding up to 12 animals each. There are associated procedure room and one feed preparation room. The entrance to this area is limited to the east end of the building. The entrance into the area is a PPE don/doff room.

Specific Animal Location conventional)
There are four, Specific Animal animal holding rooms with 14 two over two mobile racks. There is one Specific Animal Location animal holding room with 4 two over two mobile racks. There are associated procedure room and one feed preparation room. There is a cage rack storage room Specific Animal Location The Basil 4601 rack washer can hold up to two, two over two racks. The washer handles the conventional and ABSL2 caging. The centralized diet

kitchen is housed in Specific Animal the kitchen has one large walk in refrigerator and one large walk in freezer. There is a centralize[illegible]storage room capable of holding up to 18 pallets.

Specific Animal Location (ABSL3)

There are two identical ABSL3 suites. Each suite contains two, Specific Animal nimal holding rooms containing 9, one over one mobile racks. There is a large necropsy/procedure room with a down draft table. There is also a feed preparation area. Each suite has a large pass through autoclave capable of holding one, one over one rack. There is a locker/PPE don/doff room, two shower rooms and a transitional PPE room. Additionally, there is a pass through transitional vestibule room.

Specific Animal Location

This building houses the breeding colony full service hospital. The hospital has two associated animal rooms. Specific Animal Location houses up to 65 hanging cages. Specific Animal Location houses four, two over two mobile racks. The hospital also has a large feed prep room.

There are four Specific Animal Location indoor/outdoor colony runs holding up to 35 animals each. Specific Animal Location wing animal room houses up to 65 hanging cages Specific Animal Location houses up to 90 hanging cages Specific Animal Location has eight group housing pens, each capable of holding up to 8 animals each. Colony Run 7 and 8 has six group housing pens, each capable of holding up to 6-10 animals each. Specific Animal Location have 8 hanging cages for temporary support space. There is an additional feed preparation and one additional minor procedure room. Additionally, there is a break room and several office spaces.

Specific Animal Location containment area ABSL2+)

This building has a PPE don/doff room; associated shower room and transitional PPE don/doff room. There are three animal rooms holding up to 30 hanging cage spaces each. There is an associated procedure room and feed preparation room. The cage pass through autoclave can handle two cages per load. There is a rack washer Lynx LX410, capable of handling 8 cages at once.

Specific Animal Location

There are ten indoor/outdoor group housing units. Each pen is capable of holding up to 16 animals per unit. The support space can hold up to four, two over two mobile racks. There are an associated feed prep and procedure areas.

Cammack Building

This building serves as PPE centralized storage. There are two offices for husbandry staff.

Higgins Building

This building contains two large locker rooms for DCM staff.

Locker/Staff lunch Room (Holte-Fuquay-Roupp)

This building serves the DCM staff and also a centralized area for scrub/uniform storage.

Specific Animal Location

This building has a PPE don/doff room and transitional PPE don/doff room. There are three animal rooms; two rooms hold up to 32 hanging cages and the third room holds up to 28 hanging cages. There is a separate radiology room. There is a central diet prep and procedure area.

Specific Animal Location

There is one Specific Animal animal holding room capable of holding 8, two over two racks. There are four indoor/outdoor pens holding up to 6-15 group housed animals. There are two support areas each holding up to two, two over two racks. There is also one food prep room and one procedure room.

Central Cage Wash Facility

This building contains a tunnel washer used for sanitization of stainless steel hanging caging and equipment.

Computer:

The Integrated Research Information System (IRIS) on Sequel server platform contains all animal records, surgery, pathology data and sponsored projects, IACUC, and DCM administrative data including an electronic billing system for animal related charges. This includes all medical procedures as well as experimental use, reproductive history, and demographic data for the life of the animals. Transition to a new computerized NHP electronic medical record and research data management system, designated PRIMe, began implementation in 2012. An 18-month endeavor, this comprehensive data system for all ONPRC divisions and DCM units will retain information regarding every animal currently or previously maintained by the ONPRC. PCs are available in all RFO management offices for use by staff to access email and other ONPRC and OHSU sites. Number of computer assets and locations are listed below:

Location	Owner	Name
South Research Annex	Serology Office	2 desktops
South Research Annex	Serology Laboratory	2 desktops
North Research Annex	Research Support Manager Office	1 desktop 1 laptop
Research Building	Nonhuman Primate Resources Offices	4 desktops
Research Building	Facilities and Operations Manager Office	1 desktop
Research Building	Head, Resources, Facilities, and Operations Unit Office	1 desktop 1 laptop
ASB III	Lead Technician Offices	4 desktops
ASB III	Facilities and Operations Supervisor Office	1 desktop
ASB III	Technician Break Room	1 desktop
ASB III 381	Procedure Room	1 laptop
ASB II 203	Nursery	1 desktop
ASB I 126	Procedure Room	1 desktop
ASB I 136	Technician Office	1 desktop
ASB I 163	Procedure Room	1 laptop
ASA	Diet Kitchen	1 laptop
Colony Building	Research Support Manager Office	1 desktop 1 laptop
Colony Building	Facilities and Operations Supervisor Office	1 desktop
Colony Building	Lead Technician Office	1 desktop
Colony Building	Lead Technician Offices	2 desktops
Colony Building	Technician Break Room	1 desktop
Colony Annex	Technician Break Room	2 desktops
Colony Annex	Lead Technician Office	1 desktop

Office:

Sufficient office space is provided for personnel who fill leadership roles or have duties requiring a workstation. Six RFO management offices are located in the Research Building for the Unit Head, the NHP Resources group, and the Operations Manager. The Head of Colony Medicine office is located in small integrated trailer adjacent to the Colony Annex. Shared office/computer workstation space is provided for husbandry technicians on an as needed basis. Number and location of all office assets are listed below:

Building	Office	Workstation
Research	6	0
ASB1	0	1
ASB2	0	0

ASB3	1	6
ASA	0	1
Research Annex	1	3
Colony –	3	1
Colony Annex	1	0
Cammack	2	0
Locker/Staff lunch Room (Holte-Fuquay-Roupp)	0	3

Major Equipment:

Total caging

Cage name	Size	Total	Rack/Hanging
Carter	Specific Animal Location	277	R
Britz		108	R
1 over 1		144	R
Single tall		40	R
Double tall		29	R
Rolling play cage		5	R
Breeder Double		9	R
Nursery		10	R
Air		18	R
Baboon 1 over 1		13	R
ABSL3 1 over 1		40	R
Allentown		7	R
West Nile Carter		2	R
New Large Carter		16	R
Used 1 over 1's		15	R
Novo		14	R
single non-squeeze		289	H
single squeeze		78	H
single non-squeeze		130	H
single squeeze		161	H
double non-squeeze		328	H
double squeeze		150	H
double tall squeeze		10	H
single guillotine squeeze		97	H
single small squeeze		94	H
single small non-squeeze		9	H
single non-squeeze with mesh sides		22	H
single squeeze with a guillotine slant but regular door		17	H
single tall guillotine squeeze		7	H
single tall guillotine non-squeeze		2	H

Other Equipment

There are fourteen capture tunnels used for animal processing. The RFO has approximately fifty transfer boxes and 8 sedation/squeeze boxes. There are 8 electronic scales and 10 analog scales.

Vehicles

There are 13 support trucks and vans. The vans and some trucks contain secondary caging for animal transport. There are five golf carts for staff and supply transport.

Pathology Services:

Laboratory:

Necropsy facilities in the Specific Animal Location 2 necropsy rooms for routine and Biological Safety Level-3 activities (470 and 300 sq ft respectively); cold room adjacent to the conventional necropsy room for holding pathological specimens, (80 sq ft); histology laboratories in the Research Building room 142 (580 sq ft) and room 147 (284.9 sq ft), and storage room 144C (147.3 sq ft) in the Research Building.

Clinical Pathology: The clinical pathology laboratory occupies three rooms Facility Security Facility Security It is in close proximity to the Colony Hospital.

Computer:

Integrated Research Information System (IRIS) on Sequel server platform. Pentium 2, 3, or 4 PCs with supporting software linked to IRIS and other network support.

Clinical Pathology: Desktop computers with IRIS access are present in the laboratory and manager's office for data entry and retrieval and billing. Six workstations for the LIS are located in ASA Room 107, ASB1 Room 126, ASB 3 Room 324, the Colony Hospital Room 2, and Clinical Pathology laboratory Room 15. The work stations are equipped with desktop computers with IRIS/LIS access and printers to generate barcoded labels.

Pathology: Desktop computers for each of the pathologists, manager, office specialist, one in each of the necropsy rooms, three Dell optiplex computers with flat screen monitors in the Histology laboratory.

Office:

Excluded by Requester occupy offices in building Facility Security Facility Security the Research building in rooms respectively. The Pathology office (120 sq ft) is located is located in the Facility Security building in close proximity to the necropsy room where routine necropsies are conducted.

Clinical Pathology: An office for the laboratory manager is located across the hall from the clinical pathology laboratory in room Facility Security

Other:

Secretarial services are provided by the Unit's administrative assistant located in close proximity to both pathologists' offices.

Major Equipment:

Pathology: 2 Lipshaw down draft autopsy tables with hoods, Lipshaw grossing in table, 2 Ohaus platform balances, 2 Mettler Toledo balances, 2 Mettler Toledo microbalances, 2 Dell optiplex 760 with flat screen monitors, Castle surgical lights, Burton surgical lights, 1 Rittler minor surgery light, 1 Repro camera stand and 1 Bencher camera stand, 1 Marmed bone saw, 1 Rockwell 10" band saw, 2 Mopec HEPA filtered Stryker saws, 2 Manostat varistaltic pumps, 2 Nikon P90 digital cameras, 1 Nikon D80, 2 Kenmore refrigerator-freezers, Medical Illumination surgical lights, Leica stereoscope, Leica DME microscope, Leica S6D microscope, Revco -80 chest freezer, 2 Blickman mayo instrument tables.

Clinical pathology: Equipment includes an ABX Pentra 60C+ hematology analyzer by Horiba, Pentra 400 chemistry analyzer by Horiba, Merge (Fletcher) LIS, Reichert hand refractometer, two light microscopes (Leica DM1000 and Leica DME 13595XXX), Leica DFC290 camera for microscope, Nove fluorescent microscope, Fisher Scientific vortex mixer, Elix Advantage water purification system by Millipore, three incubators (VWR Scientific, Isotemp and BT Sure), IEC Centra CL2 centrifuge, Eppendorf centrifuge 5810, Mettler 70276 balance, two refrigerators (Kenmore and Whirlpool), Consolidated autoclave, and Forms Scientific biological safety cabinet.

Research Histology Laboratory: The laboratory is equipped with a Leica CM 3050S manual and automatic cryostat, Microm HM 315 rotary microtome, Microm HM 325 rotary microtome, Tissue-Tek TEC embedding center, Tissue-Tek VIP paraffin processing center, and a Leica SP 9000 knife sharpener.

PPID: 1 Olympus VS110 Slide scanner, Dell 36 TB server, 1 Minus K vibration isolation system, 1 Dell Optiplex 780 with 2 flat screen monitors, 1 HPZ400 computer with flat screen monitor.
Pathologists: 1 Leica DM 3000 microscope with dual viewing attachment, 1 Olympus Bx41 microscope with dual viewing attachment, 1 Leica DM 1000 microscope and 1 Leica DMLB microscope with dual viewing attachment.

Histology: 2 Precision-incubator ovens, 1 Microm Hm315 manual microtome, 1 Sakura-Accu-cut SRM manual microtome, 1 Leica Rm 2255 automated microtome, CSE water bath, 2 Lipshaw hot water bath, 1 Fisher brand waterbath with light, 1 Surgipath automated stainer, 1 Mettler Toledo top loading electronic scale, 1 Mettler Toledo microbalance, Sakura Tissue-tek VIP 300 tissue processor, Sakura Tissue-tek TEC tissue embedding center with cold plate, , Hewlett-Packard Deskjet 722c inkjet printer, 2 microwaves, Olympus CX31 binocular microscope, 1 CBG reagent recycler, 1 Creative waste solutions reagent recycler, 1 Surgipath block melter, 1 Premier paraffin dispenser.

Surgical Services Unit:

Clinical:

Most major and minor procedures are performed in surgery-dedicated facilities in the Facility Security Facility Security at ONPRC. Additional satellite facilities for minor procedures are maintained in containment areas (Facility Security All surgical facilities are state-of-the-art and meet or exceed federal standards and guidelines of regulatory and accrediting agencies.

Ethylene oxide gas sterilizer (3M) and steam sterilizer (Consolidated) to sterilize instruments and equipment. 3 gas anesthesia machines with vaporizer/ventilators (including an Ohmeda Modulus); 6 portable anesthesia machines to support a variety of ultrasound, MRI, and other project-related requirements. 4 Surgivet multiparameter vital signs monitors; 2 Marquette physiological monitors; 1 Propac portable physiological monitor; and 10 Nonin portable pulse oximeters for monitoring patient/subject physiologic status during anesthesia and anesthesia recovery. 1 infant incubator and 1 Snyder ICU cage with jump/squeeze cage which allow delivery of supplemental oxygen, heat and humidity for critical care cases. LifePack System 9 defibrillator unit. 7 Gaymar water blankets and 3 Bair Hugger patient therapy/warming systems. Endoscopic equipment: 6 Karl Storz 3.7mm flexible bronchoscopes, 1 Karl Storz 7.5FR ureteroscope, 1 Richard Wolf 3.0mm flexible bronchoscope and 1 Richard Wolf 2.5mm flexible bronchoscope used for infectious disease project broncho-alveolar lavage procedures and clinical diagnostics; 2 10-mm telescopes and 3 5mm telescopes for laparoscopic manipulation of the female reproductive tract (follicle aspirations, ovariectomies, etc.) and organ biopsies; 3 Pentax flexible gastroscopes and 1 Karl Storz video gastroscope for GI mucosal biopsies to support infectious disease projects as well as gain diagnostic information for clinical cases. 7 complete laparoscopic towers (4 Richard Wolf, and 3 Karl Storz), as well as 2 CO2 insufflators for laparoscopic procedures. Other equipment includes an ultrasonic instrument cleaner, 7 incubators for warming intravenous fluids, 4 vacuum regulators, 3 portable vacuum pumps, scales for weighing animals and measuring pharmaceuticals and tissue samples, a large drug safe for security of controlled substances, several wall-mounted narcotics cabinets that have been distributed to various campus work sites for storage of controlled substances. 2 I-stat blood analyzers.

Computer:

Desktop computers are provided for each veterinarian and veterinary technician. Desktop computer workstations are located in each operating room as well as in satellite procedure rooms (Kroc Rm 105, RS 4b, ASB Rm 197A, and ASB Rm 197B). All computers have electronic animal records software access as well as internet access for tools developed for computational integration of workflow and direct data entry.

Office:
Both surgical veterinarians have private offices near the surgical suites (Facility Security Members of the surgical veterinary support staff have private desks in shared office spaces just outside of the Facility Security surgery hallway Facility Security

Other:
Golf cart for transport of equipment and personnel between ASB Surgery and satellite procedure rooms on campus.

Major Equipment:
10 operating room tables of various design. 15 mayo instrument stands. Operating room lights, fixed overhead as well as portable. 6 infusion pumps used for fluid therapy as well as drug delivery. 2 Hall surgical drills and 2 cast/bandage cutters. 3 Valleylab cautery units. 2 flammable storage cabinets. 1 Digital camera and camcorder. 5 hand held clippers. 5 craftsman storage cabinets. 1 refrigerator and 1 washer and dryer set. 1 golf cart for transport to satellite facilities. 1 Freestyle lite glucometer.

Behavioral Services Unit:

Laboratory:
The BSU maintains a 631 sq. ft. diet kitchen on the west end of campus. This area is used to make food treats and other enrichment items for the colony. It contains a walk-in refrigerator and freezer, as well as storage space. It also contains a small workshop in which enrichment devices and toys are made and/or repaired. For larger projects, the BSU has access to the ONPRC Facilities unit. In addition, the BSU maintains a small 158 sq. ft. toy room in the Higgins Building (also on the west end of campus) in which toys and enrichment devices are stored. The BSU has smaller storage areas in other NHP buildings, as well as a small kitchen in ASB III.

Computer:
The BSU has 9 desktops and 3 laptop computers that are employed for statistical analysis of data and the maintenance of experimental records. One computer is dedicated to behavioral scoring (for scientific studies). All computers can access the ONPRC animal history database. In addition, the BSU has a Psion work-about (a mobile handheld computer for taking behavioral observations) and four tablets utilized for direct data entry.

Office:
Excluded by Requester has an administrative office in the Facility Security There is a separate office that contains desk space for the BSU research assistants and BSU manager in the Facility Security There is extra desk space for visiting students. Excluded by Requester has desk space in the Facility Security to enable communication with other fellows and students.

Other:
The BSU has several video cameras for recording behavior. They also have the Observer software, which is utilized for scoring videos.

Scientific Environment: The ONPRC has excellent resources to successfully complete the proposed research. Members of the BSU meet with the clinical, husbandry and scientific staff on a regular basis to ensure that the behavioral needs of the animals are met. Drs. Coleman and Gottlieb are members of the Division of Neuroscience and attend their weekly meetings.

Research, Education, and Training:

Office:
The Head of RETU, the Training Program Coordinator, the Lead Training Technician each have private offices with a workstation and two monitors. The LAM Resident has either a private office or shares an office with one other LAM Resident, and each resident has a workstation plus two monitors, plus a laptop.

The Head of RETU and the Training Program Coordinator each have laptops in addition to their workstation due to the need for work at off-campus locations, and to provide lectures and/or training modules. The Training Program Coordinator also has a scanner and overhead projector to facilitate presentations in rooms that do not have those capabilities built-in.

Other:

Lectures part of the LAM Residency Program, didactic training modules for employees, public outreach, or lectures provided to extramural institutions through contractual agreements with ONPRC, are provided at either the Research Building room 122A/B, or the Montagna Auditorium and ONPRC Learning Laboratory. Room 122A/B is equipped with a dual overhead projector, web sharing through Adobe Connect, PolyCom video teleconferencing, and a Smart board.

Clinical Medicine Unit:

Laboratory:

Clinical laboratory services, including on-site CBC and serum chemistry analysis, urine analysis, anaerobic and aerobic cultures, and cytology are provided by the Clinical Pathology laboratory. Specialized tests, including ionized calcium, vitamin levels, and endocrine tests are readily available through an associated diagnostic laboratory. Virology services and PRIMAGAM assays are available through the diagnostic virology core. Point of care testing is provided by 7 portable I-stat serum chemistry analyzers. These devices are located in the Colony hospital and ASB treatment areas, and are used in other treatment areas as needed.

A variety of imaging modalities are available on the ONPRC campus. Two radiography rooms are equipped with radiography machines and digital CR processing. One room is utilized on campus for the general population. The second radiography room is housed within the quarantine unit. This allows all new arrivals on campus to have chest radiographs before being released from quarantine to verify a negative TB status. Doppler ultrasound, a CT, DEXA scan, and MRI are also available for diagnosis and management of clinical cases.

Clinical:

The clinical medicine unit uses 12 procedure rooms or designated spaces across campus. These areas house supplies and medications necessary to treat both research assigned cage housed non-human primates and group housed breeding non-human primates. The items that are stored in the areas are used for routine clinical care, IV fluid administration, surgical repair, and emergency medical response. Devices utilized are IV fluid pumps, warm air blankets, warm water blankets, IV fluid warmers, surgical instruments, portable ultrasound, and portable anesthesia machines. Other equipment includes 6 infant incubators, a suction unit, a vacuum, scales for weighing animals and measuring pharmaceuticals and bottles, a large drug safe for security of controlled substances, and multiple wall-mounted narcotics cabinets that have been distributed to various campus work sites for storage of controlled substances.

In addition to general procedure spaces a separate room is equipped for general dentistry and oral surgery. Equipment includes a dental unit with high and low speed hand pieces, ultrasonic scaler, heated procedure table, warm air blanket, warm water blanket, anesthetic machine, and dental radiography unit.

Office:

Office space is centrally located. Each veterinarian has private office space with a computer. There are two technician offices with desks and computers. The clinical staff also utilizes an electronic medical record system that is accessible in both animal facilities and office spaces. This system is currently undergoing major revisions that are expected to increase productivity through improved user interface, increased access, and greater integration of the clinical research data.

Obese NHP Resource:

Laboratory:
The Obese Resource has 385 sq. ft of laboratory space that is used for tissue and blood sample processing. This space is a shared laboratory space for visiting scientist for primary processing of tissues. This laboratory is stocked with the basic laboratory equipment, i.e., pipettes, glassware and scales, etc.

Animal:
The Obese Resource has three cohorts of animals. 1) 71 adult female Japanese macaques housed in 7 different social cohorts. These animals are used for a breeding program. 2) 65 adult Rhesus macaques maintained in single or paired housing in the ASB. 3) 35 Cynomolgus macaques housed in single or paired housing in the ASB.

Computer:
The Obese Resource has two Dell PC desktops used by the Colony Manager and animal technicians for data entry and work order processing. These computers are also used for email communication of information to the various investigators that use the Obese Resource.

Major Equipment:
The Obese Resource has two –80 C freezers used to store tissues as a tissue band. There is also a –20 C freezer and 4 C refrigerator for storing supplies. Sorval Legend RT-plus table top refrigerator centrifuge is used for blood sample processing.

Primate Aging Resource:

Laboratory:
Excluded by Requester shares laboratory space in the Facility Security which houses the Division of Neuroscience at ONPRC. Laboratory space (1000 square ft) is in the west wing and has separate space for wet-bench experiments, microscopy and cell culture, and is also equipped with two chemical hoods, two sinks, house vacuum and gas. For heavy equipment, two -80 C freezers are in place for archiving samples for the Primate Aging Resource. The Division also shares common heavy equipment, such as centrifuges (low speed and ultra) as well as gel and Western blot readers. Other equipment within the lab includes two light microscopes, one of which is hooked up to a digital color CCD camera, a sliding microtome for primate tissue, glassware for histological staining, two Western blot setups, material for in situ hybridization, a PCR machine, table-top water baths and centrifuges, rotary tables, tissue homogenizers and mixers. The lab is fully stocked with glassware and disposables, as well as working chemicals.

Clinical:
Animal health is overseen by veterinary staff, who will also be involved in the administration of the biannual physicals. They will diagnose any problems, prescribe any treatments and document the opening and closing of clinical cases. Husbandry (feeding, cage cleaning, daily observation) will be carried out by technicians in the Division of Comparative Medicine. Any surgical interventions will be performed by staff in the state-of-the art surgical suites in the Facility Security

Animal:
The resource has oversight of the approximately 100 animals in the Primate Aging Study. These individuals are Indian-origin, males and females, and range in age from 15-30+ years of age. The middle-aged animals (15-17 years) reflect early recruitment into the resource, which facilitates a regular rate of repopulation to offset animal use and attrition.

Computer:
The resource has three desktop computers, for the primary investigator and two technical staff members. These are wired to the OHSU intranet system and are serviced by information services, hence are outfitted with standard software supported by the institution. The primary investigator also has a laptop, for working off-site.

Other:
Other Core services that may be used and include the Endocrine Core, which conducts assays on nonhuman primate samples, and also the MRI Core for *in vivo* imaging.

Major Equipment:
Two ultralow freezers are designated for the archiving of samples.

Infectious Disease Resource:

Laboratory:
Excluded by Requester laboratory is located in the ONPRC Facility Security on the OHSU West Campus and includes 1,640 sq. ft. of BSL-2 general laboratory space that contains tissue culture rooms, general laboratory bench space, dark room, cold room and shared equipment support space. Adjacent to the BSL-2 laboratory is a 460 sq. ft. BSL-3 laboratory. This lab is equipped with shower-in/shower-out facilities, Class II Type A/B3 biological safety cabinets and pass-through autoclave. The laboratories are well equipped for virus isolation/propagation, PCR-based quantitative virology methods, serology, cellular and humoral immunology assays, molecular biology/virology and flow cytometric analysis of infectious specimens.

Laboratory space available to the Resource's Laboratory Unit (LU) includes 2100 sq. ft. of general laboratory space, an additional 400 sq. ft. of BSL-2 tissue culture space, and a 200 sq. ft. freezer galley. The LU also has access to a 1200 sq. ft. BSL-3 suite (which includes a cell sorter, equipped to handle the aerosol dangers of infectious live specimens).

Clinical:
Veterinary care of nonhuman primates (NHP) assigned to Resource managed protocols and the AIDS Macaque Resource is overseen by a complement of Division of Comparative Medicine (DCM) veterinarians with advanced training and/or certification in laboratory animal medicine, surgery, veterinary practice, primate medicine and pathology. The ONPRC has state-of-the-art facilities and equipment to evaluate, hospitalize and clinically manage and treat nonhuman primate medical and surgical cases in ABSL-2, -2+ and 3 containment settings. Routine clinical care and experimental procedures are conducted in areas dedicated for these activities including examination/treatment rooms; a pre- and post-surgery holding area; hospital, intensive care and isolation wards; pharmacies, radiology, surgery, and necropsy suites. The ONPRC clinical pathology laboratory is supervised by a certified Medical Technologist and equipped with appropriate instrumentation to support clinical diagnostic hematology, parasitology, bacteriology and chemistry and the clinical diagnostic virology laboratory provides diagnostic virology and serology support. Husbandry support for Resource managed animals (feeding, cage cleaning, and daily observation) is provided DCM. Surgical procedures are performed in state-of-the art surgical suites under the supervision of DCM surgical Unit veterinarians.

Animal:
The Resource manages and provides oversight of an average census of approximately 460 NHPs assigned to grant- and contract-supported infectious disease research protocols, largely rhesus macaques. These animals are housed in Specific Animal Location containment housing as appropriate for the agent understudy. The Center has indoor ABSL-2 housing totaling approximately Specific Animal Location exclusive of support areas and corridors sufficient to support 1,980 Class III macaques. Containment housing available to support infectious disease studies include the Specific Animal Location containment animal housing suite with a capacity of 272 Class III macaques housed in 17 rooms of 16 animals each and the Specific Animal Location building with a capacity of 96 Class III macaques. Containment housing support facilities include change/locker room, shower room, decontamination/locker room, equipment and personnel airlocks, dedicated necropsy and clinical treatment/surgical rooms and pass -through equipment decontamination (autoclave) for caging. A state-of-the-art Specific Animal Location acility provides housing and support space for 72 Class III macaques in high-level containment. This facility has 2 separate animal suites capable of supporting 36 Class III macaques.

The facility is supported by a clean locker room, separate shower rooms, separate decontamination room/locker, and a pass-through autoclave. Each suite is equipped with a Class II Type A/B3 biological safety cabinet. Entry into ABSL-2+/3 and ABSL-3 animal containment facilities is restricted to Select Agent approved, appropriately trained personnel by "key-card and finger print reader controlled" access. Biosafety standards for all work with BSL-2, BSL- 2+ and 3 agents conform to NIH, CDC and OHSU Biosafety Committee guidelines.

Computer:

Excluded by Requester office and the laboratory are equipped with 16 desktop computers and two laptop computers to support the LU manager, the project manager, 12 technical staff members and equipment. The computers are networked within the ONPRC, VGTI and OHSU for secured database access, word processing, data management applications, electronic mail and direct access to the OHSU bioinformatics center on main campus. Available software includes statistical applications, graphing and graphics, word processing, spreadsheets, PAX imaging, LabKey and dongle-regulated TreeStarFlowJo flow cytometric data analysis software. Additionally, the Resources's LU is supported by analysis workstation computers all linked to a 42TB data array accessible controlled by an administered server.

Office:

Excluded by Requester has a 100 sq. ft. office adjacent to his laboratory and the Project Manager's 100 sq. ft. office. Resource technical staff has office space within, but distinct from the laboratory spaces.

Other:

Secretarial and accounting assistance are provided by the ONPRC. The ONPRC virology core provides support for viral preparation and quantification. Additionally, the ONPRC has support units core laboratories supporting DNA sequencing, gene microarray analysis, hormone assays, flow cytometry, laser capture microscopy, confocal microscopy and other imaging methods, radioimmunoassay, anatomic pathology, experimental surgery, magnetic resonance imaging, and a central library.

Major Equipment:

Major equipment available in Excluded by Requester laboratory or available in shared core space include 6 performance-monitored laminar flow biosafety cabinets, a Labconco radioisotope hood, 5 dual-chamber CO_2 incubators, microcentrifuges, 4 refrigerated low speed centrifuges, a Beckman J2-HS high speed centrifuge, a Beckman L-8 M70 ultracentrifuge and rotors, Beckman Model Optima TL ultracentrifuge and rotors, a PCR hood, Bio-Rad Tetrad 2 and Perkin-Elmer thermal cyclers, Roche MagNA Pure Compact robotic nucleic acid purification unit, Applied Biosystems 7500 Real Time PCR system. NanoDrop ND-1000 and Beckman DU-65 spectrophotometers, Thermo Max kinetic microplate reader, Bio-Rad DNA horizontal electrophoresis cells, and Bio-Rad protein II vertical electrophoresis cells with Bio-Rad Model 1000/500 power supply, Bio-Rad Trans-Blot SD semi-dry transfer cell with Model 200/2.0 power supply, constant temperature water baths, DNA concentrator, Savant slab gel dryer with vacuum pump, UV cross linker, bacterial incubator, incubator shaker, Footdyne Photosystem, Kodak X-OMAT processor, Amsco Eagle 3000 autoclave, three refrigerators, three - 20°C freezers, three ultralow (-86°C) freezers, Liquid Nitrogen frozen cell storage (Forma Scientific CryoPlus2), 5 light microscopes (3 upright, 2 inverted), high definition bronchoscopy/endoscopy units (Storz, Wolf) pulse oximeters (Nonin), iStat blood analyzers, portable ultrasound unit, dental equipment, BD ACT5 hematology machine, chemistry panel machine (Vet Scan VS2) and Pam unit.

Equipment available to the Resource's LU includes two dedicated top-of-the-line Becton-Dickinson LSR-II analysers (3-laser, 21-parameter) which can be coupled to a high-throughput 96-well plate sample loader. The LU also has access to two other LSR-II analysers, as well as a BD Aria-II sorter, through the ONPRC Flow Cytometry Core. The BSL-2 and BSL-3 laboratories are equipped with performance-monitored biosafety cabinets, CO_2 incubators, aerosol-control centrifuges, and a computer-controlled cell freezer, frozen storage (-20°C, -80°C, LN vapor). The unit also has access to four unique, custom-designed computerized incubators, capable of rapid transition from a humidified, 5% CO_2 37°C atmosphere to a refrigerated 4°C environment at user-specified clocktimes. Two of these units have 6 independently-controlled chambers.

Japanese Macaque Resource:

Clinical:
Virology and histology will be reviewed in the research laboratories of Dr. Scott Wong and Dr. Larry Sherman respectively. Neuroimaging will be carried out in the ONPRC MRI imaging facility by Dr. William Rooney. Retinal photography will be carried out by Dr. Martha Neuringer and her staff.

Animal:
This resource includes a one acre coral housing a 200 member Japanese macaque breeding colony, which will produce about 40 offspring per year. Two harem groups of 10-12 members will be established during the granting period to augment research production and potentially genetic diversity in the breeding group. Veterinary care will be provided by the DCM staff.

Computer:
JMR pedigree, genotype and phenotype data will be updated regularly by the JMR staff, using one Dell Optiplex 790 work station. Data will be stored on PRIMe, and will be accessed by DCM and JM research users for animal review and assignment.

Major Equipment:
Equipment within the MRI imaging facility (See CORE SCIENCE SERVICES-MRI)

ANIMAL SERVICES: DIVISION OF COMPARATIVE MEDICINE (DCM) SPECIFIC AIMS

The Division of Comparative Medicine (DCM) provides superior NHP animal models and research support services to the ONPRC by maintaining healthy, specific pathogen free (SPF) nonhuman primate (NHP) breeding and research populations. To ensure physically and psychologically healthy animals free from disease and genetically characterized, DCM also maintains a well trained and experienced professional, technical and husbandry staff in a collaborative and cooperative posture with the Scientific Divisions.

To successfully accomplish this mission, the DCM will:

Specific Aim 1: Provide a reliable number of healthy, genetically defined and pathogen-free source of NHPs.

Specific Aim 2: Develop improved strategies for the socialization of NHPs.

Specific Aim 3: Train the next generation of veterinarians dedicated to the advances in the understanding and improvement of NHP models.

The DCM will continue to optimize NHP breeding consistent with physical infrastructure and the anticipated need and diversification of the ONPRC scientific programs. The Division will improve management of colony genetics, and continually strive for top quality animal resources by enhanced pathogen monitoring, screening tests and diagnostic technologies, to ensure Specific Pathogen Free (SPF) animals availability. DCM will also implement management strategies to increase breeding efficiencies and provide optimium holding facilities using a systems management approach to identify bottlenecks, leverage points, and potential animal resource management changes to improve breeding program performance.

The Guide has recently been updated and housing standards have been further enhanced for these sentient species. In addition, European Union guidelines will likely expand socialization requirements, which may well influence further such requirements in the U.S. Thus, DCM will explore new opportunities for social compatibility assessment and enrichment, ensure compliance and develop strategies to improve the quality of life for the animals at the Center. Strategies will include innovative and comprehensive approaches to improving the methods of managing medical and behavioral cases, and explore novel use of caging and the design of innovative housing systems to enhance animal welfare and socialization.

Finally, a relatively small number of veterinarians possess the clinical expertise to support NHP research models. Recognizing this fact, the ONPRC has entered into a LAM resident training consortium with OSU veterinary medical school and the OHSU medical center to provide opportunities to veterinarians that wish to pursue the important experience of using the NHP model. This non-NIH funded training program will give residents an integrated and comparative approach to the value and limitations of the wide array of NHP research models, and serve as a continuing education forum for DCM veterinarians and other ONPRC interested professional staff.

ANIMAL SERVICES: DIVISION OF COMPARATIVE MEDICINE (DCM) RESEARCH STRATEGY

SIGNIFICANCE.

The Division of Comparative Medicine (DCM) provides superior NHP animal models and research support services to facilitate scientific discovery in the ONPRC's pursuit of human health advancement. To accomplish this mission, DCM maintains a robust, specific pathogen free (SPF) nonhuman primate (NHP) population, and is directly responsible for their humane care and use: animal husbandry, breeding programs, veterinary care, disease surveillance and prevention, psychological well-being, surgical and technical support, and pathology services.

Collectively, the ONPRC NHP population consists of four primary species divided into two larger breeding colonies and three small nonbreeding research-only populations:

- *Macaca mulatta* (4,221 Rhesus macaques - principally of Indian origin only for the SPF/eSPF breeding colonies, although some imported and SPF Chinese-origin; 1,483 research only)
- *Macaca fuscata* (350 Japanese macaques breeding colony of 212 animals; 138 research only)
- *Macaca fascicularis* (148 Cynomolgus macaques for research purposes only)
- *Papio anubis* (10 baboons used for research purposes only)

Total NHP population exceeded 5,000 animals in May 2012, of which approximately 2,000 are currently housed indoors. Although colony numbers are continuously adjusted, we anticipate remaining consistently at or slightly above this number of NHPs for the foreseeable future due to forecasted research needs and facility infrastructure. As of January 2013, the actual number of NHPs at the ONPRC totaled 4,729.

The primary focus of the DCM Division has been the development and provision of a proficient professional, technical and husbandry care, and to promote successful staff integration with the animal research model programs of the now four Scientific Divisions, in both supporting and contributory roles. To the extent all university requirements are satisfied, permanent veterinary staff are also adjunct faculty within the Department of Comparative Medicine at the Oregon Health Sciences University (OHSU), our host institution. In addition, the ONPRC recognizes the critical need for future veterinarians with specific expertise in NHP models, and participates in a newly organized laboratory animal medicine training consortium (OSU-ONPRC-OHSU). Recognized by the American College of Laboratory Animal Medicine (ACLAM), the initial 3-year resident was funded by the ONPRC in 2012.

As Associate Director and Chief of the Comparative Medicine Division, Excluded by Requester provides management oversight of the professional, technical and husbandry staff supporting the ONPRC, and directs the animal resource as the Attending Veterinarian. His background includes experience as an Attending Veterinarian and on-site clinical veterinarian for BSL-2 and 3 protocols using rhesus, cynomolgus and pigtail macaques for infectious disease research protocols; corporate oversight for both the Alamogordo Primate Facility (200+ chimpanzees) and an NIAID free ranging rhesus breeding colony of over 4,000 animals; and the managerial oversight for staff and resource utilization at multiple NIH institutes using nonhuman primates. Excluded by Requester is assisted in these duties by Assistant Associate Director Excluded by Requester hired in August 2011. Excluded by Requester also provides direction and mentoring for the newly established ACLAM-recognized laboratory animal medicine residency training program, as well as overall supervision of the animal care and use program, to include the management of all breeding colonies, subsequent animal allocation to research programs, and the successful provision of animal-related research support services. Since his arrival in May of 2012, Excluded by Requester practical knowledge and familiarity with the development of NHP research models has allowed him to continually maintain the ONPRC colony at the optimum target population, to provide the requisite number of animals for AIDS research, to genetically characterize the colony, and to ensure SPF colony status for future requirements.

Proper management of the animal resource is achieved through a centralized animal care program. Excluded by Requester manages a division consisting of approximately 140 personnel: 14 veterinarians (clinical, surgical, pathology, research support, residents), 1 PhD behavior professional, 62 animal husbandry technicians, 15 clinical medicine support personnel, 15 certified veterinary technicians, 7 surgical technicians, 3 pathology technicians,

5 small laboratory animal technicians, 19 NHP operations, resource management and supervisory personnel, 1 medical technologist, 8 behavior technicians, and 4 clerical positions. The staff is well trained and possesses the requisite certifications and licenses for performing animal husbandry and technical procedures; providing clinical medicine, surgical and pathology expertise; and ensuring leadership and management. The DCM currently provides service support and clinical care for approximately 115 ongoing NHP-based research projects.

INNOVATION.
From an overall Center perspective, the DCM has instituted programmatic changes to improve and enhance divisional capabilities:

Organizational Structure. The center recruited Excluded by Requester to replace Excluded by Requester when she left to take a faculty position at the University of Arizona. Excluded by Requester made significant progress at increasing veterinary and support staff, based on time-in-motion analyses that she completed in 2010 and 2011. Excluded by Requester has refined the organizational approach to optimally align staff functions for increased efficiencies, and to institute a new focus on research integration, training and professional staff development. The division has been reorganized into seven units, which are more functionally aligned to meet service support and workflow requirements. Noted improvements in organizational support and redirection include the following:

- Recognizing the need for additional executive leadership support, the position of Assistant Associate Director of DCM was created. Filled by Excluded by Requester this position assists Excluded by Requester with DCM administrative functions including regulatory compliance, IACUC membership and leadership, executive management of DCM, and proxy representation of DCM for Dr. Taylor in his absence.
- Although individuals units continue to oversee their respective budgets, overall DCM financial administration has been rolled into the ONPRC Business Office to eliminate redundancy.
- Excluded by Requester nd the colony hospital were moved from the Clinical Medicine Unit (CMU) to directly support the Resources-Facilities-Operation (RFO) Unit, primarily for breeding colony support.
- CMU now consists of four veterinarians that, to the extent possible, equally share breeding and research clinical responsibilities; each scientific division now has a dedicated clinical veterinarian assigned.
- Shortly following his arrival, Excluded by Requester established a new Research-Education-Training (RET) Unit. In addition to his administrative role, Excluded by Requester eads this Unit to provide 1) focus on the integration of DCM veterinarians as team members of the ONPRC research enterprise, and 2) a centralized approach and resource management for professional education and training of all DCM staff, including oversight of the newly established ACLAM-recognized LAM residency program.
- Finally, a Quality Assurance Specialist position has been added to generate a more focused approach on process improvements through self-directed oversight audits and incremental assessments and refinements of personnel performance and program support.

Systems Management. By contracting with local experts in systems planning from Portland State University, DCM specifically and the ONPRC collectively, will be able to simulate the multitude of parameters we must optimize to effectively forecast NHP demand, use and populations over varying time periods with changing but limited infrastructure. Because our breeding and research colonies are a highly complex system, effective management of the system must balance research needs with the health of the colony as a whole, including concerns of genetic diversity, disease management, and behavioral issues that arise when large populations of NHPs are kept in confined areas. Early indications have confirmed that although systems modeling may not remove all uncertainty, development of a computer simulation tool can be successfully used to identify bottlenecks, leverage points, and potential animal resource management changes that could be evaluated to improve the performance of the breeding program, with respect to both research and resource objectives. We anticipate that by simulating various resource management approaches *in silico*, animal resource managers and research investigators will be given the opportunity to extrapolate potential consequences of proposed changes with a degree of formalism that cannot be obtained in the absence of careful consideration of whole-system dynamics.

Quality Assurance. An often overlooked yet vital piece to building and maintaining management excellence and superior performance, even with a well functioning program, is Quality Assurance (QA). With the addition of a Quality Assurance Specialist position, DCM will institute a focused approach on improving services and outcomes, as well as to enhance the performance of personnel and program support over the next Grant cycle. With additional representatives from each DCM unit performing as self-inspection Quality Program Teams (QPTs), the "Quality Management Program" (QMP) will serve to incrementally enhance processes that are used to manage all aspects of research support resources and programs such as animal procurement, production, husbandry, and clinical care. The QPTs will audit individual activities, review processes and records, evaluate incident and accident reports, and define how well the DCM meets its programmatic obligations. The QMP will rely on the already extensive SOPs in existence, personnel training, and project management. Complementing QA, a formal training process established by the RET Unit will be used to assure that employees reach the level of proficiency required to perform the procedures in accordance with established performance standards. The QMP will be utilized to evaluate problems and advise on approaches for DCM management to readily implement corrective and preventative action.

Investigator Collaboration. DCM veterinarians maximize the research value of NHPs through supporting staff activities and individual unit expertise. Importantly, DCM manages outstanding ONPRC animal and infrastructure resources to facilitate NHP research, including the U24 resource that provides expanded Specific Pathogen Free (eSPF) rhesus macaques of Indian origin, the U42 resource to provide SPF rhesus monkeys of Indian origin for AIDS-related research, a Japanese macaque resource for promising studies of the Japanese macaque encephalomyelitis model of multiple sclerosis-like disease and the macular degeneration model or Drusen, and the unique facilities (ABSL-2/3 containment) to house and study animals infected with pathogenic agents. Additionally, several immunological reagents, molecular genetic manipulation and surgical techniques, and advanced imaging approaches have been created and validated in NHPs. These tools assist in the determination of host-pathogen interactions in NHPs that before now were only accessible with inbred rodent models through genetic knockouts. The translation of these integrated NHP studies will increase our understanding of host-pathogen interactions to develop more rationale approaches to prevent and treat infectious disease in humans. Thus, the DCM's ability to quickly recognize and address specific NHP disease states and normative processes throughout the life of an NHP permits timely contributions to the care and interpretation of NHP data and behavior collected at the ONPRC. Hence, our professional staff collaborations enhance scientific discovery when using ONPRC NHP models.

In addition to the role DCM plays with regard to each scientific division contribution, individual units within the division continue to make significant strides at investigating novel solutions, instituting cost-effective measures, and inventing new and improved solutions, examples of which are noted below:

- Maximized corral populations to increase the number of animals socially housed, and improved genetic diversity for production by dramatically increasing genetic typing prior to group formation.
- Modified the Timed Mated Breeding (TMB) program to increase efficiency and effectiveness of this resource in providing infants, while providing a more natural social environment for breeding females.
- Implemented a foster-mother program pairing abandoned or orphaned infants with older females with demonstrated success at infant rearing, which subsequently moves infants out the nursery and into a more natural parent/infant relationship, thereby reducing stress and the development of abnormal behavior.
- Enhanced electronic health records by the addition of a Master Problem category to allow more accurate tracking of disease and injury, streamlined SNOMED coding to improve the searchability of records, added a web-interface so that records could be accessed more readily, and developed SQL queries for Morbidity and Mortality and common research queries.
- Developed the Primate Pathology Image Database (PPID): ARRA Supplement awarded in 2009 in collaboration with California NPRC and BIRN, to participate in the development of a readily searchable and accessible database of images of NHP Pathology for use in teaching and research.
- Implemented novel methodologies and instrumentation to enhance the research value of procedures while minimizing invasiveness and distress: experimental induction of endometriosis, interventional MRI

platform to support Huntington's disease research, development of Roux-en-Y gastric bypass procedure for rhesus macaques.

- Computational tools were developed for high volume bronchoalveolar lavage, bone marrow aspirate, lymph node biopsy, and GI endoscopy procedures to maximize efficiency, consistency, and precision of workflow. Some funding assistance was received from the NHP Consortium, and in collaboration with the WiNPRC, Mathematica® based tools were easily adaptable and became available to other NPRCs at no cost.

Center-wide, the ONPRC scientific divisions and DCM practice a hand-in-glove approach to efficient and effective NHP and infrastructure utilization. Improvements and innovations within DCM directly contribute to scientific discovery at every level. Veterinary integration as protocol team collaborators thus allows time sensitive decisions and capture of scientific relevant data.

APPROACH.

reviewers' comments

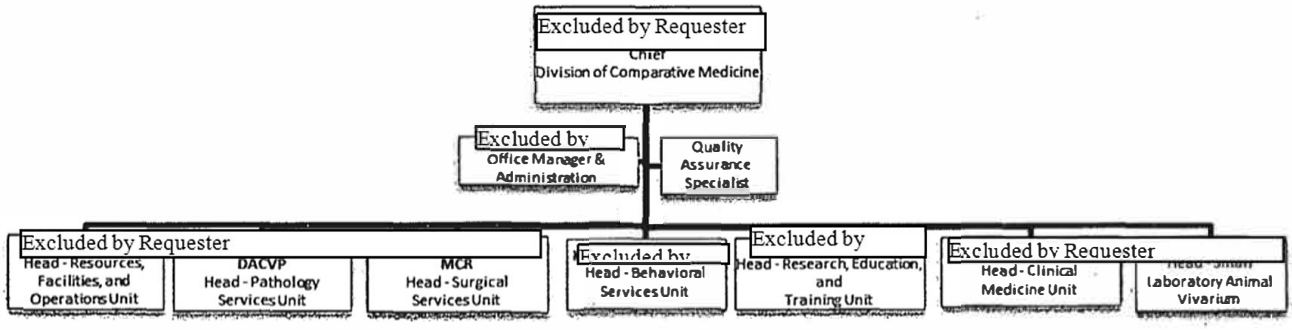
reviewers' comments

Progress Report. During the past grant interval, the DCM continued to redefine and refine their management approach and business model in order to meet animal population expansion, DCM staffing changes and continuing advances in the ONPRC science program.

- Following the last Site Visit, DCM underwent significant re-organization including elimination of the Unit Manager, Control Coordinator (product) and the Purchasing Agent. The functions of these positions were re-allocated to existing DCM units as well as to Business Services to eliminate redundancies noted by internal and external program review. The administrative functions associated with NHP colony management, allocation and animal assignments are now part of the RFO Unit headed by Dr. Excluded by Requester. New additions to the DCM team include a Containment/ABSL3 Research Support Manager, Training Program Coordinator, the RET Unit head (and Assistant Associate Director), and establishment of a Quality Assurance Specialist (process) position.
- Facility Security building is completely operational. The building contains five rooms totaling Specific Animal Location SPF NHP housing, as well as two separate Specific Animal Location NHP suites containing four total animal rooms, two necropsy/ procedure rooms and required support space. ARRA supplements funded staff increases for the newly opened facility by 15 FTE over a two-year period.
- In July 2010, the ONPRC participated in the three-year AAALAC, International site visit. The site visit resulted in Continued Full Accreditation, with seven commendations and no major deficiencies.
- DCM partnered with the Center director to develop an NPRC-wide strategic plan for future growth and expansion; clearly defined strategies and tactics are now identified for forward progression in support of the Center's mission and vision. The Director invited an external review of the macaque breeding colonies in the fall of 2011. External reviewers from Washington, Tulane and NIH provided recommendations regarding resource management, allocation, and prioritization that continue to be adopted.
- Developed and implemented an emergency mitigation plan, and participated in the emergency preparedness drills associated with the Center adopting the Incident Command System (ICS). Several DCM members are now ICS trained to the 700 level.
- DCM faculty and staff continue to lead and participate in the NPRC Consortia, including Virtual Grand Rounds, Breeding Colony Management, Pathology, Behavioral Management, IT, the Clinical and Surgical Techniques Working Group, and the Data Access Guideline Group. Consortium participation has resulted in collaborative projects, publications, grant applications, and sharing of resources, best practices and efficiencies to NPRCs at no cost.
- DCM continues to seek methods for data-driven management by partnering with the Information Technology Group. Three clinical veterinarians are directly integrated with the LabKey® transition process, and bar-coding was introduced to leverage this methodology for direct data entry and paperless operation at all levels in the vivarium.
- DCM continued focus on leadership and organizational development. Annual leadership retreats are augmented by senior and middle management leadership classes. Classified lead technicians also participate in the Lead Worker training series. All professional staff participated in a DCM Leadership Workshop in 2012 to characterize divisional strengths, and to determine priority actions and resources

for the future. Several veterinarians and technical staff have completed the OHSU Leadership Foundation training, an eight week, nine session certificate series designed to provide OHSU managers with a broad understanding of the behaviors, tools, and resources needed to be successful in a leadership role at OHSU.

Operational Efficiency. To optimize resources and infrastructure, the DCM is organized into the following seven Units under the direction of the Division Chief/Associate Director: Resources-Facilities-Operations (RFO), Pathology Services, Surgical Services, Behavioral Services, Research-Education-Training (RET), Clinical Medicine, and the Small Laboratory Animal Unit.



A snapshot synopsis of each DCM Unit is provided below to provide a quick overview of the breadth and scope of the DCM Division. However, every Unit is described separately and in far more detail than can be afforded here.

- *Administration.* Excluded by Requester is Chief of the Division. Excluded by Requester reports to Excluded by in an senior administrative capacity as the Assistant Associate Director. Also assisting Excluded by Requester the Office Manager is responsible for purchasing, record keeping, clerical support, budget development and oversight, and statistical support data entry. A new Quality Assurance Specialist position reporting to the Division Chief has been established to independently assess DCM service processes, thereby enhancing the oversight and improvement in the performance of personnel and program support.
- *Resources-Facilities-Operations Unit (RFO).* Managed by Excluded by Requester the RFO is responsible for the multiple activities related to daily care and use of NHPs, including research support, animal facility management, and equipment maintenance and replacement. Reporting to Excluded by Requester Prongay supervises the Colony Hospital and is primarily responsible for the clinical oversight and management of breeding colony NHPs, as well as clinical epidemiology. The RFO Unit also manages animal resource development and the project assignment process. The RFO consists of supervisory, lead and staff technicians assigned a variety of duties, including routine animal husbandry care and observations, support of the environmental enrichment program, weekend and evening supervision of the animal care staff, research protocol support, time-mated breeding colony management, diet preparation, and initial clinical oversight of breeding colonies.
- *Pathology Services Unit (PSU).* Managed by Excluded by Requester the PSU is responsible for diagnostic and pathology support, and operation of the clinical pathology laboratory. The PSU has four veterinary pathologists who perform gross necropsies and microscopic examination of tissues in support of animal disease diagnosis and surveillance, and participate in collaborative research and characterization of spontaneous diseases of NHPs. The unit also coordinates necropsy, histology, clinical pathology and tissue distribution services. Excluded by Requester is responsible for all activities in the clinical pathology laboratory.
- *Surgical Services Unit (SSU).* Managed by Excluded by Requester, the SSU provides surgical services for research programs and colony animal health, as well as research and clinical support as needed. Dr. Excluded by Requester and the Surgical Services Manager oversee six certified surgical technicians. This unit is responsible for conducting surgical procedures, providing anesthesia induction and

monitoring, monitoring pre- and post-operative care, providing training to other technical and investigative staff, and the supervision and leadership to subordinate surgical technical staff.

- *Behavioral Services Unit (BSU).* Managed by Excluded by Requester (NHP Behaviorist), the BSU is responsible for placing NHPs in compatible pair housing, behavior assessments, environmental enrichment, operant training, and studies that examine psychological well-being issues. Staff includes an animal behavior manager, five behavior technicians, and an environmental enrichment coordinator. The unit provides social opportunities and environmental enrichment to promote species-typical behaviors, and to promote animal well-being by developing and implementing relevant techniques, devices and procedures.
- *Research-Education-Training Unit (RET).* Directed by Excluded by Requester, the RET is principally responsible for the Laboratory Animal Medicine veterinary resident program oversight, curriculum and unit rotations; SOP coordination and approval; and DCM collaborative efforts with Scientific Divisions to continually define and refine unique metabolic and clinical differences between normal NHPs, and Special NHP Resources (aged, obese, infectious disease, TMB and Japanese macaques), integrating relevant investigator data into NHP medical records, and developing computer tools to determine more accurate diagnostic or prognostic indicators. New employee training, as well as professional and continuing education, have also been centralized under the RET Unit to improve resource allocation and training oversight.
- *Clinical Medicine Unit (CMU).* Directed by Excluded by Requester, the CMU has four veterinarians dedicated to clinical care and preventive medicine of primarily research assigned NHPs. The unit includes the CMU manager, lead veterinary technicians and junior veterinary technicians, all of which are Certified Veterinary Technicians. Excluded by Requester along with Excluded by Requester in the RFO Unit, are collectively responsible for the provision of veterinary care and research support of all NHPs.
- *Small Laboratory Animal Unit (SLAU).* This rodent and rabbit vivarium is an independent university service center not supported by the P51, and thus provides a mechanism for non-NHP animal research performed by ONPRC investigators. Under agreement from OHSU, Excluded by Requester manages this resource. Reporting to Excluded by Requester is a small laboratory animal manager and four dedicated husbandry technicians staff the facility. The SLAU provides assistance in protocol development and implementation, as well as comprehensive health care and colony health monitoring.

Research Support Services. DCM professional, technical and care staff collectively provide support across all science Divisions. As several programmatic areas overlap to varying extent, DCM cross-support capabilities are a significant strength since DCM broad-based NHP behavioral knowledge and expertise contributes to all research models. DCM veterinarians create behavioral, clinical and/or surgical therapies and techniques for each NHP model to investigate etiology and improve diagnostic protocols and treatment regimens. And specific veterinarians are assigned during the formation of interdisciplinary groups scheduled to use the NHP model in translational research. Despite economic instability, Core and Affiliate Scientists continued to enjoy remarkable success in competing for grant support for their respective research programs, with the direct support and assistance of competent and dedicated DCM professional, technical and husbandry staff. During calendar year 2011, the DCM provided housing, husbandry, veterinary care, and research support for 4,713 NHPs (as well as 15,205 rodents and 68 rabbits). Although the approximate average daily census is 4,500 NHPs, and is currently the maximum number of primates for existing ONPRC infrastructure, we have housed as many as 5,000 animals in 2012 on several occasions. Although not all inclusive, the DCM core research support program provides the following services:

- Collection of blood samples
- Multiple agent administration modalities
- Preparation and distribution of specialty diets
- Ultrasound-based reproductive evaluations
- Physical examinations, limited visual assessments and clinical case evaluations
- Dental procedures, including full cleanings, extractions, and gingival flap procedures
- Clinical laboratory testing including CBC, chemistry panels, electrolytes, and parasitological exams
- Serologic assays for NHP viral pathogens, and virus isolations in support of Center surveillance

- Provision of supplemental care and oversight for challenging infectious disease models, weight management cases, geriatric rhesus macaques, obese animal resource, and a time-mated breeding colony
- Surgery support includes surgical model development and implementation, anesthesia administration and monitoring, multimodal analgesia protocols and various research sample collection techniques including, but not limited to, bronchoalveolar lavage, lymph node biopsy, CSF aspirate, GI endoscopy and laparoscopic follicle aspiration.

Facility Infrastructure. The facilities for NHP housing and research are located in eight DCM-owned facilities, eight outdoor one-acre corrals with associated catch areas, and thirty-two Sheltered Group Housing Units. DCM also manages indoor facilities in 7 buildings. The ONPRC has added several new animal buildings for NHP housing to keep pace with the expanding research program, including four sheltered group housing units and a biocontainment building of caged housing, which includes of conventional ABSL-2 housing and of ABSL-3 space). Continued construction will bring of group and indoor housing on line in the Spring of 2013, and an expansion project in the design phase will add and six additional ABSL-2+ animal holding rooms when completed in the Fall of 2013.

Regulatory Compliance. The DCM veterinary staff is collectively responsible for the ONPRC Animal Care and Use Program, including complete implementation of applicable policies from the Public Health Service (PHS), Association for the Assessment and Accreditation of Laboratory Animal Care (AAALAC International), and the USDA Animal Welfare Act, to ensure regulatory compliance and best standards of practice. Since the DCM imports, houses, and conducts select agent research, other agencies with which the DCM interacts also includes the U.S. Fish and Wildlife Service (FWS) and Centers for Disease Control and Prevention (CDC). DCM staff use the *Guide for the Care and Use of Laboratory Animals (Guide,* 8th Ed, NRC 2011*),* as its primary document for performance standards. The ONPRC is inspected by the USDA no less than annually (more often twice a year), and has successfully maintained AAALAC Continued Full Accreditation since 1974. The Attending Veterinarian, the Associate Director of Administration, the Office of Research Integrity, the IACUC, and members of the research and veterinary staff review current local, state, and national policies and guidelines, and collectively inform the IO of any required programmatic changes.

Training and Personnel Development. The ONPRC maintains an established culture of learning and educational growth through training of professional, technical and husbandry staff. The primary focus of the DCM Division has been the development of skilled and proficient staff to promote successful integration with the program focus of the Scientific Divisions, in both support and contribution roles. As teaching and training remains a high priority for the DCM, the Center provided NHP training for 34 veterinary externs during the last grant interval, including the sponsorship of 3 veterinary residents using an R25 Nonhuman Primate Veterinary Clinical Education Program grant (completed in 2012), and together with OSU and OHSU, established an ACLAM-recognized Oregon LAM Residency Consortium; the first ONPRC sponsored veterinary resident entered this 3-year program in 2012.

Over 85 management, animal care and surgery technical staff are certified for their competency, either by the American Association for Laboratory Animal Science (AALAS), or other licensing authority, and greater than half of those certified are at the progressively more difficult levels. Forty-five of the DCM animal care or surgical technical staff have B.S. or B.A. degrees, and one has an M.S. degree. Two DCM animal care technicians have A.A. degrees in veterinary animal health technology. All surgery technicians are certified by the Academy of Surgical Research, and the PSU has 2 full-time assistant prosectors and 3 histotechnologists, one of whom has H.T. certification.

Training and education have been centralized within the Research-Education-Training Unit. Many animal care personnel have received their training through in-house classes and long-term on-the-job experience. Newly hired DCM employees participate in a series of didactic training sessions and hands-on/shadowing training prior to independent task assignments based upon Division SOPs. Training subjects include reviews of environmental health and safety topics, reviewing updated SOPs, explanation and expectation of current and future research projects that require DCM technical support, and information related to preparation for AALAS

certification.

Research personnel are required to attend Basic Primate Well-Being training prior to receiving access to areas where primates are housed. This program discusses NHP psychological well-being and basic clinical aspects of primate care. This program is considered Tier I training and is presented by the Research Integrity Officer (RIO). Research staff desiring to work directly with primates assigned to their projects must demonstrate competency in animal restraint, sedation, blood sampling, and drug administration. This is considered Tier II training and presented by various DCM staff that are subject matter experts for the specific training given. All research staff are required to be recertified every three years in these areas. Any research staff wishing to participate in surgical NHP procedures must be certified by the Head of the Surgery Unit or the Assistant Surgical Veterinarian, and must receive appropriate training from the surgical staff. This is considered Tier III training and the Head of the Surgery Unit or Assistant Surgical Veterinarian and their staff monitor all NHP surgical procedures. Staff who are expected to 1) work with the use of hazardous agents, 2) work with animal tissues or body fluids, or 3) perform anesthesia, surgery or euthanasia, must receive additional training as applicable from the Principal Investigator, clinical veterinarians, DCM supervisory personnel, or Research Safety Program/Environmental Health & Radiation Safety (RSP/EHRS) staff, as appropriate.

Electronic Animal Records System Transition (IRIS to LabKey®). The Integrated Research Information System (IRIS) contains all animal records, surgery and pathology data, sponsored projects information, IACUC records, and DCM administrative data, including an electronic billing system for animal related charges. This includes all clinical procedures as well as experimental use, reproductive history, and demographic data for the life of each NHP at the Center. IRIS has been in existence for over 40 years. Continued upgrades have maintained its utility, but programmatic limitations, serviceability requirements and inherent restrictions for future use make this database problematic in the short term and unusable in the long term. Thus, transition to a new and improved computerized NHP electronic medical record and research data management system, LabKey®, began implementation in 2012. An 18-month endeavor, this comprehensive data system for all ONPRC divisions and DCM units will retain information regarding every animal currently or previously maintained by the ONPRC. DCM personnel have begun to input data and assist with questions and data retrieval essential to the ongoing activities of the LabKey® transition. Three clinical veterinarians were front-loaded in this highly iterative process to ensure a strong clinical perspective as the DCM informatics liaison for all IT changes. The new system is more robust and user friendly, and is expected to readily facilitate data entry and extraction through complementary data management tools, while still maintaining access to historical data. LabKey® should prove to be a significant resource to the Center, and allow DCM to leverage decisions regarding animal movements, animal procurement planning, operation of the specific-pathogen-free breeding programs, preventive medicine, psychological well-being programs, evaluation and documentation of animal histories, facilities planning, and general administrative oversight of colony operations. Additionally, LabKey® will be utilized to implement billing operations within DCM for cost-recovery per diem, facilitate animal assignments and research support activities, as well as maintain detailed research protocol information such as animal numbers, approved dates, procedures and personnel. This new system is anticipated to provide a significant benefit for researchers, clinical and administrative personnel alike.

Outreach. OHSU maintains an outstanding office of Strategic Communications that interfaces with ONPRC and OHSU to promote the unique nature of the Center within the University and the community. Excluded by Requester, is the Senior Outreach Advisor, and Ms. Diana Gordon is the Education Outreach Coordinator at the ONPRC. As such, they represent ONPRC in state and local governmental organizations; coordinate outreach programs to students, teachers, and local citizens; and determine optimal community interactions via a Community Advisory Board. The ONPRC enjoys a regrettably high degree of exposure to animal extremist groups and has been targeted in the last several years. Thus, the OHSU/ONPRC partnership has been crucial to assure adequate security and accuracy of public information. ONPRC efforts at Public education have also been substantial and critical to our stature in the community, and DCM participation plays a critical role in student and teacher education of NHP biomedical research. For example, twelve veterinary and technical staff volunteered to help Excluded by Requester organize and host an all-day activity for over 70 middle school children, called "Camp Monkey", prior to the August, 2011 Society for the Study of Reproduction (SSR) meeting in Portland. Co-sponsored by SSR and ONPRC, the day included activities to learn about monkeys

and their value in research, primate reproduction and development, and issues related to reproductive health. Efforts succeeded in attracting students from several different school systems, including disadvantaged children with little science background. Its resounding success (as documented from students, parents and volunteers) led to the decision to provide this "camp" on an annual basis. Division veterinarians also participate in other educational opportunities, including presentations to secondary education science forums, veterinary school and law school classes.

Future plans. The Division of Comparative Medicine has a remarkable opportunity to broaden its impact in NHP research and training. The solid expertise of our faculty and the special resources of the ONPRC provide DCM with unique opportunities to characterize NHP models, as well as to serve as a teaching ground for professional staff dedicated to supporting these unique animal resources. While most research institutions are limited to the use of rodent animal models, research at the ONPRC includes a large contingent of NHPs with access to a small animal vivarium component. This blend of resources allows integration of research pre-clinical data and animal model information in the quest to better understand normalcy and disease in NHPs. Finally, the value of NHPs for "pre-clinical" research bridging the knowledge gap between traditional laboratory animal models and humans is receiving increasing attention as a valuable component in the portfolios of NIH institutes and pharmaceutical/biotechnology companies with research agendas in all science disciplines supported by DCM. Within this context, the Division will focus its activities on:

Specific Aim 1: Provide a reliable number of healthy, genetically defined and pathogen-free source of NHPs. The DCM will continue to optimize NHP breeding consistent with physical infrastructure and the anticipated need and diversification of the ONPRC scientific programs. ONPRC scientists and leadership is expected to mutually define the requirements based upon programmatic priorities, the need to accommodate animal containment, and the necessary limitations posed by existing and projected regulatory, budgetary, facility, technical and staffing limitations. Scientific program growth is projected:

- The Division of Pathobiology & Immunology (DPI) will expand NHP models of emerging infectious and chronic disease, a program largely supported by the Pacific Northwest Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research (RCE) (U54 RFA-AI-08-002), as a joint program between OHSU and the University of Washington. The development of vaccines for vulnerable populations and the use of functional genomics and genetics to understand pathogen-host response for biodefense organisms and emerging disease focused on multiple viral pathogens will all involve NHP components.
- Following pilot studies (2008-9) and a subsequent R21 grant from NCRR for model development (2010-12), the Division of Diabetes, Obesity and Metabolism (DOM) is anticipating the development of a new center that will use the NHP macaque model to provide new information on the actions of androgens and diet/obesity-related factors on reproductive function.
- The Division of Reproductive and Developmental Sciences (DRDS) will use the NHP model to study the causes and prevention of preterm labor and the effects on neonatal health. The NHP remains the optimal model for unraveling the mechanisms controlling pregnancy in women from implantation and establishment of the fetal-placental-maternal unit, through intrauterine fetal development, to onset of labor and delivery of the infant.
- The increased demand for adult female macaques for studies related to women's health will require continuation of the SPF breeding program as well. DCM expects that demand may likely exceed supply, thus the breeding colony will be supplemented with importation of adult female rhesus macaques, and the purchase of animals from other primate Centers to meet demand.
- A $125 million philanthropic gift from recently awarded to OHSU for cardiovascular research is expected to include an NHP cardiac catheter laboratory at the ONPRC. The resultant interdisciplinary program and new infrastructure will increase demand for a ready supply of SPF animals from the Center.

Commensurate with scientific program growth, increased demand will be met in several ways: 1) increased production when time and infrastructure permit, 2) importation for surge requirements if quarantine space and research capacity will allow, and more likely 3) a balance of careful planning, breeding and imports based upon animal utilization approvals, population management practices and selective resource allocation to avoid over

commitment without scientific prioritization based upon scientific program strategy. Frequent discussions with the NHP Resource Managers (in Aging, Obese Macaques, Infectious Diseases, and Japanese Macaques) will facilitate this planning and usage.

Historically, genetically defined primates were not critical to scientific discovery when using NHPs. However, with the advent of the genomic explosion, major histocompatibility characterization of NHP models, particularly in infectious disease research is now a must have. Specifically, the DCM intends to improve management of colony genetics by applying 3rd generation population-based genetic management tools, incorporating population-level genetic structure and heterogeneity-monitoring statistics. Since the last P51 proposal, we have substantially improved our approach to providing genetic analysis for proposed new breeding groups, the primary point at which genetic diversity may be reduced. Although genotype data at microsatellite markers has been used for many years to establish the parentage of offspring born into the breeding colony, the ONPRC will transition early in the grant cycle to using a panel of 96 single nucleotide polymorphism (SNP) markers developed for parentage analysis by the OD/ORIP-supported Genetics and Genomics Working Group. Dr. Excluded by Requester as an ONPRC member of both this group and the NHPRC Consortium, is currently transitioning the ONPRC to parentage analysis based on a 96-SNP array and analysis pipeline, and anticipates a corresponding improvement in the accuracy of pedigree data.

The RFO Unit continuously strives to improve the quality of the animal resources by improving our pathogen monitoring program, and we will continue to enhance our screening and diagnostic technologies. We also propose to improve our colony health and genetic testing capabilities to ensure Specific Pathogen Free (SPF) animals in the next funding period. Based on the continued pattern of low MTBC incidence among imports and the recognition of a continuum of MTBC clinical and immunological manifestations in macaques (Lerche 2008; Dutta 2010), our screening and diagnostic program uses multiple diagnostic tools for tuberculosis surveillance, including serial TST with clinical examinations, serological assays, and molecular diagnostic tests run in parallel. We are also anticipating approval for participation in a Private Source MTBC study and

Pending Support

Finally, with the recognition that a breeding colony is a highly complex system, effective management of this system must balance research needs with the health of the colony as a whole, including concerns of genetic diversity, disease management, and behavioral issues that arise when large populations of NHPs are kept in confined areas. To that end, a team from the Systems Science program at Portland State University has begun development of a computer simulation tool to identify bottlenecks, leverage points, and potential animal resource management practices that can then be extrapolated to forecast the performance of the breeding program, with respect to both research and resource objectives. By simulating various resource management approaches *in silico*, animal resource managers will be given the opportunity to evaluate expected consequences of proposed changes with a degree of formalism that cannot be obtained in the absence of careful consideration of whole-system dynamics. We anticipate a reduced scope validation of the model in 2013, with the likelihood of incorporating system management approaches ONPRC-wide in 2014.

Specific Aim 2: Develop improved strategies for the socialization of NHPs. Using NHPs presents unique challenges. The Guide has recently been updated and housing standards have been further enhanced. In addition, European Union guidelines will likely expand socialization requirements, which may well influence further such requirements in the U.S. In fact, the USDA has unequivocally mandated that animals must be pair housed if they do not have an IACUC approved exemption from socialization. To be in compliance with the new guidelines, exclusions from social housing must be based on the reason that the experimental design would be compromised if the animal were socially housed, an animal must be singly housed due to

incompatibility, or the animal has been determined to be overly aggressive, has contagious disease, or is debilitated.
Collectively, the above restrictions only serve to remind us of the fact that NHPs are intelligent, sentient beings deserving of focused attention on superior housing conditions when used for biomedical research. Thus, the DCM, and specifically the BSU, will explore new opportunities for social compatibility assessment and enrichment, including the use of facial recognition methodologies, the addition of exercise pens, bedding enhancements and indoor/outdoor housing improvements. To ensure compliance, BSU staff will continue to be responsible for ensuring that any exempt animals are provided with additional enrichment devices, and that non-exempt animals will be socially housed. They will also continue to use the positive reinforcement training program to enhance socialization, reduce stress, and train animals for voluntary sampling whenever possible. In addition, the Associate Director will continue to meet frequently with all DCM managers and supervisors to ensure compliance and develop strategies to improve the quality of life for the animals at the Center. Notably, the BSU has implemented a positive reinforcement training program and developed novel treatment strategies for animals with abnormal behaviors. Nevertheless, the DCM staff will continue to work with investigators and Facilities personnel to design and improve housing at the ONPRC. Further, the RFO Unit Head will lead an effort to explore novel use of caging and the design of innovative housing systems to enhance animal welfare and socialization, based on the ability to connect any of the new Group 3, Group 4, Group 5, or Group 6 cages in combination. Such flexible design enhancements will facilitate positive reinforcement training and pair housing strategies.

Specific Aim 3: Train the next generation of veterinarians dedicated to the advances in the understanding and improvement of NHP models. It is well recognized that the NHP is an important and often superior research animal that emulates human disease progression more accurately than any other preclinical species. However, there are a relatively small number of veterinarians that possess the clinical expertise to support these valuable models. Recognizing this fact, the ONPRC has entered into a LAM resident training consortium with OSU and OHSU to provide opportunities to veterinarians that wish to pursue the important experience of using the NHP model. This comprehensive training program permits access to the full spectrum of animal models across three unique academic and research institutions, giving the resident an integrated and comparative approach to the value and limitations of the wide array of NHP research models at the ONPRC. We believe that the having such an experience will give our veterinary residents a competitive edge for a broader range of future positions. And now that DCM has an established ACLAM-recognized LAM Training Program, resident-eligible DVMs will be encouraged to submit applications for positions as they become available. Typically two resident positions are filled, with selection of an additional resident every other year. The LAM Training Program also serves as a continuing education forum for DCM veterinarians and other interested professional staff not normally eligible for board certification.

Since an important part of the Division's mission is to train the next generation of veterinarians dedicated to advancing the understanding and improvement of NHP models, DCM will continue to provide opportunities for undergraduate, graduate and postdoctoral training within the division. Undergraduate training will be offered primarily as 2-4 week externships throughout the calendar year. Division veterinarians will review applications of those indicating interest in NHP and LAM. High quality students motivated to research careers will be interviewed, and several externs are typically selected. For some externs, this is their first in-depth laboratory animal medicine experience with exposure to NHPs in the context of the scientific method, modern research techniques and ethical issues of animal research. Graduate and postdoctoral fellow career development will be a continued focus of the DCM behavioral and pathology units respectfully. DCM veterinarians are also involved in mentoring trainees at several different educational levels across a broad range of NHP experiences. This experience will subsequently allow ONPRC post doctorate fellows, LAM residents, veterinary externs and graduate students to be competitive for a broad range of career opportunities in academic, government or commercial settings.

Program Director/Principal Investigator (Last, First, Middle): Robertson, Joseph E./Haigwood, Nancy L.

ANIMAL SERVICES-ADMINISTRATION DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Excluded by Requester	Dir-DCM/Assoc Dir	% Effort			Institutional Base Salary	73,677	18,419	92,096
	Admin Coord					23,933	8,377	32,310
To Be Named	Quality Assurance Specialist	6.00				27,500	9,625	37,125
	SUBTOTALS →					125,110	36,421	161,531

CONSULTANT COSTS		
None Requested	6,000	6,000
EQUIPMENT *(Itemize)*		
None Requested	0	0
SUPPLIES *(Itemize by category)*		
Office & Admin Supplies	10,000	
Software Rentals & Leases	9,000	
Minor Equipment	1,325	
Operating Supplies	1,060	
		21,385
TRAVEL		
Domestic	6,000	6,000
INPATIENT CARE COSTS		0
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		
None Requested	0	0
OTHER EXPENSES *(Itemize by category)*		
Equipment Rental & Leases	795	
Registration/Course Fees	795	
Shipping	125	
Training Program/Course Fees	530	
Maintenance - Equipment	292	
Taxes & Licenses	4,000	
Retention Program	7,950	
Telecommunications	17,490	
Memberships	4,250	
BioEng Fees	174	
		36,401
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 231,317
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 231,317

ANIMAL SERVICES-ADMINISTRATION
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	161,531	166,377	171,368	176,510	181,805
CONSULTANT COSTS	6,000	6,180	6,365	6,556	6,753
EQUIPMENT	0	0	0	0	0
SUPPLIES	21,385	22,027	22,687	23,368	24,069
TRAVEL	6,000	6,180	6,365	6,556	6,753
INPATIENTS CARE COSTS	0	0	0	0	0
OUTPATIENTS CARE COSTS	0	0	0	0	0
ALTERATIONS AND RENOVATIONS	0	0	0	0	0
OTHER EXPENSES	36,401	37,493	38,618	39,776	40,970
DIRECT CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	231,317	238,257	245,404	252,766	260,349
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	231,317	238,257	245,404	252,766	260,349
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					1,228,094

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

PERSONNEL

Associate Director, Division Chief – Excluded by Requester % Effort % Effort Provides overall supervision of the animal care and use program, to include the management of NHP colonies, subsequent support for research programs, and provision of research support services; provides oversight and direction for the laboratory animal medicine training program.

Administrative Coordinator – Excluded by Requester % Effort Responsible for centralized timekeeping and purchasing for the division, and is the primary divisional administrative support for the seven DCM core units; provides support for the DCM Incident Command System, and is responsible for DCM budget management. Other key responsibilities include acting as a liaison to other divisions and departments, unclassified employee onboarding, grants management, and database maintenance.

Quality Assurance Specialist – To be named :(12 calendar months effort: 6 ORIP, 6 Program Income). The Quality Assurance Specialist Position audits Division of Comparative Medicine unit procedures, reports, facilities, equipment and data for adherence to protocols and SOPs. This position also assists in the training of all technical staff to "quality related needs" as may be required. The Quality Assurance Specialist will thus maintain divisional systems of quality and compliance, reporting directly to the Division Chief on quality and compliance trends and possible service failures, ensuring resolution of outstanding issues while calibrating policy.

CONSULTANT COSTS

Consultant Costs: Funds are requested for the development, implementation and continuing support of a systems management simulation project for forecasting divisional resources using infrastructure requirements and scientific need.

SUPPLIES

Office & Admin Supplies: Funds are requested for office and administrative materials for all DCM units. These supplies include, but are not limited to: printer ink, bulletin boards, calendars, desk accessories, and pens for a staff of 131 employees. Area office supplies are essential to the normal operation of each unit, and are monitored for necessity at the time of purchase. Furniture purchases for new hires will also be drawn from this budget.

Software Rental & Lease: Funding is requested for a divisional subscription to online meeting software, and the accompanying long distance charges incurred during usage. GoToMeeting, the preferred meeting software provider, is indispensable with regard to the secure sharing of data across remote locations. This software also includes a teleconferencing feature that allows meeting attendees to call in toll- free, making it an extremely collaborative tool. Software is also requested in support of the Quality Assurance Specialist position and for upgrading systems currently in use by the Division Chief and Administrative Coordinator.

Minor Equipment: Funds are requested for the purchase of a desktop computer for the new Quality Assurance Specialist position, and for scheduled replacement of existing DCM administrative computers, as part of the ONPRC ITG computer life-cycle management initiative.

Operating Supplies: Funds are requested for supplies in support of the DCM Incident Command System. Supplies include: emergency vests and armbands, clipboards, flashlights, and maintenance and replacement of walkie-talkies. These supplies are necessary for communication and documentation needs during an emergency, and will allow emergency staff to respond appropriately to situations threatening the well-being of employees and animals on campus.

TRAVEL

Domestic Travel: Funds are requested for travel necessitated by the positions of Division Chief and Quality Assurance Specialist. Funds include 4 trips for the Division Chief for conferences and continued license certification, and a trip for the continued development of the Quality Assurance Specialist.

OTHER EXPENSES

Equipment Rental & Leases: Funds are requested for the maintenance and monthly rental of water machines for technician use. Water machines provide potable water to outdoor and remote DCM-monitored locations on campus, provision of which is mandated by OHSA 1910.141(b)(1)(i).

Registration/Course Fees: Funds are requested for the payment of conference and course registration related to professional development and accreditation of the Division Chief and Quality Assurance Specialist.

Shipping: Funds are requested for charges associated with the shipping of goods and services to other institutions as well as receipt of goods.

Training Program/Course Fees: Funds are requested for meetings and retreats in support of DCM leadership development and unit alignment. Senior Staff retreats and meetings allow the heads of each unit to align strategies and share common experience, providing an additional avenue for communication and cooperation.

Maintenance- Equipment: Funds are requested for the maintenance and repair of administrative equipment, including but not limited to an industrial shredder used for necessary document control, and other electronic devices not covered by warranty or supported by bio-engineering fees.

Taxes & Licenses: Funds are requested for license renewal related to the Division Chief and Quality Assurance Specialist positions, and for licensing through Fish and Wildlife and AAALAC.

Retention Program: Funds are requested for employee retention and recognition, and for the hosting of visitors sponsored by DCM in support of divisional development. DCM provides a number of avenues for which excellent service can be recognized within the division, allowing DCM to remain a desired and competitive employer. In addition, the hosting of outside presenters allows unique educational opportunities for division staff, and fosters collaboration between the division and other institutions.

Telecommunications: Funds are requested for the maintenance and usage of unit cell phone and telephone services, established centrally through the DCM Administrative department. Due to the remote location of the West Campus, cell phones are necessary to ensure normal operations are maintained, and that directions are communicated properly during all working shifts and situations.

Memberships: Funds are requested for membership fees associated with the positions of Division Chief and Quality Assurance Specialist, and for the centralized maintenance of technician memberships and testing through AALAS, necessary for the professional development of DCM technicians.

Bioengineering Fees: Funds are requested for miscellaneous repair fees associated with requests to the Facilities department.

ANIMAL SERVICES: Animal Services Administration Income Table

Last Funded Year (53)

Source	Funding (direct costs)
P51 base grant support	$275,878.97
Program income derived from P51 base grant	282,316.55
Other Sources	0
Total	$558,195.52

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$231,317.09
Program income derived from P51 base grant	231,317.09
Other Sources	0
Total	$462,634.19

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

Animal Services Administration receives salary support and support for other expenditures from program income.

RESOURCES, FACILITIES, AND OPERATIONS UNIT SPECIFIC AIMS

Non-human primates are critical animal models for basic and translational biomedical research. Supporting scientists who use NHP's in their research requires an integrated program of resource management, breeding, animal husbandry, and facilities oversight. To enhance the scientific utility, health, and well-being of ONPRC's animal resources, RFO coordinates programs of resource allocation and tracking, genetic and disease surveillance, animal husbandry and veterinary care. Working closely with other DCM units and across the ONPRC campus, RFO manages breeding colonies, animals and animal facilities, oversees animal care, animal assignment and utilization, and coordinates genetic and viral screening to ensure the health and well-being of our research resources.

Our long term goal is a population of pedigreed, disease-free animals of defined quality which matches current and future research needs. To achieve this, RFO must provide innovative resource management, excellent husbandry and clinical care, relevant genetic and viral screening, and utilize a centralized electronic health record system to document and track all aspects of animal care and management.

The specific aims for accomplishing this are:

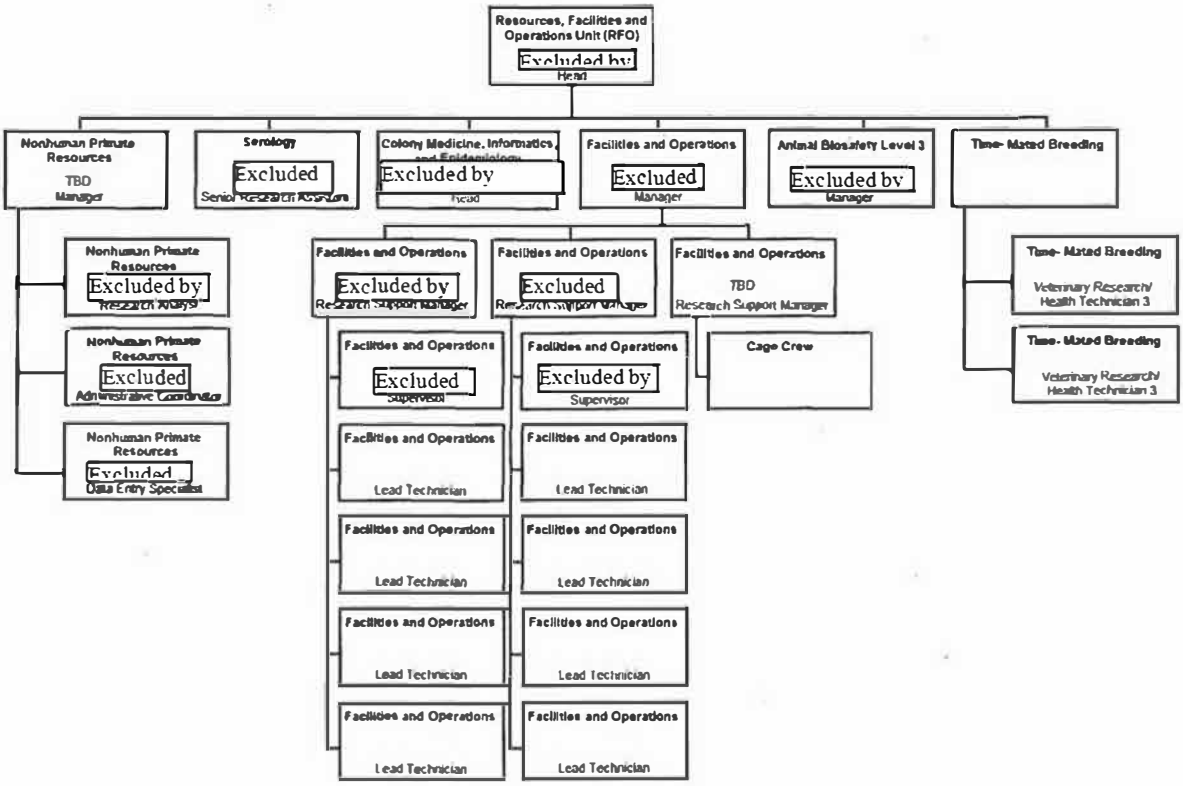
Specific Aim 1: To support scientists who use NHP's in their research by providing state-of-the-art, comprehensive management of our animal breeding and acquisition programs and centralized coordination of animal breeding, allocation, assignment, and release.

Specific Aim 2: To operate animal housing and facilities, aligning ONPRC infrastructure, space and resources for maintenance and husbandry of species for which there is a major national demand.

Specific Aim 3: To provide exemplary care to our breeding population of NHP's through an integrated program of animal husbandry, genetic and viral screening, and veterinary clinical and preventative care.

The expected outcome is a physically and psychologically healthy population of NHP's sufficient to support current and future research needs for pedigreed, genotypically and phenotypically defined, disease-free animals.

ANIMAL SERVICES: RESOURCES, FACILITIES, AND OPERATIONS UNIT RESEARCH STRATEGY.



SIGNIFICANCE.

Non-human primates are essential models for biomedical research. Only by using them are we able to discern the immunologic, molecular biologic, and biochemical pathways for developing and testing vaccines, elucidate key control and intervention points of the reproductive system, and define the neuroendocrine changes that drive obesity and substance abuse. A reliable source of disease free, genetically characterized animals provides investigators with a defined animal model for development and testing of cellular mechanisms, physiologic pathways, drugs, and vaccines. Restrictions on animal importation, and the challenge of locating disease free animals of known phenotype emphasize the need of preserving and protecting the health and well-being of non-human primates currently in research settings.

A robust program of resource management, facility maintenance and operation, and animal care and husbandry is essential to ensure adequate NHP resources for current and future research needs. *The Resources, Facilities, and Operations (RFO) unit provides state-of-the art, comprehensive resource management, integrated facilities operations and maintenance, and centrally supervised staff supporting animal care and operations.* We will improve NHP breeding and husbandry practices to enhance the utility of our research resources. We will manage resources to maximize animal use and animal well-being. We will use our clinical, epidemiologic, and genetics information and expertise to further the understanding of complex disease and disease prevention.

INNOVATION.

The RFO is committed to supporting biomedical research by developing improved practices of animal resource management, facility utilization, and animal health. Scientific research is fundamentally creative, and frequently unpredictable.[Portney and Austin 2002] The resource management strategies used to match NHP populations to research needs rarely include simulation modeling software. Relying instead on retrospective usage, resource managers must frequently make a "best guess" at the impact of decisions on breeding colonies, animal populations, and facilities utilization. Similarly, the impact of different outdoor housing designs and husbandry practices on disease incidence is not well characterized.[Hird et al. 1984] While a number of advancements have been made using the rhesus macaque pedigree to describe significant heritability for disease risk factors, this information is not integrated into current breeding management programs. Excluded by Requester

Excluded by Requester Finally, existing screening tests and diagnostic technologies to detect Mycobacterium tuberculosis infections in NHP's are have poor sensitivity and specificity. Excluded by Requester Excluded by Requester New scientific approaches are necessary to address the ongoing threats presented by this disease. New space and resource management technologies are essential to improve breeding practices.

The RFO will improve practices of animal resource management, facility utilization, and animal health in a number of specific ways in the upcoming grant cycle. First, we will continue to develop the Animal Resource Simulation (ARMs) population simulation model, and explore the utility of using this software for matching breeding colony size to research needs. Second, using data in our electronic records system, we will continue our efforts to proactively reduce chronic colitis incidence. Retrospective studies, using data from these records indicate housing type is a colitis risk factor[Prongay et al. 2012]. This baseline data will be used in the upcoming grant cycle to measure the impact of changes in housing designs and husbandry practices on diarrheal disease incidence. We will provide veterinary clinical expertise to support the Primate Genetics Program pedigree characterization of macaques affected by chronic colitis. Using a resource tracking feature in the PRIMe software, we will also develop a web-based tracking system to maximize space utilization, and continue beta testing a bar coding system for animal tracking. Finally, in collaboration with WANPRC, we will explore models of natural Tb transmission and beta-testing a seriological Tb microarray, and will continue to pursue funding for development of a *Campylobacter sp* vaccine for use in group-housed NHP's.

These efforts will directly contribute to and enhance our animal management programs. They are essential to ensure that a population of disease-free, genetically characterized animals of known phenotype is available for future generations of research scientists.

APPROACH

reviewers' comments

Progress Report

The RFO consolidates the previous Operations Unit, NHP Resources, Colony Veterinarian, and SPF Surveillance (Serology) into a single unit. This bold and visionary management strategy has had numerous positive impacts on our resource management. Teaming resource management, animal husbandry, genetic and disease surveillance, and colony medicine allowed us to develop an integrated system of population management. Collectively, RFO is responsible for colony maintenance, clinical management, and logistics including identification, assignment, monitoring, and assignment/release of research project animals; acquisition of animals for research project assignment with attention to genetic diversity of colonies and

projected future needs; animal sales in support of other NIH funded facilities and projects; management of resident rhesus and Japanese macaque breeding populations; animal facility management, maintenance and construction; animal husbandry and population oriented veterinary care.

The unit is led by Excluded by Requester an experienced primate veterinarian with extensive background in facilities operation and resource management. An Associate Veterinarian with clinical, informatics and epidemiology expertise, a PhD virologist, and an NHP Resources Manager support animal resources and utilization. The Facilities and Operations sub-unit includes an Operations Manager, two Research Support Managers, two Supervisors, and both technical and research support staffs. Coordinated communication and planning ensure the entire unit works collaboratively to ensure the highest standards of animal care and utilization are maintained and that all care and management exceeds federal, state, county, municipal, and international (CITES) regulations. To ensure continuity and consistency, routine care and treatment procedures are outlined in either Standard Operating Procedures or Guidelines. The RFO unit collaborates with DCM units, ONPRC researchers, and across the NPRC Consorsia to maintain an outstanding resource management program, robust facilities maintenance and operations programs, and a program of exemplary animal care. Revenue and charges are indicated in Table 1.

Table 1. Services and Revenue for RFO*

Service	Year 50	Year 51	Year 52	Year 53**	Year 55 Projected
Operations	5,181,887	5,484,350	5,745,208	6,034,953	6,400,000
SP Surveillance	30,632	37,200	36,265	14,846	36,548
Animal Sales	265,742	718,210	354,695	453,403	480,000
Total	5,478,261	6,239,760	6,136,168	6,503,202	6,916,548

*Detailed information on service categories, allocation, and inclusive dates is included in the XXXX section and will be available at the site visit. **Through 12/31/2012.

Resource Planning, Breeding, Acquisition, and Allocation

Overview: The needs of science necessitate a malleable resource management strategy, supported by regular communication with researchers. The Head, RFO, manages resource planning, breeding, acquisition, and allocation, supported by the Resource Manager, SPF Surveillance, and Colony Informatics and Epidemiology staff.

Planning: A number of efforts have been made to improve the lines of communication with researchers. Study Facilitation Meetings were implemented in 2009 and are chaired by the Head, RFO. These pre-grant study meetings include multiple DCM units, the principle investigator, and the Business Office. Project costs and logistical challenges are discussed. These meetings have improved cost recovery and decreased the time from grant funding to study start. Applications for animals and, when needed, purchases, are reviewed through the Animal Use Committee and Subcommittee. The Head of RFO chairs this subcommittee. Animal Assignment Forms and project tracking information, once managed on paper, are now available on the ONPRC SharePoint website and can be readily reviewed by investigators and RFO staff.

Recognizing that the high demand for ABSL3 space necessitated simultaneous space and project management planning, ABSL3 planning meetings were started in 2011. Chaired by the ABSL3 Manager, this group develops and publishes the space schedule, coordinates facilities and maintenance around active projects, and oversees ABSL3 safety and training.

Breeding: Right sizing the breeding colony (Table 2) to meet current and future uses, while protecting the genetic diversity and SPF status requires an extensive coordination across DCM and the ONPRC campus. Several process changes have significantly improved our management capability. First, the RFO Head chairs weekly meetings of the Colony Management Group. Members include representatives from RFO, CMU, BSU, ISE, Colony Genetics, and SPF Surveilence. Meeting topics include quarantines, new breeding group formations, breeding group dynamics, future studies, compliance and IACUC issues, and animal facility maintenance and repairs. Second, with the assistance from ISE, we have enhanced our utilization of IRIS electronic records to track and manage colony population, breeding, and health. Production, morbidity, and mortality reports can be generated real-time for each SPF breeding group, and can be accessed from the ONPRC SharePoint Bridge. Demographic information is used by the Colony Epidemilogy Group to track the health and social stability of individual groups, and adjust husbandry and clinical care as required. Third, the U42 colony was transitioned to RFO management. Historically, the U42 and P51 SPF breeding colonies were

managed and housed separately. Melding the colonies together has improved genetic diversity, streamlined colony management, and enhanced our ability to match production and maintaince to research needs. Forth, management of non-breeding animals within the population have been refined. We have increased the number of temporary groups, including social housing of juvenile and Primate Aging Study (PAS) animals who would otherwise be caged-housed when awaiting project assignment. We have also formalized the Cull Animal Program to include a SharePoint Bridge list and unique pool code. Animals who are clinically stable but have health issues which preclude either maintenance in the breeding colony or assignment to a research project are placed on the Cull Animal List. These resources can be used for terminal, short term, pilot projects, maximizing the use of the animal and reducing need to use healthy animals to support technique or dosing refinement.

Table 2. SPF Breeding Colony Population and Production by Grant Year*

	Year 50	Year 51	Year 52	Year 53*
Population	2324	2413	2588	2817
Production #	577	626	684	278
Production	25%	26%	26%	10%
New groups formed	10	12	18	13
Disbanded groups	4	7	35*	4

*Year 53 numbers are through 31 December 2012. A number of temporary juvenile groups were disbanded in Year 52 to support research needs and sales.

Allocation, Acquisition, and Sales: The total campus population, species population, and animal importation, sales and assignments are displayed in Table 3. Over the past funding cycle the RFO unit has synthesized and standardized the method by which researchers request and receive NHPs for research studies. Steps toward animal assignment are now clearly outlined, and include costs and timelines. Annually, a small number of animals are purchased to increase genetic diversity or in response to unique research needs. All animals undergo either a domestic or international quarantine in a dedicated building. Animal sales ensure animals without current or project research needs are available to other NHP researchers.

Resource Management

The ONPRC maintains major domestic breeding colonies of both SPF and expanded SPF Indian-origin rhesus macaques pigtail macaques, and the only domestic breeding colony of Japanese macaques. Our breeding populations are primarily maintained in corrals, sheltered housing, or harem-style breeding groups. Management of campus breeding colonies has evolved significantly during this funding cycle, and is characterized by innovations in clinical case management, group formation and maintenance, and SPF surveillance.

Table 3. NHP Population, Importaion, Sales and Assignment, Years 50- 53

	Year 50	Year 51	Year 52	Year 53*
Total NHP's	4593	4806	4886	5012
M. mulatta	4134	4348	4437	4566
M. fascicularis	46	50	87	95
M. fuscata	399	395	352	348
Papio sp.	8	13	10	3
Chlorocebus sp.	6			
Importation	76	102	71	53
Animal Sales	97	189	23	60
Project Assignments	1150	964	1288	372

*Through 1 November 2012. Population census was calculated by averaging daily population for each grant year.

Maintenance of Genetic Diversity: We have substantially improved the process of genetic analysis for proposed new breeding groups.Candidate animals are identified using the Genetic Relationsships and Information on Primates (GRIP) electronic data base. Lists are screened by the Colony Genetics group prior to inclusion in a group. Each candidate is ranked for genetic value according to estimated mean kinship with the entire living colony, and a "genetic value" assigned. This value is determined using estimated mean kinship with the rest of the living colony and additional infomormation on the location of this estimate within the distribution of mean kinships calculated for all living colony animals. Additional factors, including measure of genome uniqueness, or probability of carrying an allele with no more than 2 other copies the colony, as well as the number of living offsping and contribution of each founder are also scored. These scores are evaluated with pairwise relatedness among candidate animals. No relatedness greater than 2nd cousin is permitted between males and females, or between males proposed for new breeding groups. Candidate animals with >5offspring that remain in the colony are also removed from consideration for further breeding.

SPF4 Surveillance: The SPF Surveillance Lab is the key to maintaining the SPF status of the ONPRC NHP colonies, providing testing and expertise for both colony maintenance and research need. Based on the continued pattern of low MTBC incidence among imports and the recognition of a continuum of MTBC clinical and immunological manifestations in macaques Excluded by Requester our screening and diagnostic program uses multiple diagnostic tools for tuberculosis surveillance, including serial TST with clinical examinations, serological assays, and molecular diagnostic tests run in parallel. Serology is the single most important tool for monitoring and validating the SPF status of animals at ONPRC. Table 4 outlines the selection of assays, testing frequency and the laboratories used. This is based on over two decades of experience evolving and maintaining a large population of SPF rhesus macaques that are free of select viruses.

Table 4. SPF4 Surveillance

Pathogen	Screening Frequency	Screening Assay	Confirmatory Assay	Consequence of Positive or Equivocal Test	Isolation Release Criteria
B Virus	Annually (all SPF animals)	Intuitive Biosciences' Colony Surveillance Assay (microarray)	ELISA/Recombinant ELISA[1]	Isolate and retest entire group every 3 months	4 consecutive negative tests
SRV	Annually (all SPF animals)	Intuitive Biosciences' Colony Surveillance Assay (microarray)	Luminex/Western Blot/PCR[2]	Isolate and retest entire group every 3 months	4 consecutive negative tests
STLV-1	Annually (all SPF animals)	Intuitive Biosciences' Colony Surveillance Assay (microarray)	Luminex/Western Blot/PCR[2]	Remove animal(s) from group and retest entire group every 6 months	2 consecutive negative tests
SIV	Annually (all SPF animals)	Intuitive Biosciences' Colony Surveillance Assay (microarray)	Luminex/Western Blot/PCR[2]	Remove animal(s) from group and retest entire group every 6 months	2 consecutive negative tests

SPF Breeding Colony Management: Our SPF Indian rhesus has a 10 generation pedigree and is a primary resource for ONPRC. Historically, breeding group formation, husbandry, and clinical care were segregated and veterinary responsibility for the clinical care was rotated between veterinarians on a monthly basis. During the pervious grant cycle, we have developed an integrated management system (Figure 2).

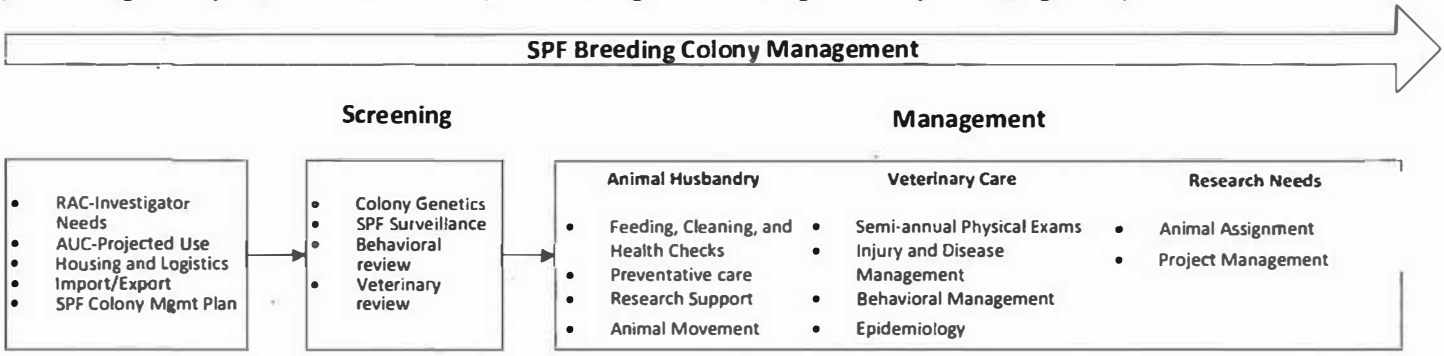


Figure 2. The resource management plan is aligned with research needs (Planning). Animal records are screened for group suitability (Screening). State-of-the-art, comprehensive management integrates animal husbandry, veterinary care, and research needs (Management).

SPF Breeding Group Formation

Since 2009 we have employed an integrated approach to group formation. Using the electronic health record system and informatics tools developed through our collaboration with the IRIS development team, unassigned, caged animals can be rapidly identified and screened. Historically, RFO has acted as the lead in the formation of new breeding groups. Our experience with the Colony Epidemiology Group (detailed below) has led to a more collaborative approach, with BSU and Colony Genetics gaining significantly larger roles in the formation and maintenance of groups. Each individual animal record is reviewed by BSU, and evaluated for successful integration into the proposed social group, animal hierarchies, and likely familial interactions. Colony Genetic reviews all available animals, and generates a prioritized list based on genetic diversity. The CMIE veterinarian also reviews each record, to identify and evaluate and previous clinical issues that may make an animal unsuitable for group introduction. These partnership efforts have resulted in less aggression

during group formation and breeder male additions, enhanced group production, and improved the genetic diversity of our colony.

During the previous five years, a concerted effort has been made to place unassigned animals who do not meet the criteria for breeding group into outdoor social groups.This temporary groups may include juvenile males awaiting project assignment, PAS animals on aging studies, and animals who have been identified for sale.

Colony Medicine, Informatics, and Epidemiology: Historically, animals from SPF breeding groups were returned to groups following treatment. No formal evaluation of the impact of these releases social group dynamics or campus resource needs was made. To improve animal welfare and enhance communication among clinical, husbandry, animal resource, and behavioral staff, we have developed an integrated case management process. Animals requiring clinical care are evaluated and treated in the Colony Hospital as outlined in the CMU component submission. The colony veterinarian provides and oversees care. As animals recover, cases are reviewed by members from the Animal Resource Unit, Husbandry Unit, and Behavior Services Unit. Led by the Colony Medicine, Informatics, and Epidemiology (CMIE) veterinarian, the Colony Epidemiology Group (CEG) discusses hospital cases from a clinical, behavioral, and animal resource management perspective before determining whether an animal should return to a breeding group or reassigned. Including all stakeholders in the discussion has enhanced animal resource utilization (Figure 3). Animals not suited for breeding groups are identified more quickly and reassigned to appropriate protocols; social groups are more actively managed, ensuring stable and productive breeding groups; and program transparency fosters trust with research scientists and across the various units within DCM.

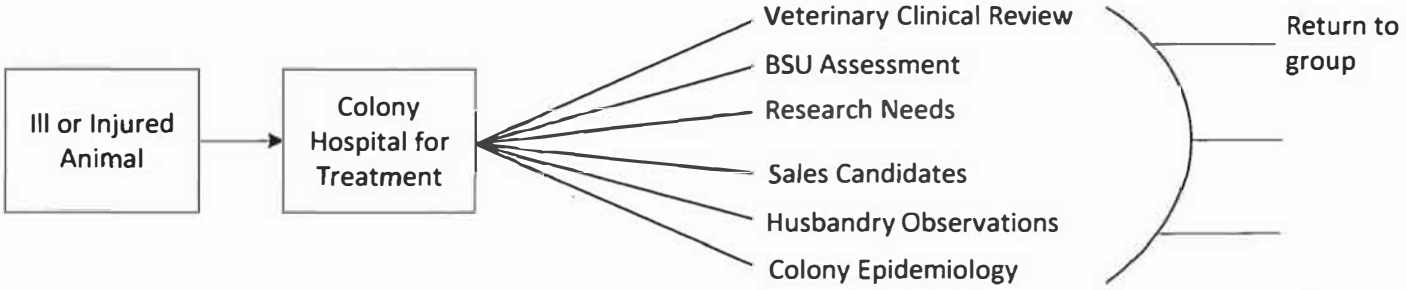


Figure 3. The Colony Epidemiology Group reviews each clinical case that enters the Colony Hospital to ensure husbandry, clinical, and resource needs are assessed prior to release.

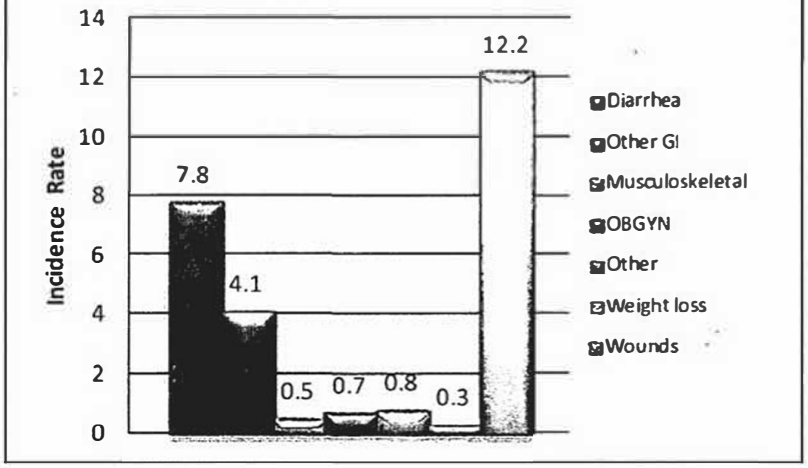
Prior to individual case review, the team discusses social group dynamics and solutions, and reviews morbidity and mortality data from the previous week. Trends generate discussion and re-evaluation of the management plan. For example, in 2010 there was large increase in the number of clinical cases from shelter breeding groups. A record review was initiated, and indicated frequent group movement may be a component. Husbandry and maintenance practices were changed, to reduce the need for such movement. Clinical case numbers declined following the decision. This system was also used to identify an outbreak of Yersinia in 2010. Excluded by Requester The new electronic records system, PRIMe, will include additional user-selected parameters and enhanced reporting features. Epidemiologic metrics will be compared across groups and times, and will include infectious disease data.

Our utilization of clinical and epidemiologic data in social group management continues to expand and evolve. In 2009, the Excluded by Requester and the Integrated Research Information System (IRIS) development team initiated a medical informatics program, to better utilize the extensive data in our electronic health record systems. Historically, codes from the Systematized Nomenclature of Medicine (SNOMED codes) were used to track clinical cases. Inconsistent uses of these codes presented significant challenges. For example, diarrhea cases could be classified with 63 different codes.To improve efficiency and preserve data integrity, user screens were redesigned, some data entry was automated, and SNOMED code use was standardized. Additionally, a broad classification system was developed. Titled "Master Problem," this system categorized cases by major body system and has significantly enhanced our ability to mine epidemiologic data to support colony management. High level sorting of cases types has also significantly improved our ability to track clinical case types, respond to information requests from researchers, and provide epidemiologic data for colony management.

Figure 4 shows the incidence of clinical cases within the breeding colony, and demonstrate the significant impact of diarrhea and wounds on colony health. Several initiatives have been made to decrease this numbers. The first was an extensive study of diarrheal risk factors conducted by Excluded by Requester (OHSU-Public Health and Preventative Medicine). Using both logistic regression and Classification and Regression Tree analysis, we demonstrated that the type of outdoor housing, age, and previous diarrhea episode were positively correlated with diarrhea risk. For example, younger animals in smaller shelters and temporary housing have a greater risk of acquiring diarrhea, and juvenile animals (0.7 to 3.9 years) have the highest mortality rate. The information from this study is being used to develop and assess mitigation strategies, and a similar study design is being used to determine risk factors for wounds.

Efforts to integrate such information into daily workflows are ongoing. Electronic health records for all NHP's are now available through both the conventional IRIS software portal, and a web interface. This allows DCM staff and investigators real-time access to patient data from any internet enabled computer. Dynamic reports, using Power Pivot, SSRS reports, and Share Point query tools have been generated to support clinical case management. For example, when an animal enters the colony hospital for treatment, a pre-designed history query indicates previous clinical case by type, breeding and rearing success, and medication history. Morbidity and mortality reports for the weekly CEG meetings are generated using a similar query.

Figure 4. Case Incidence by Type, 2010-2012



Japanese Macaque Breeding Colony: The Japanese macaque breeding troop in Corral 8. A team management approach, similar to that outlined for the SPF Rhesus colony, is used for this colony. The current JMAC troop spans 5 generations and includes over 200 members. It has been a closed troop since 1965, had no new genetic introductions, and was heavily harvested in 1985 and 201 to reduce the colony size and to lower troop stress. In 2011 the original two acre JMAC corral (commonly called North Corral) was divided in half and the troop was consolidated into the west one acre, now corral 8. Due to research needs for females since 2001, the troop continues to be male centric, so we plan on harvesting up to ten genetically, phenotypically and behaviorally unimportant males per year, so that the troop will eventually mimic a more natural group. Additionally, the demand for female project harvesting has also slowed, allowing for an improved yearly infant production. A management decision in 2005 and 2006 was made to place contraceptive implants into 33 fertile females to slow the rate of infant production, but the research demands on the females continued. As these implanted females age out and new generation of females mature, the infant production is slowly normalizing. With continued structured husbandry and medical management, we expect the troop to develop a more normal demographic within 5 to 8 years.

Timed Mated Breeding Program: Modifications to the Timed Mated Breeding (TMB) program have increased the efficiency and effectiveness of this resource in providing infants to meet scientific research needs. To augment the TMB, pregnancies within colony groups are now more closely monitored and where appropriate infants from the colony are offered in place of TMB infants. Changes to our methodology have allowed us to down-size the TMB, freeing up space for research and providing a more natural social environment for a larger portion of our breeding females. All of these adaptive, collaborative efforts have resulted in a more malleable system that allows the RFO unit, as partners, to respond to changing direction and strategic needs of the scientific divisions and center overall.

Foster Dam Program: Two exceptional examples of the innovative work within the unit are the implementation of a foster-mother program and the formation of new breeding groups. In the foster-mother program, abandoned or orphaned infants are paired with older females with demonstrated success at infant rearing. This program has successfully moved infants out the nursery and into a more natural

parent/infant relationship, reducing stress and the development of abnormal behavior. The formation of new breeding groups has allowed us to continue to meet research needs while maintaining colony genetic diversity and a more natural social environment.

Primate Aging Study (PAS), AIDS Orphanage, and Obese Resources: The RFO provides, housing and husbandry support to several unique resource groups. The *PAS resource* supplies aged NHP for researcher investigating endocrine replacement, cognitive function, macular degeneration, and post-menopausal changes. This resource is developed both from the existing population of naturally aged animals, and purchases from other NPC. Through the PAS Support Group, the RFO works with investigators to ensure selected animals match protocol needs maintains, and that unassigned animals are maintained in social groups to support natural aging and social behavior. Chronically SIV-infected animals who are maintained on antiretrovirals are housed in the *AIDS Orphanage*. This resource supports infectious disease projects, providing social housing for animals not on active infectious disease studies. The RFO provides housing, husbandry, and veterinary care for the approximately 30 animals in this colony. Additionally, the RFO maintains an *Obese Resource* for DOM. Support includes evaluation and modification of caging to meet special housing needs, modifications to group housed areas, and assistance with the development, purchase, and feeding of high fat, high carbohydrate diets.

Medical Cull Program: This program formalized the Medical Cull List, an internal list of medically stable animals with well-managed, chronic medical conditions who were unsuited for breeding programs or *long-term* project assignment. Historically, these animals could only be assigned to DCM medical or surgical training, and were then sent immediately to necropsy. In 2012, following extensive review and collaboration between the Research Advisory Committee (RAC) and the RFO, these animals were made available to researchers. Application for use is made through the RAC and use is approved by the IACUC. Typically, these animals are used for short pilot projects to answer questions prior to large grant submissions. The Medical Cull list is available on the internal, secure ONPRC SharePoint site, and can be viewed by researchers and DCM staff.

Facilities and Animal Housing

The ONPRC campus is over 250 acres and includes Specific Animal Location of indoor animal space, Specific Animal Location of sheltered housing, and Specific Animal Location of corral housing located in eight buildings, eight outdoor one and two acre corrals, and 32 Sheltered Group Housing units. The approximate average daily census is 4,500 NHP's, the optimum number for our current infrastructure. Routine facility maintenance and new construction, while necessary, can disrupt research studies and stress our NHP population. Construction and modernization projects may incorporate building design features that pose risks to animal health or endanger our animal husbandry staff. To minimize the impact of this, the RFO unit works closely with the Facilities Division on all projects. Daily communication between the groups is augmented by RFO's attendance at the Facility's hosted Weekly Shop Meeting and the monthly Construction Meetings. A web-based work request tracking system has also recently been added to the communication system. The SharePoint site displays ongoing and future maintenance issues for the entire campus, a job priority, and projected completion date. Automatic emails provide project updates and completion dates to RFO staff.

ABS and Select Agent Spaces: The first building added four, 56 cage and one 16 cage conventional NHP rooms, two large ABSL3 suites with pass-through autoclave centralized rack washer. diet kitchen, a conventional procedure room, and ABSL3 surgical and necropsy spaces. The two Specific Animal Location suites can house 32 animals per room. Funds from a C06 award were used to add 6 animal room, a diet kitchen, and common use surgical area to the ASB ABSL2+ facility. This eliminated the need to transport infected animals from containment areas to the common use surgical areas, and enabled RFO to house additional infectious disease research protocols.

Corrals: All corrals have undergone extensive modernization. Tractor access was added to all corrals, so that routine maintenance and facility improvements can be performed without removing animals from the corral. Fence skirting was added around each corral for improved vermin control. As our Japanese macaque colony size has decreased, this 2-acre corral has been divided into two corrals. Japanese macaques now occupy the west one acre, designated Special SPF Indian rhesus are housed in Specific New feed areas, play structures, cement feeding pad, drainage and irrigation systems, and tunnel systems were added in both corrals.

Shelter Housing: Fence panels in many of the shelters experienced metal fatigue and cracked welds following NHP activity. These panels have either been replaced or reinforced. Many of the floors developed cracks in the epoxy. After evaluating several flooring options, we are now grinding and polishing the floors and applying cement sealers. Several new flooring systems were evaluated. The radiant heaters have been replaced, and all shelters have been repainted.

Runs and Buildings: Facility Security Facility Security Aging plumbing in the Facility Security buildings has been upgraded, and a replacement schedule developed for other aging buildings. Structural changes in Specific Animal were made to support dry bedding. To facilitate cleaning, roof fencing was in the eSPF indoor group housing area. Cyclone fencing of Specific Animal Specific Animal replaced.

Construction, Modernization, and Abandonment: A new facility, including 12 corn cribs and a service building will be completed in early 2013. Using G20 funds, the Specific Animal was remodeled to include additional behavior suites, a large animal room, diet kitchen, and procedure room. Funds from a C06 award were to add 6 animal rooms and a diet kitchen to the Specific Animal Animal housing areas in the Specific Animal Location Specific Animal used since 1960, were closed and the space remodeled to support non-animal use.

Equipment Purchases and Modifications: Caging purchases to support new housing areas and animal social housing, and cage modifications to support housing for additional obese and ABSL3 animals have been completed in each grant year. Vehicle purchases, used for daily feeding, cleaning, and husbandry include a Class V forklift, electric golf carts, two Chevrolet Astro vans, and a half-ton cargo van. Additional purchases include transport boxes, Landa hot water pressure washer, Landa 13 hp cold water pressure washer, and calf hutches for Corrals. A complete list will be available for review during the site visit.

Operations and Animal Husbandry

There are over 5,000 nonhuman primates on the ONPRC campus, housed in cages, small group housing, sheltered group housing and corrals. Daily care, logistical management, animal transfers, project related procedures, disease screening, and semi-annual examinations requires a large and well-trained husbandry team (Table 5). To facilitate management, the campus is divided into eight major husbandry teams (Figure 1).

Staffing: The current staff includes an Operations Manager, an Assistant Operation Manager, two Research Support Managers, an Equipment Research Support Manager and a 25% FT ABSL3 Manager (remaining 75% in Small Laboratory Animal Unit). Due to the large size of the campus, the two FT Research Support Managers responsibilities are assigned geographically. Directly reporting to each Research Support Manger is a Supervisor. Supervisors are responsible for the day to day operation and management of their areas. Each Supervisor has four Lead Technicians who, who lead four to eight husbandry staff. Prior 2011, two separate teams managed cage change out and cage maintenance. To improve efficiency, the two cage change teams were merged. An Equipment Research Support Manager (Cage Crew) now oversees this staff of eight. The Cage Crew is responsible for cage change out, and cage sanitation for over 160 different areas across ONPRC. Staffing and project management of the two select agent ABSL3 suites is the responsibility of the ABSL3 Research Support Manager. Staffing needs in the ABSL3 vary with protocol and are dynamic. Currently this position does not directly oversee husbandry staff but schedules staffing through the other two Research Support Managers.

Table 5: Procedures performed by RFO staff

	Year S0	Year 51	Year 52	Year 53*
Animals Processed	6204	7526	7760	6930
Physical Exams	1550	4676	7623	3784
Tb tests	7723	8680	9891	4677
Sedations	29113	30869	33765	14756
Injections	6680	2946	2788	3510
Special diets	6720	6892	11134	11475
Blood draws	29029	32068	31871	11073
Animal transfers	17034	21575	22028	8419
Semen samples	100	120	86	12

*Through 1 November 2012.

The ONPRC continues to grow in laboratory animal space as well as in nonhuman primate population. In 2009, we transitioned from annual physical exams and preventative care for socially housed animals to semi-annual processing. This greatly improved our quality of care and preventative medicine goals but it placed much higher demands on our animal care staff. Additionally, there are higher demands on our husbandry staff due to increased participation on research projects.Two detailed time-in-motion studies as well as projecting

needs for future new laboratory animal space have demonstrated staffing deficits in all areas. To minimize the impact, the RFO unit now manages a pool of up to ten trained temporary husbandry employees. During periods of increased need, this resource is rapidly mobilized. This also has lowered overtime and improved our quality of care and compliance and lessened staff fatigue. While our overall staffing levels have increased to meet demand, they remain below levels needed to provide animal care without incurring overtime and staff burn out. Our goal is to staff at 110% in order to meet vacation and other absences and thus to limit overtime and lower staff fatigue. By Y55, we will need to add an additional eleven husbandry staff.

Exposures, Capture Team, and Incident Response Planning: Working with NHP can present risks to personnel, and the housing and maintenance of large animal populations presents significant risk management issues. Several programs within RFO have improved our capacity to manage and respond to both personnel exposures, and larger incidents. The RFO led several key initiatives that have resulted in fewer exposures and significantly decreased programmatic cost to ONPRC. The full description of changes and improvements in our Personnel Exposure plan are available in the EHRS component section. The RFO also developed and implemented a robust Capture Management plan, and regularly trains husbandry staff in NHP escape response procedures. Additionally, in 2009, RFO developed a highly detailed DCM Incident Response Plan. The plan has been adopted by the ONPRC, and includes both didactic and "live exercise" training in incident response. Responsibility for the plan was transferred to the RET in 2012. A complete description is available in the RET component of this submission.

Future Plans

Aim 1: To support scientists who use NHP's in their research by providing state-of-the-art, comprehensive management of our animal breeding and acquisition programs and centralized coordination of animal breeding, allocation, assignment, and release.

Areas of special emphasis for this funding cycle: Ensuring comprehensive resource management is a primary aim of this department. We will continue to develop processes which accuratey predict future animal needs, streamline the assignment and release process, and create a transparent space utilization matrix. Specifically, with support and collaboration from the ONPRC Information Systems Engineering (ISE), we will expand our systems management capabilities by adding predictive modeling capability to ensure animal resources match research needs and continue refinements to our Timed Mated Breeding (TMB) resource.

Research Design and Expected Outcomes:

PRIMe Development: The current animal records system is antiquated. Over an 18-month period, the ONPRC campus will transition to a new system, Primate Records and Information Management (PRIMe). Using a project management framework called "Scrum," RFO and ISE staffs will actively manage the transition process. Unlike conventional command-and-control strategies, Scrum includes a feedback loop that incorporates users in the development and implementation process. Excluded by Requester have both received formal training in this system, and are the DCM Product Owners for the transition from IRIS to PRIMe. As such, they are accountable for ensuring business value throughout the transition. In consultation with DCM users, they prioritize the User Stories into a product backlog. Phase one of this process, collecting "User Stories" that capture all points where DCM staff enter information or interactive with information in the electronic record system, was recently completed. Following the initial transition, the Scrum process will be refined to support developing business practices and to ensure these practices support state-of-the-art, comprehensive management of our animal resources.

Population Simulation Modeling: Our breeding and research colonies are a highly complex system. Management requires balancing overall colony health, genetic diversity, disease management, and current and projected research needs. Developing a computer model system which simulates all of these variables will improve our ability to balance breeding performance and needs with research objectives. With ISE, we are collaborating with Excluded by Requester a Systems Scientist from Portland State University to develop a forecasting and logistic tool for our breeding colony. The initial development is complete, and the software is

currently being beta tested. We anticipate that by simulating various resource management approaches *in silico*, animal resource managers and research investigators will be given the opportunity to work out the expected consequences of proposed changes with a degree of formalism that cannot be obtained in the absence of careful consideration of whole-system dynamics.

TMB Resource Refinement. The TMB resource has been successful in meeting its goals of providing pregnancies of known gestational age for reproductive and developmental research. However, the requirement to produce pregnancies in rhesus monkeys throughout the year has tended to reduce the production efficiency because this species has a seasonal cycle and tends to be less fertile during certain times of the year. Improvements in pairing efficiency have increased our pregnancy success. To maximize pregnancies, provide specific gestational age pregnancies at the required time, use the minimal number of females required, and limit pregnancies not used by investigators, the RFO will implement additional monitoring strategies. To improve ovulation detection, we will monitor estradiol (E_2) and progesterone (P_4) in addition to tracking menstrual bleeding. Insemination will be confirmed by vaginal swabs and microscopic observation of sperm. Post-conception monitoring will include serum hormone profiles (P_4, E_2), bi-manual palpation and ultrasound. Intrauterine pregnancy will be diagnosed following 3 consecutive weeks of P_4 elevation.

Aim 2: To operate animal housing and facilities, aligning ONPRC infrastructure, space and resources for maintenance and husbandry of species for which there is a major national demand.

Areas of special emphasis for this funding cycle: We will continue to leverage our electronic resources during the next funding cycle. Specifically, we will leverage features in the new electronic records system to improve space utilization, support resource improvement initiatives from the Consortium, and provide data and expertise for complex disease modeling.

Research Design and Specific Outcomes

Space Utilization and Planning: Our campus size, large NHP population, and diverse research environment challenges our current space monitoring capabilities. Working with ISE, we are developing a real-time, web-based space monitoring system. When complete, this system will allow DCM staff and ONPRC scientists to easily view space utilization and assignment across campus. The expected outcomes are decrease transfer errors, improve space utilization, and improved communication.

Breeding Colony Management Consortium (BCMC): The BCMC allows members to collectively study common NHP herd health, breeding issues, and management strategies, and gain from each Center's positive and negative experiences. ONPRC has been an active leader since inception, and hosted the March 2012 face-to-face meeting. During the upcoming grant cycle, we will continue a high level of involvement. In addition to submitting multiple samples to the virus testing panel, we are perusing outside funding to address deficiencies in the current SRV antigen assay. Our results will be shared across the Consortium. As part of our colony health benchmarks initiative, we have requested funding to support consultation with an Agricultural Economist. The information and population models will be shared across the BCMA. We have previously presented the Animal Resource Simulation (ARMS) project, and anticipate sharing the developed software across the Consortium. Finally, we will continue to actively share animal resources with other Centers.

Colitis Management: We have previously demonstrated that housing type influences diarrhea morbidity and mortality. Excluded by Requester We established diarrhea incidence rates and diarrhea associated mortality rates for our population, and demonstrated that young animals in smaller housing groups have the highest diarrhea associated mortality rates. We are pursuing three initiatives to reduce diarrhea in our infant and juvenile population. The first, in conjunction with the Division of Pathobiology, involves modification of a Camphylobacter vaccine. Intestinal campylobacteriosis is the most common cause of diarrhea in many NHP colonies, and can be fatal to infants. Modifying and testing a vaccine that reduced the overall incidence of Camphylobacter diarrhea in our colony may significantly reduce morbidity and mortality. Our second initiative involves dietary supplementation. Studies Excluded by Requester demonstrate oral lactoferrin may significantly reduce the duration of infant diarrhea. Lactoferrin is an iron binding glycoprotein found in

mammalian milk, and appears to inhibit cytokine production and reduce respiratory and GI inflammation. We are currently evaluating lactoferrin for use in our nursery infants, and, if validated, with use this supplement in our colony infant diarrhea protocols. Finally, using parametric and non-parametric models we recently developed and validated, and in collaboration the Early Childhood Development Program (ECHD), we will monitor how husbandry management changes influence diarrhea incidence, and adjust our processes to reduce diarrheal disease incidence. The specific outcome is a reduction in infant and juvenile diarrhea associated mortality.

Aim 3: To provide exemplary care to our breeding population of NHP's through an integrated program of animal husbandry, genetic and pathogen screening, and veterinary clinical and preventative care.

Areas of special emphasis for this funding cycle: Interdisciplinary collaboration facilitates the development of novel insights and approaches to disease and disease management. The RFO has established formal collaborative relationships with investigators in PGP, PSU, and staff in Information Systems Engineering (ISE) that will enable us to leverage these information-rich data sources to improve animal health and genetic management. Additionally, we are working with the Washington National Primate Research Center (WaNPRC) on a Mycobacterium tuberculosis model.

Research Design and Specific Outcomes

Improved Tb diagnostics and surveillance. Mycobacterium tuberculosis is a devastating, zoonotic disease to both NHP's and humans. Established testing methodology, tuberculin skin testing, often leads to both false positive and false negative reactions. Refining existing testing methodology is essential for colony health. Currently, we are beta testing a serological Tb microarray developed by Intuitive Biosciences. The assay tests for 20 M tb peptides, and may provide a reliable and cost-effective replacement for existing test. Additionally, In conjunction with the WANPRC, the ONPRC is actively pursuing funding to develop models of natural M tuberculosis transmission and methods for defining the relevant molecular characteristics of naturally transmitted mycobacteria and the interactions of such with vertebrate hosts. In collaboration with Excluded by Requester Excluded by Requester (Infectious Disease, WaNPRC),

Pending Support

Chronic Colitis Pedigree Development: We have previously developed disease risk profiles for chronic colitis. Using this information, and additional epidemiologic data, we are collaborating with Excluded by Requester (ONPRC PGP) to test the hypothesis of a genetic basis for colitis, and to provide preliminary data supporting future funding to identify causative genetic and environmental contributions to this phenotype. Excluded by Requester has already identified a focal set of 233 animals with chronic colitis, and is currently characterizing a ~900-member pedigree containing these affected animals and their relatives for genetic analysis. This analysis will be supported by peripheral biomarker and histological analysis of ~200 matching blood and gut tissue samples already collected on affected animals at necropsy by Excluded by Requester (PSU). The RFO will continue to provide clinical and bioinformatics expertise in support of this project, and ongoing collaboration with the PGP to develop pedigrees for, osteoarthritis and chronic inflammatory disease such as hepatic amyloidosis and reactive arthritis.

REFERENCES

Excluded by Requester

ANIMAL SERVICES-RESOURCES, FACILITIES & OPERATIONS DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*

Use Cal, Acad, or Summer to Enter Months Devoted to Project

Enter Dollar Amounts Requested (omit cents) for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Excluded by Requester	Mgr, Operations	% Effort			Institutional Base Salary	43,195	13,390	56,585
	Assoc Vet					42,665	10,666	53,331
	Lab Animal Tech 2					18,851	6,598	25,449
	Res Analyst 2					24,285	8,500	32,784
	Lab Animal Tech 2					21,828	7,640	29,467
	Lab Animal Tech 3-ASB Lead					21,828	7,640	29,467
	Vet Res/Health Tech 1					13,846	6,231	20,077
	Vet Res/Health Tech 1					17,517	7,007	24,524
	Vet Res/Health Tech 2/ABSL 3					20,779	7,273	28,051
	Lab Animal Tech 1					16,459	6,583	23,042
	Lab Animal Tech 1					15,169	6,068	21,237
	Vet Res/Health Tech 1					15,775	6,310	22,085
	Vet Res/Health Tech 1					15,169	6,068	21,237
	Lab Animal Tech 1					13,273	5,973	19,246
	Lab Animal Tech 1					15,511	6,204	21,715
	Lab Animal Tech 1					16,161	6,465	22,626
	Vet Res/Health Tech 1					13,846	6,231	20,077
	Lab Animal Tech 1					13,273	5,973	19,246
	Lab Animal Tech 1					15,169	5,309	20,478
	Res Asst 2					16,623	6,649	23,273
	Lab Animal Tech 1					13,273	5,973	19,246
	Lab Animal Tech 1					18,112	6,339	24,451
	Lab Animal Tech 2					21,828	7,640	29,467
	Lab Animal Tech 1					16,161	6,465	22,626
	Vet Res/Health Tech 2					18,377	7,351	25,729
	Vet Res/Health Tech 3/ABSL 3					21,761	7,616	29,378
	Lab Animal Tech 1					13,273	5,973	19,246
	Vet Res/Health Tech 3					25,036	8,762	33,798
	Lab Animal Tech 1					15,169	6,068	21,237
	Lab Animal Tech 3-Crew Lead					21,276	7,447	28,723
	Res Support Supervior					21,354	7,474	28,827
	Lab Animal Tech 1					15,863	6,345	22,209
	Lab Animal Tech 1					13,273	5,973	19,246
	Res Asst 1					15,209	6,084	21,293
	BSL3 Supervisor/Res Support Mg					9,125	2,829	11,953
	Lab Animal Tech 2					18,024	7,210	25,234
	Lab Animal Tech 1					15,511	6,204	21,715
	Lab Animal Tech 1					13,846	6,231	20,077
	Res Support Mgr					32,597	10,105	42,702
	Vet Res/Health Tech 2					17,528	7,011	24,539
	Lab Animal Tech 1					13,273	5,973	19,245
	Vet Res/Health Tech 1					18,377	6,432	24,809
	Res Support Mgr					31,585	9,791	41,375
	Lab Animal Tech 1					17,583	7,033	24,617
	Vet Res/Health Tech 2					17,220	6,888	24,108
	Lab Animal Tech 2					19,336	6,768	26,105
	Sr Res Asst					25,083	8,779	33,862
	Lab Animal Tech 1					15,511	6,204	21,716
	Vet Res/Health Tech 1					15,775	6,310	22,085
	Assoc Vet					44,883	13,914	58,797
	Lab Animal Tech 3-ESPF Lead					19,600	6,860	26,461

ANIMAL SERVICES-RESOURCES, FACILITIES & OPERATIONS
DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY

FROM 5/1/14 | THROUGH 4/30/15 | GRANT NUMBER P51 OD011092-55

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Excluded by Requester	Lab Animal Tech 2	% Effort			Institutional Base Salary	21,188	7,416	28,604
	Lab Animal Tech 2					16,800	6,720	23,521
	Lab Animal Tech 1					15,863	6,345	22,209
	Lab Animal Tech 1					17,583	7,033	24,617
	Vet Res/Health Tech 3-Lead					21,100	7,385	28,485
	Vet Res/Health Tech 2					17,903	7,161	25,065
	Vet Res/Health Tech 3-Lead					23,933	8,377	32,310
	Lab Animal Tech 1					18,112	6,339	24,451
	Lab Animal Tech 1					13,273	5,973	19,246
	Lab Animal Tech 2					21,828	7,640	29,467
	Vet Res/Health Tech 1					14,485	5,794	20,280
	Vet Res/Health Tech 1					18,377	6,432	24,809
	Admin Coord					26,788	9,376	36,164
	Lab Animal Tech 2					19,809	6,933	26,743
	Lab Animal Tech 2					18,443	7,377	25,820
	Vet Res/Health Tech 2					20,780	7,273	28,053
	Office Specialist					19,832	6,941	26,773
	Lab Animal Tech 1					15,510	6,204	21,715
	Vet Res/Health Tech 2					20,295	7,103	27,399
	Lab Animal Tech 2					21,828	7,640	29,467
	Res Support Spvr					21,354	7,474	28,827
	Vet Res/Health Tech 2					21,276	7,447	28,723
To Be Named	Vet Res/Health Tech 2/ABSL 3	6.00				20,000	7,000	27,000
To Be Named	Vet Res/Health Tech 2/ABSL 1	6.00				20,000	7,000	27,000
To Be Named	Vet Res/Health Tech 2/PENS	6.00				20,000	7,000	27,000
To Be Named	Vet Res/Health Tech 2/Shelter	6.00				20,000	7,000	27,000
To Be Named	Lab Animal Tech 1	60.00				135,002	60,751	195,752
To Be Named	Asst Operation Mgr	6.00				37,100	11,501	48,601
To Be Named	Res Support Mgr	6.00				25,000	8,750	33,750
To Be Named	Lab Animal Tech 2-PENS	6.00				20,776	7,272	28,048
To Be Named	Lab Animal Tech 2-Cage Crew	6.00				20,776	7,272	28,048
To Be Named	Vet Res/Health Tech 3	6.00				22,831	7,991	30,822
To Be Named	Mgr, NHP Res	6.00				37,100	11,501	48,601
	SUBTOTALS →					1,790,993	662,248	2,453,242
CONSULTANT COSTS								
Building Recertification Consultant							4,000	4,000
EQUIPMENT *(Itemize)*								
None Requested								
SUPPLIES *(Itemize by category)*								
Operating Supplies							16,925	
Animal Bedding							5,800	
Animal Purchase							70,000	
Chemicals-Non-Hazardous							2,500	
Rentals & Leases							140	
Laboratory Supplies							55,654	
Med Care Malts Supplies							23,850	
Pharmaceuticals							8,745	
Cleaning Cage Supplies							74,338	
Primate Food							337,500	
Fruits and Vegetables							104,940	
Diet Supplements							29,150	
Protective Clothing							78,500	808,042

ANIMAL SERVICES-RESOURCES, FACILITIES & OPERATIONS DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55	
TRAVEL				
Domestic			7,045	7,045
INPATIENT CARE COSTS				0
OUTPATIENT CARE COSTS				0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*				
None Requested			0	0
OTHER EXPENSES *(Itemize by category)*				
Shipping			4,620	
Equipment Maint & Repair			55,075	
Equipment Rentals & Leases			530	
Equipment Certification & Testing			500	
Hazardous Waste Disposal			4,233	
Vehicle Maintenance			1,750	
Vehicle Expenses			2,500	
Lab Svc Non Patient - MHC Typing			45,000	
Lab Svcs-Non Patient Care			23,130	
Lab Svcs-Internal			3,180	
Bioengineering Service Fees			1,325	
Misc Services			795	
Conference Registration			750	
Maintenance Cages			26,500	
Registration/Course Fees/Meetings			1,265	
Select Agent Processing			306	
Software Development Support			7,500	
Flow Cytometry			795	
Virology Service			265	
RIA Lab Fees			1,225	
Ultrasound Fees			2,975	
				184,218
CONSORTIUM/CONTRACTUAL COSTS			DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*				$ 3,456,547
CONSORTIUM/CONTRACTUAL COSTS			FACILITIES AND ADMINISTRATIVE COSTS	0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD				$ 3,456,547

ANIMAL SERVICES-RESOURCES, FACILITIES & OPERATIONS
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	2,453,242	2,613,139	2,691,533	2,772,279	2,855,447
CONSULTANT COSTS	4,000	4,120	4,244	4,371	4,502
EQUIPMENT	0	0	0	0	0
SUPPLIES	808,042	832,283	857,252	882,969	909,458
TRAVEL	7,045	7,256	7,474	7,698	7,929
INPATIENTS CARE COSTS	0	0	0	0	0
OUTPATIENTS CARE COSTS	0	0	0	0	0
ALTERATIONS AND RENOVATIONS	0	0	0	0	0
OTHER EXPENSES	184,218	189,745	195,437	201,300	207,339
DIRECT CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	3,456,547	3,646,543	3,755,939	3,868,617	3,984,676
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	3,456,547	3,646,543	3,755,939	3,868,617	3,984,676
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					18,712,322

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

PERSONNEL

Manager, Operations – Excluded by Requester % Effort Responsible for directing day-to-day operations including facilities, corrals, animal husbandry, coordination of research space, etc. Serves on committees, meets regularly with management staff to ensure that animal care is being conducted properly, serves as AALAC site visit liaison.

Associate Vet – Excluded by Requester % Effort Excluded by Requester has over twenty years' veterinary experience, eighteen of these in nonhuman primate care, breeding, and husbandry. His position, as head of the Resources, Facilities, and Operations unit is responsible for colony management and maintenance, facility management and maintenance, and oversight of all care and maintenance personnel. The position acts as liaison with researchers and is the point person within DCM for the development and implementation of new projects. The position provides oversight and guidance relative to animal regulatory requirements, and is an active member or ad hoc on the Institutional Animal Care and Use Committee, Institutional Biosafety Committee, ABSL3 Committee, and the Animal Utilization Committee.

Research Analyst 2 – Excluded by Requester % Effort Income). Excluded by Requester s a recent a m' welcomed addition to the unit. His computer talents are in database administration, programming, web site design and data analysis. He is integral with Lab Key development.

Laboratory Animal Technician 3-ASB Lead – Excluded by Requester Area Lead ASB): (% Effort % Effort Responsible for research project management in the ASB Building as well as responsible for the animal care of the ONPRC on one weekend day each week.

Research Assistant 2 – Excluded by Requester % Effort Responsible for managing the testing strategies for the expanded SPF (SPF 9) U24 program. (She is currently developing a western blot for SRV and has extensive experience with PCR).

Veterinary Research Health Technician 2 – Excluded by Requester % Effort Program Income). Responsible for animal care and directing animal care staff on a daily basis to accomplish animal care in the breeding corrals with approximately 1600 animals.

Veterinary Research Health Technician 3/ABSL3 – Excluded by Requester % Effort % Effort . Lead tech for ABSL3 responsible for animal care and directing animal care staff on a daily basis to accomplish animal care in the ABSL3 suites.

Veterinary Research Health Technician 3 – Excluded by Requester % Effort Program Income) % Effort is devoted to managing the TMB colony of over 65 animals. including: project coordination with DCM staff and investigative staff, evaluating and monitoring mense data, evaluating estrogen/progesterone data, breeding animals for project use, coordination of projects and medical issues with the veterinary staff, etc. Also, directly responsible for the care of the animals in the Specific Animal uilding and parts of ASB3.

Laboratory Animal Technician 3-Crew Lead – Excluded by Requester % Effort Program Income). Responsible for overseeing cage crew which cleans, moves and sterilizes all racks and cages on campus - the lead technician for the ten-person cage crew.

Research Support Supervisor – Excluded by Requester % Effort Responsible for the daily management of the animals in Specific Animal Location and overseeing four leads that are responsible for the daily husbandry and research needs of over 1900 caged and group housed animals.

Research Assistant 1 – Excluded by Requester % Effort Responsible for the HSV1/2 surrogate macacine herpes virus1 assay and managing the thousands of retained frozen serum in freezers on campus.

Research Support Manager – Excluded by Requester CMAR, LATG, CVT: % Effort % Effort appointment, devoted to the ABSL3 management and project coordination. Since the ABSL3 is not continuously occupied, overseeing staff is accomplished by the Research Support Managers.

Research Support Manager – Excluded by Requester % Effort Responsible for management of the husbandry staff for the breeding colony (over 3600 animals) as well as quarantine and animals in Specific Animal Location Building.

Research Support Manager – Excluded by Requester % Effort Responsible for management of the husbandry staff for the indoor housed animals in the Specific Animal Location buildings.

Senior Research Assistant – Excluded by Requester % Effort Excluded by Requester responsibilities include performing virology and serology assays for the detection of viral infection in nonhuman primates; data analysis and management; sample processing and management; project coordination, as well as routine laboratory duties such as maintaining inventories and equipment. As lead-person for the SPF lab she oversees and delegates tasks to the lab personnel.

Associate Vet – Excluded by Requester % Effort Excluded by Requester has fifteen years' experience in veterinary medicine and surgery, with ten years in primate medicine. She has held her current role as Head of Colony Clinical Medicine for three years. She is currently obtaining her master's degree in Clinical Research at OHSU. She is a stake holder in the Lab Key development and roll out. She is responsible for establishing and maintaining the high volume of epidemiological data for the breeding colony of over 3,700 nonhuman primates. She also manages the high medical case load of colony animals entering our veterinary hospital.

Laboratory Animal Technician 3-ESPF Lead – Excluded by Requester % Effort Program Income).). Responsible for the care of the animals in the Expanded Specific Pathogen Free (ESPF) area and ASB 3,and directing staff on a daily basis to accomplish animal care in these specific areas.

Veterinary Research Health Technician 3 - Lead – Excluded by Requester % Effort % Effort . Responsible for the care of the animals in the sheltered housing area and directing staff on a daily basis to accomplish the animal care for over 1300 animals.

Veterinary Research Health Technician 3 - Lead – Excluded by Requester % Effort % Effort Responsible for managing the processing of the breeding colony with over 3800 animals processed (sedated, bled, MOT, weights, etc.) twice per year. Also responsible for directing staff in the care of animals in the Specific Animal Location and quarantine areas.

Administrative Coordinator – Excluded by Requester % Effort Excluded by Requester has twenty years' experience with OHSU/ONPRC. His position provides administrative support for Dr. Excluded by Requester and oversees the animal requisition and allocation process, assisting investigators and their project coordinators in identifying and assigning subjects matching project requirements. In addition to these tasks, the position is responsible for the requisition and inventory of the Personal Protective Equipment for the Division of Comparative Medicine, as well as maintenance of animals records relative to the requirements of the Convention on the International Trade in Endangered Species (CITES).

Veterinary Research Health Technician 2 – Excluded by Requester % Effort Program Income). Back up to the TMB program; primarily responsible for animal care staff and proper animal care in the ASB2 area along with a supportive role in the TMB program.

Office Specialist – Excluded by Requester % Effort Excluded by Requester has twelve years of experience at ONPRC. Her position is the key data entry point for the information gathered by the animal technicians, and is responsible for the maintenance and verification of animal histories including procedures, weights, blood draws, transfers, and labs, as well as a myriad of other tracked indicators used to maintain animal health and wellbeing. Her position is responsible for the timely and accurate input of this data, which is paramount in tracking animal health.

Research Support Supervisor – Excluded by Requester % Effort Responsible for the daily operations for the outdoor breeding groups (corrals and shelters) as well as the animals in the Specific Animal Location Building.

Veterinary Research Health Technician 3 (Area Lead- ABSL3) – TBN: (12 calendar months effort: 12 ORIP, 12 Program Income). These are posted positions. The training demands are higher with this position due to the nature of the studies. These positions are primarily responsible for the two ABSL3 suites in the ASA Building. These positions are also responsible for the animal care of the entire Center on the weekend.

Veterinary Research Health Technician 2 (Shelters) – TBN: (12 calendar months effort: 6 ORIP, 6 Program Income). This is currently an open and advertised position. The area of responsibility for the position will be the care of primates in the group housing areas in Sheltered Housing.

Assistant Operations Manager – TBN (12 calendar months effort: 6 ORIP, 6 Program Income). Excluded by Requester will be Personal Info so we need someone to acquire Excluded by nvaluable knowledge. The hope is to have this position in place in Y54. Once Excluded by Requester Personal Info from the ONPRC, this person would become the Operations manager and this position would dissolve.

Research Support Manager (Cage Crew) – TBN: (12 calendar months effort: 6 ORIP, 6 Program Income). This is a newly created cage crew position targeted for Y54.The current top level position in cage crew is a unionized lead position which does not allow for discipline and full training of the rest of the cage crew staff; this leads to delays in disciple or inaction. The newly created position would report to the Operations Manager. This position will be responsible for all of the caging maintenance and sanitation throughout the Specific Animal Specific Animal Location

Manager, NHP Resources – TBN (12 calendar months effort: 6 ORIP, 6 Program Income). We are currently interviewing for this critical position. The position is responsible for breeding group formations, animal assignments, animal sales, assist in genetic management and SPF management, data mining, and consortia activities. This is a specialized position, so finding the right person can take time. We should have the position filled by February 2013.

Remaining staff to Accomplish daily Husbandry and research needs

Eight Laboratory Animal Technician 1– Cage Crew – (96 calendar months effort: 48 ORIP, 48 Program Income). Along with Excluded by Requester the cage crew consists of eight laboratory Animal technicians 1. We need this many staff in cage crew to accomplish the large number of cage and rack change outs, along with maintenance and sanitation requirements that are needed for compliance.

16 Laboratory Animal Technician 1 – (LAT1): (192 calendar months effort: 96 ORIP, 96 Program Income). These positions are needed for the daily animal care and research needs for over 5000 nonhuman primates in cages, small group housing and large breeding groups.

11 Laboratory Animal Technician 2 – (LAT2): (132 calendar months effort: 66 ORIP, 66 Program Income). These positions are needed for the daily animal care and research needs for over 5000 nonhuman primates in cages, small group housing and large breeding groups.

Nine Veterinary Research Health Technician1 (VRHT1) –: (108 calendar months effort: 54 ORIP, 54 Program Income). These positions are needed for the daily animal care and research needs for over 5000 nonhuman primates in cages, small group housing and large breeding groups.

Five Veterinary Research Health Technician 2 (VRHT2) –: (60 calendar months effort: 30 ORIP, 30 Program Income). These positions are needed for the daily animal care and research needs for over 5000 nonhuman primates in cages, small group housing and large breeding groups.

Additional Positions Needed for Y55

One Veterinary Research Health Technician 2 (ABSL3) – TBN: (12 calendar months effort: 6 ORIP, 6 Program Income). We project that the ABSL3 will be continually scheduled with complex projects. We currently have two staff members devoted full time to the ABSL3 but we will need another highly skilled laboratory animal technician to handle the increased load of work.

One Veterinary Research Health Technician 2 (PENS) – TBN: (12 calendar months effort: 6 ORIP, 6 Program Income). We need this position for the animal care of up to 180 animals in twelve corn cribs. This position is responsible and accountable for research support and animals care. Each PENS complex of twelve corn cribs requires three husbandry staff members to accomplish daily animals care and research needs.

Two Laboratory Animal Technician 1– TBN (PENS): (24 calendar months effort: 12 ORIP, 12 Program Income). We need this position for the animal care of up to 180 animals in twelve corn cribs. The projected date for animal occupation of this new area is April 2013. We did not account for this new animal area in the current grant cycle.

One Laboratory Animal Technician 2– TBN (PENS): (12 calendar months effort: 6 ORIP, 6 Program Income). We need this position for the animal care of up to 180 animals in twelve corn cribs. The projected date for animal occupation of this new area is April 2013. We did not account for this new animal area in the current grant cycle.

Two Laboratory Animal Technician 1– Corrals – (24 calendar months effort: 12 ORIP, 12 Program Income). After performing time in motion matrix in this area, we are currently understaffed in this area. This is a large geographic area overseeing eight breeding corrals of over 1800 animals. Currently it is difficult to accomplish the high level of care required in this area with our current staff.

Three Laboratory Animal Technician 1– Shelter Group Housing – (36 calendar months effort: 18 ORIP, 18 Program Income). After performing time in motion matrix in this area, we are currently understaffed in this area. There are thirty two shelters with 50 to 70 animals per unit. Currently it is difficult to accomplish daily animal husbandry requirements as well as regulatory and research needs with our current full time staff. In order to maintain breeding group dynamics, we are now medically treating more animals in their natal groups. This methodology is time consuming but beneficial.

Three Laboratory Animal Technician 1– Cage Crew – (36 calendar months effort: 18 ORIP, 18 Program Income). After performing time in motion matrix for cage crew, we are currently understaffed in this area. The cage crew is responsible for all caging sanitation on campus

Specific Animal Location
Specific Animal Location

One Laboratory Animal Technician 2– Cage Crew – (12 calendar months effort: 6 ORIP, 6 Program Income). Over this grant cycle several new caged areas will be added: PENS support housing (up to twelve two over two racks), Colony Annex remodel (12 two over two racks), seven new ASB1 ABSL2+ containments rooms (4 two over two racks per room).

One Veterinary Research Health Technician 2 (ASB1 containment expansion) – TBN: (12 calendar months effort: 6 ORIP, 6 Program Income). The ASB1 containment (ABSL2+) seven animal room expansion will be completed in 2014 (Y55). We will need these new staff members to accomplish the husbandry and research needs for up to 112 caged animals.

Proposed future expansion into PENS Y56

One Veterinary Research Health Technician 2 (PENS) – TBN: (12 calendar months effort: 6 ORIP, 6 Program Income). It is projected that another complex of PENS units consisting of twelve corn cribs will be built during this grant cycle. We will need this position for the animal care of up to 160 animals.

One Laboratory Animal Technician 1– TBN (PENS): (12 calendar months effort: 6 ORIP, 6 Program Income). It is projected that another complex of PENS units consisting of twelve corn cribs will be built during this grant cycle. We will need this position for the animal care of up to 160 animals.

Staffing Explanation

Laboratory Animal Technician 1 (LAT1) and Veterinary Research Health Technician 1 (VRHT1)
Essentially the differences between the LAT-1 and VRHT-1 are the percentage of time we expect them to spend focusing on research support and animal health care services versus Animal Husbandry. The LAT-1 tech is expected to spend more time doing animal husbandry. It doesn't necessarily mean they will always, but that is the expectation in the position description that differentiates mainly between the two.

Laboratory Animal Technician 2 (LAT2) and Veterinary Research Health Technician 2 (VRHT2)
The difference between the LAT-2 and VRHT-2 is essentially the same with percentages but has an added addition of increased responsibility and accountability related to their job specific responsibilities. The LAT-2 has more responsibility and accountability in the animal husbandry area and the VRHT-2 has more responsibility and accountability in the areas of research support and animal health care. It doesn't mean we don't expect both to be responsible and accountable for whatever they are assigned to do, this is just the area of focus that mainly separates the positions.

Laboratory Animal Technician 3 (LAT3) and Veterinary Research Health Technician 3 (VRHT3)
An LAT-3 has a higher percentage of time focused on animal husbandry and a VRHT-3 has a higher percentage of time spent focused on areas of research support and animal health care. These techs are meant to be leaders and mentors for the staff and are expected to spend a small percentage of their time in the development and writing of SOP's. Additional core competencies also apply and are expected from employees in a leadership position: Systems Thinking, Managing Resources, being a Change Leader, and Developing organizational Talent.

CONSULTANT COSTS

Building Recertification Consultant: Funds are requested for costs related to the recertification of the Animal Service and Animal Biosafety Level 3 building (ASA) as an supportive facility for projects requiring level 3 Animal Biosafety precaution. Building recertification is a requirement to maintain projects that include select agents.

SUPPLIES

Operating Supplies: Funds are requested for the purchase of consumable materials used in support of the nonhuman primate population on an ongoing basis. Specific materials in support of this aim are: technician footwear, lock purchases and recalibration, plumbing and lighting supplies not provided by ONPRC facilities, hand and power tools, and walkie-talkies for area technicians. In addition, as all ASA building consumables are required to be disposed of when each project commences, specific operating supplies are requested for the handing of exotic agents. The operating supplies budget will also support materials for an ongoing barcoding

initiative, and is critical for the maintenance of all division operating procedures. In addition supplies are needed for the ASA Clordysis decontamination unit and general cleaning supplies essential for a safe working environment.

Animal Bedding: When new breeding groups are established in sheltered group and small group housing, husbandry staff oftentimes bed down the group with pine shavings. These shavings offer enrichment to the animals and tend to lower the stress of new group formation. Each shelter house requires ten large bales of shavings and small group housing requires about 2-3 bales. The shavings are replaced every two weeks for up to eight weeks. Some indoor breeding groups for the U24 colony are permanently bedded down.

Animal Purchase: Funding is requested to purchase five to eight Indian origin SPF4 male nonhuman primates per year. The intention of this purchase is to put these animals into several of the forty plus breeding groups to improve our heterogeneity within the breeding colony. The cost plus diagnostics is approximately $7000/animal. Shipping can be as high as $15000, depending on the distance. It is the intention of the RFO to amass a yearly shipment of animals.

Chemicals-Non-Hazardous: The majority of the costs in this category are for various chemicals needed for medical use as well as for equipment support in husbandry areas.

Rentals and Leases: Rental of equipment for temporary use such as pressure washers or an extra vehicle when scheduling occasionally requires it.

Laboratory Supplies: Funding is requested for items such as water filters for the animal drinking water, wash down hoses, supplies for the bedding suction vacuum, syringes needed to sedate animals and to Tb test, and blood collection tubes. These items are for the daily husbandry of over 5000 nonhuman primates as well as to support research needs. In addition, funding is requested to support SPF4 multiplex arrays from Intuitive Biosciences and for HSV 1/2 ELISA plates from Zeus Scientific for our surrogate Herpes B ELISA. The SPF4 multiplex array costs approximately $24.50 per animal per year. The HSV plates cost $48.13/96 well plate. The SPF Surveillance laboratory tests ~ 4200 animals/year to include the breeding colony, rechecks, and imports.

Medical Care Materials Supplies: Items such as acetone, autoclave bags, tape, stainless steel cleaner, sharps containers, sharpies, syringes, and disposable towels for husbandry support. Funds are needed in this category for the daily operation of the RFO unit as well as to support research needs.

Pharmaceuticals: Funds are requested for items such as: ketamine and telazol for sedation, injectable parasitacides, and bacteriostatic water to be used as a diluent for pharmaceuticals, measles vaccine and antibiotics. These items are necessary for the daily husbandry, as well as preventative medicine for the nonhuman primates.

Cleaning Cage Supplies: Funds are necessary to purchase mainly chemicals and detergents for the cage and rack washers. We have four large rack/cage washers on campus that are in daily operation.

Primate Food: The RFO feeds approximately 680, twenty five pound bags of primate chow to over 5000 nonhuman primates per week (17,000 pounds of chow per week). We recently evaluated food wastage in our group housed areas and were able to cut back by 75 bags of chow per week. We also purchase four tons of medicated feed with a parasitacide once yearly that is fed out to all of the breeding groups for two weeks.

Fruits and Vegetables: Unless specified in a research protocol, the nonhuman primates on campus are supplemented several times per week with fruits and vegetables for added nutrition as well as for behavioral enrichment.

Diet Supplements: The RFO makes many specialty research project specific diets as well as formulated medical diets for colony nonhuman primates. Funding is requested to purchase food grade minerals, vitamins, oils, proteins and fats.

Protective Clothing (PPE) : Funds are requested to purchase the large volume of personal protective equipment needed to supply all ONPRC staff and visitors, so that they can safely work in the ABSL2, ABSL2+ and ABSL3 areas. Items include but not limited to: Tyvek suites, face shields, scrubs, latex gloves, nitrile gloves, goggles, boots, booties, hair bonnets, gauntlets, PAPR hoods, dust masks and N95 respirators. In addition, due to indigenous or exotic agents used in the ASA facility and their potentially lethal effect on employee health, funding is requested in support of personal protective equipment including; PAPR Hoods, Scrubs, and Tyvek cleanroom suits.

TRAVEL

Funds are requested to support travel to one national clinical veterinary meeting every other year per veterinarian, travel for six members of the husbandry staff to attend regional and national AALAS meetings, travel for the Serology laboratory supervisor to learn new techniques and methodologies, and ABSL-3 training and certification for the ASA manager and RFO Unit Head. Additionally, travel funds are needed to visit and inspect vendors that supply food, research animals and other regulatory items, to cover costs for ASA recertification consultants, and for mileage incurred by AFSCME technicians during non- standard shifts, payment of which is mandated by the AFSCME union contract. Travel funds provide invaluable staff experience and critical training for laboratory staff, and support the continuing education of RFO veterinary staff and managers.

OTHER EXPENSES

Shipping: Funds are requested for the shipping and receiving of large items necessary for the RFO to operate effectively, efficiently, and to maintain a high quality of care for the nonhuman primates. Items such as, feed, feed supplements, caging, chemicals, decontamination units with specialized gasses and warming huts fall under this category. Funds are also requested for the shipment of samples going to outside reference laboratories, costs for receiving goods, and sample processing by outside reference laboratories.

Equipment Maintenance & Repair: Funds are requested to maintain equipment such as: pressure washers, hand held radios, cell phones, computers, floor scrubbers, cage lifts, vacuums, heaters and fans. This equipment is necessary for the RFO to operate and communicate effectively and efficiently. Funding is also requested to support maintenance contracts for vital systems in the ASA building: the Clordysis decontamination tank, building autoclaves, the affluent decontamination system, and the building's Ceretom CT scanner. Additional funds are requested to cover costs to maintain critical Serology equipment, including repairs, annual preventive maintenance, recalibration, certification, and vendor maintenance contracts.

Equipment Rentals & Leases: Funds are requested for the monthly rental of Chlorine and Nitrogen canisters used in mandatory decontamination procedures in the ASA building, and for equipment necessary for RFO to perform daily duties and maintenance of the facility, such as: portable restroom rental, man-lift rental, pressure washer rental, trencher rental, etc.
($530 ORIP, $530 Program Income)

Equipment Certification and Testing: Funds are requested for the mandatory bi-yearly testing and certification of area laminar flow hoods and biosafety cabinets in the ASA building

Hazardous Waste Disposal: Funds are requested to pay for disposal of biological (sharps), chemical waste, and hazardous materials generated by unit centers. Charges are per the standard OHSU Environmental Health & Radiation Safety Program.

Vehicle Maintenance: Funds are needed for the maintenance (oil changes, new batteries, new tires) of our ten trucks and vans as well as three electric golf carts. This equipment is necessary to move equipment, nonhuman primates, and staff around the Center.

Vehicle Repair Expense: Funds are needed for the repair of our ten trucks and vans as well as three electric golf carts. This equipment is necessary to move equipment, nonhuman primates and staff around the Center as well as off campus.

Laboratory Services Non Patient - MHC Typing: Currently all male Indian SPF4 offspring are MHC typed so that we can supply the needs of our researchers and to better characterize our colony. The ONPRC P51 Indian rhesus breeding colony produces approximately 300 males per annum. One 13 haplotype MHC costs $150.

Laboratory Service – Non Patient Care: Along with importing NHPs specifically to add to our breeding colony, we also import 40 to 100 nonhuman primates per year to meet researches needs in reproduction, obese resource, and neuroscience. Much of the clinical and viral diagnostics are performed prior to arrival. Common offsite clinical tests are: complete blood counts, clinical chemistries, viral SPF surveillance (SRV, STLV1, herpes B, SIV), rectal cultures and Tb serological assays, and are required so that we can ensure we receive a healthy animal into quarantine. Additional laboratory services include tests on colony animals that support the epidemiology and herd health program, and the shipping of samples to various diagnostic laboratories for confirmatory viral screen testing. These tests and shipments are vital to maintain a high quality NHP model, and to assist with colony surveillance and pre-sale selection.

Lab Services-Internal: An important responsibility to the SPF Surveillance Laboratory is processing and submitting serum for estrogen/progesterone and other hormone analysis to the Endocrine Services Core. If a breeding troop is experiencing low fertility, sex hormone analysis will be requested, along with other diagnostics to ferret out the fertility issue.

Bioengineering Service Fees: Funds are needed in this category for preventative maintenance and repair of DCM operated laboratory equipment such as cage and rack washers, scales, boilers and autoclaves.

Miscellaneous Services/Supplies: Funds are requested to purchase various small items necessary for the RFO to function efficiently and effectively. Items included in this category are: zip ties, small hand tools, books, kitchen equipment, nursery items, unique foods, card holders, plastic signage and carabineers.

Conference Registration: Funds are requested for continuing education to obtain and keep staff licenses and certifications current.

Maintenance Cages: Funds are requested for cage and rack maintenance, modification and repair. We have over 750 racks and over 1400 hanging cages. Ten to thirty cage or rack related items are repaired monthly.

Registration/Course Fees/Meetings: Memberships in professional organizations are essential for maintenance of continuing education and certification. Professional conference registration includes the APV/AALAS Annual Meeting, veterinary internal medicine conferences, and specialty conferences such as for ultrasound and CT training.

Select Agent Processing: Funds are requested for the Select Agent certification for four employees per year. Select agent costs cover mandatory FBI requirements and fingerprinting costs for each individual, and are necessary to staff the ASA building.

Software Development Support: Funding is needed for requisite training and aids to maintain the data integrity and administration of the inventory and record management SQL implementations. As well, funding for SharePoint educational aids and automation solutions is needed to accurately determine the areas of greatest business need and how they could be most effectively addressed in our push for expanded intra-business media presence and transparency. Lastly, funding is needed for reporting and QA development solutions, business intelligence resource training, and analytical modeling software in an effort to provide the best possible data models and report generation for the multiple constituents NHPR has dealings with.

Flow Cytometry: Funds are requested to use the BD FACS Caliber flow cytometer from the Core. Generally we are using the cytometer 2 to 4 hrs./week to a total of ~ 4000 SRV IFA samples per year.

Virology Service: For cost savings purposes, the SPF surveillance laboratory will occasionally order reagents, chemicals, and other supplies from the Virology laboratory.

RIA Lab Fees: The TMB program also uses the Endocrine Core for estrogen and progesterone analysis. We use this data to confirm pregnancies as well as to monitor the menstrual cycle of NHPs.

Ultrasound Fees: Funds are requested for the use and maintenance of the diagnostic ultrasound machines. Ultrasonography is needed in the TMB program to confirm pregnancies as well as age the fetus and thus to make fetuses available for project use.

ANIMAL SERVICES: Resources, Facilities, and Operations Income Table

Last Funded Year (53)

Source	Funding (direct costs)
P51 base grant support	$2,941,983.20
Program income derived from P51 base grant	3,017,866.38
Other Sources	0
Total	$5,959,849.58

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$3,456,546.55
Program income derived from P51 base grant	3,544,846.55
Other Sources	0
Total	$7,001,393.10

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

Resources, Facilities, and Operations receives salary support and support for other expenditures from program income.

PATHOLOGY SERVICES UNIT SPECIFIC AIMS.

Anatomic and clinical pathology expertise and services are key elements of ONPRC's veterinary care program dedicated to the maintenance of self-sustaining populations of genetically characterized, disease-free NHPs for research. They are also essential for meeting the objectives of our research programs. The primary goals of the Pathology Services Unit (PSU) are to provide disease diagnostic and surveillance services that promote the health and safety of ONPRC's animal resources and provide research support services that strengthen the research infrastructure and contribute directly to the mission of ONPRC through participation in multidisciplinary research programs.

The specific aims for accomplishing this:

Specific Aim 1: To provide disease diagnosis and surveillance for ONPRC's animal resource through diagnostic necropsies, biopsies, clinical pathology and maintenance of databases for epidemiologic queries.

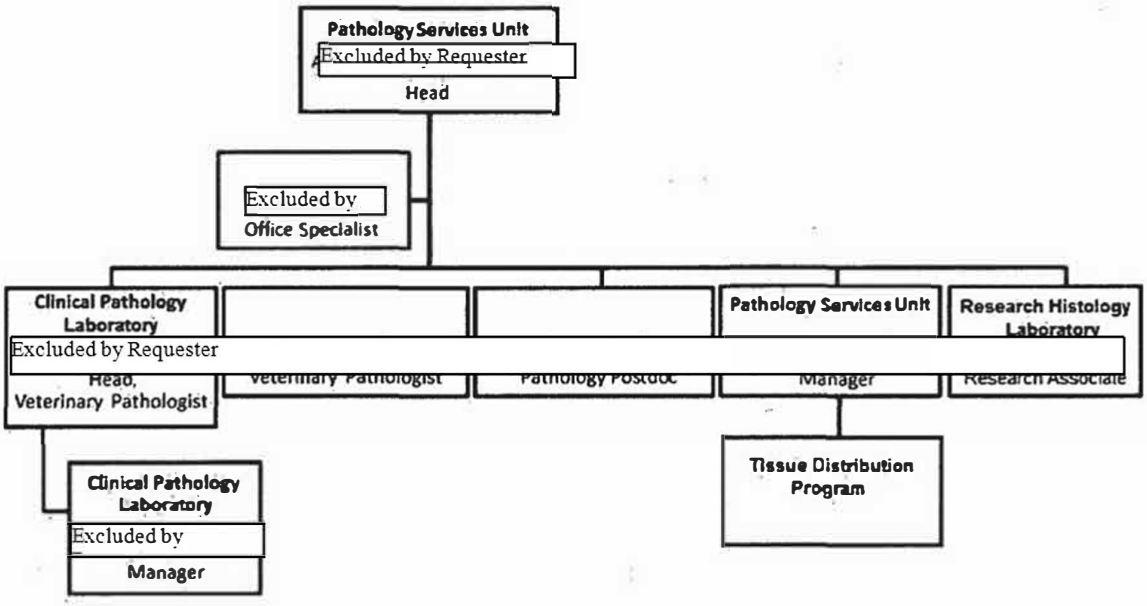
Specific Aim 2: To participate in the research mission of ONPRC by providing pathology support for research projects through necropsies, tissue distribution, clinical laboratory services and participation in study design; and through characterization of spontaneous NHP diseases potentially useful as models for human diseases.

Specific Aim 3: To act as a national resource for NHP pathology through maintenance of archived tissues, slides and blocks, databases of biological data and images.

Specific Aim 4: To serve as a resource for educating veterinarians, laboratory animal professionals and investigators, about primate pathology by participation in publication, teaching and presentation in local, national and international settings.

The expected outcome is a highly productive resource for the support of the research mission and the NHP population through centralized provision of pathology services and expertise.

PATHOLOGY SERVICES UNIT RESEARCH STRATEGY.



SIGNIFICANCE.

Disease diagnosis and surveillance, combined with husbandry practices, are keys to the maintenance of animals for biomedical research that are free of intercurrent diseases. Early diagnosis of serious contagious diseases and prompt implementation of control strategies are essential to prevent catastrophic losses such as those experienced in outbreaks of disease such as mammalian tuberculosis. Epizootics of Shigellosis and Listerial abortion illustrate that animal resources are at risk from endemic organisms. Other diseases endemic in NHPs, such as Macacine herpesvirus 1 (B virus), represent a serious human health hazard and recognition of suggestive lesions will prompt appropriate diagnostic measures. Archives of tissue, necropsy reports with gross and histologic evaluation, databases of diagnoses and tissue weights and materials coupled with pedigree data and the potential for genetic analysis of archived material provide an inestimably rich resource for the investigation of the pathogenesis of diseases, including the influence of genetics. Many of these diseases may serve as powerful models of human disease. Additionally since access to training in NHP pathology is limited, the ONPRC is an enormously valuable resource for advanced training given its large resident NHP population, expertise of the pathologists on staff, and depth of archived material.

The Pathology Services Unit (PSU) provides advanced comparative pathology services to ONPRC veterinarians, core scientists, OHSU investigators, and affiliate and external investigators. The PSU provides diagnostic capabilities through post mortem examinations, clinical pathology and microbiology services and integrative interaction with our clinical veterinarians. PSU serves the research mission through research-directed post mortem examination, tissue collection, clinical laboratory testing, support of the Tissue Distribution Program (described separately), and identification of new disease entities and characterization of recognized, but neglected, diseases in NHP. PSU provides training for pre and post graduate veterinarians through our participation in on campus externships and residencies as well as our support of a post graduate training position in NHP pathology. PSU provides these services with a highly trained group of three ACVP boarded pathologists, a postdoctoral pathology resident, an ASCP certified medical technologist and eight technical level personnel who excel at their jobs and provide both overlapping and unique skills creating a flexible and responsive work unit.

INNOVATION.

A major innovative effort of the PSU has been the development of Primate Pathology Image Database (PPID.) The PSU was awarded an ARRA Supplement to the base grant in 2009, in collaboration with California NPRC and BIRN, to participate in the development of a readily searchable and accessible database of images of NHP Pathology for use in teaching and research. The PPID is intended to serve as a national resource for the education of laboratory animal veterinarians, veterinary pathologists, and biomedical researchers. The

ONPRC effort has been to establish the initial database content, develop associated procedures, and in conjunction with the Consortium development team, enable access to the resource from the NPRCs and external research communities. Continued development of a widely available online resource of reference materials will significantly advance the training of veterinarians, comparative pathologists, and translational researchers working in the NHP model. This resource can be utilized to enhance the training of clinical and translational science knowledge of trainees. Broad accessibility to this teaching and reference resource extends the impact far beyond the host and consortium institutions.

Innovative strategies to improve PSU service in the face of an increasing work load have employed a multifaceted approach using multiple resources. Best practices shared by pathologists at SWNPRC guided us in the development of a new tissue trimming protocol. Our office specialist participated in Lean process improvement training through OHSU Career and Workplace Enhancement Center.

Innovative research collaborations included a project with Amnon Sonnenberg, MD gastroenterologist at OHSU to evaluate whether focally enhanced gastritis, a lesion present in human patients with Inflammatory Bowel Disease (IBD) was similarly present in macaques with chronic colitis, a disease with many similarities to IBD in humans. These findings were subsequently published. Additionally, we are actively involved with innovative cross center studies with members of the Consortium Pathology Working Group on projects such as the development of immunohistochemical markers of rhabdomyosarcomas and other soft tissue sarcomas (Asseff, NENPRC) and the detection of Spironucleosis in SIV-infected macaques through PCR (Miller, NENPRC). These collaborations are expected to lead to publication within the year.

APPROACH.

reviewers' comments

reviewers' comments

Progress and Accomplishments.

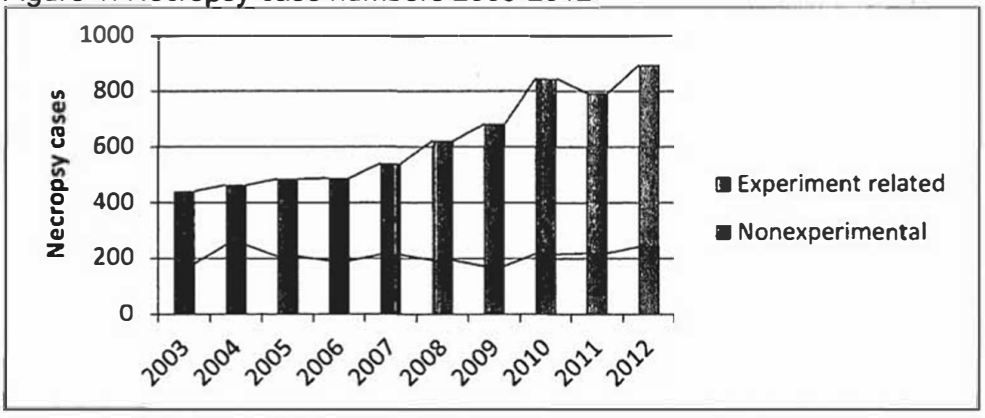
Highlights

Personnel The PSU has enjoyed an expansion of staff over the last several years as well as retention of several senior members. Excluded by Requester, Diplomate, American College of Veterinary Pathologists (ACVP), has served as Head of Pathology Services since 1999. Excluded by Requester, Diplomate, ACVP, has served as veterinary pathologist since 2001. Excluded by Requester was appointed as Head of Clinical Pathology in January of 2009 and retains her responsibilities as veterinary pathologist in PSU. Both Excluded by Requester participated in the formal ONPRC promotions process and were promoted in 2011 to the ranks of Senior Veterinarian and Associate Veterinarian respectively. Both hold faculty appointments in the OHSU Department of Comparative Medicine. Excluded by Requester joined the unit in 2009 in a newly created veterinary pathologist position. He left the PSU in June 2012 and was replaced by Excluded by Requester Diplomate, ACVP who joined the PSU in October 2012.

Other personnel changes since 2009 include a reorganization of the unit to create a manager-level position filled by Excluded by Requester who had joined the unit in 2005 as a histology technician and the creation of a part time office specialist position filled by Excluded by. The assistant prosector position held by Excluded by Requester was used to develop the postdoctoral veterinarian training position. Excluded by held the position from June 2011 through July 2012. Excluded by Requester joined the unit in October 2012. Three new technical positions were created in 2010 and 2011. Excluded by Requester was hired in the role of assistant prosector in a newly created position; a new position as assistant prosector and aide in the histology laboratory was created in 2011 and is currently held by Excluded by Requester was hired as a histology technician in 2012, Excluded by Requester was hired as a new histology technician and back up for the necropsy in 2012, replacing Excluded by Requester. We retained our senior histotechnologist, Excluded by Requester who joined the unit in 2000. Excluded by Requester has provided valuable expertise and training of new personnel throughout his tenure. Excluded by Requester the manager of the clinical pathology laboratory has 39 years of experience and often taps her deep knowledge of diagnostic laboratory principles to provide appropriate suggestions in support of veterinary and research protocols. Excluded by Requester another long term employee has been a member of the clinical pathology laboratory since 1997. Excluded by Requester was employed for the initial 2 years of the ARRA Supplement to the base grant to support the Pathology Image Database (PPID). She was replaced by Excluded by Requester in January 2012.

Efficiency A number of strategies have been employed to address the challenges of a rapidly increasing necropsy caseload. As indicated in Figure 1, the caseload has risen to over 800 necropsy case accessions annually. The majority was due to increase in the numbers of animals sacrificed for protocol and tissue distribution.

Figure 1. Necropsy case numbers 2003-2012.



A new tissue trimming protocol was established. Tissues are now trimmed and placed in pre-numbered cassettes for processing. This significantly reduces technician time required for trimming in fixed tissues at a later time, ensures uniform tissue sampling and lesion selection, reduces the total number of cassettes for most cases, and facilitates quick processing time (within 2 to 7 days post necropsy) so that tissues are both available for examination quickly and suitable for later IHC evaluation as desired. More aggressive triaging of diagnostic cases selected for full or limited microscopic evaluation has been implemented. Assistant prosectors are trained to perform routine research support necropsies under the direct supervision of the pathologists. We acquired an additional microscope for the necropsy laboratory so that the pathologists can evaluate cases and be available as necessary during these routine necropsies. The report process has been streamlined with the use of prepared templates and abbreviated (bulleted) reporting format. Our office specialist employs Lean process improvement practices for managing reports.

Immunohistochemistry (IHC) capabilities have been a priority for the PSU over the last several years. We have capitalized on the expertise of Excluded by Requester to develop a number of IHC protocols for detection of pathogens and routine tissue antigens. Excluded by Requester performs the majority of our IHC protocols and has expanded our repertoire since Excluded by Requester left. Currently, we routinely perform cluster of differentiation markers (CD) CD3, CD4, CD4, CD8, CD20, CD68; intermediate and thin filament markers such as cytokeratin, desmin, vimentin, glial fibrillary acidic protein (GFAP), smooth muscle actin; and infectious agent markers for cytomegalovirus, adenovirus, SV40 and measles matrix protein as a surrogate for the detection of *Enterocytozoon*, and the proto-oncogene c-kit.

Clinical Pathology The Clinical Pathology Laboratory, previously within the Clinical Medicine Unit, was incorporated into the Pathology Services Unit under the direction of Excluded by Requester in 2009. Expanded services to clinicians and the provision of a more rapid turnaround of results to facilitate veterinary medical care were offered with the acquisition of an in-house serum chemistry analyzer in 2009. Reference intervals were established from laboratory test results from clinically healthy rhesus macaques here at the ONPRC which allowed improved interpretation of laboratory data. In the past, the reference intervals provided by the external clinical laboratory were based on human laboratory test data. A Laboratory Information System (LIS) was acquired in 2009 to improve accuracy and efficiency with direct data entry. It facilitates test orders, prints bar-coded labels for sample containers, interfaces with the hematology and chemistry analyzers, directs the test to be run once the sample is checked in and releases results directly into IRIS. Results may be viewed either on the LIS or IRIS. A charge-back system for laboratory work performed for research projects was instituted December 2011. The relatively slow through-put and obsolete chemistry Cobas c 111analyzer was replaced with a Pentra 400 chemistry analyzer in 2012 that was more efficient to operate, had a decreased turnaround time for results and could handle the current workload with room for growth. An expanded test menu including a full lipid panel optimized research support which allowed more income to be retained within the primate center budget as well as allowing expeditious turnaround of results needed for clinical care. The Pentra 60 C+ hematology analyzer by Horiba was acquired in 2011 to replace the obsolete Pentra 60 hematology analyzer by Horiba. Reference intervals were generated for these two units on a reference population of healthy adult female rhesus macaques, adult Cambodian cynomolgus females, and combined genders of adult Japanese macaques housed at the ONPRC. Two individuals in the PSU were cross trained to ensure critical support during understaffed periods in the clinical laboratory.

Research Support Services The establishment of formal pre-study meetings with investigators by DCM has expanded the opportunities for PSU to provide more in depth support and evaluation of pathology and clinical laboratory testing portions of research protocols prior to the commencement of studies. We have also promoted more regular meetings with investigators and their staff prior to beginning of new necropsy protocols or when there are significant changes in existing protocols. This has facilitated better communication and allowed us to provide better research support. After studies are completed, we have had increased opportunities to review histological findings on an individual basis with investigators using a double-headed microscope or through review of whole slide scanned digital images.

Advanced Training in NHP Pathology. The opportunity to provide in depth post graduate training in NHP pathology, while also enhancing the capabilities of the PSU to provide service to the ONPRC community, was created by the establishment of a postdoctoral training position. The position was initially created when a technical position became vacant. The first veterinarian hired was Excluded by Requester a recent DVM graduate who had participated as an extern the previous year. The postdoctoral veterinarian position allowed us to help Dr. Excluded by Requester bridge the gap between her undergraduate veterinary training and entrance into a formal veterinary residency program while providing the advanced expertise and service capabilities of a veterinarian to the unit. After Excluded by Requester left to begin her formal residency training at Texas A&M, we were able to recruit a post DVM, PHD, board eligible veterinary pathologist. The position's role within the unit has been flexible, allowing us to consider applicants with a range of backgrounds who can be successful e.g. recent graduates and board eligible trainees.

Pathology Services

Necropsy Services. All nonhuman primates that die on the ONPRC campus receive a post mortem examination. The extent of post mortem examination is determined by the case. Factors determining the level of evaluation include but are not limited to the services requested by an assigned investigator and source of the animal. During the period 5/01/09 through 10/30/2012, 2791 NHP cases were evaluated by Pathology Services. This represents all NHPs that died during this period (including fetuses) and is inclusive of both experimentally assigned and non-experimental animals. The majority were rhesus macaques (2475 animals), followed by Japanese macaques (259), and small numbers of anubis baboons (23), vervets (6), and cynomolgus macaques (28). An additional 201 NHP surgical biopsies were evaluated during the same period.

As NHP necropsies are performed by veterinary pathologists and their staff, necropsy findings in both research assigned and colony animals are used to provide colony health information. There is close integration with the clinical and other DCM staff. Necropsy results from colony animals are reported to the clinical staff and appropriate behavioral and senior husbandry personnel at the end of each day by email in order to ensure that information pertinent to clinical and colony management is available in a timely manner. Clinical veterinarians participate in the weekly Pathology Rounds conducted with the LAM residents to present clinical aspects of cases and/or diseases discussed. SOP's addressing necropsy procedures, the use of PPE, sample collection, tissue shipping and other topics are maintained through the training program coordinator in Research, Education, and Training Unit (RETU) of DCM and reviewed annually in compliance with DCM and IACUC guidelines.

Histology The Histology laboratory provides routine tissue processing, embedding, hematoxylin and eosin (H&E) staining, and advanced techniques such as immunohistochemistry (IHC), and special histochemical staining techniques. Special stains include, but are not limited to, acid fast, Fite's acid fast, Gomori's methanamine silver, Giemsa, periodic acid Schiff's (PAS), Warthin-Starry, Perl's iron, phosphotungstic acid hematoxylin (PTAH), Brown and Brenn and McDonald's gram, Von Kossa, Alizarin red, Congo red, Masson's trichrome, luxol fast blue, Churukian-Schenk, and others. During the period 5/01/09 through 10/30/2012, 37,006 slides of tissues were processed, sectioned and stained with H&E for light microscopic evaluation by the histology laboratory in support of pathology unit activities. This includes 457 slides for surgical biopsies and 2903 slides for special stains.

Records and Reports A necropsy report consisting of gross, microscopic findings as appropriate, and associated SNOMED (Systematized Nomenclature of Medicine) codes is generated for every NHP post mortem examination. The histology laboratory is currently processing tissues and slides with a fast enough throughput rate to allow 2 week turn around for routine cases requiring microscopic evaluation. Any case requiring immediate review and surgical biopsies have one to two day turnaround. The average turnaround time for all cases is now under 4 weeks. A log of necropsy accession numbers, animal ID, associated animal data and primary diagnoses is maintained for easy reference within the unit. Provisional and final diagnoses in the form of SNOMED codes, diagnostic test results, organ weights, and tissue distribution data are maintained in IRIS, the ONPRC electronic animal record system. All of this information is linked in IRIS to the animal's record, which includes signalment, source, geographic origin, medical and surgical history and reproductive

history and the GRIP database that contains parentage and pedigree data. These functions will be integrated in PRIMe when this new animal record system is adopted.

Clinical Pathology The Clinical Pathology Laboratory provides clinical laboratory support for disease diagnosis and surveillance for ONPRC's animal resources and for research support. In-house laboratory testing capabilities include hematology, bacteriology, parasitology, urinalysis, and serum chemistry. Automated instrumentation is utilized for hematology and clinical chemistry determinations. A comprehensive chemistry panel including a full lipid panel is available in-house. Samples for assays not available in-house are processed for shipping to local or national laboratories. Tests are performed to identify endoparasites and hemoparasites. Direct fecal smears, fecal cultures, flotation and thick and thin blood smears are done. An LIS supports order entry, sample processing and reporting of laboratory results. It prints bar-coded labels for sample containers and interfaces with the hematology and chemistry analyzers and releases results into IRIS. Standards of performance are detailed in SOPs that cover all procedures for diagnostic and research support conducted in the Clinical Pathology laboratory.

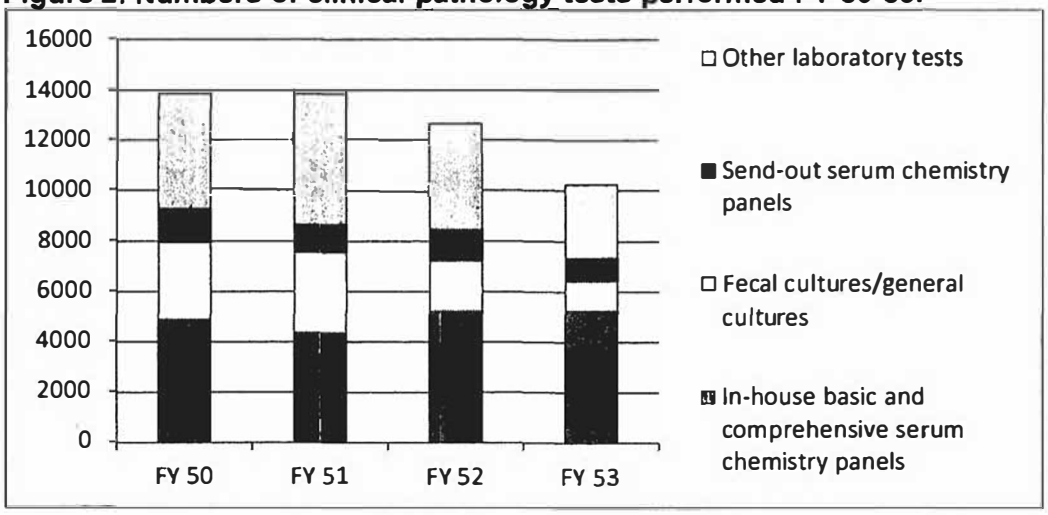
The Clinical Pathology Laboratory began providing support for research projects on a fee-for-service basis in December 2011 for work performed in-house and by outside laboratories. A processing fee is assessed for each sample that is sent out. Prior to this, investigators were only charged for the work performed by outside laboratories. A processing fee was not assessed. The top four test categories performed are specified in the following two tables showing current rates (Table 1) and numbers of tests performed (Figure 2). The "other" category includes in-house tests such as reticulocyte count, manual differential, HDL/LDL, fecal parasitology, anaerobic culture, *Yersinia* culture, occult blood, malaria screen, antibiotic sensitivity, urinalysis, dermatophyte test medium culture, and miscellaneous tests. Tests that are sent out include clotting panel, chemistry panel with amylase, lipid panel, C-reactive protein, cytology and other miscellaneous tests. The income derived from fee-for-service work and the number of investigators served is presented in Figure 3.

Table 1. Clinical Pathology Laboratory rates FY 53.

Description	Internal	Affiliate	External
Basic Serum Chemistry Panel/Comprehensive Panel	$15.00/$17.00	$26.25/$33.25	$32.80/$41.55
CBC	$9.85	$17.25	$21.55
Fecal culture/General Culture	$26.30/$26.30	$46.03/$46.00	$57.54/$57.50
Serum Chemistry Panel*/Serum Chemistry Panel with HDL*	$19.00/$27.00	$45.60/$33.75	$57.00/$42.20
Other (includes tests performed in-house and sent out)	Varied	Varied	Varied

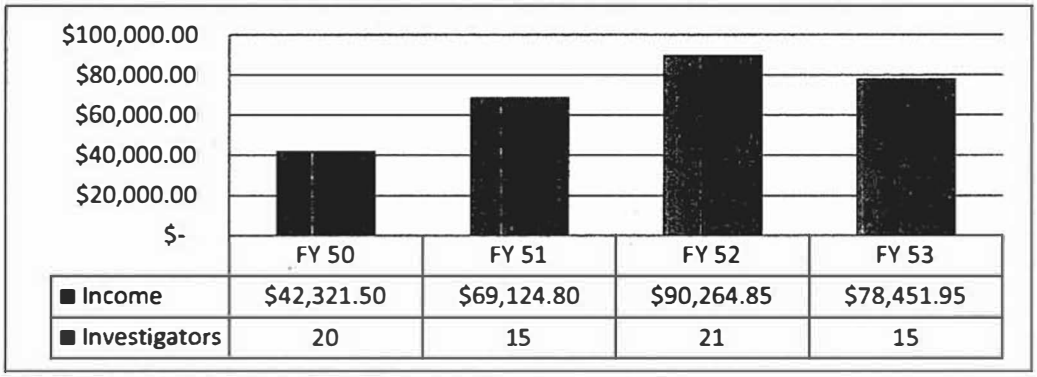
*These tests are sent to an outside laboratory and a processing fee of $8.35 is added.

Figure 2. Numbers of clinical pathology tests performed FY 50-53.



*FY 53 data are extrapolated from 8 months actual numbers

Figure 3. Income for Clinical Pathology Laboratory FY 50-53.



	FY 50	FY 51	FY 52	FY 53
■ Income	$42,321.50	$69,124.80	$90,264.85	$78,451.95
■ Investigators	20	15	21	15

*FY 53 data are extrapolated from 8 months actual numbers

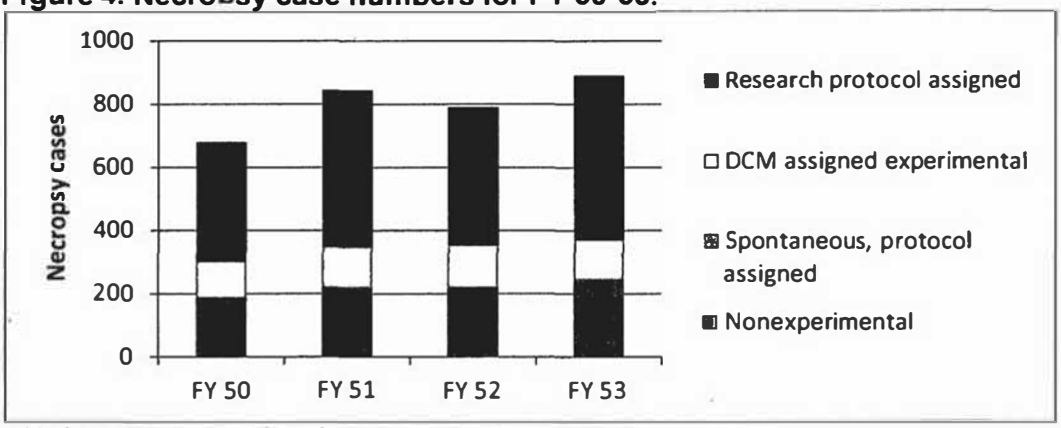
Archival Resources Archival material from necropsies include paraffin embedded blocks of tissue, limited formalin fixed tissues, frozen liver and terminal sera. As part of the support for the genetics program, liver is frozen at necropsy for each animal brought to necropsy except those assigned to infectious disease protocols. These samples are collected in replicate and are archived at -80 by Primate Genetics Support Core for future genetic analysis. Paraffin blocks are kept indefinitely in a climate controlled storage area. Glass slides are also kept indefinitely and the archives contain slides beginning in 1963. Formalin fixed tissues are bagged and stored three to five years. Additional materials from specific diseases of interest are also archived. These include mucosa and luminal content samples and OCT (Optimal Cutting Temperature compound cryo medium) embedded blocks frozen from animals with and without colitis; as well as frozen tissue of GI adenocarcinoma, and other neoplasms and synovium from reactive arthritis cases.

Digital photographs from a majority of our diagnostic cases are maintained within the Pathology Services Unit. With the availability of high quality digital photography, the number of images obtained and archived each year has risen significantly; as an example in 2011, approximately 6,800 gross images were obtained from 501 cases. Because the Primate Pathology Image Database is designed to function as federated instances of local databases, we have been able to utilize the local instance of the database and its powerful curation tools to upload the majority of our archived digital photos using mass import tools developed by BIRN and the OHSU Advance Computing Center. Our extensive archive of images is now searchable by numerous parameters such as species, gender, and selected key words. These images are completely separate from the PPID. Only a small portion of the overall collection has been selected for processing, curation and publication within the federated portion of the database. Copies of digital archives of over 1500 images of NHP diseases contributed by other institutions, including a copy of Excluded by Requester collection of photos spanning his 30 year career at Yerkes which we digitized as a collaborative project in 2009, are also archived by the PSU.

Research Support Services PSU provides a range of research support through a variety of mechanisms including gross, microscopic and clinical pathology services. Our support includes participation in formal pre-study meetings with investigators by representative members of DCM, meetings with investigators and their staff prior to beginning of new necropsy protocols, provision of expertise in complex dissection and perfusion techniques, review of histologic findings pertinent to study with investigators, provision of photomicrographs/digital images from scanned slide and digital gross images from necropsy, and evaluation of necropsy data in the context of experimental design.

Pathology Services began providing support for research projects on a fee-for-service basis in May 2004. Rates were calculated by a time and motion study to derive personnel cost with the cost of supplies also calculated. Between May 2009 and September 2012, 2725 necropsies were performed for research support. These included animals assigned to investigators on funded protocols (assessed fees for services) and animals assigned to DCM as medical culls for tissue distribution or terminally assigned for short term use, such as surgical training (no fees assessed.) Figure 4 presents the numbers of necropsy cases per year indicating the number of protocol-assigned experimental cases, DCM-assigned (short term training and tissue distribution use) experimental cases and non-experimental necropsies performed on NHP during the grant period.

Figure 4. Necropsy case numbers for FY 50-53.



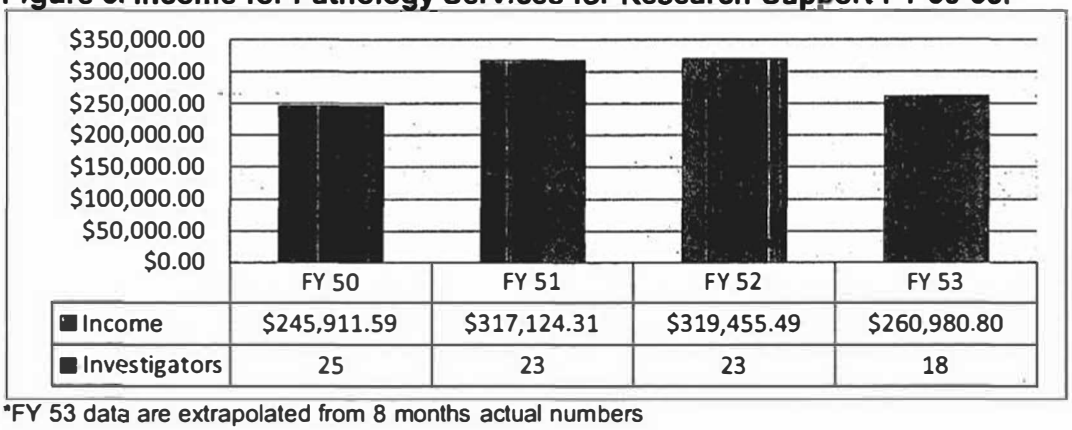
*FY 53 data are extrapolated from 8 months actual numbers

The rates for pathology services are outlined in Table 2. Three basic grades were determined by the size of the animal, numbers of tissues collected and complexity of the necropsy protocol. Additional fees are applied to specialized procedures such as fixative perfusion. Non-DCM pathologists' rates were established for situations in which the time of the pathologist performing the necropsy is paid by a grant. These rates are used for exclusively for necropsies performed by [Excluded by Requester] Diplomate ACVP whose appointment is in the Division of Pathobiology. Rates were calculated by a time and motion study to derive personnel cost with the cost of supplies also calculated. Figure 5 presents the income derived from the provision of gross and histologic support to research projects during the same time period. The decline in income with a simultaneous increase in case number in FY 53 reflects a shift from complete necropsies with slide review to gross only examination by several research laboratories with more advanced and predictable models for which necropsy histology end points are no longer critical for experiment evaluation. Income from the Tissue Distribution Program is presented separately in that section.

Table 2. Rates for Pathology Services Unit FY 53.

Description	Internal	Non-DCM pathologist	Affiliate	External
Gross Only Grade 1	$217		$327	$681
Gross Only Grade 2	$300		$600	$1,250
Gross Only Grade 3	$410		$818	$1,704
Necropsy with Histology Grade 1	$328		$655	$1,365
Necropsy with Histology Grade 2	$891		$1,778	$3,703
Necropsy with Histology Grade 3	$1,502		$2,999	$6,249
Base Necropsy Fee	N/A	$140	N/A	N/A
Additional Procedures - NHP > 2.5 kg	$142		$214	$446
Finished Stained slides	$17	$15.96	$26.17	$55

Figure 5. Income for Pathology Services for Research Support FY 50-53.



	FY 50	FY 51	FY 52	FY 53
Income	$245,911.59	$317,124.31	$319,455.49	$260,980.80
Investigators	25	23	23	18

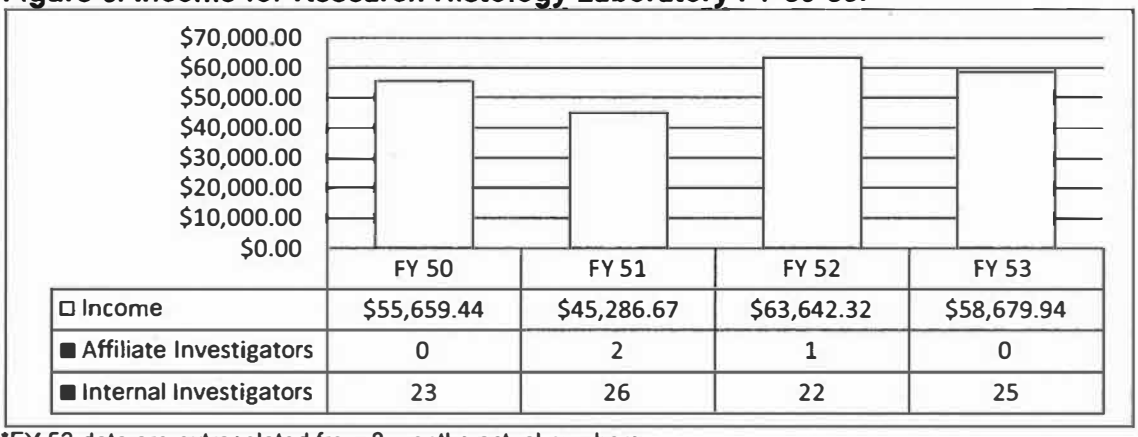
*FY 53 data are extrapolated from 8 months actual numbers

Research Histology Laboratory The Research Histology Laboratory is managed by Barbra Mason and provides support for research-specific histology techniques for ONPRC investigators, researchers at OHSU and external investigators. The priority of services provided by this laboratory within the PSU is to provide specialized histology support for research-driven objectives and to offer training and access to shared equipment for investigators' personnel to perform these functions independently. The laboratory provides technical support and training for use on various microtomes and cryostats, preparing frozen or paraffin sections of tissues, as well as training and consultation in histological experiment design and techniques. Microtomes can be reserved by the user and are backed up by staff training. General services include tissue processing, embedding, serial sectioning (cryo and free-floating) and H & E staining for paraffin, fixed-frozen, and fresh-frozen samples. Special stains and immunohistochemistry are also available. Table 3 presents the current rates for the Research Histology services and Figure 6 the income generated over the grant period.

Table 3. Rates for Research Histology Laboratory FY 53.

Description	Internal	Affiliate	External
Process 1paraffin block, cut 1 slide @ 5 microns, Stain with H&E	$7.54	$13.19	$14.40
Process 1 paraffin block only	$4.89	$8.56	$9.34
Process 1 frozen block (isopentane-quick freeze), cut 1 section	$7.54	$13.19	$14.40
Mounted series unstained (per slide)	$3.48	$6.09	$6.65
Use of cryostat (per hour)	$10.30	$18.03	N/A
Use of microtome (per hour)	$8.76	$15.32	N/A
Other histology services	Varied	Varied	Varied

Figure 6. Income for Research Histology Laboratory FY 50-53.



	FY 50	FY 51	FY 52	FY 53
□ Income	$55,659.44	$45,286.67	$63,642.32	$58,679.94
■ Affiliate Investigators	0	2	1	0
■ Internal Investigators	23	26	22	25

*FY 53 data are extrapolated from 8 months actual numbers

Teaching and Education. One of the essential missions of the NPRCs is to act as a national resource for nonhuman primate expertise. In addition to the services, tissues and data provided to internal and external recipients, the pathologists and staff at ONPRC serve an important function as educators in the broader community of veterinary pathology, laboratory animal medicine and comparative medicine. The Pathology Services Unit hosts 1 to 2 week externships for undergraduate veterinary students and veterinary pathology residents as well as supporting the general LAM externship coordinated by the Research, Education and Training Unit. During the grant period, seven undergraduate veterinary students from Colorado State, Washington State, Tuskegee, and Oregon State spent two weeks in PSU for pathology specific externships and three graduate veterinarians came for one week intensive training in NHP Pathology. Thirty six veterinary student externs spent portions of their 2 week clinical externships in PSU. We also support the Pathology rotations of the Laboratory Animal Medicine (LAM) residency training program. All the veterinary pathologists participate in the ONPRC veterinary training activities including veterinary rounds, weekly pathology rounds, continuing education lectures for technicians, lectures for Laboratory Animal Medicine residents, and LAM journal club.

Excluded by Requester MT (ASCP) has reviewed laboratory procedures with over 100 visiting veterinarians, veterinary students, veterinary residents and veterinary technology students during the last 3 ½ years. She conducted a medical camp with a group of junior high school students and taught a microbiology course to

high school students involving hands on activities and evaluation of case histories with microbiologic data. She mentored a junior high school student for a semester on an advanced science fair project.

Excluded by Requester mentored Excluded by Requester and endorsed his application to sit the American College of Veterinary Pathologists board examination. Extensive review and critique of Dr. Excluded by Requester microscopic and gross analyses were done routinely and he successfully attained Diplomate status in September 2012. Our first postdoctoral veterinarian in the training program, Excluded by Requester learned gross and microscopic description and interpretation as well as highly specific training in NHP pathology, enabling her to compete successfully for a pathology residency position in a highly competitive environment.

PSU participation in training on a national and international level occurs through mechanisms such as preparation and submission of cases for the Wednesday Slide Conference (WSC) of the Joint Pathology Center (Armed Forces Institute of Pathology) with two cases each year, NPRC Consortium Pathology Working Group (PWG) Virtual Slide Conferences (VSC) with four to five cases each year and the Primate Pathology Workshops (PPW).

Excluded by Requester taught the laboratory primate portion of the Laboratory Animal Pathology graduate course at Michigan State University in 2009 and will do so again in summer 2013 (a week long portion of the course with six contact hours) and the NHP portion of C.L. Davis Gross Morbid Anatomy Course in 2010. Dr. Excluded by Requester provided lectures and slide seminars on nonhuman primate pathology at the veterinary colleges at Washington State University (2010), Ohio State University (2010), and Iowa State University (2009).

Excluded by Requester contributed to the overall training and certification effort of the veterinary pathology community through service as a member of the ACVP Examination Committee from 2008 through 2010 and as General Chair and Chair of Anatomic Pathology of the Examination Committee in 2011.

NPRC Consortium-related Activities: Excluded by Requester serves as the chair of the NPRC Consortium Pathology Working Group (PWG). The annual PWG Face-to-Face Meeting was hosted by the pathologists at ONPRC with support from the Consortium Development Group in April 2012 in Beaverton, OR. This meeting provided an opportunity to discuss comparative solutions to shared challenges and review the Primate Pathology Image Database (PPID) progress and future directions. The PWG holds monthly Virtual Slide Conferences (VSCs) with presentations rotated through the NPRCs. The VSCs are well-attended, and consist of interactive presentations of gross images, virtual histology slides, and powerpoint summaries of interesting, challenging and unusual cases.

In addition to the opportunities for teaching and education through the PWG virtual slide conferences and the PPID, the ARRA supplement for the development of the PPID allowed us a unique opportunity to participate as mentors in several externally sponsored educational opportunities for high school and undergraduate students. Excluded by Requester served as mentors to three high school and three undergraduate students over two summers. The students worked on research questions based on ONPRC case material and data as well as participating in preparing material for inclusion in the PPID. Much of the data they collated may be used as the starting points for projected publications in the next grant cycle. Topics included a retrospective study of disease in aged rhesus macaques, incidence of prostatic disease in aged monkeys, changes in standard cardiac measurements associated with valvular endocardiosis, factors associated with the development of GI adenocarcinoma in macaques, factors associated with the development of endometriosis in laboratory rhesus macaques, and the association of amyloidosis and chronic colitis in ONPRC macaques.

Service Plan:

Specific Aim 1. To provide disease diagnosis and surveillance for ONPRC's animal resource through diagnostic necropsies, biopsies, clinical pathology and maintenance of databases for epidemiologic queries. Due to the crucial nature of this activity for the health and research suitability of the NHP resource, provision of diagnostic support for the colony will continue to be of paramount importance for PSU. We will continue to provide support through post mortem examinations, clinical pathology services, biopsies, coordination of testing for specific pathogens, and maintenance of databases. Areas of special emphasis for this funding cycle include:

- Development of further immunohistochemistry capabilities
- Establishment of clinicopathologic reference intervals for adult male rhesus macaques
- Integration of necropsy data into PRIMe allowing more robust epidemiologic queries of data
- Evaluation of further areas for efficiency in report preparation through improved reporting formats available in PRIMe

The conversion to PRIMe will occur over the intervening period between now and the start of the next grant cycle. Full implementation of PRIMe capabilities is expected to continue through the next grant cycle. We have interacted extensively with pathologists from the Wisconsin NPRC who currently use PRIMe as their electronic health record system to familiarize ourselves with its current capabilities for pathology support. During the upcoming grant period, we will be optimizing the coordination of PRIMe functions and reporting mechanisms with pathology work flow to maximize efficient use of personnel resource. This will be achieved through defining critical minimum data required for each necropsy case, evaluating ease of PRIMe data entry as it relates to current practices, and optimizing categorization and retrieval of case material through SNOMED.

Specific Aim 2. To participate in the research mission of ONPRC by providing pathology support for research projects through necropsies, tissue distribution, clinical laboratory services and participation in study design; and through characterization of spontaneous NHP diseases potentially useful as models for human diseases. We will continue to provide the high level of service to the research community through necropsy services and clinical pathology. Continued evaluation of adequate staffing levels will be an ongoing process using metrics such as case turnaround time, the availability of necropsy time slots (or how far in advance investigators are having to schedule necropsies in order to ensure desired termination dates,) and investigator satisfaction through personal interactions. The management of the Tissue Distribution Program is within PSU and this is an ongoing area of attention as described in the separate section.

Areas of special emphasis for this funding cycle include:

- Embracing and promoting a shifting paradigm within ONPRC as a whole and DCM specifically for greater inclusion and integration of the professional staff into research projects through participation in all stages of projects and inclusion as authors in publications
- Increasing the availability of the Olympus VS110 whole slide scanner to the research community through provision of technical support
- Increased submissions to the PPID
- Partnering with others to evaluate NHP spontaneous disease as models for human disease such as colitis, arthritis, and colon carcinoma
- Integration with genetics group to characterize disease phenotypes etc.
- Publication of multiple case reports and case series

Utilization of existing personnel to support the whole slide scanner and PPID activities will enhance our service to the research mission through provision of technical support for the scanner to investigators and through enhancement of the PPID as a research tool. Opportunities for collaboration with other NPRC's for input into the PPID are currently being pursued and are expected to continue. Opportunities for independent funding to support expansion of these efforts will be pursued.

Evaluation, characterization and publication of many previously unreported or underreported disease entities are a priority of the PSU for the next funding cycle. Our current level of staffing including two newly recruited pathologists with advanced training will place us in a position to realize these goals. We currently maintain electronic worksheets of potential case series which we actively curate. Current topics for publications include retrospectives of GI adenocarcinoma, intracranial neoplasms, sprue-like enteropathy, and case series of rare neoplasms in cooperation with other NPRC's such as salivary gland tumors and meningiomas. As diagnostic capabilities such as IHC have become available, we expand these worksheets with an eye to developing enough data for publication. Slides from cases being evaluated for publication are digitally scanned for ease of providing photomicrographs and are then available for inclusion in the PPID. Publication of descriptive pathology will be tremendously important as baseline material for establishing collaborative relationships with

investigators studying mechanisms of disease such as colon cancer and inflammatory bowel disease. Partnership with the Research, Education and Training Unit within DCM to facilitate publication and collaborations will be pursued.

Specific Aim 3: To act as a national resource for NHP pathology through maintenance of archived tissues, slides and blocks, databases of biological data and images. ONPRC has an extraordinary archive of pathology related materials and data spanning decades. The migration to PRIMe will be an opportunity to both preserve the data currently held in IRIS but also to develop new mechanisms for including pathology data not currently held in IRIS as well as formulate more efficient mechanisms for mining the data. The continued support of the PPID will enhance this archival resource through inclusion of gross images and whole slide scans. Digitized material is much more easily shared nationally and internationally and preserves the resource beyond its physical constraints of glass and tissue.

Areas of special emphasis for this funding cycle include:

- Continued digitizing of glass archival material through the PPID
- Inclusion of gross images for publication in the PPID

Specific Aim 4: To serve as a resource for educating veterinarians, laboratory animal professionals and investigators, about primate pathology by participation in teaching and presentation in local, national and international settings. PSU will continue to support this important activity through participation in teaching at the local level with undergraduate and veterinary students and postgraduate veterinarian externs and LAM residents. The postdoctoral position has proven to be an excellent mechanism for providing intensive experience in NHP pathology. We expect to be able to continue to attract high caliber applicants. Expansion of PPID to the larger veterinary pathology and laboratory animal communities through a registered user mechanism will greatly enhance its impact as a tool for education.

Areas of special emphasis for this funding cycle include:

- Expansion of PPID users to larger veterinary pathology and laboratory animal community
- Continued recruitment of high quality candidates for the post-doctoral training position

We will actively promote the PPID to the veterinary pathology and laboratory animal community through involvement with training coordinators, presentations at meetings and word of mouth. Mechanisms for feedback directly from users are provided through the portal. We will encourage feedback through regular email communication with registered users and prompt responses to comments.
We will enhance recruitment for post-doctoral training position through mechanisms such as the ACVP Training Program Network and through direct communication with training coordinators as well as standard advertising mechanisms. Providing training coordinators and trainees with more information regarding this unique option for advanced expertise in NHP pathology is expected to benefit programs with limited access to NHP material, which have trainees particularly interested in laboratory animal pathology. Additionally, increased interaction with other training programs is likely to increase the number of applicants for short 1 to 2 week externships.

TISSUE DISTRIBUTION PROGRAM SPECIFIC AIMS

The nonhuman primate (NHP) is, and will always remain, a limited and valuable research resource. Continued efforts to maximize distribution of NHP tissues to biomedical investigators will ensure the best possible use of this resource. Centralized coordination of tissue requests with scheduled necropsies permits support for increased numbers of biomedical research efforts with less impact on the primate resource.

Specific Aim 1: Ensure maximum and efficient utilization of the unique primate resource through continued and expanded promotion of the Tissue Distribution Program (TDP)

TISSUE DISTRIBUTION PROGRAM RESEARCH STRATEGY.

SIGNIFICANCE.

As nonhuman primates are a limited and valuable resource for biomedical research, maximal use of their tissues and organs is imperative. The Tissue Distribution Program (TDP) provides biological samples to investigators both within the institution and throughout the United States. The Tissue Distribution Program is part of the Pathology Services Unit. Having tissue distribution managed through a single program allows centralized coordination of tissue requests with scheduled necropsies. The efficiency of this process results in greater numbers of tissues being available for research without greater impact on the NHP living resource.

INNOVATION.

In response to potential concerns regarding biosafety hazards to personnel handling macaque tissues and institutional liability, the TDP is utilizing new forms regarding biohazard notice and acknowledgement which were developed in collaboration with OHSU Environmental Health and Radiation Safety (EHRS). The forms represent a novel strategy to help ensure recipient protection by requiring acknowledgement of risk inherent in macaque biological specimens that must now be signed by both the recipient laboratory and their institutional biosafety office. This is intended to help ensure adequate support for personnel in the case of an accidental exposure.

In response to increasingly complex needs of our tissue recipients, we have developed several new collection techniques. Examples include a technique developed for "mucosa enriched" sampling of the gastrointestinal tract which ensures that desired subsections of gastrointestinal tissues are obtained rapidly and in adequate volumes for research analysis of antibody and cellular components. We have also established techniques and identified landmarks for skeletal muscle dissections and a variety of specific ganglia and bones for research protocols. Similarly, the exacting research needs of an external investigator prompted development of a complex dissection protocol of the pelvic floor of adult female macaques. New techniques are documented photographically, placed in power point presentations and serve as excellent tools for pathology staff and investigators for training and to ensure consistency across subjects. A tissue array collection protocol was developed in order to maximize the use of tissue from animals considered particularly uncommon for tissue distribution such as adult male Indian-origin rhesus macaques of known SPF status. Availability is maximized by providing small samples as frozen, in OCT (Optimal Cutting Temperature compound cryo medium) or fresh tissue in media. Development of these novel tissue collection protocols make greater use of the resource, provide a potential avenue for publication for pathologists, and expand the repertoire of sample collection for ONPRC core and affiliate scientists potentially providing a competitive advantage when submitting proposals for funding.

APPROACH.

reviewers' comments

Progress and Accomplishments.

The Tissue Distribution Program (TDP) is administered through the Pathology Services Unit (PSU) within the Division of Comparative Medicine (DCM). Materials provided include tissues, fluids such as blood, CSF and

urine, and biological data such as organ weights and measurements. Tissues are collected at the request of the recipient and according to a defined, individualized protocol.

The PSU manager oversees the TDP and is responsible for receiving and coordinating requests, directing collection of tissues and overseeing shipments. The Tissue Distribution Program was formerly managed by the Pathology Services Unit administrative assistant, Excluded by Requester retirement in 2008 and the burgeoning caseload over the last five years prompted a reorganization of the administrative structure of the unit. A manager position was created with responsibilities for coordinating the TDP scheduling necropsies and supervising personnel in the necropsy and histology laboratories Excluded by Requester an enthusiastic, detail-oriented individual with excellent communication skills was promoted and ably meets the demands of this position. The creation of the manager position to administer the tissue distribution program ensures that the program has priority and frees pathologists to accomplish more academic activities. Support for the creation of this position demonstrates the importance that the ONPRC places on the program.

The TDP services are advertised on the ONPRC website and information on tissue availability is via referrals by ONPRC core and affiliate scientists, other TDP clients and NPRCs. Additional methods include notification through the offices of the Director and Associate Director by presentations at scientific meetings and through acknowledgements in publications.

Priority is given to NIH-funded investigators in accordance NIH guidelines. Prioritization beyond this is on a first come-first served basis. During this grant period, there has not been a need for a prioritization schedule but in previous years, high demand tissues have been offered on a rotational basis in order to provide equitable access among NIH-funded researchers. ONPRC and affiliate OHSU investigators receive the weekly necropsy schedule and request tissues based on availability. The TDP manager maintains a roster of tissues requested by outside investigators and fills tissue requests as appropriate animals and tissues become available.

The animals used for the TDP are both investigator-assigned animals and medical culls. Typically, medical culls are animals with a clinical diagnosis of chronic and/or recurrent diarrhea without gross evidence of systemic disease. Some of these animals are assigned to short term projects, clinical and surgical training protocols immediately prior to euthanasia and tissue collection, thus maximizing utilization of tissue. Tissues from investigator-assigned animals are provided to other investigators by permission of the assigned investigator. The PSU manager evaluates all animals scheduled for necropsy with reference to known TDP recipients to ensure suitability of tissues and to match potential recipients with newly available tissue.

ONPRC and other OHSU investigators collect their tissues at the time of necropsy. Several types of tissues (including tissues from aged animals and liver as a source of genomic DNA) are collected and stored as a resource for distribution by other ONPRC cores. These tissues are collected and frozen by PSU and transferred for storage and cataloging by the recipient programs. Off campus investigators typically receive fresh tissue shipped overnight or frozen tissues stored at -80 and shipped within 10 days of collection.

In the past three years, most TDP requests are for specific tissues and organs acquired postmortem from the following organ systems: integumentary (most often skin), musculoskeletal (specific skeletal muscles, various bones), nervous (brain, spinal cord, cerebrospinal fluid, ganglia, peripheral nervous tissue), cardiovascular (heart, various vessels), respiratory (lungs, trachea, upper respiratory structures), digestive (liver, gall bladder, and virtually all regions of the gastrointestinal tract, oral cavity structures, and esophagus), urinary (kidneys, bladder), genital (male and female, entire reproductive tracts or various portions thereof), endocrine (adrenal glands, pituitary gland, thyroid glands, parathyroid glands), special senses (eyes, whole or portions thereof,), and hemic-lymphatic (blood, serum, bone marrow, spleen, various lymph nodes) systems. In addition to tissues provided to external investigators, we also supplied biological measurement data to researchers such as full term, neonate brain and associated body weights for Japanese and rhesus macaques and digital measurements from rhesus and Japanese macaques and anubis baboons.

The available phenotypic data associated with these tissues are extensive. Each animal sacrificed receives a complete gross necropsy, the extent of which is determined by the pathologist. Gross necropsy includes complete visual exam of all organs and sectioned surfaces and collection of organ weights. This information is linked to the animal's history (i.e. IRIS) record, which includes signalment, source, geographic origin, medical, surgical, and reproductive history.

Table 1 presents the numbers of recipients and number of tissues distributed during the current grant

period. In addition to those tissues provided to on campus and external investigators, several types of tissues are collected and stored as a resource for other on campus programs. These include a variety of tissues, for the Resource for the Aging NHPs Program (RANHPP), administered by Excluded by Requester and liver samples for the ONPRC Primate Genetics Program. Tissues collected for RANHPP include blood, brain, cerebrospinal fluid, left ventricle, subcutaneous fat, adrenal, kidney, liver, thyroid, pituitary, testis, epididymis, soleus muscle, vastus lateralis muscle, and trigeminal nerve. These tissues are collected and frozen by the PSU and transferred for storage and cataloging by the respective programs.

Table1. Numbers of tissues and recipients for Tissue Distribution Program

	FY 50	FY 51	FY 52	FY 53*
ONPRC investigators (core)	34	30	32	30
OHSU investigators	5	3	4	3
Other Academic Investigators	4	7	4	4
3	7	5	5	7
Tissues to ONPRC investigators	907	1055	1077	433
Tissue to OHSU investigators	24	11	50	37
Tissue to Other Academic Investigators	15	122	96	59
Tissues to Private Sector Investigators	531	254	366	342

*FY53 represents 8 months data

List of academic institutions and private enterprises utilizing the TDP during the above period:

Academic Institutions: University of Washington, Washington National Primate Research Center, Massachusetts Institute of Technology, University of California, Los Angeles, Keck School of Medicine, Zilkha Neurogenetic Institute, Duke University, Fred Hutchinson Cancer Research Center, University of Southern California, California National Primate Research Center, Mount Sinai School of Medicine, University of Colorado, and The Mayo Clinic

Private Companies: Comparative Biosciences, Trinity Bio Tech- Life Science, Akron City Hospital/ Summa Health Systems, Georgia Dermatopathology Associates, Beutner Labs, Dermatopathology Partners, INOVA Diagnostics, Inc.

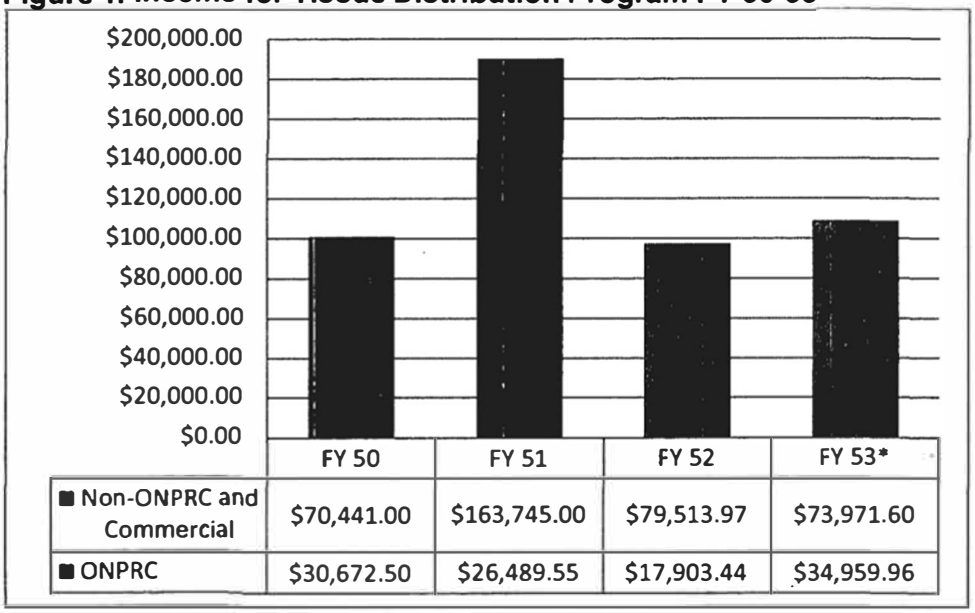
An additional eight academic and private entities have contacted the TDP and have either standing orders to be filled when the appropriate animals are available and/or have been referred to other centers who may have or are more likely to have appropriate animals to fill the requests. Examples of such requests include specific gender and/or age of species desired and gestationally aged fetuses.

The current chargeback system has been in place since 2004. OHSU investigators began paying for tissues and the external (non-OHSU) rate was changed to reflect the in-house price. Rates are listed in Table 2. Income for ONPRC and non-ONPRC recipients is listed in Figure 1. External clients are billed on a monthly basis by the PSU manager. The recipients bear the cost of shipping.

Table 2. Tissue Distribution Rates FY53

	Internal	NIH funded Non-ONPRC	Commercial
Tissue Distribution (per tissue)	$67.00	$109.00	$172.00
Brain	$133.00	$217.00	$344.00
Special procedures (fixation perfusion, etc)	$131	$214.00	$446.00

Figure 1. Income for Tissue Distribution Program FY 50-53



	FY 50	FY 51	FY 52	FY 53*
■ Non-ONPRC and Commercial	$70,441.00	$163,745.00	$79,513.97	$73,971.60
■ ONPRC	$30,672.50	$26,489.55	$17,903.44	$34,959.96

*FY53 represents projected income based on 8 months data

Service Plan:

Specific Aim 1. Ensure maximum and efficient utilization of the unique primate resource through continued service and expanded promotion of the Tissue Distribution Program (TDP). The primary intent of the Tissue Distribution Program is to provide a much valued resource to the biomedical research community with an emphasis on maximizing the utilization of individual animals while potentially reducing the overall numbers of animals used in research programs. Our ongoing efforts will be focused on continuing to provide this high quality service. We will also continue to take advantage of new opportunities for promotion of the resource through mechanisms such as Primate Portal, a web portal designed to facilitate research in the NHP model by providing information on NHP resources. We will continue to evaluate the effectiveness of our advertising through evaluation of where our new clients have heard of us and by periodically checking our visibility through web-based searches. We currently exhibit as the third entry for a google search for "nonhuman primate tissue distribution."

PUBLICATIONS

Excluded by Requester

Excluded by Requester

Program Director/Principal Investigator (Last, First, Middle): Robertson, Joseph E./Haigwood, Nancy L.

ANIMAL SERVICES-PATHOLOGY SERVICES DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Excluded by Requester	Sr. Vet/Head Path Svs	% Effort			Institutional Base Salary	63,243	15,811	79,053
	Res Asst 2					16,960	6,784	23,744
	Assoc Vet					64,652	16,163	80,815
	Res Asst 2					16,695	6,678	23,373
	Postdoctoral Trainee					26,439	9,253	35,692
	Assoc Vet					54,060	13,515	67,575
	Med Lab Tech 2					28,993	8,988	37,980
	Mgr, Clin Pathology					36,838	11,420	48,257
	Sr Res Asst					26,833	9,392	36,225
	Res Asst 2					15,500	6,200	21,700
	Res Assoc					28,705	8,899	37,604
	Office Specialist					10,815	3,785	14,600
	Res Asst 2					17,171	6,869	24,040
	Mgr, Path Svs					25,599	8,960	34,559
To Be Named	Res Asst 2	12.00				31,000	12,400	43,400
	SUBTOTALS →					463,502	145,115	608,617

CONSULTANT COSTS		
None Requested	0	0
EQUIPMENT *(Itemize)*		
None Requested	0	0
SUPPLIES *(Itemize by category)*		
Laboratory Supplies	81,249	
Pharmaceuticals	341	
		81,590
TRAVEL		
Domestic	5,500	5,500
INPATIENT CARE COSTS		0
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		
None Requested	0	0
OTHER EXPENSES *(Itemize by category)*		
Equipment Maint Contract	21,856	
Freight	957	
Hazardous Waste Disposal	7,530	
Misc Fees & Services	4,043	
Lab Svc-NonPatient Care	32,453	
Conference & Registration Fees	300	
Train/Instruction Materials	100	
Membership in Professional Org	112	
		67,350
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 763,057
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 763,057

ANIMAL SERVICES-PATHOLOGY SERVICES
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	608,617	626,876	645,682	665,053	685,004
CONSULTANT COSTS	0	0	0	0	0
EQUIPMENT	0	0	0	0	0
SUPPLIES	81,590	84,038	86,559	89,156	91,830
TRAVEL	5,500	5,665	5,835	6,010	6,190
INPATIENTS CARE COSTS	0	0	0	0	0
OUTPATIENTS CARE COSTS	0	0	0	0	0
ALTERATIONS AND RENOVATIONS	0	0	0	0	0
OTHER EXPENSES	67,350	69,371	71,452	73,595	75,803
DIRECT CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	763,057	785,949	809,527	833,813	858,828
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	763,057	785,949	809,527	833,813	858,828
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					4,051,175

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

PERSONNEL

Senior Vet/ Head Veterinary Pathologist - Excluded by Requester Diplomate, ACVP: (% Effort % Effort). Responsible for coordination of necropsy, histology and tissue distribution services, supervision of personnel, database management, and budget management; performs gross morbid and microscopic examination of tissues in support of animal disease diagnosis and surveillance; contributes professional expertise and consultation to research projects, and participates in collaborative research and characterization of spontaneous diseases of NHPs. Serves as PI on the Primate Pathology Image Database consortium, which includes all NPRCs.

Research Assistant 2 - Excluded by Requester % Effort
Responsible for developing and performing immunohistochemical staining procedures, processing tissues and preparing slides for microscopic examination in support of animal disease diagnosis and surveillance and research protocols, maintaining the histology laboratory and equipment, histology laboratory records and archival tissue block and slide files, and is responsible for necropsy room technical support on an as needed basis.

Associate Veterinarian - Excluded by Requester Diplomate, ACVP % Effort
Program Income). Responsible for providing direction, supervision of personnel and budget management of the Clinical Pathology Laboratory; performs gross morbid and microscopic examination of tissues in support of animal disease diagnosis and surveillance; contributes professional expertise and consultation to research projects, and participates in collaborative research and characterization of spontaneous diseases of NHPs. Serves as contributing veterinary pathologist on the Primate Pathology Image Database consortium.

Veterinary/Research Resident. - Excluded by Requester % Effort
Program Income). Responsibilities include gross morbid and microscopic examination of tissues in support of animal disease diagnosis and surveillance; contributes professional expertise and consultation to research projects, and participates in collaborative research and characterization of spontaneous diseases of NHPs.

Associate Veterinarian - Excluded by Requester Diplomate. ACVP % Effort
Program Income) Responsible for performing gross morbid and microscopic examination of tissues in support of animal disease diagnosis and surveillance; contributes professional expertise and consultation to research projects, and participates in collaborative research and characterization of spontaneous diseases of NHPs. Serves as contributing veterinary pathologist on the Primate Pathology Image Database consortium.

Medical Lab Technician 2 - Excluded by Requester Animal Health Technologies, LATG, CVT % Effort % Effort Responsible for providing technical support by performing standard laboratory clinical tests on samples including blood, feces, urine and other body fluids and tissues; assists in maintaining the clinical pathology laboratory and equipment, performs quality control checks to determine that equipment is functioning within acceptable limits and assists in maintaining stock of laboratory supplies.

Manager, Clinical Pathology - Excluded by Requester % Effort
Program Income). Manages and supervises all activities in the Clinical Pathology Laboratory to facilitate veterinary medical care, support animal disease diagnosis and surveillance and provide support for research programs. Key responsibilities include supervision of staff, coordination of instrument maintenance and quality control, specimen processing, performing a variety of biochemical, microscopic, microbiologic, parasitologic, hematologic, serologic and cytologic analyses and reporting test results; procures all laboratory supplies, instrumentation and equipment

Senior Research Assistant:- Excluded by Requester % Effort
Income). Responsible for processing tissues and preparing slides for microscopic examination in support of animal disease diagnosis and surveillance and research protocols, performing routine and special staining procedures, maintaining the histology laboratory and equipment, histology supplies ordering and inventory,

histology laboratory records and archival tissue block and slide files. Also trains new personnel in histological techniques.

Research Assistant 2 - Excluded by Requester % Effort
Responsible for processing tissues and preparing slides for microscopic examination in support of animal disease diagnosis and surveillance and research protocols performing special staining procedures, maintaining the histology laboratory and equipment, histology supplies and inventory, histology laboratory records and archival tissue block and slide files.

Research Associate - Excluded by Requester % Effort A manager and research associate of the Research Histology Unit of Pathology, DCM, continues to be requested for her provision of high quality, high throughput services to researchers. This includes processing of various NHP tissues for routine histological staining and immunohistochemical procedures. A major effort is preparation of paraffin-embedded and frozen sections. In addition, training in use of equipment and tissue processing is provided to students, fellows and laboratory technicians. Other duties include scheduling use of equipment by laboratory groups, accounting of fees-for-services, budget oversight, and liaison between Pathology, the unit's Oversight Committee and the Associate Director for Research.

Office Specialist - Excluded by Requester % Effort Part time position providing administrative support to the Unit including data entry, and transcription of necropsy reports; provides support for the Tissue Distribution Program, and necropsy scheduling.

Research Assistant 2 - Excluded by Requester % Effort
Responsible for performing animal prosecution and specialized necropsy procedures in support of animal disease diagnosis and surveillance, infectious disease, biosafety level 3 and other research protocols; collecting, preparing and distributing tissues in support of the Tissue Distribution Program; maintaining the containment and conventional necropsy facility, ordering supplies and inventory; maintaining the archival necropsy frozen tissue bank. He trains new personnel in necropsy duties.

Manager, Pathology Services - Excluded by Requester % Effort
Manages and organizes functional activities in the necropsy and histology laboratories of Pathology Services Unit (DCM) as well as coordinates the Tissue Distribution Program. Responsible for supervising administrative and laboratory personnel in the necropsy and histology laboratories.

Research Assistant 2 - Excluded by Requester % Effort Excluded by Requester
is responsible for performing animal prosecution and specialized necropsy procedures in support of animal disease diagnosis and surveillance and research protocols; collecting, preparing and distributing tissues in support of the Tissue Distribution Program; maintaining the necropsy facility, maintaining the archival necropsy frozen tissue bank, and is responsible for preparing slides for microscopic examination, helps maintain histology laboratory records and archival tissue block and slide files on as needed basis.

Research Assistant 2 – To be named (12 calendar months effort: 6.0 ORIP, 6.0 Program Income).
Responsible for performing animal prosection and specialized necropsy procedures in support of animal disease diagnosis and surveillance and research protocols; collecting, preparing and distributing tissues in support of the Tissue Distribution Program; maintaining the necropsy facility, maintaining the archival necropsy frozen tissue bank, and is responsible for preparing slides for microscopic examination, helps maintain histology laboratory records and archival tissue block and slide files on as needed basis.

SUPPLIES

Laboratory Supplies and Pharmaceuticals: Funding is requested to purchase a portion of the laboratory supplies and reagents to support activities relating to essential core functions including necropsy, histology,

clinical and disease diagnosis, microscopic procedures, and tissue distribution essentials.

- The supplies for necropsy include replacement instruments such as Metzenbaum scissors, rongeurs, forceps, injectable anesthetics for euthanasia, and consumables such as needles, syringes, scalpels, specimen collection tubes, and other miscellaneous items utilized in the necropsy laboratory, such as digital cameras, as well as protective clothing essential while performing the responsibilities of the unit
- The supplies for histology laboratory include organic reagents for tissue processing, paraffin, tissue cassettes, antibodies, chemicals for histochemical and immunohistochemical staining techniques and other miscellaneous items. Laboratory supplies include, but are not limited to, large quantities of microscope slides, cover glass, slide boxes, paraffin, Cytocool, mounting media, and other chemicals. Due to the hazardous nature of some chemicals, a large inventory is not maintained; supplies are replaced as needed.
- The supplies for clinical pathology include consumables and reagents for various chemical, hematologic, microscopic, parasitologic and microbiologic diagnostic testing. Also included are reagents and quality control standards for the hematology and clinical chemistry analyzers and personal protective clothing.

TRAVEL

Domestic Travel - Funds are requested to provide travel to one national meeting per pathologist annually and manager or other senior technical personnel every other year and travel to meet with research collaborators such as Pathology Working Group personnel. Pathologists will keep up-to-date with current research, communicate with peers at other institutions to promote collaboration, and travel to meet with research collaborators such as PWG personnel .

Funds are also requested to provide travel to one national meeting for the clinical pathology laboratory manager once every two years to update knowledge and skills to continue to provide essential laboratory services and invaluable direction to veterinarians and research staff.

OTHER EXPENSES

Funds are requested for:

Equipment Maint Contract: to cover costs of maintaining critical equipment including repairs, annual preventive maintenance, recalibration, certification and vendor maintenance contracts. Equipment covered includes the tissue processor, microtomes, cryostat, paraffin dispenser, solvent recycler, chemistry and hematology analyzers, the LIS, centrifuges, microscopes, centrifuges, autoclave, and fume hoods and biosafety cabinets.

Freight: includes shipping costs for samples going to outside reference laboratories as well as costs for receiving goods.

Hazardous Waste Disposal: to be used to pay for disposal of biological (carcasses and sharps) and chemical waste generated by the division laboratories that cannot be practically attributed to specific grants. Charges are per the standard OHSU Environmental Health & Radiation Safety Program.

Misc Fees & Services: for the 36 TB server which supports the Pathology Image Database (PPID which is maintained at the OHSU Advance Computing Center. Annual fees cover for storage, server hosting, backup storage, and consulting.

Laboratory Services: A number of diagnostic tests (such as *Mycobacterium* culture and identification) are necessary for diagnosis of infectious diseases critical to colony health. Many of these tests are performed sporadically and require specialized laboratory facilities and are therefore not cost effective to run in-house

Conference and Registration Fees - Funds are requested to support fees associated with conferences and meeting registration. These fees are essential to the professional development and continued certification of PSU staff. Conferences attended include the American College of Veterinary Pathologists annual meeting and the Primate Pathology Workshop. At least one or more pathologist attends each of these meeting each year in order to remain current with the field. Our histology technicians attend the National Society for Histotechnology annual meeting which provides excellent educational sessions to expand the capabilities of our laboratory. The information gained at these meetings is shared with staff members upon return through hand outs and lab meeting presentations.

Training and Instructional Materials : Funds are requested for the purchase of relevant training materials for PSU staff. The National Society for Histotechnology and American Society of Clinical Pathology provide webinars and on line resources to economically update the knowledge and skills of laboratory personnel. Participation is priced by topic rather than number of participants allowing maximized use of the resource.

Membership in professional organizations : Memberships in professional organizations are essential for maintenance of continuing education and certification. Professional organizations that PSU staff are members of include the American College of Veterinary Pathologists, American Society for Veterinary Clinical Pathology, Joint Pathology Center Wednesday Slide Conference, American Society for Clinical Pathology and National Society for Histotechnology. Professional conference registration includes the ACVP/ASCVP Annual Meeting, Primate Pathology Workshop, National Society for Histotechnology, and others as appropriate. Memberships in certifying organizations are essential for external evaluation and accreditation which serve as marks of the professional qualifications of our professional and technical staff.

ANIMAL SERVICES: Pathology Services Income Table

Last Funded Year (53)

Source	Funding (direct costs)
P51 base grant support	$630,923.69
Program income derived from P51 base grant	700,013.03
Other Sources	0
Total	$1,330,936.72

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$763,057.30
Program income derived from P51 base grant	766,917.30
Other Sources	0
Total	$1,529,974.60

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

Pathology Services receives salary support and support for other expenditures from program income.

ANIMAL SERVICES: SURGICAL SERVICES UNIT SPECIFIC AIMS

The Surgical Services Unit is a specialized, unified team delivering centralized, reliable, and consistent surgical services in a state-of-the-art surgical facility. Complete surgical service and expertise that include procedural planning and development, anesthesia, analgesia, and post-operative animal care are essential for meeting the objectives of the research programs at ONPRC as well as supporting a comprehensive clinical care program. The primary goal of SSU is to provide compassionate care for animal patients while assuring the scientific integrity of research objectives. The specific aims in support of this goal are:

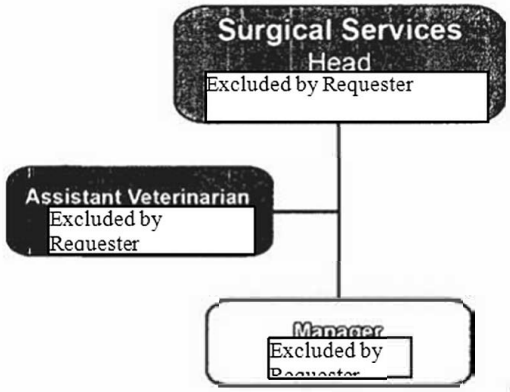
Specific Aim 1. To provide surgical support for research projects through comprehensive surgical, anesthetic, analgesic and post-operative care. Research support includes collaboration with investigators to refine surgical procedures through careful planning, proper training, and optimal instrumentation to minimize invasiveness and discomfort to the animal subjects. We will continue to provide and refine anesthesia and analgesia modalities tailoring them for specific surgical procedures, subject size, age, and species while also accomodating for physiologic factors that may compromise anesthesia, such as obesity. We will continue to find ways of providing these services while maximizing efficiency through work flow analysis and computational automation.

Specific Aim 2. To support colony health maintenance by providing diagnostic, therapeutic, and emergency surgical services for spontaneous or experimentally-induced diseases or conditions. SSU provides support for colony health maintenance through the provision of aseptic surgical suites equipped with quality anesthesia machines, instrumentation, endoscopic equipment, and experienced surgical veterinarians available for referral procedures or consult. Specific examples of routine colony health support we will continue to provide include intestinal resection and anastomosis for intestinal neoplasia, emergency Caesarian section, orthopedic fracture repair, diagnostic endoscopy and laparoscopy, and critical care.

Specific Aim 3. To serve as a resource for training veterinary students, residents, technicians, and veterinarians as well as investigative staff in all aspects of non-human primate surgical techniques, anesthesia, and analgesia practices. A significant part of this training is continued proficiency evaluation of personnel performing surgeries on animals. We will work closely with the RETU in developing interactive, software-based means of training and competency evaluation to compliment the traditional hands-on training and observational modalities currently in use. Intraoperative imaging will continue to be a primary component of the preparatory materials personnel must review prior to hands-on training, as well as a key aspect of continued proficiency assessment after initial certification.

Specific Aim 4. To expand collaborative and independent research with the goal of refining practices to minimize adverse physiological sequelae that may result from experimental interventions for the betterment of animal welfare and science. SSU will explore long-acting analgesic modalities to reduce subject distress associated with frequent post-operative injections. Current collaborations to determine the physiological effects of various anesthesia modalities on neonatal and pregnant rhesus macaques will continue. Finally, we have applied for funding to develop a means of measuring the total blood volume of rhesus macaques.

SURGICAL SERVICES UNIT RESEARCH STRATEGY



SIGNIFICANCE

The Surgical Services Unit (SSU) facilitates the ONPRC research mission through the provision of centralized surgical facilities, expertise, and reliable surgical services that are essential elements of most research programs at the ONPRC. Additionally, SSU provides surgical service and consultation for diagnostic and therapeutic procedures as key elements of the veterinary care program to promote the continued health and wellbeing of research animals. Formalized training for many surgical and clinical procedures is provided by the unit for DCM personnel, investigators, veterinary students, and residents, as well as visiting and external scientists.

INNOVATION

SSU is closely integrated with the ONPRC scientific divisions and readily implements novel methodologies and instrumentation necessary to enhance the research value of the surgical procedures while minimizing invasiveness to the animal subjects. An example of a recent innovation includes significant refinements to the experimental induction of endometriosis. Previously, endometriosis was induced by laparotomy, hysterotomy, and excision of endometrial tissues. These tissues were then sutured to the serosa of the uterus. Now, endometriosis is induced via laparoscopically guided aspiration of endometrial tissue followed by 'seeding' of endometrial cells within the abdomen. Another example is the implementation of an interventional MRI platform to support Huntington's disease research in the Division of Neuroscience. This platform enables precise targeting, trajectory determination, craniotomy, and real-time visualization of needle placement and brain target perfusion. Additionally, as part of ongoing studies in the Division of Diabetes, Obesity, and Metabolism, the Roux-en-Y gastric bypass procedure was developed and standardized for rhesus macaques. Each of these procedures were developed through in-depth communication and close collaboration with investigators followed by experimentation and refinement using necropsy specimens or live animals prior to necropsy as part of the IACUC-approved Surgical Training Protocol (Hobbs, PI). In some circumstances, the surgical procedures are less complicated, but the volume of procedures requested is large. Bronchoalveolar lavage, lymph node biopsies, and GI endoscopy with mucosal biopsies are examples of procedures performed by SSU in high volume. In these cases, the challenge lies in managing workflow to maximize efficiency, consistency, and precision. To meet challenges of this nature, computational tools were developed to integrate and automate much of the surgical workflow. By increasing the efficiency of surgical resource management, the scientific informational return on investment is maximized. Some of these computational tools were developed with funding assistance from the Nonhuman Primate Research Consortium (NHPRC) and are easily adaptable and available to other NPRCs. An additional innovation utilizing the NHPRC is the Clinical and Surgical Techniques Working Group, established May 1, 2012 and chaired by Excluded by Requester. This working group meets via monthly web conference to discuss procedures commonly performed at the NPRCs, serving as a forum to accelerate transmission of information among the NPRC veterinary staff. The goal of this popular working group with over 50 members is to improve members' procedural competency and repertoire as well as improve workflow efficiencies associated with these procedures.

APPROACH

reviewers' comments

reviewers' comments

Progress and accomplishments in the previous funding period.

Veterinary Support Staff

An experienced and talented veterinary support staff is vital in assuring the quality and consistency of surgical outcomes. Continued support for career development of the veterinary support staff has been a priority of the unit. Six of the 7 technicians are Certified Veterinary Technicians (CVT). Five of the 7 technicians are certified by the Academy of Surgical Research Excluded by Requester certified Surgical Research Specialists (SRS); and Excluded by Requester is certified as Surgical Research Technician (SRT). Additionally, six of the 7 technicians are certified by the American Association for Laboratory Animal Science (AALAS). Excluded by Requester are Registered Laboratory Animal Technologists (RLATG).

Table 5. Veterinary Support Staff of SSU

Name	Degrees and Certifications	Position Title	Years at ONPRC
Excluded by Requester	B.S., C.V.T., S.R.S., R.L.A.T.G.	Manager	9
	M.S., S.R.S	Senior Research Assistant	10
	B.S., C.V.T., S.R.S., R.L.A.T.G.	Senior Research Assistant	18
	B.S., C.V.T., S.R.S., R.L.A.T.G.	Senior Research Assistant	7
	C.V.T., R.L.A.T.G.	Veterinary Surgical Technician III	7
	C.V.T., S.R.T., R.L.A.T.G.	Veterinary Surgical Technician III	11
	B.S., C.V.T., R.L.A.T.G.	Veterinary Surgical Technician III	3

Standard Operating Procedures (SOPs) and Standardized IACUC Procedures

SSU maintains over 30 SOPs for a variety of topics including post-operative patient assessment, surgical records, operating sterilizers, endoscope cleaning and maintenance, and scheduling. These undergo annual reviews by SSU staff members as well as a final annual review by the Head of Surgery. Additionally, SSU has created over 40 Standardized IACUC Procedure descriptions that are posted on the Office of Research Integrity website, intended to aid investigators in accurately representing surgical procedures performed by SSU in their IACUC protocol submissions. These documents include detailed descriptions of preoperative care and medication, anesthesia, animal and surgeon preparation, a surgery/procedure narrative, and post-surgical care. The Standardized IACUC Procedures are reviewed annually by the Surgical Veterinarians and approved by the IACUC. Additionally, 40 Powerpoint presentations of our most-commonly performed procedures were developed for staff training purposes, but these have also been used to inform the IACUC about procedures requested within protocols. These presentations have also been shared with veterinarians at other NPRCs who request procedural information and they have been used as formal presentations in Consortium web conferences. Presentations undergo annual review and updating by the SSU staff.

Services Provided

The Surgical Services Unit provided comprehensive surgical support for IACUC-approved projects directed by 43 different investigators from May 1, 2009 to September 30, 2012. The total procedure count for this period was 26,703 cases. In addition to surgical procedures such as cesarean section, telemetry implants, laparoscopic procedures, endoscopic procedures, and craniotomies, the unit also provided support for novel surgical procedure development like Roux-en-Y gastric bypass and laparoscopic abdominal seeding of endometrial tissues as well as ancillary surgical services like anesthesia, surgical training, and equipment sterilization.

Table 6. Annual Procedure Counts

	Y50	Y51	Y52	Y53*
Total # procedure/Fiscal Yr	9162	7522	7313	2706
Total # Investigators/Fiscal Yr	37	30	34	27

*Y53: Partial data through September 30, 2012

Table 7. Service usage per investigator each fiscal year.

Y50		Y51		Y52		Y53*	
Investigator	**Usage**	**Investigator**	**Usage**	**Investigator**	**Usage**	**Investigator**	**Usage**
Excluded by Requester	9	Excluded by Requester	356	Excluded by Requester	241	Excluded by Requester	1
	307		76		33		265
	76		28		1		1
	29		70		10		20
	4		14		98		40
	59		32		22		8
	10		11		48		23
	127		195		75		144
	23		48		7		
	42		41		179		11
	295		79				4
	61		65		56		7
	27		14		20		14
	84		26		2		8
	67		13		28		14
	11		61		31		5
	55		258		37		136
	29		7		8		31
	10		9		12		2
	4		4		36		1684
	101		4974		7		42
	209		112		81		24
	6		2		206		42
	16		12		6		10
	2		47		5562		17
	6039		122		26		148
	1		793		101		5
	506		9		42		
	6		8		39		
	100		36		93		
	43				18		
	152				155		
	597				33		
	14						
	7						
	9						
	25						
Total	**9162**		**7522**		**7313**		**2706**

*Y53: Partial data through September 30, 2012

Costs

Table 8. Costs for Services

Service Category	Users	Ave Usage Per PI	Ave Unit Cost	Total Cost
Surgical Fees	64	36.0	$365	$840,341
Miscellaneous	24	10.7	$97	$25,000
Total				**$865,341**

Surgery Fees include all surgical and anesthesia services provided by the unit. A large, comprehensive list of costs and services will be provided to reviewers at the site visit. *Miscellaneous* includes pharmaceuticals, consumables, sterilization charges, equipment rental, and supplies that are purchased in small quantities through the unit.

Figure 1. Annual Procedure Counts with Procedure Types

*Year 53 values are projected.

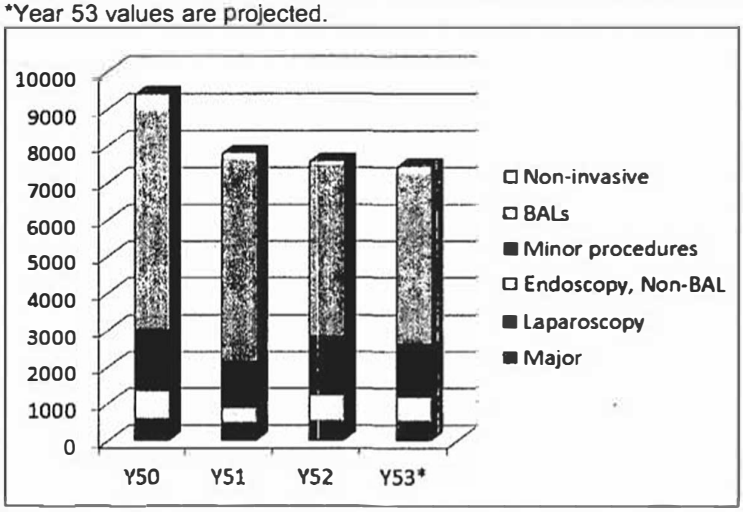


Figure 1 shows the total procedures performed in each year with color-coding indicating the general types of procedures. "Non-invasive" procedures include, but are not limited to MRI and ultrasound imaging, anesthesia studies; "BALs" are bronchoalveolar lavages; "Minor procedures" include, but are not limited to hormone implants, telemetry implants, lymph node biopsies, bone marrow biopsies, arteriovenous shunt placement, and CSF aspirates; "Endoscopy, Non-BAL" includes, but is not limited to colonoscopy with biopsy, gastroscopy, duodenoscopy with biopsy; "Laparoscopy" includes, but is not limited to ovariectomy, follicle aspirates, liver biopsies, and menstrual seeding of abdomen; and "Major" includes, but is not limited to exploratory laparotomies, cesarean sections, aortic grafting, intracranial injections, brain biopsies, middle cerebral artery occlusions, fetal catheterizations, and lutectomies. The reduction in case load that is evident between Y50 and Y51 was almost entirely due to a significant reduction in bronchoalveolar lavages (BALs) performed by SSU. Responsibilities for many of these procedures were reallocated to CMU staff or investigative staff. The reduction in BAL workload, however, was more-than-offset by the demand on the SSU for BAL training, oversight, and emergency management of BAL cases which SSU continues to provide.

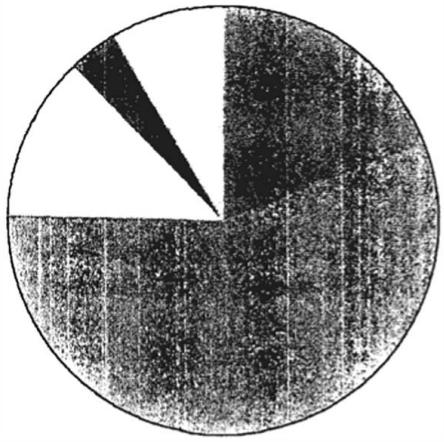
While the procedure counts above are helpful in assessing the workload of the unit, a look at unit income may provide a better breakdown of proportion of total effort the unit spends to support each of the major scientific divisions at ONPRC. The rates investigators are charged for surgical services are proportionate to the staff time and effort involved with each procedure. Figure 2 shows the proportion of total unit income that is derived from each of the major ONPRC divisions.

Continued Support of Research Protocols

SSU is closely integrated with ONPRC scientists and their collaborators to develop novel surgical techniques and to create animal models of disease that have optimal translational value. Highlights of SSU progress and strategies going forward are grouped below by scientific division. Brief descriptions of the experimental objectives associated with the surgical procedures described are included for orientation.

a. *The Division of Neuroscience*

An interventional MRI platform is currently being developed in support of Huntington's Disease research Excluded by in which *HTT* gene expression is suppressed by infusion of inhibitory RNA sequences into the putamen of subjects. This Interventional MRI platform allows visualization of intracerebral agent delivery and perfusion of neuroanatomical targets in real time with subjects under anesthesia in the MRI scanner. Traditional stereotaxic frame-based procedures rely on imaging obtained prior to surgery. Later, in the operating room, the surgeon must use coordinates associated with anatomic or fiducial markers. However, once the dura is opened, loss of cerebrospinal fluid and entry of air may combine to cause unpredictable and varying degrees of brain shift, even in deep brain tissues. The ClearPoint implantation system being adopted is based on a burr-hole mounted aiming device and trajectory guide with control software. This is a significant refinement over traditional methods to accurately deliver agents to specific targets within the brain. The current challenge is obtaining MRI-compatible instrumentation and specialized training to perform these neurosurgical procedures within the MRI suite.



An NHP model for alcohol use disorder has been developed in which NHPs undergo controlled induction of alcohol drinking followed by 12 months of daily access to alcohol and water Excluded by Requester Studies of human alcoholics suggest that a history of heavy drinking is related to increased impulsivity. The research group is studying changes in the expression of gene networks in the orbital medial and prefrontal cortex, an area implicated in impulsive behavior, as a function of chronic alcohol self-administration in monkeys. As part of this study, a 50 mg biopsy of rostral cortical area 12 is obtained by SSU via MRI-guided craniotomy before alcohol drinking and behavioral testing for impulsivity. A novel application of a clay modeling tool was developed to ensure consistent and minimally-traumatic brain tissue retrieval. Tissue from the opposite hemisphere is collected immediately prior to necropsy after 12 months of alcohol drinking and follow-up impulsivity testing.

Middle cerebral artery (MCA) occlusion surgeries associated with stroke model studies (Stenzel-Poore, PI) continue to provide challenges in terms of staff support for the procedure and post-operative patient care. Six to 8 MCA occlusion procedures are performed and supported by SSU monthly. The collaborative development and adoption of an index for endpoint determination has greatly improved communication between the veterinary and investigative staff. Preliminary results of the investigative drug intended to prevent or reduce the severity of strokes induced in the animal model are quite promising and funding support appears strong for the foreseeable future. The study was recently expanded to include female subjects and extended survival of selected animals for 28 days post-stroke surgery.

b. *The Division of Diabetes, Obesity, and Metabolism*

The Obese Resource has undergone considerable expansion in the past 3 years Excluded by Requester SSU continues to be closely integrated with the investigative staff and routinely provides consultation and oversight to minimize subject morbidity. Working with this resource has provided many opportunities to broaden our skill set by learning new procedures as well as adopting modifications necessary to provide optimal surgical, anesthetic, and post-operative support for obese NHP patients. The most notable new surgical procedure developed in support of the Excluded lab's diabetes projects was the Roux-en-Y gastric bypass, now currently performed routinely by SSU. Training for the SSU surgeons in this procedure was provided by direct instruction and oversight from a human bariatric surgeon collaborating with the investigator. Training animals were survived 1, 3, and 21 days post-operatively. Necropsies were attended by the research and surgical staff in order to refine procedures, to verify consistency among

procedures, and to identify and reduce potential morbidities. This project has provided SSU many unique challenges and problem-solving opportunities. The surgical veterinarians have presented much of their experiences at national meetings (Association of Primate Veterinarians and American Association for Laboratory Animal Science). Project endpoints are currently being analyzed by the investigators for publication. Excluded by Requester of the Excluded by lab are also collaborating with veterinarians and investigators who study diabetes and manage diabetic patients at the Wisconsin National Primate Research Center to develop computational tools to optimize the medical management of diabetic patients. This common format will allow seamless case management, information sharing, and professional collaborations among the veterinarians and investigators at the two centers. Computational tool development is partially supported by the NHPRC.

c. *The Division of Reproductive and Developmental Sciences*
SSU continues to routinely perform laparoscopic follicle aspirations and oophorectomies as well as embryo transfers, follicle injections, corpus luteum excisions, and cesarean sections in support of the Division of Reproductive and Developmental Sciences. In addition to these procedures, SSU has been closely involved in the development of several innovative experiments.

A technique for transcervical delivery of polidocanol, an agent currently used for sclerotherapy of spider veins, was developed. Transcervical delivery of polidocanol is being evaluated for use in women for elective outpatient sterilization in third-world countries where contraceptives are less available (Excluded by . The rhesus macaque cervix is narrow, tortuous and difficult to cannulate. Working cooperatively with Dr. Excluded by endoscopy was utilized to guide a rigid cannula through the cervix, an over-the-top catheter was inserted over the rigid cannula, then laparoscopy was used to verify the foaming agent (with polidocanol) infusion into the uterus and oviducts. Eventually the cervical cannulation could be achieved without endoscopy and recently laparoscopy was replaced with ultrasonography, thereby further reducing the invasiveness of the procedure.

A method for induction of endometriosis in rhesus macaques was developed and validated (Excluded by Requester In this procedure, endometrial tissue and menstrual fluid is aspirated directly from the uterus using laparoscopy to visualize and manipulate the uterus. The material is then infused (seeded) into the abdominal cavity near the uterus, where spontaneous endometriotic cysts are known to occur. This is a significant refinement over the previous, more invasive technique. Laparoscopy is used at one- to two-month intervals after seeding to evaluate the abdomen for endometriotic lesions. The successful minimally-invasive induction of endometriosis in this species is an exciting advance as progress on new therapeutic approaches for endometrioses has been slow due to limited physiologically relevant animal models. Anti-endometriotic therapies evaluated using this model could be well-positioned for translation to clinical trials. Pending Publication

d. *The Division of Pathobiology and Immunology*
The majority of the surgical procedures requested by The Division of Pathobiology and Immunology are in support of the HIV and AIDs vaccination development program. The key investigators in this division to whom SSU provides surgical support include Drs Excluded by Requester Excluded by Requester These experiments rely on the serial collection of subject tissues to assess immunological changes in response to vaccination and viral challenges. The primary tissue samples are collected via bronchoalveolar lavage, lymph node biopsy, bone marrow aspirate, and endoscopic duodenal and colonic mucosal biopsy. Because these procedures are frequently performed and highly standardized, we have focused considerable effort on workflow management to maximize efficiency and procedural quality.

Improving Workflow
Computational integration and automation have been key players in workflow management. We have developed and implemented innovative software tools that eliminate repetition, improve communication between cooperating units and investigative staff, and assure compliance with IACUC-approved protocols. These tools have also reduced human error, and improved animal care by making animal information that is relevant to surgery and anesthesia immediately accessible for each case in a format that is informative. In

addition to pre-procedure animal assessments and coordination, direct data entry modalities have been implemented to enable data entry during surgical procedures. This eliminates the time and error that is often associated with transcription. While these computational tools were initially developed to manage high-throughput procedures such as bronchoalveolar lavages, they have improved the efficiency of SSU operations in a comprehensive manner as they have been incorporated in all other aspects of the service. Small investments in software development have yielded significant returns in reduced surgical staff effort required to manage the workload. Since implementation of these computational tools in 2010, surgical staffing levels have been allowed to decrease through attrition (Table 9). This trend is expected to continue with the expansion and implementation of additional tools along with the adoption of a contemporary animal records system, Lab Key.

Implementation of the Training Program

A formal Surgical Training Program was developed with the appointment of a Surgical Training Coordinator (Excluded by Requester) with veterinary oversight provided principally by Excluded by. The purpose of the program is to provide comprehensive training resources that include written surgical descriptions, PowerPoint presentations, and hands-on instruction for Surgical Services Unit staff, investigative staff, clinical veterinary and technical staff, as well as visiting students and residents. The most common procedures for which SSU provides training include bronchoalveolar lavage, intravenous catheter placement, endotracheal intubation, subcutaneous hormone implant placement and removal, bone marrow biopsy, and lymph node biopsy. Live animal surgical training is typically conducted using animals assigned to the Surgical Training Protocol (described below). Some training of investigative staff may occur in investigator-assigned animals (survival surgery) only after thorough procedural instruction and observation and while under close supervision by a designated trainer until surgical competency has been confirmed. Training records are maintained by the SSU Manager, and final certifications of procedural competency are registered with the ONPRC Compliance Officer. The SSU training program will eventually be aligned with new RETU to centralize record keeping and consistency as well as improve efficiency. Individuals who have received surgical training by SSU from Yr 50 to present include 7 veterinary residents (4 ONPRC and 3 rotating from other NPRCs); 45 veterinary students; 15 veterinary technician students; 6 Division of Comparative Medicine staff members; and 15 investigative staff members.

Excluded by Requester is the PI on the Surgical Training Protocol (IS00000906). The purpose of this protocol is to utilize live animals to train veterinarians, veterinary technicians, and investigative staff. All animals used in this protocol are in transit to pathology for elective euthanasia generally due to unresponsive clinical conditions or poor clinical prognoses, therefore all procedures conducted are non-survival. Areas of training include development of new surgical skills or anesthetic techniques, refinement of surgical protocols, and evaluation of new equipment. These training opportunities educate and improve the skill sets of surgery staff, investigative staff, and clinical staff for performing procedures in support of research protocols. Development and perfection of surgical skills using non-survival animals reduces the likelihood of unintended surgical outcomes among healthy protocol-assigned animals. The development of novel surgical procedures as well as the development of procedural refinements using these animals reduces the number of healthy animals that would otherwise be required for procedure development, in accordance with the Three Rs.

Table 10. Annual use of animals in the Surgical Training Protocol.

	2009	2010	2011	2012*
Animals used	71	56	52	22

*Y53: Partial data through September 30, 2012

Activities

From 2009, members of SSU have authored 14 peer-reviewed papers, of which there was one first-authorship and 11 were collaborations with ONPRC investigators. In Press The first summarizes a collaborative study with scientists at the University of Arizona Excluded by Requester and the second is a collaboration with ONPRC investigators Excluded by Requester. Two non-peer-reviewed articles were published as well as one article in "Tech Talk", a publication of AALAS. In the same time period, members of SSU authored 11 posters/platform talks and were invited to give 2 symposia talks at national and international meetings. Abstracts and posters will be available for review at the site visit. SSU members also co-organized the regional District 8 of AALAS meeting and co-organized platform sessions at the National AALAS meeting and the Association of Primate Veterinarians meeting.

Outreach

Since 2009, SSU continues to be involved in outreach, within the veterinary profession, the scientific community, and the general public. SSU participated in outreach by assisting the Public Information Officer by giving presentations, campus tours, and providing opportunities to observe surgical procedures. We have given presentations at local schools and provided instruction and materials for suturing labs as part of the Science Ambassadors Program. Excluded by was an invited speaker for graduate-level biomedical ethics classes at Portland State University, the University of Portland, and Oregon Health and Sciences University.

Within the veterinary profession, DCM has maintained a structured program for veterinary students to spend 2-4 weeks rotating through the units of DCM to get exposure to clinical, surgical, pathological, behavioral, and operational facets of primate medicine. In SSU, we provide opportunities for students to utilize animals assigned to our surgical training protocol to develop basic surgical competencies in procedures such as intubation, venous and arterial catheterization, suturing, and anesthesia monitoring. Excluded by was an invited to at the Oregon State University College of Veterinary Medicine to speak to the Zoo & Wildlife Medicine and Laboratory Animal Research Clubs about career opportunities in primate medicine and surgery.

Within ONPRC, members of SSU were involved in many committees including IACUC, the Employee Recognition Committee, the IT Advisory Committee, Safety Committee, Environmental Enrichment Committee, and the Disaster Preparedness (ICS) Committee.

Additional Training Received

Excluded by Requester completed a Master's Degree in Clinical Research at Oregon Health and Science University. He was the first veterinarian to receive this degree. The degree track focuses on formal training for clinicians (typically physicians) who desire to make clinical or translational research either their predominant focus or a substantial part of their long-term career goal. Clinical research design, proposal development, biostatistics, evidence-based medicine, and computerized data management are core subjects within the curriculum. The knowledge, skillsets, and professional network gained through this coursework continue to aid Excluded by Requester in his independent clinical research, mentoring of residents, and facilitation of research.

Excluded by Requester have completed the Oregon Health and Science University Leadership Foundations Program, an eight-week, nine-session certificate series designed to provide managers with a broad understanding of behaviors, tools, and resources needed to be successful in a leadership role at OHSU.

Excluded by Requester completed the Oregon Health and Science University Conflict Management Certificate Series. The series consists of three courses that improve participants' ability to handle conflicts in the workplace by building conflict competence then transforming conflicts to a more productive dialogue.

Excluded by Requester has received advanced training in disaster preparedness and emergency response, including advanced ICS training and FEMA-sponsored classes at the Center for Domestic Preparedness. This training has enabled Excluded by Requester membership to the following organizations: Oregon Veterinary Emergency Response Team (OVERT); National Animal Health Emergency Response Corp (NAHERC); National Veterinary Response Team (NVRT); and Veterinary Medical Assistance Team (VMAT). She was recently

deployed to New York City by the National Disaster Medical System as part of the Hurricane Sandy relief effort.

Major Equipment Purchases:
1 Surgivet physiological monitor; 3 Storz Flexible Endoscopes (for bronchoscopy); 1 Wolf Flexible Endoscope (for bronchoscopy); 1 Storz 5mm telescope (for laparoscopy); 1 Storz HD Endoscopy Tower; 1 Storz Video Endoscope (gastroscope); 1 LEI Portable Anesthesia Machine; 2 Heska I-stat Blood Analyzers; 1 Smith Medical Med fusion Syringe Pump.

Specific Aims

Specific Aim 1. To provide surgical support for research projects through comprehensive surgical, anesthetic, analgesic and post-operative care.

Surgical instrumentation: Several technologic advances in minimally invasive surgical technique have occurred over the past decade. Advances in optics and imaging have enabled progressive size reductions in laparoscopes and endoscopes. While the 10mm-diameter laparoscope was once considered "minimally invasive", the 3-mm and 5-mm laparoscopes used today are capable of superior image quality through much smaller port sites. For this reason, we intend to replace our remaining 10-mm diameter laparoscopes with 3mm and 5mm diameter systems. Additionally, we plan to acquire a new 6mm endoscope for use in animals too small for 8mm endoscopes currently in use. This will broaden the age and size range of animals on which we may safely perform flexible endoscopy.

Anesthesia: We intend to purchase two refurbished Ohmeda anesthesia carts to replace the carts currently used in our two main operating suites. The carts will have modern pediatric ventilators and dual isoflurane and desflurane vaporizers. The reduced solubility of desflurane, relative to isoflurane, will improve the anesthetic recovery of our expanding caseload in support of the Obese Animal Resource.

Efficiency: A key means SSU will continue to support research objectives in a comprehensive manner is through maximizing the efficiency of our resource management through the use of computational automation. We will continue to develop and refine computational tools that interface with the electronic health records system. The efficiency resulting from automation allows reduction of surgical staffing levels. By reducing personnel expenses, surgical costs to the researchers may be lowered, thereby maximizing the value of each grant dollar. Our goal is to reduce SSU staffing levels by 25% of 2010 levels, adjusted for any change in workload. Specific goals include:

a. Update physiological monitors to allow direct data entry into electronic animal records.
b. Web page creation for commonly-performed procedures to allow rapid, real-time entry of surgical cases (surgical log, anesthesia, analgesia, and rounds) into electronic animal records. These will be based upon a prototype that is currently in use.
c. Automation of billing, census information, and drug inventory tracking.
d. Automation of critical information transmission between units, similar to the Post-surgical Cagemate re-pairing tool currently in use that generates automated email messages to husbandry staff after surgical cases are closed. This tool streamlines communications between SSU and Operations to aid BSU in the maintenance of social pairs.

Specific Aim 2. To support colony health maintenance by providing diagnostic, therapeutic, and emergency surgical services for spontaneous or experimentally-induced diseases or conditions.
Surgical support for colony health maintenance consistently provides a source of professional challenge, often requiring creativity and resourceful thinking. Objectives discussed in Aim 1 also benefit SSU support of colony health maintenance. To improve upon the services we currently provide, one objective is to obtain equipment and training for orthopedic bone plating. Many fractures are poorly amenable to our current methods of fracture casting, pinning, or external skeletal fixation. Bone plating will improve fracture outcomes and allow faster return of animals to their social groups.

SSU also intends to incorporate remote video monitoring of critical cases in the post-operative period. By removing the influence of the observer, an animal's behavior may be more accurately assessed. The monitoring system will also allow night time assessments of patients by veterinarians via mobile devices to increase the frequency of monitoring and thereby improve animal care.

Specific Aim 3. To serve as a resource for training veterinary students, residents, technicians, and veterinarians as well as investigative staff in all aspects of non-human primate surgical techniques, anesthesia, and analgesia practices.
A comprehensive surgical training program was developed within SSU and is currently operational. We plan to merge this program with that of RETU for training congruency and record keeping efficiency. One area that will require more development is routine software-based competency evaluation modalities. Since surgery is visual and process-oriented, we plan to obtain and incorporate high-quality intraoperative images of our more common procedures into our didactic training materials and computer-based competency evaluations as they are developed. These images will also be made available to investigators for presentation and publication.

Specific Aim 4. To expand collaborative and independent research with the goal of refining practices to minimize adverse physiological sequelae that may result from experimental interventions for the betterment of animal welfare and science.
Buprenorphine SR: We are exploring a collaborative study with SR Veterinary Technologies to establish the efficacy of Buprenorphine SR (single, long-acting dose) in comparison to buprenorphine HCl (given at established dosing intervals).

Anesthesia: We are continuing our collaboration with Excluded by Requester to determine the physiological effects of various anesthesia modalities on neonatal and pregnant rhesus macaques. This is a retrospective study using data generated from previous protocols that evaluated the neuroapoptotic effects of common anesthetics on fetal and neonatal rhesus macaque brains.

Blood Volume: Pending Support
Pending Support By measuring blood volume in a cross-section of animals of various ages and body conditions, a valid means of accurately predicting blood volume may be derived, filling a current gap in our knowledge of this species. Then limitations of benign blood withdrawal may be explored, characterized, and applied in a practical manner to nearly every experimental protocol involving this species.

Program Director/Principal Investigator (Last, First, Middle): Robertson, Joseph E./Haigwood, Nancy L.

ANIMAL SERVICES-SURGICAL SERVICES DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*

Use Cal, Acad, or Summer to Enter Months Devoted to Project

Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Excluded by Requester	Head Surgical Serv/Sr Vet	% Effort			Institutional Base Salary	66,494	16,623	83,117
	Mgr, Surgery Unit					31,800	9,858	41,658
	Vet Surgical Tech 3					30,933	9,589	40,523
	Sr. Res Asst					19,818	6,936	26,754
	Asst Vet					39,188	12,148	51,337
	Sr. Res Asst					14,882	4,614	19,496
	Vet Surgical Tech 3					28,905	8,961	37,866
	Vet Surg Tech 3					31,859	9,876	41,736
	Sr Res Asst					23,273	8,145	31,418
	SUBTOTALS →					287,153	86,751	373,904

CONSULTANT COSTS		
Surgery Consultant	0	0
EQUIPMENT *(Itemize)*		
None Requested	0	0
SUPPLIES *(Itemize by category)*		
Minor Equipment	3,202	
Pharmaceuticals	31,300	
Operating Supplies	12,455	
Surgery/Autopsy/Histology Supplies	44,619	91,576
TRAVEL		
Domestic	2,400	2,400
INPATIENT CARE COSTS		0
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		
None Requested		0
OTHER EXPENSES *(Itemize by category)*		
Maintenance - Equipment	5,500	
Conference/Registration	1,900	
Hazardous Waste Disposal	524	
Laboratory Services	436	
Registration/Course Fees	2,155	
Freight	1,312	11,827

CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 479,708
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 479,708

ANIMAL SERVICES-SURGICAL SERVICES
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	373,904	385,121	396,675	408,575	420,833
CONSULTANT COSTS	0	0	0	0	0
EQUIPMENT	0	0	0	0	0
SUPPLIES	91,576	94,324	97,154	100,068	103,070
TRAVEL	2,400	2,472	2,546	2,623	2,701
INPATIENTS CARE COSTS	0	0	0	0	0
OUTPATIENTS CARE COSTS	0	0	0	0	0
ALTERATIONS AND RENOVATIONS	0	0	0	0	0
OTHER EXPENSES	11,827	12,182	12,547	12,924	13,311
DIRECT CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	479,708	494,099	508,922	524,190	539,915
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	479,708	494,099	508,922	524,190	539,915
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					2,546,834

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

PERSONNEL

Unit Head/Surgical Veterinarian – Excluded by Requester % Effort;Excluded by Requester
Program Income). Responsible for budget management, supervision of personnel, major equipment decisions, and computational software development and maintenance; performs surgical procedures in support of research programs and veterinary care activities; manages the post-operative care of NHP with the aid of the Assistant Surgical Veterinarian, Surgery Manager, three Veterinary Surgical Technicians, three Senior Research Assistants. Contributes professional expertise and consultation to research projects and participates in collaborative and independent research. As a voting member of the IACUC, reviews the surgical components of protocols to verify their accuracy and suggests refinements of techniques when necessary, to reduce invasiveness of procedures planned. Serves as PI on the ONPRC Surgical Training Protocol and serves as PI on the Clinical and Surgical Techniques Working Group consortium, which includes all NPRCs.

Manager, Surgical Unit – Excluded by Requester % Effort
Income) Responsible for directly managing the Senior Research Assistants and Veterinary Surgical Technician III staff; performs surgical procedures, both major and minor, in support of research programs; assists in the post-operative care of NHPs; assists the Unit Head with administrative responsibilities; manages the surgery schedule; manages Surgical Services Training Program for Unit technicians as well as PI staff; maintains equipment inventory; provides billing information to Business Services; and coordinates unit activities.

Veterinary Surgical Technician 3 – Excluded by Requester % Effort
Program Income). Responsible for performing anesthesia, assisting in major procedures, and performing minor surgical procedures in support of research protocols and clinical care of NHPs, providing anesthesia monitoring; assisting surgeons; monitoring pre- and post-operative care; and providing training and other technical support to investigative staff. Also manages pharmaceuticals and consumables inventory for the unit.

Senior Research Assistant – Excluded by Requester % Effort
Program Income). Responsible for performing anesthesia and surgical procedures, both major and minor, in support of research programs; maintaining animal medical and surgical records; managing pre- and postoperative care; training professional and technical staff in proper sterile surgical techniques; providing surgical support to surgery staff; and providing training and other technical support to investigative staff. support.

Assistant Veterinarian – Excluded by Requester % Effort
Income). Responsible for performing surgical procedures in support of research programs and veterinary care activities and manages the post-operative care of NHPs, along with Surgical Technicians. Contributes professional expertise and consulting to research project; participates in collaborative and independent research; provides veterinary oversight and instruction for the surgical training program; reviews the surgical components of IACUC protocols to verify accuracy and suggests refinements of techniques when necessary, to reduce invasiveness of procedures planned. Also, serves on the IACUC (an alternate); coordinates the Veterinary Technician Continuing Education Program as well as the Laboratory Animal Technologist Preparatory course for technicians seeking AALAS certification; serves as a contributing veterinarian on the Clinical and Surgical Techniques Working Group consortium.

Senior Research Assistant – Excluded by Requester % Effort
Part time position, responsible for performing anesthesia and surgical procedures, both major and minor, in support of research programs; maintaining animal medical and surgical records; managing pre- and postoperative care; training professional and technical staff in proper sterile surgical techniques; providing surgical support to surgery staff; and providing training and other technical support to investigative staff.

Veterinary Surgical Technician 3 – Excluded by Requester % Effort
Program Income) Responsible for performing anesthesia, assisting in major procedures, and performing minor surgical procedures in support of research protocols and clinical care of nonhuman primates, providing

anesthesia monitoring; assisting surgeons; monitoring pre- and post-operative care; and providing training and other technical support to investigative staff. Also responsible for controlled substances ordering, inventory, and record-keeping.

Veterinary Surgical Technician 3 – Excluded by Requester % Effort
Program Income). Responsible for performing anesthesia, assisting major procedures, and performing minor surgical procedures in support of research protocols and clinical care of nonhuman primates, providing anesthesia monitoring; assisting surgeons; monitoring pre- and post-operative care; and providing training and other technical support to investigative staff. Also coordinates all anesthesia machine maintenance and services.

Senior Research Assistant – Excluded by Requester % Effort
Program Income). Responsible for performing anesthesia and surgical procedures, both major and minor, in support of research programs; maintaining animal medical and surgical records; managing pre- and postoperative care; training professional and technical staff in proper sterile surgical techniques; providing surgical support to surgery staff; and providing training and other technical support to investigative staff. Also manages equipment rental for the unit.

SUPPLIES

Minor Equipment: Funds are requested for divisional computers to be replaced at four year intervals, thus four per year in years one through four.

Funding is requested to purchase supplies to support activities essential for core-related surgical functions.

- Pharmaceuticals: pharmaceuticals such as analgesics, anesthetics, and emergency drugs;
- Operating Supplies: sterile drapes, smocks, and gloves, masks, safety glasses, and hair bonnets; cleaning supplies; and image capturing and image storage devices.
- Surgical/Autopsy/Histology Supplies: includes instrumentation such as various forceps, Metzenbaum scissors, needle holders, retractors, etc.;

TRAVEL

Funds are requested to provide travel to one national meeting per surgical veterinarian annually to keep up-to-date with current surgical practices, communicate with peers at other facilities, and promote collaboration and information-sharing.

Funds are also requested to provide travel to one national meeting for the Unit Manager and senior technical personnel once every 2 years to take exams for certifications (such as the Surgical Research Technician and Surgical Research Specialist certifications of the Academy of Surgical Research), update knowledge and skills, communicate with peers at other facilities, and gain industry insights.

OTHER EXPENSES

Funds are requested for:

Maintenance - Equipment: These funds cover repair and refurbishing of the delicate endoscopes used for bronchoalveolar lavage procedures; repair and maintenance of flexible endoscopes used for gastroscopy, endoscopy, and colonoscopy; and repair and maintenance of rigid endoscopes used for laparoscopy. Endoscopy towers that support the illumination, imaging, and insufflation for these procedures also require occasional maintenance. Sterilization equipment including ethylene oxide and steam sterilizers are maintained on annual preventive maintenance contracts. Anesthesia machines, including vaporizers and ventilators, are maintained, tested, and calibrated biannually.

Conference /Registration: Funds are also requested for fees for Manager and senior technical personnel to take exams for certifications (such as the Surgical Research Technician and Surgical Research Specialist certifications of the Academy of Surgical Research), update knowledge and skills, communicate with peers at other facilities, and gain industry insights.

Hazardous Waste Disposal: These funds are to be used to pay for disposal of sharps and outdated controlled substances.

Laboratory Services: These funds are for the occasional use of outside laboratories for diagnostic tests not available within DCM facilities or ONPRC service cores.

Registration/Course Fees: Essential for maintenance of continuing education and certification as well as providing professional outreach. Professional organizations include the American Veterinary Medical Association, the Association of Primate Veterinarians, the American Association for Laboratory Animal Science, the Academy of Surgical Research, and the Portland Veterinary Medical Association.

Freight: Costs for receipt and shipment of goods.

ANIMAL SERVICES: Surgery Income Table

Last Funded Year (53)

Source	Funding (direct costs)
P51 base grant support	$407,184.32
Program income derived from P51 base grant	497,669.72
Other Sources	0
Total	$904,854.04

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$479,707.84
Program income derived from P51 base grant	479,707.84
Other Sources	0
Total	$959,415.69

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

Surgery receives salary support and support for other expenditures from program income.

ANIMAL SERVICES: BEHAVIORAL SERVICES UNIT SPECIFIC AIMS

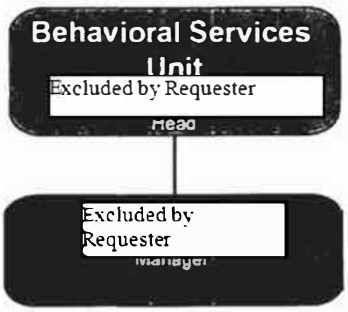
The Behavioral Services Unit (BSU) is a service unit in the Division of Comparative Medicine. The BSU is responsible for overseeing behavioral management of the nonhuman primates (NHPs) at the ONPRC, including providing social opportunities, enrichment, and positive reinforcement training and attending to animals with behavioral problems. As such, the BSU plays a major role in ensuring that the ONPRC is compliant with both the Animal Welfare Act and the *Guide for the Care and Use of Laboratory Animals*. The primary objectives of this unit are to provide social opportunities and environmental enrichment promoting species-typical behaviors for the monkeys, to assess and try to decrease abnormal behaviors and to promote animal well-being by using and developing techniques, devices and procedures that contribute to their psychological health. Pursuant to these objectives, the specific aims of this unit are:

Specific Aim 1. Reduce the number of single housed animals. A major goal of the ONPRC is to further reduce the number of single housed animals . Social housing increases the opportunity for animals to engage in many species typical behaviors, including play, feeding, and grooming, and is considered one of the best ways to promote their psychological well being. We will continue to explore and further define the factors that positively influence pair or group success.

Specific Aim 2. Improve and expand upon our NHP training program. Training animals to cooperate with procedures such as injections or blood draws reduces the stress associated with these procedures. In addition, by reducing the stress associated with husbandry and handling procedures, interindividual variation in stress response may also be reduced, enhancing the use of NHPs as research subjects. Training can also allow experimental animals to be housed in social groups as opposed to cages. Therefore, a major objective of our program is to expand upon our Positive Reinforcement Training training, including training group housed monkeys to come to the front of their pen for injection or blood draw. We are currently undertaking studies geared at increasing training success, and will continue to investigate ways to improve and expand these efforts.

Specific Aim 3. Improve wellbeing and decrease abnormal behavior in NHPs. Abnormal behaviors, including self-injurious behavior and stereotypical behavior, can be indicators of compromised well-being in captive NHPs. Therefore, a major goal of the BSU is to reduce the occurrence of abnormal behaviors in our NHPs by improving conditions that promote well-being and decreasing situations known to compromise well being (such as nursery rearing). To achieve this aim, we plan to: 1) Improve early rearing for orphaned infants by providing opportunities for them to be with foster females (i.e., non-lactating females trained to allow infants to feed from a bottle); 2) Provide a wider variety of enrichment options to NHPs, particularly for singly housed monkeys; and 3) Work with the Clinical Medicine Unit, the Behavioral Management Consortium and others to develop novel treatments for these behavioral problems.

ANIMAL SERVICES: BEHAVIORAL SERVICES UNIT RESEARCH STRATEGY.



SIGNIFICANCE

The Behavioral Services Unit (BSU) is a service unit in the Division of Comparative Medicine (DCM). The BSU consists of staff responsible for overseeing behavioral management of the nonhuman primates (NHPs) at the ONPRC, including providing social opportunities, enrichment, and positive reinforcement training and attending to animals with behavioral problems. As such, the BSU plays a major role in ensuring that the ONPRC is compliant with both the Animal Welfare Act and the *Guide for the Care and Use of Laboratory Animals*. The primary objectives of this unit are to provide social opportunities and environmental enrichment promoting species-typical behaviors for the monkeys, to assess and try to decrease abnormal behaviors, and to promote animal wellbeing by using and developing techniques, devices, and procedures that contribute to their psychological health. Since many of these objectives overlap with those of other services units within the Division of Comparative Medicine, the BSU works closely with the other units, particularly the Clinical Medicine unit (CMU) and the Resources, Facilities and Operations (RFO) unit. The BSU also interacts directly with the scientific staff.

INNOVATION.

In the last funding period, the BSU was reorganized to include a full-time Training Specialist position (2009) and an additional FTE to manage social groups (2009). In 2011, the BSU Supervisor position was changed to BSU Manager. In 2012, the BSU added a postdoctoral trainee, to reflect the importance of research to the unit. We continually strive to improve the psychological wellbeing of the NHPs at the ONPRC. Innovations to the BSU over the past 5 years include improvements to social housing (utilizing a team-based approach to managing group-housed animals and enhanced monitoring of social group and pairs), the expansion of our positive reinforcement training program to train NHPs to cooperate with husbandry, clinical and/or research procedures, and the establishment of a program to reduce nursery rearing by pairing orphaned infants with non-lactating females trained to allow the infants to bottle feed. In the past 5 years, the BSU has been active in the NIH Behavioral Management Consortium (BMC), taking a lead role in the implementation of the BMC Self-Injurious Behavior (SIB) Scoring system, a tool designed to help standardize terminology and assessment of SIB. Finally, in 2011, the BSU co-hosted the International Conference on Environmental Enrichment with the Oregon Zoo, and has begun to increase communication and collaborations with members of the zoo community.

APPROACH

reviewers' comments

reviewers' comments

Progress and accomplishments in the last funding period.

Staffing

The BSU currently contains a NHP Behaviorist who oversees the unit, a BSU manager who is responsible for managing the BSU staff, a "Training Specialist" who oversees the NHP training program to train caged and group-housed monkeys to cooperate with husbandry and/or research procedures, an "Enrichment Coordinator" who oversees the environmental enrichment program, and four "Behavior Technicians" responsible for providing social opportunities for monkeys, assessing and monitoring animals with behavioral problems, and checking the monkeys on a daily basis. Each of the behavior technicians is assigned to a specific area on campus (e.g., Colony, ASA, ASB 1, 2, or 3). They interact with husbandry staff in those areas on a daily basis, and thus can keep informed of what is going on with the monkeys in their areas. One behavior technician is assigned to monitor group-housed monkeys. The BSU also has a postdoctoral fellow to help collect, analyze and publish data. Table 1 details the BSU staff.

Table 1: Current BSU members, degrees, position titles and length of time in the unit.

Name	Degree and Certifications	Position Title	Years in the BSU
Excluded by Requester	Ph.D.	Head	11
	MS, LAT	Manager	10
	LAT	Enrichment Coordinator	11
	BS, ALAT	Training Specialist	0.5
	MS, LAT	Behavior Technician	7
	BA, LATg	Behavior Technician	9
	BS, ALAT	Behavior Technician	6
	Ph.D.	Postdoctoral Fellow	0.5
TBD		Behavior Technician	

Social housing

The major goal of the BSU has been and continues to be to socially house as many of the NHPs as possible, either in groups or pairs. Currently, over 84% of our NHP population is socially housed.

Group housing:

Over the last funding period, the BSU has taken on additional responsibilities with group-housed animals. In 2009, a new position was added to the BSU to monitor group-housed animals, assess group dynamics, and interpret dominance relationships to ensure that animals important to group stability are not inadvertently removed. In 2010, we established weekly meetings with the clinical, husbandry, and resource staff to discuss individual animals and/or groups of concern. These meetings have resulted in a team-based approach to the management of these animals, which has improved the care provided to them. The weekly meetings provide a forum for direct and clear communication between the interested parties, and allow everyone to have a voice in animal care. While metrics for the success of this team-based approach to animal care are still being evaluated, the length of hospital stays for group-housed animals decreased from an average of 18 days in 2007 to approximately 10 days in 2012.

The BSU also has a greater role in group formation than 5 years ago. We now work closely with the DCM RFO and CMU as well as the ONPRC Genetics Core to help assess potential candidates for each new group, particularly males, with the goal of producing stable groups. In any given group, up to half of the males may have to be permanently removed from the group due to aggression. For the past 4 years, the BSU has examined factors that might predict whether or not males will be successful in their new groups. For example, we found that males reared in cages were more likely than those reared in outdoor corrals to suffer trauma within a year of being introduced to a new group Excluded by Requester In addition, we currently perform temperament tests on adult males before introducing them into groups in an effort to determine if there are

personality traits that can predict male success (in terms of fitness and ability to survive in the group). To date, we have assessed temperament in 119 males prior to group introduction.

We are also working closely with the other DCM units to find other methods to reduce aggression and maintain group stability. We make every effort to keep animals in their home groups whenever possible, even if they need medication or other clinical treatments. In 2010, we started to work with husbandry technicians to train group-housed monkeys to accept medications, which allowed the animals to stay in their group (as opposed to being moved to the clinic hospital). We now utilize this kind of training whenever possible. In 2012, we had a "satellite cage" built. This freestanding, mobile monkey cage can be placed next to a sheltered housing unit, and allows treatment of sick or injured animals while providing them with visual contact with the rest of their group. The use of this cage has facilitated re-integration back into the home group.

Pairing:
Pairing caged animals has been a top priority of the BSU since 2009. The number of pair attempts has increased dramatically in this time period. In FY 50, the BSU attempted 484 pairs, and in the following fiscal year we attempted over 800 (Fig. 1). Of the animals currently singly housed, approximately 24% have IACUC approved scientific exemptions, approximately 3% are behaviorally unsuitable, and 8% have clinical exemptions. Animals are deemed behaviorally unsuitable after three unsuccessful pairing attempts with three different partners. These animals, along with animals singly housed for clinical reasons, are assessed monthly. The other 65% are in queue to be paired.

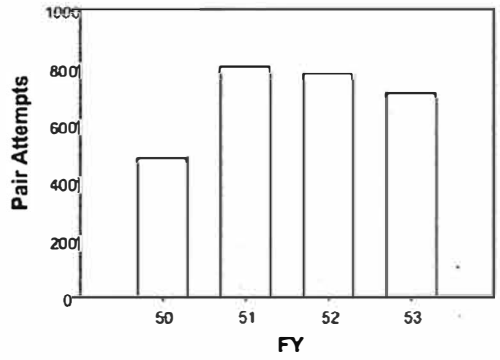


Figure 1: Number of pairing attempts by BSU staff from FY 50-53. Numbers for FY 53 include projections.

In 2010, we identified the primary obstacles of pair formation and maintenance. Since that time, we have made great strides towards overcoming these challenges. Some of the challenges and improvements include:

- Increased communication: One major obstacle to pair housing was the lack of appropriate caging (i.e., caging that allows pair housing), particularly for our larger animals. In addition, we often formed pairs only to have them separated soon after because one or both partners was assigned to a research project or sold. In 2010, the BSU Head and Manager began to meet with RFO Head and Colony Manager on a regular basis to discuss these issues. We identified our caging needs and have started procurement of new caging. RFO staff now informs BSU about animals about to go on assignment and, when possible, assign paired animals to the same project, allowing the pair to remain together. This increase in communication has had a great impact on our ability to form lasting pairs.
- Increased data keeping: Prior to 2010, information about which animals had IACUC approved exemptions was not readily available to the behavior technicians involved in pair housing, and thus they had to contact individual investigators for this information. This process often took a great deal of time. We now maintain a detailed "Single-housing list" in which *all* singly housed animals are identified along with the reason for their single housing. This list is currently generated monthly. We are working with the IS group to make this a dynamic list that can be updated daily. The list has allowed BSU technicians to more easily determine which animals need to be paired. It also allows us to track animals singly housed for more than a month.
- Increased notification: An obstacle to maintaining social housing was the inadvertent separation of pairs. Animals separated for surgical or clinical reasons were not always re-united in a timely manner. The IS group designed an automatic notification that is sent to BSU (and other units) when animals separated for

surgical reasons can be re-united. This notification has helped to reduce the number of pairs inadvertently separated.

- Increased monitoring: In 2012 we instituted a system of observations in which we observe new pairs throughout the first couple of weeks. These data will help us determine behaviors that might indicate the long-term outcome of the pair (i.e., whether or not they will fight).

As a result of this effort, the percent of caged animals that are paired has risen dramatically since 2009. In FY 53 (May-Dec 2012), on average, over 57% of our caged animals were paired, an increase from the previous fiscal year, in which 52% of caged animals were paired (Fig 2).

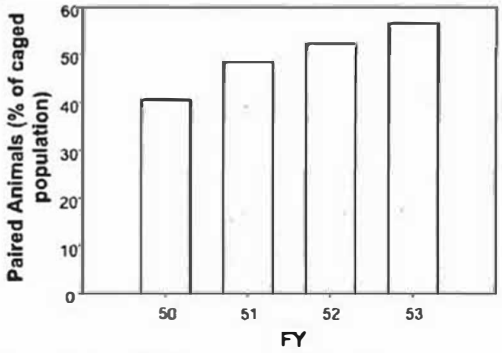


Figure 2: Average percent of caged animals that were pair housed from FY 50-53.

All pairing attempts (successful and unsuccessful) are entered into the animals' permanent records. We try to find less traditional partners for animals that do not appear compatible. For example, we have increased the number of pairs consisting of an adult and juvenile monkey. These efforts, along with having an experienced and stable staff, have increased the success rate of our pairing attempts from approximately 50% in 2002 to over 80% in 2012. Pairs are considered successful if the partners do not immediately (i.e., within 2 weeks) fight or show excessive aggression or fear towards each other. Table 2 illustrates the number of pairs we attempted in FY 53. Our pairing success has decreased somewhat because we have attempted more difficult pairs (i.e., pairs involving animals singly housed for long periods of time). Because the behavior technicians spend several hours observing pairs after they are formed, injuries rarely occur during pair attempts. In 2012, less than 2% of pair attempts resulted in injury to one partner.

Table 2: Number of pairs attempted in FY 53 (to Dec 31) by age and sex class of the partners. The number in parentheses represents the percent of attempts that were successful.

	Adult	Juvenile	Adult/juvenile
Female-Female	220 (71%)	36 (100%)	13 (92%)
Male-Male	112 (78%)	81 (99%)	18 (94%)
Female-Male	0	3 (66%)	3 (100%)

While full pairs are the preferred method of pairing at the ONRPC, it is not always possible to maintain them in this fashion. We utilize grooming-contact slides, which permit tactile interactions between the pair when full contact between the pair is not desirable due to experimental or animal welfare concerns. Half of the grooming contact slide is a solid panel while the other half consists of bars wide enough to permit grooming.

Environmental enrichment

Our enrichment program focuses on providing animals with opportunities to express species-typical activity patterns such as exploration and foraging. All primates, including caged and group-housed monkeys, are provided with novel toys and devices that encourage these behaviors. Currently, the environment of each caged monkey is enriched with cage furniture (e.g., perches) and a different manipulatable object (i.e., toy)

rotated every two weeks. Novel toys are continually substituted as they are purchased or designed. The toys remain with the cages for sanitation.

In an effort to increase the amount of time our monkeys spend foraging, we provide caged monkeys with devices that promote foraging and manipulation (i.e., foraging manipulanda) on a regular basis. These devices are hung on cages and are changed every two weeks, giving animals access to new foraging manipulanda every other week. The devices are filled with trail mix, grain, and/or produce every other day.

Additional enrichment provided to the monkeys includes:

1. Providing foods that utilize their cognitive and foraging skills, including use of frozen foods (which increases consumption time), placing food on the top of the cage, and hiding food (in larger group housing).
2. Providing additional auditory and visual stimulation including television, radio, and computers with randomly generated screen saving programs.
3. Enriching the structure and substrate to allow species-typical behavior, including substrate through which NHPs may forage. Monkeys in some of the smaller pens receive wood shaving substrate in which they can forage. In 2012, we undertook a study in which we examined the use of shavings in both the sheltered housing units and other areas. We found that the use of substrate can help reduce aggression and excessive self-grooming behavior, as well as increase foraging In Press
4. Increase the use of novel enrichment, such as a 'porch' (a small cage that is hung on the outside of the monkey's home cage, increasing the individual's visual field of view) and a "tunnel" (a stainless steel structure that connects two cages, allowing movement between the two). We found that the porch reduced the incidence of abnormal behavior including feces smearing Excluded by Requester

We document and evaluate enrichment so that we can determine whether or not it is being utilized. This evidence-based approach guides our decisions to maximize the use of our resources for the benefits of the NHPs in our care. Evaluation includes monthly assessments of randomly chosen animals, as well as small research projects in which use of the new device is objectively quantified. Currently, this information is maintained by BSU. In the future, we plan to utilize LabKey, a dynamic and integrated electronic health record system, to maintain this information and facilitate program improvement.

NHP Training

In 2009, the BSU changed our 0.5 FTE position of "Training Coordinator," to a full-time position (currently titled "Training Specialist", to be consistent with other NPRCs). This position oversees our NHP training program in which we use positive reinforcement training (PRT) to teach monkeys to cooperate with husbandry, clinical and/or research procedures. Such training decreases the stress associated with procedures (e.g., blood draws) for both the monkeys and caretakers, thus producing a better research model. Our goal is to train as many monkeys (both group housed and caged) as possible. Training monkeys within their social groups is particularly important, as it allows animals to remain in groups thus reducing stress associated with social separations. In addition to training animals, the Training Specialist is responsible for teaching technicians to train using PRT, developing training plans and maintaining records. To date, over 35 husbandry, clinical, and behavioral technicians have undergone the PRT training course allowing them to act as NHP trainers. Since 2010, we have trained over 500 monkeys for procedures including entering a tunnel (for group housed animals), presenting a thigh or other body part for injection, presenting for vaginal swabbing, and remaining stationary for blood draw. Many of these animals were trained as part of PI studies (Table 3). Because training can be time consuming, the BSU has conducted studies examining ways to make training more effective and efficient. For example, we found that animals learn more quickly if they watch others perform in the same task Excluded by Requester

Table 3. Number of animals trained for various tasks for ONPRC PIs over the past four years. (Number for FY 53 includes projections).

Training task	PI	FY 50	FY 51	FY 52	FY 53
Blood draw	Excluded by Requester	8			
					55
					3
Present for injection					25
Present for vaginal swab			9		
					73
Desensitize to primate chair		9	4		
Shift (group housed animals)		10			
			20		

Assessment of abnormal behaviors

The BSU continues to assess and monitor abnormal behavior in caged monkeys. Common behavioral problems include excessive stereotypical behavior, excessive self-grooming and hair plucking, and self-injurious behavior (SIB) resulting in bruising or bite wounds. Currently, we have approximately 120 animals with open cases for these behavioral problems. Of these, 51 have exhibited some sort of SIB. Most of the SIB does not involve wounding; fewer than 15% of these SIB animals have caused injuries that have required veterinary attention at some point during the past year. Monkeys with open behavior cases are assessed regularly (at least every 1-2 weeks, depending on the severity) by the behavior technicians. Data are entered into the animal's medical records using objective criteria that describe the current status of the animal, which allows us to monitor and assess treatment progress. The behavior technicians provide these animals with therapeutic devices designed to displace the behavior. For example, animals that engage in hair plucking might be provided with a paint roller they can groom. The BSU works closely with the CMU to care for animals that wound themselves, as these animals often require pharmacological intervention. In 2010, the ONPRC created a Self Injurious Behavior Endpoint Policy. The veterinarians make decisions based on the severity and frequency of SIB events. The BSU is currently collaborating with the Behavioral Management Consortium to establish common definitions of abnormal behaviors as well as standards of care across facilities.

Because it can be very difficult to fully treat abnormal behaviors once they have begun, we emphasize prevention to avoid the development of these behavioral problems. We conduct standardized annual behavioral assessments to ensure that each animal is examined. In the past year, we have assessed over 1,100 caged animals.

One of our main preventative measures is to increase social housing, especially for our younger monkeys. Early rearing without appropriate socialization is one of the biggest risk factors for the development of abnormal behavior in macaques Excluded by Requester To this end, we try to reduce nursery rearing by pairing orphaned infants with adult females. Whenever possible, orphaned infants are paired with a lactating female if one is available (e.g., a female that recently lost her own infant). While this approach is most often successful, the supply of available lactating foster mothers does not always meet the demand. In 2009, we began a program with the CMU and RFO to examine the use of operant conditioning to train non-lactating female rhesus macaques to act as foster mothers to abandoned infants. The females are trained to allow the infants to come to the bottle for feeding. To date, we have trained 9 non-lactating females to allow the infants to feed from the bottle, and have attempted to pair 16 orphaned infants with these foster females. Of these, 14 were successful and resulted in long-term foster mother-infant pairs. Clinically, infants on these non-lactating foster females gain weight at a rate equal to naturally reared infants, and foster-reared infants show significantly less cases of diarrhea compared to non-foster reared nursery infants Excluded by Requester Further, we have seen no indication of any behavioral problems typical of nursery-reared infants, such as stereotypical rocking or digit sucking. Thus, it appears that foster-reared infants behave similarly to mother-reared infants at the ONPRC. These behavioral benefits likely last into adulthood. We house our foster females in the nursery to facilitate training and feeding. We believe having adult females displaying normal primate behavior in the

nursery will also benefit the other infants housed there. We are currently collecting data to evaluate this hypothesis.

Personnel training

The BSU is involved in providing training on primate behavior to ONPRC staff. Currently, the BSU Manager and Enrichment Coordinator conduct one-on-one training sessions with all new DCM employees, covering items such as basic NHP behavior, how to recognize abnormal behavior, and how their actions might influence the animals. We also work with technicians when they have problems with animals (e.g., aggressive animals, etc.).

Training of BSU staff includes mandatory attendance at bi-monthly sessions presented or sponsored by the DCM staff. They are encouraged to attend ONPRC seminars. In addition, BSU staff organizes and participates in monthly journal clubs, where they read papers relevant to animal welfare issues. Currently, all of the BSU technicians have AALAS Certification (1 LATg, 3 LAT, and 2 ALAT). Standard operating procedures (SOPs) and guidelines describing various animal care and use activities have been created or extensively revised. The ONPRC Behavioral Management Plan will be available for the site visit. In addition, the following SOPs will be available:
AC-002: Environmental Enhancement
AC-050: Social Housing Formation and Maintenance

The following Guidelines will also be available:
GL 052: Clicker Training
GL 055: Behavior Case Guidelines
GL 064: BSU Pairing Guidelines

In the past 5 years, BSU staff members have attended scientific meetings including the American Association of Laboratory Animal Science, the American Society of Primatology, and the International Conference on Environmental Enrichment.

Research support and collaborative research

The BSU has increased collaborative work in the last grant period. In the past five years, we have collaborated with investigators both inside and outside of the ONPRC, including Excluded by Requester (ONPRC; "Ovarian steroid regulation of serotonin in primates", "Steroid regulation of serotonin in male macaques", "Postmenopausal monkey resource"), Excluded by Requester (ONPRC; "Effects of a high fat diet on the behavior of infant Japanese macaques"), and Excluded by Requester (OHSU; "Long-term outcome of anesthesia exposure of infant monkeys"). Our role in these projects has been to perform standardized temperament testing and behavioral assessments, perform observations on social behavior, and perform infant behavioral and neurodevelopmental testing. In addition to these efforts, for which we have received salary support, we also provided behavioral services to PIs at the ONPRC (Table 4).

Table 4: Behavioral services provided to ONPRC PIs during the past 4 years. (FY 53 includes projected services).

Service	PI	FY 50	FY 51	FY 52	FY 53
Temperament test	Excluded by Requester	14	25	22	29
Temperament test		6	0	0	0
Neonatal neurodevelopmental assessments		0	91	0	55

The BSU continues to conduct independent research designed to examine behavioral management and psychological well-being issues as well. Many of these projects are collaborative. Excluded by Requester is a co-PI on a collaborative NIH grant ("Self-Injurious Behavior and Primate Well-Being"), involving the New England NPRC, the Washington NPRC, the Southwest NPRC, and the ONPRC. She is also co-PI on an NSF grant ("Computational Models for the Automatic Recognition of Non-Human Primate"), a collaborative study between

the ONPRC and OHSU. She was the PI on a Private Source grant ("Factors underlying alopecia in rhesus macaques"). In addition to these funded projects, we have conducted other research aimed at examining new enrichment and evaluating methods for making positive reinforcement training more efficient. Such research activities have resulted in several abstracts and publications. Since 2009, members of the BSU authored 22 posters/platform talks at national and international meetings, of which 6 were collaborations between the ONPRC and other Behavioral Management Consortium (BMC) members and 4 were collaborations with ONPRC investigators. In the same period, BSU team members were invited to give 6 symposia talks at national and international meetings and 3 plenary/keynote addresses at national conferences. Of note, 17 of these talks/presentations were authored by BSU team members other than the BSU Head, and one of the plenary invitations was extended to the Enrichment Coordinator. BSU team members also co-organized one workshop (with other BMC members) and one symposium at the 2012 American Society of Primatologists meeting. Since 2009, the BSU has published 9 peer-reviewed papers/book chapters (3 BMC collaborations, and 2 were collaborations with ONPRC investigators), 2 non-peer reviewed book chapters (both collaborations with BMC or others), and one article in "Tech Talk", a publication of AALAS. Under Review

Outreach

Since 2009, we have continued to be involved in outreach, both within ONPRC and in the greater scientific community. During this time period, members of the BSU participated in over 100 hours of outreach, including assisting the Outreach Coordinator with campus tours and giving presentations about our program to visiting groups. Each year since they started, Excluded by Requester has given a talk on animal care at the ONPRC Public Tour. We also assisted in other outreach endeavors, including the Science Ambassadors Program. We have given presentations at local schools and organized symposia (e.g., the Annual Math, Science & Technology Conference for Middle School Girls and the Washington County Gender Equity Team). From 2007-2010 Dr. Excluded by Requester was a presenter for the OHSU TIES (Teacher Institute for the Experience of Science; an NIH Science Education Partnership Award) program, giving several talks a year to middle school students. Members of BSU have also as judges at local science fairs and as a mentor for a high school student as part of a local Science, Technology, Engineering and Math program (STEM). Many of these outreach efforts, including the mentorship, were undertaken by BSU technicians.

Since 2009 Excluded by Requester has served as a mentor to 3 undergraduate students, 1 high school teacher (through the M.J. Murdock Partners in Science program), 2 graduate students (one PhD student from UC Davis, and one MS student from Texas State University, San Marcos), and one recent PhD from Kyoto University.

Members of the BSU were involved in many committees, both inside and outside of the ONPRC. Internal committees include the Safety Committee, Employee Recognition Committee, and the ONPRC IACUC, on which the BSU Head serves as co-chair. External committees include the Research Committee and the Captive Care Committee (ASP) and the International Committee (Shape of Enrichment). In 2011, the BSU co-hosted the International Conference on Environmental Enrichment (ICEE) with the Oregon Zoo. This was the first time this conference was co-hosted by a research facility.

In 2010, Excluded by Requester served as a consultant for Private Source Singapore, and, in 2012, she consulted at the Private Source She gave invited lectures at the SCAW Advanced IACUC meeting (2009) and the Large Animal Handling Course, SingHealth, Singapore (2010). She was also invited to talk at Dowling College, NY in 2012.

Specific Aims.

Specific Aim 1. Reduce the number of single housed animals.

The primary objectives of this unit are to reduce the number of animals living singly in cages, expand our training program to train monkeys to cooperate with research and/or husbandry procedures, try to reduce the occurrence of abnormal behaviors, provide behavioral expertise supporting primate-related research, and provide training to the investigative staff in the care and use of laboratory animals. Many of the aims of this unit overlap with other service units within DCM.

Social housing

Increasing social housing remains an important goal of the BSU (as well as other units within the DCM). Macaques are social animals and providing social housing is our best means of optimizing their psychological wellbeing [Excluded by Requester] As mentioned above, we have made great strides towards this goal in the past grant period. We will continue to address the social needs of our animals and plan to decrease our singly housed animals by at least 60% in the next five years.

Group housing

We will continue to work closely with the RFO and CMU to promote and retain group formations. One obstacle that is inherent with social housing is aggression. We are working on a collaborative grant with members of the Behavioral Management Consortium (BMC) to examine aggression in group-housed animals. This study will give us information on factors that might predict when aggression. In addition, we are currently assessing temperament in males before introducing them into groups, to determine whether these traits may predict whether males are successful in the groups. We hope to expand this to females in the coming years. We also plan to examine factors that might help reduce stress in the groups. As detailed above, we recently submitted a paper to *JAALAS* describing the effects of wood shaving substrate on aggression in group-housed animals. We also plan to determine whether making husbandry events consistent and therefore predictable helps to reduce stress associated with routine husbandry activities. Finally, we hope to increase our ability to monitor group-housed animals, particularly when fighting occurs. To this end, we hope to procure a camera system that will allow us to remotely monitor animals in groups and determine which individual is instigating the aggression. Such a system is important, because animals often behave differently when humans are present than when we are not present.

Pair housing

As detailed above, we have made great strides in reducing the number of singly housed animals. However, despite our increase in pair attempts, in FY 53 an average of 63% of single housed animals do not have behavioral, clinical, or IACUC exemptions. Our goal is to dramatically reduce this number in the next five years. We plan to approach this goal from two directions; improve pairing success and decrease pair separations.

To help improve pair success, we have begun to implement pair assessments, as detailed above. We will continue and expand these assessments in an effort to determine early behaviors that might predict whether or not the pair will be successful. Further, it will allow us to make better pairs. We currently define pairing success by lack of aggression; however that does not imply that the animals actually show pro-social behavior such as grooming. These pair assessments will help us ensure that the pairs we make are benefiting the animals. We will also continue to work with RFO and IS to help overcome the challenges associated with finding appropriate caging. We are requesting funds to hire a "Socialization Specialist" to help oversee the pairing process. For the most part, the behavior technicians currently pair animals with others in their areas. However, it is possible that the compatible partner might be located across campus. The Socialization Specialist would have knowledge about all animals on campus. This person will work closely with the RFO to determine cage availability and assignment status of the animals. Because many animals are assigned to scientific protocols in which pairing can only occur during specific phases of the study, the Socialization Specialist will work closely with investigative staff as well. Having a central person organizing pairing, as well as our continued efforts at pairing, will help ensure that we meet our goal to significantly reduce animals in single housing.

Another important factor involved in increasing socialization is reducing pair separations. A high percentage of our pairs are separated within 12 months of being formed. Of the pair separations in 2012, less than 10% were due incompatibility issues. The majority of these were separated because one or both partners were assigned to a protocol or new group or sold. Pairs are sometimes separated inadvertently (e.g., the pair is not re-united after separation for medical or scientific reasons). We have started to address these issues, and will continue to do so in the coming years. The new LabKey animal records system, along with barcoding, will greatly aid our ability to keep pairs from being inadvertently separated.

Specific Aim 2. Improve and expand upon our NHP training program.

NHP Positive Reinforcement Training:

Another important goal of the BSU over the next five years is to improve and expand upon our training program. Training animals to cooperate with procedures such as injections or blood draws reduces the stress associated with these procedures. In addition, by reducing stress and variability associated with maintenance procedures through training, NHPs can become better-defined research subjects, thereby increasing the value of the animal model and the research. Training can also allow experimental animals to be housed in social groups, as opposed to cages.

While the use of training is beneficial to both the animals and the caretakers, there are obstacles that make widespread implementation difficult. First, training is very time consuming; it can take several weeks or even months to train animals to accept venipuncture, for example. Further, individuals vary a great deal with respect to trainability; some individuals learn tasks quite readily, while others take longer to reliably perform tasks. To that end, we have begun, and plan to continue, research to address these issues in a systematic manner. We published a study Excluded by Requester demonstrating that shy rhesus macaques are more difficult to train than bolder animals. We are currently examining whether this finding holds true with cynomolgus macaques as well. Further, we will look at other factors that might affect trainability, such as age, dominance status, or even rearing history. Knowing which individuals may be relatively easy to train can help us assign them to projects where such training would be useful, such as studies in which frequent blood draws are necessary. Further, knowing that some animals may be hard to train can help us develop alternate ways to get them to perform the tasks. We have begun studies to examine how to train these shy animals.

In addition to the research into training, we also hope to train animals proactively, as opposed to reactively (i.e., when they are assigned to a research protocol). For example, we have recently begun to train all imported animals to enter a transfer box while they are still in Quarantine. This training acclimates the monkeys to caretakers, making them easier to work with. We hope in the next five years to train all imported monkeys for tasks such as present for injection and present for vaginal swab (for females), which will help reduce stress for the animals when they are ultimately assigned to research studies.

Specific Aim 3. Improve wellbeing and decrease abnormal behavior in NHPs.

Abnormal behaviors, including self-injurious behavior and stereotypical behavior, can be indicators of compromised well-being in captive NHPs. Therefore, a major goal of the BSU is to reduce the occurrence of abnormal behaviors in our NHPs by improving conditions that promote well-being and decreasing situations known to compromise well-being. We will approach this aim from several directions. It is well known that once behavioral problems start, it is very difficult to ameliorate them. Thus, one objective of our program is to prevent the occurrence of these behavioral problems from the beginning. One of the primary risk factors for developing self-injurious and other abnormal behaviors in macaques is being reared without appropriate close social contact with conspecifics. Therefore, we hope to expand upon our "foster mother" program in which orphaned infants are paired with non-lactating females trained to allow the infants to bottle feed (see above). We hope to get more females trained as foster dams, and to increase the number of staff involved in the process. We also believe that housing the adults in the nursery will help the weanlings and other non-fostered infants learn appropriate monkey behavior so that they are more socially adept later in life. We are investigating this hypothesis.

In addition, we also plan to increase the amount and type of enrichment provided to the monkeys, particularly the singly housed animals. We plan to add more exercise options and cognitive enrichment. Cognitive enrichment can include "games" in which the subject uses a touchscreen computer to view images or control various aspects of their environment (such as whether or not music plays). We have applied for funding from OHSU to purchase a touchscreen computer that can be used as enrichment, to test its efficacy. Cognitive enrichment has not been empirically evaluated to the same degree as food based or other forms of enrichment, but it is thought to promote well-being by providing a sense of environmental control to subjects (e.g., Excluded by Requester

We will also work with the CMU and others to develop novel treatments for animals with behavior problems. Such treatments could involve novel pharmacological interventions, or novel enrichment strategies. For example, we recently found that positive reinforcement training can help reduce stereotypical behavior in some, but not all, rhesus macaques [Excluded by Requester] It is possible that there are different etiologies underlying stereotypy, each of which might respond to different treatment strategies. [Pending Support] Discovering novel treatments for behavior problems is also a goal of the Behavioral Management Consortium working group, and we will continue to collaborate with BMC members. We are currently collaborating with colleagues from three other NPRCs (2 of whom are BMC members) on a grant examining self-injurious behavior and alopecia in rhesus macaques. This collaboration has resulted in one published paper [In Press] We hope to expand upon our collaborations.

Finally, as indicated above, we will continue to develop and expand upon our research program to address psychological well-being issues. The addition of a postdoctoral fellow, and increasing the managerial role of the BSU manager will greatly aid in this aim. We will continue to collaborate with others from the ONPRC and the NIH Behavioral Management Consortium.

REFERENCES

Excluded by Requester

Program Director/Principal Investigator (Last, First, Middle): Robertson, Joseph E./Haigwood, Nancy L.

ANIMAL SERVICES-BEHAVIORAL SERVICES DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cent s)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Excluded by Requester	Staff Scientist 3	% Effort			Institutional Base Salary	28,095	8,710	36,805
	Sr Res Asst					19,123	6,693	25,816
	Postdoctoral Fellow					10,405	3,642	14,047
	Sr Res Asst					22,260	7,791	30,051
	Res Asst 2					17,038	6,815	23,853
	Mgr, Behavioral Svc					28,898	8,958	37,856
	Prog Tech 1					25,036	8,762	33,798
	Res Asst 2					21,500	7,525	29,024
To Be Named	Socialization Specialist	6.00				20,000	7,000	27,000
To Be Named	Res Asst 2	6.00				16,066	6,427	22,493
	SUBTOTALS →					208,421	72,323	280,744
CONSULTANT COSTS								
None Requested							0	0
EQUIPMENT *(Itemize)*								
None Requested								0
SUPPLIES *(Itemize by category)*								
Operating Supplies							2,604	
Cage Enrichment Devices							7,429	
							0	
								10,033
TRAVEL								
Domestic							2,590	2,590
INPATIENT CARE COSTS								
OUTPATIENT CARE COSTS								
ALTERATIONS AND RENOVATIONS *(itemized by category)*								
None Requested							0	0
OTHER EXPENSES *(Itemize by category)*								
Shipping							514	
Maintenance - Equipment							4,043	
Hosting Groups & Guests							147	
Miscellaneous Services							406	
Conference Registration							690	
Telecommunications							38	5,838

CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 299,205
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 299,205

ANIMAL SERVICES-BEHAVIORAL SERVICES
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	280,744	289,166	297,841	306,776	315,980
CONSULTANT COSTS	0	0	0	0	0
EQUIPMENT	0	0	0	0	0
SUPPLIES	10,033	10,334	10,644	10,963	11,292
TRAVEL	2,590	2,668	2,748	2,830	2,915
INPATIENTS CARE COSTS	0	0	0	0	0
OUTPATIENTS CARE COSTS	0	0	0	0	0
ALTERATIONS AND RENOVATIONS	0	0	0	0	0
OTHER EXPENSES	5,838	6,013	6,194	6,379	6,571
DIRECT CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	299,205	308,181	317,426	326,949	336,758
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	299,205	308,181	317,426	326,949	336,758
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					1,588,519

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

PERSONNEL

Unit Head, Nonhuman Primate Behaviorist and Staff Scientist 3 – Excluded by Requester % Effort % Effort Responsible for overseeing all activities of the unit which includes creating, reviewing and updating all guidelines, SOPs, reports and other documents including the ONPRC Behavioral Management Plan; creating and reviewing BSU budget management. In addition, responsible for overseeing research undertaken in the BSU, including the design, data collection, statistical analysis, and manuscript preparation of scientific studies pertaining to the behavior and well-being of captive NHPs.

Senior Research Assistant- Excluded by Requester % Effort . Responsible for forming and monitoring groups and pairs of NHPs, assessing behavior of NHPs and implementing treatment plans and interventions to modify and prevent abnormal behaviors, maintaining records, data entry, and communicating with investigative and clinical staff. Also, utilizes Positive Reinforcement Training (PRT for training NHPs to cooperate with husbandry and research procedures.

Research Assistan2 – Excluded by Requester % Effort Responsibilities include forming and monitoring pairs of NHPs, monitoring groups of NHPs, assessing behavior of NHPs and implementing treatment plans and interventions to modify and prevent abnormal behaviors, maintaining records, data entry, and communicating with investigative and clinical staff. Assists in the NHP training program, utilizing PRT to train NHPs to cooperate with husbandry and research procedures, and assists in the design and implementation of research devoted to NHP well-being.

Manager – Excluded by Requester % Effort Responsible for supervising the performance of the staff members in BSU, maintaining BSU records, interacting with PIs, attending study coordination meetings as the BSU representative, and training new DCM staff in macaque behavior and behavioral management. Assists in NHP group formations by assessing potential candidates, developing and evaluating strategies for keeping animals in groups and working closely with RFO and CMU staff to discuss the disposition of animals removed from groups. Performs behavioral assessments on caged animals and assists in the design and implementation of research devoted to behavioral management issues.

Senior Research Assistant – Excluded by Requester % Effort Income). Responsible for overseeing the NHP training program, including training monkeys (using predominantly PRT techniques), teaching technicians and others to train, maintaining training records, and working with investigative staff to develop appropriate training protocols. Also assists in the design and implementation of research devoted to PRT.

Program Technician 1- Excluded by Requester % Effort Income). Responsible for overseeing the environmental enrichment program, including ordering enrichment, developing new enrichment devices, ensuring that there is enough enrichment in each area, developing schedules for the provision of enrichment, and working with investigative staff to ensure enrichment needs are met. Also responsible for documenting and evaluating enrichment devices, and modifying as necessary; helps to form and monitor pairs of NHPs.

Senior Research Assistant:- Excluded by Requester % Effort Income). Responsibilities include forming and monitoring pairs of NHPs, assessing behavior of NHPs and implementing treatment plans and interventions to modify and prevent abnormal behaviors, maintaining records, data entry, and communicating with investigative and clinical staff. In addition, Provides research support to investigative staff, including temperament assessments and standardized behavioral observations.

Postdoctoral Fellow – Excluded by Requester % Effort Responsibilities include design and implementation of scientific studies pertaining to the behavior and well-being of captive NHPs and responsible for study design, data collection, entry and analysis, and writing manuscripts.

Senior Research Assistant - TBN: (12 calendar months effort: 6 ORIP, 6 Program Income). This is a new position designed to help facilitate the formation of pairs and small groups of NHPs. This position will be responsible for coordinating pair attempts among the other BSU staff. It will also be responsible for maintaining data on single housed animals and the reason for the housing (e.g., IACUC-approved protocols, behavioral exemptions, etc). The position will work closely with RFO staff to determine factors the feasibility and longevity of potential pairs, including cage availability, assignment status of the partners, etc. It will also assist in the design and implementation of research devoted to issues around social housing.

Research Assistant 2 - TBN: (12 calendar months effort: 6 ORIP, 6 Program Income). This existing position is responsible for providing behavioral management for group housed NHPs, including assessing and monitoring group dynamics, evaluating dominance hierarchies, and using PRT techniques to train NHPs. This position works closely with clinical and husbandry staff to determine disposition of animals in the group. This position also assists in the design and implementation of research devoted to NHP well-being.

SUPPLIES

Funding is requested to purchase supplies necessary to provide enrichment and other items necessary for the behavioral management of the NHPs.

- Operating Supplies include items such as new cage enrichment devices, including rawhide bones, paint rollers, and special enrichment items utilized for animals with behavioral issues. While the majority of the food items used as enrichment is supplied through the RFO budget, the BSU is responsible for items used for animals with behavioral issues. Operating supplies also include training supplies (e.g., clickers), stopwatches, video cameras for monitoring animals, tablets such as iPads for taking behavioral observations and binoculars for taking behavioral observations.

- Cage Enrichment Devices include items such as NHP cage toys, foraging and other devices, radios and televisions, and swings and other enrichment for our group housed animals.

TRAVEL:

Funds are requested to provide travel for Unit Head to one national or international meeting annually and manager or other senior technical personnel every other year. Funds are also requested to send newly hired personnel to appropriate training opportunities (such as the Primate Training and Enrichment Workshop)

OTHER EXPENSES

Funds are requested for:

- Shipping: These funds cover the shipping costs of enrichment items.

- Maintenance - Equipment: Includes items such as chain, PVC tubing, and other materials necessary for maintaining enrichment structures and devices.

- Hosting Groups & Guests: The BSU typically hosts 1-2 visitors each year, including scientists and staff from neighboring NPRCs. Modest funds are requested to provide lunch or dinner for these guests.

- Miscellaneous Services: Includes membership for organizations such as the American Society of Primatologists, the Animal Behavior Society and the International Society for Applied Ethology.

- Conference Registration: Registration costs for conferences including the annual conference of the American Society of Primatologists and the American Association of Laboratory Animal Science.

- Telecommunications: Funds are requested for long distance calls made by BSU staff to colleagues.

ANIMAL SERVICES: Behavioral Services Income Table

Last Funded Year (53)

Source	Funding (direct costs)
P51 base grant support	$231,684.29
Program income derived from P51 base grant	258,342.08
Other Sources	0
Total	$490,026.37

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$299,204.72
Program income derived from P51 base grant	301,404.72
Other Sources	0
Total	$600,609.44

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

Behavioral Services receives salary support and support for other expenditures from program income.

RESEARCH, EDUCATION, AND TRAINING SPECIFIC AIMS

The Research, Education, and Training Unit (RETU) is a newly formed unit that functions in an integrated and coordinated fashion with all other DCM units. RETU consolidates management of training and education for all ONPRC personnel involved in Animal Services, as well as research efforts within the Division of Comparative Medicine. The RETU objective is to support and optimize research support services and animal health and well-being through refinements and innovations from scientific discovery within the field of Comparative Medicine, and structured programs of continuing education, training, and informational resources for technical and professional staff. The veterinary residency and externship programs extend this goal beyond the bounds of practices within ONPRC to the national, or international, laboratory animal medicine and research community as a whole. The following specific aims are designed to contribute to that central objective.

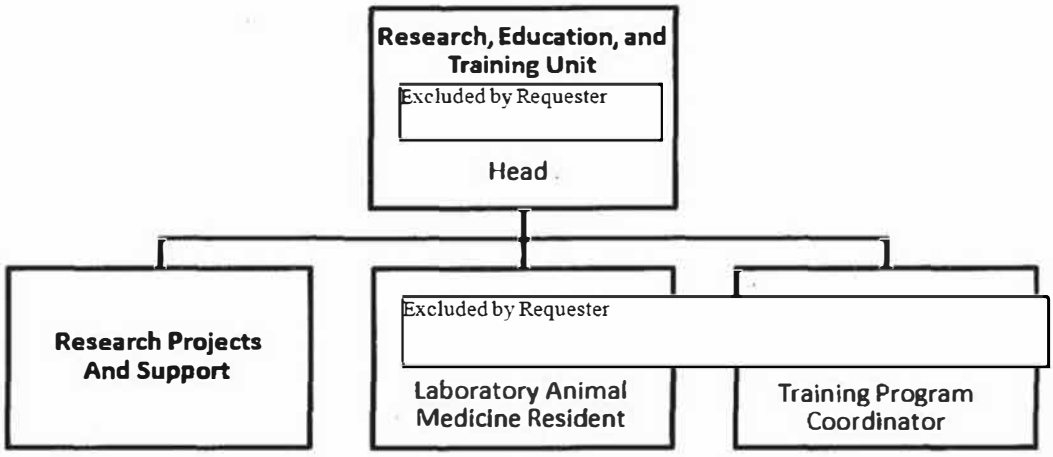
Specific Aim 1: Continually assess and refine the ACLAM-recognized residency training program in Laboratory Animal Medicine and Comparative Medicine research, including accepting additional residents every 1-2 years at ONPRC, as well as the veterinary externship program.

Specific Aim 2: Develop and continually refine programmatic training, continuing education, guidelines, and SOPs for new and existing technical and professional staff through optimal software, intranet, and web-based tools, and organizational structure.

Specific Aim 3: Provide administrative and collaborative research support as necessary to assist DCM veterinary faculty and staff in conducting and publishing research related to clinical medicine, surgery, pathology, or colony management issues of laboratory animals.

Specific Aim 4: Provide administrative and collaborative research support as necessary to the ONPRC Special Resources and other DCM units to promote and facilitate further phenotypic characterization of NHP models to optimize research utility, and clinical prognostication and management.

RESEARCH, EDUCATION, AND TRAINING RESEARCH STRATEGY.



SIGNIFICANCE.

The formation of the Research, Education, and Training Unit (RETU) occurred in August 2012 and was part of other reorganization within the Division of Comparative Medicine. RETU supports the DCM mission by operating in an integrated and coordinated fashion with all other DCM units, consolidating administrative support and management of training and education for all ONPRC personnel involved in Animal Services, as well as research efforts within the Division of Comparative Medicine. The rationale for this consolidation was a response to both internal review, and previous core grant critique. The anticipated outcomes are: 1) improved consistency and refinement of continuing education and training across units; 2) optimized academic and administrative support and management for the nascent ACLAM-recognized laboratory animal medicine residency program, which also provides important training infrastructure for DCM veterinarians pursuing ACLAM board certification and; 3) optimized administrative and research support for scientific projects and subsequent publication by DCM veterinary faculty and staff.

INNOVATION.

Training for all ONPRC personnel involved in animal care or use includes components as delineated in 9 CFR, Part 2, Subpart C, Section 2.32(c) of the Animal Welfare Regulations, with the Research Integrity Officer (RIO) and Attending Veterinarian (AV) overseeing all training. The RETU additionally oversees, administers, coordinates, and manages training, working interactively with the RIO, AV, Environmental Health and Radiation Safety (EHRS) and DCM Unit Heads and managers to determine training objectives and standards for the respective units and ONPRC as a whole. This centralized but integrated organizational structure is an innovative approach that aims to improve consistency and refinement. Records for training have been maintained and managed on the Training Database on IRIS, which is the current electronic health records (EHR) system. ONPRC will be transitioning to LabKey as a more dynamic EHR system beginning the first quarter of 2013. Another innovation involves significantly extending the functionality for training by investing in Moodle, an open source Learning Management System (LMS) software package which will support content creation, administration, documentation, tracking, and reporting. This will be a significant improvement from the current IRIS Training Database, which only supports tracking. Information Services (IS) will integrate Moodle into the ONPRC SharePoint infrastructure, allowing seamless communication with LabKey. Centralizing administrative and research support for scholarly activities of faculty and staff within DCM is considered another innovative organizational approach. In addition, the strategic decision to implement an ACLAM-recognized residency training program at ONPRC through a consortium partnership with the OHSU Central campus and the Oregon State University College of Veterinary Medicine, in addition to several other ancillary research facilities, is innovative. This arrangement will provide an enormous breadth of experience to residents in various laboratory animal species, clinical and experimental techniques, and veterinary and scientific expertise. DCM veterinarians pursuing ACLAM board certification will also benefit tremendously from this infrastructure.

APPROACH.

Personnel

Unit Head, ONPRC Assistant Associate Director, Associate Professor of Comparative Medicine – Excluded by Requester has been at ONPRC in his current position since August 2011, and has 9 years experience in nonhuman primate and comparative medicine, and is Personal Info 2013. He completed the ACLAM-recognized training program in Comparative Medicine and his PhD in Molecular Pathology at Wake Forest University (WFU) School of Medicine and Primate Center in 2008 and 2009 respectively. He previously worked as a Research Fellow and the Staff Veterinarian for the WFU School of Medicine main campus from 2008-2011, which included extensive participation in the residency training program. He reports to Excluded by Requester and is responsible for sharing, assisting, and acting as his proxy when needed, in the duties related to regulatory and administrative oversight of the animal resource, and the professional and technical DCM staff supporting the ONPRC. He is alternate for Excluded by Requester and regularly attends and participates in both ONPRC and OHSU Central Campus IACUC meetings and protocol reviews. He is also a member of the cross campus IACUC Leadership Team (ILT) and the OHSU IACUC Advisory Committee (OIAC) which discusses regulatory issues and generates OHSU Policy. As Head of the RETU, Dr. Excluded is responsible for coordination and management of two main areas: 1) education and training of all DCM faculty and staff, including the new ACLAM-recognized Oregon State Laboratory Animal Medicine Residency Consortium program under the oversight of Excluded by Requester for the ONPRC campus and; 2) conducting, and facilitating through administrative support and collaboration, research by DCM veterinarians in pursuit of refinement and innovation of best practices within the field of Comparative Medicine.

Training Program Coordinator - Excluded by Requester has worked in DCM for 10 years and was promoted to the newly created training coordinator position in 2012, which was more recently moved under RETU. His responsibilities include creating and managing training modules including but not limited to: creation of content in close coordination with other DCM unit heads and managers; administering and delegating online and in-person training; entry of trainer and trainee tracking through ONPRC's training database; onboarding new DCM and research staff and; oversight of training compliance. He maintains an understanding, with input and oversight from Excluded by of occupational health, animal health and well being, AAALAC, IACUC, ONPRC, OHSU, and state and federal guidelines. He also acts as a liaison, in addition to Excluded by Requester between DCM and the ONPRC RIO, EHRS, investigative staff, Administration, and Human Resources. Additionally, he measures efficacy of training methods through internal audits, surveys, and direct observations, and directly supervises the Training Lead.

Veterinary Research Technician-3 Training Lead - Excluded by Requester has worked in DCM for 11 years and was promoted to the newly created training lead position in 2012, which was more recently moved under RETU. Her responsibilities include training DCM and research staff, assisting with on-boarding new employees, maintaining training compliance of current staff, and playing a key role in creating and refining SOPs and Guidelines, as directed by the Training Program Coordinator. She's also responsible for providing research support, health care and husbandry for laboratory animals at ONPRC, and coordinating tasks to meet investigator, clinical and operational needs. These responsibilities require strong leadership and knowledge base in DCM functions and training. She maintains proficiency of manual and technical skills directly related to research support and animal care requiring regular professional contact with investigative staff.

Laboratory Animal Medicine Resident – Excluded by Requester is the first resident of the newly formed ACLAM-recognized residency program at ONPRC which is a consortium with Oregon State University College of Veterinary Medicine, and the OHSU Central campus. The residency is three years with the first two involving intensive rotations in clinical medicine, surgery, and pathology, as well as additional involvement in behavior, operations, regulatory compliance, journal review, didactic coursework and, planning and starting a research project in collaboration with an ONPRC staff scientist. Excluded by Requester provides essential assistance in managing clinical and surgical cases during the first two years. Her third year will be dedicated to finishing her research project, which will be expected to eventuate in a first-authorship publication in a peer-reviewed scientific journal.

Laboratory Animal Medicine Residents 2013-1018 – To Be Named: New residents expected to be recruited 1-2 per year. Structure of future residents' responsibilities will be identical to [Excluded by Requester] subject to minor refinements as individual and residency needs are continually assessed. In addition to the valuable role the residency program provides in training new veterinarians in primate and comparative medicine and providing an academic infrastructure for continuing education and ACLAM board preparation for faculty veterinarians, LAM Residents provide essential assistance with an ever-increasing clinical caseload, as well as surgical cases secondarily.

reviewers' comments

Pages 655-658 (Reviewers' comments) Removed

reviewers' comments

Progress – Training and Continuing Education (CE)

Specific Aim 2: Develop and continually refine programmatic training, continuing education, guidelines, and SOPs for new and existing technical and professional staff through optimal software, intranet, and web-based tools, and organizational structure.

Training for all ONPRC personnel involved in animal care or use includes components as delineated in 9 CFR, Part 2, Subpart C, Section 2.32(c) of the Animal Welfare Regulations, with the Research Integrity Officer (RIO) and Attending Veterinarian (AV) overseeing all training. The RETU additionally oversees, administers, coordinates, and manages training, working interactively with the RIO, AV, Environmental Health and Radiation Safety (EHRS) and DCM Unit Heads and managers to determine accurate training and proficiency objectives as well as compose SOPs, Policies, Guidelines and on-line and in-person training modules (**Figure 1**) to establish optimal standards for the respective units and ONPRC as a whole. The Training Program Coordinator (TPC) is responsible for managing and coordination of DCM authorship of SOPs by the individuals with the respective expertise; RETU proofs SOPs for readability prior to sending to Dr. Taylor for approval, and subsequently submits to IACUC for SOPs directly related to animal handling and care. The TPC additionally manages inventory of the original signed SOPs in addition to scanned copies. This centralized but integrated organizational structure is an innovative approach that aims to improve consistency, refinement, compliance, and recordkeeping. Administration of training modules (both online and in-person) is either done or delegated by the TPC, or by the respective DCM Unit in some cases of more specialized training such as surgery. Several other technicians in DCM who have demonstrated proficiency in a certain area(s) and completed the Trainer training module, are qualified to conduct certain training modules. The TPC and the Training Lead are responsible for overseeing and sanctioning trainers. Regardless of who administers training, the TPC manages and tracks information about employee completion and progress of training and disseminates that information to the ONPRC Research Integrity Office for compliance purposes, as well as appropriate Unit Heads; there is reciprocal communication from the RIO and DCM Units to the TPC (**Figure 1**). Records for training have been maintained and managed on the Training Database on IRIS, which is the current electronic health records (EHR) system. ONPRC will be transitioning to LabKey as a more dynamic EHR system beginning the first quarter of 2013. RETU is currently coordinating with IS, RIO, and EHRS to significantly extend functionality for training by investing in Moodle, an open source Learning Management System (LMS) software package which will support content creation, administration, documentation, tracking, and reporting for training (**Figure 1**). This will be a significant improvement from the current IRIS Training Database, which only supports tracking. Information Services (IS) will integrate Moodle into the ONPRC SharePoint infrastructure, allowing seamless communication with LabKey.

Once the LMS is operational, which is expected before the first quarter of 2013, it is expected that workflow will be considerably enhanced. **Figure 1** outlines this workflow as it is envisioned with an operational LMS. This is essentially the same workflow that currently exists, with the exception that there are no automated notifications or enrollments, and is done by the TPC or by the respective units in communication with the TPC. Another exception is that communication regarding training is done directly by all involved parties, rather than having

any additional intranet communication tools. The latter are expected to augment, but certainly not replace direct communication. The five functionality components within each DCM Unit which interface with RETU are outlined in **Figure 1**:

- Standardized Documentation is an avenue for simple creation of set standards of document appearance, and design within DCM.
- Automatic & Manual Enrollment is the ability to automatically set trainings when specific predefined parameters are met.
- Automatic Notification of Upcoming Refresher Trainings is a system to track individual employee timelines, and provide training refreshers as outlined by Unit.
- Administrative and End User Interfaces refers to customizable access to each user based on position and responsibilities.
- Communication Hub refers to relaying information between TPC and RETU Unit Head with other DCM Units; LMS will augment this through enhanced communications intranet-based tools, including a centralized platform to discuss training, document development, and review training progress.

Onboarding New Employees

Training for new employees has been successful over the years and has included mandatory training prior to any animal contact in animal handling, husbandry, proper animal care and use, and biosafety for animal care technicians and staff. This is, once again, a coordinated effort with the RIO, HR, EHRS, and the respective DCM units to identify appropriate training according to the specific job description. It is expected that with the full implementation of an LMS, a matrix of required training per specific job title can be automated.

Specific CE Programs

Continuing education has been formalized for technical personnel who are encouraged to seek certification or advancement via participation in annual AALAS technician/technologist training courses. Each level of certification results in guaranteed pay increases. **Table 4** gives a breakdown of various certifications which are specifically facilitated through structured CE courses and wage incentives. Emerging Leaders and Leadership Foundations are each provided by Oregon Health and Science University central Human Resources and involve one day per week for eight weeks, designed to provide managers with a broad understanding of behaviors, tools, and resources needed to be successful in a leadership role at OHSU.

Table 4.

Certification	Number of technical staff
ALAT	43
LAT	42
LATg	27
RLATg	5
CMAR	2
Emerging Leaders	5
Leadership Foundation	>4
Surgical Research Specialist	4
Surgical Research Technician	1

General CE Programs

There are a variety of continuing education programs for professional veterinary faculty and staff, which do not have the specific focus of a certification or outcome but rather provide a general edification on a breadth of topics relevant to maintaining proficiency in the respective field. These include the CE program for veterinary technicians managed by Excluded by Requester with participation from all DCM veterinary faculty in the form of

weekly lectures, which qualifies as professional CE for technicians to maintain their licensure. For veterinary faculty, in addition to the lectures provided by the residency, there are Virtual Grand Rounds (VGR) and the Clinical and Surgical Working Group (CASTWG; initiated and managed by Excluded by Requester through the NPRC Consortium; ONPRC veterinarians participate in both through presentation and attendance. In addition, Dr. Excluded by Requester is the PI for the Clinical Training protocol (IS000002560).

The purpose of VGR is to contribute to, and take a leadership role in, promoting the exchange of clinical or operational case presentations of NHPs amongst NPRCs and other contributing institutions to foster a collegial and communicative environment amongst these institutions, and ultimately promote best practices. ONPRC faculty veterinarians and residents have consistently presented timely and important clinical and operational case presentations and broader topics at the VGR Seminar series. Presentations, attendance, and participation in discussion are expectations of the residency programs at ONPRC. In addition, faculty veterinarians are actively encouraged to present and often do; attendance and participation in consortium discussion is also expected. Excluded by Requester oversees the VGR component of consortium activities including scheduling and ensuring that residents and faculty have appropriate resources to gather, process, and present the material. In addition to providing exchange of information and promotion of best practices in general, VGR presentations also provide training and practice for residents and faculty alike in speaking to, and fielding questions from, a larger inter-institutional audience. Presentation topics have often progressed into poster presentations and papers submitted to peer-reviewed journals.

Excluded by Requester is the PI on the Clinical Training protocol (IS000002560) and its purpose is to utilize live animals to train veterinarians, veterinary technicians, residents, externs, and investigative staff. All animals used in this protocol are in transit to pathology for elective euthanasia generally due to unresponsive clinical conditions or poor clinical prognoses. Areas of training include various invasive to semi-invasive procedures, development of new techniques, refinement of techniques, and evaluation of new equipment. The primary audience is for those that require initial training on a procedure they have not previously performed, or no longer feel proficient for any reason. These training opportunities educate and improve the skill sets for performing procedures in support of research protocols. Development and perfection of invasive to semi-invasive procedures using non-survival animals reduces the likelihood of unintended outcomes among healthy protocol-assigned animals. The development of new procedures as well as the development of procedural refinements using these animals reduces the number of healthy animals that would otherwise be required for procedure development. List of currently covered procedures on this protocol: intubation, phlebotomy, cystocentesis, IV catheter, intraosseous catheter, suturing, tattooing, venous cutdown, skin flaps and grafts, central venous catheter, CSF collection, arthrocentesis, lymph node biopsy, bone marrow biopsy, tracheostomy, thoarcocentesis, nasogastric and esophagogastric tube placement, nasal-oxygen tube placement, chest tube placement, peritoneal lavage, hepatic biopsy, renal biopsy, gastric lavage, skin biopsy, epidural analgesia, nasal flush, peritoneal dialysis.

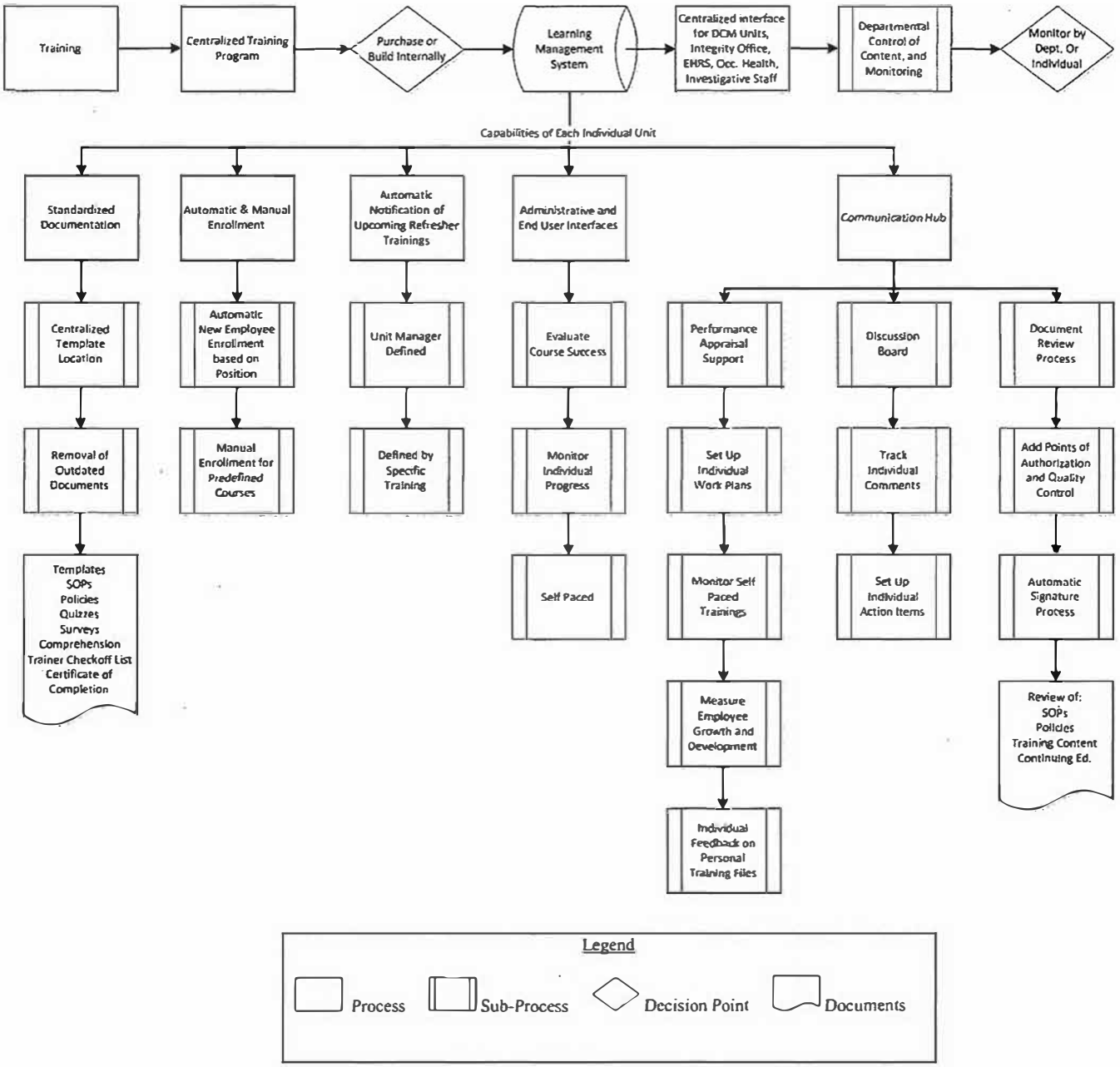


Figure 1. Organizational workflow for training within RETU and integration and communication with other DCM Units, and other components of ONPRC incorporating an LMS to automate and augment some current components.

Program Director/Principal Investigator (Last, First, Middle): Robertson, Joseph E./Haigwood, Nancy L.

ANIMAL SERVICES-RESEARCH, EDUCATION & TRAINING DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested (omit cents) for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Excluded by Requester	Asst Assoc Director	% Effort			Institutional Base Salary	68,900	17,225	86,125
	LAM Resident					20,810	7,283	28,093
	Training Program Coord					27,950	9,783	37,733
	Training Lead/VRHT 3					22,037	7,713	29,750
To Be Named	LAM Resident	6.00				20,810	7,283	28,093
	SUBTOTALS →					160,507	49,287	209,794

CONSULTANT COSTS		
SOP Development Consultant	4,000	4,000
EQUIPMENT *(Itemize)*		
None Requested	0	0
SUPPLIES *(Itemize by category)*		
Minor Equipment	2,622	
Training Materials & Supplies	991	
Operating Supplies	250	
		3,863
TRAVEL		
None Requested		0
INPATIENT CARE COSTS		
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		
None Requested		0
OTHER EXPENSES *(Itemize by category)*		
Conference Registration	6,100	
ACLAM Test & Application Fees	800	
LMS Server & Maintenance	500	
Membership in Profesnl Org	325	
		7,725
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 225,382
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 225,382

ANIMAL SERVICES-RESEARCH, EDUCATION & TRAINING
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	209,794	216,088	222,571	229,248	236,125
CONSULTANT COSTS	4,000	4,120	4,244	4,371	4,502
EQUIPMENT	0	0	0	0	0
SUPPLIES	3,863	3,979	4,098	4,221	4,348
TRAVEL	0	0	0	0	0
INPATIENTS CARE COSTS	0	0	0	0	0
OUTPATIENTS CARE COSTS	0	0	0	0	0
ALTERATIONS AND RENOVATIONS	0	0	0	0	0
OTHER EXPENSES	7,725	7,957	8,195	8,441	8,695
DIRECT CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	225,382	232,144	239,108	246,281	253,670
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	225,382	232,144	239,108	246,281	253,670
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					1,196,585

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

PERSONNEL

Unit Head, DCM Assistant Associate Director – Excluded by Requester % Effort % Effort Responsible for sharing, assisting, and acting as back up to Division Chief when needed, in the duties related to regulatory and administrative oversight of the animal resource, and the professional and technical DCM staff, regularly attends and participates in the IACUC, is a member of the cross campus IACUC Leadership Committee (ILC) and the OHSU IACUC Advisory Committee (OIAC). Responsible for coordination and management of two main areas: 1) conducting, and facilitating through administrative support and collaboration, research by DCM veterinarians in pursuit of refinement and innovation of best practices within the field of Comparative Medicine, and 2) overseeing centralized resource management for professional education and training of all DCM staff, including the new ACLAM-recognized Oregon State Laboratory Animal Medicine Residency Consortium program.

Laboratory Animal Medicine Resident – Excluded by Requester % Effort Income). Excluded by Requester is the first resident of the newly formed ACLAM-recognized residency program which is a consortium including ONPRC, Oregon State University College of Veterinary Medicine, and OHSU. The residency is three years with the first two involving intensive rotations in clinical medicine, surgery, and pathology, as well as additional involvement in behavior, operations, regulatory compliance, journal review, didactic coursework and, planning and starting a research project in collaboration with an ONPRC staff scientist. Excluded by Requester provides essential assistance in managing clinical and surgical cases during the first two years. The third year will be dedicated to finishing a research project, which will be expected to eventuate in a first-authorship publication in a peer-reviewed scientific journal.

Training Program Coordinator - Excluded by Requester % Effort Income). Responsibilities include creating and managing training modules including but not limited to: creation of content in close coordination with other DCM unit heads and managers, administering and delegating online and in-person training, entry of trainer and trainee tracking through ONPRC's training database, onboarding new DCM and research staff, and oversight of training compliance. Also acts as a liaison between DCM and ONPRC Compliance Officer, EHRS, investigative staff, Administration, and Human Resources. Additionally measures efficacy of training methods through internal audits, surveys, and direct observations.

Veterinary Research Technician-3 Training Lead - Excluded by Requester % Effort % Effort Responsibilities include training DCM and research staff, assisting with on-boarding new employees, and maintaining training compliance of current staff. Also responsible for providing research support, health care and husbandry for laboratory animals, coordinating tasks to meet investigator, clinical and operational needs while demonstrating strong leadership, and knowledge base in DCM functions and training. Maintains proficiency of manual and technical tasks directly related to research support and animal care requiring regular professional contact with investigative staff and plays key role in creating and refining SOPs and guidelines, and both online and in-person training modules.

Laboratory Animal Medicine Residents 2013-1018 – To Be Named: (12 calendar months effort, 6 ORIP, 6 Program Income). Structure of future residents' responsibilities will be identical to Excluded by In addition to the valuable role the ONPRC LAM residency program provides in training new veterinarians in primate and comparative medicine and providing an academic infrastructure for continuing education and ACLAM board preparation for faculty veterinarians, LAM Residents provide tangible essential assistance with an ever-increasing clinical caseload, as well as surgical cases secondarily. Alternative extramural funding will be sought to fund residency positions when possible. In order to be competitive for such grant applications, funding sources generally evaluate programs based on consistency and number of residents successfully completing the program.

CONSULTANT COSTS

SOP Development Consultant. Creating and managing Standard Operating Procedures (SOPs) is a critical component of optimizing occupational health, animal health and well-being, maintaining regulatory compliance, and training new and existing employees. Given that numerous individuals within DCM are needed to write

and refine SOPs according to the respective diverse areas of expertise, training is required to standardize approach to SOP writing to best practices. Funds are requested for an external consultant to conduct a two-day workshop on writing SOPs.

SUPPLIES

Funds are requested for:

- Minor Equipment.
  - Computers – laptop computers for [Excluded by Requester] in support of performing some portion of their job responsibilities from an external location when outside regular ONPRC operating hours. In addition, laptops are essential for providing didactic presentations in support of training and education. In addition, a desktop computer plus two monitors are requested for the new LAM resident each year.
  - Scanner and portable projector – projector for use in conference rooms without a projector, which is a common occurrence given that specific training must consistently be provided to individuals and small groups. Scanner needed to scan documents including but not limited to SOPs and Guidelines for backup and management purposes.

- Training Materials & Supplies. Specific training supplies, various AALAS books with accompanying CDs: ALAT, LAT, LATg , Management of Laboratory Animal Care and Use Program, Managing the Laboratory Animal Facility (2), CMAR Animal Resources Exam Kit, AALAS in a Flash. ACLAM core texts will be purchased as current versions become outdated.

- Office & Admin Supplies. Funding is requested for office supplies related to training and education as well as other material related to performance of RETU operational responsibilities.

OTHER EXPENSES

Funds are requested for:

- Conference Registration: Conferences and memberships attended include more extensive training workshops for LAM residents such the Charles River Short Course, and the NC State Workshop in Laboratory Animal Medicine. Others include but are not limited to the Association of Primate Veterinarians, and the AALAS National Meeting.
- ACLAM Test & Application Fees: The RETU centralizes educational and financial support of all DCM faculty veterinarians pursuing ACLAM board certification. Funds are requested for a test application fee and exam fee for two DVMs per year. In addition, the RETU plans to cover registration for two workshops specific to ACLAM board preparation for two faculty DVMs per year. Examples include the Charles River Short Course, and the NC State Laboratory Animal Medicine Workshop.
- LMS Server & Maintenance: Learning Management System (LMS) server and maintenance, using the open-source program Moodle. An LMS is required for computer and online-based creation, administering, tracking, and managing training within DCM and ONPRC as a whole. Fees are for server hosting, storage, and backup. $1000 per year. Estimations of cost of initial development of an LMS is based on extensive discussion with ONPRC Information Services, other vendors offering competing commercial products to open-source Moodle, and other institutions using LMS including the OHSU School of Nursing who chose another open-source LMS, Sakai. Funds are requested for costs relating to service and support, consulting, training, and any upgrade costs. In addition, estimated development costs are congruent with a 2010 eLearning Guild survey polling over 900 institutions utilizing an LMS.
- Membership in Professional Organizations: Membership in professional organizations and attendance of national conferences and workshops for RETU staff are essential for continuing education and certification. The RETU maintains an institutional membership to AALAS which allows access to key journals, JAALAS and Comparative Medicine, as well as allots four individual memberships for each member of the RETU.

ANIMAL SERVICES: Research, Education and Training Income Table

Last Funded Year (53) (New Unit – no prior funding comparison)

Source	Funding (direct costs)
P51 base grant support	$
Program income derived from P51 base grant	
Other Sources	
Total	$

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$225,382.16
Program income derived from P51 base grant	232,582.16
Other Sources	0
Total	$457,964.32

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

Research, Education and Training receives salary support and support for other expenditures from program income.

CLINICAL MEDICINE UNIT SPECIFIC AIMS

Non-human primates are critical animal models for basic and translational biomedical research. Enhancing the scientific utility, health, and well-being of these populations requires an integrated program of clinical care, animal husbandry, genetics, and psychological health. Working closely with other DCM units, CMU maintains animal health through preventative care and clinical care, ensuring the health and well-being of our research resources while supporting our breeding populations of genetically characterized, disease-free NHP's.

Our long term goal is efficient and humane management of ONPRC's NHP colonies using innovative techniques and procedures to identify, treat, and manage disease and abnormalities. To achieve this, the CMU must provide disease surveillance, diagnosis and treatment, work with ONPRC investigators to ensure experiments are well-planned and have clear scientific and humane endpoints, provide veterinary emergency care both during working hours and afterhours, and utilize a state-of-the art electronic health record system for documenting and managing animal care.

The specific aims for accomplishing this are:

Specific Aim 1. To provide preventative care and clinical care to ONPRC's laboratory animals through annual physical examinations, reproductive health monitoring, geriatric wellness programs, and weight management programs; and to provide rapid diagnosis and treatment of disease, illness, and injury.

Specific Aim 2. To provide clinical veterinary support for NHP related research, including technical assistance with protocol development, protocol review, animal model development, veterinary medical research, and resource management to optimize the NHP resource for current and future research use.

Specific Aim 3. To serve as a resource for educating pre- and post-graduate veterinarians, researchers, and technicians about clinical veterinary care and veterinary support of NHP research, including teaching, mentoring, collaborating, and presenting in local, national and international settings.

The expected outcomes are physically and psychologically healthy animals for support of biomedical research, and a population of disease free, genetically characterized NHP's sufficient to support current and future research needs. These outcomes support scientists who use NHPs, while ensuring the highest level of veterinary care for all NHP species at ONPRC.

CLINICAL MEDICINE UNIT RESEARCH STRATEGY.

SIGNIFICANCE.

Non-human primates are essential models for biomedical research. Only by using them are we able to discern the immunologic, molecular biologic, and biochemical pathways for developing and testing vaccines, elucidate key control and intervention points of the reproductive system, and define the neuroendocrine changes that drive obesity and substance abuse. A reliable source of disease free, genetically characterized animals provides investigators with a defined animal model for development and testing of cellular mechanisms, physiologic pathways, drugs, and vaccines. Restrictions on animal importation and the challenge of locating disease free animals of known phenotype emphasize the need of preserving and protecting the health and well-being of non-human primates currently in research settings.

A robust program of animal care is essential to maintain animal health and well-being and to ensure the highest quality animals are available for research. *The Clinical Medicine Unit provides veterinary clinical care, supports and educates the scientific staff in research protocol development and implementation, and educates the public and professionals on the humane care and use of our laboratory animals.* Through our program of wellness, research support, and education, we will continue to refine diagnostic and treatment modalities that maintain and enhance disease prevention and early intervention. We will ensure that research techniques are state of the art and maximize animal use while minimizing pain and discomfort. We will educate ourselves to the highest standards while educating the next generation of laboratory animal veterinarians.

INNOVATION.

The Clinical Medicine Unit (CMU) is committed to supporting biomedical research by continuously refining and improving clinical practices for NHP health, husbandry, and model characterization. The available literature regarding common ailments, best treatment practices, and appropriate diagnostic evaluation of captive NHP is sparse compared to companion or food animals, and much of NHP medicine remains an interpretation of human physiology and treatment or an inference from information garnered about other laboratory animal species. The impact of utilizing secondary rather than primary literature assumptions on the science involving our primates should not be underestimated. Our large, multivariate population allows many opportunities to explore relevant questions for basic NHP medical research that can be used to improve the care and utilization of this important species. Having a deeper understanding of our primary use species will benefit all who use NHP's in biomedical research.

The CMU seeks to contribute to primate medicine in a number of specific ways in the upcoming grant cycle. One way is defining the unique metabolic and clinical differences between a normal NHP population and research models who are obese, aged, or both. Another goal is to refine the macaque AIDS model by defining objective measures of end point criteria based on clinical and research data and collaborating with researchers to develop novel uses of the model, such as performing homologous stem cell transplantation to effect a cure for SIV infection. We will continue integrating relevant investigator data into our medical records and develop computer tools to more efficiently monitor the health of our protocol-assigned animals, particularly the SIV, aged and obese populations. We will increase collaboration with BSU and investigators to refine our psychological well-being to improve animal well-being. Collaborating with BSU and RFO, we will further refine techniques and equipment for facilitating humane, safe, un-sedated sample collection, and perform data analysis on common lab results from sedated vs. unsedated animals to determine the impact of common chemical restraints. Finally, we will continue to train our veterinary technicians in advanced procedures, so that we can support additional research protocols.

Expanding the depth of our knowledge about our primary species and specifically our primary animal models can only lead to a more nuanced understanding of disease processes, treatment capabilities, and other relevant biomedical research issues. Expanding the intertwining between research and clinical personnel improves the quality of protocols developed, improves the welfare and care of the animals used for protocols, and expands the knowledge of staff on both sides.

APPROACH.

reviewers' comments

Progress Report

The CMU provides veterinary care of animals within the Division of Comparative Medicine (DCM). The four unit veterinarians, one clinical manager, and twelve veterinary technicians work to collaboratively provide preventative and general veterinary care to both the breeding colony and research assigned animals, support

research protocol development and implementation, and provide training and education at ONPRC and nationally. The Head of CMU is responsible for unit leadership and administration, including developing, implementing and maintaining veterinary care and preventative medicine programs and provision of research support to the ONPRC scientific staff. Three assistant veterinarians provide clinical care, preventative medicine, and research support to the Neuroendocrine, Pathobiology, Reproductive, and Diabetes, Obesity, and Metabolic Disease Divisions. The Head of Colony Medicine, Informatics, and Epidemiology (CMIE) regularly interacts with the four unit veterinarians to streamline and align care for the SPF and non-SPF breeding population, and utilizes CMU technicians. This position is described in the Resources, Facilities, and Operations (RFO) component

The Manager of CMU oversees the daily veterinary care provided by 12 veterinary technicians and is responsible for supply and equipment ordering and inventory, unit budget, and the controlled drug inventory. Two Clinical Veterinary Technician lead personnel provide direct leadership of the veterinary technicians and are responsible for providing complex clinical and research procedure support. Ten Clinical Veterinary Technicians provide routine wellness care and perform manual and technical tasks directly related to the clinical support of laboratory animals. To ensure continuity and consistency, routine care and treatment procedures are outlined in either Standard Operating Procedures or Guidelines.

Excellent animal care is our core mission, and has produced many innovations including: increased focus on preventative medicine and well patient care; comprehensive care to ill or injured animals; and enhanced communication to ensure judicious use of animal resources. We now provide semi-annual preventative screening for the eSPF and SPF breeding colonies, NHP Aging Study, SIV, and obese animals, and annual preventative screening to all other animals. Chronic diseases are more aggressively screened for and, when identified, are actively managed through our dental care, weight management, and osteoarthritis programs. Aligning veterinary staff with particular research divisions and assigning IACUC protocol review to the associated division veterinarian has generated technique and procedural refinements.

Preventative Care. From 2009 through 2013, CMU provided veterinary care for an annual average of 4,200 NHPs. All NHP's in outdoor breeding colonies receive a semi-annual physical examination. Young, healthy, indoor housed animals receive an annual examination, while our geriatric animals and any animals with an active disease process receive a semi-annual physical examination. This screening allows us to identify and proactively manage clinical conditions such as weight gain or loss, musculoskeletal disease, reproductive abnormalities, and dental disease. A tailored management plan is developed for each clinical condition, and response is tracked and monitored using the IRIS electronic health record. Animals assigned to research protocols also receive regular examinations, including additional disease screening necessitated by the protocol. In year 50, approximately 5,400 physical examinations were performed. In each subsequent year, over 8,000 physical examinations were performed. This increase reflects increases in our population, and an increase in the number of animals assigned to protocols.

Breeding Colony. In addition to preventative care, the CMU provides clinical care and breeding support to our SPF, Indian origin rhesus population, the Japanese macaque colony, the Timed-Mated Breeding (TMB) Colony, and the expanded SPF (eSPF) colony. Prior to new group formation veterinary staff review the medical record of each animal to ensure any previously identified clinical issues have been resolved. This information is reviewed with the behavioral staff and the research staff prior to group formation. Ongoing CMU support of these groups includes wellness examinations, reproductive management, and clinical general care. Gestational age and fetal viability of animals in the TMB and eSPF colonies are regularly assessed with ultrasound. Occasionally, newborn infants in these groups are either rejected by dams or the dam's health precludes proper care. A foster team, consisting of specially trained behavioral and animal care staff and a veterinarian, assesses the infant's health and support needs. The infant is paired with a lactating female from the same or similar social group. If a lactating female is not available, the infant is fostered to one of our trained, non-lactating foster dams. This ensures all infants are reared by an adult, and avoids the maladaptive behaviors and chronic colitis associated with nursery rearing.

Veterinary Clinical Care: Increases in our NHP population over the last five years have resulted in increases in our clinical case load and has exposed some limitations of the IRIS *electronic health record*. Historically, codes from the Systematized Nomenclature of Medicine (SNOMED codes) were used to track clinical cases. Inconsistent uses of these codes presented significant challenges. For example, before consolidation in 2009, 63 different codes were used to classify diarrhea cases. A broad classification system titled "Master Problem" was developed in November 2009 to categorize cases by major body system. These changes have significantly enhanced our ability to track clinical cases by number and type. (Figure 1) Wounds and diarrhea remain the leading cause of clinical treatment. Adjusted for population size, the incidence of both has declined 8% over the past two years, primarily due to reductions in animal movement and refinements. in treatment protocols.

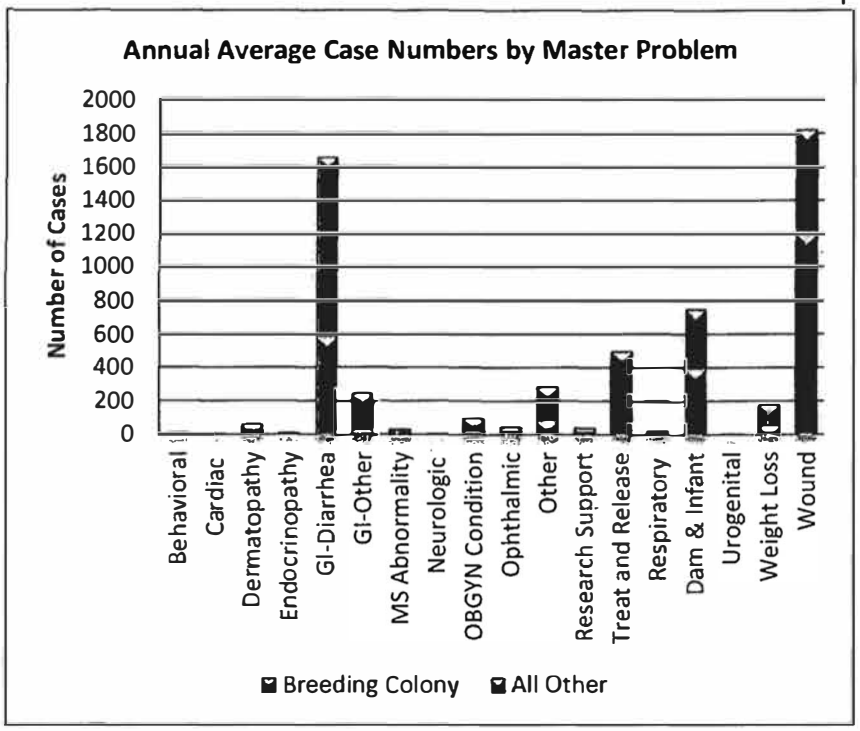


Figure 1: Annual average clinical cases displayed by Master Problem. Numbers represent case average from 01 January 2010 through 31 December 2012. The SPF breeding colony is displayed in blue and all other cases are displayed in red.

A new dental system, ultrasound unit, and digital radiograph were added to the campus in 2010, and use of these modalities has significantly enhanced our case management. The use of these diagnostic and treatment modalities continues to expand (Figure 2), as has our use of MRI and CT. Funding requested for the upcoming grant cycle would continue to expand CMU's technological capacity by adding a digital x-ray developer, advanced anesthetic monitoring capabilities throughout campus, and a portable ultrasound unit to better provide for high level diagnostic capabilities for all animals.

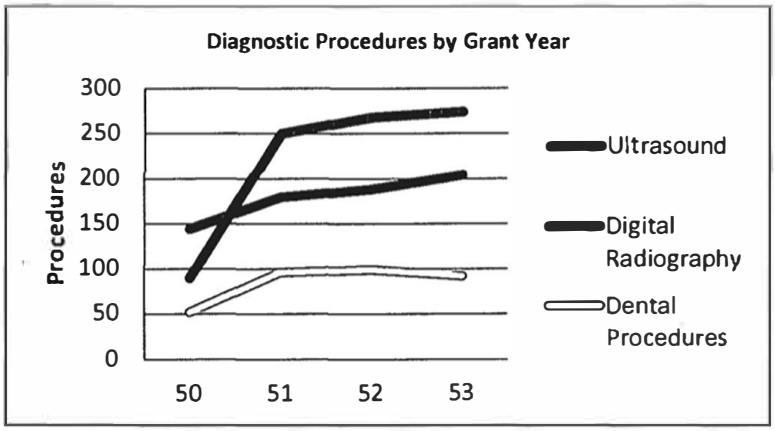


Figure 2: Number of ultrasounds, digital radiographs, and dental procedures by grant year, with year 53 estimated numbers.

Research Support: Veterinarians actively partner with research staff, developing project specific guidelines to ensure consistency for research models and humane care of assigned animals. The number of researchers supported, and total number of animals assigned increased throughout the grant period (Figure 3)

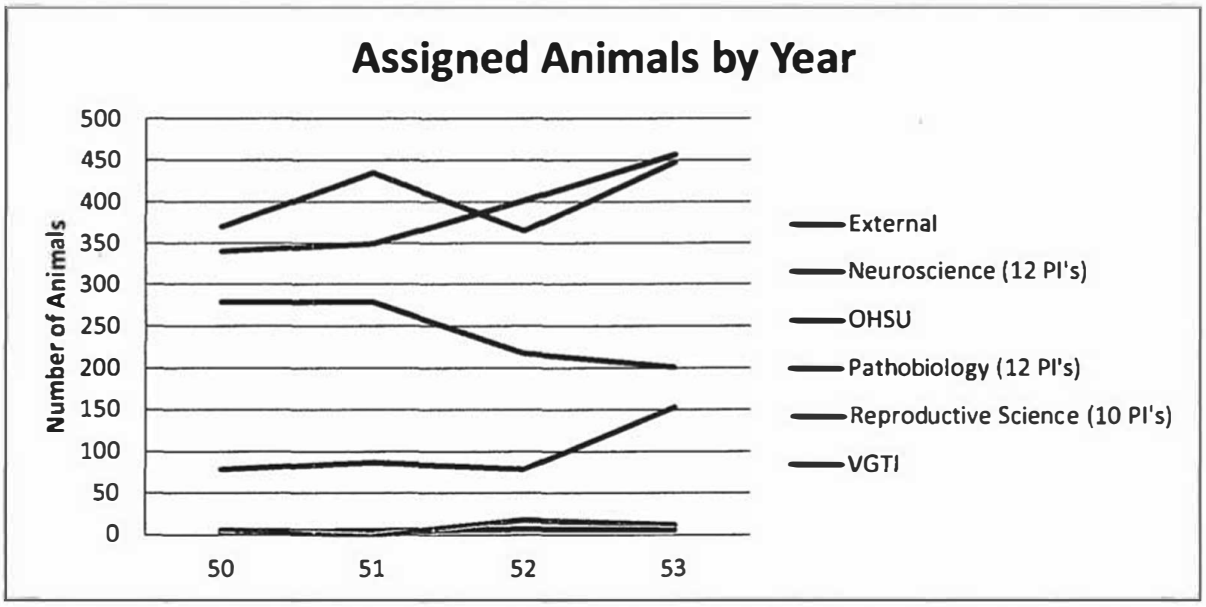


Figure 3: Animal assignments by grant year, including the number of PI's within each division. Year 53 numbers are estimated.

Unit veterinarians collaborate with investigators to ensure the highest animal welfare standards with minimal research disruption, to provide education regarding medication and treatment options, and to evaluate the potential impact of clinical issues or treatments on the research outcome. Additionally, veterinarians review research protocols prior to formal IACUC review to ensure animal well-being, optimal utilization of our NHP resources, and that medical treatment standards and monitoring are maintained. Support for protocol review and addendums increased significantly in year 51 and year 52 (Table 1), and is expected to increase in year 53.

Table 1. Number of Protocols and Addendums by Grant Year.
Year 54 is estimated through September 2012.

Protocols Reviewed	Year 50	Year 51	Year 52	Year 53 (to date)
New, annual, substantial revisions	144	163	106	37
Addendums	93	140	142	42

During this period, the complexity of protocols and the associated level of veterinary support increased. To support this, an additional assistant veterinarian position was added. Realignment of paraprofessional staff shifts and adding a night veterinary technician have enabled us to expand our routine veterinary clinical care program from eight hours daily to fourteen. Emergency and critical care support is available 24 hours a day. These changes have enhanced our human resource utilization, improved our veterinary care, and our increased our ability to support more complex research projects including staffing the neonatal intensive care unit.

Division of Diabetes, Obesity, and Metabolism. Excluded by Requester provides veterinary care and support to the Neuroendocrine Division. Excluded by Requester works closely with investigators during the protocol development phase, and proactively manages assigned animals to ensure both animal welfare and consistent research outcomes. In 2012 anesthetic protocols were reviewed and updated to include induction drugs, monitoring equipment and

parameters necessitated by obese patients. Post-surgical management, in coordination with SSU, of Roux-en-Y gastrojejunostomy patients was initiated in 2012. A subset of these animals developed vitamin and protein deficiencies caused by protocol related alterations in absorption. Early diagnosis of the condition and appropriate supportive care, nutritional supplementation and additional monitoring ensured the rapid recovery of all affected animals and the preservation of critical research information.

Key initiatives to improve the research potential and clinical monitoring of the obese population are the development of obese population laboratory reference ranges, metrics, and applications to better manage these resources. Enhanced monitoring of caloric intake of assigned animals and defined intervention points helped maintain research data integrity and obese research subject health, ensuring obese animals with unexplained or unsustainable declines in caloric consumption were rapidly identified, monitored, and treated. This will allow better definition of the metabolic changes that happen in obesity and weight loss. Additional integration of veterinary input and support into all phases of the protocol design from development through resource disposition will increase patient monitoring, research safety, and the ability to leverage the obese resources data into clinical publications supporting the expansion of primate medicine.

Neurology and Primate Aging Study: Screening of all older NHP on campus for identification and management of animals with either age induced or genetically induced retinal changes was initiated in 2009. Most animals eighteen and older undergo color fundus photography and optical coherence tomography. A subset of nineteen Japanese macaques with age related degeneration receive further quarterly retinal mapping by Adaptive Optics at the OHSU Casey Eye Institute. Consultation with ophthalmologists on the OHSU main campus resulted in further refinements to our screening process, diagnostics, and both clinical and research management programs.

The ONPRC has a unique population of Japanese macaques that are used in research on macular degeneration, Japanese macaque encephalomyelitis, and maternal obesity studies. While this population presents unique opportunities, it also presents challenges because of the lack of primary literature on the species, including clinical reference ranges for hematologic and serum chemistries. This project is currently in final phases. This will allow us to better support research protocols and clinically monitor and treat the population. Refinements to our understanding of Japanese macaque encephalomyelitis were initiated in 2010 with the formation of a working group composed of research scientists and clinical veterinary staff, resulting in development of a diagnostic protocol. This protocol has been used to screen and characterize the disease progression in nine animals since 2010 with the goal of developing a model representing aggressive human multiple sclerosis.

We have continued to refine our preventative care program for animals in the Primate Aging Study. In 2010, a concerted effort was made to place all unassigned geriatric animals in outdoor social groups. This senior group demonstrated improved muscle mass, increased mobility, and significant increases in activity within sixty days of outdoor assignment. Assigned animals presented a greater challenge, as many begin to develop secondary conditions including kyphosis and spontaneous type 2-diabetes. While many kyphosis patients responded well to glucosamine, NSAIDs, and increased exercise, the spontaneous type 2 diabetes patients responded poorly to traditional insulin management. These animals were trained to ambulate on a treadmill, and monitored to determine if exercise would improve glucose management. Initial results were encouraging, and emphasized the importance of starting this training earlier in life. The results were presented in a poster at the 2011 AALAS meeting.

Reproduction. Excluded by Requester provides veterinary care and research collaboration for the Division of Reproduction and Development (DRDS). The use of the cynomologus macaque as a reproductive model introduces unique challenges and opportunities due to the menstrual and breeding patterns that more closely mimic humans than those of the rhesus macaque. Excluded by Requester seven years of experience with this animal model will help to ensure the best outcomes for complex research protocols, and addresses a previous critique that DRDS lacked veterinarians with reproductive research experience.

Managing social housing of breeding animals is particularly complex for assigned animals. Determining standard approaches to ensure maximal social housing for breeder males, pregnant females, and juveniles will help ensure regulatory compliance, planning for animal's social needs, and the utilization of housing exemptions only when absolutely necessary. A plan is being developed to create a collaborative approach that ensures maximal social housing and animal safety without sacrificing research expediency and integrity (i.e. pairing or grouping of appropriate research subjects). During this upcoming grant cycle, the goal will be to develop a written baseline plan that can be inserted into most IACUC protocols, and adjusted where necessary for scientific integrity. Relevant to the issue of housing is the issue of premature infants, which pose both clinical and social housing challenges. A special care nursery was developed in 2011 to support these projects, and provides 24 hour advanced infant care, including enteral and parenteral nutrition, nasal oxygen, ventilator, and IV fluid therapy. To support normal social development, these infants, once stable, will be moved to the Nursery, and fostered to one of our trained foster dams.

Determining valid, measurable endpoints can be particularly complex in reproductive studies, particularly those utilizing pregnant females or neonates. Excluded by Requester has begun working with the DRDS PIs to better capture relevant specific indices of pain and distress in this vulnerable population. This will ensure an easier determination of regulatory compliance, and allow better assessment of specific animals in common or emerging situations. Development of standard criteria that can be fine-tuned as appropriate for each protocol, and updated using modifications when necessary is a primary goal of this research section during the upcoming grant cycle. A formal guideline describing General Endpoints for Protocols that represents the consensus of all ONPRC clinical DVMs was recently finalized and will help facilitate this goal.

Developing methods to obtain higher quality data at increased sampling intervals without requiring invasive techniques that in themselves may increase risk to the pregnancy or hormonal profiles is another goal for this unit. Collaboration with BSU may allow training to allow some data collection from unsedated animals, Excluded by Requester Excluded by Requester without a resultant increase in human or animal injuries or stress. The RFO is working to develop a restraint device that will allow greater animal manipulation than the current tower assemblage without compromising human or animal safety. Excluded by Requester An example of a recent step taken towards achieving higher quality data is the development of completed laboratory reference intervals for our cynomologus macaque population. A number of DRDS protocols require blood sampling of this population, and have previously relied on references ranges generated for rhesus macaques.

Division of Pathobiology and Immunology (DPI). Excluded by Requester support investigators in the DPI. This includes assisting with animal protocol development and implementation, clinical care for project-assigned animals, assistance in implementation of experiments, and refinement of NHPs as models of infectious diseases. Recent examples include improving the CT scan technique for a TB vaccine study, defining blood typing requirements for whole blood transfer in SIV studies, and selection of injection sites for a HIV vaccine study. Many DPI studies are terminal, and require clearly defined and humane endpoints. This represents an area of ongoing refinement, focusing on such quantifiable metrics as SIV viral loads, CMV viral loads, and CD4 T-cell counts.

Multiple infectious disease animal models are in used by DPI investigators, including simian immunodeficiency virus (SIV), simian varicella virus (SVV), rhesus cytomegalovirus (RhCMV), and *Mycobacterium tuberculosis*. The SIV-infected macaque model is the largest portion of infectious disease research, with 17 active protocols and between 100 to 200 SIV-infected animals assigned at any given time. This is the primary animal model of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) in humans and is utilized by DPI investigators to study the pathogenesis of lentivirus infection, viral immune evasion, and novel lentivirus treatment strategies, including antiretroviral therapy and vaccine development. SIV-infection is a chronic, often debilitating disease with sequelae ranging from mild reversible clinical signs to advanced simian acquired immunodeficiency syndrome (SAIDS). CMU veterinarians manage SIV infected animals using methods that do not conflict with the experimental protocol. For example, antiretroviral therapy, the cornerstone of human AIDS treatment, cannot be employed in these patients. This requires innovative alternative treatment strategies, including nutritional support, dermatitis treatment, and transfusion therapy.

Simian varicella virus (SVV), an analog to varicella zoster virus in humans, is being used to develop a shingles-like reactivation of virus that mimics human shingles. Immune suppression is induced using T-cell depletion and total body irradiation (TBI). Developing protocols to support these immunocompromised patients during and following treatment required close integration between investigators and veterinary staff. These protocols will also be used for future immune suppressive studies.

In addition to these models, new infectious models are being developed. A dedicated ABSL3 building was certified in 2011, and pilot projects have included *Francisella tularensis*, Yellow Fever virus, Chikungunya Virus, Simian Hemorrhagic Fever virus, Monkeypox virus, West Nile virus, and *Mycobacterium tuberculosis*. Input from the veterinarians was critical during the preparation period for each project for maintaining the well-being of the animals, as well as the safety of the investigators and DCM staff. The clinical veterinarians provide training for skill acquisition and maintenance, and, when appropriate, may also train investigative staff to perform simple procedures.

The CMU continually endeavors to improve its clinical practices to better serve the animals and the investigators in the Division of Pathobiology and Immunology. This includes improved clinical monitoring utilizing computer software and increased data sharing with investigators. Retrospective analysis of this data along with input from our veterinary pathologists will help develop more accurate diagnostic and prognostic indicators for the patients assigned to our infectious disease protocols. Excluded by Requester Excluded by Requester There is particular need for these studies to better understand the more common disease manifestations of SIV infection, including chronic diarrhea, weight loss, cholangiopathy, pneumonia, and lymphoma. Excluded by Requester We hope to improve our therapeutic strategies for these symptoms through increased collaboration with the Consortium.

Veterinary Technician support of Research Projects. CMU's certified veterinary technical team supports multiple aspects of animal care and research at ONPRC by providing technical procedural assistance to the research divisions in addition to providing primary care for ill or injured animals. Use of CMU's CVT team for these types of procedures began to be formalized in 2009, when it was clear that there was a demand for qualified procedural personnel beyond what the research staff was capable of realistically providing. After identifying and quantifying investigator needs, CMU paraprofessional staff was trained in multiple technical procedures, improving consistency and enhancing research outcomes associated with these procedures.

Efficient utilization of this qualified, educated human resource allows the researcher to focus on primary research aspects without compromising animal care by needing to learn multiple complex animal care procedures. This shift to veterinary staff performing complex procedures has reduced anesthetic and procedural complications, resulted in better NHP recovery post-procedure, and improved the quality of data from acquired samples. Additionally, almost all animal procedures within the ABSL3 facilities are performed by certified veterinary technicians, decreasing human health risks by restricting staff needing to enter this highly controlled area. Procedures commonly performed by veterinary technical staff include but are not limited to the imaging of animals using the MRI unit, CT imaging, bronchoalvelar lavage, bone marrow biopsy, lymph node biopsy, anesthetic support for complex research procedures (e.g. retinal imaging),and off campus transportation and sedation.

Costs for protocol driven (as opposed to clinically driven) procedures are funded by the individual research grants. A cost-per service for research support was implemented in Year 51. Procedures per grant year are shown in Figure 5, with revenue displayed in Table 2. Services include veterinary and technician time, lymph node biopsies, bronchioalveolar lavage, anesthesia monitoring and recovery, and critical care. A 10% annual growth rate is projected from Y53-Y58. As research protocols increase in complexity, an increase in demand for high quality technical assistance with animal procedures is also expected to increase, making this a projected growth area during the upcoming grant cycle. This type of support is expected to capitalize on the additional equipment requested (e.g. monitoring equipment, diagnostic equipment, and an additional anesthetic unit), by increasing and improving anesthetic capabilities and animal evaluation capabilities campus wide.

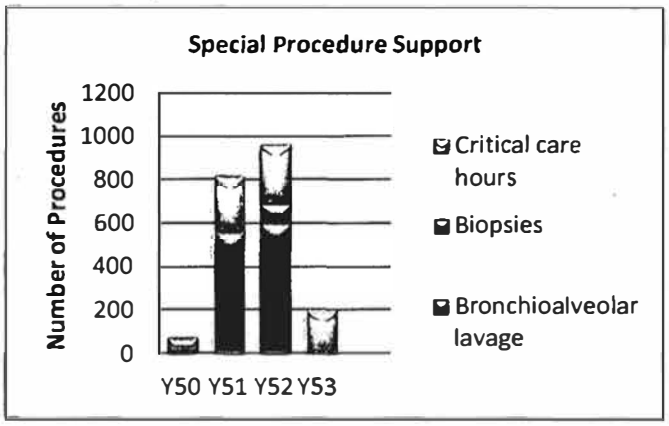


Figure 5: Number of biopsies, bronchioalveolar lavages, and critical hours provided by CMU technicians. Year 53 is through September, 2012

Table 2: Revenue and Service Utilization

Grant Year	Revenue	Pathobio	Repro	DOM	Neurology
Year 51	$59,202.20	3	4	1	4
Year 52	$72,623.41	4	2	1	4
Year 53*	$33,367.68	5	2	1	5

Year 53 numbers are through 1 1/01/12. The average procedure cost was $2.23 and the average procedure cost per PI was $28.99.

Outreach: Our educational and training programs have also expanded. A two year primate residency program began in 2009, and supported three residents each for two years. In collaboration with OHSU and OSU, we began an ACLAM approved residency in 2012. A veterinary internship program with the Oregon State University College of Veterinary Medicine was initiated in 2010 and annually provides training for 8-12 veterinary interns from OSU and other veterinary colleges. In 2011, the cooperative veterinary technician student training program was expanded to include Stanford Brown College in addition to PCC. A second cooperative program with PCC, for zoo keepers, was established in 2012.

Future Plans

Aim 1: To provide preventative care and clinical care to ONPRC's laboratory animals through annual physical examinations, reproductive health monitoring, geriatric wellness programs, and weight management programs; and provide rapid diagnosis and treatment of disease, illness, and injury. In support of this aim, our unit has close and continuous interaction between the service units within DCM, other service and research units at ONPRC and OHSU, as well as with other national primate research centers.

Areas of special emphasis for this funding cycle: Providing high quality, evidence based medicine is a primary aim of this department and an imperative in any animal research facility. The level of primary care provided directly impacts the welfare and health of our animals, and may have profound implications for the quality of the science for the research projects involving those animals. Illness and treatment introduce variability that can make data interpretation difficult or misleading. Confounding this, many of our clinical therapies are built on anecdote or interpretation from medical research in humans, companion, or other laboratory animal species. Expansion of science driven, evidence based approaches to breeding, husbandry, medical care, and population management will enhance both animal care and research quality. For example, recently we established in-house reference ranges for cynomologus macaques and Japanese macaques. Future projects include quantifying differences in CBC and serum chemistry values for our obese population, aged population, and a comparison of un-sedated animals to animals sedated using alternate sedation modalities.

Research Design and Specific Outcomes: To improve the level of primary care, treatment based SOPs and guidelines will be reviewed and updated annually. As much as possible, anecdotal treatment modalities are replaced with science driven, evidence based plans. Where multiple approaches are viable, the veterinarians will form a consensus about a tiered treatment plan, to better achieve consistency. This consistency should help both with practicalities such as technician clarity about preferred treatment plans, and enable us to perform better retrospective case analyses to create data sets for treatment modality evaluation. Collaboration with RETU ensures appropriate and timely training of all staff concurrent with issuance of updated or new SOPs and guidelines.

Establishing a formal collaborative relationship between BSU and CMU with the goal of reducing the incidence of self-injurious behavior that results in the premature euthanasia or restriction of project use of animals is another CMU goal. Modeling the RFO Colony Case Management Meeting, we now include clinical, BSU, RFO and research staffs in bi-monthly case management meetings for the eSPF breeding colony and the SIV study animals. Members collectively discuss cases, evaluate grouping potential, enrichment opportunities, and monitor for chronic health and psychological wellbeing issues.

A primary goal for the veterinary technician group is to continue to improve the efficiency of technical staff, specifically, decreasing the amount of time from request to completion of technical procedures. These procedures include routine and advanced dental care, blood collection, and non-urgent diagnostic procedures. Through innovative staffing, training, and efficiency revisions, this time can be appreciably decreased to an average of less than 3 business days over the upcoming grant period. Additionally, decreasing or eliminating situations where mis-dosing of animals by veterinary technicians (e.g. providing foods or medications not allowed by project) occurs to zero or near zero is an important goal in the near term. While the incidence of such occurrences is rare, the effects can be potentially devastating, and represent poor customer service to the PIs CMU serves. This goal can be met by introducing relative stability in responsible personnel for each project, utilizing available technology and communications mechanisms (e.g. signage etc.), and improving communication both between CMU and the labs and amongst members of CMU about relevant project issues.

Potential Problems and Alternative Strategies. In order for ONPRC to remain on the cutting edge of primate research, basic medical research in primate medicine is imperative. It is vital for researchers utilizing this important species to have a good understanding of normal when they develop their projects, and the veterinary staff is best equipped to pursue this aspect of research. Having a deeper understanding of our primary use species will benefit not just OHSU, but primate centers in specific and biomedical research in general.

Specific Aim 2: To provide clinical veterinary support for primate related research, including technical assistance with protocol development, protocol review, animal model development, veterinary medical research, and resource management to optimize the NHP resource for current and future research use. In support of this aim, CMU provides veterinary oversight and medical expertise to researchers utilizing nonhuman primates at ONPRC. Veterinary input and guidance in protocol development, procedural and treatment standards, individual animal care, pharmacokinetics, physiology, and the appropriate utilization of humane endpoints dramatically improves the quality of data gained from research using nonhuman primates.

Areas of special emphasis for this funding cycle: In support of this, the unit has established formal collaborative relationships with investigators in which CMU veterinarians are actively involved in project inception, development and implementation. A primary CMU goal is for these types of collaborations to result in veterinary authorship of three peer-reviewed publications over five years.

Research Design and Specific Outcomes.
Increased Monitoring of SIV-infected Animals: Refinement of the SIV animal model will be achieved through early detection and management of SIV-associated opportunistic infections and other AIDS defining conditions through increased frequency of routine health examinations and more thorough examinations using abdominal ultrasonography. Currently, physical examination of SIV-infected animals occurs on an annual basis until the animal shows clinical illness associated with the infection, at which time physical examinations occur semi-annually unless clinical indications exist to examine the animal more frequently. Additionally, abdominal ultrasonography occurs only when clinically indicated. We plan to perform physical examination and abdominal ultrasonography of SIV infected macaques every six months until abnormalities associated with lentivirus infection occur, then the animals will be examined quarterly. This change will refine the SIV animal model by detecting animals that meet animal protocol end point criteria as soon as possible, allow earlier management of SIV-associated morbidity, and will result in publishable data that will add to the paucity of literature describing abdominal ultrasonography of rhesus macaques, especially those infected with SIV.

Immunologic Correlates of Socially Housing SIV-infected Rhesus Macaques: We will leverage the existing knowledge of researchers within the Division of Pathobiology and Immunology to study the underlying mechanisms that contribute to an altered immune response to infection in rhesus macaques undergoing stress due to changes in social housing. While it is known that changes in social housing do result in differences in survival rates of SIV-infected rhesus macaques. Excluded by Requester The mechanisms underlying these differences remain unknown. We plan to collaborate with investigators within the Division of Pathobiology and Immunology and the Behavioral Services Unit to conduct both retrospective and prospective studies using existing reagents, assays, and animal models to assess altered immune responses to lentivirus infection between groups of macaques housed in various social groups.

Obese and Aging Resources: Literature regarding clinical prognostic indicators and measures of health and disease in NHPs is sparse, particularly with regard to aged or obese animals, which are models especially beneficial for human disease. The ONPRC is in a unique position to further define and refine the use of these NHP models and develop indicators of clinical health and disease. Better diagnostic and screening tests need to be developed for both clinical care and research validity. For example, minimal research into determining proper reference ranges for the obese and aged populations have been performed. Reference ranges for the Japanese macaques are non-existent in the literature. NHP with normal serum chemistry values can have severe renal or hepatic disease evident at necropsy. Reference information for some screening indicators such as Hba1c for diabetes have been performed, but not in conjunction with obese and aged resources. More specific diagnostics like reactive proteins, cardiac tropins, and genetic information are almost non-existent. Routine ultrasound screening of aging females may provide earlier diagnoses for common conditions such as endometriosis Excluded by Requester allow us to develop a reference range for normal measurements in this unique population (current literature is focused on younger breeding age females) Excluded by Requester may allow more specific resource management when assigning aged females to projects, and can potentially assist with more definitive diagnosis of female reproductive senescence. Further research into the utility, ranges, and predictive value of these and other markers of disease would greatly improve our ability to provide care for our NHP populations and refine our utilization of NHP as a research model.

Diarrhea management: The gut microbiome has been implicated in human research as a potential contributor for chronic diarrhea, inflammatory bowel disease (IBD), clostridial overgrowth, diabetes mellitus, and obesity. Currently there is one published paper on the NHP gut microbiome Excluded by Requester and numerous human papers showing possible uses of fecal microbial transplantation to help with obesity, IBD, clostridial overgrowth, and other problems that translate well to the NHP model and are major causes of morbidity in both our NHP colonies and human populations. Statistical models for the morbidity and mortality of diarrhea in our colony have recently been developed and submitted for publication. Excluded by Requester This information along with our expertise in obesity and diabetes, put ONPRC in an excellent position to not only develop the NHP as a microbiome model but to test clinical treatments and potentially reduce morbidity and mortality.

Specific Aim 3: To serve as a resource for educating pre- and post-graduate veterinarians, researchers, and technicians about clinical veterinary care and veterinary support of primate research, including teaching, mentoring, collaborating, and presenting at local, national and international settings. This aim focuses on education and training of our staff, and educational outreach to the broader community.

Education and Training areas of special emphasis for this funding cycle: Educational goals for CMU dovetail with the Research, Education and Training Unit (RETU) of the ONPRC. With RETU's assistance, CMU plans to continue to ensure the attainment of the highest level of AALAC certifications possible for all technical staff. As newer staff gains the experience levels required for higher certification levels, RETU will work with CMU to ensure that they are properly prepared to take and pass the certification tests. The goal for the upcoming grant period will be to have all technical staff at the highest attainable certification level within one year of eligibility. CMU's collaborative goal with RETU is to devise and document a formal training plan for all new technical staff that will ensure both a logical progression of skills and a more practical evaluation of skill set for both hiring and performance evaluation purposes. This program will consist of methods for objectively determining whether staff meets skill level expectations for each required procedure that reduces skill level differences between

staff, as well as a stepwise plan for acquiring skills that ensures necessary basic skills are attained prior to attempting more complex procedures. Documentation of completion of these training plans will make staff evaluations easier for managerial staff and for those participating in research or evaluating IACUC protocols.

CMU plays a critical role in the education and training provided to veterinary student externs and residents, as many of their educational rotations are done with CMU veterinarians working in the various research sectors. Schedules for externs and residents are coordinated through the RETU. Well planned rotations ensure students the most well rounded experience with regard to the medical challenges faced with varying research goals, as well as a chance to experience medical approaches from multiple veterinary viewpoints. A chance to observe and learn the complexities of the veterinarian/researcher collaborative relationship in person is essential for giving these students the skillset required to go on to be successful lab animal veterinarians themselves. Working with RETU, CMU aims to establish a formal detailed plan for the extern and resident rotations to ensure that the educational value for the student is as high as possible while maintaining unit efficiency.

Finally, collaboration between CMU and RETU will ensure the highest level of regulatory compliance. Regular SOP, guideline, and policy review are done in collaboration with the RETU unit. Evaluation of work processes and unit policies for adherence to AAALAC, IACUC, ONPRC, OHSU, and state and federal guidelines will involve CMU leadership working closely with RETU to make sure interpretations are consistent throughout ONPRC, and that learning opportunities that arise in other departments are capitalized on by CMU and vice versa. This team approach to regulatory compliance ensures superior quality research, and excellent medical care for our research.

Outreach areas of special emphasis for this funding cycle: The Clinical Medicine Unit carries a unique set of responsibilities with regard to public outreach and education. Clinical veterinarians are in a singular position to articulate the level of care given to research animals and put a human face to those who provide this quality service. Veterinarians are well suited to describe both the regulatory requirements and the practical approaches used at ONPRC to evaluate and ensure animal health and welfare, making them an approachable entity that connects well with the public.

Public outreach goals for the upcoming grant cycle involve increasing outreach and public education for both staff on site and the public at large provided by CMU staff. CMU vets will collaborate with PIs to produce and deliver presentations related to research projects, to educate the staff involved in the daily care of the animals about the content and the value of the research being conducted on site. This program's aim is to provide 4-6 CE programs yearly, and could potentially be incorporated in an already existing Technician CE program with DCM. Another goal is to increase the number of public outreach events attended by the veterinarians to at least 3 events per vet per year, and to have at least 3 outreach events attended by veterinary technicians. These goals can be accomplished by leveraging the relationships established by Diana Gordon, ONPRC Education Outreach Coordinator. Outreach provided from veterinarians involved in biomedical research can be particularly informative, as our primary mission is to balance the research objectives with the welfare of the animals involved in the research project. School events or other outreach opportunities attended by veterinary technicians that provide opportunity for interaction with kids may also be particularly impactful, as they provide students a chance to visualize career opportunities in research without graduate school requirements.

REFERENCES

Excluded by Requester

Program Director/Principal Investigator (Last, First, Middle): Robertson, Joseph E./Haigwood, Nancy L.

ANIMAL SERVICES-CLINICAL MEDICINE DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Excluded by Requester	Assoc Vet/Clin Med Head	% Effort			Institutional Base Salary	53,000	13,250	66,250
	Clin Vet Tech 2					19,810	6,934	26,744
	Clin Vet Tech 2					21,761	7,616	29,378
	Clin Vet Tech 2					20,780	7,273	28,053
	Clin Vet Tech 3					28,993	8,988	37,981
	Clin Vet Tech 2					17,710	6,199	23,909
	Asst Vet					42,400	13,144	55,544
	Clin Vet Tech 2					20,780	7,273	28,053
	Clin Vet Tech 2					21,232	7,431	28,664
	Mgr, Clin Med					29,947	9,283	39,230
	Clin Vet Tech 2					22,831	7,991	30,822
	Clin Vet Tech 2					12,556	4,395	16,951
	Asst Vet					43,460	13,473	56,933
	Clin Vet Tech 3					23,933	8,377	32,310
	Clin Vet Tech 1					16,459	6,583	23,042
	Clin Vet Tech 2					21,761	7,616	29,378
	Asst Vet					45,506	14,107	59,613
To Be Named	Asst Vet	6.00				45,000	13,950	58,950
To Be Named	Lab Aide	6.00				12,024	5,411	17,435
To Be Named	Clin Vet Tech 2/PENS	12.00				34,980	13,992	48,972
	SUBTOTALS →					554,925	183,286	738,210

CONSULTANT COSTS		
None Requested	0	0
EQUIPMENT *(Itemize)*		
None Requested	0	0
SUPPLIES *(Itemize by category)*		
Laboratory Supplies	39,607	
Pharmaceuticals	42,135	
		81,742
TRAVEL		
Domestic	2,400	2,400
INPATIENT CARE COSTS		
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		
None Requested		0
OTHER EXPENSES *(Itemize by category)*		
Conference Registration	1,000	
Laboratory Services	2,500	
Licences	450	
Maintenance & Repair -Equipment	10,300	
Registration/Course Fees	3,400	
Freight	180	
Books & Periodicals	410	
Bioengineering Service	546	18,786
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 841,138
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 841,138

PHS 398 (Rev. 6/09) **Form Page 4**

ANIMAL SERVICES-CLINICAL MEDICINE
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	738,210	760,357	783,167	806,662	830,862
CONSULTANT COSTS	0	0	0	0	0
EQUIPMENT	0	0	0	0	0
SUPPLIES	81,742	84,194	86,720	89,321	92,001
TRAVEL	2,400	2,472	2,546	2,623	2,701
INPATIENTS CARE COSTS	0	0	0	0	0
OUTPATIENTS CARE COSTS	0	0	0	0	0
ALTERATIONS AND RENOVATIONS	0	0	0	0	0
OTHER EXPENSES	18,786	19,350	19,930	20,528	21,144
DIRECT CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	841,138	866,372	892,363	919,134	946,708
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	841,138	866,372	892,363	919,134	946,708
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					4,465,715

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

PERSONNEL

Associate Veterinarian/Clinical Medicine Head – Excluded by Requester % Effort % Effort Responsible to provide unit administration and leadership, including developing, implementing and maintaining veterinary care and preventative medicine programs and provision of research support to the ONPRC scientific staff, provide clinical care for animals involved in DRDS protocols, as well as providing veterinary oversight for protocol development and refinement within the DRDS group.

Assistant Veterinarian – Excluded by Requester % Effort Responsible for providing clinical support for the NHP Neurology/DOM research units and mentors other members of the veterinary staff by providing instruction in both simple and sophisticated clinical procedures. Primary veterinary care includes: medical, preventative, and emergent care, management of breeding colonies and research animals, animal suitability assessments, allocation to research programs, IACUC protocol reviews, and research related support services.

Manager, Clinical Medicine Unit – Excluded by Requester % Effort Responsible for managing the veterinary technician team and providing clinical support for the animals in the Pathobiology research unit, providing administrative support for the CMU department including budget management, inventory, billing services, and purchasing, as well as oversight of the controlled substances program and providing regular outreach for future veterinary technicians through multiple local technician education programs.

Assistant Veterinarian – Excluded by Requester % Effort Responsible for providing clinical support for the NHP Pathobiology research unit and mentors other members of the veterinary staff by providing instruction in both simple and sophisticated clinical procedures including providing clinical care for animals involved in infectious disease protocols, providing veterinary pre-review of IACUC protocols involving infectious diseases, and working with investigators in establishing novel NHP animal models of infectious diseases, as well as refining established animal models.

Assistant Veterinarian – Excluded by Requester % Effort Provides clinical support for the NHP Pathobiology research unit and mentors other members of the veterinary staff by providing instruction in both simple and sophisticated clinical procedures including using various NHPs models including tissue transplants, vaccines, SIV, and other infectious diseases. Additionally, position is part of the management team for the expanded SPF colony, including investigating effective clinical therapies for chronic idiopathic diarrhea in macaques.

Clinical Vet Tech 3 – Excluded by Requester % Effort Income). – Responsible for providing hands on care for NHP both for clinical and research support, performing routine and complex procedures and sophisticated animal assessments. Lead technicians provide scheduling, day-to-day operations support, and mentoring duties for the other technicians of the unit.

Clinical Vet Tech 2 – Excluded by Requester Excluded by Requester and To be named % Effort % Effort Technicians provide hands on care for NHP both for clinical and research support, performing routine and complex procedures and sophisticated animal assessments. This midlevel position allows the experienced technicians to provide high level support for advanced animal procedures, and to serve as veterinary "eyes and ears" in emergency situations. All technicians have current CVTs, and are minimally ALAT certified, with most in this strata LAT and some LATg certified.

Clinical Vet Tech 1 – Excluded by Requester % Effort – Technician provide hands on care for NHP both for clinical and research support, performing routine and complex procedures and sophisticated animal assessments. This entry level technician position allows staff without prior NHP experience to become accomplished in routine activities. All technicians have current CVTs, and ALAT certification is expected within the required experience requirement time frame.

Assistant Veterinarian – To be named (12 calendar months effort: 6 ORIP, 6 Program Income). With the additional indoor animal housing and research focus expected over the next few years, additional veterinary staffing will be required to ensure the continuation of excellent animal care for all NHP on site. Current ratio is considered max for excellent animal care at ~500 NHP/clinical vet.

Lab Aide – To be named (12 calendar months effort: 6 ORIP, 6 Program Income). – This entry level departmental position performs multiple routine activities for the department, including medication preparation, cleaning, laundry, supply stocking, expiration date checks, and other entry level activities.

SUPPLIES

Funds are requested for:

- Laboratory Supplies to purchase the laboratory supplies necessary to provide appropriate veterinary care to the colonies of NHPs includes medical supplies such as injectable anesthetics, antibiotics, analgesics, anti-inflammatories, needles, syringes, blood collection tubes, catheters, intravenous fluids, fluid delivery devices, gauze, bandage material, radiographic film, radiographic tape, and radiographic cassettes, and other miscellaneous items utilized in daily veterinary care while dental supplies includes replacement instruments for dental packs (e.g., periosteal elevators, extracting forceps, manual scalers, periodontal probes, prophy angles, etc.), replacement PAPR hoods, and replacement disposable water circulating heating pads.
- Pharmaceuticals to purchase the pharmaceuticals required to provide appropriate veterinary care for ill or injured animals housed at the ONPRC.

TRAVEL

Funding is requested to support travel for continuing education opportunities. four veterinarians and 13 Certified Veterinary Technicians require annual continuing education to maintain licensure as required by job descriptions. Two domestic trips per year per veterinarian, plus funds for limited travel for the manager and technicians is needed to ensure continuous licensure/certification, up to date education, and to provide professional networking opportunities that ensure the ONPRC remains current and ahead of the curve with regard to industry standards, regulatory interpretation, and research opportunities.

OTHER EXENSES

Conference/Registration: Funding is requested to support professional memberships for veterinarians, including APV, AALAS, AVMA, etc. Memberships frequently result in lower costs for conference registrations or journal subscriptions.

Laboratory Services: Funding is requested to support lab services required to be sent to outside laboratories for processing. The ONPRC laboratory, while substantial, cannot realistically provide processing and interpretation for all possible samples, and medical diagnostics and animal care require occasional use of outside laboratories for uncommonly run samples.

Licenses: Funding is requested to ensure that all licenses and certifications required by job descriptions are kept up to date (DVM and CVT). Veterinary licenses are ~$150-200 per DVM, and Technician Licenses are $30 each starting 2013.

Maintenance & Repair – Equipment: Funding is requested to support maintenance and repair of equipment used by CMU, including $17,000/year for software maintenance of the digital radiography unit, one of the most frequently used pieces of equipment on campus.

Registration/Course Fees: Funding is requested to support continuing educational costs for 4 veterinarians and three certified veterinary technicians. Costs range from ~$50 for local technician CE to ~$1000 for ILAM, Charles River Short Course, etc. Average DVM CE fee is ~ $500-800 per conference.

Freight: Funding is requested to pay for shipping of required supplies.

Books and Periodicals: Funding is requested to ensure that adequate references are available for veterinarians and technicians providing clinical care for NHPs. An institutional membership to AALAS allows the department to receive JAALAS and Comp Med, journals that are the bedrock of the newest information in this industry.

Bioengineering: Funding is requested to ensure that to maintain the autoclaves and other such equipment required for sterilization of medical supplies used at ONPRC.

ANIMAL SERVICES: Clinical Medicine Income Table

Last Funded Year (53)

Source	Funding (direct costs)
P51 base grant support	$675,727.10
Program income derived from P51 base grant	675,727.10
Other Sources	0
Total	$1,351,454.20

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$841,137.79
Program income derived from P51 base grant	847,037.79
Other Sources	0
Total	$1,688,175.58

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

Clinical Medicine receives salary support and support for other expenditures from program income.

ANIMAL SERVICES: RESOURCES OBESE NHP RESOURCE SPECIFIC AIMS

The Obese NHP Resource is closely linked with the newly established Division of Diabetes, Obesity, and Metabolism, and exploits the macaque model of diet-induced obesity (DIO) developed at ONPRC to provide qualified internal and external investigators access to metabolically characterized animals and clinical samples for a variety of studies in metabolism, obesity, pre-diabetes, and co-morbidities. Through provision of the services and expertise supported by this Resource, it fulfills the mandate of the ONPRC to serve as a national resource for valuable NHP models. In furtherance of this goal, the Resource will pursue the following Specific Aims:

Specific Aim 1. Maintain a healthy and well-characterized DIO macaque colony. Since diet-induced obesity is a serious disease state, the animals become more susceptible to health complications when maintained on the Western-style diet used to produce weight gain. Therefore, the progression of disease state is accomplished through the quarterly measurement of body weight, adiposity (by DEXA), and glucose tolerance (through intravenous glucose tolerance tests and HbA1C determinations).

Specific Aim 2. Expansion of animal availability. There is an ever-expanding demand, both locally and nationally, for the macaque DIO model. Resource constraints will be addressed by targeting short-term studies supported by industry to maintain animals during phenotype development and the establishment of a cynomolgus DIO model.

Specific Aim 3. Increased collaboration with the ONPRC Primate Aging Resource. Most current ongoing studies using the Obese NHP Resource focus on early developmental programming or the young adult. However, one of the major challenges that clinicians will face in the future is the management of aging, obese patients. To address this issue, Obese Resource staff will cooperate with Aging Resource personnel to evaluate the metabolic status of aged animals as well as making older Obese Resource animals available for studies as they reach the appropriate age.

ANIMAL SERVICES: RESOURCES: OBESE NHP RESOURCE RESEARCH STRATEGY

SIGNIFICANCE

Obesity is a growing worldwide epidemic that increases the likelihood for many associated diseases, decreases the quantity as well as quality of life, and significantly increases medical care costs. In 2010, over 72 million adults in the U.S. were classified as obese, with nearly 2/3rd being classified as overweight and at risk for associated complications [1]. These associated complications primarily include type 2 diabetes (T2DM) and cardiovascular disease; however, obesity also increases the risk for cancer, immune/inflammatory diseases, dyslipidemia, stroke, liver disease, sleep apnea, infertility, and osteoarthritis. Together, these diseases and complications are referred to as metabolic diseases. While it is clear that the availability of highly palatable and calorically dense foods, as well as a decrease in activity levels, are major contributors to these diseases, genetics, early developmental programming, and even natural aging also significantly contribute to this epidemic. Besides the impact on human health and quality of life, these diseases also have a serious impact on our economy. Being obese raises a person's average annual medical costs by $2741. The total direct health care costs of obesity are estimated at $260 billion per year. The total annual costs of diabetes and obesity together in the US exceeds $500 billion, 30% of all medical costs [2]. Because of the broad health implications, the impact on the quality of life, and the financial costs, it is imperative that we gain a better understanding of the pathogenesis, treatment, and prevention of metabolic diseases.

To date, the majority of research investigating obesity and T2DM is performed in rodent models. However, there have been several issues with translating rodent findings to human pathophysiology, making the NHP a critical preclinical model for understanding disease mechanisms, as well as for the development of therapeutics. Furthermore, there are distinct differences between rodents and primates (human and nonhuman) in: 1) the ontogeny of the development of metabolic systems; 2) the cytoarchitecture of the pancreas, liver, gastrointestinal tract, and brain; 3) the regulation of energy expenditure; and 4) the progression of complications of metabolic diseases.

The macaque model of diet-induced obesity (DIO-NHP). While there have been various versions of obese and diabetic macaque models developed, our Center has chosen a DIO-NHP model. These animals are generated by chronically feeding adult macaques a palatable diet high in fats and calories, similar to the Western-Style diet (WSD). The DIO-NHP is one of the few models that develops the full spectrum of metabolic complications associated with obesity in humans, including similar inflammatory/immune responses, hyperlipidemia, and cardiovascular complications. Furthermore, the NHP has a similar developmental ontogeny, making them especially relevant for the investigation of the development of metabolic systems, as well as the developmental origins of adult diseases- commonly referred to as DOHAD.

INNOVATION

The goal of the Obese NHP Resource is to provide access of this powerful research model to the ONPRC/OHSU and national research community. Over the last 5 years, researchers using these models have made numerous significant findings and advancements that have direct health relevance to the obesity/diabetes epidemic in the US. Below are a few selected examples of significant advancements using this resource.

1) Developmental programming of psychiatric disorders: There are several investigators currently using the breeding colony of Japanese macaques that are maintained on either a standard chow or the WSD. This cohort models the impact of poor maternal nutrition and metabolic health on the risks for development of a wide variety of health complications in the offspring [3-12]. For example, Excluded by Requestor (Division of Diabetes, Obesity, and Metabolism) and colleagues have demonstrated that chronic consumption of the WSD during pregnancy, *independent of maternal obesity and insulin resistance*, increases anxiety [13] and autism-like behavior in the offspring. These studies have identified a new risk factor, chronic consumption of a diet high in saturated fat, for the development of psychiatric diseases in children. Excluded by Requestor has already developed collaborations with clinical investigators in the Department of Psychiatry at OHSU to further expand the behavioral testing protocols for the analysis of different psychological disorders. Importantly, they will be

combining these behavioral studies with various noninvasive imaging techniques, such as fMRI and PET. Using these powerful techniques and protocols will make this research immediately translatable to the clinic.

2) Development of bariatric surgery models: Using our well-characterized adult rhesus DIO-NHP model, Drs. Excluded by Requester;Private Source Boston, MA), Excluded by Excluded by Requester (University of Texas Southwestern, Dallas, TX) (Univ. Cincinnati, OH), and Excluded ONPRC) have developed an NHP model of Roux-en Y gastric bypass (RYGB). The protocol for this surgical procedure was taught to the ONPRC veterinarian surgeon, Dr. Excluded by Excluded by by highly experienced surgeons from Massachusetts General Hospital, ensuring the procedure was consistent with the human surgeries. Along with the surgical procedure, we also needed to develop a safe and stress-free recovery protocol for the animals. Amazingly, within 24 horus after the surgery, these animals are active, alert, and consuming small amounts of fluid nutrients.

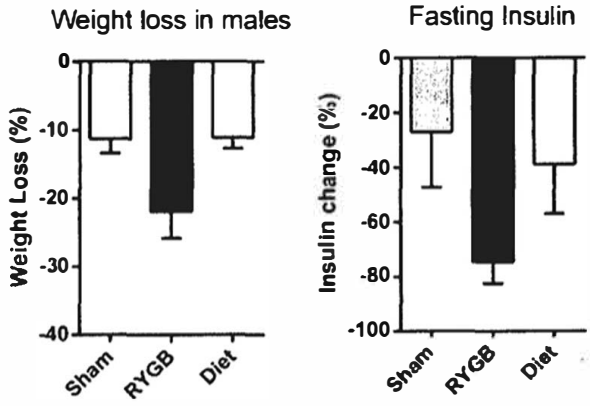


Figure 1. Weight loss and improve insulin levels in DIO Rhesus macaques unde rgoing RYGB, compared to sham-pair fed animals or in response to 50% caloric restriction (Diet). Sham- n=5, RYGB- n=6, Diet- n=20

To date, these investigators have performed this procedure on 15 animals with no major issues, and with survival out to 3 months (as designed in their approved NIH grant). These investigators have been able to demonstrate that, like in humans, RYGB can elicit significant weight loss and improved insulin sensitivity over three months (Figure 1). Interestingly, these improvements are more significant than achieved in sham pair-fed animals, or animals maintained on 50% caloric restriction for 3 months (Figure 1). Furthermore, RYGB also corrected diabetes in animals with complete diabetic phenotypes (not shown). These investigators are now performing an extensive integrated analysis of the metabolic and hormonal changes that occur in these animals, under carefully controlled conditions. This could lead to the discovery of novel targets or strategies for the treatment of obesity and diabetes.

3) Cardiovascular imaging: The Obese Resource has been collaborating with several investigators to develop new non-invasive imaging technologies and diagnostics. For example, Excluded by and Excluded by (Cardiology, OHSU) have been using the DIO-NHP model to characterize the progression of inflammation and plaque formation using noninvasive contrast-enhanced ultrasound (CEU) imaging ([14]. For this technique, radio-opaque microbubbles (the size of red blood cells) are injected into the animal and can be visualized with US, making them useful for microvascular reperfusion analysis. Furthermore, these microbubbles can be labeled with antibodies against inflammatory markers (Figure 2), allowing for the visualization and early detection of plaque formations in arteries. These studies will result in the development of advanced imaging techniques for the early detection of atherosclerosis. This technique and others being developed by Excluded by and colleagues, will be valuable as research tools as well as for clinical diagnostics. *For additional advanced imaging technologies see Research Strategy section for the Division of Diabetes, Obesity & Metabolism*

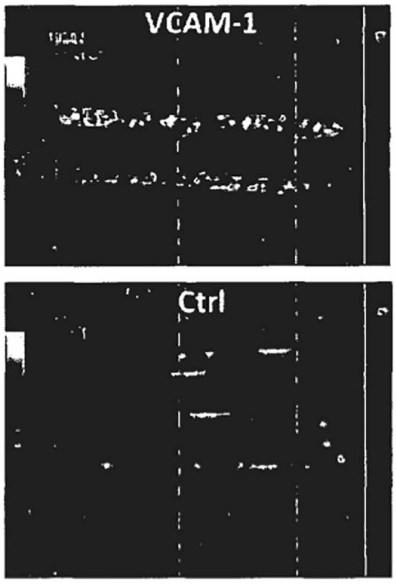


Figure 2. Examples of targeted CEU imaging of the common carotid artery of a macaque on HFD. Background-subtracted pseudo-color images are shown 5 min after injection of microbubbles conjugated with VCAM-1-antibody (top) or unconjugated (bottom). Animals on control diet showed no increase in with VCAM labeling over that observed with unconjugated micobubbles (not shown).

APPROACH.

reviewers' comments

Progress Report.

Currently, the Obese NHP Resource (OR) is maintaining 65 adult rhesus macaques, 32 adult cynomolgus macaques, and 71 adult Japanese macaques. Almost 100% of the animals in the OR have been used at some point over the past 3+ years for funded research projects. Currently, 100% of the offspring (approx. 30 offspring per year) from the DIO Japanese macaque colony are leased each year by NIH projects ($1.2M direct costs/year). During the last funding cycle, 12 independent investigators at 7 different universities have used these animals and/or tissue samples generated from these animals. One third of the adult DIO rhesus macaque animals are assigned to NIH-funded projects to investigators at ONPRC, as well as three external universities ($1.1M direct costs/year). Approximately 40% of the animals are assigned to long-term industry-sponsored research projects ($1.4M direct costs/year). Finally, two-thirds of the adult DIO cynomolgus animals are reserved for projects that will start in early 2013.

Cumulatively, during the last funding cycle, 32 independent investigators at 16 different universities/companies have used these animals and/or tissue samples generated from these animals, and/or OR personnel to assist in their funded projects (Table 1). Since 2009, research using this resource has also generated 25 peer-reviewed publications, with several more in submission. It is the primary goal of the OR to maintain sufficient well-characterized DIO macaques to meet the ever-expanding demands from the research community. However, this needs to be done under the constraints of limited animal space availability. Furthermore, it needs to be cost-effective, not only for ONPRC, but also for the end-users. We believe that we are currently meeting the majority of the needs of our research community, and providing good access to this valuable and powerful research model.

Table 1: Usage of Obese Resource animals, tissues and/or personne.

Investigator	Institute	Funding
Excluded by Requester	ONPRC	NIH, SRA
	ONPRC	NIH, SRA
	ONPRC	NIH, SRA
	ONPRC, Univ. Portland	NIH, OHSU
	ONPRC, OHSU	NIH
	ONPRC	NIH
	ONPRC	NIH, SRA
	OHSU	NIH
	OHSU	NIH
	OHSU	NIH, Private Source
	OHSU	OHSU
	OHSU	NIH
	Univ. Texas Southwestern	NIH
	Univ. Cincinnati	NIH
	Massachusetts General	NIH
	Vanderbilt	NIH
	Univ. Massachusetts	NIH
	Univ. Colorado, Denver	NIH
	Univ. Colorado, Denver	NIH
	Baylor	NIH
	Eli Lilly, U.S.A.	SRA
	Merck, U.S.A.	SRA
	Merck, U.S.A.	SRA
	Genentech, U.S.A.	SRA
	Ipsen, Rhythm Pharm., U.S.A.	SRA
	Regeneron, U.S.A.	SRA
	Johnson & Johnson, U.S.A.	SRA
	GUBRA, Copenhagen	NIH
	Novo Nordisk, Copenhagen	SRA
	Novo Nordisk, Copenhagen	SRA
	Novo Nordisk, Copenhagen	SRA
	Novo Nordisk, Copenhagen	SRA

NIH includes funding from NIDDK, NICHD, and NIHLBI; OHSU indicates funding from institutional pilot programs; Private Source SRA indicates sponsored research agreements. Private Source

Oversight Committee.

The OR has been heavily used over the last funding period by ONPRC, OHSU, and external scientists. Furthermore, there are limitations on the availability of animal space and support resources to maintain these animals, as well as limitations in the availability of animals that can be assigned to this program. Therefore, it is important to have a strong, consistent, and logical oversight committee to help manage the sustainability of this resource. ONPRC has an Animal Utilization Committee that consists of representatives from all of the Division (Scientific Divisions, DCM and the Business office). This committee makes all final decisions about animal use; however, this group relies on input from the oversight committees for the specialized animal resources. The two most critical functions of the OR oversight committee will be to 1) set the priorities for utilizing this valuable resource and 2) planning for the maintenance and expansion of this resource to meet the future needs of the users. These functions are critical for the long-term success of this resource. For this, it is important to note that it can take up to 2+ years to generate animals with the necessary metabolic phenotype needed for particular studies and these animals are very expensive to generate and maintain.

By mandate, the highest priority for the use of the OR is to support academic grants. However, when animals are available, it is important to also support sponsored research agreements for collaborations with

research groups from industry. These interactions are an important aspect of translational research. Furthermore, these Industry partnerships give ONPRC/OHSU investigators access to more advanced research tools and diagnostics. There are several factors that are taken into account for prioritizing use of animals in the OR, such as:

1. Multi-PI research consortiums make efficient use of these valuable animals, and are thus given a higher priority than single investigator studies. For example [Excluded by Requester] in collaboration with several investigators at ONPRC, OHSU, University of Colorado at Denver, and Baylor have several grants using the same animals generated from the Japanese Macaque breeding cohorts maintained chronically on a HFD (see animal models).
2. Length of study- studies supporting animals for longer periods of time are given a priority over short-term studies. This provides better sustainability of the resource. For example, study supporting an animal for 1 year is given priority over a study using an animal for 1 month.
3. Impact on animal status- Animals at ONPRC are categorized into three main categories- naive, protocol-restricted, and surgically restricted. Studies that do not change this status are given priority over studies that result in limitations to the use or termination of the animals. For studies that do require termination, the Obese Resource oversees the necropsy and banks all tissue not required by the study investigators. These tissues are then made available to the research community, for a fee, through a tissue bank. Since the animals become more fragile the longer they are maintained on the HFD, it is important to eventually perform terminal studies on the animals at points when the animals are still healthy enough to obtain informative endpoints. This also provides an opportunity to establish a new cohort of animals that then can be investigated through different stages of the metabolic complications.
4. Source of funding and cost recovery- NIH-funded projects are given priority over industry or foundation-supported studies. Funding sources that provide full indirect cost recovery are given priority over funding sources that have limits for indirect costs (i.e., some foundation grants). *It should be noted, that since this is a NIH-subsidized resource, that industry-sponsored studies are required to pay a higher rate for use of these studies to ensure full cost recovery.*

The oversight committee consists of faculty members from the Division of Diabetes, Obesity and Metabolism (ONPRC), DCM, and two faculty from OHSU. Currently the committee is made comprised of [Excluded by Requester] Ph.D. (Chair; Division Chief, Division of Diabetes, Obesity, & Metabolism), [Excluded by Requester] Ph.D. (Associate Director Research), [Excluded by Requester] Ph.D. (Associate Director of the Obese Resource and Staff Scientist, Division of Diabetes, Obesity, & Metabolism), [Excluded by Requester] (Professor, Department of Cardiology, OHSU), [Excluded by Requester] (Assistant Professor, Department of Cardiology, OHSU), [Excluded by Requester] Head, Resources, Facilities and Operations Unit [RFO], DCM), and [Excluded by Requester] attending veterinarian for the OR colony), [Excluded by Requester] and [Excluded by Requester] also sit in on the meetings, as they are the colony managers for the rhesus and cynomolgus macaque and the Japanese macaque breeding cohorts, respectively. A member of the ONPRC Business Office also attends these meetings to provide insight into cost structures for the use of this Resource. Because of the cost to generate and maintain these animals, the oversight committee, in conjunction with the Business Office, has developed a special use rate for this colony of animals.

Animal Models

All of the animals maintained in the OR are fed a custom HFD that consists of approximately 36% of calories from fat, 45% from carbohydrates and 18% from protein (TAD Primate Diet, 5L0P, LabDiet, Purina). The diet has a caloric density of 4.72 kcal/gm, with the primary fat source being preserved animal fat (lard). The cholesterol content is 612 ppm. The diet is balanced with appropriate vitamins and minerals and a quality protein. This diet was designed to model the typical American diet (TAD). As comparison, the standard chow diet (Monkey Diet, 5027, LabDiet, Purina) approximately 13% of calories from fat, 69% from carbohydrates, and 18% from protein. This diet has a caloric density of 3.89 kcal/g and the cholesterol content is 75 ppm. It should be noted that the while the standard diet has sucrose as the sugar source; the TAD Primate Diet uses both sucrose and fructose. Animals maintained on the HFD are also supplemented with calorically dense treats (< 5% of daily caloric intake). A cohort of the HFD animals also have access to 500 mls of 10% fructose in KoolAid™ 3-4 times a week, to mimic soda consumption (depending on the requirements of assigned

studies). To facilitate care of these animals, when these animals are assigned to the Obese Resource we initiate training of the animals for voluntary presentation for blood samples. This training is done using positive reinforcement, which reduces the stress to these animals and, in the long run, significantly reduces the need to sedate animals for research protocols.

Rhesus Macaque: Currently, we have 65 adult rhesus macaques (8-14 yrs of age) being maintained as part of the OR, with 50 males and 15 ovariectomized females. The majority of these animals are maintained primarily in single housing (see below), to enable daily monitoring of food intake. At this time, we have animals that have been on the HFD for up to six years, with six animals developing full diabetes. These diabetic animals are maintained on a combination of glargine and metformin, as directed by the veterinary staff. See Aim 1 for discussion of monitoring and maintenance procedures for these diabetic animals.

A smaller cohort (5 females and 5 males) is being housed in pairs in newly designed modular cages (with a total dimension of 2m x 2m x 2m) (Figure 3). This new cage system is being tested for its ability to socially house animals (in pairs) while still retaining the control to be able to monitor individual daily food intake and for the training of the animals for voluntary presentation for blood sampling. This system is designed to house pairs of animals with weights up to 25 kg each.

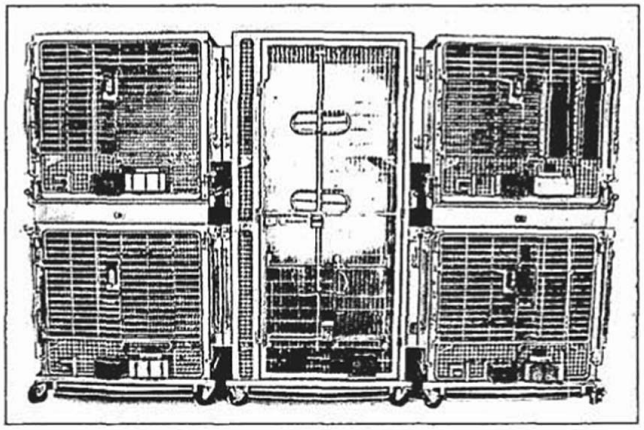


Figure 3. Modular paired housing cages designed by ONPRC and Carter[2] Systems. The full deminsion of this system is 2 x 2 x 2m.

We have over 10 years of experience working with this model, and have collected extensive data on the progression of obesity and diabetes in animals over several years (up to 6 years). This includes close regular analysis of food intake, body weight, body fat, changes in circulating hormone levels, and changes in lipids and cytokines. During the past 10 years, animals have been euthanized as part of planned studies. The OR has collected a broad array of tissue and blood samples for a tissue bank. These samples have been made available for the scientific community, both for academic and industry scientists.

Cynomolgus Macaque: Currently, we have 32 young adult (6-10 yrs of age) male cynomolgus macaques that have been maintained on the HFD for 6 months to 2 yrs. These animals are maintained in single housing for close monitoring of food intake. Currently, 4 of these animals have full diabetes. These diabetic animals are maintained on a combination of glargine and metformin, as directed by the veterinary staff. To this date, we have only been utilizing this model for the past 2 years. However, other groups have used this model extensively, such as at the Wake Forest primate facility, pharmaceutical companies and contract research organizations. An advantage to this model is the relative availability of this species, compared to the rhesus macaque. Furthermore, obese cynomolgus macaques are often still less than 15 kg, which allows for use of smaller cages and more efficient housing than the rhesus macaque.

Japanese Macaque: Currently, we have 71 adult Japanese macaques (6-14 yrs of age), with the majority (63) of these being intact cycling females. These animals are maintained in group-social housing in cohorts of 10-12 (8-10 females and 2 males). The primary purpose of these animals is a breeding facility to produce offspring that are investigated by a developmental programming research consortium involving investigators at ONPRC, OHSU, the University of Colorado at Denver, and Baylor. These animals are assigned to this program at approximately 5-7 years of age and then maintained in the breeding harem for 6 to 7 yrs.

Obese Resource Personnel

Excluded by Requester Resource Director. Excluded by Requester has 15 years' experience in the study of metabolic diseases, and 10+ years using NHP models of obesity and diabetes. He provides oversight for the long-term planning of these colonies of animals.

Excluded by Associate Director. Excluded by Requester is a senior staff scientist that has 5+ years of experience of working with obese and diabetic monkeys. Furthermore, he has spent his entire research career studying metabolic diseases. Excluded by is responsible for the data analysis and management of all of the metabolic phenotype data of the animals within the Obese Resource. Excluded by also provides support and consultation for the submission of IACUC applications for investigators utilizing this resource.

Excluded by Requester Resource Support. Excluded by is a senior staff scientist with more than 15 years of experience working with NHPs. Excluded by is the manager of the Collaborative Research Unit, which is responsible for facilitating external investigator utilization of animal resources at ONPRC. He also provides support and consultation for generation of budgets and invoicing for animal resource utilization by external investigators.

Excluded by Requester has functioned as the Animal Resource Manager of the Obese Resource since its inception. She has more than 10 years of experience working with NHP, and is an expert in positive reinforcement training of animals for voluntary presentation for blood sampling and injections. Excluded by Requester is responsible for managing and supervision of all procedures performed on Obese Resource animals. She is also responsible for management of the RA I scheduling. Finally, she is responsible for monitoring of metabolic phenotypes of the animals and coordinating with veterinary staff for the treatment of any and all health conditions that arise in these animals, including the maintenance and monitoring of the treatment of diabetes.

Excluded by Requester are Research Assistants that will be involved in the day-to-day direct animal handling and management. They are responsible for daily monitoring of food intake and scheduled body weight measurements and transport of animals for procedures. They also assist research staff in blood sampling and performing metabolic phenotype procedures on the animals.

SPECIFIC AIMS

Specific Aim 1. Maintain a healthy and well-characterized DIO macaque colony. Since we are inducing a serious disease state, these animals become more susceptible to health complications the longer they are maintained on the WSD. Therefore, it is important to carefully track the progression of their disease states. This is accomplished through the scheduled measurement of food intake, body weight, adiposity (by DEXA), glucose homeostasis (through intravenous glucose tolerance tests (ivGTT) and HbA1c determinations), and insulin sensitivity (through insulin tolerance tests and euglycemic clamp studies). We also carefully monitor blood chemistry to track possible hyperlipidemia that may contribute to cardiovascular issues, as well as for liver and renal function. During the first year of being maintained on the WSD, the animals undergo these procedures at 1, 3, 6, 9, and 12 months. Blood samples from these animals are obtained monthly and banked for distribution through the tissue/blood bank. After the first year, the animals undergo the metabolic phenotyping biannually, but with blood chemistry being evaluated quarterly. Furthermore, a full metabolic phenotype and clinical physical are performed on the animals prior to being assigned to any research protocol.

OR technicians work closely with the veterinarians to provide the best health monitoring of these animals. We have developed several standard operating procedures to reduce risks of unanticipated complications during experimental procedures. For example, because some of these animals reach upwards of 50% body fat, they are susceptible to respiratory stress during sedations with Ketamine or Telezol. Thus, we monitor blood oxygen levels, respiration rate, and heart rate in animal during these procedures. We have oxygen available for administration to the animals in case blood oxygen levels drop and have antidotes ready for reversing the sedations if necessary. Finally, we ensure that adequate technicians are available to monitor all animals under sedation until full recovery.

In animals that present with blood glucose levels above 90 mg/dL, we initiate a protocol to carefully monitor the progression to diabetes. This involves analysis of monthly blood samples for fasting insulin, fasting glucose, HbA1c, complete blood chemistry with a full lipid analysis (triglycerides and cholesterol). Furthermore, we perform a glucose curve on the animals whereby a blood sample is taken every 2 hrs during

the day to determine postprandial glucose fluxes. An animal is classified as diabetic if they present with blood glucose above 1 mg/dL, HbA1c above 8%, and area under the curve for the daily glucose curve of 150 (arbitrary units). We also take into consideration other parameters such as blood chemistry, lipids, and insulin secretion during an ivGTT. When animals are classified as diabetic, we first initiate a dietary intervention whereby the animals are removed from the WSD and placed back on standard monkey chow. If the animal does not regain glucose homeostasis after 1 month, we initiate pharmaceutical treatment, which includes treatment with glargine (Lantus, starting at 0.5 U/kg SID subcutaneously) and/or metformin (starting at 12 mg/kg orally BID). The clinical treatment of these animals is carefully coordinated with the veterinary staff.

Specific Aim 2. Expansion of animal availability. As mentioned above, there is an ever-expanding demand, both locally and nationally, for the DIO animal model. While we currently have 168 animals associated with this resource, the vast majority of these are assigned to long-term research programs, which limits our ability to meet demands for new projects. We face several challenges for the expansion of this colony: 1) to generate a stable obese animal requires approximately 6 months on the WSD; however, for development of the more severe aspects of metabolic disease, such as diabetes and cardiovascular disease, it can require up to 4 years on the WSD. This long-term animal maintenance is costly. We have offset these costs by making these animals available for shorter-term studies involving collaborations with industry partners. This typically covers the cost of maintaining these animals until they develop the complex diseases that are often the focus of NIH-funded research, such as the RYGB studies. 2) DIO animals require larger cages to meet USDA standards, which mean fewer animals are housed per square foot. To partially deal with this, we have focused on development of a DIO cynomolgus macaque model. These animals are smaller (approximately 10 kg vs. 15-25 kg for the DIO rhesus) and can, therefore, be housed in smaller cages. The DIO cynomolgus has been extensively used for research on cardiovascular disease and is commonly used by industry for preclinical studies. The cynomolgus develops obesity and associated diseases in a similar manner to the rhesus and are readily available. Secondly, the OR has been working with local cage builders to design new paired/group housing for DIO macaques that meets USDA standards, but allows for more efficient housing of the animals, while maintaining our ability to closely monitor these animals, such as measuring individual animal food intake and blood sampling (Figure 3). Furthermore, recently, OHSU has recently received a large donation to expand cardiovascular research at OHSU (see Research Strategy for the Division of Diabetes, Obesity, & Metabolism), including at ONPRC. With this increased focus, it is expected that, over the next three years, we will need to more than double the number of animals in the OR. This expansion will focus on the DIO cynomolgus macaque, which is a common species used for cardiovascular research. This donation will also fund the expansion of caging and group housing at ONPRC, as well as our imaging capabilities.

Specific Aim 3. Increased Collaboration with the Aging Resource at ONPRC. Most of the current ongoing studies using the OR focus either on early developmental programming or on the young adult. Considering the number of obese and overweight people in the US, one of the major challenges that clinicians are going to face in the future is the management of aging, obese patients. This is further exacerbated by the natural changes in metabolic systems associated with aging. Since ONPRC has a well-established Aging NHP resource and a critical mass of researchers focusing on diseases associated with aging, it only makes sense to develop animal models and tools to focusing on aging, obese animals. To meet this future need, OR technicians will work with the Aging Resource group to monitor metabolic health in their aging animals that are maintained on standard chow. This will provide key benchmarks for investigating the OR animals as they age. Currently there are investigators working in the Aging field that are interested in immune function, reproductive function, neurodegenerative diseases, neuropathies/retinopathies and cardiovascular function. The aging obese animals, with and without diabetes, will provide not only a critical tool, but will make our investigators uniquely competitive for funding in this area. Finally, these animals will also be available for the national research community.

REFERENCES

Excluded by Requester

Program Director/Principal Investigator (Last, First, Middle): Robertson, Joseph E./Haigwood, Nancy L.

RESEARCH RESOURCES-OBESE DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Excluded by Requester	Sr. Scientist	% Effort			Institutional Base Salary	4,493	1,123	5,616
	Res Assoc					12,296	4,304	16,600
	Res Asst 1					14,331	5,732	20,064
	Staff Scientist 3					4,031	1,249	5,280
	Res Asst 1					14,629	5,852	20,481
	Staff Scientist 2					13,992	4,338	18,330
	SUBTOTALS →					63,771	22,598	86,369

CONSULTANT COSTS		
None Requested	0	0
EQUIPMENT *(Itemize)*		
None Requested	0	0
SUPPLIES *(Itemize by category)*		
Laboratory Supplies	31,800	
Laboratory Reagents	1,855	
Pharmaceuticals	3,180	
		36,835
TRAVEL		
Domestic	1,060	1,060
INPATIENT CARE COSTS		0
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		
None Requested	0	0
OTHER EXPENSES *(Itemize by category)*		
RIA Lab Fees	10,600	
Morphology Fees	636	
Lab Services	5,300	
Shipping Charges	530	
Hazardous Waste Disposal	265	
Maintenance & Repair	530	
Misc Internal Service	530	
Misc Other Expenses	5,300	
		23,691
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 147,955
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 147,955

RESEARCH RESOURCES - OBESE
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	86,369	88,960	91,629	94,378	97,209
CONSULTANT COSTS	0	0	0	0	0
EQUIPMENT	0	0	0	0	0
SUPPLIES	36,835	37,940	39,078	40,251	41,458
TRAVEL	1,060	1,092	1,125	1,158	1,193
INPATIENTS CARE COSTS	0	0	0	0	0
OUTPATIENTS CARE COSTS	0	0	0	0	0
ALTERATIONS AND RENOVATIONS	0	0	0	0	0
OTHER EXPENSES	23,691	24,402	25,134	25,888	26,664
DIRECT CONSORTIUM/CONTRACTUAL COSTS					
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	147,955	152,394	156,966	161,675	166,525
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	147,955	152,394	156,966	161,675	166,525
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					785,514

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

BUDGET JUSTIFICATION – YEAR 55

Resource Director Senior Scientist - Excluded by Requester % Effort Program Income): Excluded by Requester functions as the Director of the Obese Resource. He has 15 years of experience in the study of metabolic diseases, and 10+ years using NHP models of obesity and diabetes. As the director, he is responsible for the overall management of the Resource; this includes the review of metabolic phenotype data and the overview of the utilization and maintenance of animals within the Resource. Directs monthly meetings to review animal utilization and health.

Research Associate Excluded by Requester % Effort
Responsible for the management and supervision of all procedures performed on Obese Resource animals; management of the RA 1 scheduling and monitoring of metabolic phenotypes of the animals; coordinates with veterinary staff for the treatment of any and all health conditions that arise in these animals, including the maintenance and monitoring of the treatment of diabetes.

Research Assistant 1 (RA1) - Excluded by Requester % Effort
Responsible for daily monitoring of food intake, scheduled body weight measurements and transport of animals for procedures. In addition, assists research staff in blood sampling and performing metabolic phenotype procedures on the animals.

Staff Scientist 3 - Excluded by Requester % Effort
Responsible for coordination of external requests for access to Obese Resource animals, including animal and/or sample availability and responsible for the submission of invoices for utilization of animals and/or samples from the Obese Resource.

Research Assistant 1 (RA 1) - Excluded by Requester % Effort
Responsible for daily monitoring of food intake, scheduled body weight measurements and transport of animals for procedures. In addition, assists research staff in blood sampling and performing metabolic phenotype procedures on the animals.

Staff Scientist - Excluded by Requester % Effort Responsible for data analysis and management of all of the metabolic phenotype data of the animals within the Obese Resource. Provides consultation for investigators performing protocols on Obese Resource animals. Monitors protocols and provides assurances they are in adherence with IACUC approval. Directs weekly meetings with the animal care staff to review protocols, procedures and any animal health incidences. Responsible for coordination and supervision of IACUC application submissions for protocols from external investigators, in addition to the coordination and supervision of protocols being sent to the Research Advisory Committee, which provides a peer-review of all protocols that are not reviewed by a federal funding agency (i.e., NIH study section).

SUPPLIES

Laboratory Supplies: Funds are requested for the purchase of general laboratory supplies needed for the processing and storage of samples obtained from the Obese Resource animals. This includes gloves and protective gear, pipette tips, tubes, freezer/storage boxes, vacutainer tubes (for blood sampling), syringes, butterfly needles/catheters, sharps containers, autoclave bags/bins, saline/ringers bags, glucose/HbA1c monitoring strips, enrichment supplies, solution filters, etc.

Laboratory Reagents: Funds are requested for the purchase of general laboratory reagents and buffers for processing blood and tissue samples, which includes, phosphate buffered saline, ethanols, and various fixatives.

Pharmaceuticals: Funds are requested for the purchase of insulin and metformin for the treatment of the diabetic monkeys and for performing insulin tolerance tests; ketamine and telezol for the sedation of animals during experimental and animal care procedures.

TRAVEL

Funds are requested to support travel for the Research Associate and Assistants to training conferences. As the regulations for housing NHPs become more restrictive, new ways to training animals for physiological measures and for technical advances for improvement of monitoring the metabolic health of the animals is continually being investigated.

OTHER EXPENSES

RIA Lab Fees: Funds are requested for the hormone analysis needed for the monitoring of the metabolic phenotype of the animals. This includes the monitoring of a broad array of hormones, including insulin, leptin as well as various other biomarkers of metabolic diseases. These are provided as part of metabolic profiles to investigators utilizing these animals.

Morphology Fees: Funds are requested for pathological analysis of tissues from animals that are either sick or spontaneously die from complications of the metabolic diseases.

Lab Services: Funds are requested for the monitoring the blood chemistry of the animals being chronically maintained on the Obese Resource, this includes monitoring of triglycerides, cholesterol, as well as liver enzymes, and indicators of kidney function. These measures are determined, on average, quarterly on all animals in the Obese Resource. These funds also cover the quarterly DEXA of each animal to monitor lean and fat mass.

Shipping Charges: Funds are requested for shipping charges related to shipping samples for analysis (used for metabolic monitoring of animals). In addition, funds are requested for the shipment of equipment and/or devices for modification and/or repair.

Hazardous Waste Disposal: Funds are requested for the disposal of hazardous biological waste; which includes contaminated syringes and needles as well as excess or outdated tissue samples.

Maintenance & Repair: Funds are requested for the maintenance and repair of equipment used by the Obese Resource staff, including centrifuges for processing of blood samples and refrigerators and freezers used to store samples.

Misc. Internal Service: Funds are requested for the internal facilities services for the maintenance, repair and minor modifications of space and/or cages used by the Obese Resource. For example, modifications of electrical outlets, doors and cages to fit the specific needs of the Obese Resource.

Misc. Other Expenses: Funds are requested for the purchase or replacement of small equipment and supplies that need to maintain and monitor animals in the Obese Resource. This includes primate collars, activity monitors, bottle holders (to administer specialized drinks), video cameras (and associated supplies), pipettes, O2 monitors, scales, ice boxes, etc.

ANIMAL SERVICES: Obese Resource Income Table

Last Funded Year (53)

Source	Funding (direct costs)
P51 base grant support	$137,836.93
Program income derived from P51 base grant	175,428.83
Other Sources	0
Total	$313,265.76

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$147,955.12
Program income derived from P51 base grant	149,955.12
Other Sources	0
Total	$297,910.24

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

The Obese Resource receives salary support and support for other expenditures from program income.

ANIMAL RESOURCES: PRIMATE AGING RESOURCE SPECIFIC AIMS

The Primate Aging Resource (PAR) has been in existence since 1999 and manages the Primate Aging Study (PAS) colony, which is a NIA-supported nonhuman primate resource at ONPRC. The PAS colony serves the research community by identifying, maintaining, and supplying projects with aged Indian rhesus macaques. To further facilitate this process and strengthen the resource for the future we propose the following specific aims:

Specific Aim 1. Formalization of organizational ties with the Division of Comparative Medicine (DCM). To integrate the goals of the PAR with DCM operations, strong and direct connections of PAR with senior management in animal resources, facilities, research, clinic, surgery and pathology departments will be necessary for smooth PAR operations.

Specific Aim 2. Leveraging of Information Services (IS) and other computational resources. The ongoing evolution and expansion of the IS department will be highly beneficial for PAR and will result in the development of management tools for tracking of replacement animals, database management (LabKey project) and the data mining of archival animal records.

Specific Aim 3. Enhancement of husbandry practices. Physicals exams (PE) of old animals are more frequent (biannual) and will now be used to capture biomarkers of inflammation and evaluate the prevalence of aging pathology, arthritis and obesity. This data will better define the model and inform clinical practice.

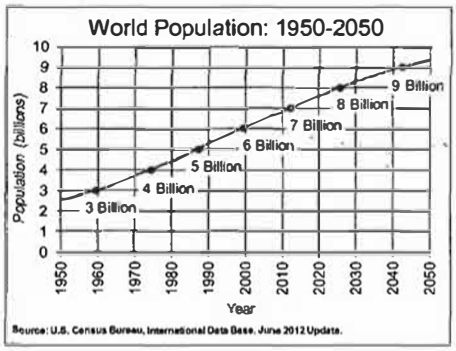
Specific Aim 4. New model development. We will use PE results to discover the extent and level of arthritis in the PAS colony and evaluate the possibility of model development. A second project leverages on-campus expertise and scientific collaborations to develop a model of alcohol abuse in aged animals.

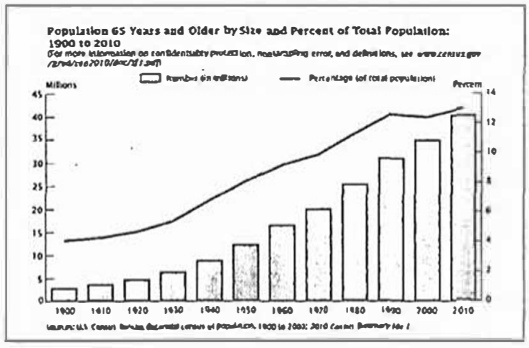
Specific Aim 5. Expansion of archival projects. Continuation of one of the long-term projects in PAR is the collection tissues for our archives. Moreover, we propose to continue to build our archive of MRI brain images to better define the patterns of normative aging.

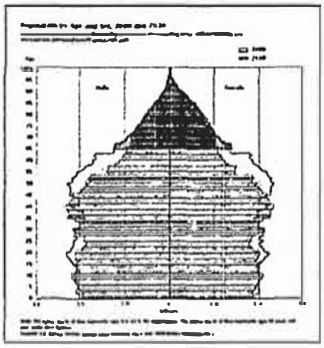
ANIMAL RESOURCES: PRIMATE AGING RESOURCE RESEARCH STRATEGY

SIGNIFICANCE

It has long been recognized that technological advances in food production (1) have been instrumental in avoiding Malthusian predictions of widespread famine and aiding in explosive population growth (Figure 1). In addition, accompanying this overall numerical increase, medical and public health interventions have also lead to a dramatic increase in longevity (2), such that the elderly are currently the fastest-growing portion of the U.S. population (Figures 2, 3). Recognition of the socioeconomic consequences of an expanding, older population resulted in the founding of the National Institute on Aging (NIA) in 1974, whose mission is to help prevent, reduce and treat diseases and conditions of aging (3). To this day, meeting the challenges of a rapidly expanding aging population, both here and abroad, continues to represent one of the greatest debates in society.







Figures 1-3 (left to right): 1.) U.S. Census Bureau data on the rapid increase in the world's population since 1950 and projected out to 2050. While the rate of overall population growth is slowing, peak levels are still decades away. 2.) U.S. census of the increase of the elderly since 1900. The population over age 65 is currently the fastest-growing portion of the U.S. population. 3.) Demographic increase of elderly men and women in 2000 and 2010. Baby boomers (born between 1946 and 1964) account for the large "bulge" of people between the ages of 48 and 66 in 2010.

Studying the health challenges of the elderly fits the mission of ONPRC extremely well, which is tasked to develop biomedical technologies to improve human health (4). However, several additional factors have been put into place to facilitate nonhuman primate (NHP) aging research at ONPRC, the first of which is programmatic support of the animal resource. One of the long-term goals of the NIA is the development of animal models for aging research, and they have historically provided funding to ONRPC for aged monkeys through the Primate Aging Study (PAS). The NIA funding for PAS is through a supplement to the Core grant, with the charge to create a colony of aged monkeys for translational research. Primate Centers, with their large breeding programs and specialized infrastructure, are ideally positioned to create and maintain such a resource. The PAS colony at ONPRC is composed of about 100 male and female, Indian-origin rhesus macaques, which are long-lived, phylogenetic relatives of humans that share a similar anatomy, physiology and central nervous system (5), which differentiate the NHP from other animal model systems.

To facilitate research in the area of aging by leverage of the PAS resource, ONPRC created the Primate Aging Resource (PAR) in 1999. Headed by [Excluded by Requestor] PAR was tasked with the management of the PAS colony. Specific tasks included PAS colony maintenance, which meant the tracking, selection and induction of animals into the resource. In addition, another of PAR's mission was to assist with the generation of projects revolving around the PAS resource. To this end, NHPs models that examined hormone replacement and cognitive behavior, immune dysfunction and rejuvenation, stroke, macular degeneration and effects of diet have been implemented over the past few years

Finally, the most recently added factor that has contributed to the maturation of aging research at ONPRC has been the creation of the Biology of Aging Program (BoA). This collection of research scientists at ONPRC and OHSU provides multidisciplinary, programmatic, and intellectual support to help accelerate and diversify aging research at ONPRC while providing a bridge to clinical programs at OHSU. We anticipate that additional programmatic areas of research involving PAS animals will arise from BoA interactions; including studies on the alleviation of the vasomotor response (hot flashes) and the examination of functional physiological changes due to age-related modification of the circadian rhythm system. In combination, the BoA and PAR have

combined to generate a substantial research portfolio involving the PAS resource. A direct reflection of this scientific success has been the continuous support of PAS by the NIA, which has trebled over the past decade and is now poised to increase further over the duration of the next P51.

To anticipate the health needs of the elderly population, which may be addressed by the usage of the NHP model, we again refer to the current NIA Strategic Plan (3). In this document there is an emphasis on the study of the genetic, biochemical, and physiological factors that contribute to arthritis, cardiovascular disease, cancer, diabetes and neurodegeneration (Alzheimer's disease). While we currently already have programmatic coverage in some of these areas, the list is instructive and will be further addressed within PAR with the development of new models. For example, we plan to examine the level and extent of arthritis in the PAS colony. In addition, PAR will also take advantage of on-campus academic expertise and other resources, as we also plan to interact with programs that examine metabolic disorders and alcoholism, both growing problems that have been identified in the aged population.

Other significant gains in PAR will occur with integration into the Division of Comparative Medicine (DCM). Formalization of managerial ties for the enhancement of PAS husbandry, recruitment, and tracking will help to increase usage and efficiency. To assist with the transition, it is also envisioned that the creation and expanded use of computer tools produced by Center-wide resources, such as Information Services (IS) and Research Informatics, will assist in increased efficiency and improved data archiving and mining of animal records. Enhanced scrutiny of the PAS resource will advance animal health and facilitate model development, leveraging existing ONPRC technology to unmask the extent and prevalence of pathologies. Thus, these subtle enhancements will create a stable platform from which to conduct aging studies into the future and maximize the gathering of descriptive information on the model.

INNOVATION

With the complexities of running a large and sustainable NHP resource at ONPRC, research efforts have benefited from the specialization of the process to include the generation of several models, including specific-pathogen-free, obese, Japanese, and aged primates. This evolution reflects specific research needs, such as with aging research and the creation of PAR. The mission of PAR has historically been multifold, to provide management of the PAS colony and to also provide assistance to aging projects from their inception. The latter includes discussion of resource requirements, identification of candidate animals, the facilitation of potential collaborations, assisting with administrative matters and providing scientific input. To this end, we have found that centralization of information through PAR significantly increases efficiency as redundancy of effort is reduced, while aiding in the reduction of administrative errors. The implementation of functional interfaces of PAR with the many facets of DCM, including resource management for tracking animal recruitment and usage, clinical staff for discussions on treatment and scheduled protocols, surgery for potential health interventions, and pathology for tissue collection, will track with the operational reorganization in DCM. Historically, this arrangement has successfully met project demands for animal usage and, hence, these interactions with DCM management will continue to be emphasized. Moreover, PAR will also benefit from adaptation of DCM practices, such as the formalization of protocol development so that critical institutional memory is protected in a formalized manner. In summary, the planned interactions with DCM managers will help provide the best PAS resource possible for investigators conducting aging research.

Excluded by Requester

PAR manager, has Ph.D. research experience in gerontology. This facilitates the generation of formal reports for ONPRC and NIA and aids in project design and prognostication for animals recruited into PAS. Moreover, updates on current aging research are attained through the attendance at relevant annual scientific meetings and participation on organizational and editorial boards, which also provide opportunities to consult with similar programs that can inform practices at ONPRC. Recent publications indicate the importance of lifestyle and diet on primate longevity and the expression of pathology in the NHP (6, 7). These practices will insure the continued availability of aged animals, while continuing to improve health metrics. Enhanced interactions (consultations) with other similar resources can synergize efforts to provide critical information to participants that can also be communicated to relevant outside programs, and to create new research opportunities for the future. Given the rarity of aged NHPs, collective efforts will enable improvement of husbandry practices and standardization of research practices across institutes and accelerate discovery in this model, including defining normative as well as pathological changes that occur as a function of aging.

Beneficial interactions with other ONPRC programs include leveraging IS efforts in following colony demographics in an effort to efficiently identify and track candidates for PAS in real-time. To this end,

computer modeling of prognostication tools predictive of breeding efficiency also indirectly provide a cutting-edge tool for monitoring aging trends in any middle-aged breeders, a source of animals for PAS recruitment. The installation and implementation of LabKey also appears advantageous for PAR operations. For example, for database management, the generation of LabKey workbooks will have the capacity to help organize the tracking of tissue sample archiving and usage, while concatenating parallel, descriptive information of interest. Along these same lines, we have started a relationship with the manager of Research Informatics at ONPRC, who will be designing and refining tools that will help rapidly organize historical animal data (for example, clinical, reproductive and housing histories) in a manner that will speed the vetting of animal for PAS induction, as well as for subsequent project assignment. Moreover, this same relationship will help generate computer searches of the animal information system to mine historical data that will provide information on the effects of aging on normative changes, as well as pathology. Secular trends can also be mined, as the database is extensive in scope of time and the number of animals. This will provide a window on aging trajectories of our animals and provide "normative" ranges for various clinical measures.

PAR will also take advantage of local expertise in expanding the repertoire of ONPRC NHP models of aging. A specific example is the initiation of a NHP model of alcohol abuse as a component of the PAS resource. Excluded by Requester Chief of the Division of Neuroscience and an expert in primate models of alcoholism, in collaboration with collaborators at the Wisconsin NPRC and with the support of NIAAA, will oversee the transfer of animals previously engaged in alcohol research from WNPRC to ONPRC. Pilot studies from the first transferred cohort will commence by time of submission of this P51 proposal, and future cohorts will be continually transferred to ONPRC over the following 5 years. This highly characterized resource is timely, as alcohol abuse is on the increase in the elderly (8) and will constitute our attempts to address a major health concern of the elderly in the immediate future.

PAR will also regularly consult with the Primate Genetics Program to maintain an out-bred resource, maximizing its translational potential and with the Behavioral Services Unit for enhanced animal wellbeing. We will also coordinate with DCM, biannual PAS physical examinations, bringing closer scrutiny to body condition (weight, arthritis, periodontal issues), and will leverage the ONPRC imaging capabilities (X-ray, DEXA, and MRI) to measure these factors, while utilizing the Endocrine Core to identify serum biomarkers of inflammation and perimenopause. This information will greatly aid in achieving another critical P51 objective, the development of models of human disease, and this will modernize resource development and management, increasing speed and accuracy, while maximizing potential.

APPROACH

reviewers' comments

reviewers' comments

Progress Report

Aging studies at ONPRC have recently examined macular degeneration, hormone therapy for females and males (with endpoints of cognition, vasomotor response), changes in circadian rhythm, immune senescence, a model for shingles, a new R24 project that explores the interaction of estrogen and Western diet, and the creation of a monkey model of reversible central nervous system stroke. Examples of the NIH-funded grants are shown in Figure 5, but to conserve space additional private and pilot grants are not shown. The emergence of multi-investigator grants (for example, Excluded by Requester R24) greatly increases the efficiency of animal use, as multiple investigators will examine the same experimental groups of animals. These successes were facilitated by improved PAS availability, specialized project training of ONPRC staff, and the addition of new, interested investigators. Adaptation of infrastructure has been important for progress, and some examples include specialized group caging and the specialization of rooms for testing of various behavior/cognitive domains. Expansion of imaging capabilities (for example- MRI), have also greatly enriched the research effort. In addition to the build of programmatic areas, other forms of productivity have been fruitful. For example, the Head of PAR has been active in this process, and has participated on 25 original, peer-reviewed papers involving primate aging in the past 4 years, with additional papers and projects expected in year 5 of the P51. This represents only a fraction of the total output of overall research effort on aging NHPs. Finally, several other pilot research efforts are underway that could lead to future funding, as well as pending grants that under review.

Principal Investigator	Funding Source	Grant No.	Project Description
Excluded by Requester	NIH/NIA	R01 AG029612	Interacting Impact of Adrenal and Ovarian Aging on the CNS
	NIH/NIA	R01 AG036670	Cognition in Rhesus Macaques in Relation to Age and Endocrine Status
	NIH/NINDS	U01 NS064953	Development of Toll-Like Receptor Agonists as Neuroprotectants in Brain Ischemia
	NIH/NIAID	R01 AI082529	Rejuvenation of the T-cell Compartment in Aging Primates

Excluded by Requester	NIH/NIAID sub in w/ Pac NW Regional Ctr Excellence	U54-AI081680	Yellow Fever Vaccination of the Aged and Immunocompromised
	NIH/NIAID sub in w/ Pac NW Regional Ctr Excellence	U54-AI081680	Yellow Fever Vaccination of the Aged and Immunocompromised
	NIH/NIA	R01 AG037042	Impact of Immune Senescence of Herpes Zoster in a Nonhuman Primate model.
	NIH/NIAID sub in w/ Pac NW Regional Ctr Excellence	U54-AI081680	Determination of Age-related defects and Chik Virus Infections
	NIH/Office of the Director	R24-OD011895	Post-menopausal Monkey Resource

Figure 5. Current funded NIH projects proposing to use PAS animals. These include projects that study the neuroendocrinology of aging and the effect of hormone replacement therapy on cognitive function, and the interaction of hormones on metabolism, interventions for reducing the effects of ischemia in the brain and potential factors modulating immune aging, rejuvenation & susceptibility. The PAS colony provides a vital buffer that can supply research studies with large groups of the appropriate aged animals. (Smaller grants not shown)

SPECIFIC AIMS

Specific Aim 1. Formalization of organizational ties with the Division of Comparative Medicine (DCM). The Head of PAR will interact with DCM for optimizing housing of PAS animals, the Behavioral Services Unit for issues of animal behavior and preferred housing (usually pairing), the NHP Resource for discussions of PAS enrollment and projected usage on scientific projects, and with the heads of Clinical and Surgical care for individual cases of health interventions. SOPs are being generated for inclusion into the DCM library. For example, protocols are already in place with pathology if an aged animal is sent to necropsy. We will work with DCM to coordinate the enhanced biannual physical exams on PAS animals (see husbandry, below). As in the past, programmatic direction will be discussed directly with Excluded by Requester Chief of DCM. Frequent discussions with individuals from the various departments ~~are scheduled on~~ an *ad hoc* basis, which are supplemented with more complex face-to-face meetings when warranted. The clinical staff is well versed in procedures for contacting the PAR prior to interventions of any kind and to coordinate for surgical interventions or tissue harvesting, in the event of a clinical cull situation.

Specific Aim 2. Leveraging of Information Services (IS) and other Computational resources. As outlined elsewhere, IS has undergone an expansion recently and has begun to integrate new software solutions for a variety of issues, including prognostication of breeding and laboratory database development. For the former, the maturation of animals in the breeding colony will be monitored with algorithms being constructed that allow for long-range prognostication on productivity of the breeding colony. It is important to note that the construction of breeding groups usually includes a sub-population of older adults, which function as "peacekeepers", providing social stability to a new group. The tracking of the older strata of adult breeders will be a focus for identifying PAS candidates, to be inducted at middle age upon the eventual take-down of the breeding group over time. Aside from the practical aspects of monitoring future PAS animals, the recorded breeding information is valuable for emerging projects that desire normally breeding, aged animals. This historically has been a programmatic strength for aging research at the center, assisting efforts by our scientists who examine the effects of hormones on aging processes. Hence, the addition of these tools will provide an additional mechanism for labeling PAS candidates from breeding stock.

Another component of this specific aim is that, for database management, the rollout of the LabKey software promises to provide a platform for the upload and organization of files and data. The "workbook" design will be helpful for better management of our extensive tissue archive and will allow for the organization of on-going projects. Critically, this system will have the capacity for secure storage, as well as the capacity for a facilitated exchange of information (Figure 6). As the current animal information database is gradually replaced by LabKey, integration of PAR operations with this platform will become increasingly important.

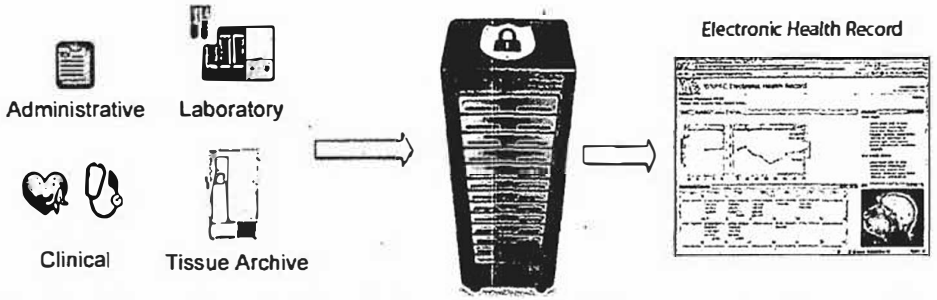


Figure 6. LabKey workflow at ONPRC. Computer solutions for the storage and access of administrative data, animal records (e.g., clinical data), laboratory results and our tissue archive database will be explored through the IS department. Our expectation is that specialization of existing LabKey tools will facilitate both search and storage of information in a secure fashion.

Another facet of interfacing with the existing IRIS animal database, which will also be plausible with the future Labkey environment, are efforts being driven by the manager of Research Informatics. Functionally, the great wealth of archival animal data can be accessed using algorithms in the MATLAB environment. For example, historical body weight data can be overlaid across time with clinical tests and prognoses, which offer rapid information on clinical histories and correlations with other health metrics (Figure 7). This is an important tool for the vetting of animals for induction into PAS, as well as for the downstream assignment of PAS animals onto projects with specific requirements or disqualifying conditions/past histories. Moreover, the establishment of stable adult weight and subsequent fluctuations will inform clinical decisions on possible husbandry interventions. Alternatively, identifying variation in weight or other variables can be useful in study design or assessing experimental variation in outcomes. Any number of terms in the animal records system can be queried and compared, for example historical data on pathology assessments and organ harvest weights. This easily accessible data is critical for the establishment and further description of the aging NHP model and allows for comparisons to data from other centers and their resources. For example, brain weights collected at necropsy here show no diminution with age (Figure 7), corroborating and extending data from the Yerkes Primate Center (9). This data verifies that the aging brain of NHPs are stable and supports the contention that overt neurodegeneration is not evident in this model system. The model is strengthened since similar outcomes occur at different locations (environments). Similar perusal of the IRIS database can also reveal historical trends, prevalence rates and age distributions of pathologies of interest, for example, arthritis and rates of obesity.

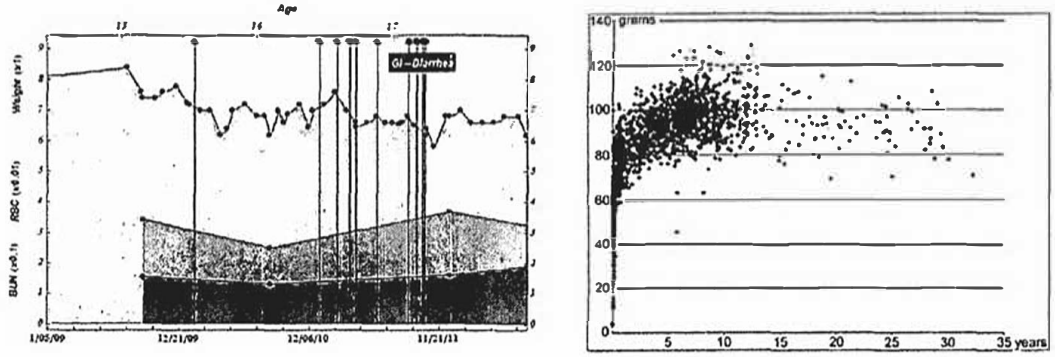


Figure 7. Left: Overlay of weight, RBC and BUN across time and age. Vertical bars denote clinical episodes, in one case, diarrhea. Right: Brain weights from 2003-2012, both sexes. No overt loss is observed post-maturity, validating no gross atrophy with old age.

Specific Aim 3. Enhancement of husbandry practices. Our third aim focuses on husbandry for aged animals and includes biannual physicals where we propose to capture additional information on systemic inflammation, which has been associated with chronic infection, immunosenescence, reduced longevity (10), metabolic disturbances, periodontal disease and osteopenia (11), maladies of aging that are reduced by caloric restriction in rhesus (12, 13). Systemic inflammation is reflected by elevated serum levels of C-reactive protein, interleukin 6 and tumor necrosis factor-α (14) and samples from PAS animals collected during regular physical exams will be assayed by the Endocrine Core at ONPRC. In addition, estrogen loss with aging is associated with increased inflammation (14), hence, anti-mullerian hormone (AMH), a predictor of menopause, will also be measured in females by the Endocrine Core. We have unpublished longitudinal data that shows that the age decline of AMH is a better predictor of the onset of perimenopause (Figure 8). The AMH data will also be extremely valuable information for projects trying to control for reproductive menstrual cyclicity and it is superior to the costly and repetitive serum sampling needed for measuring gonadal steroids or gonadotropins in the determination of menopause.

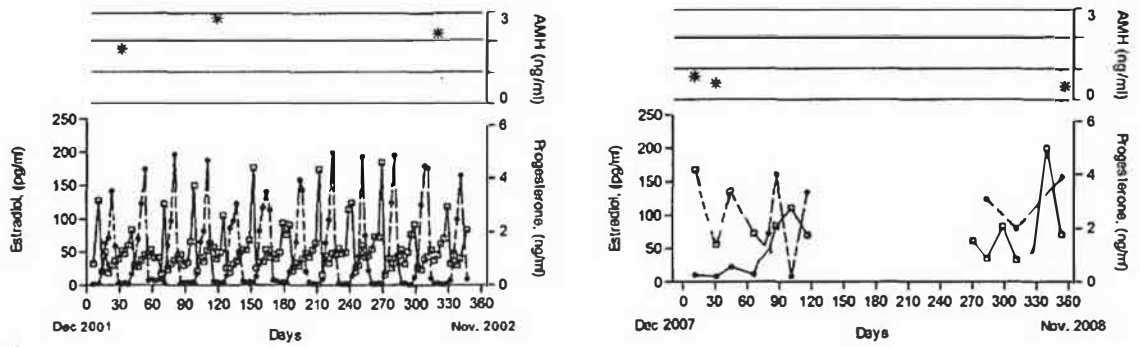


Figure 8. Longitudinal data on menstrual cyclicity. Left- Serum is assayed every 3 days for estradiol (dashed line) and progesterone (solid lines) in order to show cycle regularity. AMH levels are shown on the same graphs (asterisks, average=2.36 ng/ml). Right- Six years later, cyclicity in the same animal has become more sporadic with the average AMH=0.69 ng/ml. This pattern has been replicated in other animals. AMH would require less frequent blood sampling since the timing during a regular or irregular cycle is not critical.

Excess weight is associated with inflammation and reduced rhesus longevity (15), and is prevalent at other NHP colonies (16). Collecting data on our colony animals will be critical for the management of body weight. Conversely, differentiating animals with regards to fat, or any of the other aforementioned variables can potentially enrich future experiments. Quantitatively, lean and fat mass will be measured with DEXA scans (lean/fat ratio) and MRI will determine the levels of visceral fat in PAS (Figure 9).

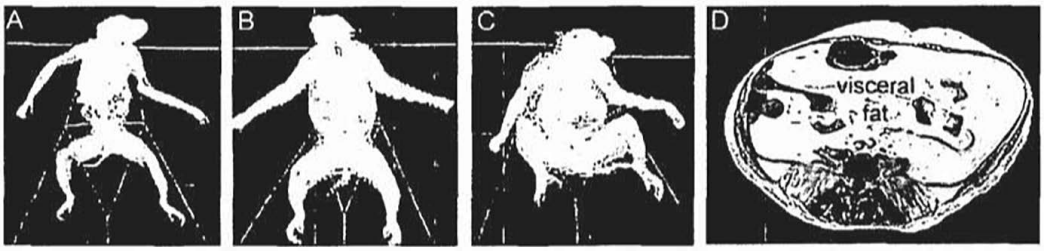


Figure 9. A, B, C: DEXA scans of progressively fatter, old female rhesus macaques, taken on the Hologic fan beam system at ONPRC. D. Internal visceral fat can be quantitated using the on-campus 3T MRI system.

These measures are complementary and will inform clinical assessment of the source of metabolic disturbances. The MRI system is also capable of doing proton MR spectroscopy, which may be important for studies, as intrahepatic fat levels appears to be a marker for insulin resistance in our monkeys (17). It would be possible to maintain PAS animals of various levels of obesity as a variable for future studies. It is also important to note that natural interactions with the **Obese NHP Resource** are expected, as overlap in techniques, expertise, as well as animal models, will be on the in the increase in the coming years.

Since inflammation is also related to periodontal disease and osteoarthritis (OA), these factors will also be assessed during the biannual physical exams (level of gingivitis and knee range of motion). X-rays (18) and MRI will also be used to directly examine musculoskeletal changes with age, like the loss of cartilage with OA and plans are being discussed with DCM clinicians. Discussions are also underway with the Advanced Imaging Research Center at OHSU to develop MRI tools for measuring the extent of osteoarthritis. The establishment of normative values of these factors will be informative for clinical intervention and overall animal health. Moreover, this degenerative process is high on the NIA list of health problems for the elderly. We have also received inquiries from the pharmaceutical companies on the development of this model of disease and hence would like to characterize prevalence and severity in the PAS colony.

Specific Aim 4. New model development. Our fourth specific aim is to develop two new models of NHP aging, one of which involves bringing in monkeys from the Wisconsin NPRC (WNPRC), exposed perinatally to alcohol (19). Excluded by Requester an expert on NHP models of alcohol abuse, will assist in the transfer with fiscal support from NIAAA. Interest in this model is high (see PA-12-291), questioning the impact of early alcohol exposure on diseases of aging. A current group of animals, already at ONPRC, will be used for pilot study, followed by cohorts of aged animals over the next five years. Accompanying the animals will be a comprehensive archive of *in vivo* data collected at WNPRC, where these animals were originally on a study of

alcohol. It is our intent to collect enough preliminary evidence for an application that will use the future, successive WNPRC cohorts.

The second model of interest, mentioned above, will be generated by data gleaned from the enhanced biannual physical exams, which will gather information on systemic inflammation. Levels of serum inflammatory cytokines will be correlated with the level and distribution of fat, periodontal disease and arthritis (range of knee motion). We will develop on-campus imaging modalities for model definitions, which will also be useful for the clinical staff. These studies will interface with the efforts of Excluded by Requester who is examining the genetics of inflammation, including some PAS animals that are senior members of large family groups. Because inflammatory markers have been correlated with metabolic disease, arthritis, cardiovascular problems, osteopenia and cognitive decline, profiles will be extremely useful for future proposals and as secondary cofactors in other studies.

Specific Aim 5. Expansion of archival projects. Archiving of *in vivo* scans and tissue samples is a low-cost and valuable service that helps spur the development of the aging primate model and can be easily shared with research efforts within OHSU and with the general research community, and represent our fifth specific aim. For example, MRI scans have demonstrated that monkeys experience *normative* brain aging (Figure 10) without the degeneration seen with Alzheimer's or Parkinson's disease. It has been proposed that functional changes in motor and cognitive function coincide with mild white matter atrophy (20). But, anatomical MRI brain scans of aged monkeys are still rare, especially longitudinal scans that can verify the progression of changes in this complex brain model, which are currently just inferred with cross-sectional studies. Over the years, we have collected at low frequency, cross-sectional MRI scans, an archive that was easily obtainable, non-invasive and turned out to be a valuable commodity for a cross-center analysis and generation of a macaque-specific atlas (21).

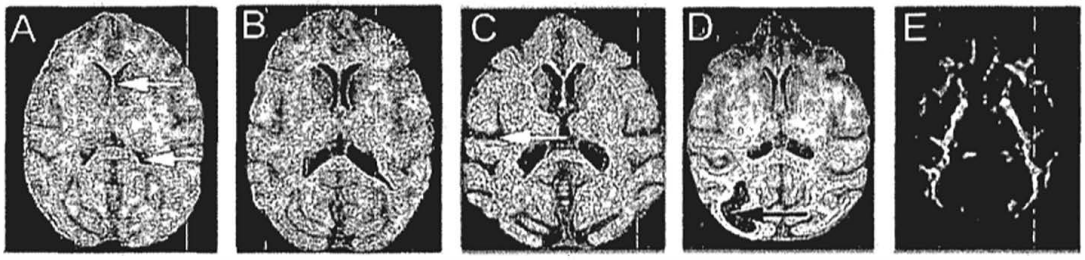


Figure 10. MRI changes with age in the NHP. A. Anatomical MRI scan of a 24-year-old macaque. The arrows denote normal sized ventricles. B. Ventriculomegally (enlarged ventricles) in a 25-year-old macaque. The increase of CSF is not associated with neuronal loss with age. It is suspected that gray and white matter volumes shrink with age. C. Ventriculomegally and dilation of sulci (white arrow) in a 38-year-old macaque. Unlike examples A and B, this animal also has shrunken gyri that result in wider sulci. D. Aged animal with an aberrant loss of occipital lobe mass. E. Diffusion tensor image of white matter tracts in an old animal. This technique allows tract-specific analysis of white matter connectivity between brain regions.

It is proposed that longitudinal MRI brain scans of PAS animals, males and females, be taken to better describe general age-related changes in the NHP model. This would involve primarily T_1-weighted anatomical scans and also diffusion tensor imaging, which parcels out white fiber tracts. It is expected that a subpopulation of aged animals exhibit noticeable volumetric changes, but that others would be resilient (successful agers?). The use of this data would be multifold, as it would inform studies of brain-based function, which would know to co-vary results as a function of volumetric differences. Also, by scanning both sexes, eventually, with sufficient numbers, an age x sex atlas could be constructed for public use. If age-related and or sex-related brain changes turn out to be consistent, this suggests that for aging studies, better fit of data could be accomplished with an atlas that accounts for these differences. On some occasions, anomalies are noted (Figure 10D), which may disqualify animals from specific projects. Excluded by Requester relationship with the OHSU Advanced Imaging Research Center will greatly facilitate this effort and has already resulted in set MRI protocols for this aim. A long-term goal is to generate an archive that will be available to outside scientists, along with any analysis tools that we will build. In the recent past we have had discussions with leaders of shared resources, such as the Biomedical Informatics Research Network, who agree that such efforts would be enriching for the research community.

Finally, a long-term project for PAR, since its inception, has been the archiving of tissue samples collected at necropsy. Although originally envisioned as a repository of central nervous tissue (also including serum and CSF), it has more recently evolved to include peripheral tissue samples as well. The latter include frozen, unfixed biopsies of muscle, fat, heart, kidney, liver, and adrenals. The brain samples collected are, in some cases, perfused-fixed, cryo-protected, cut into blocks and then undergo a controlled freeze for archiving. These blocks are in excellent condition for histological techniques. Some brain samples are also frozen and archived as unfixed samples. These are dissected into sub-regions and include areas of the cortex, hypothalamus, hippocampus, midbrain areas (raphe, nigra), cerebellum, and caudate-putamen and also include the pituitary. Finally, some brains are flushed with saline and the left hemisphere is blocked and prepared for immersion fixation and further processing for freezing (archiving) and eventually histology. The right hemisphere is dissected into same sub-regions listed above, then frozen and archived for biochemical uses. We have hundreds of samples representing a wide-range of ages and both sexes, as periodically younger adult animals are also collected as comparisons to aged individuals. Information on the archive is housed in a Microsoft Access database, built and maintained by PAR personnel. In the near future, adaptation to LabKey will occur to settle the platform where the archive will reside. Historically, this archive has served many projects, primarily at ONPRC, but also including OHSU, NIA Intramural and other outside investigators. Periodically we entertain inquiries for tissues (as well as animals), but it is also impossible to anticipate beforehand what will be in demand from outside sources.

The current application proposes to continue to collect samples, but will now also include fixed, paraffin-embedded brain tissue, as a complement to our extensive frozen archive. We will restrict this effort to brain tissue since this is the area most highly in demand. This tissue will be better for high-resolution (thin section) histology and will provide a stable and less expensive media in which to store samples reflecting limitations of the current archived, fixed-frozen tissue. We will, however, continue to collect unfixed samples from other animals, for biochemical-based studies. The annotation in the archive will of course reflect methodology for the preparation of samples (immersed/perfusion-fixed) along with the standard information on date of preparation, animal, region and so forth. As a footnote, we also continue to contribute normative aging data to the Primate Aging Database (PAD) at WNPRC. PAD is accessible via the internet (iPAD) once credentials are granted. An archival database, iPAD serves as a national resource of normative physiological changes across age in monkeys (22,23), an effort that the Head of PAR helped in its origination. Because the vetting of incoming data from many sources is difficult, it was agreed between the different contributing centers that only high-grade information should be accumulated. Both easily attainable measures (for example, body weight) are provided, and clinical data, which is analyzed by calibrated certified machinery, is also collected. Of course, the redundancy of data across age and sex provides the most reassuring measure of the precision of the measures. iPAD is instructive for our efforts of data-mining of our own animal database, as we seek more complex interactions, which are not necessarily available through iPAD.

In summary, this proposal for PAR will seek to enhance and enlighten the development of the rhesus macaque as a model of aging. The development of new clinical and husbandry practices, models of aging, description of comorbidities, as well as readily available data and tissue archives, will serve the local and national research interests into the future. As one of the few institutes in the world with specialized infrastructure, highly trained staff, and sophisticated technology, the NPRCs are best positioned to define the aging NHP model and develop models to further explore health issues that plaque the elderly. ONPRC, with PAS support, is even better positioned to explore and define the aging NHP as it is one of the few places in the world to have a self-perpetuating colony. We fully expect that, over the course of this next P51 grant, that we will to continue to contribute unique information to this effort, as well as provide models for research that will help alleviate the health challenges associated with aging.

REFERENCES

Excluded by Requester

ANIMAL RESOURCES: PRIMATE AGING RESOURCE BIOHAZARDS

Daily maintenance of animals in the Primate Aging Study (PAS), such as feeding, cage cleaning and health monitoring will be carried out by staff members of the Division of Comparative Medicine (DCM). For personnel in the Primate Aging Resource (PAR), Biosafety training will be required for data collection during biannual physical exams (PE), tissue collection during medical culls of PAS animals and for tissue handling in the laboratory setting. In addition, PAR personnel will be under the supervision of veterinary staff well-versed in pertinent hazards during PEs and tissue collection. A Biosafety manual is available and annual training will be based upon recommended safety practices, including the use of personal protective equipment (PPE), proper disposal, and spill response. Medical surveillance is also provided upon need. Protocols are reviewed and approved by the IACUC, including worker safety and health concerns. Incidents that may result in exposure are evaluated and treated, and reported to the lab supervisor and the Biosafety Officer.

PEs and tissue collection will be performed in restricted, Biosafety Level 2 facilities, as recommended by the *Biosafety in Microbiological and Biomedical Laboratories*, 5th edition. These buildings are equipped with inward opening, self-closing doors and are designed for easily cleaning and decontamination. They are equipped with eyewash stations and sinks for hand washing. PPE (gowns, gloves, and eye and face protection) is provided, as are disposal receptacles. Policies are in place for the safe handling of sharps. No eating, drinking or food storage is permitted. Signage at entry points provides information on the biosafety level, potential hazards and entry/exit requirements.

Tissue handling and archiving will occur in laboratories that are also considered at the Biosafety Level 2. Hence, they also are designed with surfaces that are easily cleaned and decontaminated and are equipped with eyewash stations and sinks for hand washing. A biosafety cabinet is used for all manipulations of potentially infectious material, is operationally certified annually, and is located in an isolated space in the lab. PPE is provided, which is removed before entering non-laboratory areas. Personnel are trained for safety practices, use of PPE, proper disposal, and spill response. Incidents that may result in exposure are evaluated and treated, reported to the lab supervisor and the Biosafety Officer Medical with surveillance provided when necessary. The proper disposal of biological and chemical waste is done in consultation with the Biosafety officer to achieve compliance.

Program Director/Principal Investigator (Last, First, Middle): Robertson, Joseph E./Haigwood, Nancy L.

RESEARCH RESOURCES-AGING DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Excluded by Requester	Sr. Staff Scientist	% Effort			Institutional Base Salary	37,680	11,681	49,361
	Sr. Res Asst					8,956	3,583	12,539
	Res Asst 2					18,020	6,307	24,327
	SUBTOTALS →					64,657	21,570	86,227

CONSULTANT COSTS		
Consulting	500	500
EQUIPMENT *(Itemize)*		
None Requested	0	0
SUPPLIES *(Itemize by category)*		
Laboratory Supplies	1,000	
Office & Admin Supplies	250	
		1,250
TRAVEL		
Domestic	625	625
INPATIENT CARE COSTS		0
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		
None requested		0
OTHER EXPENSES *(Itemize by category)*		
Morphology Fees	250	
MRI Fees	3,240	
DEXA Scans	700	
Necropsy Fees	2,000	
RIA Lab Fees	1,250	
Equipment Maint & Repair	159	
Software Maint Contract	212	
Misc Other Expenses	265	
Memberships	100	
Registration & Conference Fees	292	
		8,468
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 97,069
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 97,069

RESEARCH RESOURCES - AGING
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	86,227	88,814	91,478	94,222	97,049
CONSULTANT COSTS	500	515	530	546	563
EQUIPMENT	0	0	0	0	0
SUPPLIES	1,250	1,287	1,326	1,366	1,407
TRAVEL	625	644	663	683	703
INPATIENTS CARE COSTS	0	0	0	0	0
OUTPATIENTS CARE COSTS	0	0	0	0	0
ALTERATIONS AND RENOVATIONS	0	0	0	0	0
OTHER EXPENSES	8,468	8,722	8,983	9,253	9,530
DIRECT CONSORTIUM/CONTRACTUAL COSTS					
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	97,069	99,981	102,981	106,070	109,252
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	97,069	99,981	102,981	106,070	109,252
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					515,355

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

PERSONNEL

Senior Staff Scientist - Excluded by Requester % Effort % Effort Responsible for overseeing and coordinating all of the Primate Aging Resource (PAR) activities which includes regular consultation with the Resource Manager, to ensure the PAS colony is populated with ideal animals for future study; genetics to ensure maintenance of an out-bred genetic background; clinical staff for review of husbandry issues, including responses to acute illness/injury and chronic problems; Behavioral Services Unit- to optimize housing and animal interactions; Pathology- to optimize tissue collection from cull animals; DCM research to enhance biannual physical exams to gain a better perspective of systemic (e.g., inflammation) and focal aging changes; for interactions with Information Services and Research Informatics

Senior Research Assistant - Excluded by Requester % Effort Income) Responsible for interacting with clinical staff during the biannual physical exams, which will necessitate record-keeping, associated imaging and the collection of tissue samples, processing of samples, submission for assay and tissue archiving; ordering of minor equipment and supplies; maintenance of required buffers and other common-use solutions and cleaning and storage of equipment and glassware.

Research Assistant 2 - Excluded by Requester % Effort Responsible for assisting in the archiving of tissue and data; responsible for tissue handling from animal culls which includes handling, processing (sub-dissection, fixation, freezing, paraffin-embedding) as well as serving as gatekeeper for the tissue archive. Day-to-day activities also include the maintenance of supplies and equipment and general house-keeping of the general lab areas.

CONSULTANT COSTS

Funds are requested to bring in leaders in the field of primate aging to advise us on husbandry (the NIA Intramural program) as well as technology specialization (University of Wisconsin for MRI protocols).

SUPPLIES

Laboratory Supplies: Funds are requested for chemicals for fixatives, buffers and disposables. In addition, pipets, shakers, stir plates and vortexes wear out and require periodic replacement.

Office & Admin Supplies: Funds are requested for standard office supplies, such as paper, pens, folders, printer cartridges, etc.

TRAVEL

Funds are requested for attendance at the Society for Neuroscience or the American Aging Association.

OTHER EXPENSES

Morphology fees: Funds are requested for a subgroup of perfused-fixed tissue samples to be paraffin-embedded and available for thin sectioning for high-resolution light microscopy.

MRI fees: Funds are requested for scans for fat distribution and arthritis to be performed and brain-based scans to be collected for the aging archive. Once developed, the archive will be made available for the research community and will include a cross-section of males and females from young, middle-aged and old animals.

DEXA Scans: In concert with biannual physical examinations, a subgroup of 25 animals per year will be given DEXA scans to yield information on body composition (lean/fat) and bone density. This will provide valuable information for future projects, as well as inform the clinical staff of excessive weight in individuals.

Necropsy Fees: PAR tissues for younger NHPs will be collected, 10/year, in order to provide cross-sectional comparisons for end-tissue users.

RIA Lab Fees: Systemic markers of inflammation (CRP, IL6, TNF ☐) and will be assayed by the Endocrine Support Core in order to better characterize the PAS colony.

Equipment Maint & Repair: Funds are requested for minor repair or maintenance of equipment for refrigerators and freezers.

Software Maint Contract: Funds are requested for computer programs not covered by IS (for example, MRI imaging software) are made available with an annual fee from the servicing businesses.

Misc. Other Expenses: Funds are requested for printing costs for posters for scientific conferences, registration for local conference.

Memberships: Funds are requested for fees for Society for Neuroscience and the American Aging Association.

Registration/Conference fees: Funds are requested for fees for Society for Neuroscience and the American Aging Association.

ANIMAL SERVICES: Aging Resource Income Table

Last Funded Year (53)

Source	Funding (direct costs)
P51 base grant support	$164,595.63
Program income derived from P51 base grant	0
Other Sources	0
Total	$164,595.63

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$97,069.41
Program income derived from P51 base grant	99,569.41
Other Sources	0
Total	$196,638.82

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

The Aging Resource receives salary support and support for other expenditures from program income.

ANIMAL SERVICES: RESOURCES INFECTIOUS DISEASE RESOURCE SPECIFIC AIMS

This is a resource not described in the prior funding period that brings together a number of assets and capabilities that were previously in other Center entities, but which shared a focus on infectious disease research. In light of the significant focus on this research area and the concurrent presence of specialized SPF colonies supported by U24 and U42 grants, as well as the SIV-infected long-term survivor cohort, this resource was established to provide expertise to investigators who are performing infectious disease research and who would benefit from assistance with project performance.

Specific Aim 1. Model development. The *Plasmodium knowlesi* (PK) challenge model in rhesus macaques will be developed with the assistance of Excluded by Requester Naval Medical Research Center (11). Macaques will be intravenously inoculated with 100 sporozoites obtained 14 days after *Anopheles dirus* mosquitos are fed on a Pk-infected macaque using the Ozaki method. Beginning 6 days after sporozoite challenge, blood will be taken daily by ear prick at 1 pm. Pk infections are highly synchronized in the blood. Daily ear prick blood (10 µL) will be used for a PCR blot onto filter paper and for thin and thick malaria smears stained with Giemsa stain to quantify the percent of infected red blood cells according to standard procedures. When parasitemias exceed 2%, monkeys will be treated by IM injection of chloroquine 15 mg/kg on days 1, 3, and 5, and a single IM dose artesunate (AS; 5 mg/kg) to prevent death.

Specific Aim 2. Development of an autologous bone marrow transplant model. This rhesus macaque model will be developed with the assistance of Excluded by Requester and his transplant staff at the Fred Hutchinson Cancer Research Center (12, 13). Briefly, macaques will be habituated to a jacket-tether system. Recombinant human granulocyte colony-stimulating factor (rhG-CSF, 100 µg/kg) will be given daily as subcutaneous injections for 5 days. On day 5, bone marrow will be harvested from the humeri and/or femora and cryopreserved. In preparation for transplant, a femoral vein catheter will be placed for continuous intravenous (iv) hydration with continuous iv administration of broad-spectrum antibiotics (cetazadime, vancomycin, gentamicin) and an antiviral agent (acyclovir) and the animals will receive myeloblative total-body irradiation. Twenty-four hours after transplantation, the animals will be started on intravenous G-CSF at 100 µg/kg daily until the animals have attained stable neutrophil engraftment with an absolute neutrophil count of greater than 0.5×10^9/L (500/µL). Standard supportive care, including blood product transfusions, fluid and electrolyte management, and antibiotics will be given as needed.

Specific Aim 3. Development of state-of the art immunological assays and analysis. We will make services available to support subcontracted grant work in the NHP model (design and implementation of full immunological studies), custom sample processing (isolation, counting, and cryopreservation of cells, fluids, and nucleic acids), performance of optimized and validated flow cytometric assays (phenotype staining, ICS, CFSE, tetramer, TruCount), specialized and customized high-throughput analysis, economies-of-scale reagent purchasing, and archiving of cryopreserved samples. This operation was previously the Cellular Immunology Unit of the Immunology Support Core during the previous grant period, but was felt to be more appropriate to function as a component of the IDR, and will continue to be managed by Excluded by Requester.

Specific Aim 4. Maintenance of a National AIDS Macaque Resource. The resource will maintain a pool with an average census of 60 clinically stable and immunologically and virologically characterized SIV-infected macaques that have completed their initial research assignment. This pool of animals represents a unique and increasingly valuable research resource because of their value for priority research to identify strategies to eliminate HIV reservoirs (14). These animals will be made available to the US AIDS research community along with sufficient virologic and immunologic data to permit the identification of animals that are suitable for inclusion in additional studies. To maintain adequate immunologic characterization, animals in the pool will be bled and bronchoalveolar lavage will be performed at three week intervals to obtain serum, plasma, peripheral blood leukocytes and lung lymphocytes for virus-specific antibody, cellular immune, cellular proliferation and virus load analyses. The immunologic assays will be performed by the IDR. The ONPRC Molecular Virology Service Core will perform real-time PCR assays to quantify plasma SIV RNA.

ANIMAL SERVICES: RESOURCES: INFECTIOUS DISEASE RESOURCE RESEARCH STRATEGY

SIGNIFICANCE.

A significant expansion of nonhuman primate (NHP) research at the Oregon National Primate Research Center has been in the area of infectious diseases, due to the uniqueness of the NHP model in the study of AIDS and the current emphasis on bioterrorism. The ONPRC has one of the most highly respected programs in AIDS immunology and vaccine development. The cytomegalovirus-based vectors developed in this program have shown great promise as an AIDS vaccine in the SIV/macaque model and are now being evaluated as potential vaccine strategies for tuberculosis and malaria (1). Other infectious disease NHP models under study within the Division of Pathobiology and Immunology include rhesus and Japanese macaque rhadinoviruses (2,3) and simian varicella (4). The Vaccine and Gene Therapy Institute's Pacific Northwest Regional Center of Excellence for Biodefense and Emerging Infectious Diseases Research (PNWRCE) has a major research program on development of vaccines for vulnerable populations and has utilized an ABSL-3 NHP infectious disease models system including monkeypox virus (5, 6), west Nile virus (7,8), yellow fever virus (9), and chikungunya virus (10). The AIDS program in particular includes projects with large cohorts of animals and highly complex protocols involving multidisciplinary investigators in multiple laboratories investigating several hypotheses in parallel. To meet the challenge of this exponential expansion in infectious disease research and the specialized expertise required to conduct ABSL-2/3 and ABSL-3 infectious disease studies in NHPs, the ONPRC created a preliminary version of the Infectious Disease Resource (IDR) in 2007, and headed by Dr. Excluded by Request a veterinary pathologist who received his Ph.D. in viral pathogenesis at the Ohio State University. The IDR was formalized in 2012 as a new Resource Program. The goals of the IDR are to: 1) aid new investigators in their transition from research focused on small animals or humans to NHP; 2) facilitate accomplishment of multiple programmatic goals; 3) promote efficient use of the animal resource and advance cross-correlation of the pathologic, virologic and immunologic features of these unique models; 4) manage the SIV macaque resource as a national resource; 5) provide expertise in managing NHPs used in infectious disease studies to ensure safety for personnel and study animals; 6) provide access to state-of-the-art immunological assays and analysis for studies in the NHP model; and 7) provide a management core for hosting NHP infectious disease studies for off-site and collaborating investigators. The IDR has been highly successful since its inception and now provides support for over 400 animals assigned to infectious disease-related research grants.

INNOVATION.

We propose to develop new NHP infectious disease models, provide access to state-of-the-art immunological assays and analysis for studies in the NHP model, and maintain the National AIDS Macaque Resource. These resource enhancements will facilitate research program growth in vaccine development and in the priority area of AIDS reservoir research. Provision of state-of-the-art immunological assays will enhance the IDR's ability to host and provide immunologic support to collaborative projects. Maintenance of the AIDS macaque resource as a national resource will make these animals available to a wider scientific community.

Model Development- As a primary objective of the NPRC, we propose to expand our current portfolio of NHP infectious disease models. Two areas are targeted for development, the addition of a rhesus macaque/*Plasmodium knowlesi* challenge model for malaria vaccine efficacy testing and addition of an autologous bone marrow model in rhesus macaques with antiretroviral therapy-suppressed SIV infection to facilitate the evaluation of therapeutic vaccines and drugs aimed at elimination of the SIV reservoir.

State-of-the-art immunological assays and analysis supporting studies conducted in NHP models- The IDR makes available techniques and expertise under continual development in the state-of-the-art immunological laboratory of Excluded by Requester This includes access to top-end flow cytometric analyzers, cell sorters, parameter-pushing staining panels for phenotyping, tetramer staining, ICS assay, and sorting. It also includes the expertise to carry out large-scale trials, handling blood, lung wash, biopsy samples (lymph node, intestine, colon, bone marrow), and myriad tissues available from necropsy dissection.

Maintenance of a National AIDS Macaque Resource- The current SIV+ rhesus macaque resource will be managed as a national resource for rhesus macaques with stable, virologically and immunologically characterized SIV infection ready for assignment to research project requiring them. The availability of these

animals reduces overall use of rhesus macaques and provides a substantial cost savings to grants over infecting naive animals and maintaining them for 1-2 years to obtain a project-usable animal.

APPROACH.

reviewers' comments

Progress Report.

The number of animals on infectious disease protocols supported by the IDR increased 30.6% from 602 in 2009 to 786 in 2011; 729 animals were supported to date in 2012. The census of animals on study increased 13.1% from 405 in 2009 to 458 in 2012. The animals supported derived from Center individual research grants and program projects, collaborative projects subcontracted to Center investigators including eight subcontracted to IDR staff Excluded by Requester New NHP infectious disease models were developed for the following select agents and other ABSL-3 pathogens in rhesus macaques to support grant-supported research protocols: monkeypox virus, yellow fever virus, chikungunya virus, *Francisella tularensis* and *Mycobacterium tuberculosis*. The core also acquired expertise in new immunization technology (electroporation, new low-dose mucosal exposure, bronchoscopic delivery of pathogens to the lung) and a highly effective 5-drug antiretroviral protocol to support AIDS reservoir research and scaled up staffing sufficient to handle large projects with group sizes of 30-50 animals. The resource provided immunology support for three collaborative projects. Innovations to improve efficiency included temperature-changing incubators allowing complex ICS timings, custom-built inserts for centrifuge buckets to enable scaling up of sample number, a cheaper formula for our standard permeant, and new ways of homogenizing tissue for bacterial load analysis. The AIDS Macaque Resource provided 81 SIV-infected macaques to research projects during the reporting period.

Future Plans.

Our goals over the next funding cycle are:

Specific Aim 1. Model development. The *Plasmodium knowlesi* (PK) challenge model in rhesus macaques will be developed with the assistance of Excluded by Requester Naval Medical Research Center (11). Macaques will be intravenously inoculated with 100 sporozoites obtained 14 days after *Anopheles dirus* mosquitos are fed on a Pk-infected macaque using the Ozaki method. Beginning 6 days after sporozoite challenge, blood will be taken daily by ear prick at 1 pm. Pk infections are highly synchronized in the blood. Daily ear prick blood (10 µL) will be used for a PCR blot onto filter paper and for thin and thick malaria smears stained with Giemsa stain to quantify the percent of infected red blood cells according to standard procedures. When parasitemias exceed 2%, monkeys will be treated by IM injection of chloroquine 15 mg/kg on days 1, 3, and 5, and a single IM dose artesunate (AS; 5 mg/kg) to prevent death.

Specific Aim 2. Development of an autologous bone marrow transplant model. This rhesus macaque model will be developed with the assistance of Excluded by Requester and his transplant staff at the Fred Hutchinson Cancer Research Center (12, 13). Briefly, macaques will be habituated to a jacket-tether system. Recombinant human granulocyte colony-stimulating factor (rhG-CSF, 100 µg/kg) will be given daily as subcutaneous injections for 5 days. On day 5, bone marrow will be harvested from the humeri and/or femora and cryopreserved. In preparation for transplant, a femoral vein catheter will be placed for continuous intravenous (iv) hydration with continuous iv administration of broad-spectrum antibiotics (cetazadime, vancomycin, gentamicin) and an antiviral agent (acyclovir) and the animals will receive myeloblative total-body irradiation. Twenty-four hours after transplantation, the animals will be started on intravenous G-CSF at 100 µg/kg daily until the animals have attained stable neutrophil engraftment with an absolute neutrophil count of greater than 0.5×10^9/L (500/µL). Standard supportive care, including blood product transfusions, fluid and electrolyte management, and antibiotics will be given as needed.

Specific Aim 3. Development of state-of the art immunological assays and analysis. We will make services available to support subcontracted grant work in the NHP model (design and implementation of full

immunological studies), custom sample processing (isolation, counting, and cryopreservation of cells, fluids, and nucleic acids), performance of optimized and validated flow cytometric assays (phenotype staining, ICS, CFSE, tetramer, TruCount), specialized and customized high-throughput analysis, economies-of-scale reagent purchasing, and archiving of cryopreserved samples. This operation was previously the Cellular Immunology Unit of the Immunology Support Core during the previous grant period, but was felt to be more appropriate to function as a component of the IDR, and will continue to be managed by Excluded by Requester

Specific Aim 4. Maintenance of a National AIDS Macaque Resource. The resource will maintain a pool with an average census of 60 clinically stable and immunologically and virologically characterized SIV-infected macaques that have completed their initial research assignment. This pool of animals represents a unique and increasingly valuable research resource because of their value for priority research to identify strategies to eliminate HIV reservoirs (14). These animals will be made available to the US AIDS research community along with sufficient virologic and immunologic data to permit the identification of animals that are suitable for inclusion in additional studies. To maintain adequate immunologic characterization, animals in the pool will be bled and bronchoalveolar lavage will be performed at three week intervals to obtain serum, plasma, peripheral blood leukocytes and lung lymphocytes for virus-specific antibody, cellular immune, cellular proliferation and virus load analyses. The immunologic assays will be performed by the IDR. The ONPRC Molecular Virology Service Core will perform real-time PCR assays to quantify plasma SIV RNA.

REFERENCES

Excluded by Requester

Program Director/Principal Investigator (Last, First, Middle): Robertson, Joseph E./Haigwood, Nancy L.

RESEARCH RESOURCES-INFECTIOUS DISEASES DETAILED BUDGET FOR INTIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Excluded by Requester	Assoc Scientist/Head	% Effort			Institutional Base Salary	4,493	1,123	5,616
	Res Asst 2					20,017	7,006	27,022
	Res Assoc					6,976	2,442	9,417
	Project Mgr					18,388	5,700	24,088
	Staff Scientist 3/Lab Dir					21,880	6,783	28,663
To Be Named	Staff Scientist	6.00				47,700	14,787	62,487
	SUBTOTALS →					119,453	37,840	157,293

CONSULTANT COSTS		
None Requested	0	0
EQUIPMENT *(Itemize)*		
None Requested	0	0
SUPPLIES *(Itemize by category)*		
Personal Protective Equipment	700	
Laboratory Supplies	1,500	2,200
TRAVEL		
Domestic	800	800
INPATIENT CARE COSTS		0
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		
None Requested	0	0
OTHER EXPENSES *(Itemize by category)*		
Bronchoalveolar Lavage	8,280	
Plasma SIV RNA Assay	2,131	
Serum Chemistry & Blood Collection	3,894	
Pathology Fees	26,532	
Equipment Maint & Repair	5,000	
		45,837
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 206,130
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 206,130

RESEARCH RESOURCES-INFECTIOUS DISEASES
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	157,293	162,012	166,872	171,878	177,035
CONSULTANT COSTS	0	0	0	0	0
EQUIPMENT	0	0	0	0	0
SUPPLIES	2,200	2,266	2,334	2,404	2,476
TRAVEL	800	824	849	874	900
INPATIENTS CARE COSTS	0	0	0	0	0
OUTPATIENTS CARE COSTS	0	0	0	0	0
ALTERATIONS AND RENOVATIONS	0	0	0	0	0
OTHER EXPENSES	45,837	47,212	48,628	50,087	51,590
DIRECT CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	206,130	212,314	218,683	225,244	232,001
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	206,130	212,314	218,683	225,244	232,001
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					1,094,373

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

PERSONNEL

Associate Scientist/Head - Excluded by Requester % Effort Program Income). Responsible, as the Infectious Disease Resource (IDR) Core Director, for program projects conducting infectious disease studies in NHPs. Also interacts with the principal investigators in planning and conducting IDR protocols to insure research objectives are met. Responsible for supervising the staff, including the IDR project manager. Other management responsibilities include oversight of the AIDS Macaque resource, oversight of the model development objectives, oversight of the budget, preparation of IACUC and Biosafety documents, preparation of progress reports and participation in grant and manuscript preparation. Assists in technical aspects of the projects when necessary including animal sampling procedures, health assessment and anatomic pathology.

Research Assistant 2 - Excluded by Requester % Effort Responsible for obtaining blood, urine, saliva, bronchoalveolar lavage and lymph node biopsy samples from NHPs in ABSL 2/3 and -3 containment settings, as necessary to support projects hosted by the IDR. Other responsibilities include assisting with acquisition and processing of tissues at necropsy for immunological and virological studies, animal health monitoring and entry of procedures into individual animal records as required by the Animal Welfare Act. Is the IDR laboratory technician responsible for new primary cell line derivation and identification of viral agents recovered from study animals. .

Research Associate - Excluded by Requester % Effort Responsible for performing the assays in the LU assay portfolio, participating in the optimization and scaling up of all the techniques offered, and is an expert on the antibody reagents used in flow cytometry. Constitutes the pre-trained 'standing staff' of the IDR-LU, available to assist in planning a study, conducting pre-study R&D, and then fully performing all technical work associated with the required immunologic assessments.

Project Manager - Excluded by Requester % Effort esponsible for scheduling and coordinating day-to-day IDR project activities including animal selection, animal assignments, immunization/challenge procedures, sample acquisition and processing, necropsies, sample distribution, and monitoring individual animal blood sample volumes, complete blood counts, serum chemistry procedures and weight to assess animal health, and individual animal health observations. Responsible for providing quality assurance for staff training and adherence to standard operating procedures developed to maintain personnel and animal safety and the integrity of the study

Staff Scientist 3/Lab Director - Excluded by Requester % Effort Income). Responsible for directing the IDR's laboratory unit (IDR-LU) devoted to providing immunology support for Center investigators who's NHP infectious disease studies and laboratories are not primarily focused on immunology but required immunologic assay support, and immunology support for off-site investigators' projects. Responsible for (1) interacting with interested outside investigators to explore possible work and serving as the subcontracting principal investigator for studies that extensively utilize immunologic assessments, (2) helping investigators prepare funding proposals, (3) conducting any necessary R&D to customize or optimize or develop new assays, (4) coordinating study protocols with other IDR staff (5) organizing the laboratory logistics prior to initiating a study, and supervising it thereafter, (6) QC-checking, analyzing, and reporting all data, and (7) co-authoring any publications from the work.

Staff Scientist – To be named. (12 calendar months effort: 6.0 ORIP, 6.0 Program Income). A doctoral level scientist or veterinarian will be recruited to assist Excluded by in managing the Resource. The growth in NHP infectious disease research activities hosted by the IDR has outstripped its professional personnel resources and additional professional expertise is critically needed to reduce Excluded by workload. The staff scientist will assume responsibility for a portion of the IDR, participate in the oversight of IDR research protocols and assist investigators with budget preparation, preparation of IACUC and Biosafety documents.

SUPPLIES

Personal Protective Equipment: Funding is requested to purchase tethering equipment (tether jackets, tethers and tether endplates) necessary to support development of a bone marrow transplant model in rhesus macaques. Training of the animals to adapt to tether restraint and maintaining them in tether restraint is necessary to provide the post-transplant critical care required.

Laboratory supplies: Funding is requested to ensure working stocks of consumable supplies and reagents including: Vacutainer® blood tubes, needles, syringes, cryovials, cryovial storage boxes, ketamine HCl, sodium pentobarbital and reagent packs for hematology and serum chemistry analyzers, and disposable protective clothing.

TRAVEL

Travel funds are requested to cover the cost of consultant travel. It is necessary for our consultants to be onsite for development of both the malaria vaccine challenge model and the bone marrow transplant model.

OTHER EXPENSES

Funds are requested to pay for the following services:

Bronchoalveolar lavage: Requested for bronchoalveolar lavage procedures performed by the Division of Comparative Medicine's (DCM) Surgery unit to obtain bronchoalveolar fluid necessary to monitor SIV-specific T-cell responses. The average census of the resource is 30 animals and bronchoalveolar lavages will be performed eight times annually at 6 week intervals.

Plasma SIV RNA Assay: Requested for quantitative real-time polymerase chain reaction quantification of plasma SIV RNA performed by the ONPRC Virology Core to monitor SIV loads. The average census of the resource is 30 animals and SIV loads in the animals will be determined eight times annually at 6 week intervals.

Serum Chemistry & Blood Collection: Requested for serum chemistry health monitoring panels and complete blood counts (CBC) performed by the DCM clinical pathology laboratory. The average census of the resource is 30 animals and serum chemistry and CBCs will be evaluated eight times annually at 6 week intervals to monitor animal health.

Pathology Fees: Requested for necropsies performed by DCM's pathology unit. Twenty-five necropsies with full histologic evaluation are anticipated annually on AIDS Macaque Resource animals due to disease progression.

Equipment Maintenance/Repair: Funds are requested to defray the cost of maintaining service contracts on hematology and serum chemistry analyzers and laboratory centrifuges, and maintenance and repair of the Resources bronchoscopy equipment.

ANIMAL SERVICES: Infectious Disease Resource Income Table

Last Funded Year (53)

Source	Funding (direct costs)
P51 base grant support	$0
Program income derived from P51 base grant	285,926.06
Other Sources	0
Total	$285,926.06

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$200,514.53
Program income derived from P51 base grant	200,514.53
Other Sources	0
Total	$401,029.06

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

The Infectious Disease Resource receives salary support and support for other expenditures from program income.

ANIMAL SERVICES: RESOURCES JAPANESE MACAQUE RESOURCE SPECIFIC AIMS

The ONPRC Japanese Macaque Resource is increasingly recognized as an important reservoir of animals with unique phenotypes (presumably resulting from specific genetic susceptibilities) relevant to multiple sclerosis and age-related macular degeneration.

To maintain an appropriate population to exploit these features, the Resource is pursuing the following steps in the next funding period:

Specific Aim 1. Expand breeding production, by rebalancing the demographic distribution, using best practices to optimize colony and genetic health.

Specific Aim 2. Employ Information Systems (IS) capacities to model and an inform JMR colony management decisions.

Specific Aim 3. Characterize colony members for pedigree relationships and risk for genetic diseases.

Specific Aim 4. Maintain centralized genetic and phenotypic records of the JMR to inform colony management decisions.

ANIMAL SERVICES: RESOURCES: JAPANESE MACAQUE RESOURCE RESEARCH STRATEGY

SIGNIFICANCE

The ONPRC Japanese macaque (*Macaca fuscata,* Snow Monkey; JM) captive breeding colony was established in 1965 with a gift of 55 animals from the Japanese government. The founders originated from the Hiroshima prefecture and have produced over 1600 descendants. The current troop spans 5 generations and includes 190 members. To the best of our knowledge, this is the largest and oldest JM captive-bred colony in the world. The newly defined Japanese Macaque Resource (JMR) serves as a unique research resource, offering the opportunity to study naturally occurring and biomedically important disease models not available in other NHP species or even in other JM colonies. Moreover, the ONPRC JM colony serves as an essential resource for multiple research programs, generating $13,371,910 in grant and contract total costs for JM research over the past 4 years.

The JMR supports several distinct lines of research at the ONPRC. One disease model is Japanese macaque encephalomyelitis (JME), which recapitulates both the etiological and pathophysiological processes that occur in multiple sclerosis (MS) and related demyelinating diseases. To our knowledge, this disease only occurs in the ONPRC JM colony. Only a subset of JMR family lineages is susceptible to this disease, suggesting genetic predisposition for JME; there is also strong evidence for the involvement of a viral trigger, similar to findings in MS (1). Isolation of the viral agent associated with JME, and subsequent intracranial introduction of the virus into JMs, has demonstrated that the virus can trigger inflammation and demyelination in high risk family lineages. Thus, the JMR provides an unprecedented opportunity to investigate both spontaneous and inducible MS-like demyelinating disease in non-human primates. Moreover it offers a unique resource to test the safety and efficacy of drugs designed to prevent demyelinating attacks, as well as agents aimed at repairing demyelinating lesions.

An independent subset of individuals within the JMR exhibits a retinal disease phenotype that closely parallels human "dominant drusen" syndromes, such as Malattia Leventinese/Doyne honeycomb dystrophy. The phenotype and pathophysiology of this syndrome closely resemble age-related macular degeneration

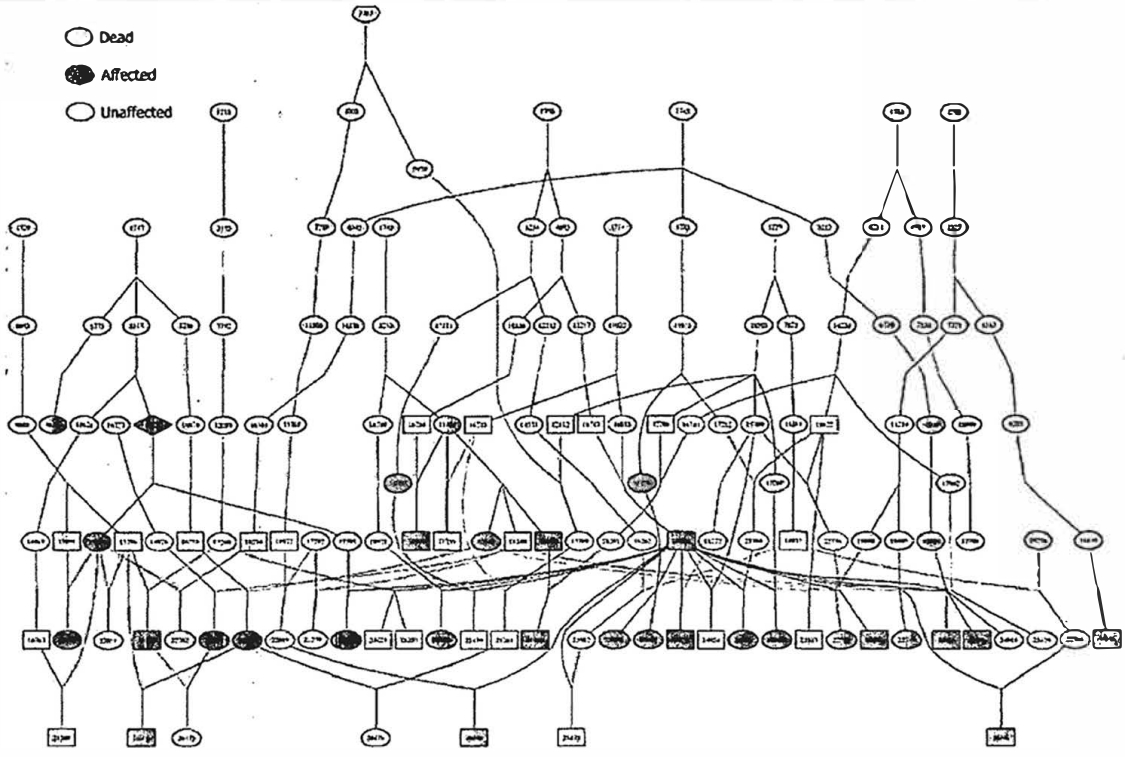


Figure 1. Partial JM pedigree, demonstrating the dominant inheritance of the drusen trait. Individuals with confirmed drusen are shown in green, individuals unaffected by drusen are in yellow, unknown status are in white, and dead are shown in grey. Males are indicated by boxes and females by circles.

(AMD), the leading cause of vision loss in the elderly, with prevalence expected to increase over 50% by 2020. The hallmark of both dominant drusen and AMD is the presence of the sub-retinal deposits called drusen. Dr. Excluded by Requester laboratory has shown that drusen deposits in the JM model have all the morphological and molecular characteristics seen in human AMD, the most prevalent cause of blindness in the elderly (2). Distinct advantages of this model are that it is transmitted as a simple Mendelian, dominant trait, can be propagated through selective breeding, and is detectable in juveniles as young as three years old (3). A portion of the JM pedigree illustrating the dominant pattern of this trait is shown in Fig. 1. The identification and documentation of this phenotype provided the basis for substantial funding that is now in place to further characterize this model as an optimal resource for preclinical testing of AMD therapies.

The JMR troop maintains a strong, matrilineal social structure, and the social and behavioral interactions within this colony have a long documented history. These unique social data has been leveraged by Excluded by R to investigate the effects of experimental manipulations, such as hormonal changes associated with ovarian loss or failure, on individual temperament and social interactions (4). The behavioral data have also been correlated with neurophysiological, cellular and gene expression profiles (5, 6), providing insights into the molecular mechanisms underlying behavioral and temperamental changes.

JMs have been utilized in diet-induced obesity (DIO) studies for the past several years, focusing on the significant effects of high-fat diet on maternal and child health (7-10). The ONPRC Obese Resource depends on the JM colony to supply new animals as JMs age out of the DIO studies or are terminated. The maternal and child health study design has also required the removal of more than half of the breeding-age females from the main troop, resulting in a significant drop in production within the JMR. Thus, the critical and overarching goal of the JMR is to restore the health and demographic balance of the JMR during the next funding cycle. This effort will be essential to capitalize on the unparalleled disease models in the JM colony and to fulfill the multiple research programs that are dependent on this resource.

INNOVATION

Given the unique history of the founding colony, coupled with the nearly 50-year history of captive breeding, the JMR represents a genetically unique resource for biomedical research. The JMR supports innovative and interdisciplinary research that cannot be replicated in other NHP colonies. As an example, a research program recently funded by the Congressionally Directed Medical Research Programs (through the Department of Defense) Multiple Sclerosis Program involves a team of ONPRC investigators in the fields virology Excluded neurobiology and demyelination Excluded by Re genetics Excluded by and NHP brain aging Excluded by Requester and included OHSU collaborators contributing expertise in NHP brain imaging Excluded by Requester and multiple sclerosis Excluded by The JM dominant drusen studies led by Excluded by Requester involve close collaborations with the ONPRC Primate Genetics Program as well as several investigators at OHSU's Casey Eye Institute (Excluded by Requester). Both of these JM-specific disease models and multidisciplinary research approaches offer exceptional opportunities to determine the origins of two human diseases that affect millions of individuals worldwide, and for developing novel therapies for these diseases.

APPROACH

reviewers' comments

SPECIFIC AIMS

Specific Aim 1. Expand breeding production, by rebalancing the demographic distribution, using best practices to optimize colony and genetic health. The JMR currently comprises 190 individuals, including 115 females and 75 males, with 91 individuals under the age of five. The free-ranging colony resides within a 1-acre corral; a fixed population limit of 190 individuals maximizes the health and wellbeing of animals in the corral. However, research demand for the JM population has steadily increased over the past 5 years, exceeding the capacity of this population. Overharvesting of animals has resulted in a decrease of breeding-age females (n=41), and accordingly, a drop in offspring production (28-32 offspring/year). Meanwhile, the imbalanced ratio female to males has led to increased aggression and injury in the troop. To restore the demographic distribution of the population and to increase production rate, we will retain the majority of juvenile and breeding age females, while selectively reducing the male population. This plan aims to

rebalance the corral population with a female to male ratio to 3:1. As the number of breeding females increases, and production reaches the target goal of 42-47 newborns per year (projected for 2015), a maintenance harvest plan for both males and females will be implemented (see Aim 2).

In addition, we aim to supplement the pool of research JMs, and to simultaneously increase genetic diversity in the JM, by establishing additional small breeding groups outside of the corral. Specifically, we will purchase 4-5 males in years 1 and 3, and pair these males with up to 12 breeding females retired from compatible research studies. Thus breeding females that served as controls for the DIO studies (not on high-fat diet), or participated in dominant drusen studies, or are known carriers of JME risk can be re-purposed to produce additional generations of research animals. Since adult JMs are not accepted back into the corral after a long period of absence, small group housing provides a critical means to extend the utility of valuable breeding females and to augment JM production. Moreover, by including purchased male JMs as breeders in these groups, we have opportunity to introduce additional genetic diversity into the JMR. Thus, a subset of the offspring will be introduced into the corral as young juveniles, while they are still accepted by the JM troop.

Finally, the JMR Oversight Committee will annually review progress towards meeting the goals of improving colony health, diversity and production in the JMR. The JMR Oversight Committee includes leadership from DCM, Primate Genetics, and the Behavioral Sciences Unit (BSU), as well as two members of the OHSU research community, initially Excluded by Requester

Specific Aim 2. Employ Information Systems (IS) capacities to model and an inform JMR colony management decisions. Due to the limited number of JMs in this resource, it will be critical to consistently evaluate the impact of potential harvest plans on colony health, stability and diversity. The ONPRC IS group is developing population-modeling capabilities, with the JMR being one of the first target populations for implementation. Population modeling will allow us to evaluate the predicted consequences of harvesting different numbers of males, females, and affected or unaffected individuals on future population projections. Annual census data will be collected and reviewed to maintain accurate demographic projections, and observed changes in production and attrition rates will be incorporated annually. The modeling will inform the specific harvest strategy each year. Modeling of our current population identifies a sustainable harvest rate of 5 females and 15 males per year. We project the harvest rates to increase 50-70% as the colony population is restructured, producing the target goal of 30-34 research animals per year.

The selection of specific individuals for removal will require careful evaluation. The primary goal is to select animals in a manner that maximizes genetic diversity and social stability of the JMR. Thus, the selection process will be informed by validated pedigree data, calculated kinship values, and founder representation to identify individuals with genetic overrepresentation (See Aim 3). Second, social stability in the JMR is achieved by maintaining critical dominant individuals that serve as "peace-keepers" (evaluated by the BSU), and by limiting the size of the male population. The process of selection thus will require input from DCM colony managers, Genetics, BSU, and the JMR leadership.

Once a harvest list is developed, research assignments will take into account the current genetic requirements for research studies, with JME-susceptible animals having priority for JME studies, drusen-positive animals for the AMD study, and so forth. Healthy control subjects will be selected to be age and sex-matched. Studies that do not have specific genetic risk requirements will receive the balance of remaining animal assignments per year. The JM Users Group, composed of funded researchers making use of the resource, as well as DCM, Genetics, BSU, and JMR personnel, meet twice a year to discuss the availability of animals and to discuss research needs. Additionally, the Users Group meeting provides opportunity to coordinate research studies to maximize the utility of each animal, for example making available the collection of eyes for drusen studies at the end of compatible, terminal research protocols.

Specific Aim 3. Characterize colony members for pedigree relationships and risk for genetic diseases. Validated pedigree relationships are critical for informing colony management decisions and research animal assignment of JMR animals. JM parent-offspring relationships are determined using a 28-microsatellite panel, with genotyping analysis performed by the Veterinary Genetic Laboratory in Davis, CA. Newborns are screened against all potential sires and dams to ascertain the true parents; the genotypes and validated parental assignments are uploaded into the Labkey/PRIMe database. The pedigree relationships are used to calculate the evaluate colony genetic diversity measures, which will be monitored annually using established

methods implemented throughout the ONPRC P51 colony management plans. The pedigree data is also critical for identifying the most appropriate animals for research study assignment (See Aim 4).

Phenotypic characterization of individuals within the JMR is required for appropriate research assignment to the JME and dominant drusen projects. Although direct genetic screening for disease risk of these pathologies would be ideal, the critical risk alleles for these traits have not yet been identified. However, biomarker assays and imaging have been shown to successfully identify high-risk individuals for these two traits. Thus, during the regularly scheduled annual physical exams, we will screen JMR individuals for molecular evidence of demyelinating disease by collecting cerebral spinal fluid (CSF), bronchioalveolar lavages and serum in up to 50 individuals per year. These samples are used to measure for Japanese macaque rhadinovirus load by real time PCR, immune responses to myelin components (myelin oligodendrocyte glycoprotein, myelin basic protein, and proteolipid protein), and to detect the presence of oligoclonal bands in the CSF over time, with elevated levels correlated with risk for spontaneous JME and response to virally induced demyelination. Analysis of the assay results will be provided by JME investigators.

The JMR will also assist with the characterization and recovery of spontaneous JME cases. A recently established standard operating procedure is on file with the Division of Comparative Medicine (DCM) and describes the clinical phenotype (limb weakness, blindness, difficulty in eating or drinking), which will trigger the protocol. Briefly, participating members will be notified and will then coordinate with clinical staff the procurement of blood and CSF samples for analysis. Moreover, if a physical exam does not rule out JME, *in vivo* diagnosis and prognosis of the case will be assisted with a series of MRI scans. Clinical support will attempt to recover the animal with an acute attack of JME, so that it can be put back into the colony and the natural history of JME can be more completely defined. If these efforts fail, then protocols for central nervous system collection, high-field MRI scans, and subsequent tissue processing are also in place. Although the original index cases of spontaneous JME included animals of a range of ages, more recent cases have been composed of primarily young animals. We speculate that the index cases represent the introduction of a suspected agent into the colony, with genetically susceptible individuals of all ages being quickly affected. In subsequent years, genetically susceptible juveniles were most likely to be exposed to an etiological agent for the first time, and therefore formed the majority of new JME cases. However, MRI scans of portions of the JM colony have revealed white-matter scars with a similar spatial distribution as observed for acute JME lesions in 10% of the adult animals that may indicate survivorship from earlier remitting cases of JME in this population. A more overt example of a clinical JME case in an adult animal is shown in Fig. 2, a 14-year-old male that

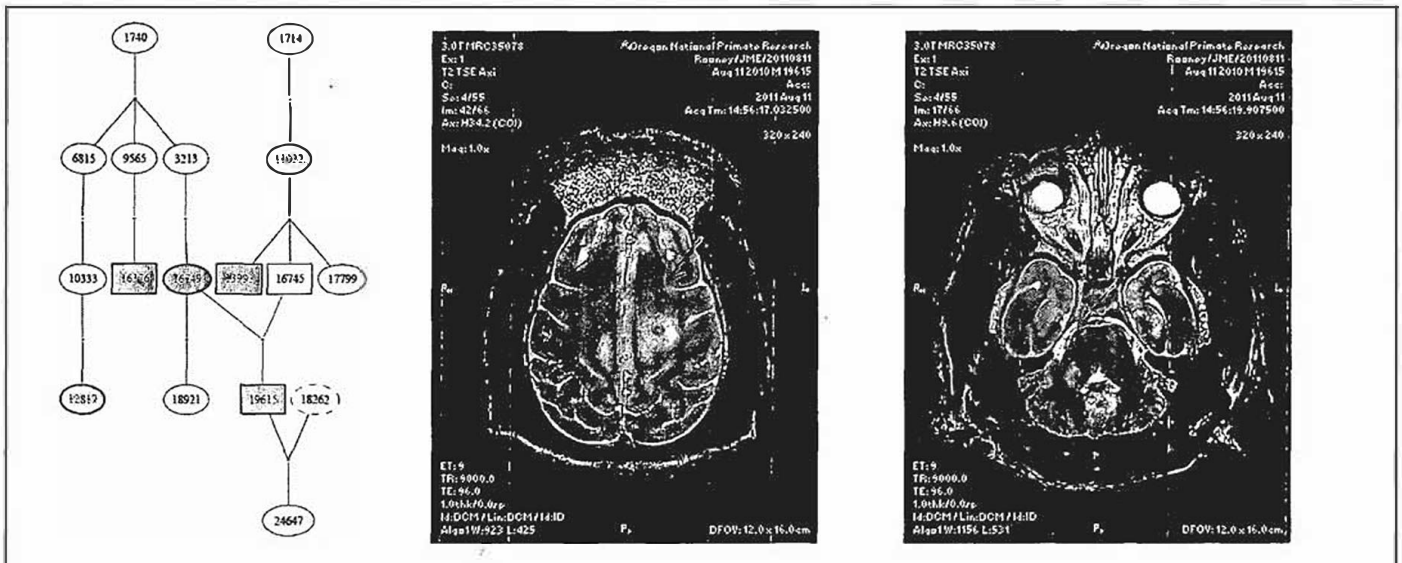


Figure 2. Pedigree (left) and MRIs (middle and right) from a 14-year-old JM with JME symptoms. This animal, identifier number 19615, was produced from two matrilines that had previously exhibited cases of JME. In fact, his dam, 16749, had survived from her initial JME episode and was returned to the colony, but relapsed several months later. For 19615, two lesions (red arrows) were discovered by MRI analysis, in the forebrain (middle) and the sub-cerebellar white matter (right).

exhibited ataxia in both hind limbs as well as a head-tilt. The latter data suggests that older adults may have survived a primary attack(s), but secondary triggers can spark disease relapse.

We will also continue to use retinal photography to screen up to 50 individuals per year for the drusen phenotype and to evaluate disease progression. If validated genetic risk alleles for either trait are identified over the next 5 years, direct genetic screening would replace these indirect screening approaches. Protocols are well-established for retinal phenotypic screening using retinal fundus photography. The procedure requires sedation but is noninvasive and requires 10-15 minutes per animal. Screening is accomplished as part of the semi-annual roundups. Fig. 3 shows three examples of photographs of the back of the eye in affected individuals with a range of drusen severity. Studies in progress are examining the impact of the disease on retinal function as measured by the electroretinogram and on photoreceptor density as measured *in vivo* by the new high-resolution imaging method of adaptive optics, as well as the possible influence of a high fat diet on disease progression. Studies of postmortem retinal tissue obtained from the Tissue Distribution Program has documented that drusen in these animals express several key molecular markers of drusen as described in human AMD patients.

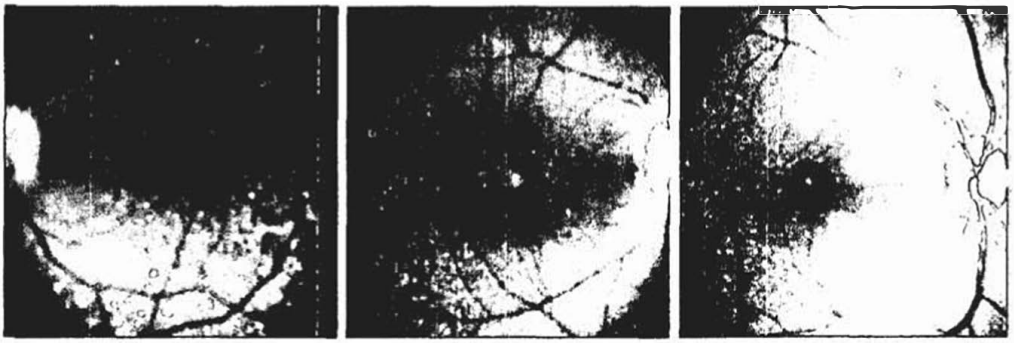


Figure 3. Retinal fundus photographs of 3 Japanese macaques affected with the dominant drusen phenotype, ranging from very severe (left) to moderate severity (right). The fovea/macula is in the center, and the optic nerve (large white oval) is at the far left in the left-hand photograph (left eye) and at the far right in the other two (right eyes). Drusen are seen as white dots throughout the retina, often with particularly high density in the central macula.

Specific Aim 4. Maintain centralized genetic and phenotypic records of the JMR to inform colony management decisions. We will deposit all pedigree and phenotypic data into the Labkey/PRIMe genetic database to establish a specific comprehensive resource for evaluating and managing the JMR. The data will also be used to update the historical JM pedigree, and to overlie phenotypic data to enable tracking of disease prevalence and transmission. As an example, a selected portion of the JM pedigree, with drusen phenotype data incorporated, is shown (Fig. 1). This composite pedigree resource is critical for accurately monitoring kinship relationships, genetic representation, and phenotypic traits, for both colony management purposes and research assignment. If new biomedical traits are discovered in the JMR, they will also be incorporated into the pedigree data as well. The JM trait data are currently curated by a dedicated manager Excluded by Requester who receives updates on affected status from each JM investigator to insure consistency and accuracy in data reporting and management. She also contributes to the process of animal selection for study assignment, by reviewing the composite pedigree and phenotypic data.

REFERENCES

Excluded by Requester

ANIMAL SERVICES: RESOURCES JAPANESE MACAQUE RESOURCE BIOSAFETY

All Japanese Macaque (JM) sample handling will be conducted in accordance with Biosafety Level 2 standards, in adherence to the criteria outlined in *Biosafety in Microbiological and Biomedical Laboratories*, 5th edition, including all standard microbiological practices. Each laboratory has locking, self-closing doors, is designed to be easily cleaned and decontaminated, and has an eyewash station and a sink for hand washing. A biosafety cabinet that is certified annually is used for all manipulations of potentially infectious material. Personal protective equipment is provided for use in the laboratory, and is removed before entering non-laboratory areas. A laboratory-specific biosafety manual is available that outlines safety practices, use of personal protective equipment, proper disposal, and spill response. Personnel are trained in accordance with this manual, and are provided with medical surveillance. Access to the laboratory is restricted when work is being conducted and signage at the laboratory entrance provides information regarding the biosafety level, potential hazards and entry/exit requirements. Incidents that may result in exposure are evaluated and treated, and reported to the lab supervisor and the Biosafety Officer.

All physical evaluations of JMs will be performed at Animal Biosafety Level 2, in adherence to the criteria outlined in *Biosafety in Microbiological and Biomedical Laboratories*, 5th edition, including all standard microbiological practices. In addition, access to the facility is restricted, all personnel have specific training in performing procedures and the handling of animals, and are supervised by individuals with knowledge of potential hazards, animal manipulations. All protocols are reviewed and approved by the IACUC, and when applicable by the IBC, including worker safety and health concerns.

The facility has inward opening, self-closing doors, is designed to be easily cleaned and decontaminated, and has an eyewash station and a sink for hand washing. Personal protective equipment, including uniforms or gowns, gloves, and eye and face protection is provided for use in the facility, and is removed before leaving the facility. A biosafety manual is available that outlines safety practices, use of personal protective equipment, proper disposal, and spill response. Personnel are trained annually in accordance with this manual, and are provided with medical surveillance. Eating, drinking, and food storage are not permitted in the facility, and policies are in place for the safe handling of sharps. Signage at the laboratory entrance provides information regarding the biosafety level, potential hazards, and entry/exit requirements. Incidents that may result in exposure are evaluated and treated, and reported to the lab supervisor and the Biosafety Officer.

Program Director/Principal Investigator (Last, First, Middle): Robertson, Joseph E./Haigwood, Nancy L.

RESEARCH RESOURCES-JAPANESE MACAQUES DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Excluded by Requester	Assoc Scientist	% Effort			Institutional Base Salary	4,700	1,175	5,875
	Sr. Res Assoc					4,240	1,484	5,724
	SUBTOTALS →					8,940	2,659	11,599

CONSULTANT COSTS		
None Requested		0
EQUIPMENT *(Itemize)*		
None Requested	0	
		0
SUPPLIES *(Itemize by category)*		
NHP Imports	27,500	
		27,500
TRAVEL		
None Requested		0
INPATIENT CARE COSTS		
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		
None requested		0
OTHER EXPENSES *(Itemize by category)*		
Parentage Analysis	1,750	
Phenotype Characterization	4,161	
MRI Fees	5,540	
Retinal Characterization	530	
Quarantine Housing	1,021	
Small Group Housing	9,697	
		22,699
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 61,798
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 61,798

PHS 398 (Rev. 6/09) **Form Page 4**

RESEARCH RESOURCES-JAPANESE MACAQUES
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	11,599	11,947	12,305	12,675	13,055
CONSULTANT COSTS	0	0	0	0	0
EQUIPMENT	0	0	0	0	0
SUPPLIES	27,500	28,325	29,175	30,050	30,951
TRAVEL	0	0	0	0	0
INPATIENTS CARE COSTS	0	0	0	0	0
OUTPATIENTS CARE COSTS	0	0	0	0	0
ALTERATIONS AND RENOVATIONS	0	0	0	0	0
OTHER EXPENSES	22,699	23,379	24,081	24,803	25,547
DIRECT CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	61,798	63,651	65,561	67,528	69,554
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	61,798	63,651	65,561	67,528	69,554
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					328,092

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

PERSONNEL

Associate Scientist - Excluded by Requester % Effort
Responsible for overseeing and coordinating the Japanese Macaque Resource activities which includes working closely with the DCM staff to review and update both short-term and long-term goals of the resource, and, accordingly, evaluating genetic diversity measures and phenotypic data to help prioritize animals for colony breeding or study assignment. Also responsible for overseeing the genetic characterization and pedigree analysis, database management and user group forums to discuss planned and ongoing JM research needs.

Sr. Research Associate - Excluded by Requester % Effort
Responsible for collecting and evaluating JM parentage and pedigree data; monitoring and updating the phenotypic data, as needed, to insure all spontaneous JME cases, JME first-degree relatives and drusen cases or other disease model data are accurately recorded; contributing to the selection of animals for research assignment, by generating phenotypic tables and pedigree relationships required to inform animal disposition.

SUPPLIES

NHP Imports: Funds are requested to obtain 5 breeding-age, male JMs in years 1 and 3 for small breeding groups to produce offspring that can augment the research pool, or be introduced into the corral to increase genetic diversity. The acquired males will be co-housed with breeding age females retired from compatible research projects. Costs for acquiring the JMs, as well as initial quarantine and subsequent husbandry costs of two 10-12 animal breeding groups, are averaged over the 5-year period.

OTHER EXPENSES

Parentage Analysis: Funds are requested for blood draws, sample shipping, and STR genotyping fees for all offspring born each year in both the corral and small group housing.

Phenotype Characterization: Funds are requested for the analysis of viral load and myelin biomarkers by collecting saliva, EDTA blood, bronchioalveolar lavage, and cerebral spinal fluid (50 animals/year) and by using MRI scans to detect lesions/scars suggesting an inflammatory event (12 animals/year). For macular disease characterization, retinal photography will be used to detect or measure progression of drusen (50 animals/year).

MRI fees: MRI imaging is requested for the characterization of up to 12 JMs/year to evaluate history and risk for JME inflammation. This analysis provides critical information for both study and breeding animal selection in the JMR.

Retinal Characterization: This analysis provides information on the status and progression of macular disease in the JMR individuals, informing the selection of animals for research and breeding purposes.

Quarantine Housing: Two groups of up to 5 imported JMs acquired in years 1 and 3 will be held in quarantine prior to inclusion in common housing, as is required for all NHPs.

Small Group Housing: Both imported male JMs and appropriate female JMs retired from research protocols will be housed in harem groups for breeding purposes, both to supplement the research pool and to introduce genetic diversity into the JMR corral breeding group.

ANIMAL SERVICES: Japanese Macaque Resource Income Table

Last Funded Year (53) (New Unit – No prior budget)

Source	Funding (direct costs)
P51 base grant support	$0
Program income derived from P51 base grant	0
Other Sources	0
Total	$0

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$61,797.55
Program income derived from P51 base grant	61,797.55
Other Sources	0
Total	$123,595.10

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

The Japanese Macaque Resource receives salary support and support for other expenditures from program income.

TITLE: ASSISTED REPRODUCTIVE TECHNOLOGIES SUPPORT CORE

CORE-SUPPORTED PERSONNEL:

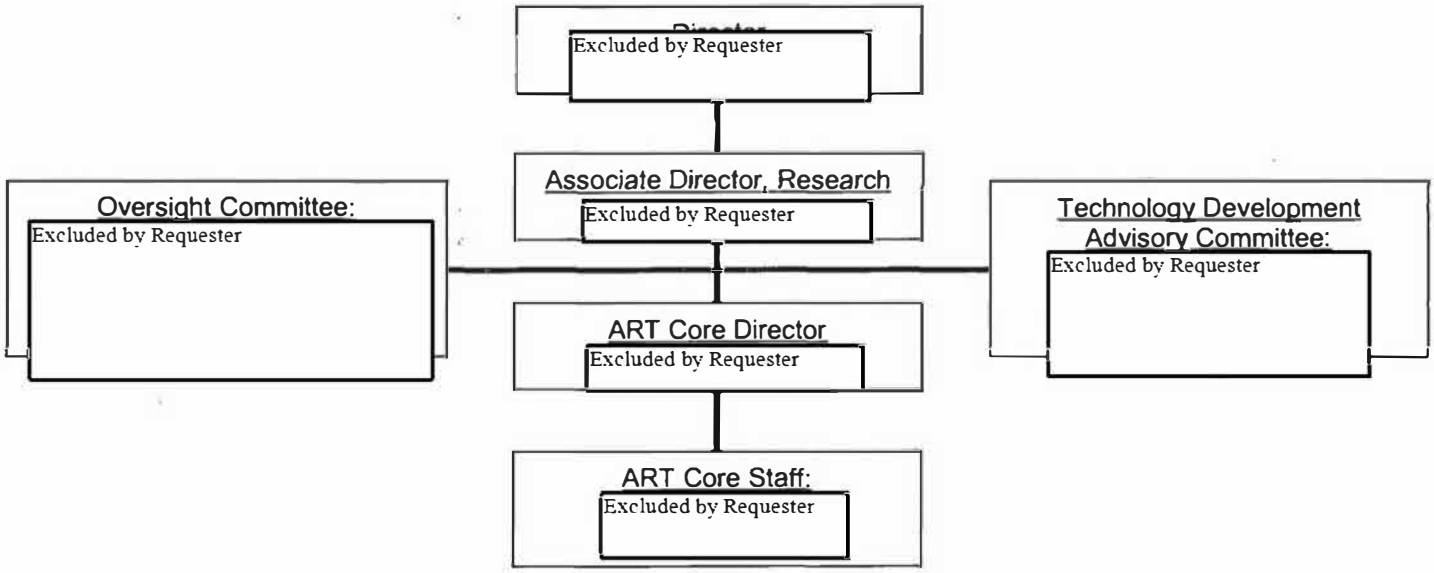
Core Scientists (See Biographical Sketch, listed alphabetically in the Overview of the ONPRC)

Excluded by Requester	Associate Scientist

Research Support

Excluded by Requester	Staff Scientist I
	Senior Research Assistant
TBN	Lab Aide

ASSISTED REPRODUCTIVE TECHNOLOGIES (ART)
Organizational Chart



ART SUPPORT CORE PERSONNEL AFFILIATION AND ROLE

Core Scientist

Excluded by Requester

Associate Scientist, Core Director

Staff Scientist

Excluded by Requester

Staff Scientist 1

ASSISTED REPRODUCTIVE TECHNOLOGIES (ART) SUPPORT CORE

DESCRIPTION:

The Assisted Reproductive Technologies (ART) Support Core provides gametes and embryos, ovarian follicular cells and fluid, pregnancies, and fetal tissues to scientists in support of investigations on gamete and ovarian follicle function, contraception, fertilization, early embryogenesis, implantation, fetal development, and the creation of NHP disease models. During the previous funding period, the Core provided expertise and training in all aspects of ART and embryology research to scientists located at ONPRC and throughout the country. ART Core operations are periodically evaluated by the oversight committee consisting of Excluded by Requester committee chair Excluded by Requester which, in turn reports to the Associate Director, Excluded by Requester In addition, the technology development component of the Core is guided by the Core Director with input from a committee of ART Core users that includes Excluded by Requester Excluded by Requester Future plans for the Core include continued support for ONPRC scientists and collaborators requiring ART services to advance their understanding of reproductive and developmental processes in primates, as well as the refinement and development of new technologies that optimize and enhance the Core's ability to offer such services.

ASSISTED REPRODUCTIVE TECHNOLOGIES SPECIFIC AIMS

The overall objective of the ONPRC Assisted Reproductive Technologies (ART) Support Core is to provide ONPRC researchers as well as national and international scientists the expertise and materials necessary for the efficient use of nonhuman primates (NHPs) in studies relevant to human health and disease. Specifically, the ART Core offers investigators the means to acquire difficult to obtain NHP ovarian specimens (granulosa cells, follicular fluid), germ cells (sperm, oocytes), and embryos for research purposes. Embryos are generated by the ART Core using established in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) techniques. Additionally, the ART Core provides the expertise and technical support necessary to perform embryo transfers, such that the developmental potential of experimentally manipulated embryos can be evaluated based on the presence or absence of a successful pregnancy. Established ART Core embryo transfer and cryopreservation protocols also allow investigators to maintain animal lineages with valuable genotypes/phenotypes. Lastly, the ART Core also provides researchers with media and reagents that are necessary to culture nonhuman primate germ cells and embryos.

To ensure that the ART Core possesses the most up-to-date means to provide the afore-mentioned services in an efficient and cost-effective manner, continual refinement of existing protocols and the development of new technologies are required. Thus, the Core strives to be at the cutting edge of NHP ART by developing new techniques and protocols that will fully support ONPRC scientists and collaborators focusing on primate reproduction and development. An active technology-development arm of the Core enables the addition of services and expertise that advance the use of the NHP as a manipulatable and translationally relevant model system.

Therefore, to attain the same level of high quality and cutting-edge services provided in the previous funding interval, the ONPRC ART Core proposes the following objectives through the next 5-year period of support:

Specific Aim 1: To provide an efficient, responsive, and transparent operating structure that allows for the delivery of high-quality NHP ART services and support. The Core aims to offer the necessary services and expertise for researchers seeking to utilize NHPs as models for the treatment of diseases and regulation of fertility in humans. To achieve this goal, the Core will focus on maintaining current high standards of service and quality control, ensuring an uninterrupted source of nonhuman primate gametes, embryos, ovarian materials, and germ cell/embryo culture media. Regular review of resources, personnel training and performance, as well as quality of services offered will be performed by the Core director, oversight committee, and the ONPRC Associate Director for Research to ensure continued success of the Core.

Specific Aim 2: To develop new ART reagents, services, and expertise that advance the use of the NHP as a translationally relevant model system. The Core will develop the following tools and resources to advance the utility of NHP ART for ONPRC and external research projects. Technology development objectives for the next funding interval include: a) the identification of biomarkers in ovarian follicles that yield oocytes with the greatest potential to undergo fertilization and embryonic development; b) the development and optimization of ART protocols in cynomolgus macaques, an NHP species that is emerging as a valuable model system at ONPRC, as well as; c) to apply state-of-the-art molecular methodologies to the manipulation of the NHP genome, which will allow for the development of models of human disease critically important for advancing reproductive, regenerative, and stem cell-based medicine.

ASSISTED REPRODUCTIVE TECHNOLOGIES (ART) RESEARCH STRATEGY

SIGNIFICANCE

Assisted reproductive technology (ART) relevant to nonhuman primates (NHP) is essential for studies that aim to advance our understanding of reproduction and development in translationally relevant model systems. The requisite years of experience and expertise, as well as the technological infrastructure, make most standard ART services/activities inaccessible to the average laboratory. Proven ART expertise and services are essential for supporting studies that assess events critical for the release of functional germ cells, fertilization, and embryo formation and development, as well as embryo implantation and subsequent fetal development. Since the NHPs share human endocrine, reproductive tract, germ cell, and embryo biological activities, the services provided through the ART Support Core are critical for supporting studies addressing pressing questions regarding human reproduction, development, and stem cell/regenerative medicine.

INNOVATION

Innovative aspects of the Core include the development of ART to support the use of a tractable NHP animal model in studies relevant to reproduction and development. The ART Core provides researchers with NHP gametes, embryos, follicular cells, and other ART-related services in support of studies investigating oocyte development, fertilization and contraception, early embryogenesis, pregnancy initiation, fetal development, stem cell biology, and cell-based therapy of human disease, as well as the creation of disease models in NHPs (1-9). Innovative aspects of the ART Core include its use of specialized protocols/methods (controlled ovarian stimulation and multiple oocyte retrieval; sperm collection; IVF; embryo culture), technologies (ICSI; embryo transfer), and information/expertise (translation of the results from NHPs to the design of clinically relevant experiments). Moreover, the Core actively develops technologies that advance NHP ART and the utility of NHP models in biomedical research. The innovative technology-development objectives proposed for the coming period of support include: 1) increasing the efficiency of ART by determining markers and characteristics of ovarian follicles that yield oocytes with the greatest capacity to undergo fertilization and/or embryonic development; 2) optimizing ART in cynomolgus macaques, a NHP species important for pharmacokinetic and pharmacodynamic studies; and 3) developing the tools to manipulate the NHP genome to allow for the study of primate physiology and the creation of NHP models of human disease.

APPROACH

reviewers' comments

reviewers' comments

Progress and Major Accomplishments.

In addition to accommodating service requests to both internal and external investigators (see below for list of services offered, users, and the amount of revenue generated), the Core was successful in obtaining updated equipment and dedicated laboratory space, and completing the major technology development aims in the previous grant interval.

New Equipment: The ONPRC continuously supports modernization of its Core facilities and equipment. With the transfer of the Core directorship from Excluded by Requester new laboratory space was renovated for the ART Core (see Resources) to allow efficient completion of ART Core functions without competition for resources from individual research programs. Thus, the equipment detailed in **Table 1** was purchased to upgrade old or outdated items and to provide for a more independent ART Core laboratory.

Table 1. New equipment purchases.

Item	Cost
Zeiss Axiovert A1 w/ DIC and Fluorescence	$21,965
Digital Camera w/ Spot 5.0 Imaging Software	$9,457
Narishige Micromanipulators (2X)	$31,000
Narishige Microinjectors (2X)	$5,820
Thermo Heating Plate/Stage	$4,125
Zeiss Discovery V8 Stereo Microscope (2X)	$21,402
Nuaire Self-Sterilizing Incubators (2X)	$10,378
Olympus Anti-Vibration Table	$4,194
Norlake Scientific Upright Freezer	$1,768
Isotemp Laboratory Refrigerator	$8,232
Straw Insert for BioCool Controlled Rate Freezer	$1,350
Thermo Heated Cell Transporter	$1,630

Technology Development Progress:

Objective 1: Develop approaches for the production of genetically identical monkeys using SCNT. Since initial application of SCNT in a rhesus model, the efficiency of the procedure was dramatically improved through the previous grant period by optimization of standard SCNT protocols (11, 13). Other beneficial protocol modifications include implementation of additional steps that aid in epigenetic reprogramming using histone deacetylase inhibitors during the process of oocyte activation. While early pregnancies have been established with SCNT embryos at a reasonable rate, efficient in vivo development of monkey SCNT embryos following transfer to recipient animals remains limited, since most pregnancies failed to progress beyond the first trimester. It is possible that SCNT blastocysts (inner cell mass and trophectoderm) are deficient in their ability to contribute to functional extraembryonic tissues, since they contain significantly lower numbers of cells expressing extraembryonic endoderm markers In Press

reviewers' comments

reviewers' comments

Comprehensive in vivo studies were performed to address this possibility through the injection of well-characterized monkey ESCs into blastocysts and their subsequent transfer to recipient females. Eight offspring were generated, but none of them possessed ESC contributions to any of the tissues analyzed. In contrast, chimeric monkey offspring were generated by injecting non-cultured embryonic cells freshly isolated from preimplantation embryos into recipient blastocysts (12). These results suggest that monkey ESCs lose their ability to contribute to chimeras during derivation and culture; i.e., more "interactive" cells capable of cell-cell-interaction or fully totipotent, "naïve" cells from earlier embryos may need to be established for the chimera generation in NHPs.

Objective 2: Create rhesus macaque ES cell lines containing reporter genes for cell tracking in vitro and in vivo. Several rhesus ESC lines were transduced with a lentiviral vector carrying a green fluorescence protein (GFP) reporter gene downstream of the pSin-EF2-Puromycin resistance sequence (Addgene, Inc.). After transduction (24 hr), ESCs were cultured with puromycin-resistant mouse embryo fibroblasts (mEFs) feeders in medium containing 2 µg/ml puromycin. Following two passages, all ESCs within each colony highly expressed the transgene. ESCs remained GFP-positive after in vitro differentiation into various phenotypes. These genetically tagged cell lines were critical in the tracking of injected cells in chimeric fetuses (12).

Progress was also made in generating ESCs that express GFP under the control of the endogenous OCT4 promoter. A knock-in construct was generated using a recombinant adeno-associated virus (rAAV) vector. This construct was composed of rhesus homology arms that flank an internal ribosomal entry sequence followed by the gene encoding GFP and a selectable puromycin-resistance cassette driven by PGK. ESCs

were transduced and selected by culturing in the presence of puromycin. Several recombinant clones were identified by PCR analysis and are currently being tested for GFP expression.

Objective 3: Improve efficiencies and capabilities of the monkey ARTs by oocyte in vitro cryopreservation. The feasibility and outcomes of rhesus macaque oocyte cryopreservation were assessed using a commercially available vitrification kit (CRYOTOP) developed for human IVF. Survival and recovery of mature rhesus metaphase II (MII) oocytes post-thaw was high and 72% fertilized, while only 6% formed blastocysts. Thus, the cryopreservation method compromises blastocyst development, as fertilization of fresh oocytes from the same cohort was 97% and blastocyst formation was 52%. Reciprocal spindle transfers between fresh and frozen-thawed monkey oocytes were conducted to pinpoint where in the transition from a zygote to a blastocyst the cryopreservation effect occurs. When fresh spindles were transplanted into vitrified cytoplasts, fertilization after ICSI was impaired (50%) compared to controls (91%). All embryos in this group arrested before reaching the blastocyst stage, while 57% of fertilized controls progressed to blastocysts. However, when spindles from vitrified oocytes were transferred into fresh cytoplasts, fertilization (88%) and blastocyst formation (68%) rates were similar to fresh controls. These results suggest that vitrification causes damage within the cytoplasm rather than to the spindle apparatus itself, thus preserving the genetic potential of the embryo. To further evaluate developmental potential, 4 spindle transfer blastocysts from vitrified spindles were placed into one recipient, resulting in a singleton pregnancy and the timely birth of a healthy female infant (14). These landmark findings resulted in the rapid translation of the spindle transfer approach from NHPs to human studies, which are now on-going in a collaborative effort involving Excluded by and members of the OHSU Department of Obstetrics & Gynecology. Moreover, these findings will allow the ART Core the prospect of long-term storage of oocytes obtained from genetically valuable animals.

Objective 4: Create an ART/ESC Core website to advertise and disseminate available resources and services. During the previous funding interval, ONPRC has revamped and modernized websites available to external and internal investigators. Potentially interested external users now have access to updated contact information and available services through a publically available Core website. Internal users now can access ART Core service lists and associated prices, as well as relevant protocols and an ART Core listserv for announcements of ongoing Core activities through the newly created ONPRC intranet.

Services Provided/User Info During Previous Grant Period. Controlled ovarian stimulation (COS) protocols were performed using rhesus macaque females assigned to the Core laboratory or to individual principal investigators at ONPRC, resulting in the collection of follicular fluid, granulosa cells, and oocytes for Core users. Oocytes retrieved from these experiments, along with sperm collected from rhesus males assigned to the ART Core are commonly used for IVF or ICSI in the generation of embryos. Requests also included the transfer of Core or investigator-generated embryos to recipient animals to determine their developmental competency. **Table 2** provides a detailed accounting of all services performed or provided by ART core staff through the previous grant period. Training activities of the Core also included training Excluded b Excluded by Reque Assistant Clinical Investigator, NICHD/NIH) with regard to NHP COS protocols, oocyte retrieval, and oocyte fertilization.

Table 2. Number of services offered yearly by the ART Core through the previous funding interval.

SERVICE	Number for the Indicated Year			
	5/09-4/10	5/10-4/11	5/11-4/12	5/12-present
Controlled Ovarian Stimulations (COS)[1]	64 (53)	91 (74)	37 (15)	22 (19)
Semen Samples	99	133	86	34
Granulosa Cells	12	15	3	2
Ultrasounds	176	197	163	38
In Vitro Fertilization (IVF)	2	5	20	7
Intracytoplasmic Sperm Injection (ICSI)	66	78	64	8
Recipient Monitoring[2]	48	117	24	3
Embryo Transfers[1]	16 (11)	39 (32)	8 (8)	0
Media Requests	94	123	128	25

(1) The values in parentheses represent the number of protocols performed using ART Core animals out of the total number performed. (2) Represents the number of animals being monitored for the proper time in the menstrual cycle for embryo transfer as requested by Core users.

Revenue Generated as ART Core Program Income

An overview of program income obtained by the ART Core through the

Table 3. Yearly income generated from ART Core services through the previous funding interval.

Year	$ Amount
5/09-4/10	$190,341
5/10-4/11	$287,687
5/11-4/12	$82,940
5/12-present	$43,000
TOTAL	$603,968

previous funding interval is provided in **Table 3**.

The Number/Affiliation of Users in the Previous Grant Period

The ART Core provided services for 7 investigators at ONPRC and 4 external researchers affiliated with other OHSU departments and non-OHSU entities (**Table 4**).

Table 4. ART Core users through the previous funding interval and their respective affiliations.

User	Affiliation
Excluded by Requester	Internal, ONPRC
	Internal, ONPRC
	Internal, ONPRC
	Internal, ONPRC
	Internal, ONPRC
	Internal, ONPRC
	Internal, ONPRC
	External, OHSU
	External, University of Pittsburgh
	External, Private Source
	External,

Specific Aims/Service Plan for Next Grant Period.

Aim 1: To provide an efficient, responsive, and transparent operating structure that allows for the delivery of high-quality NHP ART services and support.

Oversight and administration. ART Core personnel strive to maintain a high level of quality control (QC) in all laboratory settings and protocols. Our QC efforts include daily documentation of temperature and gas compositions for incubators, as well as the temperature for microscope stage warmers, water baths, and the culture room. Culture media and reagents prepared by Core personnel are monitored routinely for pH, osmolarity, and sterility, with the results logged into electronic records that are regularly backed up. Oocytes, sperm, embryos, and ES cells are routinely examined for normal growth, development and other cell-specific parameters. Standard operating procedures are followed to ensure proper sterilization of lab utensils and to ensure maintenance of a clean environment in the dedicated culture room (e.g., use of proper laboratory attire, regular changing of sticky mats and air purifiers, certification of hoods).

User satisfaction is reviewed annually through the anonymous survey of Core users. The satisfaction survey results, Core services offered, service chargeback fees, equipment needs and any quality control issues are presented to the ART Core Oversight Committee semiannually, which are summarized and reported to the ONPRC Associate Director for Research, Excluded by Requester The Oversight Committee is comprised of faculty representatives from 3 of the 4 ONPRC scientific divisions Excluded by Requester Reproductive & Developmental Sciences; Excluded by Requester Neuroscience; and Excluded by Requester Immunology & Pathobiology. Any deficiencies or conflicts in terms of Core services or fees are presented to the oversight committee so a corrective plan can be developed. Implementation and progress made towards any corrective measure will be communicated routinely to Excluded by and Excluded by Chargeback fees are determined by calculating cost-recovery for staff time and effort as well as animal and supply costs. All ART Core chargeback fees are reviewed and approved by the oversight committee, Excluded by Requester and the ONPRC Associate Director for Administration.

Services to be Offered: The Core plans to continue providing ONPRC scientists as well as national and international collaborators ART and ART-related services, including, but not limited to, controlled ovarian stimulation, oocyte retrieval, granulosa cells and follicular fluid, sperm, IVF, ICSI, embryo transfer, ultrasonography, and oocyte/embryo culture. In addition to our regular services, Core personnel will provide individual, hands-on training and expertise in all aspects of the aforementioned ART protocols. In contrast, services related to the embryonic stem cell (ESC) portion of the core will no longer be available, as its use was becoming minimal over the last two years of the previous funding interval. The costs associated with maintaining and managing ESCs were too great relative to the limited number of users or requests for these services. Investigators requiring ESCs for their research programs will be directed to Excluded by Requester as he is willing to provide interested individuals access to NHP ESCs via a collaborative arrangement.

Aim 2: To develop new ART reagents, services, and expertise that advance the use of the NHP as a translationally relevant model system.

Technology development objectives will include identifying methods to optimize IVF/ART success rates in terms of embryo generation and development, advancing ART in other NHP species that are valuable research models and evaluating recently developed molecular techniques that likely represent an efficient means to generate genetically modified monkeys.

Objective 1: To identify follicular markers of oocyte quality. Current ovarian stimulation protocols result in the development of multiple follicles from which tens of oocytes can be collected for subsequent studies. While

such protocols provide sufficient numbers of oocytes for research purposes, they are of varying quality due to the fact that exogenous gonadotropins result in the development of additional follicles that would not survive the normal selection process and/or are at different stages of follicle maturation (15, 16). Thus, it is imperative that those oocytes with the potential to generate a competent embryo be identified so as to limit the effect of the stimulation as a confounding factor on embryo development when trying to assess the outcome of a particular experimental manipulation. Moreover, having assayable indicators of oocyte quality would also allow the Core to increase efficiency in generating valuable NHP offspring following embryo transfer.

The oocyte and surrounding follicular granulosa cells coordinate activities critical for oocyte maturation through the factors they secrete and the transfer of small molecules via intercellular channels (17, 18). Therefore, the metabolic (e.g., glucose, fatty acids) and paracrine-acting factors (e.g., steroids, eicosanoids) within the follicular fluid likely serve as key indicators of the overall competency of the oocyte; i.e., its ability to fertilize and yield a pregnancy. To systematically identify biomarkers that predict an oocyte's competency, a metabolomic evaluation will be performed on the follicular fluid and granulosa cells within individual rhesus macaque follicles that develop following a COS protocol. Female macaques will be stimulated by standard ART Core techniques (9, 19, 20) and oocytes, follicular fluid, and granulosa cells will be collected from individual follicles by needle aspiration. The oocytes will be retained for standard IVF and subsequent culture to blastocyst stage. Follicular fluid (average of 150 µl per follicle) and granulosa cells (average of 1 X 106 cells) from each follicle will be separated and flash-frozen for metabolomics analyses. Metabolomic analyses will be performed by Metabolon (Durham, NC) using ultra-high pressure liquid chromatography coupled to positive and negative ionization mass spectroscopy (MS) as well as gas chromatography (GC) MS (21). Using this approach, an average of ~485 metabolites can be identified by automated spectra fitting to a standard library of experimentally derived spectra (22-24). Follicular metabolite presence and concentrations will be compared between oocyte groups that: 1) develop to blastocyst stage; 2) undergo asynchronous division(s) following fertilization and fail to develop to the blastocyst stage or yield a poor quality/fragmented blastocyst; or 3) fail to fertilize. To provide 55 individual oocytes and their corresponding follicular fluid and granulosa cells, which was calculated to provide sufficient power to determine a 2-fold change in an individual metabolite between groups ($p<0.05$), 6 females will be stimulated (10 to 20 oocytes are typically retrieved per stimulation). The outcome of oocytes derived in this manner is distributed across the 3 categories with about 50% developing to the blastocyst stage (Group 1) and then approximately 30% in Group 2 and 20% in Group 3 (based on ART Core historical data). A selected group of blastocysts obtained from group 1 will be transferred to recipient animals to establish their ability to yield a term pregnancy and a viable offspring. Although pregnancy outcomes would be the optimal endpoint for comparison against the metabolomic profiles for each individual oocyte, the resources necessary for conducting such an expensive and animal intensive study are prohibitive. Once an association between key metabolic pathways and optimal early embryonic development is established, subsequent focused studies to determine whether markers of blastocyst development correlate with implantation and term pregnancies can be performed. Furthermore, comparisons can be made between the metabolomic profile that is obtained from the multiple follicles that develop following ovarian stimulation protocols and the single follicle that is naturally selected through the course of each cycle (25). It is anticipated that from these studies, key metabolic fingerprints will be discovered that are critical for the development of a fertilizable oocyte, which in turn will be valuable in determining the quality and likelihood of successful pregnancy outcomes of valuable research embryos.

Objective 2: To advance ART in cynomolgus macaques. Cynomolgus macaques have long been a valuable NHP model system, primarily in terms of preclinical pharmacokinetic and pharmacodynamic studies (26-29). The usefulness of cynomolgus macaques also stems from the fact that, unlike rhesus macaques, they do not have anovulatory periods in the summer, thereby allowing investigators to conduct year-round studies. Through the previous funding interval, the utilization of cynomolgus macaques at ONPRC in the Division of Reproductive & Developmental Sciences has increased significantly, including for use in the development of novel contraceptive targets [Excluded by Requester] and for treatments of heavy menstrual bleeding [Excluded by] Moreover, propagation of cynomolgus macaques with unique phenotypes are also important for future ONPRC studies focused on obesity and metabolic disorders (Dr. [Excluded by Requester] Division of Metabolism, Obesity, & Diabetes) as well as alcohol addiction [Excluded by Requester] Division of Neuroscience) (29, 30). Thus, the objective of these studies will to be to optimize ART such that oocyte collection, fertilization, in vitro embryo development, and embryo transfer can be performed efficiently in cynomolgus macaques.

Information regarding ART for cynomolgus macaques is limited, with only a few reports detailing IVF and in vitro embryo culture. In vitro culture of cynomolgus embryos to the blastocyst stage is not possible without a feeder cell co-culture system and results in only a very low percentage of the embryos undergoing compaction and blastocoel formation (15-20%) (31). Of those blastocysts transferred to recipient animals, the pregnancy rate is low (21% of transfers to recipient animals) (32). Most culture media used for IVF produced embryos are typically buffered physiological salt solutions with little or no supplementation to support the different phases of development. Thus, extensively supplemented media, which are now clinically available for use at precise stages of human embryo growth, will be systematically evaluated for the first time with regard to promoting cynomolgus blastocyst formation in vitro. Cynomolgus females will undergo COS protocols and presumed MII oocytes will be collected by follicle aspiration. On average, we can anticipate retrieval of 10 to 15 oocytes from every aspiration, of which 66% will be expected to have reached MII of meiosis. Immature oocytes also collected from the aspirate can undergo additional in vitro maturation of which 54% will progress to MII for inclusion in subsequent procedures (31). Oocytes will be fertilized by ICSI and cultured to the blastocyst stage in one of the following commercial media representing both sequential and non-sequential culture strategies: 1) macaque specific KSOMaa Evolve® (Zenith Biotech, Guilford, CT); 2) G1/G2TM sequential media (Vitrolife, Englewood, CO); 3) G1/G2TM PLUS sequential media; 4) Quinn's Advantage® sequential media (Sage, Trumbull, CT); 4) HECM-9 (Control medium, optimal for rhesus macaque embryo culture (33)). Embryo culture will be carried out for 7-10 days allowing time for blastocyst development and blastocoel formation. Development of each embryo will be documented daily and quantitated for growth analysis. At the conclusion of culture, resulting embryos will be preserved for fluorescence confocal imaging to visualize spindle morphology and chromosome integrity. Proof-of-principle for the optimal media will also require production of a live offspring, which will be attempted via embryo transfer using the media that results in the best blastocyst development. Identification of an efficient in vitro embryo culture system will be a critical advancement in supporting research projects at ONPRC and other NPRCs that use cynomolgus macaques.

Objective 3: To develop efficient methods for manipulating the rhesus macaque genome. The ability to create genetically modified offspring would greatly facilitate the use of NHPs in biomedical research by advancing the development of models for a variety of human diseases as well as providing the tools necessary for understanding the cellular and molecular processes required for NHP development. Recent advances have occurred with regard to the delivery of transgenes in non-primate model systems via transposon-based approaches (34). One such system includes a hyperactive, synthetic transposable element termed Sleeping Beauty 100X (SB100X) (35-37). SB100X has the advantages of a) being active in different somatic tissues of a wide range of vertebrate species, b) providing long-term transgene expression, c) integration efficiencies that are comparable to viral vectors, d) integrating on average only 1 to 2 times per genome, e) preferentially integrating outside of intragenic regions, in contrast to what often occurs with viral-derived vectors, f) not being susceptible to epigenetic silencing, and g) integrating prior to chromosomal segregation, thereby limiting mosaicism. The latter is critical for transgene delivery in rhesus macaques due to their long generation time and the inability to evaluate and maintain founder animals. SB100X has the added utility of delivering a construct expressing a short-hairpin (sh) RNA that inhibits the expression of a specific target gene (38).

To test the utility of the SB100X system in rhesus macaques, fertilized oocytes will be co-injected with circular plasmid DNA consisting of an enhanced GFP (Venus)-tagged transposon (pT2/CAGGS-Venus; 0.4 ng/ml) and SB100X transposase (5 ng/ml) as described (36). The SB100X transposase expression plasmid and the transposon delivery vector (pT2/CAGGS) were kindly provided by Private Source,Excluded by Requester Private Source Transgenic embryos positive for Venus fluorescence at day 7 postinjection and with no apparent sign of mosaicism will be identified and transferred to recipient animals. Implantation will be monitored by determination of sustained progesterone levels and subsequent fetal development will be assessed every other week by ultrasound. Initial successful pregnancies will be allowed to proceed to term (155 days), at which point a cesarean section will be performed to obtain the fetus for subsequent necropsy. Fetal morphology and tissue-specific transgene expression will be evaluated in a comprehensive panel of tissues. After initial studies confirm systemic transgene expression throughout the animal, any subsequent pregnant recipients will be allowed to deliver transgenic animals so that normal development and sustained transgene expression can be monitored through the first year of life. Collectively, these studies will provide a powerful genetic tool for the manipulation of the NHP genome such that models of human disease and development are available to interested scientists.

REFERENCES:

Excluded by Requester

Excluded by Requester

Excluded by Requester

Excluded by Requester

ASSISTED REPRODUCTIVE TECHNOLOGIES (ART) VERTEBRATE ANIMALS

An overview of the routine housing and care of NHPs at the ONPRC are provided in the general Vertebrate Animal section of the renewal application (see ANIMAL SERVICES). The following information is specific to the ART Core service protocols and technology development objectives.

1. Female and male rhesus monkeys (*Macaca mulatta*) are used to provide the requested ART Core services. The number of female rhesus macaques maintained per year varies with the number of ongoing projects and the estimated ART Core use provided by investigators at the beginning of each breeding season (September). The Core has maintained between 10 to 20 females and 4 to 6 males over the past funding interval. To complete the technology objective that aims to advance ART in cynomolgus macaques (*Macaca fascicularis)*, 5 female and 2 male cynomolgus monkeys will be used per year for the next 5-year funding interval.

All protocols will be performed under the direction of the veterinary staff and with the assistance of the laboratory animal technicians in the Division of Comparative Medicine, ONPRC, OHSU, Beaverton, Oregon. The veterinary and support staff is experienced in the handling and housing of both rhesus and cynomolgus macaques.

ART Core Protocols:

a. Controlled Ovarian Stimulation/Oocyte Collection

Multiple preovulatory follicles will be stimulated by administering recombinant human gonadotropins for ~9 days. This protocol will utilize a daily injection of 60 IU rhFSH (30 IU 08:00 and 16:00, i.m.) for 6 days, with 30 IU LH also being administered (i.m.) at 08:00 and 16:00 h (60 IU total per day) on days 6 and 7. The GnRH antagonist acyline will be given on day 6 at 16:00 h to prevent an endogenous LH surge (75 μg/kg, i.m.; NICHD). Numbers and size of growing follicles will be monitored by ultrasonography at day 6 to 7 of treatment, and subsequently as needed. When ≥ 6 follicles of 4 mm diameter or greater are present, typically day 8, hCG may be given to obtain mature MII oocytes for subsequent fertilization. Laparotomy will be performed prior to or 36 h post-hCG injection, with the follicular contents aspirated by suction using a stainless-steel needle attached to a 3 cc syringe.

b. Sperm Collection

Electro ejaculation of NHPs is performed to obtain semen samples for the ART Core when requested by investigators or needed for the generation of embryos. The IACUC approved semen collection method at ONPRC includes penile band electro stimulation. For this procedure, male monkeys are trained to wear collar restraints and to sit quietly in a chair. At least one hour prior to initiating the electro ejaculation procedure, acetaminophen (80 mg PO) will be administered to prevent any possible discomfort. At the discretion of the veterinarian, diazepam (2-4 mg PO) may also be given to reduce any possible anxiety. After the animal has been restrained appropriately, the negative and positive leads will be attached to gel electrodes secured to the penis. The pre-sized negative electrode will be wrapped around the base of the penis, whereas the second positive electrode will be positioned immediately behind the glans. The penis will be positioned over a collection beaker and a low voltage is applied to act as priming stimulus. Voltage will be slowly and steadily increased until a slight erection, engorgement of the glans, or elevation of the testicles into the inguinal region is observed. Typically, ejaculation will occur at 10-20 V. The applied voltage will not exceed 35 V. The date, time of day, peak output current, length of time electrical current was delivered, drugs administered, behavioral observations, and technician initials will be entered into a logbook. If no ejaculate is obtained, the stimulation process may be repeated within 1-3 minutes. No more than three consecutive stimulus attempts are made per monkey on a given day, and each monkey is given a rest period of at least 48 hours between collections.

c. Embryo Transfer

Adult, multiparous females monitored for menses will be used as recipients. Daily blood samples will be collected beginning on day 8-10 of the menstrual cycle and serum levels of estradiol are to be quantitated by automated electrochemiluminescence assays in the Endocrine Technologies Support Core. The day following the peak in serum estradiol is considered the day of ovulation (day 0). The pregnancy success rate depends

on the synchrony between the age of the transferred embryos, as measured by culture time in vitro, and the host endometrium, relative to the predicted day of ovulation. The optimal timing for blastocyst transfer is day 4 after ovulation, while cleavage stage embryos at a culture age of 1-4 days can be optimally transferred into a day 2 recipients. Recipient females within 1 to 4 days after ovulation will be anesthetized and prepared for laparoscopic embryo transfer utilizing the same basic laparoscopic approach and anesthesia as described for follicular aspiration. A catheter and Hamilton syringe will be loaded with the embryos (2 to 6) in TH3 media while maintaining sterility. The surgeon will advance the catheter through the fimbria into the oviduct to a distance of 0.5-1.0 cm and slowly expel the embryos into the oviduct. To detect pregnancy, serum levels of estradiol and progesterone will be monitored 2 weeks and 3 weeks after embryo transfer. A rise in both estradiol and progesterone at this time indicates that pregnancy has been achieved, which will be confirmed by ultrasound approximately 30 days post-transfer and monitored periodically throughout gestation.

d. Pregnancy Termination

If an embryo transfer is successful, it will be up to the discretion of the investigator that requested the transfer to determine when or if a pregnancy should be terminated. For those that seek to prove only successful implantation of experimentally manipulated germ cells/embryo, the pregnancy can be terminated within the first trimester (i.e., before 55 days) using a pharmacological approach. After a third week of sequential progesterone, a fetal heartbeat will be verified by ultrasonography. The afternoon following a confirmatory ultrasound, any pregnant female will be placed in single housing during the pregnancy termination period. Each pregnant female will be dosed with 20 mg mifepristone suspended in Captex oil via an intramuscular injection. Following the administration of mifepristone (48 h), the pregnant animal will be given 200 µg of crushed misoprostol orally. To minimize any pain and discomfort, animals will simultaneously receive a burprenex (0.03 mg/kg, im) injection at the time of misoprostol administration. DCM staff will monitor the animal closely for passing of tissue. An ultrasound will be performed 7 days after the initiation of the pregnancy termination protocol, and then weekly thereafter, until complete passage of the fetal tissue has occurred.

For investigators interested in obtaining fetal tissue beyond the first trimester, a caesarean section will be performed by the DCM surgical staff as per standard procedure at the requested day of gestation to obtain the necessary fetal specimens.

As per ONPRC IACUC guidelines, multiple surgeries are allowed on each monkey. Experience indicates that 4 ovarian biopsies (e.g., follicle aspirations) and 3 embryo transfers can be performed per female NHP without any adverse problems. Males can also undergo a maximum of twice weekly semen collections without causing adverse outcomes. This repetitive, but certainly not excessive, use of each monkey permits optimal scientific use of a highly valuable research species to (a) decrease experimental error, (b) increase the statistical power of each experiment, and hence (c) increase confidence in the scientific findings. The repetitive use also allows the P.I. to maintain a small cohort of monkeys that are carefully monitored for normal menstrual cycles, and assures provision of ovarian tissues characteristic of normal follicular and luteal structure-function.

2. The aforementioned protocols will allow the Core to fulfill all service requests. These protocols will allow for the collection of gametes and embryos, ovarian follicular cells and fluid, pregnancies as well as fetal tissues to scientists in support of investigations on gamete and ovarian follicle function, contraception, fertilization, early embryogenesis, implantation, fetal development, and the creation of disease models in NHPs. Since information must be obtained from complex tissues (i.e., ovary, testis, fetus), there is no alternative to using animals and collecting ovarian samples for these experiments.

With the ultimate goal of relating this research on ovarian function to the regulation of human reproduction, macaques are uniquely qualified as surrogate human models. In contrast to many laboratory and domestic animals, the characteristics of the ovary during the nonfertile cycle and early pregnancy are very similar to those in women. Characteristics distinguishing the human and Old World monkey follicle and corpus luteum from that of many other species, include: (a) women and macaques are monovular species, forming only one mature follicle and corpus luteum per cycle, (b) the interval from onset of the ovulatory gonadotropin surge to cumulus-oocyte maturation and follicle rupture is much longer, (c) the primate corpus luteum is functional during the nonfertile cycle, regulated primarily by the pituitary hormone LH, not prolactin, and secretes substances (e.g., estrogen, inhibin A) not produced by nonprimate luteal tissue, (d) a uterine luteolytic

mechanism is absent in primates, and (e) the rescue of the corpus luteum in early pregnancy by chorionic gonadotropin only occurs in primates. Therefore, the adult female macaque remains the model of choice for studying periovulatory events and the corpus luteum during the menstrual cycle, essentially as preclinical trials of direct relevance to controlling human ovarian function and reproduction.

3. & 4. Aseptic surgery involving either a mini-laparotomy or laparoscopy will be performed on anesthetized animals by trained, experienced personnel under the supervision of the surgical veterinarian in the Surgical Unit, Division of Comparative Medicine ONPRC. In all surgical protocols, ketamine is initially administered to sedate the monkey, followed by gaseous anesthesia (isoflurane gas vaporized in 100% oxygen) in the operating room. Medication is routinely administered to relieve postoperative pain (buprenorphine). Laparoscopy or laparotomy results in minimal trauma; the animal is awake, mobile and eating fruit within a few hours. Of over 200 surgeries performed in the last four years for these protocols, no incidence of infection has occurred. The veterinarians in the DCM at ONPRC routinely check all animals for infections and diseases, and are well equipped to handle any problems.

5. Female and male macaque monkeys will not be killed during these studies. Rather, animals will be used in protocols that involve aseptic surgery. After four major surgeries (e.g. laparotomies), according to ONPRC IACUC guidelines, animals will be returned to the ONPRC colony.

RESOURCES

ASSISTED REPRODUCTIVE TECHNOLOGIES (ART) Core Resources:

Laboratory:
The ART Core relocated to dedicated and newly renovated laboratory space located on the first floor (Room #1114) of the ONPRC/VGTI Building (total area of 465 sq ft). The main laboratory space contains a NuAire laminar flow safety cabinet for filtering media and preparing semen samples, a Norlake -20 C freezer, two refrigerators, and centrifuges for processing blood and semen samples. Housed within this space is an embryology lab/warm room of 90 sq ft equipped with an independent heating unit and integrated HEPA filter heater for maintaining a temperature of 85 F and a clean work area. All embryology services are conducted within this space that includes sorting of oocytes from surgical aspirates, fertilization by in vitro fertilization or intracytoplasmic sperm injection, in vitro culturing and preparation of embryos for transfer, etc. The room is equipped with a set of Nuaire stacking incubators, Zeiss dissecting scopes with thermoplates/stage warmers, Zeiss Axiovert A1 inverted microscope equipped with Narishigi manipulators for performing intracytoplasmic sperm injection, as well as a desktop computing system for capturing photos and videos. A Primetech piezo drill for assisted embryo hatching as well as a Sutter pipet puller and Narishige microforge are also available. Other general-use areas are available in this building, and include four standard and ultracold (-80 C) freezers (Rm 2119), seminar room (Rm 1100) and classroom (Rm 2001) for research laboratory meetings, and washing/autoclaving glassware (Rm 3125). The ART Core facilities are located close to the ONPRC laboratories that utilize this Core, including Excluded by Requester and as well as to animal housing and surgery facilities.

Clinical: NA:

Animal:
The ONPRC houses over 4000 rhesus monkeys in state-of-the-art facilities for breeding and research purposes. The Division of Comparative Medicine (Excluded by Requester Chief) includes 15 veterinarians and over 100 full-time staff involved in animal care and research support. The animal facilities and care programs are fully accredited by the American Association for the Accreditation of Laboratory Animal Care (AAALAC), and operations are inspected regularly by representatives of the United States Department of Agriculture (USDA). Adult, female rhesus monkeys will be pair-housed in the Animal Services Building (ASB), adjacent to the ART Core. One clinical care veterinarian, Excluded by Requester has oversight of research protocols and animals assigned to scientists in the Division of Reproductive & Developmental Sciences and the ART Core.

Office:
The Core Director has an office Facility Security in the ONPRC/VGTI building near the ART Core laboratory. Additionally, adjacent office space is available for staff scientists and research associates Facility Security The offices are equipped with desktop computers for word processing, electronic mail, etc.

Other:
The ART Core owns two laparoscopic systems with camera and accessories for follicle aspiration and egg pickup by the surgery team, Division of Comparative Medicine. Facilities, equipment, and assistance for immunocytochemistry, in situ hybridization and confocal microscopy are available through the Imaging & Morphology Support Core laboratory Excluded by Requester Director). The Endocrine Technology Support Core supervised by Excluded by Requester has the equipment and technical help for providing assays of steroids and gonadotropin hormone levels in collected samples. The Molecular & Cellular Biology (MCB) Support Core, directed by Excluded by Requester assists with sequencing and provides reagents support for gene expression analyses.

Scientific Environment:
The ONPRC provides an exceptionally supportive environment for the performance of the services offered by the ART Core. Major strengths of the institution that directly impact our ability to successfully conduct nonhuman primate ART include the number of investigators in both the Divisions of Reproductive &

Developmental Sciences and Neurosciences with long-standing expertise in reproductive biology, as well as the availability of the infrastructure and expert veterinary support necessary to operate such a specialized core.

Program Director/Principal Investigator (Last, First, Middle): Robertson, Joseph E./Haigwood, Nancy L.

CORE SCIENCE SERVICES- ART-ESC DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*

Use Cal, Acad, or Summer to Enter Months Devoted to Project

Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Excluded by Requester	Assoc Scientist	% Effort			Institutional Base Salary	17,910	4,477	22,387
	Staff Scientist 1					8,014	2,484	10,498
	Sr. Res Asst					28,389	9,936	38,325
To Be Named	Lab Aide	3.30				7,276	3,274	10,550
	SUBTOTALS →					61,589	20,172	81,761

CONSULTANT COSTS		0
EQUIPMENT *(Itemize)*		
None Requested		0
SUPPLIES *(Itemize by category)*		
Laboratory Supplies	5,500	
Office & Admin Supplies	440	
Primates	11,770	
Animal Protocol Supplies	4,950	
Animal Lease and Set up Fees	38,006	
		60,666
TRAVEL		
None Requested	0	0
INPATIENT CARE COSTS		0
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		
None Requested		0
OTHER EXPENSES *(Itemize by category)*		
Surgery Fees	13,805	
NHP Per Diem (16 @$9.44X365 days)	43,587	
Drug Admin & Sample Collection	6,909	
Semen Collection	1,790	
Equipment Maint Contract	6,836	
Endocrine Services	7,241	
		80,168
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 222,595
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 222,595

CORE SCIENCE SERVICES - ART-ESC
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	81,761	84,213	86,740	89,342	92,022
CONSULTANT COSTS	0	0	0	0	0
EQUIPMENT	0	0	0	0	0
SUPPLIES	60,666	62,486	64,361	66,291	68,280
TRAVEL	0	0	0	0	0
INPATIENTS CARE COSTS	0	0	0	0	0
OUTPATIENTS CARE COSTS	0	0	0	0	0
ALTERATIONS AND RENOVATIONS	0	0	0	0	0
OTHER EXPENSES	80,168	82,573	85,050	87,602	90,230
DIRECT CONSORTIUM/CONTRACTUAL COSTS					
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	222,595	229,273	236,151	243,235	250,532
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	222,595	229,273	236,151	243,235	250,532
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					1,181,786

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

PERSONNEL

Associate Scientist - Excluded by Requester % Effort
Responsible for the overall coordination and execution of ART Core Service operations and technology-development projects, results interpretation, and manuscript and progress report preparation; advising of ART Core activities, performance, and plans to the ART Core Oversight Committee; responsible for overseeing technology-development objectives, including studies that serve to identify follicular markers predictive of oocyte quality, advancing ARTs in cynomolgus macaques, and the development of new strategies for the manipulation of the macaque genome.

Staff Scientist 1- Excluded by Requester % Effort
Responsible for the development, optimization, and evaluation of ART protocols, training investigators, coordinating ART services, and preparation of presentations and reports as well as work towards the advance of the Core's technology-development objectives.

Senior Research Assistant - Excluded by Requester % Effort
Responsible for the day-to-day activities of the ART Core, including the management of the Core's assigned macaques, ovarian stimulations, and oocyte collections (performance of transabdominal ultrasound imaging of follicles, and assisting surgical staff during oocyte recovery/embryo transfer procedures), preparation of embryo culture media and daily quality control, oocyte recovery, collection of sperm from semen samples, and embryo culture and cryobanking, as well as maintenance of supplies and equipment for the ART Core

Lab Aide - To be named (6 calendar months effort: 3.3 ORIP, 2.7 Program Income). Responsible for processing blood samples for subsequent steroid hormone analysis (e.g., estradiol, progesterone), transporting specimens for steroid measurement, and collecting the resulting data; reviewing steroid hormone data with the Senior Research Assistant to allow for monitoring and coordinating animal protocols; assist in media preparation, stocking and inventory of laboratory supplies, and monitoring incoming service requests.

SUPPLIES

Laboratory Supplies: Funds requested include consumables for tissue/embryology culture, including plastic culture dishes/flasks, buffers, media, media supplements, reagents for cryopreservation, compressed gasses, and liquid nitrogen. Reagents are also needed for the technology development goals of the Core and include molecular biology reagents for plasmid manipulation/construction, and RNA/protein extraction or tissue sectioning. Laboratory supplies also include injectable anesthetics, bench paper, glass and capped plastic tubes, needles and syringes, serological pipettes and pipette tips, as well as disposable gloves and masks.

Office & Admin Supplies: Funding is requested for office supplies (paper, pens, folders etc.) to cover the administrative activities of the Core.

Primates: To develop the use of ARTs in cynomolgus macaques, an emerging nonhuman primate model system at ONPRC, the core will purchase 3 regularly cycling females and 1 adult male.

Animal Protocol Supplies: Funds are requested for injectable anesthetics and hormones as well as needles and syringes. Consumables for blood/serum processing and storage are also needed, including serological pipettes, centrifuge tubes and storage vials, as well as gloves, masks, and face shields/masks.

Animal Lease and Set Up Fees:

Animal Leases: Funds are requested each year for the use of ten adult female and one adult male rhesus monkeys. The group of regularly cycling females (assigned based on menses records) will permit the necessary protocols/year to cover service requests from Core users and the Core's technology development activities. Through IACUC-approved sequential protocols, each monkey will be used for one to two years and then released and replaced.

Animal Set-up Fees: Set-up fees to recover costs related to performing physical examinations prior to assigning animals to investigators. Purchased cynomolgus macaques require a 3-month quarantine period and pre-assignment physical assessment by veterinarian staff.

OTHER EXPENSES

Surgery Fees: Funds requested include the effort of the surgical veterinarian and two assistants, sterile surgical supplies, plus pre- and post-operative care. Aspiration of ovarian follicles for oocyte, granulosa cell and/or follicular fluid collection will be performed by laparoscopy. Following the completion of all IACUC approved ovarian stimulation and embryo transfer protocols, the animals will be ovariectomized bilaterally by laparoscopy. Embryo transfer protocols will be performed by laparoscopy.

NHP Per Diem: Monkeys will be pair-housed (female:female) for social enrichment in the ONPRC Animal Sciences Building during the proposed studies.

Drug Admin & Sample Collection: Funds are requested for DCM fees for drug administration and blood collection to recover costs associated with technical assistance and staff personal protection.

Semen Collection: Funds are requested for fees charged for the collection of macaque semen cover expenses associated with animal handling and technical assistance.

Equipment Maint Contract: Since the ART Core performs ultrasounds for other investigators and oversees the use and management of the ONPRC-owned GE Voluson ultrasound system, funds are requested to cover its service contract. The service contract is necessary to ensure optimal function of the ultrasound system, 24/7 access to technical support, and unlimited probe replacements.

Endocrine Services: Funds are requested for services from the Endocrine Technology Support Core for each steroid analyzed. Estradiol and progesterone will be assayed in samples collected daily from mid-follicular phase through the duration of the controlled ovarian stimulation and controlled ovulation regimens to ensure protocol success.

CORE SCIENCE SERVICES: ART-ESC Support Core – Service Income Table

Last Funded Year (53)

Source	Funding (direct costs)
P51 base grant support	$303,367.52
Program income derived from P51 base grant	113,658.00
Other Sources	0
Total	$417,025.52

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$222,594.72
Program income derived from P51 base grant	181,749.54
Other Sources	0
Total	$404,344.26

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

ART-ESC Support Core receives salary support and support for other expenditures from program income.

TITLE: ENDOCRINE TECHNOLOGY AND SUPPORT CORE LABORATORY (ETSL)

CORE-SUPPORTED PERSONNEL:

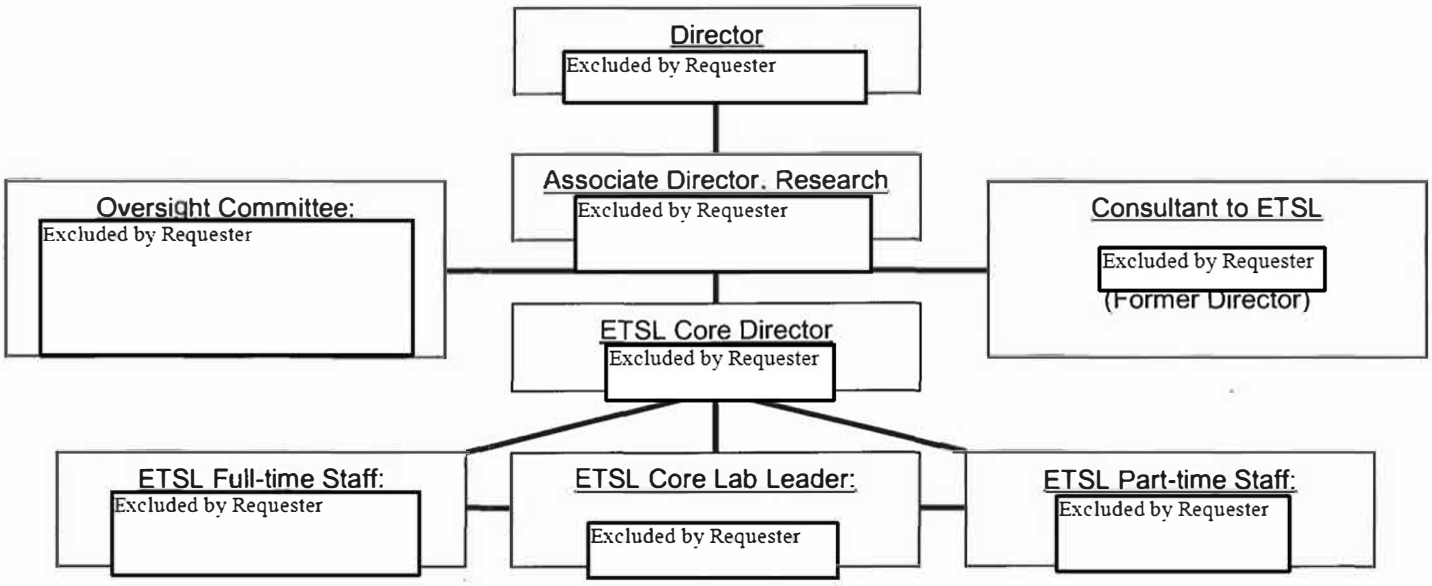
Core Staff (See Biographical Sketch, listed alphabetically in the Overview of the ONPRC)

Excluded by Requester	Senior Staff Scientist

Research Support

Excluded by Requester	Senior Research Assistant Laboratory Aide Laboratory Aide Research Assistant 2 Research Assistant 2

ENDOCRINE TECHNOLOGY SUPPORT CORE (ETSC)
Organizational Chart



ENDOCRINE TECHNOLOGY SUPPORT CORE PERSONNEL AFFILIATION AND ROLE

Staff Scientist:

Excluded by Requester	Senior Staff Scientist, Core Director

ENDOCRINE TECHNOLOGY SUPPORT CORE (ETSC)

DESCRIPTION:

The Endocrine Technology Support Core (ETSC) at ONPRC has provided services and support to intra and extramural investigators for 39 years with analysis of protein and steroid hormone content in blood as well as in biological tissues and fluid. At present, the ETSL routinely provides 5 assay technologies:

1. Traditional radioimmunoassay (RIA) that requires radioiodination to generate tracers for use with in-house antibodies, NIH-NHP reagents or developing an assay for new antibodies.
2. Organic solvent extraction (Ext) and/or Sephadex LH-20 liquid chromatography (LC) prior to in-house RIAs for purification/separation/analysis of single or multiple steroids in samples for many species.
3. Immunochemiluminescense technology using automated clinical platforms (i.e., Roche Cobas e411 and E170) for sensitive, reliable and high-throughput analyses for human and NHP hormones following complete validation.
4. XMAP-based technology (i.e., Luminex 200) using laser to recognize antibody-coded beads for multiplexing protein assays, e.g., 28 cytokines/chemokines in 50 µl of NHP serum.
5. Enzyme immunoassays (EIA), i.e., enzyme-linked immunosorbent assay (ELISA) or enzyme-linked fluorescent immunoassay (ELFA), for a wide range of commercial assays (validated for NHP).

The ETSL also performs, upon request, mouse interstitial cell testosterone bioassay (MICT) for analyzing monkey luteinizing hormone (LH) in chronological and frequent samples with minute volumes.

The function of the ETSC is advised by an Oversight Committee comprised of Excluded by Requester Ov Excluded by Requester Business meetings or email conferences with the ETSC Director are held twice a year to help improve ETSL operations on key issues about the efficiency of operation, directions for research support, including fee structure, technology development, and core facility infrastructure (i.e., space and equipment). The progress of the ETSC is reported to the Associate Director for Research, Dr. Excluded by Requester

Requesting ETSC services by internal or external investigators is easily accessed on line, by phone or via email. The operation relies on a master spreadsheet for sample requests from the investigator which will be used by the ETSL to generate assignment number, assay protocol, data analysis, results reporting, and chargeback billing information, i.e., "one-form-for-all".

In the past 40 months, Core income has increased every year by an average of 14% without significant increase in charge rates to internal and academic clients. About 79% of all samples are originated from NHPs and 14% are from humans. Approximately 74% of all samples are related to research in areas of reproduction, metabolism, stress and alcohol addiction. A total of 69 different assays were provided for 91 internal and exterunal investigators, from all ONPRC research division, OHSU departments, plus external programs, including industry.

Future plans for the Core include continued support for ONPRC, OHSU and external scientists requiring endocrine services for their research, publications and grant applications. Validation of new assays for NHP research, developing and extension of our services in Multiplex NHP platforms, and sharing of our services and experiences with other NPRCs will also be our main goals.

ENDOCRINE TECHNOLOGY SUPPORT CORE SPECIFIC AIMS

The goal of the ONPRC Endocrine Technology and Support Core (ETSC) is to provide intramural (ONPRC and OHSU) and external (academic and industry) scientists with the expertise and facilities necessary for obtaining quality data supporting clinical and pre-clinical research using nonhuman primates (NHPs) and other species in studies relevant to human health and disease. Specifically, the ETSC provides services and support in traditional and new assay technologies, including radioiodination, radioimmunoassay (RIA), organic solvent extraction (Ext), Sephadex LH-20 liquid chromatography (LC), immunochemiluminescense technology using automated clinical platforms, XMAP-based technology (i.e., Luminex 200) for multiplexing protein assays, enzyme immunoassays (EIA), enzyme-linked immunosorbent assay (ELISA), enzyme-linked fluorescent immunoassay (ELFA), and unique bioassays such as those developed for mouse interstitial cell testosterone bioassay (MICT) and monkey luteinizing hormone (LH). Furthermore, the ETSC supports continuous developments in NHP research by validating commercial or existing assays using human antibodies, by developing new assays with antibodies generated in academia, and by partnering with companies to develop and validate single or multiplex assay panels specifically for NHPs. Regular review of resources, personnel training and performance, as well as quality of services offered will be performed by the Core director, oversight committee, and the ONPRC Associate Director for Research to ensure continued success of the Core.

To continue the high-quality services for NHP and non-NHP research provided in the previous funding period, the ONPRC ETSC proposes the following objectives through the next 5-year period of support:

Specific Aim 1: To provide a transparent operating structure for efficient and responsive services for NHP research programs with quality and validated analyses. This will be achieved through cooperation between the Core Director and his staff, the Core Oversight Committee, and the ONPRC Business office. Over the past 40 years, the ETSC has developed or validated more than 50 assays suitable for NHP serum, plasma, cell culture medium, or tissue extract samples. We expect to continue the high standards of service by maintaining close attention to all reagents and procedures, including multiple internal quality controls in all assays, and by enhancing our operation with electronic interactions with users, including sample requests, assay schedules, assay protocols, assay analysis, data reports, and invoicing. Immediate data-return, within an hour or less if necessary, is provided for time-dependent research projects, such as daily monitoring of the menstrual cycle in female NHPs. Regular review of resources, fee structure, performance and quality of services will be performed by the Core Director, the Core Oversight Committee, and the ONPRC Business office to ensure continued success of the Core.

Specific Aim 2: To support internal and external programs for clinical and basic sciences research. The ETSC focuses on providing scientists and clients with state-of-the-art equipment, knowledge, experience, reliability, skills, reasonable rates and well-proven technologies. The Core has acquired and validated assays on both a bench-top (e411) and a high-throughput (e170) Roche clinical automatic platform for analyzing large number of primate samples in clinical and basic research. The Core will continue to provide the capacity to analyze multiple steroid or protein hormones for primate and non-primate species, using chromatography and Luminex technologies, respectively, and to analyze a single steroid or protein parameter by traditional RIA and EIA methods following isolation and purification as necessary.

Specific Aim 3: To develop NHP-specific assays and share with NPRCs and other scientific institutions. The ETSC has initiated cooperation or partnership with academic laboratories or commercial companies to develop NHP-specific assays or panels, including custom-made multiplex monkey cytokine kits, appropriate multiplex metabolic hormonal panels, as well as steroid biosynthesis panels to monitor steroid intermediates and products in a single serum sample. The results of these developments will be shared with all NPRCs as well as the scientific community through specific organizations, NIH-sponsored programs, scientific annual meetings, and on our website (http://www.ohsu.edu/xd/research/centers-institutes/onprc/research-services/research-support/endocrine-technology.cfm).

ENDOCRINE TECHNOLOGY SUPPORT CORE RESEARCH STRATEGY

SIGNIFICANCE

Nonhuman primate (NHP) research is a chosen path to translate experimental data from bench to bedside. Analyses of protein and steroid hormones in NHP studies rely on specific assays performed by skilled operators for reliable results. These assays must be validated for NHP samples in the form of serum, plasma, tissue extracts, cell culture, saliva, urine, etc., as each may contain components incompatible with a given assay. The ETSC's mission is to validate, develop, perform and share endocrine technologies that support NHP research at the local, national and even global level. We strive to find and offer the best-quality assays for our internal and external investigators with the most reliable, efficient, and economical solutions available within the budget for the researcher and the ETSC. In the past 42 months (5/1/2009-10/31/2012), 45 internal investigators at ONPRC (27) or OHSU (18), and 46 external scientists in academia (30) or companies (16) have used ETSC's services. External scientists send samples both from within the USA (38) and abroad, from Canada (3), Germany (2), South Korea (1), Sweden (1) and Switzerland (1). External users, including several other NPRCs and governmental institutions such as UC-Davis, Harvard, and NIH, have used same-day or next-day services for their studies on NHPs. In addition, several clinical contraceptive projects at the Women's Health Research Unit (WHRU) at OHSU have also taken advantage of quick data-return time for screening research subjects.

Reproductive research has been a focus at ONPRC for 5 decades, and the ability to analyze monkey LH and FSH continues to define the ETSC as a unique contributor to the NPRC system. Because most antibodies against human LH or FSH do not cross-react with monkey gonadotropins, the currently available homologous cynomolgus RIA kits from Excluded by Requester at UCLA-Harbor/NHPP are critical tools for measuring monkey LH and FSH. These are traditional RIAs that require iodination of purified hormones with radioactive ^{125}I, a procedure that is still performed routinely in the ETSC. About 10% of our samples and 15% of our income came from analyses for monkey gonadotropins, including requests from industrial pre-clinical or pharmaceutical research projects. Another unique service that the ETSC continues to provide is the extraction-LH-20 chromatography-RIAs for single or multiple steroid determinations, particularly vital for non-primate species in smaller volumes.

The ETSC has been an active advocate, forming strategic partnerships with companies such as Life Tech, IBL, CalBiotech, ALPCO, Cayman, and Ansh Labs, in the quest for developing or validating specific assays for NHP research. These projects include multiplex NHP cytokine assays, multiplex steroid assays, inhibin-B, anti-Mullerian hormone, and other investigator-initiated EIAs and RIAs. We share our experience with other NPRCs and scientists (via organizations, website or inquiries).

INNOVATION

Multiplex cytokines for NHPs: Since the installation of a Luminex 200 in 2011, we have been associated with and trained by Life Tech (28-Plex NHP cytokines) and Millipore-EMD (23-plex NHP cytokines). The two kits were compared using a set of monkey samples specifically prepared for assay validation (provided in part by the Division of Comparative Medicine with samples taken from rhesus macaques in the sick bay). We also plan to run a narrowed-down version with 5 cytokines in an ETSC-made kit with materials supplied by Life Technologies, Inc., for Excluded by Requester pilot project on phenotyping ONPRC rhesus macaques with a pedigree for heritage diseases. This is innovative because we will make our own multiplex cytokine kits and be able to test values for each cytokine against individual ELISA. This project would lay the groundwork for us to develop more multiplex kits for NHP research.

Multiplex steroids for many species: Steroids are the foundation of many physiological and pathological conditions across all species, including aging, obesity, polycystic ovary syndrome, infertility and cancer. The path of biosynthesis from cholesterol to all 15 steroids has been known for decades. Many steroid-related disorders or functions are linked to their precursors or metabolites, but usually they can only be analyzed individually, making difficult for scientists to see the whole picture in one step. We have teamed up with Life Technologies Inc., who will develop all 15 steroid antibodies into multiplex kits; the ETSC will validate kit performance with our traditional techniques. The results could benefit not only NHP research, but also clinical and basic science research in developmental, reproductive, cancer, and metabolic disorders.

Chorionic gonadotropins for NHPs (mCG): For many years, measuring macaque (m)CG has been limited to mostly qualitative assays performed at a few institutions, notably UC-Davis. We recently established a

heterologous traditional RIA for mCG that is quantitatively superb, with a sensitivity of less than 0.01 ng/ml. This will allow studies to identify early pregnancies critical for developmental and drug treatment studies. **Other new or validated assays for NHPs:** We also developed a kisspeptin RIA and validated 11 other assays for NHPs, including the only ELISA that works for monkey steroid hormone binding globulin (SHBG).

APPROACH

reviewers' comments

Progress and Major Accomplishments.

As detailed below, the ETSC has seen a 30% increase in the number of samples processed and a 73% increase in chargeback income during the past 42 months, compared to the previous grant period (2004-2008). In the past 42 months, the ETSC served 91 internal and external clients with 69 assay modalities (TABLE 3 below), developed or validated 14 new assays for investigators, and encouraged companies to develop NHP-specific assays, such as multiplex monkey cytokines and multiplex steroids assays. Services unique for NHPs included homologous cynomolgus LH and FSH assays validated for other macaque species and a heterologous, quantitative monkey CG assay. We have streamlined our operation system to be completely electronic, with investigator-prepared electronic sample request forms for assay assignment, protocol, analysis, results, and data reports. We have also extended services to international investigators.

Services Provided/User Info During Previous Grant Period (42 months from 5/1/2009-10/31/2012).

As shown in TABLE 1, a total of 196,070 samples were processed and $1,744,437 was received as chargeback income. These samples came in 11 species and were processed for 69 different assay types. 78% of samples came from internal investigators of ONPRC and OHSU. The average chargeback rate was

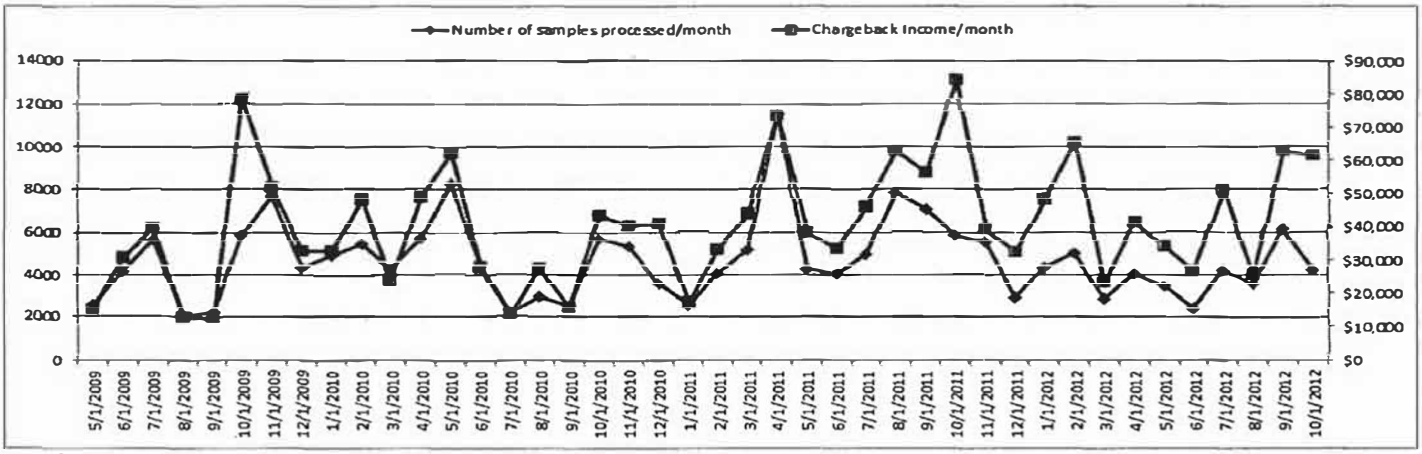
$7.10 and $15.14 per sample for internal and external projects, respectively. 79% of all samples originated in NHPs, and 14% were from clinical trials with human subjects. These NHP and human samples combined for 91% of total income.

The number of samples processed monthly (Figure 1) Varied between 2,000 and 13,000. However, the average number of samples processed per month over each year was stable (TABLE 1).

TABLE 1: Number of Samples Processed and Chargeback Income Received

From 5/1/2009 -10/31/2012 (42 months)	No. of samples	Chargeback Income	Charge/sample
Total	196,070	$1,744,436.92	$8.90
Internal	152,274	$1,081,563.07	$7.10
External	43,796	$662,873.85	$15.14
Average per month	4668	$40,581.83	$8.69
Averaged Internal per month	3626	$25,752.50	$7.10
Averaged External per month	1043	$15,783.00	$15.13
Internal % of total	78	62	
External %of total	22	38	
Monthly average in 2009 (8 months)	4332	$34,355.06	$7.93
Monthly average in 2010 (12 months)	4611	$35,568.46	$7.71
Monthly average in 2011 (12 months)	5480	$46,785.64	$8.54
Monthly average in 2012 (10 months)	4032	$44,134.73	$10.95

Fig. 1: Monthly sample processed and Chargeback Income



Of the 69 assay types serviced, the 10 most frequently used include 6 Roche assays, 3 RIAs and 1 ELISA; all but 2 were for NHPs (the other 2 were for human samples). The top 2 assays were the Roche estradiol and progesterone assays, which, with their excellent sensitivity, proven consistency, and fast data turn-around time, are uniquely suited for monitoring menstrual cycle stages in NHPs for same-day decisions about surgery, MRI, follicle aspiration, in vitro fertilization, tissue removal, drug treatment, or vaccine inoculation (TABLE 2).

Table 2: Services by Assay Types provided from 5/1/2009 to 10/31/2012

Sorted by Quantity of Samples

	Hormones Processed	Assay Technique	Code	Quantity	Income	% Total Samples	% Total Income
1	Progesterone	Roche	P4	41577	$272,579.30	22.13	17.20
2	Estradiol-17b	Roche	E2	39989	$262,111.04	21.29	16.54
3	Insulin	Roche	INS	12952	$76,643.38	6.90	4.84
4	Luteinizing Hormone	RIA	LH	11281	$143,207.44	6.01	9.04
5	Follicle-stimulating Hormone	RIA	FSH	8910	$103,944.52	4.74	6.56
6	Cortisol	Roche	CSL	6400	$39,139.84	3.41	2.47
7	Adrenocorticotropin	Roche	ACTH	5099	$31,984.32	2.71	2.02
8	Luteinizing Hormone	Roche	LH	4640	$35,965.99	2.47	2.27
9	Androstenedione	ELISA	A4	3827	$24,933.70	2.04	1.57
10	Levonorgestrel	RIA	LNG	3715	$133,740.00	1.98	8.44

Sorted by Chargeback Income

	Hormones Processed	Assay Technique	Code	Quantity	Income	% Total Samples	% Total Income
1	Progesterone	Roche	P4	41577	$272,579.30	22.13	17.20
2	Estradiol-17b	Roche	E2	39989	$262,111.04	21.29	16.54
3	Luteinizing Hormone	RIA	LH	11281	$143,207.44	6.01	9.04
4	Levonorgestrel	RIA	LNG	3715	$133,740.00	1.98	8.44
5	Follicle-stimulating Hormone	RIA	FSH	8910	$103,944.52	4.74	6.56
6	Insulin	Roche	INS	12952	$76,643.38	6.90	4.84
7	Cortisol	Roche	CSL	6400	$39,13984	3.41	2.47
8	Luteinizing Hormone	Roche	LH	4640	$35,965.99	2.47	2.27
9	Anti-mullerian Hormone	ELISA	AMH	1802	$33,711.28	0.96	2.13
10	Adrenocorticotropin	Roche	ACTH	5099	$31,984.32	2.71	2.02

Table 3: ETSC services used by 91 internal and external scientists in 39 institutions.

Last Name	First Name	Source	Institution	Department	Location	Sector
Excluded by Requester		External	Private Source	Research & Development	Minneapolis, MN, USA	Industry
		External		Research & Development	Minneapolis, MN, USA	Industry
		External		Research & Development	Minneapolis, MN, USA	Industry
		External		Vaccine Research	Boston, MA, USA	Academic
		External		Research & Development	Reno, NV, USA	Industry
		External		Research & Development	Reno, NV, USA	Industry
		External		Research & Development	Reno, NV, USA	Industry
		External		Research & Development	Reno, NV, USA	Industry
		External		Research & Development	Munster, Germany	Industry
		External		Biological Science	Pittsburgh, PA, USA	Academic
		External		Research & Development	Cupertino, CA, USA	Industry
		External		Research & Development	New York, NY, USA	Non-profit Org
		External		Neurosciences	Stockholm, Sweden	Academic
		External		American Institute for Goat Research	Langston, OK, USA	Academic
		External		Toxicology	Albuquerque, NM, USA	Academia
		External		Cellular and Molecular Physiology	Chicago, IL, USA	Academic
		External		Reproductive Endocrine Unit	Boston, MA, USA	Academic
		External	National Institute of Health	Viral Evolution and Genomics Core	Frederick, MD, USA	Government
		External	New England Primate Center/Harvard Univ.	Pathology	Boston, MA, USA	Academic
		External	Northwestern U	OB/GYN-	Chicago, IL, USA	Academic
		External	Oregon State U	Physiology	Corvallis, OR, USA	Academic
		External	Portland State U	Biological Science	Portland, OR, USA	Academic
		External	Private Source	Reproductive Science	Washing DC, USA	Academic
		External		Developmental and Reproductive Toxicology	Everett, WA, USA	Industry
		External		Developmental and Reproductive Toxicology	Everett, WA, USA	Industry
		External		Research & Development	Seoul, South Korea	Industry
		External		Research & Development	Seoul, South Korea	Industry
		External		Neonatology	Palo Alto, CA, USA	Academic
		External		Endocrinology	Toronto, Canada	Academic
		External	Tulane Primate Center	Veterinary Medicine	Covington, LA, USA	Academic
		External	Tulane Primate Center	Veterinary Medicine	Covington, LA, USA	Academic
		External	Private Source	Structural and Cellular Biology	New Orleans, LA, USA	Industry
		External		OB/GYN-Reproductive Sci	Winnipeg, Canada	Academic
		External	U Mississippi School of Med	Psychiatry	Jackson, MS, USA	Academic
		External	U of Colorado Denver	OB/GYN-Reproductive Endocrinology and Infertility	Denver, CO, USA	Academic
		External	U of Zurich-Irchel	Evolutionary Biology and Environmental Studies	Zurich, Switzerland	Academic
		External	Private Source	Center for the Interaction of Animals and Society	Philadelphia, PA, USA	Academic
		External	U Texas SW Med Center	Internal Medicine-Arthritis	Dallas, TX, USA	Academic
		External	U Vermont	Orthopaedics and Rehabilitation	Burlington , VT, USA	Academic
		External	Private Source	Maternal, Fetal and Newborn Health	London, ON, Canada	Academic
		External		Molecular Neurobiology	Heidelberg, Germany	Academic
		External	University of Pittsburgh	Physiology	Pittsburgh, PA, USA	Academic
		External	UT Southwestern Medical Center	Molecular Genetics	Dallas, TX, USA	Academic
		External	Private Source	Veterinary Science	Blacksburg , VA, USA	Academic
		External		Neurobiology and Anatomy	Winston-Salem, NC, USA	Academic
		External	Yerke Primate Center/Emory U	Developmental and Cognitive Neuroscience	Atlanta, GA, USA	Academic
		Internal	OHSU	SM Surg Urology	Portland, OR, USA	Academic
		Internal	OHSU	Molecular Microbiology and Immunology	Portland, OR, USA	Academic
		Internal	OHSU	Physiology	Portland, OR, USA	Academic
		Internal	OHSU	Physiology	Portland, OR, USA	Academic
		Internal	OHSU	Stem Cell Center	Portland, OR, USA	Academic
		Internal	OHSU	OB/GYN-WHR	Portland, OR, USA	Academic
		Internal	OHSU	Anesthesiology	Portland, OR, USA	Academic
		Internal	OHSU	Anesthesiology	Portland, OR, USA	Academic
		Internal	OHSU	Anesthesiology	Portland, OR, USA	Academic
		Internal	OHSU	OB/GYN-WHR	Portland, OR, USA	Academic
		Internal	OHSU	Orthopedics	Portland, OR, USA	Academic
		Internal	OHSU	Physiology	Portland, OR, USA	Academic
		Internal	OHSU	OB/GYN-WHR	Portland, OR, USA	Academic
		Internal	OHSU	Anesthesiology	Portland, OR, USA	Academic
		Internal	OHSU	Neurology	Portland, OR, USA	Academic
		Internal	OHSU	Behavioral Science	Portland, OR, USA	Academic
		Internal	OHSU	Physiology	Portland, OR, USA	Academic
		Internal	OHSU	Physiology	Portland, OR, USA	Academic
		Internal	ONPRC-OHSU	Animal Science	Portland, OR, USA	Academic
		Internal	ONPRC-OHSU	Reproductive Sciences	Portland, OR, USA	Academic
		Internal	ONPRC-OHSU	Reproductive Sciences	Portland, OR, USA	Academic
		Internal	ONPRC-OHSU	Animal Science	Portland, OR, USA	Academic
		Internal	ONPRC-OHSU	Reproductive Sciences	Portland, OR, USA	Academic
		Internal	ONPRC-OHSU	Neuroscience	Portland, OR, USA	Academic
		Internal	ONPRC-OHSU	Neuroscience	Portland, OR, USA	Academic
		Internal	ONPRC-OHSU	Neuroscience	Portland, OR, USA	Academic
		Internal	ONPRC-OHSU	Reproductive Sciences	Portland, OR, USA	Academic
		Internal	ONPRC-OHSU	Animal Science	Portland, OR, USA	Academic
		Internal	ONPRC-OHSU	Reproductive Sciences	Portland, OR, USA	Academic
		Internal	ONPRC-OHSU	Neuroscience	Portland, OR, USA	Academic
		Internal	ONPRC-OHSU	Neuroscience	Portland, OR, USA	Academic
		Internal	ONPRC-OHSU	Neurosciences	Portland, OR, USA	Academic
		Internal	ONPRC-OHSU	Immunology	Portland, OR, USA	Academic
		Internal	ONPRC-OHSU	Reproductive Sciences	Portland, OR, USA	Academic
		Internal	ONPRC-OHSU	Neuroscience	Portland, OR, USA	Academic
		Internal	ONPRC-OHSU	Animal Sciences	Portland, OR, USA	Academic
		Internal	ONPRC-OHSU	Neuroscience	Portland, OR, USA	Academic
		Internal	ONPRC-OHSU	Reproductive Sciences	Portland, OR, USA	Academic
		Internal	ONPRC-OHSU	Neuroscience	Portland, OR, USA	Academic
		Internal	ONPRC-OHSU	Reproductive Sciences	Portland, OR, USA	Academic
		Internal	ONPRC-OHSU	Neurosciences	Portland, OR, USA	Academic
		Internal	ONPRC-OHSU	Reproductive Sciences	Portland, OR, USA	Academic
		Internal	ONPRC-OHSU	Reproductive Sciences	Portland, OR, USA	Academic
		Internal	ONPRC-OHSU	Reproductive Sciences	Portland, OR, USA	Academic
		Internal	ONPRC-OHSU	Reproductive Sciences	Portland, OR, USA	Academic

Specific Aims/Service Plan for Next Grant Period.

Aim 1: To provide a transparent operating structure for efficient and responsive services for NHP research programs with quality and validated analyses.

To accomplish **Aim 1**, user satisfaction will be reviewed annually through the anonymous survey of Core users. The satisfaction survey results, Core services offered, service chargeback fees, equipment needs and any quality control issues are presented to the Endocrine Core Oversight Committee semiannually, which are summarized and reported to the ONPRC Associate Director for Research [Excluded by Requester] The Oversight Committee is comprised of faculty representatives from 2 of the 4 ONPRC scientific divisions [Excluded by Requester] Reproductive & Developmental Sciences; and [Excluded by Requester] Neuroscience). Any deficiencies or conflicts in terms of Core services or fees are presented to the oversight committee so a corrective plan can be developed. Implementation and progress made towards any corrective measure will be communicated routinely to [Excluded by Requester] Chargeback fees are determined by calculating cost-recovery for assay kits, staff time, and effort, as well as lab supply costs. All Core chargeback fees are reviewed and approved by the oversight committee, [Excluded by Requester] and the ONPRC Associate Director for Administration.

We will also continue to perfect our electronic operation system. The one-form-for-all system works well for general assay requests in basic science jobs that are organized into separate experiments. However, in chronological and clinical studies where samples are being sent to us at different times over months or years for the same hormonal measurements, a new operation format for data analysis and recording is needed. Furthermore, many jobs require specific sample identifications and duplicate measurements, with requested data report in individual and mean values. We have been utilizing a "Master file" in spreadsheet format that was largely satisfactory for our clients. We will develop needed "Macros" in spreadsheets to eliminate repeated calculations and errors. Moreover, we will work with the ONPRC IT group to enhance our operating system with the application of data management software (LabKey), and to facilitate internal communications via the OHSU Intranet based on SharePoint. As our workload increases, so does the labor for sample entry, sample processing, data analysis, results reporting and chargeback billings. These chores, while critically important, are taking away time that we should be spending it on assay operations. We will focus first on using the LabKey software for efficient sample identification, input and data management for the Roche automatic platform and the Luminex 200, as those equipments generate large amount of data and lend themselves best to developing an electronic interface. We shall achieve precision efficiently for years to come with our commitment to better data management.

We have been involved in many cases where scientists inquired about what we can do to help their research in reproductive disorders, aging, metabolic diseases, new drug testing, cancer research, environmental changes, development, gene knock-outs, etc. Recommendation of ETSC from our users to new clients is common. Many of these services materialized after favorable interactions between the clients and the Core Director solved issues of assay specificity, sensitivity and selectivity. These interactions led to an expansion of our client base, which now includes the USA, Canada, Europe, Australia and Asia. We will continue to serve our internal and external investigators and to provide high quality assay services for which our lab is recognized.

Aim 2: To support internal and external programs for clinical and basic sciences research.

To accomplish **Aim 2**, we will continue our services to internal and external clients for our existing assays. NHP samples for estradiol, progesterone, LH, FSH, insulin and cortisol are predicted to be the top services. A new contraceptive clinical trial with the ETSC as the Central Lab should begin in 2013, for which we will use a high-throughput Roche E-170 automatic platform to complete the project on time. In the next 5 years, while our priority is NHP research, we will continue to bid for jobs in clinical research, but only through the participation and recommendation of our internal scientists. Both scientific and economic aspects of new projects and new Core techniques will be considered. We predict that the needs for phenotyping and multiplexing will explode in the next 5 years. With the purchase of a Luminex 200, we are in position not only to use pre-mixed commercial kits, such as the 23-plex NHP cytokine panel, but also to develop new NHP multiplex panels in our lab for ongoing projects, including reproduction, obesity, diabetes, alcohol addiction, and stem cell research. We are involved in an ONPRC pilot project with [Excluded by Requester] that involves phenotyping of 5 cytokines in pedigreed monkeys. We will use this opportunity to develop our experience in making custom-mixed multiplex monkey cytokine kits, so that we may be able to develop other multiplex custom kits

for our clients. Our signature monkey LH and FSH RIAs will continue to be valued by basic and pre-clinical research with NHPs. Traditional RIAs requiring ^{125}I radioiodination will continue for their robust reliability and relatively low cost. Multiple steroid determinations for NHP and non-NHP samples using Sephadex LH-20 columns will continue. While these are labor-intensive techniques and did not generate major income, they are one of the reasons for our national and international reputations.

Aim 3: To develop NHP-specific assays and share with NPRCs and other scientific institutions.
To accomplish **Aim 3**, we will continue to share our experience with NHP assays and data management with other NPRCs and colleagues in the scientific community. The ETSC has participated in several informational programs, including the "Eagle i" program and the Western Association of Core Directors Meeting at OHSU. However, neither of these two programs focuses exclusively on NHP research and hormonal assays. The Internet becomes ever more important in facilitating our sharing of assay knowledge and NHP experience. Our experiences with the new Sharepoint intranet will form a framework for future social networking developments on the broader Internet. We did have communications with the NPRCs in Tulane, Massachusetts, Wisconsin, and California, primarily through assay requests and conversations with the investigators there. Recommendations of Assay Core labs among NPRCs are common and we expect such recommendations to continue as we develop new techniques and continue to offer traditional services. We will continue to send our newsletters to our clients, associates updating them with our experiences in NHP and non-NHP assays. Likewise, we welcome the opportunity to participate in meetings specifically designed to enhance NHP research with assays.

ENDOCRINE TECHNOLOGY SUPPORT CORE PUBLICATIONS:

Excluded by Requester

Endocrine Technology Support Core Biosafety Protection

Research conducted at the ETSC does not include microbiological practices. The lab primarily handles serum or plasma samples of primate and non-primate species, as well as cell culture media and tissue extracts. The laboratory has 4 fume hoods with closing doors and timers for organic solvent extraction, including column chromatography. The benches for handling biohazard samples are designed to be easily cleaned and decontaminated. These benches are dressed with two layers of absorbant papers: the lower layer with disposable full-length white absorbant paper lining with plastic bottom, and the top layer is protected by 2x3 feet disposable absorbant paper with plastic bottom for easy removal. All benches are provided with biohazard containers to hold pipet tips and test tubes suitable for autoclaving. The lab has two eyewash station and sinks for hand washing. Dedicated benches for handling radioactive materials are clearly labeled with radioactive material markers and tapes, dressed similarly with two layers of disposable absorbant papers as described above. A monthly meter as well as swipe test survey are performed and recorded. Personal protective equipment is provided for use in the laboratory, and is removed before entering non-laboratory areas. A laboratory-specific biosafety manual is available that outlines safety practices, use of personal protective equipment, proper disposal, and spill response. Personnel are trained in accordance with this manual, and are provided with medical surveillance. Access to the laboratory is restricted when work is being conducted and signage at the laboratory entrance provides information regarding the biosafety level, potential hazards and entry/exit requirements. Incidents that may result in exposure are evaluated and treated, and reported to the lab supervisor and the Biosafety Officer.

RESOURCES

Endocrine Technology and Support Core

Laboratory:
The Core occupies 1450 sq. ft. of space on two floors of the Research Building. First floor: Roche platforms, 400 sq. ft., Luminex room, 150 sq. ft. Second floor: four laboratories (two of 300 sq. ft., and 2 each of 150 sq. ft).

Animal:
N/A

Clinical:
N/A

Computer:
Four PC-based data collection and assay calculation stations as well as four personal desktop computers for Excluded by Requester OHSU LAN and WIFI are available for data exchange, storage and/or Internet access.

Office:
One 150-sf office for the core director and one 160-sf for ETSC staff (4 desks) are located in the Research Building.

Major Equipment:
A Packard B5005 5-channel gamma counter, two Beckman LS6500 with electronic data storage, three centrifuges (a Beckman J6B, a Beckman J6-MI, a Sorvall RC3Bplus), three Dubnoff temperature-controlled incubator and shakers; two water baths with external controllers and forced air manifolds, 80 Sephadex LH-20 microchromatography columns with racks; three Hamilton automatic sampling/diluting pumps, five refrigerators, six -20C freezers, one -80C freezer, access to a walk-in freezer, access to liquid nitrogen storage, a Molecular Devices microplate reader with analysis software; a Luminex LX-200 with analysis software, a Roche Cobas e411 bench-top clinical immunoassay platform, and a Roche modular E-170 high-throughput clinical immunoassay platform. Research).

Scientific Environment:
The ONPRC provides an exceptionally supportive environment for the performance of the services offered by the Core.

Program Director/Principal Investigator (Last, First, Middle): Robertson, Joseph E./Haigwood, Nancy L.

CORE SCIENCE SERVICES - ENDOCRINE DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Excluded by Requester	Sr Staff Scientist/Lab Mgr	% Effort			Institutional Base Salary	58,241	14,560	72,801
	Sr. Res Asst					21,775	7,621	29,396
	Laboratory Aide					3,173	1,428	4,601
	Laboratory Aide					17,280	6,912	24,192
	Res Asst 2					9,844	3,938	13,782
	Res Asst 2					18,529	7,412	25,941
	SUBTOTALS →					128,843	41,871	170,714

CONSULTANT COSTS		
None Requested		0
EQUIPMENT *(Itemize)*		
None Requested		0
SUPPLIES *(Itemize by category)*		
Office & Admin Supplies	350	
Laboratory Supplies	58,883	
Radioactive Antigens	1,290	
Small Lab Animals	201	
		60,723
TRAVEL		
Domestic	921	921
INPATIENT CARE COSTS		0
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		
None Requested		0
OTHER EXPENSES *(Itemize by category)*		
Membership in Profesnl Org	437	
Telecommuication	332	
Freight & Moving	1,166	
Equipment Maint & Repair	14,118	
Animal Per Diem	93	
Biohazard Waste Disposal	985	
		17,132
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 249,490
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 249,490

CORE SCIENCE SERVICES - ENDOCRINE
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	170,714	175,835	181,110	186,544	192,140
CONSULTANT COSTS	0	0	0	0	0
EQUIPMENT	0	0	0	0	0
SUPPLIES	60,723	62,545	64,421	66,354	68,345
TRAVEL	921	948	977	1,006	1,036
INPATIENTS CARE COSTS	0	0	0	0	0
OUTPATIENTS CARE COSTS	0	0	0	0	0
ALTERATIONS AND RENOVATIONS	0	0	0	0	0
OTHER EXPENSES	17,132	17,646	18,175	18,721	19,282
DIRECT CONSORTIUM/CONTRACTUAL COSTS					
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	249,490	256,974	264,684	272,624	280,803
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	249,490	256,974	264,684	272,624	280,803
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					1,324,575

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

PERSONNEL

Senior Staff Scientist - Excluded by Requester % Effort
Responsible for the overall progress of the ETSL Core, reviewing and implementing directions with the approval of the Oversight Committee and leadership team, submitting annual progress reports, providing methodological descriptions and quality control data to scientists for publications or grant submissions, keeping contacts with scientists and clients through emails, telephone and newsletters, heading staff meetings monthly and lab meetings routinely to prioritize assay schedules and discuss lab issues, finalizing assay schedules and protocols, analyzing data, reporting results, sending billing information to the administration, maintaining quality controls for all assays, and managing day-to-day activity of the Core. Also leads the development of new assays, validation of commercial assays for NHPs, and negotiation with company representatives for reagent discounts.

Senior Research Assistant Excluded by Requester % Effort
Income). Responsible for day-to-day assay assignment and schedule, distributing assay work load, reinforcing technical instructions, and completing assay assignments; responsible for technical training and supervision of new members of the Core, and for maintaining team work and quality; communicating with clients on assay questions, trouble-shooting, and training of staff.

Laboratory Aide - Excluded by Requester % Effort
Responsible for assisting with sample and reagent preparations, monitoring lab safety with monthly swipe test, handling disposal of bio-hazardous and radioactive waste, and maintaining lab cleanliness.

Laboratory Aide - Excluded by Requester % Effort
Responsible for handling operation of the daily E&P program and the Roche automatic platforms, handles sample receiving, storage and inventory, assists with sample and reagent preparations for assay analysis, records raw data and assists in purchasing.

Research Assistant 2 - Excluded by Requester % Effort
Responsiblefor extraction and analysis of steroids in NHP hair, saliva, and urine, and also develops new techniques, assists in operation of the Roche automatic platforms for large projects, and communicates with clients on assay questions.

Research Assistant 2 - Excluded by Requester % Effort
Responsiblefor the daily E&P electronic operation and report, is the primary operator of commercial assays, supervises the use of the Roche automatic platforms, performs assay analysis and validation, assists with electronic data reporting, communicates with clients on assay questions, assists in assay validations, purchasing and billing.

SUPPLIES

Office & Admin Supplies: Funding is requested to purchase printer inks, paper, chairs, binders, tapes and labels.

Laboratory Supplies: Funding is requested for purchasing chemicals, organic solvents, assay reagents, assay kits, quality controls, calibrators, accessories for operating the Roche platforms, the Luminex 200 and ELISAs, pipets and tips, assay and extraction tubes, sample vials, storage racks and boxes, glass columns for radioiodination and chromatography, and small equipment such as shakers, a sonification bath and water baths.

Radioactive Antigens: Funding is requested for purchasing, handling, and disposal of radioactive ^{125}I for radioiodination and tritium and ^{14}C radioactive tracers for radioimmunoassays.

Small Lab Animals: Funding is requested to purchase mice for the interstitial cell bioassay for measurement of NHP luteinizing hormone in small sample volumes.

TRAVEL

Funding is requested to attend one domestic annual meeting on NHP research or on technical training for new technologies that would benefit our services in NHP research.

OTHER EXPENSES

Membership in Profesnl Org: Funding is requested for membership in professional scientific organizations.

Telecommunication: Funding is requested to make local, long-distance and conference calls with clients regarding research projects, assay recommendation, sample preparation, experimental design, chargeback price, data report, and description of materials and methods for publications and grant proposals.

Freight & Moving: Funding is requested for overnight sample shipping on dry ice (return to clients only) as well as shipping and handling fees for assay kits and reagents.

Equipment Maintenance & Repair: Funding is requested for maintenance and repair of equipment, including the Roche platforms, Luminex 200, a gamma counter, two liquid scintilation counter and three refrigerated centrifuges.

Animal Per Diem: Funding is requested for per diem for mice to perform the MICT bioassay for monkey LH determinations.

Biohazard Waste Disposal:
Funding is requested for disposal of blood, saliva, urine and cell culture samples.

CORE SCIENCE SERVICES: Endocrine Support Core Income Table

Last Funded Year (53)

Source	Funding (direct costs)
P51 base grant support	$109,168.91
Program income derived from P51 base grant	307,512.59
Other Sources	0
Total	$416,681.50

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$249,489.79
Program income derived from P51 base grant	205,478.63
Other Sources	0
Total	$454,968.41

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

Endocrine Support Core receives salary support and support for other expenditures from program income.

TITLE: FLOW CYTOMETRY CORE

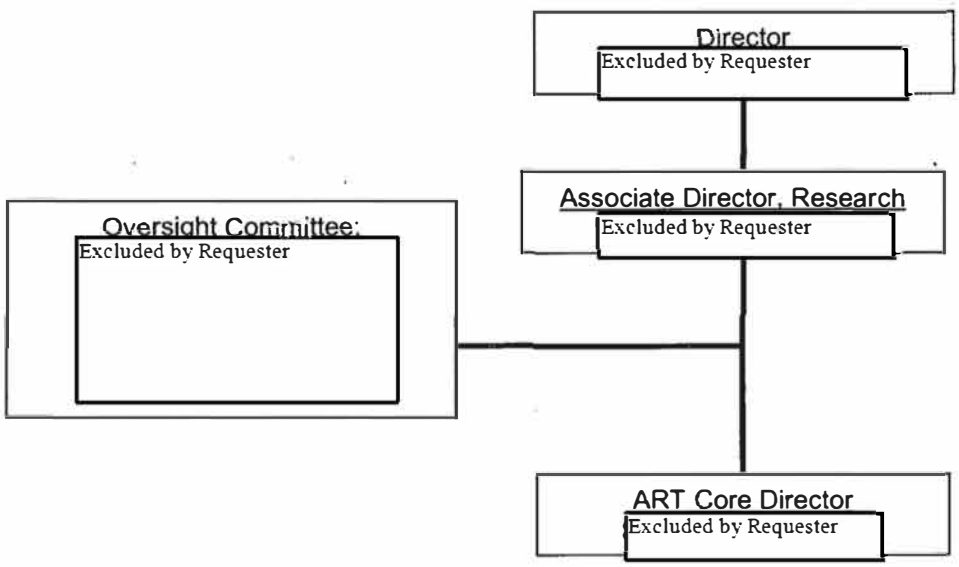
CORE-SUPPORTED PERSONNEL:

Core Staff (See Biographical Sketch, listed alphabetically in the Overview of the ONPRC)

Excluded by Requester

Staff Scientist 3

FLOW CYTOMETRY SUPPORT CORE
Organizational Chart



FLOW CYTOMETRY CORE PERSONNEL AFFILIATION AND ROLE

Staff Scientist:

Excluded by Requester	Staff Scientist 3, Core Director

FLOW CYTOMETRY SUPPORT CORE

DESCRIPTION:

The Flow Cytometry Core of the Oregon National Primate Research Center (ONPRC) was created during the mid 1980s in response to the AIDS epidemic and subsequent discovery of an animal model in nonhuman primates; i.e., simian AIDS or SAIDS. Starting with a Coulter EPICS C analyzer/sorter, the Flow Core currently contains two Becton-Dickinson (BD) FACS Calibur analyzers, two BD LSR2 analyzers and a BD Aria II cell sorter. The Flow Core is used by reseachers in all four research divisions (Neuroscience, Diabetes, Obesity and Metabolism, Reproductive & Developmental Sciences, and Pathobiology & Immunology), animal care staff in the Division of Comparative Medicine, and collaborators from outside institutions. The Flow Core is overseen by an Oversight Committee chaired by [Excluded by] (Chair) (Division of Pathobiology and Immunology; Vaccine and Gene Therapy Institute), [Excluded by] (Division of Pathobiology and Immunology; Vaccine and Gene Therapy Institute), [Excluded by Requester] (Vaccine and Gene Therapy Institute), [Excluded by Requester] (Division of Reproductive and Developmental Sciences), and Dr [Excluded by Requester] (Division of Neuroscience).

The Flow Cytometry Core plays a significant role in the ONPRC. Since its inception, the Core has spent over 2 million dollars purchasing equipment. Thus, This expense was not placed entirely upon individual laboratories that required flow capabilities. In addition, the Flow Core provides consistent training to all personnel and has the responsibility of maintaining the Core's equipment.

FLOW CYTOMETRY SUPPORT CORE SPECIFIC AIMS

The Flow Cytometry Support Core was created during the mid-1980s in response to the increase in non-human primate AIDS research. Both the technical capabilities and user base of this Core have significantly expanded in the intervening years, and the Core is now used by researchers from each of the ONPRC's scientific research divisions, animal care staff from the Division of Comparative Medicine, and collaborators from outside institutions.

The Specific Aims of the Flow Cytometry Core are:

Specific Aim 1: Provide an efficient, responsive, and transparent operating structure. Starting in 2012, the Core Director directly interacts with the users, the Core Oversight committee, the ONPRC business office, and manufacturers. In the last funding period, the Flow Cytometry Core was a unit of the Immunology Support Core, which also included the Cellular Immunology Unit, under the overall direction of [Excluded by Requester]. The latter unit has been transferred to the Infectious Disease Resource and the flow cytometry component has resumed its historical status as an independent support core. This new organization improves the efficiency, responsiveness and transparency of the Core's operation. As Core Director, [Excluded by Requester] will interact with the Core oversight Committee, the Associate Director for Research, and the ONPRC Business Office to ensure appropriate provision of core services, regular assessment of chargeback fees, and assessment of technology needs.

Specific Aim 2: Provide, maintain, and upgrade the Flow Core's equipment. The Flow Core currently has the same flow cytometers it had at the beginning of the 5-year grant; i.e., two BD FACS Calibur analyzers, two BD LSR2 analyzers, and a BD Aria II cell sorter. The analyzers will be available to all users on a self-serve basis, while the sorter will be available only to a limited number of well-trained users. We will continue to have a full maintenance contract with BD to keep the cytometers in peak working condition. During the coming 5-year grant period, we will explore efforts to replace the two aging BD FACS Caliburs with a BD Verse and add to our cell sorting capabilities by purchasing a cell sorter that can sort very large cells.

Specific Aim 3: Train users to operate the equipment in the Flow Core. We will continue training personnel to operate the analyzers on a self-service basis. The analyzers are available on a 24/7 basis to the users. Since the beginning of the Flow Core, the cell sorter has been operated by Flow Core personnel only. However, starting in 2009, we started training selected laboratory personnel to operate the Aria II sorter. The Aria II proved to be much easier to operate than the FACS Vantage. This change made the sorter available for longer sorting runs, some of which ended in early morning.

FLOW CYTOMETRY CORE RESEARCH STRATEGY

The Flow Cytometry Support Core operation was a unit of the Immunology Support Core in the previous funding period, along with the Cellular Immunology Unit (CIU). The CIU activities are proposed to become a component of the new Infectious Disease Resource for the next funding period, so that the flow cytometry unit will now revert to its previous status as an independent support core. The response to the previous critique and progress report for both the CIU and flow cytometry are included in this section, while the plans for the CIU operation for the next funding period are described in the Infectious Disease Resource section of the proposal.

SIGNIFICANCE

The Flow Cytometry Support Core is a critical technical resource at the ONPRC, and is used by researchers from all of the ONPRC research divisions, animal care staff from the Division of Comparative Medicine, and several collaborators from outside institutions. Since its inception, this Core has spent over $2 million in the acquisition of new equipment. In addition, the Core provides consistent training to all personnel and has the responsibility of maintaining the Core's equipment. The Core also revised its charge rate structure and instituted an annual review of the rate to place the Flow Core on firm financial grounds and to make possible future expansion.

INNOVATION

On-Line Scheduler: the laboratory of Excluded by Requester has developed an online scheduler for the Flow Core, which replaced an obsolete wall-calendar based system. Users can now reserve time on the analyzers from their desk computers. In addition, the core director can review the analyzer usage schedule and generate usage tables from the scheduler.

Charge Rates: a new charge system for usage of the Flow Core's services was initiated during the 2010-2011 fiscal year. The new system includes an annual review of charge rate with any changes starting at the beginning of the fiscal year. The increase in charges for the 2011-2012 fiscal year was 12% to make up for previous years of no increases. The rate was increased another 3% starting on May 1, 2012 (i.e., beginning of the 2012-2013 fiscal year).

Training of Personnel: prior to 2009, the cell sorters (EPICS C, FACS Vantage and Aria II) were operated solely by personnel of the Flow Core. However, early that year, we began to train selected laboratory personnel to operate the Aria II for two reasons: (a) the Aria II was much easier to operate since the it had fixed laser and mirror alignment and did not require re-alignment before or during each sorting run; and, (b) longer sorts were being done that often ended early next morning. This change in the training of the sorter users greatly increased its availability (24/7) and, thus, its usage.

APPROACH

reviewers' comments

reviewers' comments

Progress and Major Accomplishments.

CIU progress-

Projects completed or ongoing in the closing grant cycle include:

1. A project with the University of Washington, in which the goal was to assess the value of oral administration of an anti-SIV vaccine relative to a conventional intramuscular administration of the same vaccine, with readouts emphasizing GI tract (rectal) immunological parameters (24 rhesus monkeys in one study). This study culminated with a low-dosage rectal SIV challenge, infecting and following all 24 animals, with samples sent to collaborators for analysis of viral loads (NCI) and secretory antibodies (LSU). Results have been reported at two conferences, by presentation and poster, and a manuscript is currently in preparation.
2. A two-study project with an investigator at the Providence Health Franz Cancer Research Center, in Portland, OR, in which the goal was to take a promising anti-cancer treatment from the mouse to the NHP model. The studies evaluated three OX40 (CD134)-directed reagents for their affects on T cell effector function and memory cell generation, first in a 16-monkey study, then in a 10-monkey study. This original study was several months in preparation, and then the two connected studies spanned from early 2010 until winter 2011. The data has been analyzed, and a manuscript is currently in preparation.
3. This small (6-monkey), ongoing pilot study for an investigator at UCLA School of Medicine is assessing whether immunogenicity of HIV vaccines would be improved by use of small conserved regions of the SIV genome. This study was originally proposed in 2010, but delayed for more than a year while its complicated and innovative vaccine reagents were being prepared. After several months of preparation at the CIU the study began in Summer 2012, and will finish in Spring 2013.
4. This ongoing follow up study to project 1 is underway with 21 monkeys, and, like the first, is assessing whether oral vaccination improves vaccine-induced memory responses in the tissues. This study refines the earlier work several ways, but notably by including females, allowing the assessment of secretory antibodies at vaginal mucosa. This study currently is not funded to include a challenge phase. It started in January 2012, and is slated to end in January 2013.

Flow cytometry progress-

1. On-line scheduler developed as described above.
2. New charge rates recently implemented as described above.

Services Provided/User Info During Previous Grant Period.

Fiscal Year Starting in	Number of Laboratories	Affiliated with ONPRC
2009-10	20	17
2010-11	17	15
2011-12	17	15

Cytometer usage hours:

Fiscal Year Starting in	Analyzer Usage (hours)	Sorter Usage (hours)
2009-10	1843	422
2010-11	1716	352
2011-12	978	207

There was a slight decrease in the total hours of usage for both the analyzers and the sorter from 2009-10 to 2011-11. During 2011-12, usage of both the analyzers and sorter decreased significantly.

5. Cytometer use frequency: Number of recorded/charged uses of analyzers and sorter.

There was a general increase in the number of recorded/charged uses for both the analyzers and the sorter from 2007 to 2010. During 2011, the number for both the analyzers and sorter decreased.

Annual analyzer and sorter income:

Fiscal Year	Analyzers ($)	Sorter ($)	Total ($)

Fiscal Year	Analyzer Usage Number	Sorter Usage Number
2009-10	1209	117
2010-11	1310	157
2011-12	931	117

2009-10	68,100	28,300	96,400
2010-11	67,400	32,300	99,700
2011-12	34,400	17,800	52,200

Annual income of both the analyzers and sorter remained about the same from 2009-10 to 2010-11. During 2011-12, the income for both analyzers and sorter decreased.

The general trend during 2009-10 to 2010-11 was an increase in usage (hours, times used, income). Both the analyzers and the sorter showed increases in usage, but the sorter usage showed the more dramatic increase. There were two reasons for this increase in sorter usage, the purchase of the Aria II sorter during 2008 which made sorting of T cell subsets possible using 4-way 8-color staining, surpassing the 2-way, 4-color limitation of the older FACS Vantage sorter, and an increase in the number of necropsy samples due to studies reaching their terminal stages.

The 2011 fiscal year showed a drop in both analyzer and sorter usage. The drop in analyzer usage can be explained by the loss of two heavy users, Excluded by Requester left the ONRPC to take a new position at another university. Also, Excluded by Requester purchased his own analyzer and thus stopped using the Flow Core except for emergency uses. The drop in sorter usage is explained by a decrease in the number of necropsies.

It should be noted that, during the first five months of the current 2012-2013 fiscal year, sorter usage has dramatically rebounded due to a large increase in the number of necropsies. Analyzer usage is also rebounding by the addition of a new faculty member Excluded by Requester and general increase of usage by other laboratories.

Specific Aims/Service Plan for Next Grant Period.

Specific Aim 1. Provide an efficient, responsive, and transparent operating structure.

As described above, in the previous funding period, the Flow Core was folded into an overall Immunology Core that also included the Cellular Immunology Unit (CIU), which was directed by Excluded by Requester who also served as overall Immunology Core Director. The operations of the CIU were more in the nature of performing specialized assays for outside infectious disease investigators who desired access to particular techniques developed in the laboratory of Excluded by Requester As such, this was not clearly definable as a support core service per se; thus, it is being proposed that this operation be transferred to the new Infectious Disease Resource directed by Excluded by Requester remaining in charge of the former CIU procedures. As a result, the Flow Cytometry operation will resume its former status as a distinct support core with its original Director.

An Oversight Committee has been organized to reflect the Flow Core's new independent status, and consists of Excluded by (Chair) (Division of Pathobiology and Immunology; Vaccine and Gene Therapy Institute), Excluded by (Division of Pathobiology and Immunology; Vaccine and Gene Therapy Institute), Excluded by Excluded (Vaccine and Gene Therapy Institute), Excluded by Requester (Division of Reproductive and Developmental Sciences), and Excluded by Requester (Division of Neuroscience). The Committee's responsibilities are to: 1)

Evaluative the scope and efficacy of the Flow Cytometry Core and the Core's director; 2) Approve and/or recommend changes in the operational procedures of the Flow Core; and, 3) Approve and/or recommend the purchase of new equipment for the Flow Core. The committee will meet at least once a year and as needed.

We will continue our annual review of the rate charged to users of the Flow Core. The guiding principle of the rate charge has been to cover the cost of the maintenance agreement for all our instruments. We feel that, for the optimal effectiveness of the Flow Core, the cytometers must be kept in prime operating condition. Thus, aside from our responsibility for maintenance, we have always kept our instruments under full maintenance agreements with the manufacturer so we can have any problems quickly fixed. Upon approval of the oversight committee, changes in charge rate will be initiated on May 1st, the beginning of our fiscal year.

Specific Aim 2. Provide, maintain, and upgrade the Flow Core's equipment.
Analyzers: The Flow Core's has 4 analyzers: two 2-lasers, 4-color BD FACS Caliburs (one with the tube-autoloader option); a 3-laser, 10 color BD LSR 2; and, a 4-laser, 18 color BD LSR 2. When each analyzer was purchased, the new one did not replace the older one(s), but increased the Flow Core's analytic capabilities. Thus, we still have all 4 analyzers we purchased over the past 14 years.

The LSR2s should provide adequate service during the next 5-year grant period since we don't expect to exceed the 18-color limit of our newer LSR2. However, the FACS Caliburs will be replaced. But, instead of replacing the Caliburs with an instrument that just matches the Calibur's capabilities, we plan to replace them with an instrument that exceeds the Calibur's capabilities: the BD Verse. The Verse can be configured with up 3 lasers and detect up to 8 colors. It can also be equipped with BD's new Universal Loader that can automatically load samples from tubes or plates. Thus, the Verse will not only provide service for all the current Calibur users (including tube-autoloader users), but also serve as an 8-color backup for the LSR 2 users and provide automatic loading from tubes and plates (that our LSR2s are not equipped to do).

Sorter: The Flow Core has a 3-laser, 14-color BD Aria II cell sorter. This is the third sorter the Core has had, following a Coulter EPICS C and a BD FACS Vantage SE. Each new sorter replaced the older one; thus, the Flow Core has only the Aria II sorter. During the next 5-year grant period, we anticipate that the Aria II will provide adequate sorting of PBMCs and smaller diameter cell lines (<40 □m diamet
several ONPRC laboratories have shown interest in sorting very large cells (>50 □m diam
exploring the acquisition of a sorter capable of sorting large cells. The maximum nozzle diameter of our Aria II sorter is 130 □m.
efficient sorting, the Aria II's limit is about 40 □m, a smaller nozzle would have
limit of about 70 □m.

Three options will be explored: (i) A sorter, such as a BD Jazz, specifically built to sort large cells. Although mainly equipped with a 100-□m nozzle for PBMC sorting, the Jazz can be reconfigured with a 200-□m nozzle for large cell sorting. The Jazz cannot be reconfigured with the smaller nozzle by the user. The cost of a 200-□m Jazz is about $250,000. (ii) A main-line sorter that has been stripped down to meet the requirements for large cell sorting. The basic requirement for a large cell sorter is the availability of a 200-□m (or larger) nozzle diameter. However, the number of color detectors for most large cell use is far below that required for PBMC use. Thus, a 2-laser, 4-color sorter with a 200-□m nozzle would be adequate. The lower number of lasers and color detectors dramatically reduces the price of the sorter. Both BD (the Influx) and Beckman Coulter (the Astrios) can be configured into a $350,000 large cell sorter. Since both sorters also come with easily installed smaller nozzles, both sorters can be easily reconfigured for sorting PBMCs but limited to just 4 colors. Another advantage is that both sorters can be upgraded by the addition of more lasers and color detectors. (iii) A 3-laser, 14-color sorter configured to sort PBMCs and large cells. Both the Influx and Astrios can be configured to sort all the cell types we can anticipate by increasing the number of lasers and color detectors. Such a sorter costs about $600,000. An additional advantage of such a sorter is that it can serve as a backup if the Aria II breaks down or as an additional sorter when large numbers of cells are sorted (>4 x 10^7). It takes about 10 hours to sort 4 x 10^7 cells with the Aria II.

Specific Aim 3. Train users to operate the equipment in the Flow Core.
We will continue to offer the use of the analyzers on a self-serve basis and the sorter(s) on a core-run and limited self-serve basis. This procedure has proven effective since the analyzer users have been very careful about the daily clean up and shutdown procedures. With these trained users, the analyzers are available 24/7. The limited access to the sorter has also proven effective in maintaining the performance of the sorter while increasing its accessibility to well-trained users. The smaller number of sorter users makes maintaining sort performance much easier.

Biohazard Procedures: Flow Cytometery Core

Flow Cytometric Analysis: Uninfected murine cells may or may not be fixed with paraformaldehyde prior to analysis. Infected murine cells are fixed prior to analysis. All NHP cells are fixed prior to analysis whether they are infected or not. The cytometer's fluidics is a closed system that deposits waste fluid into a vessel containing 500ml of 100% bleach. The fluidics is cleaned monthly with 10% bleach.

Flow Cell Sorting: The Aria 2 cell sorter is located in a BSL-3 laboratory (VGTI Room 1215B). Both infected and non-infected cells of murine and NHP sources are sorted. The BSL-3 room is of standard design with filtered air in and out, negative pressure inside the room(s) relative to the outside, eye wash stations, and one-way pass autoclave. The room is constantly monitored to assure that the systems are functioning properly. Access to the BSL-3 room is limited to only essential personel.

The Aria 2 cell sorter is equipped with a Becton-Dickinson Hazard Management Option (HMO) that provides additional biohazard protection. The HMO creates a negative pressure in the sort chamber preventing aerosol from entering the room. Air in the BSL-3 room is filtered prior to entering the sort chamber and air from the sort chamber is passed through a HEPA filter prior to re-entering the room. Waste fluid is collected in a vessel containing 500 ml of bleach.

RESOURCES

Flow Cytometry Core Resources:

Laboratory:
VGTI/ONPRC Room 1211 serves as the core director's office and houses a 10-color LSR2 and a 4-color FACS Cailbur analyzer. The room is equipped with a sink, variable lighting controls, high capacity HVAC system, three computers and internet and telephone connections. A small refrigerator just for flow use is located in this room.

VGTI/ONPRC Room 1215B is a BSL-3 room that houses the Aria 2 cell sorter. Besides the biohazard containment capability of the room, the Aria 2 has an additional Biohazard Maintenance Option that filters air that moves pass the sheath stream. This option prevents aerosols from leaving the sort chamber providing extra biohazard containment. The site contains three biohazard hoods for sample handling and an autoclave to decontaminate waste and used tissue culture ware. Internet and phone connections are provided. The Flow Core shares a refrigerator located in this room.

VGTI/ONPRC 3119 houses the 18-color LSR 2 analyzer. This room is part of a common equipment room, but is separated by a double door; thus, is suitable isolated from the other instruments. The common room has water and sink availability. A small refrigerator just for Flow Core use is located in this room.

Clinical:
N/A

Animal:
N/A

Computer:
The core director has an Apple iMac office computer with standard OHSU internet connection and virus protection. All the flow cytometers have dedicated PC computers that have no virus protection and are, thus, not connected to the internet. The cytometer's computers are isolated from the internet because the BD operating system runs at a slower rate with virus protection on.

Office:
The core director's office is in room Facility Security /GTI/ONPRC.

Other:
N/A

Program Director/Principal Investigator (Last, First, Middle): Robertson, Joseph E./Haigwood, Nancy L.

CORE SCIENCE SERVICES- FLOW CYTOMETRY DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Excluded by Requester	Staff Scientist 3	% Effort				42,747	13,252	55,999
SUBTOTALS →						42,747	13,252	55,999

CONSULTANT COSTS		
None Requested	0	0
EQUIPMENT *(Itemize)*		
None Requested	0	0
SUPPLIES *(Itemize by category)*		
Laboratory Supplies	6,600	
		6,600
TRAVEL		
None Requested	0	0
INPATIENT CARE COSTS		0
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		
None Requested	0	0
OTHER EXPENSES *(Itemize by category)*		
Equipment Maint Contract	49,231	
		49,231
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 111,830
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 111,830

PHS 398 (Rev. 6/09) **Form Page 4**

CORE SCIENCE SERVICES - FLOW CYTOMETRY
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	55,999	57,679	59,409	61,192	63,027
CONSULTANT COSTS	0	0	0	0	0
EQUIPMENT	0	0	0	0	0
SUPPLIES	6,600	6,798	7,002	7,212	7,428
TRAVEL	0	0	0	0	0
INPATIENTS CARE COSTS	0	0	0	0	0
OUTPATIENTS CARE COSTS	0	0	0	0	0
ALTERATIONS AND RENOVATIONS	0	0	0	0	0
OTHER EXPENSES	49,231	50,708	52,229	53,796	55,410
DIRECT CONSORTIUM/CONTRACTUAL COSTS					
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	111,830	115,185	118,640	122,200	125,866
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	111,830	115,185	118,640	122,200	125,866
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					593,721

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

PERSONNEL

Staff Scientist 3- Excluded by Requester % Effort

Responsible for training of all new users of the flow analyzers, which provides a consistency of initial training and helps to maintain the cytometers in good working conditions. Supports researchers by assisting in the introduction of flow cytometry into ongoing research. Responsible for reviewing the Flow Core's charge rate, along with Admin-Business Services, to adjust accordingly.

SUPPLIES

Laboratory Supplies: Funds are requested for sheath fluid to pass samples through the analyzers/sorter, control beads to perform standardization tests to verify the cytometer performance, sample and collection tubes, sample pre-filters, disposal cytometer spare parts (e.g., gaskets, sorter nozzles) and printer ink.

OTHER EXPENSES

Equipment Maint Contract: Funds are requested to continue the full maintenance agreement with the cytometer's manufacturer. Since the Core serves many users with varying flow needs and schedules, one of the Flow Core's goals is to have the facilities available at all times. Having a full maintenance agreement helps the Flow Core fulfill this goal by assuring that the cytometers are in peak working order.

CORE SCIENCE SERVICES: Flow Cytometry Support Core Income Table

Last Funded Year (53)

Source	Funding (direct costs)
P51 base grant support	$94,416.72
Program income derived from P51 base grant	99,324.24
Other Sources	0
Total	$193,740.96

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$111,830.03
Program income derived from P51 base grant	93,087.29
Other Sources	0
Total	$204,917.32

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

The Flow Cytometry Support Core receives salary support and support for other expenditures from program income.

TITLE: PRIMATE GENETICS SUPPORT CORE

CORE-SUPPORTED PERSONNEL:

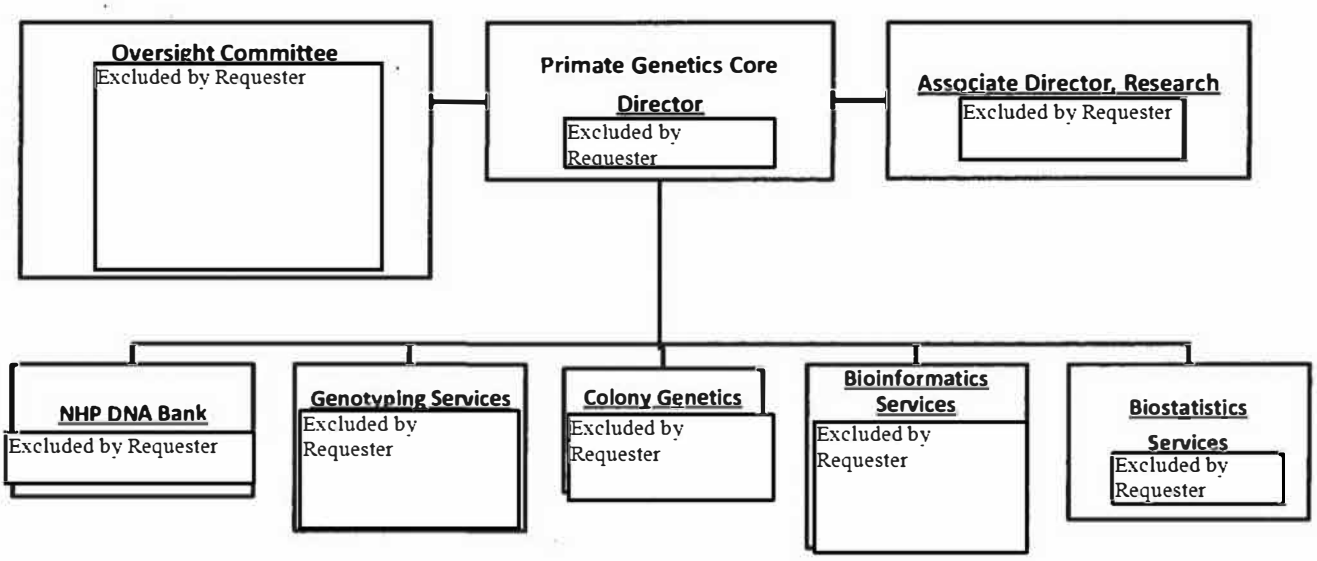
Core Scientists (See Biographical Sketches, listed alphabetically in the Overview of the ONPRC)

Excluded by Requester	Assitant Scientist Associate Scientist Assistant Scientist

Research Support

Excluded by Requester	Senior Research Associate Senior Research Associate Assistant Professor Research Assistant Research Associate Research Associate Research Assistant Research Associate

PRIMATE GENETICS SUPPORT CORE
Organizational Chart



PRIMATE GENETICS SUPPORT CORE PERSONNEL AFFILIATION AND ROLE

Core Scientists:

Excluded by Requester	Associate Scientist, Core Director
	Assistant Scientist
	Assistant Scientist

Visiting Scientists:

Excluded by Requester	Biostatistics & Bioinformatics Shared Resource, OHSU

PRIMATE GENETICS SUPPORT CORE

DESCRIPTION:

The Primate Genetics Support Core (PGSC) provides services to support the genetic and genomic analysis of NHPs for both colony management and research applications. Genetic characterization services are increasingly fundamental and essential for cutting-edge NHP management and research. To maximize efficiency, the PGSC provides a logical umbrella of services as follows: 1) The PGSC maintains a centralized ONPRC NHP DNA Bank to provide the high quality genomic material needed for both colony and research analysis; 2) The PGSC provides NHP-focused genotyping assays necessary for macaque MHC expressed-allele identification, SNP-based ancestry analysis, and SNP-based parentage analysis; 3) The PGSC provides the bioinformatics and biostatistics necessary to analyze the genotype and sequence information it generates; 4) The PGSC uses the genomic information it generates to evaluate and interpret NHP genetic diversity measures and to inform colony management decisions; and 5) The PGSC leverages its necessary biostatistics expertise to help other primate center investigators.

The services previously associated with the Primate Genetics Program are now formalized as the Primate Genetics Support Core, reflecting the expansion of critical genetic and analysis services provided to all ONPRC Divisions. It further reflects the need for efficient, centralized, and integrated services to support the genomic characterization of NHPs for both colony management and research needs. The underlying technologies and analysis methods are rapidly evolving, and a dedicated staff to stay current in evolving methods is essential. Further, this service core interacts closely with the Molecular and Cellular Biology Support Core (MCBSC) to ensure the availability of complimentary genomic analysis support.

PRIMATE GENETICS SUPPORT CORE SPECIFIC AIMS

The rapid development of the scope and sophistication of a number of capabilities in the Primate Genetics Program over the past funding period has justified their incorporation into a new Primate Genetics Support Core. The focus of the next grant period will include the systematic delivery of these services, using state-of-the-art methods to meet the expanding emphasis on genetic analysis in NHP management and research. Incorporation of next-generation sequence (NGS) methods and high-throughput genotyping analysis will continue to require integration to insure the seamless and efficient use of service resources. Our specific aims are as follows:

Specific Aim 1: Provide an efficient, responsive, and transparent operating structure. This will be achieved through cooperation between the Core Director and their staff, the Core Oversight Committee, and the ONPRC Business office.

Specific Aim 2: To collect and manage a comprehensive ONPRC NHP DNA Bank. The DNA Bank is a centralized resource to insure the availability of high quality genomic material for both colony and research analysis.

Specific Aim 3: To provide state-of-the-art genotyping services. Genotype assays to establish macaque parentage, ancestry and MHC expressed allele haplotypes inform colony management decisions. Additional genotype analyses, such as for TRIMCyp and 5-HTTLPR, are available as needed.

Specific Aim 4: To provide state-of-the-art bioinformatics services. Dedicated bioinformatics personnel provide state-of-the-art support for the analysis of high-density data, such as MHC expressed-allele analysis, user support for the Illumina MiSeq sequencer (operated by the MCBSC), and ONPRC genomics research applications.

Specific Aim 5: To provide comprehensive colony genetic analysis. This critical service informs ONPRC colony management decisions for breeding group formation and potential animal sale or research assignment, and to evaluate genetic diversity overall.

Specific Aim 6: To provide biostatistics support. This service leverages the Core's biostatistics expertise to evaluate NHP health measures and treatment efficacy, as well as pre- and post-award research grant support.

PRIMATE GENETICS SUPPORT CORE RESEARCH STRATEGY

SIGNIFICANCE

Genetic characterization of NHPs is critical to monitoring population genetic diversity and for informing breeding colony management. The ORIP-sponsored Genetics and Genomics Working Group (GGWG) of the Non-human Primate Research Consortium (NHPRC) set as initial goals the development of SNP genotyping assays to enable standardized parentage and ancestry characterization of rhesus macaques across all of the NPRCs. The Primate Genetics Support Core Director, Excluded by Requester, was a leader in that effort, and has since established genotyping services for implementation of both the parentage and ancestry assays for the ONPRC, and, as requested, for other NPRCs. A current goal of the GGWG is to establish population-analysis methods and metrics to evaluate colony genetic health at each NPRC, reflecting the importance of using state-of-the-art approaches to evaluating genetic diversity in our macaque populations. Excluded by Requester is a leader in this GGWG effort. Similarly, genomic characterization is an increasingly essential component of NHP-based biomedical research, as growing numbers of genetic variables that influence disease risk or rate of progression are identified, as with HIV, endocrine dysfunction, addiction, or macular disease. Next-generation sequencing (NGS) advances have also provided a quantum leap in the resolution of rhesus macaque MHC alleles and haplotypes, by enabling expressed allele quantitation at an affordable cost. These examples highlight the rapid pace of genetic and genomic advances, and underscore the importance of having the tools and skilled staff available to meet the evolving colony genetic and NHP analysis needs at the ONPRC.

INNOVATION

The Primate Genetics Support Core (PGSC) is an innovative support core that aims to maximize efficiency and integration between multiple aspects of genomic characterization, from DNA collection to genomic typing and data analysis. Centralized resources and skilled personnel meet the genomic analysis needs of both research and colony management groups, yielding a synergistic benefit to both. The PGSC personnel are also supported in part by grant-funded research programs, assuring that the staff interacts with other colleagues, attends topical conferences, and keeps current with new approaches to genomic analysis. This team of experts is thus informed and able to adjust to changing technologies, as evidenced by the recent incorporation of new NGS approaches for MHC haplotype analysis to meet colony management needs and for exon-seq analysis to meet research needs.

APPROACH

reviewers' comments

reviewers' comments

Progress Report and Major Accomplishments.
Though this core service was not established at the time of the previous grant submission, some basic services were provided, including ONPRC NHP DNA Bank management, Colony Genetic and Demographic services, and custom genotyping services. In the last few years, the advance of genomic technologies has resulted in substantial need for more sophisticated genetic characterization approaches to meet both colony genetic and research needs. This group was tasked with addressing those expanding technological and analysis needs. As a result, we now have in house capabilities to perform MHC expressed-allele analyses, to provide SNP-based parentage and ancestry analysis, to support NGS analysis of NHPs, and to perform more comprehensive and sophisticated colony genetic assessment. The restructuring of these services as a Core, now streamlines fee-for-service work, and increases the efficiency and availability of the skilled genetic and genomic services.

Services Provided/User Info During Previous Grant Period
Services provided in the previous grant period.

	Number	Revenue
ONPRC NHP DNA Bank samples	1356	$27,120
Macaque ancestry SNP assays (since *2010*)	1292	$58,140*
Macaque parentage SNP assays (since *2012*)	1920	$72,960*
Biostatistics Services Projects	87	$51,776
Bioinformatics Services Projects (since *2011*)	11	$35,786

*Genotyping costs for P51 animals are covered by the PGPSC budget, and not reported in Revenue.

The number and affiliation of users in the previous grant period.

	ONPRC	Non-ONPRC
ONPRC NHP DNA Bank	14	10
Macaque ancestry SNP assay (since *2010*)	DCM	8
Macaque parentage SNP assay (since *2012*)	DCM	4
Biostatistics Services	24	-
Bioinformatics Services (since *2011*)	8	-

Specific Aims/Service Plan for Next Grant Period.
Specific Aim 1. To provide an efficient, responsive and transparent operating structure. This will be achieved through cooperation between the Core Director and their staff, the Core Oversight Committee and the ONPRC Business office.

Personnel. The PGSC is under the overall direction of Excluded by Requester who has directed the Primate Genetics Program for the past 5 years. Excluded by has also led the development of the National NHP DNA Bank, and worked with the ORIP-sponsored GGWG in the development of the macaque ancestry and parentage SNP arrays for use across all 8 NPRCs. Excluded by Requester brings a wealth of NHP population research experience to her role as Head of Colony Genetics Unit, and also leads the current efforts to establish standardized metrics for colony genetic health for all NPRCs through the GGWG. Excluded by Excluded by PhD is the head of the Bioinformatics Services Unit, applying her expertise in cutting edge genomic analysis of NHPs. Excluded by Requester provides support for biostatistics services. His primary appointment

at OHSU is to provide biostatistics services to the Oregon Clinical and Translational Research Institute (OCTRI) and the OHSU Knight Cancer Center.

Oversight. Oversight of the PGSC is provided by the Oversight Committee, consisting of [Excluded by Requester] (Chair), [Excluded by Requester] (OHSU) and [Excluded by Requester] (OHSU). The Oversight Committee assists with charting strategic direction, advising on approaches, setting priorities and budgets. As needed, the core also seeks advice from outside experts regarding technical issues or longer-range planning. Day to day trouble shooting and management of services are supervised by Drs. [Excluded by Requester] Group meetings of each service unit are held weekly to review project data. The leaders of each service unit meet together once a month to discuss changes, challenges and project progress.

Quality Control. Positive and negative quality controls are incorporated into all genotype assays. The reproducibility of standard controls is monitored to insure the reliability of all assay data. Bioinformatics approaches and summary data are reviewed for logic and accuracy by [Excluded by] and at least one staff member. Initial parentage assignments are reviewed by analysis using the NHPRC Consortium web-based parentage analysis tool, with all discrepancies reviewed by [Excluded by Requester] on an individual case basis. The ONPRC NHP breeding colonies are also reviewed annually to evaluate genetic diversity metrics.

Chargebacks. Chargebacks for delivered services are developed by personnel and are in keeping with market costs for similar services at other institutions and NPRCs. Charges are set in coordination with the Oversight Committee and ONPRC business office.

Specific Aim 2. To collect and manage a comprehensive ONPRC NHP DNA Bank.
The ONPRC NHP DNA Bank is a centralized resource that was established in 2004 to insure the availability of high quality genomic material for both colony and research analysis. The DNA bank currently includes archived samples from >10,000 NHPs, comprising 9 species and more than 27,000 samples. The systematic collection of blood samples from breeding colony newborns insures that the DNA Bank remains current. Blood samples of offspring are collected and DNA is either extracted immediately for genotype analysis, or buffy coat cells are concentrated for storage at -80 degrees until needed. A second source of NHP DNA is received at necropsy, when a liver sample is collected and reserved for the DNA bank, unless infectious disease status or research aims preclude collection. The DNA bank-LabKey database is used to track date and volume of blood/tissue sample received, date of DNA extraction, and amount and concentration of DNA stored. The ONPRC NHP DNA bank has served as a model for the establishment of the National NHP DNA Bank, which was established across the 8 NPRCs, through the NHPRC, and under the direction of [Excluded by Requester] The National NHP DNA Bank includes a subset of DNAs from each species available at each NPRC; that resource can be searched through the public NHPRC web portal. As a result of this national DNA resource, there has been increased awareness of the more expansive ONPRC NHP DNA Bank, and, accordingly, an increase in number of external requests for DNA samples. The importance and value of the ONPRC NHP DNA Bank is evidenced by its growing use. It is commonly tapped to support large-scale NHP genomic studies at national institutions, and by investigators who wish to query genotypes with potential impact on research outcomes. Since 2009, more than 1,356 NHP DNA samples have been distributed for research use.

Specific Aim 3. To provide state-of-the-art genotyping services.
Three main genotyping assays are performed in support of NHP characterization for colony management. First, the macaque ancestry assay is a SNP-based assay that distinguishes Indian-origin and Chinese-origin rhesus macaques. It was developed by [Excluded by] in partnership with the CNPRC, through the NHPRC-GGWG consortium to enable standardized ancestry validation of rhesus macaques across all NPRCs. Since the ONPRC aims to include only Indian-origin rhesus in the social breeding groups, and purchased animals can be misidentified as either Chinese or hybrid rhesus macaques, this assay has been used to screen all rhesus macque breeders. As new breeders are purchased, they are also screend with this assay. A 128-SNP panel, which includes SNP alleles that are either rare or absent in one of the two geographic populations, is used for the analysis. Genotypes are assayed in the ONPRC Molecular and Cellular Biology Support Core (MCBSC) using the LifeTech QuantStudio 12K Flex. DNAs from 2 individuals previously genotyped are

included as positive controls and a water as negative control for each assay run. The full set of genotypes are then analyzed using STRUCTURE software in combination with genotype data from a set of 75 previously characterized Indian and Chinese reference animals. The reference set includes 35 Chinese rhesus purchased from 5 different sources, 35 unrleated Indian rhesus and 4 hybrid controls. STRUCTURE analysis reports include 90% credible intervals and mean point estimates. Individuals with 10% or more missing genotype information are classified as indeterminant. This macaque ancestry assay has been used by the PGPSC to evaluate rhesus macaque ancestry for the ONPRC, and as a fee for service for the TNPRC, WNPRC, NEPRC, WaNPRC, and NIH.

Rhesus macaque MHC expressed-allele assay has recently been launched at the ONPRC, in response to the growing demand for high resolution MHC analysis. The assay makes use of methods pioneered by Excluded by Requester at the WNPRC, leveraging the power of targeted RNA-seq to identify both major and minor MHC Class I alleles in macaques. The assay involves PCR amplification of exons 2 and 3 of the Class I alleles from cDNA, sequencing on the MCBSC Illumina MiSeq using 250-bp PE reads, then analyzing the products for both allele identity and relative expression level. We have worked closely with Excluded by Requester to transition this assay to our center, initially by our staff receiving hands-on training at the WNPRC. In addition, a former Excluded by lab member Excluded by joined the ONPRC, and established an analogous LabKey-based MHC sequence analysis pipeline. Finally, we validated our assay techniques by independently MHC typing 30 ONPRC rhesus macaques that were previously characterized in the O'Connor lab. A postivie control (previously characterized sample) is included with each new each set of samples processed, to insure that the expected MHC alleles are consistantly identified. We plan to MHC type up to 620 ONPRC rhesus macaque offspring per year. Additional samples will be processed, as requested for research purposes or for other facilities, as a fee for service. Having this MHC technology available in house enables the timely processing of samples and reduces the costs for service for the ONPRC. Expansion or modifications of the MHC assay will be considered as they become standardized and accepted by the NHP field.

Rhesus macaque parentage was previously validated using a 28-marker STR panel, performed at the Veterinary Genetics Laboratory in Davis, CA. We recently adopted a plan to transition to an SNP-based parentage assay, both because SNP genotyping has a lower error rate than STR typing, and because, as a consortium, the NHPRC-GGWG agreed to transition all NPRCs to this method for parentage assessment. The SNP assay was developed in partnership with the ONPRC, the CNPRC, and the SNPRC. Specifically, 96 SNP loci were selected based upon chromosome location and allele frequency and by testing 480 potential parent/offspring rhesus macaques from 7 NPRCs. For this assay, blood is collected from offspring, as well as from potential sire/dams that have not previously been SNP-typed. DNA is extracted using the robotic capabilities of the Eppendorf 5075 provided by the MCBSC. Genotyping makes use of a custom 96-SNP Illumina BeadExpress assay, which is performed at Igenix, Inc. (Bainbridge Island, WA). This external genotyping service was selected as it has been proven to be reliable, timely, and cost-effective. The genotype data are then uploaded to an analysis pipeline for evaluating simple Mendelian inheritance, a resource established by the NHPRC-GGWG to enable standaradized methods across NPRCs. We launched this assay in 2012, and have thus far performed genotype analysis of more than 2400 animals for the ONPRC, WNPRC, TNPRC, and NEPRC. Future updating of the SNP assay will be done in coordination with the NHPRC-GGWG.

Finally, we remain flexible for meeting the supplemental genotyping needs for colony management and research purposes. We provide custom genotype analysis for both SNP haplotypes and variable number tandem repeat (VNTR) alleles, as a fee-for-service function. Specific examples include TRIMCyp, 5-HTTLPR and MAOA-LPR, common variants associated with either S/HIV replication or temperament/anxiety.

Specific Aim 4. To provide state-of-the-art bioinformatics services.
This service was initiated in 2011, in response to the rapidly expanding use of high thoughput data assays by both the PGSC services and NHP scientific research programs. This onsite resource insures the ready availability of bioinformatic expertise, including strategies to maximize the usefulness of public NHP genomic resources. The personnel also support the analysis of PGSC genotype data for the genetic characterization of macaques (MHC expressed-allele, parentage SNP, and ancestry SNP assays). Moreover, this service group interfaces with the MBCSC to provide user support for the Illumina MiSeq sequencer, recently purchased by

the ONPRC. Individual research projects that require support for study design or bioinformatic analysis are available as a fee for service. Within the first year of service, reseach support was provided to scientists in all research divisions, including viral resequencing, pathogen detection, DNA methylation analysis, mitochondrial DNA heteroplasmy analysis, exon-seq based variant discovery and transcriptome characterization. Three part-time bioinformatics personnel are included in this P51 proposal, with more staff to be added if the need and fee for service use warrents it. The current bioinformatics analysts have complementary expertise in the analysis of whole genome sequence, exon-seq, methyl-seq, RNA-seq and database development. They have established analysis pipelines for several macaque genomic studies, including *de novo* and guided sequence assemblies, SNP variant discovery, and DNA methylation analysis. They have also spearheaded research and development projects to evaluate different genomic approaches. For instance, they completed a comparative analysis of three human-based exon-capture methods for macaque exon enrichment showing that this is a viable approach to be applied in NHP. In addition, they have deeply investigated the difference between four different approaches to study DNA methylation in rhesus. The lead bioinformatics analysts make great effort to stay current in their field by participating in national genomics meetings, by carrying out bioinformatics journal clubs locally, and by interacting with other computational biologists at OHSU. Common computational resources have been established to support user needs, including centralized servers and storage units to accommodate the data analysis and short-term data storage needs. The bioinformatics group meets every week with Excluded by Requester in order to discuss progress with each project and troubleshoot when needed. The bioinformatics analysts are physically located nearby Excluded by Requester office allowing for frequent one-to-one discussions.

Specific Aim 5. To provide comprehensive genetic management support to NHP colony managers. The Colony Genetics Unit provides critical analysis to support ONPRC colony management decisions on breeding group formation, potential animal sales, and the assignment of animals to research.

Parentage analysis to characterize the ONPRC pedigree: For the past 8 years, rhesus and Japanese macaque parentage has been determined using simple Mendelian inheritance at up to 28 microsatellite markers. Genotyping and initial parentage assignment has been conducted by the Veterinary Genetics Laboratory (Davis, CA). All initial parentage assignments are reviewed upon receipt of genotype data, and Mendelian discrepancies between genotypes for likely parent(s) and offspring resolved by a review of the raw genotype data. The strength of evidence supporting final parentage assignments is indicated with "genetic" parentage assignment having no discrepancies, and "provisional" parentage assignment having at most a single unresolvable discrepancy, in which there is more than a single bp difference between putative parent and offspring. Cleaned genotype data and parentage assignment are uploaded into the Genetics Resource & Informatics Program database (GRIPdb), or, as available, the LabKey database. Although genotype data at microsatellite markers has been used to establish the parentage of offspring born into the P51 core grant breeding colonies, we will transition over the next year to using a panel of 96 SNP markers for parentage analysis. Unlike microsatellite markers, SNP markers are found in much larger numbers in the genome, and genotyping is easily automated, thus reducing the relatively high error rate found in microsatellite genotypes. As detailed in Specific Aim 2, the ORIP-supported GGWG has developed a 96-SNP marker array specifically for parentage analysis, to work in conjunction with the NHPRC web-based parentage analysis pipeline. Dr. Excluded by Request as a member of the GGWG, has been an active participant in the development of this analytical pipeline. She will transition the ONPRC to parentage analysis based on the 96-SNP array and analysis pipeline over the next year, with an anticipated corresponding improvement in the accuracy of pedigree data.

The calculation of genetic value to inform new breeding groups, animal sales, and the assignment of animals to research: The primary goal of genetic management in the Colony Genetics unit of the PGSC is to maximize the retention of genetic diversity in the ONPRC NHP colonies. A focal point for maximizing genetic diversity is in the formation of new breeding groups. Candidate animals available for breeding groups are screened initially for behavioral and clinical problems, and then evaluated for a number of important genetic criteria using pedigree analyses, including mean kinship with the colony as a whole, the standard deviation of the individual animal's mean kinship to the grand colony mean kinship (i.e., z-score), the relatedness between candidate males, relatedness between candidate males and females, and total number of current living offspring for candidate breeders. Candidate males are not recommended for a new breeding group if they exhibit pairwise

relatedness above the level of 2nd cousin (r ≥0.03) to another male, or to proposed females, and all candidate breeders with >5 offspring remaining in the colony are not recommended for further breeding. The retention of allelic diversity from founder animals is also considered by calculating genome uniqueness, or the probability that the focal animal contains rare founder alleles within the colony, as well as the percent of each founder represented in each candidate breeder. These metrics are considered in full during the formation of new breeding groups, and where appropriate to inform the sale or cull of genetically less-valuable animals where needed, or to assign such animals to research. To support these analyses, we have adopted the use of PedScope commercial software (Tenset Technologies, Ltd., Cambridge, UK), which has the capacity to support pedigree and population genetic analyses on extended pedigrees containing many thousands of individuals. To ensure that appropriate genetic management is implemented, we conduct annual reviews of all socially housed breeding groups in relation to the above criteria, and results from this annual review are discussed with Excluded by Requester Ph.D., ONPRC Director Excluded by Requester Associate Director for Comparative Medicine, and Excluded by Requester head of colony operations.

Specific Aim 6. To provide biostatistics support. This service leverages its biostatistics expertise to evaluate NHP health measures, treatment efficacy, as well as research pre- and post-grant award support.

This service provides comprehensive biostatistics support to the basic and clinical science research at the ONPRC. The primary goal of the biostatistics unit is to enhance scientific quality and rigor of research through consultation and collaboration at all phases of research. The Biostatistics Unit is led by Excluded by Requester who evaluates NHP health measures, treatment efficacy, and pre- and post-award support. Pre-award support includes assistance in study design, power and sample size analysis, statistical data analysis plans, and protocol development. Post-award support includes data management, statistical data analysis, and manuscript preparation and review. Typically, exploratory data analysis includes visualization, descriptive statistics, and data mining such as cluster analysis, identifying association, sequential patterns of trends, and implementing classification and regression trees (CART). Model-based statistical inferences are frequently applied for NHP studies. Since many NHP studies are conducted in a time/spatial dependent setting, the unit provides statistical model-based analyses that implement temporal/spatial dependency of the data, such as general/generalized linear/nonlinear mixed models. Weekly biostatistics drop-in sessions provide investigators access to our biostatistician for immediate and effective support. During the last three years, the Biostatistics Unit supported dozens of grant applications and produced 15 co-authored publications with ONPRC researchers in fields including vaccine development, immune senescence, endocrine dysregulation, brain imaging, and therapeutic translational research. Excluded by Request is on site one day each week to meet with PIs to discuss planned or ongoing analyses. He also hosted a series of workshops for ONPRC members on topics of common interest: sample size and power analysis, general linear mixed models, and microarray data analysis. We will continue to maintain a versatile, accessible biostatistical resource in the PGPSC to support both colony management and research applications.

PRIMATE GENETICS SUPPORT CORE PUBLICATIONS

Excluded by Requester

Excluded by Requester

GENETICS BIOSAFETY

All JM sample handling will be conducted in accordance with Biosafety Level 2 standards, in adherence to the criteria outlined in *Biosafety in Microbiological and Biomedical Laboratories*, 5th edition, including all standard microbiological practices. Each laboratory has locking, self-closing doors, is designed to be easily cleaned and decontaminated, and has an eyewash station and a sink for hand washing. A biosafety cabinet that is certified annually is used for all manipulations of potentially infectious material. Personal protective equipment is provided for use in the laboratory, and is removed before entering non-laboratory areas. A laboratory-specific biosafety manual is available that outlines safety practices, use of personal protective equipment, proper disposal, and spill response. Personnel are trained in accordance with this manual, and are provided with medical surveillance. Access to the laboratory is restricted when work is being conducted and signage at the laboratory entrance provides information regarding the biosafety level, potential hazards and entry/exit requirements. Incidents that may result in exposure are evaluated and treated, and reported to the lab supervisor and the Biosafety Officer.

All physical evaluations of JMs will be performed at Animal Biosafety Level 2, in adherence to the criteria outlined in *Biosafety in Microbiological and Biomedical Laboratories*, 5th edition, including all standard microbiological practices. In addition, access to the facility is restricted, all personnel have specific training in performing procedures and the handling of animals, and are supervised by individuals with knowledge of potential hazards, animal manipulations. All protocols are reviewed and approved by the IACUC, and when applicable by the IBC, including worker safety and health concerns.

The facility has inward opening, self-closing doors, is designed to be easily cleaned and decontaminated, and has an eyewash station and a sink for hand washing. Personal protective equipment, including uniforms or gowns, gloves, and eye and face protection is provided for use in the facility, and is removed before leaving the facility. A biosafety manual is available that outlines safety practices, use of personal protective equipment, proper disposal, and spill response. Personnel are trained annually in accordance with this manual, and are provided with medical surveillance. Eating, drinking and food storage are not permitted in the facility, and policies are in place for the safe handling of sharps. Signage at the laboratory entrance provides information regarding the biosafety level, potential hazards and entry/exit requirements. Incidents that may result in exposure are evaluated and treated, and reported to the lab supervisor and the Biosafety Officer.

PRIMATE GENETICS SUPPORT CORE VERTEBRATE ANIMALS

Proposed use of animals in this project: To enable genetic characterization of macaques within the ONPRC breeding colonies, we will collect up to 10 ml blood in two EDTA vacutainers for the purposes of parentage testing, MHC analysis, and DNA Bank archiving, as needed. Newly acquired rhesus macaques will have up to 4 ml blood drawn into one EDTA vacutainer for the purpose of ancestry testing. The bloods will be processed to extract RNA and DNA. IACUC approval (0492) has been in place for these blood collections for nine years. The blood is drawn by DCM staff during a regularly scheduled physical exam, while an animal is already sedated. Once blood is collected, it is transported to the PG Support Core for processing.

Limiting discomfort, distress, and pain: Due to the minimally-invasive nature of the standard sampling procedures, significant discomfort, pain or distress is not anticipated. However, DCM animal care staff will take appropriate measures to alleviate any observed discomfort, distress, or pain, according to accepted veterinary medical practices.

RESOURCES

Primate Genetics Core:

Laboratory:
The PGSC core consists of one dedicated room of 500 square feet for DNA processing, a restricted portion of the Ferguson research lab for RNA processing, a 100 sq ft BSL-2 approved cell culture room for all NHP tissue handling, and access to shared core space within the Cooley building. These laboratory spaces are adjoining, and overlap with the Excluded by Requester laboratories. The computer laboratory for bioinformatic and colony genetic analysis is located in 4 adjacent office cubicles within the office space of the Cooley Building.

Clinical:
N/A

Computer:
All laboratory staff are equipped with PC or Macintosh computers with access to analysis software, including Sequencher, Life Technologies Primer Express, Digital Suite, Expression Suite and Genotyper software. All computers are networked and are linked to the Labkey database. Bioinformatics staff also make use of a dedicated server for PGPSC projects, a Dell PowerEdge R510 with 96GB of RAM, and 8 3TB hot-swappable HDDs, configured in a RAID6 format, resulting in 18TB of usable storage for short-term raw and intermediate file data storage. By configuring with two-hex-core multithreaded processors, this machine is able to run 24 parallel instantiations. An additional, similar sized server is requested through the infrastructure portion of this P51 application to support anticiapted growth in bioinformatic services. Two attached storage disk arrays (PowerVault MD1200 with 12 x 2TB 7200 RPM SAS drives) are available for offloading and storing raw and key intermediate files and are attached to a dedicated, networked server. A portion of the storage capacity serves as a short term holding site for sequence files downloaded directly from the ONPRC miSeq sequencer. LabKey points to this unit for upload of MHC expressed sequences for downstream allelic analysis. Due to the expanding services dependent on the attached storage, we have requested an additional attached storage disk array, also through the infrastructure portion of this P51 proposal. The servers and storage arrays are supported by the Advanced Computing Center (OHSU), which provide system administration and data back up services.

Office:
The core director also has her office in the Cooley Building.

Major Equipment:
We have the essential equipment required to conduct laboratory based assay PGPSC work, including a Diagenode Biorupter, Bio-Rad C-1000 PCR machine, Bio-Rad MJmini, ABI gene ampPCR system 9700, Life Technologies Qubit 2.0 fluorometer, Eppendorf 5810R table top centrifugre, Eppendorf microfuge, gel electrophoresis equipment, water baths, shaker tables, 2 ultra low freezers (-80), 1 -20 freezer, 1 refrigerator and 1 biosafety cabinent. In addition, we are located immediately adjacent to the MCB service core, which includes relavent shared equipment such as the Illumina MiSeq DNA Sequencer, ABI 3730xl 96-column capillary DNA sequencer, Eppendorf EpMotion 7075 Vac liquid handling robot, Life Technologies Quantstudio 12 K Flex Real-time PCR system and an Aglient Bioanalyzer.

Scientific Environment:
The ONPRC provides an exceptionally supportive environment for the performance of the services offered by the Primate Genetics Core.

Program Director/Principal Investigator (Last, First, Middle): Robertson, Joseph E./Haigwood, Nancy L.

CORE SCIENCE SERVICES-PRIMATE GENETICS SERVICES DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*

Use Cal, Acad, or Summer to Enter Months Devoted to Project

Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Excluded by Requester	Asst Scientist	% Effort			Institutional Base Salary	8,298	2,074	10,372
	Sr. Res Assoc					22,165	7,758	29,922
	Assoc Scientist					22,325	5,581	27,907
	Sr. Res Assoc					14,575	5,101	19,676
	Asst Professor					11,988	2,997	14,985
	Res Asst 2					19,239	7,696	26,935
	Res Assoc					29,150	10,203	39,353
	Res Assoc					19,239	5,964	25,203
	Res Asst 2					17,490	6,996	24,486
	Asst Scientist					19,422	4,856	24,278
	Res Assoc					16,324	5,060	21,384
	SUBTOTALS →					200,215	64,286	264,501

CONSULTANT COSTS		
Consultant, MHC	1,100	1,100
EQUIPMENT *(Itemize)*		
None Requested		0
SUPPLIES *(Itemize by category)*		
Laboratory supplies	29,656	
Office & Admin Supplies	875	
Software	770	
		31,300
TRAVEL		
Domestic	2,798	2,798
INPATIENT CARE COSTS		
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		
None Requested		0
OTHER EXPENSES *(Itemize by category)*		
Genotyping: MHC, Ancestry, Parentage	63,451	
ACC Annual Maint Contract	4,400	
Shipping	990	
		68,841
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 368,541
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 368,541

CORE SCIENCE SERVICES - PRIMATE GENETICS SERVICES
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	264,501	272,436	280,609	289,027	297,698
CONSULTANT COSTS	1,100	1,133	1,167	1,202	1,238
EQUIPMENT	0	0	0	0	0
SUPPLIES	31,300	32,240	33,207	34,203	35,229
TRAVEL	2,798	2,882	2,969	3,058	3,150
INPATIENTS CARE COSTS					
OUTPATIENTS CARE COSTS					
ALTERATIONS AND RENOVATIONS					
OTHER EXPENSES	68,841	70,906	73,033	75,224	77,481
DIRECT CONSORTIUM/CONTRACTUAL COSTS					
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	368,541	379,597	390,985	402,714	414,796
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	368,541	379,597	390,985	402,714	414,796
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					1,956,632

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

PERSONNEL

Assistant Scientist, Excluded by Requester % Effort Excluded by Requester Income). leads the Bioinformatics Services Unit, which provides support for next generation sequencing (NGS) analysis to both investigators and core services. She meets with PIs and PGSC staff to identify specific approaches for experimental design, data analysis, and to review analysis results. Excluded by Requester interacts regularly with other computational biologists at OHSU, and is the leader of the international consortium for the sequencing and analysis of the gibbon genome, enabling her to regularly interact with leaders in the NHP genomics field and to stay current with state-of-the-art bioinformatics approaches.

Associate Scientist, Excluded by Requester % Effort Excluded by Requester Income). is Director of the Primate Genetics Support Core. She is responsible the overall coordination of services. In conjunction with the PGSC service unit leaders, the ONPRC Business Office, and the Core Oversight Committee, Excluded by Requester annually reviews the core's services and charge rates, updating accordingly. She is also directly responsible for the Genotyping Services and ONPRC DNA Bank components of the PGSC. Specifically, she oversees the development and implementation of the genotype assays (i.e., ancestry, parentage, MHC expressed-allele assays), including sample processing, data analysis and management. She oversees all aspects of the ONPRC NHP DNA Bank, including sample collection and processing, inventory management, and sample distribution. In this capacity, she interacts regularly with both DCM staff and the extended NHP genetics community concerning evolving genotyping approaches to NHP genetic characterization.

Sr. Res. Associate, Excluded by Requester % Effort Income). Responsible for coordinating all purchasing and billing for the genotype assay services; managing the DNA Bank, including tracking sample collection, database management and DNA distribution to internal and external users; responsible for management and data interpretation of the macaque ancestry assay, which is run for both internal and external users.

Assistant Professor, Excluded by Requester % Effort Income). Responsible for providing statistical analysis one day a week during Drop-In sessions;, supports PGSC needs, NHP treatment analyses for DCM veterinary staff, as well as both pre-grant study design and post-grant award analysis for research investigators. Also provides educational services to staff and investigators regarding use of statistical analyses in research. Excluded by primary appointment is at OHSU, where he provides biostatistics services for the Oregon Clinical and Translational Research Institute (OCTRI) and the OHSU Knight Cancer Center.)

Res. Assistant,2, Excluded by Requester % Effort Income). This position reports to Excluded by within the Bioinformatics Services Unit Excluded by provides support to both Excluded by Requester by performing routine data management, running routine scripts, and creating graphical representation of final data.

Res. Associate, Excluded by Requester % Effort Income). Responsible for the analyses required to implement appropriate genetic management of the breeding colonies. Therefore, responsibilities include the identification of candidate animals for breeding, sale, cull, or research from the animal records database; producing summary data of colony genetic health and diversity for management on a regular basis, and for external grant proposals upon request; responsible for review and approval of genetic marker data for inclusion in the databases.

Res. Associate, Excluded by Requester % Effort
Income). Responsible for NGS analysis, including DNA variant detection and RNA-seq. Provides support to both research investigators and, as needed, pipeline development for PGSC genotyping assay analyses. Interacts with other bioinformaticists at ONPRC and at OHSU through her grant-supported NHP genomic studies.

Sr. Res. Associate, Excluded by Requester % Effort
Program Income). Responsible for the MHC expressed allele assay, from sample receipt to processing, sequencing, analysis, and allele reporting; performs fee-for-service MHC analyses for both the ONPRC and WaNPRC.

Res. Assistant, Excluded by Requester % Effort (
This position reports directly to Excluded by Requester is responsible for DNA extractions for the DNA Bank and genotype assays. She is responsible for tracking all parentage assays from sample receipt through genotype analysis and data reporting. She processes samples for the rhesus macaque ancestry assay. Both parentage and ancestry assays are run routinely for the ONPRC, and for other NPRCs as requested.

Assistant Scientist, Excluded by Requester % Effort
Income). Excluded by leads the Colony Genetics Unit, which supports all population genetic analysis for ONPRC NHP colony management and for research purposes, as requested by investigators. She is responsible for development, implementation, and oversight of genetic management strategies at the ONPRC, including development of appropriate population genetic metrics to estimate genetic diversity and health, strategies for new breeding group formation, ongoing characterization of accurate NHP pedigrees at ONPRC, and the application of this pedigree information to genetic research in diseases relevant to colony health. Excluded by Requester oversees Excluded by Requester work in this area, and meets regularly with colony managers, the leadership of both DCM and the ONPRC to present ongoing reviews of genetic health for all NHP colonies at the ONPRC.

Res. Associate, Excluded by Requester % Effort
This position reports to L. Carbone within the Bioinformatics Services Unit. Excluded by is a bioinformatics analyst with exceptional experience in DNA methylation analysis and data base design and management. He provides bioinformatics support for research investigators, and as needed, for users of the in house Illumina miSeq sequencer, operated by the MCBSC. He interacts with other members of this group, as well as other bioinformaticists at OHSU through his work on grant-supported research.

CONSULTATION

Funds are requested to bring one consultant per year, to obtain expert support for the expected enhancements to the MHC expressed allele assay, or other new genomic assays that are brought on line during the next grant period. We also plan occasional bioinformatics consultations to discuss the rapidly evolving approaches to NGS bioinformatic analysis.

SUPPLIES

Laboratory Supplies: Funds are requested to support the genotyping aims of this PGSC, including parentage analysis for 620 offspring, including DNA extraction kit reagents and 96 well PCR plates for

assay. Ancestry analysis for 96 acquired animals per year, including DNA extraction kit reagents, PCR plates and reagents for LifeTech QuantStudio SNP genotype assay. DNA Bank storage supplies for 1000 individuals per year (both blood and liver samples), including cryovials, freezer boxes and freezer racks. Common laboratory supplies required for all genotype assays, including plastic serological pipettes, pipette tips, conical spin tubes, Eppendorf tubes, latex gloves and biohazard protection and disposal supplies (Years 1-5).

Office & Admin Supplies: Funds are requested to provide routine supplies such as paper, pens, pencils, markers, calculators, printers, monitors.

Software: Funds are requested for twelve 1 Tb harddrives per year for secondary data storage by the Bioinformatics Unit; fees for annual software licenses to support bioinformatic (Novoalign, MetaCore) and pedigree analysis (PedScope).

TRAVEL

One domestic trip for one member each of Colony Genetics, Bioinformatics and Genetic Services to attend training workshops or to participate in a conference related to the core service.

OTHER EXPENSES

Genotyping: MHC, Ancestry, Parentage: Funds are requested for blood draw fees for 620 offspring and up to 96 purchased rhesus macaques per year for DNA Bank, parentage or ancestry assay. SNP genotyping service fees comprise ancestry analysis using the LifeTech QuantStudio custom SNP assay (MCBSC) as well as parentage analyses using an Illumina custom SNP assay (Igenix, Inc.).

ACC Annual Maint Contract: Funds are requested for system administration fees for Bioinformatics Unit servers and data storage back up (Advanced Computing Center). System administration fees are requested for two Dell PowerEdge R510 servers configured to support the needs of bioinformatic analyses; service fees for system administration and tape backup of data (1 month retention) are requested for a server and two PowerVault MD1200 storage units, used for short and intermediate-term storage of data generated from the Illumina miSeq and bioinformatics data analyses.

Shipping: Funds are requested for monthly shipping of parentage samples, which are genotyped off-site.

CORE SCIENCE SERVICES: Primate Genetics Service Core Income Table

Last Funded Year (53)

Source	Funding (direct costs)
P51 base grant support	$284,971.58
Program income derived from P51 base grant	236,732.60
Other Sources	0
Total	$521,704.18

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$368,540.63
Program income derived from P51 base grant	307,202.73
Other Sources	0
Total	$675,743.36

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

The Primate Genetics Service Core receives salary support and support for other expenditures from program income.

TITLE: IMAGING AND MORPHOLOGY SUPPORT CORE

CORE-SUPPORTED PERSONNEL:

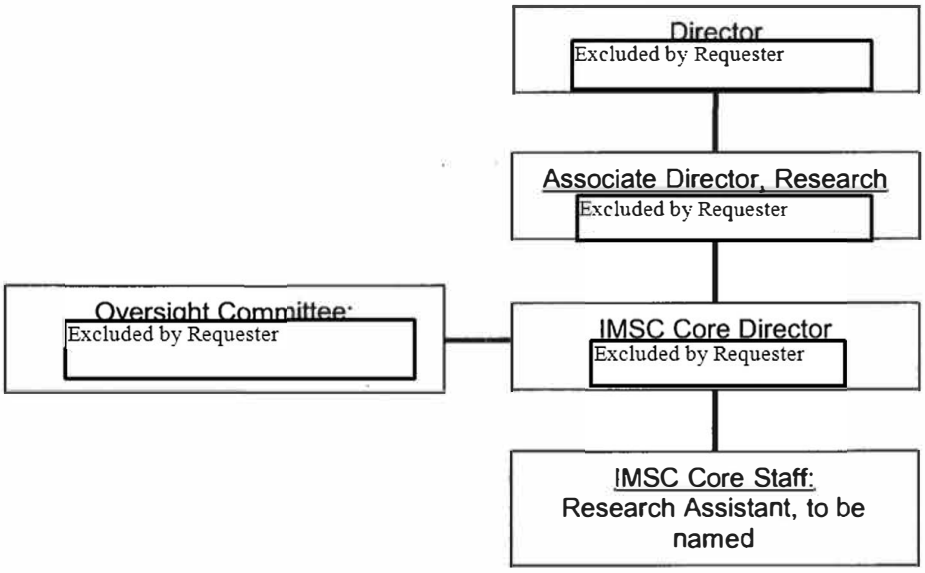
Core Staff (See Biographical Sketch, listed alphabetically in the Overview of the ONPRC)

Excluded by Requester	Senior Staff Scientist

Research Support

TBN	Research Technician

IMAGING AND MORPHOLOGY SUPPORT CORE (IMSC)
Organizational Chart



COMPONENT PERSONNEL AFFILIATION AND ROLE

Staff Scientist:

Excluded by Requester	Senior Staff Scientist, Core Director

IMAGING AND MORPHOLOGY SUPPORT CORE (IMSC)

DESCRIPTION:

The Imaging and Morphology Support Core (IMSC) provides ONPRC investigators access to state-of-the-art instruments, expertise, and services in support of their light microscosopy imaging and analysis needs. The goal of IMSC is to offer advanced imaging services at the molecular and cellular level, specialized for the need of non-human primate research. Major groups of services offered include confocal microscopy for studies of molecular localization and interactions, stereology for quantitative analysis of morphometric tissue features, and laser-capture microdissection for gene expression analyses in specific cells.

- Confocal imaging is based on a Leica SP5 AOBS equipped with 5 lasers providing 405, 476, 488, 496, 514, 561, 594 and 633nm excitation lines. Detection by four photomultipliers is prism-based spectral. A motorized Marzhauser stage and adequate software allow 3D montages of larger areas, uniform random sampling (URS), and point revisiting in time-lapse imaging. FRET and FRAP modules facilitate fluorescence resonance energy transfer studies of molecular interactions and respectively fluorescence recovery after photobleaching studies of motility. Three different spectral unmixing protocols may be used to separate fluorophores with overlapping spectra and, particularly important in non-human primates, isolate lipofuscin autofluorescence. A Tokai-Hit stage-top microincubator ensures temperature and CO2 concentration control for live cells and tissues.
- Ratiometric imaging for FURA2 quantitative calcium imaging and for CFP/YFP FRET is based on a Marianas imaging workstation by Intelligent Imaging Innovation based on a Zeiss 200M with a DG-4 fluorescence source and an ASI motorized stage. The same instrument, offering color brightfield and 3D widefield fluorescence with deconvolution, is used for live cell imaging, multi -well plate highthrouput, and for imaging large area montages of fixed tissue sections. As in the confocal case, this is particularly important for NHP studies in which areas of interest tend to be much larger than the corresponding organs in mice and other model animals.
- Stereology, based on fluorescence or brightfield, is used in most quantitative studies, using the confocal, the Marianas or an MBF Biosciences system equipped with StereoInvestigator and Neurolucida and based on a Zeiss Axioscope. Uniform random sampling is applied whenever the area of interest is too large to image exhaustively and subsampling is necessary.
- Laser microdissection is done with an ArcturusXT, equipped with a UV laser for cutting and ablation in addition to the IR laser used for capturing selected cells or tissue.

For each service, IMSC offers full support, providing images and analysis data, or consultation and training, allowing trained users round the clock access to all instruments.

All IMSC microscopy systems are covered by service contracts, are maintained in perfect working order with minimum downtime and subjected to frequent and stringent quality control procedures. The core is overseen by a committee that decides on rules, regulations, and fees, and that makes suggestions for new equipment and service needs. The Core Director keeps informed on new developments in the field, analyzes them in terms of benefit to ONPRC investigators, presents them to the committee and, if approved, identifies potential sources to finance the purchase.

During the last grant period, IMSC has moved to new and much-improved space in the West Wing of the ONPRC/VGTI building, where it occupies 5 rooms totaling 638 sq. ft. The Leica SP5, ArcturusXT, and the MBF systems were all added after the move. During this time, the projects of 40 principal investigators were supported by IMSC and more than 100 scientists were trained in one or more of the technologies offered. New imaging methods and analysis protocols were implemented or developed by the core in collaboration with interested scientists.

All core services are open to scientists from OHSU and other local institutions, when not in use by ONPRC. IMSC supports the ONPRC outreach program by hosting students, tours and lectures to visitor groups.

IMAGING AND MORPHOLOGY SUPPORT CORE (IMSC) SPECIFIC AIMS

The overall goal of the Imaging and Morphology Support Core (IMSC) is to provide the ONPRC scientific community access to state-of-the-art instruments, expertise, and services in support of their light microscopy image acquisition and analysis needs. The IMSC offers advanced imaging, specialized for the needs of nonhuman primate (NHP) research, at the molecular and cellular level. Major groups of services include confocal microscopy and derived fluorescence techniques for studies of molecular localization and interactions, stereology for quantitative analysis of morphometric tissue features, and laser-capture microdissection for gene expression analyses in specific cells. Major instruments used to support IMSC goals include a Leica SP5 AOBS confocal (Leica Microsystems, Wetzlar, Germany), a Marianas digital workstation (Intelligent Imaging Innovations, Denver, CO), an MBF Bioscience system (Williston, VT) and an ArcturusXT (Life Technologies, Carlsbad, CA). Core personnel provide expertise in experiment planning and choice of most adequate instrument and method, training for instrument use customized for each specific need, technical support in image acquisition and troubleshooting, and image analysis and stereology.

Specific Aim 1. Provide an efficient, responsive, and transparent operating structure. This will be achieved through cooperation between the Core Director and her staff, the Core Oversight Committee, and the ONPRC Business office.

Specific Aim 2. Provide state-of-the-art instruments that satisfy the major, most common needs for advanced microscopy techniques NHP studies. To this aim, the core is responsible for identifying instrument needs, procuring funds, and purchasing instruments. The Core currently offers a Leica SP5 AOBS confocal, a 3I's Marianas Imaging workstation, and an MBF Bioscience system. All instruments are covered by service contracts and undergo stringent periodical quality-control procedures to ensure optimum function. For each instrument, users receive a minimum three hours of one-on-one training before gaining independent access.

Specific Aim 3. Provide expertise, tools, and training for quantitative image analysis. To this goal, the IMSC has developed stereology and digital image processing and automated analysis expertise. The MBF system and the Marianas are the most appropriate tools for running a stereology-based analysis as they have the routines for uniform systematically subsampling large areas and (particularly the StereoInvestigator within MBF) collections of probes for estimating numbers, lengths of fibers, surface area, volumes, etc. Neurolucida is used for neuron tracing and analysis. ImageJ and FIJI are the tools of choice for image analysis for which the core offers basic and advanced training and automation macros. Volocity is used primarily for advanced 3D rendering.

Specific Aim 4. Provide expertise, training, and access to laser-capture microdissection (LCM) for the isolation of pure populations of cells. To this goal, IMSC maintains a list of protocols for tissue processing, an Arcturus XT LCM system and a close collaboration with ONPRC's Cell and Molecular Support Core and OHSU's Microarray Core to facilitate downstream applications for the microdissected materials.

Specific Aim 5. Act as an expert resource in microscopy and digital image analysis by providing consultation in experiment planning and execution, general microscopy and image-analysis knowledge, benefiting primarily the ONPRC and OHSU communities, but also serving as a regional resource in the field. To this goal, the IMSC keeps up-to-date with new methods, tools and applications, organizes periodic seminar and workshops and hosts trainees and student interns.

IMAGING AND MORPHOLOGY SUPPORT CORE RESEARCH STRATEGY

SIGNIFICANCE

Nonhuman primate (NHP) research relies heavily on microscopy to reveal the morphology of tissues, as well as the localization, interaction, and dynamics of cells, organelles, and molecules. Fluorescence microscopy in particular is a fast-evolving field, with many new instruments and technologies that are powerful but costly and specialized for fewer tasks. Pooling them into one unit under expert oversight is the most efficient way to make needed technologies available to all investigators. One significant development is the shift from purely descriptive to quantitative analysis of microscopy images. For example, several projects at ONPRC study changes in the NHP hypothalamic production of hormones and neuropeptides and their correlation with development, diet, addiction, and disease. Quantitative imaging requires much more stringent controls of experimental methods, and the IMSC offers the instruments and the expertise to ensure that measurements are reliable and bias free. Live-cell imaging reveals more accurate information on physiological processes such as active transport of glucose and fatty acids, mitochondrial transmembrane potential and dynamics, calcium signaling, and protein interactions, but requires specialized equipment and tightly controlled environmental and light exposure conditions. Gene-expression studies based on quantitative PCR or microarray with RNA isolated from blocks of tissue with heterogeneous cell populations may miss changes that happen in a specific sub-group of cells. Laser microdissection allows for more reliable and precise findings of gene expression changes that will result in a better understanding of signaling mechanisms in normal and disease states. The IMSC ensures that each ONPRC scientist has access to the instrument and method most appropriate to each study. If a needed instrument is not available in the IMSC, the core director may facilitate access to a Core that does. To this goal, a close collaboration is maintained with the Advanced Light Microscopy Core and the Electron Microscope Core at OHSU, which ensures that we have complementary instruments, with overlap of only the most heavily used ones.

INNOVATION

The IMSC is primarily a support core and, therefore, innovation is primarily in the area of the technologies made available. In the last grant period, IMSC purchased a new Leica SP5-AOBS confocal and a new Arcturus XT laser-capture microscopy (LCM) system, both based on funded shared instrumentation grants. An MBF Bioscience system, including the Stereoinvestigator and Neurolucida, was added to an older preexisting Zeiss microscope to expand our stereology services and add neuron tracing and morphometry. This enabled us to image whole brain sections from rhesus monkeys, and measure volume, thickness, and surface area of the cerebral cortex for comparison and validation of MRI measurements. We introduced confocal 3D imaging of Golgi-stained neurons in the developing cerebral cortex of rhesus macaques and correlated the dendritic branches' orientation with diffusion tensor measured by MRI in a collaboration with Excluded by Requester Director of the MRI Core (Excluded by Requester). More recently, Golgi staining was recently replaced by DiOlistics for the same types of MRI correlations. In support of Excluded by Requester research, we designed protocols to image fatty acid uptake in single cells of fat explants Excluded by Requester and implemented a PKA redistribution assay for glucagon receptor activation based on imaging 96-well plates on the Marianas and using Slidebook for automatic analysis, as a first example of our "mini-high throughput" imaging capabilities. In collaboration with Excluded by Requester from VGTI, we optimized an LCM protocol for the isolation of GFP-expressing cells in frozen tissue. Image analysis protocols and macros were designed for the automated identification and measurement of isolation of fibers and cell bodies and measurement of peptide expression in fluorescence images of hypothalamic nuclei Excluded by Requester. A novel method based on Advanced Weka Segmentation Excluded by Requester (The Weka Data Mining Software: an Update; SIGKDD Explorations, Vol. 11, Issue 1) implemented in FIJI (open-source software, "Fiji is Just ImageJ") was designed to identify and measure drusen load in fundus photographs of the retina of an NHP model of age-related macular degeneration, in support of Excluded by Requester research, a significant improvement over the mostly qualitative methods currently used in ophthalmology.

APPROACH

reviewers' comments

reviewers' comments

Progress and Major Accomplishments.

In the previous grant period, the location of IMSC moved from the Cooley building into larger and better-organized and equipped space in the West wing of the ONPRC/VGTI building. Each microscope has a dedicated room with sufficient space for training and countertop for sample preparation. Ventilation and electric power supply were custom modified to accommodate the needs of our instruments. The space consists of a three-room imaging suite on the first floor Figure 1), close to the office of the Core Director, and one room on the second floor, totaling 638sq.ft.

Figure 1. The front room of the Imaging Suite showing the confocal in the middle, access to the Marianas room on the left, and to the LCM room to the right, next to hood and analysis workstation. Despite initial concerns, traffic to the back rooms has not perturbed confocal work.

A new Leica SP5 AOBS confocal was purchased to replace an old Leica SP. A new AructurusXT is replacing the old Pixcell IIe. Both these instruments were supported by NCRR shared instrumentation grants. An MBF Bioscience system including StereoInvestigator, Neurolucida and Solid-state module was added to an old Zeiss Axioscope microscope, dramatically enhancing its capabilities. The Marianas was updated with a new 64-bit computer and Sedat filters, and a new Coolsnap HQ2 camera is on order. More than seventy publications Excluded by Requester

Excluded by Requester

Services Provided/User Info During Previous Grant Period.

Services offered by the IMSC are largely accounted for in relationship to the instrument used (Table 1). The IMSC offers confocal imaging, Marianas imaging, MBF Bioscience imaging, LCM, image analysis, training for each of the services mentioned, and full assistance for each of the services. Consultation on experiment planning, choice of instrument and method for imaging and for image analysis as well as design of macros for analysis are all offered free-of-charge, with the goal of supporting and encouraging imaging work of the best quality possible. Confocal services include multi-channel 3D immunofluorescence, time-lapse live cell imaging, FRET, FRAP, transport of nutrients, proteins or organelles, mitochondrial membrane potential and dynamics, co-localization, spectral unmixing, etc. Marianas services include live-cell imaging, FURA-2 calcium quantitative imaging, CFP/YFP FRET, 96-well plate based high-throughput, 3D fluorescence imaging with deconvolution, large-area montages of fixed sections and uniform random subsampling for non-biased stereology. Both the Marianas and the MBF Biosciences systems are used for stereology and Neurolucida for neuron tracing and analysis and cell mapping. Tissue processing and sectioning services were removed from the IMSC list, as the unit's histology operations were moved to the Research Histology section of Pathology Services, in response to the previous critique's suggestion of that program. The Medical Illustrations unit was closed and medical art design, poster preparation, and printing were also removed from the list of services.

Table 1. Services offered and hours used per year.

*Data for 2012 includes only the first 3 months of the grant year

service	2009	2010	2011	2012*
confocal imaging	655	750	550	117
Marianas imaging	450	343	325	150
MBF imaging	NA	175	357	69
LCM	31	102	52	80
Training (persons)	16	22	26	10
assisted imaging	146	165	51	35
assisted image analysis	0	92	42	67

Over the period reported, May 1, 2009, to July 31, 2012, members of 40 research groups have been users of the IMSC (Table 1). Table 2 shows the names and department affiliations as well as the chargeback fees as an indication of the volume of use. All 40 investigators are from OHSU, and the majority is from ONPRC, but the VGTI (Vaccine and Gene Therapy Institute), OHSU SOM (School of Medicine), and Physiol/Pharm (Department of Physiology and Pharmacology) are also represented.

Outside users have been accommodated through their collaboration with an internal PI and the IMSC did not have any direct external collaborators during this time interval.

Table 2. Users and their affiliations in the previous grant period.

#	Last name	First name	Department	May1, 2009-April 30, 2010	May1, 2010-April 30, 2011	May 1, 2011-April 30, 2012	May 1, 2012-July 31, 2012
1	Excluded by Requester		Phys/Pharm	$0	$4,080	$0	$0
2			SOM	$220	$0	$200	$0
3			Phys/Pharm	$0	$0	$1,785	$0
4			Neuroscience	$5,141	$6,720	$4,580	$1,010
5			SOM	$0	$925	$0	$0
6			Neuroscience	$0		$815	$0
7			VGTI	$0	$200	$120	$145
8			VGTI	$0	$0	$585	$0
9			DRDS	$0		$735	$40
10			Neuroscience	$5,125	$7,255	$12,190	$3,993
11			DRDS	$210	$0	$0	$0
12			OGI	$0	$195	$0	$0
13			SOM	$0	$855	$1,140	$0
14			DRDS	$0	$0	$1,260	$0
15			Neuroscience	$903	$670	$2,092	$0
16			DRDS	$505	$60	$0	$50
17			Neuroscience	$120	$670	$460	$570
18			Phys/Pharm	$1,700	$380	$0	$0
19			VA	$0	$0	$150	$0
20			DRDS	$1,830	$730	$350	$520
21			SOM	$0	$1,120	$0	$0
22			VGTI	$0	$35	$0	$0
23			VGTI	$0	$0	$175	$0
24			Neuroscience	$0	$0	$6,400	$13,140
25			Neuroscience	$2,365	$1,598	$900	$0
26			Neuroscience	$940	$1,045	$670	$0
27			Neuroscience	$2,955	$1,700	$4,455	$2,103
28			Neuroscience	$880	$0	$0	$0
29			Phys/Pharm	$8,310	$5,500	$240	$0
30			Neuroscience	$2,485	$4,405	$2,995	$263
31			DRDS	$0	$0	$0	$2,680
32			VGTI	$0	$0	$85	$0
33			Neuroscience	$450	$2,365	$685	$1,260
34			Neuroscience	$2,260	$180	$150	$420
35			DRDS	$1,940	$920	$510	$170
36			Neuroscience	$0	$4,985	$0	$0
37			SOM	$0	$130	$0	$0
38			Neuroscience	$0	$445	$0	$0
39			DRDS	$375	$1,260	$0	$0
40			DRDS	$505	$670	$785	$762
	total/year			$39,219	$49,098	$44,512	$27,126

• Data for 2012 includes only the first 3 months of the grant year.

Specific Aims/Service Plan for Next Grant Period.

The Imaging and Morphology Support Core (IMSC) is a well-established core whose general goal is to meet current and future needs of non-human primate research at ONPRC in the field of microscopy and image analysis. In general, the core will continue its basic operation through provision of the following services in the next grant period. All current microscopy image acquisition and analysis services will continue to be offered in the next grant period. These include confocal imaging, wide-field fluorescence with deconvolution, bright-field, large area montages, 96 and other multi-well plates, Calcium imaging, live cell imaging, FRET, FRAP, stereology, quantitative image analysis and laser capture microdissection. Training for independent use and/or assistance by core personnel will be offered for each of these services. We plan to extend and enhance support for image analysis using FIJI, test and introduce feature recognition and training algorithms whenever basic segmentation is not adequate. We are now in the process of evaluating adding lightsheet microscopy

and FLIM (fluorescence lifetime imaging) to our list of services. Lightsheet illumination will allow imaging larger specimens faster and with less photodamage. This will be particularly useful for research projects within DRDS, allowing imaging of NHP embryo and follicle development in vitro, plus whole mounts of blocks of tissue fixed and cleared. Zeiss is preparing to launch the first commercial lightsheet instrument, and we are arranging a demonstration to test how well it will fit our needs. There are many options for FLIM capabilities, with the least expensive being an addition to the Marianas. We will test it for FRET and for separating fluorophores with overlapping spectral emissions and autofluorescence. For services already existing at OHSU, such as electron microscopy, fluorescence super-resolution (SIM and PALM/STORM), multi-photon imaging, and TIRF, we will collaborate more closely with the main campus's shared facilities, to ensure easy access for our users. This will help us avoid the duplication of infrequently used services that require large investments. Closer collaboration with other facilities will also streamline services for IMSC. For example, for LCM, ONPRC's Cell and Molecular Core will offer RNA quality tests and quantitative PCR, and the OHSU's Gene Profiling Core will offer microarrays. IMSC will continue to help the ONPRC community keep up with new developments and prepare for the future by organizing specialty seminars and workshops introducing new technologies as they appear. We will also continue the yearly presentation by Molecular Probes for new fluorophores, on new LCM protocols, and stereology.

In the next funding period, the IMSC will also pursue the following specific aims:

Specific Aim 1. Provide an efficient, responsive, and transparent operating structure. This will be achieved through cooperation between the Core Director and their staff, the Core Oversight Committee, and the ONPRC Business office. The IMSC Director reports to [Excluded by Requester] Associate Director for Research and overseen by a committee composed of [Excluded by Requester] chair, [Excluded by] Division of Diabetes, Obesity and Metabolism, [Excluded by] from the Division of Reproductive and Developmental Sciences, [Excluded by] from the Division of Pathobiology and Immunology, [Excluded by Requester] from the Division of Neuroscience and [Excluded by Requester] Director of the Advanced Light Microcopy Core at OHSU. The Oversight Committee will meet at least twice a year and communicate as frequently as necessary to decide operation rules and regulations for IMSC, users' fees, the addition or termination of services, needs for new instruments or for upgrades to the existing ones, and to solve potential scheduling conflicts. Dr. [Excluded by Request] will be responsible for the day-to-day operation of the IMSC, for ensuring all instruments are in good working order, for quality control procedures, regular maintenance and quick repair by manufacture's' service engineers when needed. She will also be responsible for training new users before they gain access to instruments, for training in image analysis and non-biased stereology procedures, and for consulting in experiment planning and analysis. A part-time technician will be hired to help with day-to-day operation and routine quality control procedures. Quality control will include daily procedures for the intensity and stability of confocal lasers and Marianas' DG-4 using a protocol developed by IMSC that is in press. Objectives are tested and cleaned weekly. Troubleshooting will be, of course, done on demand. The IMSC will continue to be open 24/7 for trained users that can reserve time using an on-line Google calendar administered by Dr. [Excluded] Reservations will be available on a first-come/first-served basis, but advance reservation during normal working hours (9-5, M-F) is restricted to maximum 4 hours/day blocks of time, morning or afternoon. Live-cell experiments requiring longer time intervals will be performed after hours. Special situations, longer experiments, or imminent deadlines will be discussed with the Core Director and accommodated whenever possible. Scheduling conflicts that are not easily resolved will be managed by the Oversight Committee. The IMSC is a fee-for-service facility, with chargeback fees reducing the proportion of the total operating cost that comes from the P51 Core grant. Currently, a training fee of $150 is charged for training and initiating access to any instrument. After training, charges are $35/hour during normal working hours for the confocal and the Arcturus LCM and $20/hour for the Marianas and the MBF system. Fees for all instruments are $10/hour outside normal working hours. Consultation, planning and training in image analysis are offered free-of-charge, imaging by core personnel is charged $65/hour for any instrument and image analysis $60/hour. Fees will be revisited yearly by the Oversight Committee. Hours of use for each instrument by each user, read off the Google calendar, are currently used to populate a monthly spreadsheet that is sent to the ONPRC Business Office for processing. We are currently working with IT on plans to switch to SharePoint calendars and automate the accounting of hours and streamline charging procedures, making them less labor intensive. The IMSC will continue to observe strict safety procedures: all instruments have protections preventing laser

light from reaching the operator. Work with volatile solvents, for example Xylene for LCM sample preparation, will be performed under a fume hood. Most samples are fixed and mounted and, therefore, pose no risk, and only pathogen-free live specimens will be accepted.

Specific Aim 2. Provide state-of-the-art instruments that satisfy the major, most common needs for advanced microscopy techniques in NHP studies. Techniques supported include bright-field, DIC, and fluorescence microscopy. For all techniques, the core offers the possibility of acquiring large area montages, particularly important for the NHP organs, generally larger than rodent or other small research animals, and multi-well plates. For fluorescence microscopy the IMSC offers wide-field epi-fluorescence, deconvolution by theoretical or measured point spread function, and laser-scanning confocal. The wide-field offers a wide selection of filters for most commercially used fluorophores. This includes, besides common DAPI, FITC, Cy3 and Cy5 filters, rapid changing filter-wheels for FURA2 ratiometric calcium imaging and CFP/YFP FRET. The confocal microscope is equipped with 405, 458, 476, 488, 496, 514, 561, 594 and 633nm excitation lines, AOBS and spectral detection. This ensures the ability to image any combination of fluorophores and identification and separation of autofluorescence, particularly lipofuscin, a prevalent problem in fluorescence imaging of NHP tissues. To help with this problem, the confocal system is equipped with several spectral unmixing routines and Image J Spectral Unmixing plugin is used off-line for wide-field images. Both confocal and deconvolution may be used for multi-dimensional imaging: 3D, in time and multi-channel, advanced fluorescence techniques, such as fluorescence resonance energy transfer (FRET) and fluorescence recovery after photo-bleaching (FRAP, confocal only).

Specific Aim 3. Provide expertise, tools, and training for quantitative image analysis. To this goal, IMSC has developed stereology and digital image processing and automated analysis expertise. The MBF system and the Marianas are the most appropriate tools for running a stereology based analysis as they have the routines for uniform systematically subsampling large areas and (particularly the StereoInvestigator within MBF) collections of probes for estimating numbers, lengths of fibers, surface area, volumes, etc. Neurolucida is used for neuron tracing and analysis. Image J and FIJI are the tools of choice for image analysis for which the core offers basic and advanced training and automation macros. Volocity is used primarily for advanced 3D rendering.

Specific Aim 4. Provide expertise, training, and access to LCM for the isolation of pure populations of cells. To this goal, IMSC maintains a list of protocols for tissue processing, an Arcturus XT LCM system and a close collaboration with ONPRC's Cell and Molecular Support Core and OHSU's Microarray Core to facilitate downstream applications for the microdissected material and for quality-control analysis of resulting RNA or DNA.

Specific Aim 5. Act as an expert resource in microscopy and digital image analysis and provide consultation in experiment planning and execution and general microscopy and image analysis knowledge, benefiting primarily the ONPRC and OHSU communities, but also serving as a regional resource in the field. To this goal, IMSC keeps up-to-date with new methods, tools and applications, organizes periodic seminars and workshops and hosts trainees and student interns. As new methods or instruments are introduced, they will be evaluated for potential use on NHP research, discussed with the Oversight Committee and presented to the ONPRC scientific community. If a new instrument is found necessary, the core will coordinate the procurement of funds, usually through shared instrumentation grants or internal contribution, oversee demonstrations for selection of the most appropriate brand, and finalize the purchase. IMSC supports ONPRC outreach programs by hosting tours and contributing images.

Pages 835-839 (Publications) Removed – Excluded by Requester

RESOURCES

Imaging and Morphology Support Core (IMSC)

Laboratory:
The IMSC occupies 5 rooms in the West Wing of the ONPRC/VGTI building, totaling 638 sq.ft., easily accessible to most of its users. The three-room suite (413 sq.ft.) on the first floor houses the Leica SP5 AOBS confocal, the Marianas digital imaging workstation, the ArcturusXT laser capture microdissection (LCM) system and two image analysis and processing workstations- a Mac and a Windows-based Dell. The suite includes custom-enhanced ventilation to dissipate heat created by lasers and other fluorescence light sources, a hood and flammable storage cabinet needed for the LCM chemicals, xylene and alcohols for example, a mini-incubator necessary for maintaining live cells at 37 degrees and for the first step in RNA isolation of LCM-procured cells. The building provides compressed air for floating the airtables protecting the confocal and Marianas microscopes from vibrations. The room (93 sq.ft.) housing the MBF system is located on the second floor of the same building. All rooms include ample desk-top and storage space for sample preparation, supplies and accessories. The office (123 sq. ft.) of the IMSC Director is located on the first floor, in the vicinity of the Imaging suite and provides space for small group meetings for consultation and image processing and analysis training.

Clinical:
N/A

Computer:
Two computers may be used for image processing and analysis using ImageJ, FIJI, Slidebook (Intelligent Imaging Innovations, Denver, CO), Volocity (Perkin Elmer, Waltham, MA). Images are transferred to users' labs either through internal server or using external harddrives (Passport, WD). The Core Director's office is equipped with a Dell Optiplex 990 computer and a Dell Latitude 620 laptop.

Office:
The core director occupies an offfice immediattely adjacent to the core facilities in the ONPRC/VGTI Building.

Major Equipment:
Includes a Leica SP5 AOBS confocal (Leica Microsystems, Wetzlar, Germany), a Marianas imaging workstation by Intelligent Imaging Innovations (Denver, CO), an ArcturusXT LCM (Life Technologies, Carlsbad, CA), and a MBF Bioscience system (MBF Bioscience, Williston, VT).

1. The Leica confocal is equipped with 5 lasers providing 9 excitation lines ranging from 405nm to 633nm, a collection of objectives including dry, oil and glycerol immersion, a Marzhauser motorized stage and Mark and Find and Matrix software modules, special software modules facilitating FRAP (fluorescence recovery after photobleaching), FRET (fluorescence resonance energy transfer), spectral unmixing, and 3D viewer. We added a TMC airtable and a Tokai Hit stage-top incubator with temperature and gas control and objective heater.

2. The Marianas includes, in addition to standard features, an ASI motorized stage, three algorythms for deconvolution, ratiometric imaging for FURA2 Calcium quantitatitative imaging and for FRET (CFP/YFP and green/red), and a stereology module, an assortment of objectives, including a water-immersion 40x

3. The MBF Bioscience system is equipped with StereoInvestigator 10.0 and Neurolucida 10.0 and Solid Module, installed on a Zeiss Axioscope equipped with fluorescence and a color Retiga 2000 camera.

Other:
All IMSC instruments are supported by service contracts. The IMSC collaborates closely with similar facilities at OHSU to ensure that ONPRC users have easy access to instruments not available on the West Campus, for example electron microscopes, structured illumination (SIM) and photoactivation localization (PALM/STORM) super-resolution micorscopes, two-photon micorscopes and total internal reflection (TIRF).

Program Director/Principal Investigator (Last, First, Middle): Robertson, Joseph E./Haigwood, Nancy L.

CORE SCIENCE SERVICES - ADVANCED IMAGING DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Excluded by Requester	Sr. Staff Scientist	% Effort			Institutional Base Salary	40,273	12,485	52,758
To Be Named	Res Technician	1.32				5,830	2,041	7,871
	SUBTOTALS →					46,103	14,526	60,629
CONSULTANT COSTS								
None Requested								0
EQUIPMENT *(Itemize)*								
None Requested								0
SUPPLIES *(Itemize by category)*								
Office & Admin Supplies							292	
Laboratory Supplies							3,498	
								3,790
TRAVEL								
Domestic							875	875
INPATIENT CARE COSTS								0
OUTPATIENT CARE COSTS								0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*								
None Requested								0
OTHER EXPENSES *(Itemize by category)*								
Maintenance - Equipment							31,213	
Registration Fees							385	
Software Upgrade							1,925	
								33,522
CONSORTIUM/CONTRACTUAL COSTS						DIRECT COSTS		0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*								$ 98,815
CONSORTIUM/CONTRACTUAL COSTS						FACILITIES AND ADMINISTRATIVE COSTS		0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD								$ 98,815

PHS 398 (Rev. 6/09) **Form Page 4**

CORE SCIENCE SERVICES - ADVANCED IMAGING
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	60,628	62,447	64,320	66,250	68,238
CONSULTANT COSTS	0	0	0	0	0
EQUIPMENT	0	0	0	0	0
SUPPLIES	3,790	3,903	4,020	4,141	4,265
TRAVEL	875	901	928	956	984
INPATIENTS CARE COSTS	0	0	0	0	0
OUTPATIENTS CARE COSTS	0	0	0	0	0
ALTERATIONS AND RENOVATIONS	0	0	0	0	0
OTHER EXPENSES	33,523	34,528	35,564	36,631	37,730
DIRECT CONSORTIUM/CONTRACTUAL COSTS					
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	98,815	101,779	104,833	107,978	111,217
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	98,815	101,779	104,833	107,978	111,217
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					524,621

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

PERSONNEL

Senior Staff Scientist – A Excluded by Requester % Effort
Responsible to provide support to scientists for microscopy-based experiments and will be responsible for day-to-day operations, making sure equipment is in good working order, quality control and troubleshooting, training new users, consultation on experiment planning, stereology, and image analysis protocols, and identifying needs for new equipment and new technological developments that could benefit research.

Research Technician – To be named (2.4 calendar months effort on this project: 1.32 ORIP, 1.08 Program Income). Recruitment is taking place to hire a research assistant who will be trained to perform some of the routine tasks regarding equipment maintenance and quality control, and to assist users with imaging and analysis experiments.

SUPPLIES

Office & Admin Supplies: Funding is requested for standard office supplies (paper, pens, folders etc.) and USB storage devices for image transfers.

Laboratory Supplies: Funding is requested to purchase laboratory supplies necessary to provide appropriate microscopy imaging services to scientists, including replacement of expensive halogen light bulbs for microscopes and fluorescence sources, the HBO bulb for the Zeiss Axioscope, and the two xenon sources for the confocal and the Zeiss Axiovert 200M on the Marianas. In addition, funds are required for slides, coveslips, and incubation chambers for training purposes, a stock of fluorophores of general interest, pipette tips, chem-wipes, cleaning supplies for objectives, microscopes and lab surfaces, including RNAse away and drierite for LCM.

TRAVEL

Funds are requested for domestic travel for attendance at one meeting each year, alternating between the meeting of the International Society for Stereology, when meeting in the US, or the Meeting of the Microscopy Society of America or the Biophysical Society meeting.

OTHER EXPENSES

Maintenance-Equipment: Funds are requested to maintain annual service contracts for the Leica confocal, the Marianas, the ArctutrusXT LCM, and the MicrosBrightfield system.

Registration Fees: Funds are requested to cover registration for the annual meeting attended, for the Biophysical Society and International Society of Stereology memberships.

Software Upgrades: Funds are requested to provide regular upgrades to StereoInvestigator, Neurolucida and Volocity.

CORE SCIENCE SERVICES: Advanced Imaging Income Table

Last Funded Year (53)

Source	Funding (direct costs)
P51 base grant support	$119,916.47
Program income derived from P51 base grant	39,966.76
Other Sources	0
Total	$159,883.23

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$98,814.73
Program income derived from P51 base grant	81,433.32
Other Sources	0
Total	$180,248.05

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

Advanced Imaging receives salary support and support for other expenditures from program income.

TITLE: MOLECULAR AND CELLULAR BIOLOGY SUPPORT CORE

CORE-SUPPORTED PERSONNEL:

Core Scientist (See Biographical Sketches, listed alphabetically in the Overview of the ONPRC)

Excluded by Requester	Senior Scientist

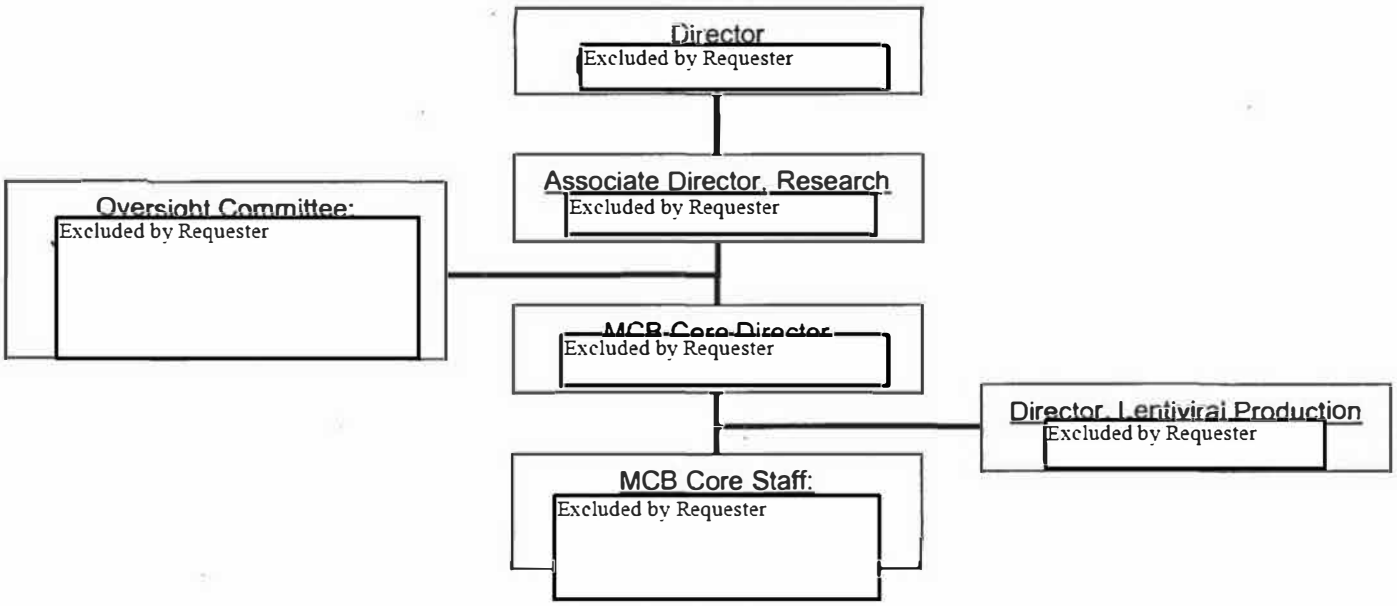
Core Staff (See Biographical Sketches, listed alphabetically in the Overview of the ONPRC)

Excluded by Requester	Staff Scientist 3

Research Support

Excluded by Requester	Research Associate
	Research Associate
TBN	Research Assistant 1

MOLECULAR AND CELLULAR BIOLOGY
Organizational Chart



MOLECULAR AND CELLULAR BIOLOGY PERSONNEL AFFILIATION AND ROLE

Core Scientist

Excluded by Requester	Senior Scientist, Core Director

Staff Scientist

Excluded by Requester	Staff Scientist 3

MOLECULAR AND CELLULAR BIOLOGY SUPPORT CORE

DESCRIPTION:

The Molecular and Cellular Biology Support Core (MCBSC) provides services in support of molecular biology and cell culture for ONPRC investigators. The goal of the MCBSC is to provide flexible, state of the art, time-effective, cost-effective services to facilitate ONPRC investigators' utilization of molecular and cellular biology. Such services are absolutely fundamental to cutting-edge nonhuman primate research. Molecular biology services include both NextGen and capillary DNA sequencing, high-throughput genotyping, high-throughput real-time quantitative PCR, digital PCR, preparation of monkey genomic DNA, generation of monkey-specific cDNAs, establishment of monkey-specific, real-time quantitative PCR assays, large-scale plasmid and phage preparation, fully automated small-scale DNA and RNA preps, and supply of a limited number of reagents and training. Cell biology services include preparation of lentiviral vectors, specialized media and reagents, storage, freezing and amplification of cell lines, preparation of coated culture ware and cover slips, transfection and cloning of cell lines, establishment of primary cell lines, training and access to specialized equipment including liquid handling robots, real-time quantitative PCR platforms, scanning fluorometer, bioanalyzer and plate readers.

Changes implemented to meet the prior review include a revamped web page to provide detailed descriptions of provided services; an improved database to allow detailed tracking of services used; and expanded sequencing services.

Highlights of the previous grant period included bringing high-throughput genotyping for rhesus monkeys online using the LifeTechnologies QuantStudio 12Kflex, offering medium-scale NextGen sequencing on the Illumina MiSeq, and offering lentiviral vectors for both expression and knockdown.

Focus of the next grant period will include delivery of existing services, provision of more automated and high-throughput services, delivery of medium-scale NextGen sequencing services consistent with the MiSeq, working closely with the ONPRC primate genetics program for ancestry, parentage and MHC genotyping, and meeting new needs of primate center investigators. Our specific service aims for the next period are as follows:

MOLECULAR AND CELLULAR BIOLOGY SUPPORT CORE SPECIFIC AIMS

The Molecular and Cellular Biology Support Core (MCBSC) provides services in support of molecular biology and cell culture for ONPRC investigators. The goal of the MCBSC is to provide flexible, state of the art, time-effective, cost-effective services to facilitate ONPRC investigators' utilization of molecular and cellular biology. Such services are absolutely fundamental to cutting-edge nonhuman primate research. Molecular biology services include both NextGen and capillary DNA sequencing, high-throughput genotyping, high-throughput real-time quantitative PCR, digital PCR, preparation of monkey genomic DNA, generation of monkey-specific cDNAs, establishment of monkey-specific, real-time quantitative PCR assays, large-scale plasmid and phage preparation, fully automated small-scale DNA and RNA preps, and supply of a limited number of reagents and training. Cell biology services include preparation of lentiviral vectors, specialized media and reagents, storage, freezing and amplification of cell lines, preparation of coated culture ware and cover slips, transfection and cloning of cell lines, establishment of primary cell lines, training and access to specialized equipment including liquid handling robots, real-time quantitative PCR platforms, scanning fluorometer, bioanalyzer and plate readers.

The focus of the next grant period will include continued delivery of existing services, provision of more automated and high-throughput services, delivery of medium-scale NextGen sequencing services utilizing the core's newly acquired Illumina MiSeq, working closely with the ONPRC primate genetics program for ancestry, parentage and MHC genotyping, and meeting new needs of primate center investigators. Our specific aims for the next period are as follows:

Specific Aim 1: To provide an efficient, responsive, and transparent operating structure.

Specific Aim 2: To provide state-of-the-art, competitively priced molecular biology services.

Specific Aim 3: To provide state-of-the-art, competitively priced cell biology services.

Specific Aim 4: To work closely with the Primate Genetics Program to enhance colony management.

Specific Aim 5: To work closely with similar cores at the OHSU main campus and Oregon State University to leverage delivered services.

MOLECULAR AND CELLULAR BIOLOGY CORE RESEARCH STRATEGY

SIGNIFICANCE

Essentially all research utilizes fundamental methods of molecular and cellular biology that can be assisted by services provided by the MCBSC. Many of these methods, including sequencing, high-throughput analyses and robotics require expensive equipment best operated in a core environment. In addition, best practices of the management of the monkey colony now require specific monkey genotype information that is supported by services of the MCBSC. Thus, the operation of the MCBSC is fundamental to both research and husbandry operations of the ONPRC. Critically, the core stresses training of ONPRC personnel to use the core's equipment except for the most sensitive or complex instrumentation as an important multiplier of the services the core can deliver to core, affiliate, and visiting scientists alike.

INNOVATION

The MCBSC strives to provide state-of-the-art support for molecular and cellular biology procedures at competitive prices. To do this we have implemented the following new services. 1) Medium-throughput NextGen sequencing using an Illumina MiSeq. This provides a whole new level of DNA sequencing support for projects that are too big for capillary and not large enough for the massive throughput of the Illumina HiSeq. Sample applications include sequencing viral genomes, MHC typing, and targeted sequencing of specific genomic loci. 2) High-throughput genotyping using a LifeTechnologies QuantStudio 12K Flex real-time PCR system that allows assay of thousands of genotyping or RNA quantification assays in a single day. This allows for parentage analysis performed by the Primate Genetics Program and provides the capacity for analyzing large panels of RNA phenotypes for multiple animals. 3) The MCBSC provides lentiviral vectors for gene expression or knockdown using multiple vector types to support the needs of investigators.

APPROACH

reviewers' comments

Progress and Major Accomplishments.

Major progress was made in the prior grant period both in terms of services delivered and modernization. As detailed in section 4 below, services were delivered to the overwhelming majority of primate center investigators. Key accomplishments included major modernization of services provided by the Core through the acquisition of a MiSeq for medium throughput NextGen sequencing (see section 7 below for further discussion), the acquisition of a LifeTechnologies QuantStudio Flex 12K for high throughput genotyping, and acquisition of an Eppendorf 5075 Vac liquid handling robot for fully automated DNA and RNA preps. Thus, in the last project period, we have fully modernized our fundamental services for sequencing, real-time PCR, genotyping, and nucleic acid preparations with an emphasis on medium-scale, high-throughput procedures, a scale ideally suited for a primate center. In addition, the core has added lentiviral vector production used for *in vivo* gene delivery, knockdown, and *in vitro* experimentation. It is also important to note that, in the last grant period, real-time PCR has rapidly evolved from an exotic new technique to a fundamental procedure used by all investigators, and, while the core maintains instruments for users, it now encourages users to provide their own reagents and consumables, consistent with "commoditization" of the technique. We consider this strong adoption of real-time PCR by ONPRC investigators a significant accomplishment.

Services Provided/User Info During Previous Grant Period.
Services provided in the previous grant period. In the current grant period, from 5/1/09 to 9/30/12, approximately 144,000 transactions and reactions were processed, equaling billing of $380,000. By comparison in the equivalent time period of the previous grant period, 114,000 transactions and reactions were processed, representing a 25% increase in volume in the current grant period over the previous grant period. Work provided included 43,000 sequencing reactions (capillary); 87,000 real-time PCR reactions, 2500 bioanalyzer samples and 31 custom constructs prepared. Notably, 62 procedures were performed for lentiviral vector production, a new service begun this period. In addition, 6800 DNA or RNA sample preps, 170 freezing and thawing of cell lines was performed, and 15 primary cell cultures were established in conjunction with investigators from the Neuroscience and Reproductive and Developmental Science divisions. As an illustration of the importance of equipment provided by the core to investigators, the core nanodrop is typically used at least 20 times per day, and the core cell counter (LifeTechnologies Countess) is used 2-3 times per day. While we do not record exact hours because we do not bill for routine training, significant time was spent in training users on real-time PCR and basic and advanced cell culture techniques. Thus, this large volume of usage shows how important the services provided to ONPRC investigators are.

ONPRC laboratories using the MCBSC

Neuroscience	Repro	PathoBio
Excluded by Requester		

**Now part of the new Division of Diabetes, Obesity, and Metabolism. Names highlighted in grey are affiliates.*

The number and affiliation of users in the previous grant period. As stated above, the MCB core is used by an overwhelming majority of primate center investigators. About 90% of the core's work is performed for ONPRC investigators and affiliates, while the remaining 10% is performed for investigators located at the OHSU main campus, the Oregon Graduate Institute (adjacent to the ONPRC and now part of OHSU), and the Neurological Sciences Institute (NSI, formerly part of OHSU and adjacent to the ONPRC), but now dissolved. Laboratories at the ONPRC using the MCBSC in the previous grant period are shown in the adjacent table. In addition, 13 laboratories from OHSU, 7 laboratories from the OGI, 4 laboratories from the NSI, 1 laboratory from Portland State University, and 1 commercial entity also used the MCBSC in the previous grant period.

Specific Aims/Service Plan for Next Grant Period.
The MSBSC is dedicated to delivering outstanding services to ONPRC core, affiliate, and visiting scientists as specifically proposed below.

Specific Aim 1. To provide an efficient, responsive, and transparent operating structure.
Efficient, cost-effective operation of the MCBSC will be achieved through cooperation between the Core Director and their staff, the Core Oversight Committee, and the ONPRC Business office. These components are summarized below.

a. Personnel. The MCBSC is under the overall direction of Excluded by Requester who has directed the core since its inception in 1994. Excluded by Requester is an experienced investigator who uses essentially all the techniques of the MCBSC in his own research, which helps ensure that the techniques of the core remain up to date and are geared to investigators' needs. The lentiviral production component of the MCBSC is directed by Excluded by Requester Ph.D. who was one of the first users of lentiviral vectors for *in vivo* modification of gene expression in rhesus monkeys at the ONPRC. The MCBSC is staffed by two highly experienced, masters-level technicians, both with years of experience working for the core. Excluded by Requester has primary responsibility for molecular applications, including DNA sequencing and high-throughput applications. Ms. Excluded by Requester has primary responsibility for cellular applications, including lentiviral vector production. Critically, Excluded by Requester are cross-trained to allow for continuation of all services during

vacation time and to allow each to pitch in and help when unusual demand in one area of service requires extra effort.

b. Oversight. Oversight of the MCBSC is provided by an Oversight Committee consisting of Excluded by Requester Excluded by Requester (chair) Excluded by Requester The Oversight Committee assists with setting chargebacks, charting strategic directions, suggesting new technologies, solving problems, and setting priorities. When needed, the oversight core will also seek outside expertise for issues of management and functioning of the core. Day-to-day core functioning, trouble-shooting and actual development of new techniques come under the direction of the heads of the MCBSC and the MCBSC personnel. As needed Dr. Excluded will also consult with the ONPRC business office on financial and budgetary issues and with Dr. Excluded by Requester Associate Director for Research on scientific and service issues.

c. Evaluation of services provided. Each year, Excluded by Requester will review patterns of usage with the Oversight Committee to decide if existing services should be eliminated, scaled down, or expanded. As needed, scientists at the ONPRC are polled regarding existing services and desired new services. Criteria for adding and maintaining services include value to investigators, cost-effectiveness, and efficiency of providing the services in the core versus investigators performing services in their laboratory, or outsourcing of the services. This approach has proved very effective in allowing the core to continue to provide the most needed services since its founding in 1994.

d. Development of new services. The continued success of the MCBSC since its founding in 1994 has reflected its continued evolution and adaption of new technologies. In the next grant period, the core will similarly evolve and adapt to new and changing technologies. Planned areas we expect to expand include more targeted NextGen sequencing, bringing the advantages of massively parallel sequencing projects to smaller projects via capture arrays and overlapping amplicons. We also expect the use of digital PCR as a means for absolute quantification of RNA/DNA levels to grow. Similarly, we expect more demand for high-throughput genotyping and real-time applications and will continue to develop those techniques and assist in their adoption. There will, of course, be unexpected innovations, and we will adopt those as appropriate. Most of all, the core will continue to listen to its users and provide them with what seems is most needed.

e. Chargebacks. Chargebacks for delivered services are developed by MCBSC personnel in coordination with the Oversight Committee and the ONPRC business office.

Specific Aim 2. To provide state-of-the-art, competitively priced molecular biology services. Though services are divided into molecular and cellular, it should be noted that this is to some extent an arbitrary distinction that has the advantage of allowing the core's two technicians to concentrate on developing maximum expertise in their specific areas. As stated above, both technicians are cross-trained and help each other as needed.

a. DNA sequencing. DNA sequencing is fundamental to almost all laboratory procedures. The MCBSC offers both conventional capillary sequencing with a 96-capillary ABI 3730 XL and NextGen sequencing with an Illumina MiSeq.

While NextGen sequencing has revolutionized DNA sequencing, capillary sequencing remains essential for construct construction and verification, and analysis of plasmids and PCR products. For such small projects rapid turnaround is essential. The MCBSC offers 24 to 48-hour turnaround on capillary sequencing with pricing that is as low or lower than commercial sources. Thus, capillary sequencing fills an essential need, provides more rapid turnaround than commercial sources, and is cost-competitive. As in index of the popularity of this service, sequencing has held constant over the current grant period at about 11,000 reactions per calendar year. The two largest users of capillary DNA sequencing have been the Haigwood laboratory, the Mitalipov laboratory, and the Primate Genetics Program.

Since the last P51 renewal, DNA sequencing has undergone a revolution and NextGen sequencing (i.e., massively parallel) methods are becoming commonplace. The recent introduction of desktop NextGen

sequencers has brought the technology to medium-scale projects that heretofore were too small for a single lane of a HiSeq and much too big for capillary sequencing. To address the need for medium-throughput NextGen sequencing, the core has just purchased an Illumina MiSeq. With the newly provided upgrade to the MiSeq, the capacity of the MiSeq is 8.5 GB with 2 x 250-bp paired-end providing a unique combination of relatively long runs, high capacity, excellent data quality, and economical run costs. Reflecting the value ONPRC investigators place on the MiSeq, the majority of the cost of the system was actually contributed by multiple investigators, with only a portion of the system cost covered by the ONPRC. Expected major users of the MiSeq are Excluded by Requester for methylation analysis, Excluded by Requester for analysis of viral genomes, Excluded by Request for analysis of the nicotinic receptor gene locus in cynomolgus monkeys, and the Primate Genetics Program as discussed further in specific aim 3 below.

b. Real-time PCR applications. As discussed above, real-time PCR has become a routine technique used by almost all laboratories. Up until about 1 year ago, the core provided machines (two ABI 7900 HT and one ABI 7500 fast), reagents, and consumables to investigators and charged per reaction. With the routine use and standardization of real-time PCR, as well as a university-wide quote from major suppliers, the core now encourages users to supply their own reagents and the core concentrates on training new users and maintaining the instruments. If desired, the core still supplies reagents to users who only occasionally perform realtime PCR. The most common uses of the systems are for quantitation of RNA's and genotyping.

An important new development in real-time PCR applications is the recent development of high-throughput systems that can perform thousands of assays in a day. The core has recently purchased such a system, the ABI QuantStudio 12K flex, which runs four 3000-well plates at a time. Each well holds 33 nl and the plates are loaded with a dedicated robotic system. Applications for the system will be high-throughput phenotyping of medium-sized cohorts of animals and high-throughput genotyping. This system will also be used by the Primate Genetics Group (discussed below). The system can also perform digital PCR, which is a new technique that is particularly suited for viral titering. As part of the purchase of this system, the MCBSC traded in its ABI7500 fast, which, unlike the ABI7900's, could not run both 96- and 384-well plates. When the QuantStudio is not being used for high-throughput use, it will also be available for use as a general real-time PCR instrument as it is also equipped with standard 96 and 384-well plates.

c. Nucleic acid preparations. With the core's Eppendorf 5075 Vac liquid-handling robot, the MCBSC offers: fully automated plasmid minipreps; genomic DNA preps from mouse tails, cell cultures, and blood samples; and RNA preps from cell culture and small tissue samples. Samples can be done in multiples of 8, providing flexibility, or in a 96-well format for maximum flexibility. Prices are competitive with manual methods and the savings on labor for labs is significant. The robot is also used by the core to set up capillary sequencing reactions and is also available for use by ONPRC investigators as needed. For laboratories that make extensive use of the robot, we will train personnel in its operation and allow independent use once we are satisfied with their level of expertise. The core also performs large-scale plasmid preparations. This is particularly important for providing high-quality starting material for lentiviral vector preparations.

d. Custom monkey cDNA construct preparation. For laboratories lacking the technical expertise to make their own constructs the core will prepare constructs for them. For some constructs, it can be more cost-efficient to have the needed inserts chemically synthesized by the low-cost service available from companies such as Genscript, and, in those instances, we will suggest that approach instead to ensure the most cost-effective delivery of services.

e. Provision of specialized equipment and training (See entry under cell biology services below).

Specific Aim 3. To provide state-of-the art, competitively priced cell biology services.

a. Traditional cell culture service. A basic function of the cell culture core is to provide basic services in support of cell culture. While not glamorous or high-tech, this is a basic service fundamental to many investigators. The core provides freezing, storage and thawing of cell lines, generation of primary cell lines (with immortalization as an option using telomerase transfection), specialized media production, back-up

assistance for vacation and emergencies and training for new personnel. The core also produces media that are not commercially available.

b. Lentiviral vector production. In 2010, lentiviral vector production was moved from the existing virology core to the MCBSC because of its primary use as a tool to modulate gene expression rather than as a tool for vaccine and immunology investigations. At that time, Excluded by Requester, who initiated lentiviral production by the virology core, became part of the MCBSC core and directs lentiviral production by the MCBSC. Lentiviral vector production by the MCBSC has proven highly successful and popular providing rapid turnaround for vectors designed to mark cells, increase gene expression, or knock down gene expression. Because so much of lentiviral vector production involves cell culture techniques, this has proved a valuable and logical addition to the core. After production, lentiviral preps are titered by flow cytometry or real-time PCR, and we are currently investigating the use of digital PCR for more precise titers. Viruses are provided either as concentrated preps (most often) or conditioned media as requested. In producing vectors, we exchange information and share equipment such as ultracentrifuges and rotors with the current Molecular Virology Support Core (MVSC) virology core directed by Excluded by Requester which is focused on CMV vector production as well as other virology services in support of immunology and vaccine production. We are proposing that lentiviral services remain in the MCBSC for now, but will evaluate this arrangement in conjunction with monitoring the development and capacity of the MVSC.

As well as producing vectors, the core will transduce cell lines with lentivirus and purify infected cell lines by cell sorting or antibiotic selection depending on the vector. The core has also modified existing vectors to provide vectors expressing GFP, mCherry, mVenus, and BFP to allow multiple infection protocols.

c. Provision of specialized equipment. A key function of the core is to provide access to essential equipment that can be shared by multiple users and therefore is best supported in a core environment, thereby avoiding pointless duplication between multiple laboratories. Equipment supplied and maintained by the laboratory includes real-time PCR instruments (see above), a Molecular Devices M5 multimode plate reader (luminescence, fluorescence, and absorbance), a Molecular Devices flex station for fluorescence kinetics with automated pipetting, multichannel nanodrop, QBit fluorometer for DNA quantification, Agilent Bioanalzyer, LifeTechnologies Countess for cell counting, and shaking incubators.

d. Synergy between molecular and cell biology services. The combination of services offered by the MCBSC offers efficiency of service delivery. Examples are as simple as sequencing of plasmids and constructs prior to maxipreps and sequencing robotic minipreps to as complex as preparing lentiviral shuttle vectors, maxiprepping the vectors, then preparing the lentiviral vector, infecting desired cell types and achieving homogeneity of expression by cell sorting. This gives the core the capability to perform fairly complex tasks from start to finish as well as provide investigators advice on all aspects of projects.

Specific Aim 4. To work closely with the Primate Genetics Program (PGP) to enhance colony management. As colony management and animal selection becomes more guided by animal genotype, the role of the PGP in assisting colony management has become more critical and, as a result, the MCBSC has increasingly worked closely with the PGP. This occurs in 3 main ways. First, as described elsewhere in this application, the PGP now has responsibility for MHC genotyping, which requires use of the MCBSC Illumina MiSeq. For MHC typing, an amplicon spanning exons 2 and 3 of the MHC class I genomic region will be sequenced. Currently, amplicon sizes between 198 and 422 bp are being evaluated. The ability of the MiSeq to perform 2x250 paired-end sequencing uniquely allows the longer amplicon size. Currently, up to 72 samples are multiplexed per run, but with the recently upgraded capacity of the MiSeq to greater than 8 Gb, increased multiplexing is possible. During the MiSeq sequencing process, BaseSpace is used to follow data acquisition and sequence quality prior to its transfer to the PGP analysis pipeline. Second, the PGP utilizes the MCBSC's QuantStudio for genotyping panels for parentage analysis both for the ONPRC and other primate centers. For this, PGP personnel deliver the DNAs to the core, where MCBSC personnel perform the robotic loading of the genotyping arrays, run the arrays, and then deliver the data back to the PGP. Third, the PGP utilizes the MCBSC for smaller-scale analyses that rely on the capillary sequencer or standard real-time PCR systems.

Specific Aim 5. To work closely with similar cores at the OHSU main campus and Oregon State University (OSU). To prevent unneeded duplication of services and to expand the services available to ONPRC investigators, we work closely with the OHSU Integrated Genomics Laboratory and the OSU Center for Genome Research & Biocomputing and have reached an agreement to offer services to each other's investigators at internal prices. Thus, the MCBSC does not offer microarray services and, instead, directs users to OHSU. Likewise, for sequencing projects that require the output of the Illumina HiSeq, we direct them to OHSU or for 454 sequencing, to OSU. For projects for which the MiSeq is optimum, users from OHSU or OSU can be directed to us. Naturally first priority is reserved for ONPRC investigators, but this allows greater usage of expensive resources. This also prevents needless duplication of expensive resources.

Molecular and Cellular Biology Biohazards

Research conducted at Biosafety Level 2 is performed in adherence to the criteria outlined in *Biosafety in Microbiological and Biomedical Laboratories*, 5th edition, including all standard microbiological practices. The laboratory has locking, self-closing doors, is designed to be easily cleaned and decontaminated, and has an eyewash station and a sink for hand washing. A biosafety cabinet that is certified annually is used for all manipulations of potentially infectious material. Personal protective equipment is provided for use in the laboratory, and is removed before entering non-laboratory areas. A laboratory-specific biosafety manual is available that outlines safety practices, use of personal protective equipment, proper disposal, and spill response. Personnel are trained in accordance with this manual, and are provided with medical surveillance. Access to the laboratory is restricted when work is being conducted and signage at the laboratory entrance provides information regarding the biosafety level, potential hazards and entry/exit requirements. Incidents that may result in exposure are evaluated and treated, and reported to the lab supervisor and the Biosafety Officer.

RESOURCES

Molecular and Cellular Biology Support Core (MCB)

Laboratory:
The MCB core consists of two dedicated rooms of 250 square feet each for molecular biology and cell culture, and access to shared core space within the Cooley building. Adjacent to these rooms is core space for additional equipment. Both rooms are approved for BSL-2 procedures. In addition, a separate 100 square foot BSL-2 cell culture room is used for lentiviral procedures.

Clinical:
N/A

Computer:
The core is equipped with PC and Macintosh computers running Database software; Sequencher; Life Technologies Primer Express, Digital Suite, Expression Suite and Genotyper software; DNAstar; and online access to GeneSifter. All systems are connected to the OHSU network. In addition the MCB core works closely with the Primate Genetics Program for Next Generation DNA sequence analysis and the Illumina MiSeq is networked for connection to the Illumina BaseSpace.

Office:
The core director Excluded by Requester has an office adjacent to the core operations space, and core staff have descks in the core lab areas.

Major Equipment:
Illumina MiSeq DNA Sequencer, ABI 3730xl 96-column capillary DNA sequencer, Eppendorf EpMotion 7075 Vac liquid handling robot, Life Technologies Quantstudio 12 K Flex Real-time PCR system, ABI 7900HT realtime PCR, Bio-Rad C-1000 PCR machine, MJ PTC 200 PCR machine, Agilent Bioanalzyer, BioTek Epoch spectrophotometer with Take3 micro-volume plate, LifeTechnologies Countess Cell Counter, Life Technologies Qubit 2.0 fluorometer, Molecular Devices Flex station, Molecular Devices M5 multimode plate reader, 3 laminar flow hoods, tissue culture incubators, inverted phase contrast microscope, Milipore Mili-Q water system, and liquid nitrogen freezer. Located in adjacent core space are ultra, medium, and slow-speed centrifuges, shaking incubators, 37 degree incubator for bacteria, -85 degree freezers, and beta and gamma counters.

Program Director/Principal Investigator (Last, First, Middle): Robertson, Joseph E./Haigwood, Nancy L.

CORE SCIENCE SERVICES-MOLECULAR & CELL BIOLOGY DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*

Use Cal, Acad, or Summer to Enter Months Devoted to Project

Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Excluded by Requester	Sr. Scientist/Lab Director	% Effort			Institutional Base Salary	11,681	2,920	14,601
	Staff Scientist 3					4,434	1,374	5,808
	Res Associate					35,910	11,132	47,043
	Res Associate					30,367	10,628	40,995
To Be Named	Res Asst 1	3.30				13,055	5,222	18,277
	SUBTOTALS →					95,447	31,277	126,724

CONSULTANT COSTS		
None Requested		0
EQUIPMENT *(Itemize)*		
None Requested		0
SUPPLIES *(Itemize by category)*		
Laboratory Supplies	42,851	
		42,851
TRAVEL		
Domestic	1,201	1,201
INPATIENT CARE COSTS		
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		
None requested	0	0
OTHER EXPENSES *(Itemize by category)*		
Maintenance-Equipment	30,250	
Flow Cytometry	1,516	
		31,766
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 202,542
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 202,542

PHS 398 (Rev. 6/09) **Form Page 4**

CORE SCIENCE SERVICES - MOLECULAR & CELL BIOLOGY
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	126,724	130,526	134,442	138,475	142,629
CONSULTANT COSTS	0	0	0	0	0
EQUIPMENT	0	0	0	0	0
SUPPLIES	42,851	44,136	45,460	46,824	48,229
TRAVEL	1,201	1,237	1,274	1,313	1,352
INPATIENTS CARE COSTS	0	0	0	0	0
OUTPATIENTS CARE COSTS	0	0	0	0	0
ALTERATIONS AND RENOVATIONS	0	0	0	0	0
OTHER EXPENSES	31,766	32,719	33,700	34,711	35,753
DIRECT CONSORTIUM/CONTRACTUAL COSTS					
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	202,542	208,618	214,876	221,323	227,962
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	202,542	208,618	214,876	221,323	227,962
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					1,075,321

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

PERSONNEL

Senior Scientist – Excluded by Requester % Effort Excluded by Requester serves as Director of the Molecular and Cellular Biology Support Core (MCBSC). Responsibilities include automated sequencing, genotyping, realtime PCR, microarrays, gene expression, and cell culture; overall direction of the MCBSC and directing the adoption of new technologies and procedures as appropriate; prioritization of work; serves as liaison to MCBSC Oversight Committee.

Staff Scientist 3 – Excluded by Requester % Effort
Responsible for directing lentiviral vector production services, which represents a small component of the MCBSC.

Research Associate – Excluded by Requester % Effort
Responsible for molecular biology services including real time PCR, cloning, automated DNA sequencing (both capillary and NextGen), and DNA sequence analysis. Provides back up service to cell culture procedures when required by demand.

Research Associate – Excluded by Requester % Effort
Responsible for cell biology services and lentiviral production; provides highly experienced expertise in cell biology, cell culture techniques, and media preparation, combining those techniques for the needed expertise for lentiviral vector production; provides back up service in DNA sequencing and real time PCR when required by demand.

Research Assistant 1 – To Be Named. (6 calendar months effort: 3.3 ORIP, 2.7 Program Income). With the addition of the MiSeq sequencer and increased lentiviral production, there is need for FTE in the MCBSC. A half-time Research Assistant will be hired for simpler tasks such as media and reagent preparation and plasmid preps necessary for lentiviral production.

SUPPLIES

Laboratory Supplies: Funds are requested to purchase supplies essential for MCBSC operation including reagents for DNA sequencing; conventional and quantitative PCR; plasmid, DNA and RNA preps; lentiviral preps, cell culture; and various other molecular and cell biology procedures.

Travel: Funds are requested for travel to meetings or other laboratories to learn new techniques relating to applications of molecular or cellular biology relevant to non-human primate research.

OTHER EXPENSES

Maintenance-Equipment: Funds are requested to continue service contracts and repairs to the sophisticated equipment essential to operation of the MCBSC. The equipment located in MSBSC includes the sequencers, robot, realtime PCR machines, centrifuges and plate readers. This also covers the required annual certifications of the MBCSC's biosafety cabinets.

Flow Cytometry: Funds are requested to pay fees from Flow Cytometry Support Core to titer lentiviral preps when the vector has a fluorescent reporter gene. Flow cytometry is also used to purify cells after infection with lentiviral vectors expressing fluorescent reporter genes.

CORE SCIENCE SERVICES: Molecular and Cellular Biology Support Core Income Table

Last Funded Year (53)

Source	Funding (direct costs)
P51 base grant support	$95,626.61
Program income derived from P51 base grant	263,125.44
Other Sources	0
Total	$358,752.05

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$202,541.64
Program income derived from P51 base grant	146,209.93
Other Sources	0
Total	$348,751.57

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

The Molecular & Cellular Biology Support Core receives salary support and support for other expenditures from program income.

TITLE: **MOLECULAR VIROLOGY SUPPORT CORE (MVSC)**

CORE-SUPPORTED PERSONNEL:

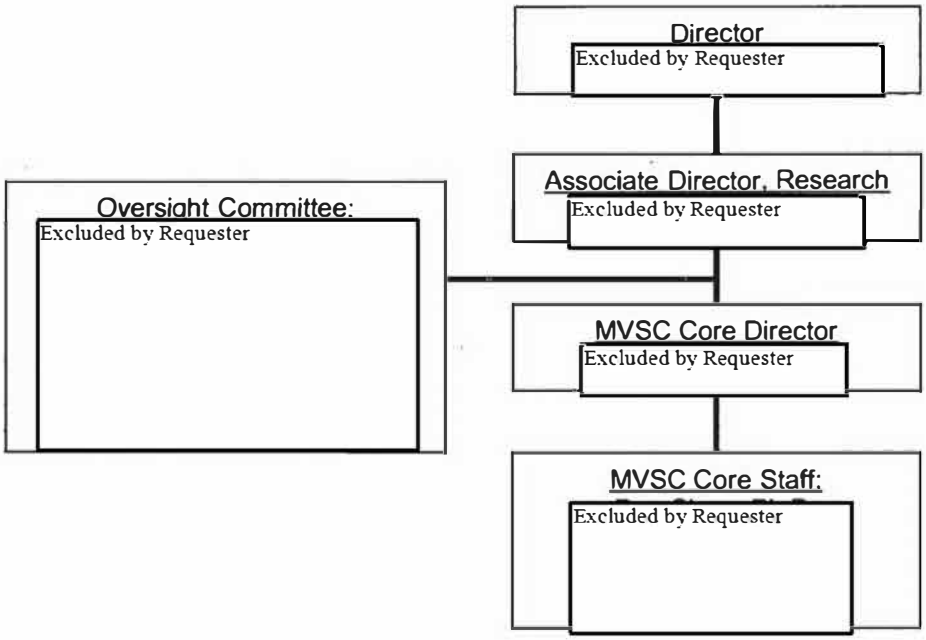
Core Staff (See Biographical Sketches, listed alphabetically in the Overview of the ONPRC)

Excluded by Requester	Senior Staff Scientist
	Senior Research Associate

Research Support

Excluded by Requester	Research Assistant 2
	Research Assistant 2

MOLECULAR VIROLOGY SUPPORT CORE (MVSC)
Organizational Chart



MOLECULAR VIROLOGY SUPPORT CORE (MVSC) PERSONNEL AFFILIATION AND ROLE

Core Scientist:

Excluded by Requester	Senior Staff Scientist, Core Director

Research Support:

Excluded by Requester	Senior Research Associate

MOLECULAR VIROLOGY SUPPORT CORE (MVSC)

DESCRIPTION:

The Molecular Virology Support Core (MVSC) will provide expert virology support to ONPRC, VGTI, OHSU, and collaborative scientists utilizing ONPRC facilities. The goal of the MVSC is to provide specialized virology services that are critical for non-human primate (NHP) research, cost-effective, efficient, and state-of-the-art, along with expertise, infrastructure, and training. Key specialty areas are production of virus stocks, viral vectors, and viral antigens, virus identification and quantification in clinical specimens, as well as the provision and development of key reagents and standardized assays. A steering committee composed of MVSC users regularly reviews core priorities for services and guides new research and development and service initiatives.

Among the criteria considered in setting priorities are 1) the need to facilitate new investigators in transitioning their infectious disease research program from common laboratory species to NHPs; 2) the need to support multiple programmatic goals such that established programs are sustained and new initiatives are facilitated; 3) centralizing work with hazardous agents within our facilities with appropriate equipment and expertise; and 4) enhancing ONPRC's national research resource mission by extending MVSC services and expertise to off-site, collaborative investigators utilizing ONPRC facilities.

The MVSC Oversight Committee is composed of Core users representing all ONPRC divisions as well as ONPRC executive leadership to provide guidance from a diversity of viewpoints: Excluded by Requester (Associate Director for Research), Excluded by Requester (Neuroscience), and Excluded by Requester Excluded by Requester (Pathobiology & Immunology). The Oversight Committee reports to Excluded by Requester and is charged with reviewing MVSC activities for compliance with ONPRC policy for appropriate cost recovery and broad use.

MOLECULAR VIROLOGY SUPPORT CORE (MVSC) SPECIFIC AIMS

The overall purpose of the Molecular Virology Support Core (MVSC) is to provide high quality, affordable, and state-of-the-art virology services to support the local and national mission of the Oregon National Primate Research Center (ONPRC) that is centered on non-human primate (NHP) research. NHPs are an invaluable model for studies of viral pathobiology and immunology and for the evaluation of recombinant vaccines and viral gene therapies. The Core supports investigators through an array of specialized virology services and the provision of technical expertise. Key focus areas are 1) custom production and quality control of viral vectors, viral stocks, and antigens; 2) sensitive viral diagnostic assays to study virus spread after infection, to monitor viral tissue distribution, and to assess viral antibodies; and 3) provision and development of key reagents and standardized assays. In addition, the Core offers user training in virology techniques and safe handling of infectious agents, and assists in maintaining proper compliance with local institutional biosafety requirements.

In the the previous grant period, the MVSC underwent structural and programmatic changes in order to position itself for success in a rapidly changing research environment and to best meet the virology needs of the local scientific community. In particular, the Core has made improvements to its management and infrastructure and has begun developing an array of new state-of-the-art virology services that capitalize on its expertise in viral production and diagnostics. Early indicators of success have been an increase in service utilization and user diversity. During the next grant period, we will continue building on these gains by further improving and tailoring our services to the programmatic needs of the ONPRC. To that end, the following specific aims are proposed:

Specific Aim 1. Provide an efficient, responsive, and transparent operating structure. This will be achieved through cooperation between the Virology Core Director and staff, the MVSC Oversight Committee, and the ONPRC Business office. The MVSC will further improve lab efficiency and administration in order to facilitate core operations, service use, and information flow. Key efforts will be 1) continuation of current efforts to standardize methods and improve efficiency in the MVSC laboratory through optimized protocols and automated procedures; 2) development and implementation of a viral load service module in the new campus-wide LabKey animal record and scientific database system to facilitate service requests, data analysis, and data sharing; and 3) evaluation of other potential LabKey service and administrative modules (e.g., billing, laboratory notes, inventory and freezer management, internal data storage, etc.) that would most benefit the Core and users.

Specific Aim 2. Provide high-quality virology services and to appropriately expand services and expertise in support of ONPRC's mission. The Core will continue to implement and improve its ongoing and new services, focusing on areas that foster growth of ONPRC's scientific programs and that are most important to investigators. These include cytomegalovirus (CMV) and HIV/SIV AIDS research, as well as gene transfer and gene therapy using adenoviral and adeno-associated virus (AAV) vectors to support diverse research areas such as neuroscience, reproduction, and metabolic disease. The goals, progress, service quality, and organization of the MVSC will be regularly reviewed by the MVSC Director, the Core Oversight Committee, and the Associate Director for Research.

MOLECULAR VIROLOGY SUPPORT CORE (MVSC) RESEARCH STRATEGY

SIGNIFICANCE

The purpose of the Molecular Virology Support Core (MVSC) is to provide high quality and state-of-the-art virology services to support the local and national mission of the ONPRC that is centered on non-human primate (NHP) research. NHPs represent a unique model for comparative research of human biology, physiology, and disease. They are critical for research in infectious viral diseases, such as HIV/SIV AIDS, and for the study of viral pathobiology, immunology, vaccination, and treatment. NHPs are also used in various gene therapy and gene transfer protocols. Advances in genetic engineering and virology have made possible the specific modification of viruses, such as adenovirus, cytomegalovirus (CMV), and adeno-associated virus (AAV), in order to be used as gene transfer vectors. Sensitive viral diagnostic methods have been developed to study virus spread after infection, monitor virus and viral vector tissue distribution, and assess viral antibodies. These are highly specialized methodologies that require appropriate technical expertise and experience with biosafety containment and cannot easily be done in individual investigators' laboratories. Therefore, they can best be provided by trained staff and through a centralized Core facility.

INNOVATION

The MVSC is constantly evolving to address the need for state-of-the-art, affordable, and easily accessible virology services in the light of rapid scientific progress and a changing research environment. In this renewal application, the Core will continue to offer and expand its expertise through a specialized and innovative array of virology services and resources, in order to support a broad range of research. Particular service innovations include: 1) improved production of viruses and viral vectors, such as next-generation (i.e. attenuated, single-cycle, multiply-deleted, multigene) rhesus CMV (RhCMV) vectors, SIV challenge stocks, custom-made adenoviral and AAV vectors; 2) large-scale NHP tissue processing methods for ultrasensitive virus detection using nested quantitative PCR; and 3) improved sample processing and viral load detection. Also, data handling and Core administration need to be improved in innovative ways to achieve better integration within ONPRC and collaboration with the user community. For instance, the Core will be implementing the new ONPRC-wide LabKey animal records and database system to more efficiently process service requests and store and disseminate research data more effectively as discussed further below.

APPROACH

reviewers' comments

Progress and Major Accomplishments.

In order to best serve the mission of the ONPRC to advance NHP research, the MVSC has been undergoing major operational and programmatic changes. Specific initiatives and strategic goals were developed with guidance by the Oversight Committee and in discussion with a wide range of users conducting NHP studies,

thus reflecting a broader consensus. These have been: 1) hiring of a new Core director; 2) central re-focus on primary Core strengths and expertise in virology; and 3) expansion and diversification of the Core user base.

Personnel. In March 2010 (end of Yr. 50) Excluded by Requester was hired as the new MVSC director to replace the interim directorship of Excluded by Requester The recruitment of a permanent Core director was a major initiative proposed during the previous grant period to bring in dedicated leadership and specialized expertise and to develop and leverage the Core's unique strengths. Excluded has a wide range of research experience in virology (viral vector development, gene therapy, vaccines, virus diagnostics), in both academic and industry settings.

Progress overview. The previously rather broad and somewhat generic Core service menu has been reshaped and newly focused to respond to the changing needs of the NHP research community. Generic, redundant, and unused services were eliminated, and new services have been in development starting in Yr. 51. Core priorities are based on: 1) services are necessary and relevant to a sufficient range of users across the institution; 2) services are specialized and capitalize on the Core's unique virology expertise; and 3) services are state-of-the-art and/or can be done more efficiently and cost-effectively at the Core, rather than in individual investigators' laboratories. Care was taken to solicit feedback from a wide range of investigators and obtain guidance from the Core Oversight Committee to select the most appropriate services. The Core has also increased advertisement of its services to reach a broader research community. Examples are institutional websites (ONPRC, VGTI, and OHSU), specialized core sites (Eagle-Eye, ScienceExchange), campus newsletters, regular updates, seminars, and peer-to-peer networking. New service initiatives were prioritized in close consultation with the Oversight Committee, and detailed plans were made to assure timely implementation. In the case of novel or complex methodologies, the help of outside subject-matter experts was solicited. New methods were extensively tested and validated before coming on-line as services. Improvements were made gradually and in phases to ensure continuity of operations. To improve infrastructure, the MVSC laboratory was consolidated and remodeled (see Resources Section). To maximize effectiveness, Core laboratory operations were redesigned in several ways. Individual responsibilities for service projects were assigned to create a sense of ownership and provide accountability and coupled with extensive cross-training to ensure uninterrupted service coverage. Particular attention was paid to increase service efficiency and provide standardization of results where possible, such as through standard request forms, optimized lab protocols, standard operating procedures, and by taking advantage of centralized processing, new equipment, and economies of scale. As a result of these extensive efforts, the Core has begun developing state-of-the-art services, primarily in the areas of CMV, SIV/AIDS, and adenoviral and AAV gene transfer vectors, which capitalize on the Core's unique blend of expertise in viral diagnostics and viral production.

Specific service improvements. An important research focus at the ONPRC in recent years has been the development of viral vectors based on BAC-cloned RhCMV to study NHP infectious disease, pathogenesis, viral immunogenicity, and vaccines. The MVSC has been involved in an extensive and broad collaboration with a diverse team of CMV investigators from ONPRC's Pathobiology & Immunology Division and VGTI (in particular Excluded by Requester resulting in important contributions to the field [1-6]. As part of these efforts, the MVSC has implemented a service for large-scale production of RhCMV vector stocks for use in a wide range of NHP studies. For diagnostics, real-time PCR assays were developed to sensitively detect RhCMV in clinical samples and to distinguish exogenous vectors carrying foreign antigens from endogenous wild-type RhCMV strains. Notably, the MVSC is the designated virology core on a recent multi-investigator HIVRAD P01 ("Development of an effector-memory T cell AIDS vaccine"; 5P01AI094417) program project grant that includes a designated budget of on average $34,000/year for MVSC services and 10% in salary support for the MVSC director for five years.

A significant effort was spent on the development of novel tools for supporting HIV/SIV AIDS research. First, an SIV plasma viral load (PVL) quantitative PCR assay was recently established to support local AIDS researchers. This assay is a crucial resource that was not previously available at the ONPRC, allowing cost-effective NHP screening and quantification of SIV loads. The assay was developed with the help of Dr. Excluded by Requester (NCI, Frederick, MD), a leader in quantitative SIV PCR methods [7-9], and standardized and

cross-validated with his reference laboratory. We then further improved our process by adopting semi-automated nucleic acid purification methods (Maxwell 16, Promega) for more rapid sample turnaround (one day for urgent samples), and high detection sensitivity (<50 viral copies/ml) from only 0.3 ml plasma. Second, the study of SIV spread early in infection and tissue distribution in the NHP model has taken on renewed importance to better understand viral pathogenesis and to improve efficacy of vaccines and treatments. With the help of Excluded by a cutting-edge technique was very recently established at the MVSC allowing large-scale tissue processing at cryogenic temperatures (up to 1 gram per sample, GenoGrinder, SPEX) for ultrasensitive virus detection by nested quantitative PCR [8]. This service has now been used in several pilot studies and usage is expected to grow. Finally, the MVSC has developed more extensive capabilities and methods for production of large SIV virus stocks to facilitate standardization of challenge studies in the NHP AIDS model.

To broaden its reach, the MVSC has started a particular focus on supporting gene delivery and gene therapy studies at the ONPRC. Excluded by Request the new Core Director, has a background in gene therapy and brought in specific expertise in viral vector development, quality control, and large-scale production, in particular adenoviral vector development. Several new adenoviral services have been since brought on-line. First, the MVSC offers adenoviral recombination cloning and vector production using the well-established Ψ5 adenovector system [10, 11]. Ψ5 vectors allow controlled transgene expression using an inducible promoter, which we have exploited for our users to express toxic proteins. A second vector system is based on Gateway recombination technology (Invitrogen, Life Technologies) that allows greater flexibility in the expression cassette design and also expression of shRNA. Third, the Core now provides standardized testing for replication-competent adenovirus (RCA) in vector stocks to satisfy OHSU institutional requirements for the use of these vectors *in vivo*. A notable example of specific MVSC involvement is a recently started collaboration with Excluded by Requester (Reproductive & Developmental Sciences Division) as part of a U54 Contraceptive Research & Development Center Grant, in order to develop shRNA adenoviral vectors to target proteases necessary for ovulation and oocyte release. Finally, the MVSC is currently setting up AAV vector production capabilities, which is further described in the Approach Section.

Services Provided/User Info During Previous Grant Period.

An overview of Core services provided during the last grant period can be found in **Table 1**, with the number of services provided and the resulting Core income from charge-backs up to the most recent date available. In order to focus the MVSC on its specific virology expertise, underutilized services were eliminated from the service menu by the end of Yr. 50. In virtually all cases, eliminated services were generic and redundant in nature, such as routine cell and molecular biology services and banking of clinical samples, and are now performed elsewhere. Services that were eliminated due to Core re-focusing are marked "discontinued". Since Yr. 51, improved and newly developed services have been gradually implemented into the service repertoire, leading to significant overall increases in service utilization and increasing income from charge-backs in Yrs. 52-53. Newly developed services are denoted with asterisks. Note that the lentiviral vector production service was integrated with the Molecular & Cell Biology Core for programmatic reasons and is further discussed in the Molecular & Cell Biology Core section.

Table 1 - Overview of MVSC Services from May 1, 2009 to October 1, 2012

Service	Yr.50		Yr.51		Yr.52		First Five Months of Yr.53	
	Services	Income	Services	Income	Services	Income	Services	Income
Virus Production Services								
Adenoviral Vector Stock Production (incl. titration and characterization)*	N/A	N/A	1	$694	6	$7,556	1	$834
Adenoviral Vector, In-Stock*	N/A	N/A	1	$50	31	$1,039	10	$600
CMV, RRV, or SFV Large Stock or Antigen Production (incl. titration)	3	$8,369	20	$10,238	59	$87,033	50	$57,376
SIV Stock Production					1	$5,876		
SIV, In-Stock	8	$280	3	$121				
SIV Titration	13	$2,882	14	$3,114	12	$5,478		
Vaccinia (MVA), In-Stock*			2	$4,448	2	$1,489		
Virus Diagnostic Services								
CMV DNA Processing	269	$3,007	331	$3,232	320	$2,426	318	$4,064
CMV Coculture	131	$7,453	168	$4,989	79	$2,169	12	$339
CMV qPCR Assay	120	$842	359	$1,704	348	$4,224	324	$4,047
CMV Antibody ELISA	179	$11,103	21	$605	35	$1,038		
Large Tissue Processing for Ultrasensitive Virus Detection*	N/A	N/A	N/A	N/A	N/A	N/A	138	$6,170
SIV Plasma Processing*	N/A	N/A	N/A	N/A	259	$3,573	145	$1,767
SIV Plasma Viral Load qPCR Assay*	N/A	N/A	106	$2,074	353	$7,346	145	$2,622
Miscellaneous Services								
Sample Prep	923	$1721	Discontinued					
Sample Banking	Discontinued							
Generic Services	Discontinued							
Totals:	1,629†	$40,792†	1,040	$31,672	1,470	$129,247	1,143	$77,819
Internal Users:	5† (4/0/0/1)		6 (5/0/0/1)		9 (6/1/1/1)		6 (4/1/1/0)	
External Users:	2		1		4		1	

Table 1 Legend: * = Newly developed service; N/A = Service not available; † = Totals do not include lentiviral vector production, as this service was integrated into the Molecular & Cell Biology Core after Yr.50;
The totals for "Internal Users" are followed by a more detailed breakdown according to departmental affiliation inside the parentheses (Division of Pathobiology & Immunology/Division of Reproductive Sciences/Division of Neuroscience/OHSU Main Campus)

Specific Aims/Service Plan for Next Grant Period.

Specific Aim 1. Provide an efficient, responsive, and transparent operating structure. This will be achieved through cooperation between the Virology Core Director and staff, the MVSC Oversight Committee, and the ONPRC Business office. The MVSC is directed by Excluded by Requester who has over 10 years of virology research experience spanning both viral vector development and diagnostics. Excluded is responsible for day-to-day Core operations and management, as well as the development and implementation of new services. General oversight will be provided by the MVSC Oversight Committee composed of Excluded by Requester (Neuroscience), and Excluded by Requester (Pathobiology & Immunology), with additional input from business administration and research leadership as needed. The committee will help Dr. Excluded by with strategic and financial planning, reviewing service usage, development of new services and technologies, recharge rate setting, resolving issues, and addressing user feedback and satisfaction.

The MVSC laboratory staff has been growing to a current total of 2.5 FTE. Excluded by Requester has been the Core's senior lab research associate since 2001. He is joined by experienced research assistants. Excluded by Requester

has been involved in the development and use of many of the Core's specialized methodologies and in providing virology training to new staff. Importantly, each MVSC lab worker is cross-trained in multiple viral diagnostic and production methods to provide flexibility and efficiency and to ensure uninterrupted service coverage during vacation and sickness. Standardized protocols, SOPs, and work schedules are in place to guide laboratory operations and training (such as all laboratory services and techniques, routine instrument and lab maintenance, sterile tissue culture techniques, proper laboratory attire, proper biocontainment, etc.). Based on user feedback and, as detailed in SA2, we expect a continued growth in service usage during the next grant period. To keep up with growing demand, we will be adding additional technical personnel as needed, in close consultation with the Oversight Committee and the Business Office.

With the increasing service demand, a main goal for the MVSC will be to maintain and improve lab efficiency and administration, in order to better facilitate core operations and service use. The ONPRC has recently launched a major campus-wide initiative to improve its animal records and create a scientific database system using a single software platform: LabKey which will be implemented over the next few years. We have been working with Excluded by Requester in ONPRC's IT unit to develop new software modules in LabKey. These will integrate MVSC service requests, data analysis, and sharing of results with users. The first module already in development is for our SIV Viral Load Service. A similar LabKey program is already in operation at the Wisconsin National Primate Center (Excluded by Requester Virology Services Core) and serves as the basic template for our efforts. For the first time at the ONPRC, this module will integrate Core-generated viral load data with the Center-wide NHP animal records system to provide better data transparency on SIV infections and ease-of-use. This may also help improve animal clinical care and better protect the safety of animal caretakers. Based on these initial efforts, we will, together with ITG and the Oversight Committee, prioritize and evaluate other service and administrative modules (for example billing, laboratory notes, inventory and freezer management, internal data storage, etc.), with an emphasis on areas that would most benefit the Core and users. Overall, we expect that these efforts will be feasible and will significantly improve the effectiveness of the Core. We will also continue our current efforts to improve efficiency in the laboratory, mainly by optimizing and standardizing protocols and by moving toward automated procedures wherever possible. For example, we have recently implemented a Maxwell 16 nucleic acid purification system that decreases processing times by up to 5 hours compared to manual methods. For the next grant period, we hope to enhance our PCR diagnostic sample capabilities and throughput by upgrading to different formats (such as 384 wells) combined with automated plate setup. Funds for improvements and modernization are proposed as part of the Center-wide I&M budget plans for the next grant period, and if approved should be available in the first year of the new grant. If implemented, these efforts will result in greater sample throughput and lower service costs that can be passed on to users.

Specific Aim 2. Provide high-quality virology services and appropriately expand services and expertise in support of ONPRC's mission.

Overview. The MVSC will continue offering highly specialized virology services, consultation and training to ONPRC and collaborative scientists using NHPs. As described above, the Core has been through a major restructuring and re-focusing effort and has started multiple new service initiatives. We will solidify these gains and continue improving and tailoring our services to best meet the programmatic needs of the ONPRC, its research divisions and scientific working groups. Services will be prioritized and priced in close consultation with the MVSC Oversight Committee, with the pricing striking a balance between low cost to the user and adequate cost recovery through chargebacks. The Committee will also have the final authority to resolve any conflicts. The principal focus will be on areas and services that foster the growth of ONPRC scientific programs and that are most important to investigators. Priorities and service development will be regularly reviewed by the Oversight Committee. It is expected that core target areas will be: 1) cytomegalovirus (CMV) research; 2) HIV/SIV AIDS research; and 3) gene transfer and gene therapy using adenoviral and adeno-associated (AAV) vectors to support diverse research areas, such as in neuroscience, reproduction, and metabolic disease. Within each of these areas, our particular focus will be on virus production and diagnostics that are key areas of Core strength and user demand; i.e. production of viruses and viral vectors for NHP studies, such as SIV challenge stocks, next-generation rhesus CMV (RhCMV) vectors, adenoviral and AAV vectors, and viral sample and large-scale tissue processing and quantitative PCR (qPCR).

Rhesus CMV (RhCMV). The Core has acquired specialized expertise in this area, with well over 100 RhCMV large-scale vector stocks successfully produced for *in vivo* NHP studies during the last grant period. More recently, this includes so-called next-generation (such as attenuated, single-cycle, conditional, multiply-deleted, or multigene) RhCMV vectors, which sometimes require very specific cell types and growth conditions. Therefore, efforts will be made to: 1) derive, test, and bank new primary rhesus fibroblast lines to replenish the limited supply of highly permissive producer cells and help develop complementing cell lines for production of attenuated vectors; 2) support translational research efforts to produce advanced human CMV vectors based on next-generation RhCMV designs; and 3) further improve processing and diagnostic detection methods to selectively and sensitively detect RhCMV vectors *in vivo*. With the historically strong focus on herpesvirus research at ONPRC and an outstanding local and collaborative research group, we expect to remain a critical CMV resource due to the Core's experience and ability to centralize and standardize many aspects of CMV production and diagnostics.

HIV/SIV AIDS. We will continue our diagnostics efforts to quantify SIV plasma viral loads and provide large-scale tissue processing. Additional capabilities will be developed as needed, such as for detection of cell-associated virus. We will also continue production of SIV challenge stocks for NHP studies, including advanced constructs such as the recently developed molecularly tagged $SIV_{mac239}X$, which can be used to trace founder viruses. Regrettably, there has been so far no national or integrated reagent resource for production of standardized SIV and SHIV stocks, a drawback that seriously hampers better standardization of NHP AIDS studies. Therefore, we plan to further improve our SIV stock production and titration protocols by cross-validating methods with investigators and cores at other primate centers to achieve better standardization. We will explore if the MVSC can potentially contribute to the establishment of a dedicated national SIV resource.

Adenovirus & AAV. The Core has already started offering an adenoviral vector production service. In consultation with our users we are currently expanding our capabilities to provide greater flexibility and to make custom vectors for specialized applications, such as shRNA expression. Finally, due to very significant local demand, we are currently working to establish a dedicated AAV vector production service. The Core has already obtained appropriate plasmids, reagents and methodologies for production and quality control from AAV experts at the University of Pennsylvania Excluded by Requester and University of Florida Excluded by Excluded by At this point, we have established initial AAV vector production and titration capabilities for several prototype vectors and are now in the final development stage, which includes fine-tuning purification protocols and validating methods. We will be launching a limited service within the next few months. As we gain experience with the AAV system and various user needs, we will progressively expand our service coverage to a wider range of users and improve our capacity to include the commonly used AAV serotypes 1-9 and custom gene expression cassettes.

Simian pathogen-free (SPF) colony screening. At the onset of the prior grant period, the SPF screening service unit was integrated into the former Division of Animal Resources (DAR; now designated the Division of Comparative Medicine (DCM) coincident with the recruitment of the new Division Chief, Excluded by Requester due its particular specialization and close overlap with routine clinical efforts. The MVSC continues to consult and provide virology expertise and viral reagents to the SPF service unit. The MVSC director is involved in ongoing efforts to expand SPF screening to cover additional viral antigens and to implement state-of-the-art multiplex SPF screening technologies to advance SPF colony development and surveillance, and to increase efficiency and lower the cost of sample testing. These efforts are further described under the separate SPF screening unit section.

REFERENCES

Excluded by Requester

MOLECULAR VIROLOGY SUPPORT CORE (MVSC) PUBLICATIONS

Excluded by Requester

Excluded by Requester

MOLECULAR VIROLOGY SUPPORT CORE (MVSC) Biohazards

reviewers' comments

RESOURCES

Molecular Virology Support Core (MVSC)

Laboratory:
The MVSC laboratories are located in the Research Building centrally located at the ONPRC. The MVSC laboratory (over 1,000 sq. ft.) contains a tissue culture room with two six-foot laminar flow hoods and four CO2 incubators, as well as molecular virology and general laboratory space. The laboratory is divided into a Biological Safety Level (BSL)-2 space and a separate BSL-2+ laboratory (315 sq. ft.) used for work with infectious HIV and SIV samples. The laboratories are well equipped for virus isolation/propagation, PCR-based quantitative virology methods, serology/immunology, and molecular virology under BSL-2 and BSL-2+ containment levels.

Clinical:
N/A

Animal:
N/A

Office:
The Core Director has a dedicated office in the Research Building and core staff have desks in the main laboratory.

Computer:
The Director and core staff each have desktop PCs with internet and printer access.

Major Equipment:
Major MVSC equipment includes Applied Biosystems 7500 Real Time PCR System with a PC P4 computer and supporting software, PCR clean hood, Applied Biosystems 9700 thermocycler, Promega Maxwell 16 robotic nucleic acid extraction robot, Roche MagNA Pure Compact robotic nucleic acid purification unit, Roche MagNA Lyser, SPEX GenoGrinder, fume hood, Virtis sonicator, Nanodrop ND-2000 spectrophotometer, BioTek Synergy Mx monochromator-based multi-mode microplate reader, BioTek ELX405UCWS microplate and cell washer, Li-Cor Odyssey Infrared Western Blot Imaging System, Beckman Model L7-65 ultracentrifuge and rotors, Beckman Model J2-21 refrigerated centrifuges with rotors, Beckman 22R microcentrifuge, Beckman Model Allegra 6R refrigerated centrifuge and rotors, Bio-Rad 3000xi power supplies, Bio-Rad DNA horizontal electrophoresis cells, and Bio-Rad protein II vertical electrophoresis cells with Bio-Rad Model 1000/500 power supply, Bio-Rad Trans-Blot SD semi-dry transfer cell with Model 200/2.0 power supply, constant temperature water baths, Siemens Purelab Ultra Genetic water purification system, DNA concentrator, UV cross linker, bacterial incubator, incubator shaker, Sanyo MCO-38AIC-UV CO2 Incubators, Nuaire NU 425-600 and Labgard ES laminar flow hoods, Leica DMIL LED FLUO fluorescence microscope, autoclave, refrigerators, -20°C freezers, Sanyo MDF-U74V -80°C freezer, Sanyo CBS V-3000AB liquid nitrogen freezer, and balances.

Other:
N/A

Program Director/Principal Investigator (Last, First, Middle): Robertson, Joseph E./Haigwood, Nancy L.

CORE SCIENCE SERVICES - MOLECULAR VIROLOGY DETAILED BUDGET FOR INTIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Excluded by Requester	Sr. Staff Scientist/Lab Direc	% Effort			Institutional Base Salary	54,320	13,580	67,899
	Res Asst 2					23,320	8,162	31,482
	Sr Res Assoc					32,733	10,147	42,880
	Res Asst 2					17,927	7,171	25,098
	SUBTOTALS →					128,299	39,060	167,359

CONSULTANT COSTS		
None Requested	0	0
EQUIPMENT *(Itemize)*		
None Requested	0	0
SUPPLIES *(Itemize by category)*		
Laboratory Supplies	57,298	
Med Care Matls & Supplies	962	
Office & Admin Supplies	292	
		58,551
TRAVEL		
Domestic	875	875
INPATIENT CARE COSTS		0
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		
None Requested		0
OTHER EXPENSES *(Itemize by category)*		
Equipment Maint & Repair/Contract	12,870	
Freight	455	
Laboratory Services	1,166	
Hazardous Waste Disposal	262	
Telecommunications	1,085	
		15,838
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 242,623
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 242,623

PHS 398 (Rev. 6/09) **Form Page 4**

CORE SCIENCE SERVICES - MOLECULAR VIROLOGY
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAIL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	167,359	172,380	177,551	182,878	188,364
CONSULTANT COSTS	0	0	0	0	0
EQUIPMENT	0	0	0	0	0
SUPPLIES	58,551	60,308	62,117	63,980	65,900
TRAVEL	875	901	928	956	984
INPATIENTS CARE COSTS	0	0	0	0	0
OUTPATIENTS CARE COSTS	0	0	0	0	0
ALTERATIONS AND RENOVATIONS	0	0	0	0	0
OTHER EXPENSES	15,838	16,313	16,802	17,306	17,826
DIRECT CONSORTIUM/CONTRACTUAL COSTS					
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	242,623	249,901	257,398	265,120	273,074
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	242,623	249,901	257,398	265,120	273,074
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					1,288,116

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

BUDGET JUSTIFICATION

PERSONNEL

Senior Staff Scientist - Excluded by Requester % Effort
Income) Responsible for operations of the Virology Core facility which includes hiring, training and supervising of technical personnel, interacting with researchers in the development and completion of research projects, and spearheading Core service development and improvement.

Research Assistant 2 - Excluded by Requester % Effort
Responsible to carry out the various specialized Virology Core services, such as virus detection by co-culture and quantitative real-time PCR, virus and viral vector production, purification, and quality control, viral antigen generation, viral immunoassays and serology, large and small tissue processing, and virus nucleic acid purification. Will also be in charge of routine tissue culture, maintenance of cell lines and primary cells, proper maintenance of lab equipment, liquid nitrogen and -80˚C storage, ordering and restocking of laboratory supplies, organizing, maintaining and updating records, databases for laboratory samples and systems, data reporting and management, and general laboratory duties.

Senior Research Associate - Excluded by Requester % Effort
Responsible for working closely with the Core Director on new assay, method, and service development. Responsible for directing the day-to-day operations of the Virology Core together with the lab assistants and helps coordinate and train the more junior technicians according to established SOPs. Assists in directing and performing key services in viral diagnostics and virus stock, vector, and antigen production described below.

Research Assistant 2 – Excluded by Requester % Effort
Responsible to carry out the various specialized Virology Core services, such as virus detection by co-culture and quantitative real-time PCR, virus and viral vector production, purification, and quality control, viral antigen generation, viral immunoassays and serology, large and small tissue processing, and virus nucleic acid purification. Will also be in charge of routine tissue culture, maintenance of cell lines and primary cells, proper maintenance of lab equipment, liquid nitrogen and -80˚C storage, ordering and restocking of laboratory supplies, organizing, maintaining and updating records, databases for laboratory samples and systems, data reporting and management, and general laboratory duties.

SUPPLIES

Laboratory Supplies: Funds are requested for tissue culture flasks and cell culture chambers, well-based plates, dishes, serological pipettes, pipette tips, reagent reservoirs, transfer pipettes, media bottles, receiver and filtration flasks, micro-centrifuge tubes, centrifuge and ultracentrifuge tubes, micro plates, PCR tubes and caps, cell scrapers, tissue grinding and processing supplies.

Medical Care Materials & Supplies: Funds are requested for

- Reagents/buffers: cell culture media, cell culture buffers and supplements, serum, trypsin, transfection reagents, PCR primers, probes, enzymes and buffers, virus nucleic acid isolation reagents and kits, protein assay reagents, gel electrophoresis reagents, restriction enzymes, antibodies, ethanol/isopropanol, salts and various chemicals, modifying enzymes, antibiotics.
- Personal protective equipment: gloves, disposable sleeves, disposable gowns, shoe covers, tyvek suits.
- Miscellaneous: tube racks and boxes, dissection tools, storage jars, biohazard bags, wiping tissues, etc.

Office & Admin Supplies: Funds are requested for standard office supplies (paper, writing implements, monitors, labels, tablets, etc.).

TRAVEL

Funds are requested for one trip per year to a key national virology meeting to keep up-to-date on important developments in non-human primate virology research (e.g. Symposiums on NHP Models for AIDS).

OTHER EXPENSES

Equipment Maintenance & Repair/Contract: Funds are requested for routine maintenance not covered under maintenance contracts such as freezers, refrigerators, microscopes, microcentrifuge, etc as well as contract maintenance for laboratory equipment that includes laminar hoods, incubators, biosafety cabinets, nucleic acid isolation robot, quantitative real-time PCR system.

Freight : Funds are requested for sample shipping and shipping costs incurred in receipt of goods.

Laboratory Services: Funds are requested for cost of services that the Core laboratory is unable to perform in-house.

Hazardous Waste Disposal: Funds are requested to be used to pay for disposal of biological and chemical waste generated by the Core.

Telecommunications: Funds are requested for long distance telephone charges, pagers and cell phones

CORE SCIENCE SERVICES: Molecular Virology Support Core Income Table

Last Funded Year (53)

Source	Funding (direct costs)
P51 base grant support	$207,293.80
Program income derived from P51 base grant	55,285.69
Other Sources	0
Total	$262,579.49

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$242,622.62
Program income derived from P51 base grant	198,509.43
Other Sources	0
Total	$441,132.05

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

The Molecular Virology Support Core receives salary support and support for other expenditures from program income.

TITLE: MRI SUPPORT CORE

CORE-SUPPORTED PERSONNEL:

Core Staff (See Biographical Sketches, listed alphabetically in the Overview of the ONPRC)

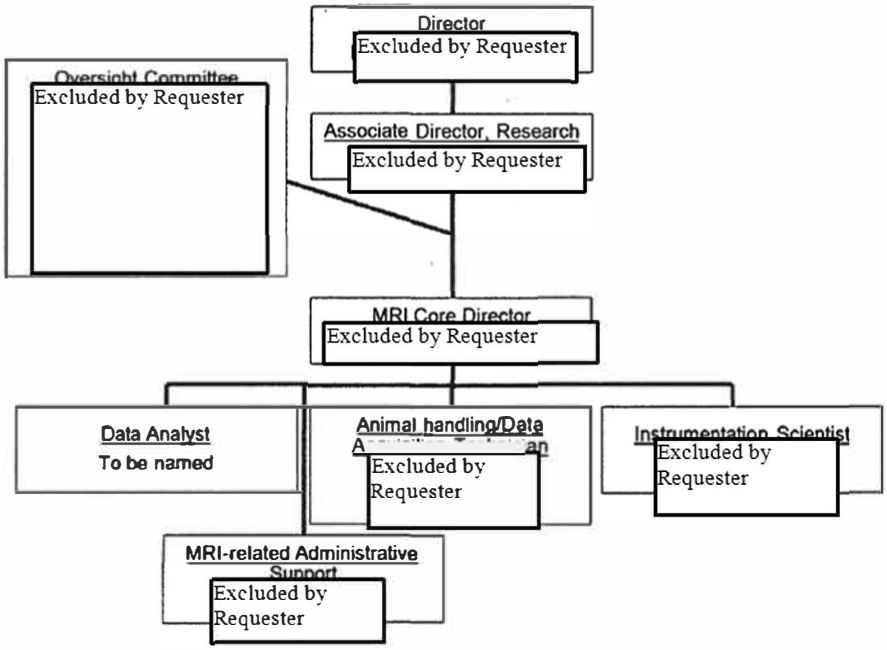
Excluded by Requester	Associate Scientist

* Indicates a partial core appointment

Research Support

Excluded by Requester	Senior Staff Scientist
	Clinical Vet Technician 2
	Financial Manager
	Director, Advanced Imaging Research Center
	Medical Lab Tech
TBN	Staff Scientist

MAGNETIC RESONANCE IMAGING SUPPORT CORE
Organizational Chart



MAGNETIC RESONANCE IMAGING SUPPORT CORE PERSONNEL AFFILIATION AND ROLE

Core Scientists:

Excluded by Requester	Associate Scientist, Core Director

Affiliate Scientists:

Excluded by Requester	Director, Advanced Imaging Research Center, OHSU Senior Staff Scientist, Advanced Imaging Research Center, OHSU

Research Support:

Excluded by Requester	Animal Handling/Data Acquisition Technician
To Be Named	Animal Handling/Data Acquisition Technician
	Data Analyst, Staff Scientist

MAGNETIC RESONANCE IMAGING SUPPORT CORE (MRISC) SUPPORT CORE

DESCRIPTION:

The magnetic resonance imaging (MRI) support core provides access to instrumentation and expertise for the design and implementation of MRI studies involving nonhuman primate research subjects. The MRI support core is located in a 2500 sq. ft. facility that is within 100 feet of the ONPRC surgical facilities. It houses a nonhuman-primate-dedicated Siemens magnetom Tim trio 3T MRI system, and instrumentation and space necessary for conducting imaging experiments, including equipment and supplies for anesthesia and MRI-compatible physiological monitoring and regulation. Additionally, the MRI support core benefits from a mutually-beneficial relationship with the OHSU Advanced Imaging Research Center (AIRC) to provide infrastructure and technical support. During the previous funding period, the core provided expertise and training in all aspects of MRI research to scientists within all ONPRC scientific divisions, as well as several researchers in the broader OHSU research community. Additionally, NIH shared instrumentation grant support was obtained provide a major (>$600k) upgrade to incorporate total imaging matrix (Tim) technology; and support services were expanded to facilitate the analysis as well as acquisition of MRI data. The core operations are periodically evaluated by the oversight committee consisting of members from all ONPRC divisions as well as the AIRC. Future plans for the core include continued support for ONPRC scientists and collaborators requiring MRI services, as well as specific plans for further expansion of the data analysis capabilities.

MAGNETIC RESONANCE IMAGING SUPPORT CORE (MRISC) SPECIFIC AIMS

The Magnetic Resonance Imaging Support Core (MRISC) operates a Siemens Magnetom Tim Trio 3T whole-body MRI system housed in a free-standing, 2500-sq. ft. facility in close proximity to the Animal Services Building. The MRISC's objective is to capitalize on the translational value of MRI-based investigations in non-human primate (NHP) research. The Core's mission is to enhance existing ONPRC research programs by providing flexible MRI facilities and expertise that are optimized for NHP subjects, enabling investigators to undertake strategies analogous to human clinical practices, and to utilize the close similarity between human and NHP anatomy and physiology to develop new MRI research and in vivo diagnosis techniques and applications. In order to facilitate these goals, the MRISC relies heavily on a mutually beneficial relationship with the OHSU Advanced Imaging Research Center (AIRC), in which the MRISC supports the efforts of several AIRC faculty and staff to provide infrastructure and technical support of the ONPRC MRISC.

The fundamental service provided by the MRISC to ONPRC investigators is assistance performing MRI exams of sedated NHP subjects. MRISC staff are available for each exam. Equipment and supplies for anesthesia and MRI-compatible physiological monitoring and regulation are provided by the MRI facility. A veterinary "on-call" system has been arranged with ONPRC surgical staff to address complications such as adverse reactions to anesthesia or experimental procedures immediately prior to, or during, the MRI exam. Imaging infrastructure services provided by the AIRC include safety and operator training sessions for ONPRC scientists, the construction of MRI-related instrumentation specialized for NHP MRI experiments, maintenance of computer resources for data access and archiving, quality/assurance oversight for the system, interface with ONPRC facilities staff to manage system requirements (such as electrical power, chilled water, etc.), and maintenance of a web-based scheduling system.

The overall goal of the MRISC is to provide ONPRC investigators state-of-the-art magnetic resonance imaging and spectroscopy services through pursuit of the following specific aims:

Specific Aim 1: Organization. Provide an efficient, responsive, and transparent operating structure. This will be accomplished by providing access to projected fees for MRISC for a 5-year period extending 5 years and through regular meetings with the MRISC oversight committee.

Specific Aim 2: Project Design. Provide the ONPRC research community with consultation and advice on appropriateness and/or feasibility of MRI experiments, and to assist with optimizing experiment design.

Specific Aim 3: Data Acquisition. Assist researchers in the development of data acquisition procedures, most typically through the development and implementation of imaging protocols.

Specific Aim 4: Data Analysis. Assist users of the ONPRC MRISC in the development of data analysis procedures, and train ONPRC personnel, either within the MRISC or within an investigator's laboratory, in implementation of the data-analysis plan.

MAGNETIC RESONANCE IMAGING SUPPORT CORE (MRISC) RESEARCH STRATEGY

SIGNIFICANCE

Research supported by the ONPRC MRISC leverages anatomical, physiological, and behavioral similarities among NHP species to perform experiments of high translational relevance to the development of future clinical practice. The imaging techniques developed and implemented at the ONPRC MRISC provide essential links for the "forward" translation of principles of research with NHPs to applications in human subjects. Two examples of significant forward translational research supported by the ONPRC MRISC are:

1. Stroke. Animal modeling is essential for the preclinical evaluation of neuroprotective drugs for the treatment of stroke. Rodent studies have provided substantial understanding of the pathophysiology of stroke and efficacy of interventions to protect the brain against ischemic injury. However, despite these successes, the recent efforts to translate pre-clinical neuroprotective strategies from rodents to humans have been disappointing. Some therapeutic trials have actually led to increased mortality [1]. Such considerations have lead to the creation of Stroke Therapy Academic Industry Round Table guidelines (http://www.thestair.com/) and recent recommendations for preclinical testing of neuroprotective agents in NHPs. The ONPRC MRISC supports NIH-funded research in collaboration with OHSU investigators to assess efficacy of a Toll-like receptor agonist as a neuroprotective agent in human stroke therapy.

2. *Japanese macaque encephalomyelitis.* A spontaneous demyelinating disease has been characterized in Japanese macaques resident at the ONPRC, Japanese macaque encephalomyelitis (JME). This disease bears many similarities to demyelinating disease entities in humans, including multiple sclerosis [2]. The ONPRC MRISC is supporting the highly integrated, collaborative effort between many investigators at ONPRC and OHSU who have been investigating JME. Specifically, the team has contributed to our understanding of a role for an identified γ-herpesvirus, which could act as a trigger in MS.

The imaging resources provided by the MRISC also serve the "reverse" translational process of facilitating the ability to interpret imaging measurements performed on human subjects through leveraging imaging strategies with longitudinal biological experimental measurements in NHP models. Examples of this approach include:

1. *Brain changes with chronic alcohol exposure.* It has long been known that the brains of humans who consume large amounts of alcohol undergo atrophy. However, questions remain regarding biological source of this change (e.g., loss of neurons vs. change in shapes/sized of neurons), as well as its temporal dynamics (e.g., how much alcohol exposure is enough to cause brain atrophy?). Longitudinal studies of brain changes associated with voluntary alcohol drinking are currently being conducted through the ONPRC MRISC to address these questions.

2. *Resting-state functional connectivity.* Resting-state functional connectivity MRI (rs-fcMRI) is based on the discovery that spontaneous low-frequency (less than ~0.1 Hz) blood oxygen level-dependent signal fluctuations in functionally related brain regions show strong correlations at rest. These connectivity signals offer the potential to provide a biomarker for brain disturbances in mental disorders that do not cause overt structural or physical abnormalities [3, 4]. While the versatility of rs-fcMRI has caught the collective attention of the scientific and clinical community, the work has predominantly been conducted in humans. Application of rs-fcMRI to NHPs is critical for characterizing the physiological mechanisms responsible for the measured signals. Novel research conducted at the ONPRC MRISC has led to the development of an experimental preparation for measuring rs-fcMRI in sedated NHP subjects. This protocol is now used by many ONPRC and OHSU laboratories to characterize the biological phenomena that underlie rs-fcMRI.

INNOVATION

The imaging-based services provided by the MRISC are non-invasive, which is unique compared to many other experimental methods for characterizing NHP subjects. As a result, imaging outcomes may be repeatedly measured on individual research subjects, providing increased sensitivity to addressing a scientific question with fewer subjects than is necessary with a cross-sectional design. In addition, approaches that

have yet to be adopted in human procedures, and that can't be easily developed in small-animal models due to significant species differences, can be evaluated in NHPs. In these cases, the MRISC supports the development of new data acquisition and analysis schemes, with the expectation that many such practices will lead to future developments of measurement procedures applicable to human subjects. Specific examples are:

1. *Fetal brain development.* Recent advances in methodology to correct for the effects of subject motion during data acquisition in image reconstruction calculations [5] are revolutionizing the utility of fetal brain MRI for neurodevelopmental research and clinical practice [6]. As a result, high-resolution 3D human fetal brain MRI data are enabling dramatic improvements in the precision of fetal brain biometric data, and facilitating qualitative changes in the sets of parameters that can be monitored. High-resolution 3D brain MRI of the fetal brain can potentially be of significant value in characterizing neurodevelopmental disorders, particularly with regard to early diagnosis. Therefore, with the objective of extending the utility of fetal MRI from normal brain growth to a diagnostic tool for brain growth disorders, the MRISC is employing animal models of neurodevelopmental disease such as exposure to maternal infection and maternal alcohol consumption.

2. *Vascular organization of the primate placenta.* Abnormalities of the placenta are linked to virtually every obstetric complication, including pregnancy loss, fetal growth abnormalities, preterm labor, and preeclampsia. However, the rodent placenta differs dramatically in its anatomical organization from that of NHPs, and, as a result, data obtained from mouse studies are often not of immediate relevance to human physiology. The MRISC is developing dynamic contrast enhanced MRI methods to map the primate-specific cotyledonary organization of the maternal component of the placental vasculature.

APPROACH

The fundamental service provided by the MRISC to ONPRC investigators is assistance performing MRI exams of sedated NHP subjects. However, this service is of highest value to the ONPRC research community if it is provided in the context of the ability to consult with ONPRC scientists on experimental strategy planning, for training personnel in data acquisition and analysis procedures, and where necessary, and to assist with implementation in cases where individuals/laboratories do not have personnel to perform required tasks.

To meet these objectives, the MRISC maintains a staff with a diverse array of expertise in a cost-effective manner through a mutually beneficial relationship with the Advanced Imaging Research Center (AIRC), which is located on the OHSU Marquam Hill campus. Excluded by Requester has an appointment to the AIRC with a joint appointment to the ONPRC. This situation allows for close coordination with Excluded by Requester the Director of the AIRC, as well as other AIRC staff in maintaining the interface between the AIRC and the MRISC.

reviewers' comments

reviewers' comments

Progress and Major Accomplishments.

1. *Upgrades to the MRI instrument.* In the summer of 2010, a $500,000 NIH S10 award was obtained to upgrade the 3T Trio to a Trio with "Total imaging matrix" (Tim) technology. The Tim upgrade was completed in the fall of 2010. In the spring of 2011, the 3T Tim Trio was enhanced with multinuclear capabilities, including acquisition of a broadband radiofrequency (RF) amplifier for non-^{1}H applications.
2. *Enhancements of RF capabilities.* To optimize sensitivity of NHP applications, a 15-channel "extremity" RF transmit/receive coil was purchased for most routine procedures. Further, Excluded by Requester has constructed several customized ^{1}H and ^{31}P surface coils for specific applications at the MRISC.
3. *Software and computer infrastructure.* Over the past three years, the AIRC staff has built an extensive computational infrastructure. Through its association with the AIRC, ONPRC MRISC users have free access to key resources, which are supported by AIRC staff, and continually documented through the local AIRC wiki pages. These resources include a Candelis ImageGrid DICOM appliance (15TB capacity) that is used to store all DICOM MRI data. Two highly expandable generic file servers with RAID arrays are used to run a number of virtual machines. These virtual machines provide services such as network file storage (35TB capacity) and backup, a backup PACS system, remote authentication and user profiles for Linux machines, version control for in house software development, and a wiki page for documentation and collaboration. The AIRC provides a Linux environment that can be accessed at local workstations on the ONPRC or remotely over the campus network. This environment has a wide variety of analysis packages installed and ready to use. Examples of the provided software include: FSL, FreeSurfer, 3DSlicer, AFNI, Analyze, SPM, Pmod, DCMTK, LCModel, CMTK, Caret, Camino, JIM, jMRUI, ImageJ, Matlab, IDL, Python, R, and many more. All of this software can also be run on our computing cluster with 72 cores, 136 GB of RAM, and an Nvidia Tesla GPU. This cluster will be expanded as needs dictate.
4. *Benefits derived from Siemens research agreement through AIRC.* The AIRC staff (and, hence, MRISC) have access to IDEA, the Siemens pulse sequence programming software environment. This has been used in consultation with Excluded by Requester who is a Siemens Applications Scientist with office space located in the AIRC, to modify several pulse sequences to optimize them for NHP applications. Examples include reducing the minimal voxel volume for localized spectroscopy pulse sequences and reducing the minimal slice thickness for echo-planar imaging (EPI) pulse sequences. The MRISC additionally makes use of several Siemens "works in progress," with examples being tools for performing diffusion tensor imaging (DTI) using either segmented EPI (e.g., "RESOLVE"), or a stimulated echo (e.g. "tSTEAM DTI"). The MRISC has also utilized the Siemens C2P mechanism to have access to constant time spiral chemical shift imaging tools developed and made available by Excluded by Requester at the Massachusetts Institute of Technology. In all of the above cases, the added capabilities are made freely available to the entire MRISC user community.
5. *Data analysis services.* Since the spring of 2010, the MRISC has supported a 0.5 FTE technician to provide assistance in developing data-analysis procedures and training in their implementation. This individual also hosts regular "drop-in" sessions, in which users are welcome to bring specific questions, or a presentation is prepared on a specific theme. This individual is also available on a fee-for-service basis, at $50/hr. In the majority of cases, however, data-processing procedures are implemented by users' laboratory personnel.
6. *Improved documentation of MRISC policies and practices related to animal handling.* In the spring of 2010, data recorded in association with all MRI procedures were interfaced with ONPRC's centralized database. This ensures that data related to IACUC compliance, billing, and physiological data recorded for sedated

animals, are logged in a consistent manner. In addition, this situation provides MRISC technicians access to medical history data, such as tolerance or adverse reactions to various types of sedation, the existence of implants, and special handling requirements, for all monkeys prior to initiating an MRI study. In the fall of 2010, standard operating procedures for all animal-handling procedures performed by MRISC were written and approved by ONPRC veterinary staff. These procedures are available to MRISC users.

Services Provided/User Info During Previous Grant Period.

Usage and hourly fees are given for the past 5 years in Table 1. MRISC users are distributed across ONPRC divisions and the greater OHSU research community, with 47% being derived from the Division of Neuroscience, 37% derived from Pathobiology and Immunology, 4% derived from Reproductive and Developmental Sciences, 1% from Comparative Medicine, and 11% from OHSU investigators. The 26 research projects supported by the MRISC over the previous grant period are listed in Table 2. Each of the Table 2 projects underwent the development process described in aims 2-4, in coordination with MRISC staff.

Table 1. Usage and Hourly Fees.

Year	Hourly Rate ($)	Hours Billed
48	200	350
49	300	440
50	375	636
51	425	500
52	475	598

Table 2. Research Projects Supported by the MRISC Over Previous Grant Period

Project Name	PI	Project Dates	Grant Support/Publication
1. Stroke Study	Excluded by Requester	2007 - present	U01 NS064953, [7]
2. Brain Aging		2007 - present	R01 AG036670, [8, 9]
3. Brain Ethanol MRS		2007 - 2010	R21 AA018039, [10, 11]
4. Stroke Blood Brain Barrier		2008	
5. Surgical Planning		2008	[12]
6. Pelvic Floor		2008 - 2010	Industry support
7. T-cell Rejuvenation		2008 - 2009	
8. Perfusion of Ovary		2008 - 2010	
9. Ethanol Volumetric Changes		2008 - present	U01 AA013510, [13]
10. Fetal Brain Infection		2009 - 2010	
11. Fetal Brain High Fat Diet		2009 - 2010	
12. Japanese Macaque Encephalomyelitis		2009 - present	DOD CDMRP 00486280, [2]
13. Placenta Perfusion		2009 - present	R21 Percentile
14. Alcoholism tissue resource		2009 - present	R24 AA019431, [14]
15. Carotid Plaque		2010	
16. phMRI, Aging Brain		2010	[15]
17. Visual fMRI		2010	
18. Fetal Development Infection		2010 - present	R01 HD069610
19. Brain ^{31}P MRS		2011	
20. Gene Therapy		2011 - present	Foundation support, [16]
21. Perinatal Sedation		2011 - present	Foundation support
22. Fetal Brain Development		2011 - present	R01 AA021981, [17]
23. Ovarian Hormone Replacement		2012 - present	R24 OD011895
24. Leg Muscle		2012	Industry support
25. Resting State Functional Connectivity		2012 - present	Private Source
26. ONPRC Clinical Support	Div. Comp. Med.	2007 - present	

Specific Aims/Service Plan for Next Grant Period.

The quantity and diversity of research projects supported by the MRISC provide evidence that the Core's objectives have been successfully met over the previous grant period. As the set of MRISC-supported projects mature, the core staff has recognized areas of overlap between users. Developments planned for the next grant period are to capitalize on this overlap to create high-level data acquisition and analysis tools that benefit multiple research groups and thereby create the opportunity for research groups to leverage the large number

of animals being characterized with similar imaging procedures to provide a broad base of control subjects for future experiments.

Specific Aim 1. Organization.

Administration. Projected MRISC rates for coming years are given in Table 2. These are available to ONPRC scientists through the internal web site, and are routinely used by OHSU researchers as they plan studies and submit budgets for grant applications. The MRISC staff provides safety training for responsible behavior near a strong magnetic field and other potential hazards, such as compress gas, present in the ONPRC MRI facility. Individuals are granted key access to the MRI facility only after completing the safety training session.

Oversight. The MRISC is overseen by a committee consisting of Excluded by Requester Division of Neuroscience, Excluded by Requester Division of Reproductive and Developmental Sciences, Excluded by Requester Division of Pathobiology and Immunology, Excluded by Requester Division of Comparative Medicine, Excluded by Requester Advanced Imaging Research Center, and Excluded by Requester Advanced Imaging Research Center. The Oversight Committee meets annually to review usage and future plans for improvements in instrumentation and support for data analysis services. This committee is also charged with setting priorities in the event that mutually exclusive services are requested of the MRISC (e.g., if multiple users wish to utilize MRISC services at the same time). To date, however, such conflicts have been resolved between users and with the MRISC staff.

Specific Aim 2. Project Design. At the beginning of each project involving use of the MRISC, ONPRC scientists typically meet with the MRISC head and staff to discuss project feasibility and to define specific outcomes desired from the study. In cases in which a promising course of action is identified, subsequent meetings are planned to outline data acquisition and analysis strategies.

Specific Aim 3. Data Acquisition. Prior to the beginning of a study, the project PI and laboratory staff meet with the MRISC staff to build a data acquisition protocol. This involves defining the animal preparation procedure, building an MRI protocol on the image acquisition computer, and agreeing on typical lengths of scan time used for the protocol. In several cases, MRISC staff and the PI agree that a series of pilot studies are needed to establish feasibility prior to initiation of the study. In cases where such pilot studies involve establishing new techniques for the MRISC, the PI is not charged for the MRI time. By the conclusion of the data acquisition/planning phase, key members of the MRISC staff and the PI's laboratory staff are trained in implementing the study protocol.

Specific Aim 4. Data Analysis. In parallel with the design of the data acquisition protocol, the data-analysis procedure is defined. During the initial stages of the data acquisition phase of each study, MRISC staff are available to train staff from the PI's laboratory in the analysis of the acquired data. If the PI wishes instead to utilize the data processing scientist on a fee-for-service basis to analyze data, an estimate of the length of time for data analysis is made based on the first acquired dataset.

In the next grant period, the effort of the MRISC data-processing scientist will focus development of a database system and data-processing solutions for volumetric, DTI, and rs-fcMRI data. Preliminary steps toward the first objective include the implementation of a PACS data-archiving system in coordination with the AIRC. The necessity for data-processing tools has been driven by the maturation of MRISC-supported projects in which commonalities in data acquisition and analysis procedures warrant the creation of high-level tools that can be applicable to several ONPRC research efforts. As an example, projects 2, 9, 22, and 25 (Table 3) all involve brain volumetric, DTI, and rs-fcMRI measurements, to be analyzed in the context of longitudinally designed experiments. Centralized data analysis tools to generate a common set of outcome measures from each of these experiments would be advantageous for several reasons. First, availability of high-level analysis routines would improve accessibility of these MRI measures to multiple research groups. Second, centralized tools would improve the reliability of analyses because it would facilitate automated execution, rather than current practices of individual procedures in several laboratories involving multiple manual steps. Last, common data processing strategies will enable researchers to utilize each other's data as control animals, where appropriate (for example, studies from the aging colony, project 2 in Table 3, could serve as controls for hormone replacement animals in project 23). Thus, standardization of MRI protocols and

data analyses will increase efficiency and create the capacity for synergism between projects. The ready availability of similar, archived projects will also create an opportunity for additional comparisons.

REFERENCES

Excluded by Requester

MAGNETIC RESONANCE IMAGING SUPPORT CORE (MRISC) PUBLICATIONS

Excluded by Requester

MAGNETIC RESONANCE IMAGING SUPPORT CORE (MRISC) VERTEBRATE ANIMALS

1. Description of the use of animals: Standard Operating Procedures for all functions involving vertebrate animals in the MRI support core are documented and approved by the ONPRC Division of Comparative Medicine.

A synopsis of these procedures is as follows:

Objective: To define standard anesthesia management of animals during MRI procedures.

I. Induction
- A. The MRI subject will be given an induction agent while in the home cage. Typically, the induction agent is Telazol (Tiletamine-zolazapam) 3-5 mg/kg IM or ketamine 10-20 mg/kg IM.
- B. Once sedated, the subject is removed from the home cage and transferred to the MRI prep room where an endotracheal tube is placed. For adult rhesus macaques, 4.0 to 5.5 mm i.d. endotracheal tubes are typically used.
- C. If the MRI is scheduled for several consecutive animals, the animal will be started on 1.5% isoflourane. The animals pulse rate, blood oxygen saturation, and $ETCO_2$ levels will be monitored until it is transferred to the magnet. An animal cannot be left unattended while under anesthesia.

II. Gas anesthesia set-up
- A. Due to the magnetic field in and around the MRI Scanner, a precision vaporizer is located outside of the MRI Scanner room, in the control room. A long (3 meter) non-rebreathing tube is utilized which extends from the anesthesia machine, through the wall of the control room, into the MRI room, where it connects to the subject. This set-up also allows for adjustments to the oxygen flow rate and anesthetic gas delivery to the subject from the control room.
- B. Because of the length of the non-rebreathing tube, high oxygen flow rates are necessary to avoid rebreathing of the exhaled gases in the tube. Typically the oxygen flow rate is set at 1-2 liters/minute.
- C. Ventilator (when used, tidal volume calculation, how to set up, pressure max, recovery from ventilation to spontaneous breathing).
  1. Under several circumstances, it is advantageous for the MRI Scanner to obtain images during specific phases of the respiratory cycle to eliminate the effects of respiratory motion on image creation. The ventilator may also be used in cases of dyspnea, hypoxemia, or hypoventilation.
  2. To engage the ventilator:
     a. Remove the blue tube from the pop off valve and connect to the exhaust port at rear of ventilator. Close pop off valve. Remove the black bag from the universal control arm. Connect clear breathing system tube from back of ventilator to where the black bag was attached. Start the ventilator.
     b. To disengage ventilator: Turn ventilator off. Open pop off valve. Remove blue tube from exhaust at rear of ventilator and connect this to pop off valve. Remove clear breathing system tube from universal control arm. Connect black bag to universal control arm.
  3. Inspiratory volume during mechanical ventilation is determined by maximum pressure during inspiration (Pressure-limited ventilation). Inspiratory pressure target is typically 15 cm H2O. This should be monitored throughout ventilation and can be adjusted by increasing or decreasing tidal volume.

III. Anesthesia monitoring
- A. From the control room, a trained individual will be able to visualize the animal in the MRI Scanner, monitor respiratory rate, pulse rate, end tidal CO2, and oxygen saturation.
- B. The trained individual will record these physiological parameters (RR, HR, O_2 Sat, $EtCO_2$) every 10 minutes throughout the procedure.

C. Approximate normal values:

Respiratory rate: 10-20 breaths/min
Heart rate: 110-170 beats/min
O_2Sat (while breathing 100% O_2): 95-100%
$EtCO_2$: 35-45 mmHg
NOTE: These are approximate values. Variables such as animal size, sex, and species affect heart rate and respiratory rate. Trends are more important than absolute numbers when monitoring these parameters.

IV. Anesthesia Recovery

A. After completion of the MRI study, the subject will be disconnected from the rebreathing tube (endotracheal tube left in) and transferred to the MRI Prep room for recovery.
B. In the MRI Prep room, the subject will be connected to a pulse-oximetry/$EtCO_2$ monitor where monitoring will continue until the endotracheal tube can be removed (jaw movement, pink mucous membranes, swallowing observed).
C. If the animal was mechanically ventilated, close monitoring with supportive ventilation (bagging) while on 100% oxygen will be conducted in the prep/recovery room until spontaneous breathing is observed.
D. After removal of the endotracheal tube, the subject will be placed into a transfer box and returned to the home cage.
E. If animal is returning to surgery, it will remain on isoflourane anesthesia and transported via the anesthesia cart while monitored with pulse oximeter/$ETCO_2$.

V. Emergency Contacts

A. The veterinarian who oversees the MRI facility should be immediately contacted if the MRI technician has any concerns regarding abnormal physiological readings, anesthetic equipment malfunction, or any animal health concerns. A current list of On-Duty Veterinary Contacts is posted above the telephone in the MRI control room.

2. Justification of animals: Suitable justification of the use of nonhuman primate research subjects in the research projects served by the MRI support core is necessary to obtain IACUC approval. It is a prerequisite to have IACUC approval of the MRI procedures in order to be scheduled in the MRI system reservation system.

3. Veterinary care: Medical Care will be supervised by ONPRC and will be assisted by post-DVM fellows and certified laboratory animal technologists. OHSU/ONPRC is committed to providing a high-quality program of animal care in compliance with state and federal Animal Welfare Acts and the standards and policies of the Department of Health and Human Services including the NIH documents entitled "Principles for Use of Animals" and "Guide for the Care and Use of Laboratory Animals." The medical school has central animal facilities and a unified program of care that are accredited by the American Association for Accreditation of Laboratory Animal Care. A faculty Animal Care and Use Committee composed of at least five members including a veterinarian maintains oversight of the animal facilities and procedures.

4. Procedures to monitor stress and minimize discomfort: Throughout the induction and recovery from anesthesia for MRI, monkeys show no signs of discomfort. There is no anticipated discomfort. We are experienced in carrying out all procedures proposed in this application. The Clinical Pathology capabilities within the Animal Resources Program will be utilized to provide health profile data, and our pharmacy provides a full range of antibiotics and other pharmaceuticals for the treatment of sick monkeys. The faculty and staff provide many years of experience in primate medicine.

5. Euthanasia: Euthanasia is not required or performed by the MRI support core.

RESOURCES

MAGNETIC RESONANCE IMAGING SUPPORT CORE (MRISC)

Laboratory:
The Core is housed in a 2500-sf facility that includes office space for MRI support core staff, laboratory space, an animal preparation/procedure room, and shared computer facilities.

Clinical:
N/A

Animal:
The animal preparation room within the ONPRC MRI facility is equipped with instrumentation necessary to induce, maintain, and recover non-human primates from anesthesia; as well as perform intravenous contrast reagent administration, or other intravascular injections as requested by ONPRC scientists. Physiological monitoring instrumentation for while animals are in the MRI system are described in the Major Equipment section.

Computer:
There is a PACS system and a Linux-based data server that is maintained by Excluded by Requester for long-term data storage and exchange of data with Excluded by Requester at the University of Washington (Co-I). All personnel are supplied with up-to-date PC's and computing resources, including the software programs Matlab and Photoshop. Other software programs used in the proposed studies (Caret, ITK-Snap, FSL, etc.) are freely available, and are maintained in cooperation with computer support staff.

Office:
The MRI support core head has offices at the ONPRC and on the main OHSU campus in the OHSU Advanced Imaging Research Center (AIRC). Additional contributors to the proposed work have office space at ONPRC or AIRC.

Major Equipment:
The primary instrument in the MRI support core is the ONPRC 3T Siemens Tim Trio. The support core is also equipped with an MRI compatible In Vivo Precess physiological monitoring system, which enables measurement of pulse rate, arterial oxygen, respiration rate, end-tidal carbon dioxide partial pressure, expired isoflurane concentration, and non-invasive blood pressure of nonhuman primate research subjects while sedated. An isoflurane delivery system, respiratory ventilation control, and various RF electronic equipment are interfaced specifically with nonhuman primate subjects. Additionally, the MRI support core manages a Caliper Quantum FX Micro computed tomography (micro CT) instrument for in vivo rodent and ex vivo nonhuman primate tissue imaging. This instrument is located in a room adjacent to the ONPRC small animal vivarium.

Other:
The MRI support core staff utilize the AIRC electronic equipment laboratory, which houses a 500 MHz four-channel oscilloscope (Tektronix), a three-in-one network analyzer (Agilent), an MRI-compatible RF sweeper (Morris), a power meter, a Gauss meter, and a precision component analyzer (Wayne-Kerr). Also within this laboratory space is a machine shop containing a band saw, drill press, and lathe, which are utilized for constructing customized RF instrumentation for post mortem MRI experiments. This information is used to assess the capability of the organizational resources available to perform the effort proposed.

Program Director/Principal Investigator (Last, First, Middle): Robertson, Joseph E./Haigwood, Nancy L.

CORE SCIENCE SERVICES-MRI DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*

Use Cal, Acad, or Summer to Enter Months Devoted to Project

Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Excluded by Requester	Assoc Scientist	% Effort			Institutional Base Salary	14,365	3,591	17,956
	Sr. Staff Scientist					18,893	4,723	23,616
	Clin Vet Tech 2					6,612	2,314	8,926
	Financial Mgr					2,339	725	3,064
	Director-AIRC					5,391	1,348	6,739
To Be Named	Staff Scientist	3.96				14,620	5,117	19,737
Excluded by Requester	Medical Lab Tech	% Effort				30,971	9,601	40,572
	SUBTOTALS →					93,190	27,419	120,609

CONSULTANT COSTS		
None Requested		0
EQUIPMENT *(Itemize)*		
None Requested		0
SUPPLIES *(Itemize by category)*		
Laboratory Supplies	4,081	
Office & Admin Supplies	466	
		4,547
TRAVEL		
None Requested	0	0
INPATIENT CARE COSTS		0
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		
None Requested		0
OTHER EXPENSES *(Itemize by category)*		
Equipment Maint Contract	103,037	
Maintenance Contract-Software	360	
		103,397
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 228,554
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 228,554

PHS 398 (Rev. 6/09) **Form Page 4**

CORE SCIENCE SERVICES - MRI
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	120,609	124,227	127,954	131,793	135,747
CONSULTANT COSTS	0	0	0	0	0
EQUIPMENT	0	0	0	0	0
SUPPLIES	4,547	4,684	4,824	4,969	5,118
TRAVEL	0	0	0	0	0
INPATIENTS CARE COSTS	0	0	0	0	0
OUTPATIENTS CARE COSTS	0	0	0	0	0
ALTERATIONS AND RENOVATIONS	0	0	0	0	0
OTHER EXPENSES	103,397	106,499	109,694	112,985	116,375
DIRECT CONSORTIUM/CONTRACTUAL COSTS					
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	228,554	235,410	242,473	249,747	257,239
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	228,554	235,410	242,473	249,747	257,239
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					1,213,423

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

Budget Justification

PERSONNEL

Associate Scientist - Excluded by Requester % Effort Excluded by is an Associate Core Scientist in the Division of Neuroscience and of the MRI support core. Responsibilities include development of data acquisition and analysis protocols in coordination with investigators conducting MRI-related research on NHP research subjects, and training staff within the MRI support core and in investigators' laboratories in the implementation of the acquisition and analysis procedures. Oversees routine maintenance and quality control activities related to MRI Support Core instrumentation, and manages equipment upgrades in coordination with the MRI Support Core Oversight Committee. Administrative activities include oversight of billing, ensuring that studies are in compliance with MRI support core standard operating procedures, and providing interface between ONPRC and the Advanced Imaging Research Center (AIRC).

Senior Staff Scientist Excluded by Requester % Effort Income). Responsibilities include designing and constructing specialty radiofrequency (RF) coils for in vivo applications (he oversees the electronic shop, machine shop, and magnet cryogenic services at the AIRC). Dr. Excluded works closely with Excluded by Requester to expand research capabilities on the 3T MRI instrument, including the design and construction of application specific RF coils, routine quality assurance measurement, and user training and education.

Clinical Vet Tech 2 - Excluded by Requester % Effort Responsible for conducting MRIs, or the animal handling component of the majority of MRI Support Core procedures. Available as a backup to Medical Lab Technician ande to investigators who cannot provide an individual to perform either the MRI or animal handling components of an MRI experiment.

Financial Manager – Excluded by Requester % Effort Responsible for administering the Siemens service contract for all research-dedicated MRI instruments and manages the research agreement between OHSU and Siemens to support access to newly-available software through Siemens "Works in Progress" and "Customer to Customer" exchanges.

Director, AIRC - Excluded by Requester % Effort Dr. Excluded by Reques is Senior Scientist and Director of the AIRC on main campus. In his role on this project, Excluded by Requester coordinates with Excluded by to work with NHP investigators on all aspects of MR study design including acquisition and processing aspects Excluded by Requester develops procedures and tools for the routine application of MR guided histology of NHP brain. works to maintain and expand the AIRC data storage and computing infrastructure and improve access ease for the ONPRC MR users. Excluded by Requester maintains and expand the Master Research Agreement with Siemens Medical Solutions (the ONPRC 3T instrument vendor) and coordinate support of advanced packages that benefit the NHP MR users.

Staff Scientist - To be named (7.2 calendar months effort: 3.96 ORIP and 3.24 Program Income)
A research associate will be hired to assist with data management and analysis. This individual will replace Mr. Excluded by whose duties were to develop data analysis procedures in coordination with Excluded by Requester and investigators, to train staff in investigators laboratories in implementing data analysis procedures, to provide overall training sessions in monthly drop-in sessions, and to contribute freely-available software tools to the AIRC wiki web site. In future years, to capitalize on redundancies in data acquisition procedures between laboratories, this individual will create centralized tools for common NHP data processing procedures.

Medical Lab Tech - Excluded by Requester % Effort Excluded by Requester is a MRI Support Core technician who assists with all investigations that utilize Core instrumentation. As per the standard operating procedures, two staff members are necessary to conduct MRI experiments on NHP subjects: one individual operates the MRI system and the other performs the animal procedures, including induction of anesthesia, intubation for the administration of isoflurane, intravenous

catheterization when necessary, monitoring and recording physiological information from the sedated animal throughout MRI procedures, and recovering the animal from sedation. Excluded by Requester is trained to perform the MRI-system-related, or animal-handling-related procedures for all experiments conducted at the MRI Support Core. Additionally, Excluded by Requester performs monthly quality assurance measurements on MRI Support Core instrumentation, offers monthly safety training to investigators who request access to the MRI facilities, and manages scheduling of the MRI Support Core instrumentation.

SUPPLIES

Laboratory Supplies: Funding is requested for anesthesia, pressurized gasses to operate the isoflurane vaporizer, maintenance of the anesthesia machine (provided by manufacturer), and supplies for animal procedures such as intubation and intravenous catheterization.

Office & Admin Supplies: Funding is requested for routine office supplies such as paper, pens, folders, printing, etc.

OTHER EXPENSES

Equipment Maintenance Contract: Funds are requested for the Siemens service contract. This covers routine preventative maintenance and hardware-related repairs of the MRI system, as well as supplies and services to maintain cryogen levels.

Maintenance Contract -Software: Funds are requested for software license fees for software related to data management and analysis, including Matlab, Adobe products, and Analyze.

CORE SCIENCE SERVICES: MRI Support Core Income Table

Last Funded Year (53)

Source	Funding (direct costs)
P51 base grant support	$147,835.43
Program income derived from P51 base grant	216,392.35
Other Sources	0
Total	$364,670.78

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$228,553.85
Program income derived from P51 base grant	187,366.84
Other Sources	0
Total	$415,920.69

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

The MRI Support Core receives salary support and support for other expenditures from program income.

TITLE: DIVISION OF NEUROSCIENCE

CORE-SUPPORTED PERSONNEL:

Core Scientists (See Biographical Sketches, listed alphabetically in the Overview of the ONPRC)

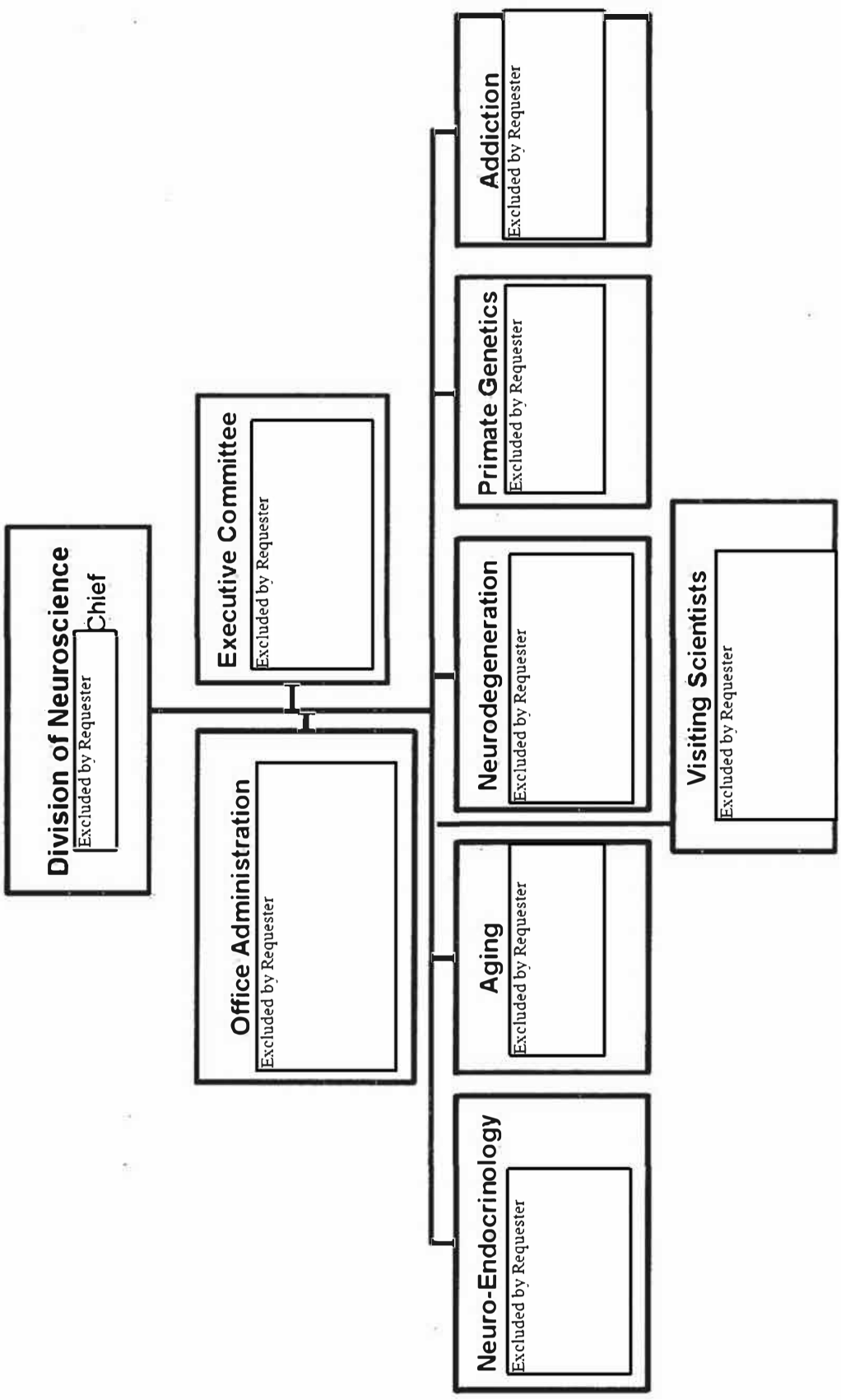
Excluded by Requester	Division Chief/Senior Scientist
	Assistant Scientist
	Senior Scientist
	Associate Scientist
	Associate Scientist
	Assistant Scientist
	Senior Scientist
	Senior Scientist
	Senior Scientist
	Senior Scientist
	Assistant Scientist
TBN	Associate Scientist
TBN	Assistant Scientist

* Indicates a partial core appointment

Administrative Support

Excluded by Requester	Administrative Assistant
	Administrative Coordinator
	Administrative Assistant
TBN	Administrative Coordinator

Division of Neuroscience
Organizational Chart



DIVISION OF NEUROSCIENCE PERSONNEL AFFILIATION AND ROLE

Core Scientists:

Excluded by Requester	Senior Scientist, Division Chief
	Senior Scientist
	Senior Scientist
	Senior Scientist
	Senior Scientist
	Senior Scientist
	Senior Scientist
	Senior Scientist
	Associate Scientist
	Associate Scientist
	Assistant Scientist
	Assistant Scientist
	Assistant Scientist
	Assistant Scientist

[1] Primary appointment Department of Behavioral Neuroscience, OHSU
[2] Joint appointment with the Division of Reproductive & Developmental Sciences, ONPRC
[3] Joint appointment with the Division of Diabetes, Obesity and Metabolism, ONPRC
[4] Primary appointment with the Advanced Imaging Research Center, OHSU
[5] Primary appointment, Department of Molecular and Medical Genetics, OHSU
[6] Primary appointment with the Advanced Imaging Research Center, OHSU
[7] Joint appointment with the Department of Physiology & Pharmacology, OHSU
[8] Joint appointment with the Department of Cell & Developmental Biology, OHSU
[9] Joint appointment, Department of Molecular and Medical Genetics, OHSU

Affiliate Scientists:

Excluded by Requester	Dept. of Biomedical Engineering, OHSU
	Dept. of Biomedical Engineering, OHSU
	Dept. of Physiology & Pharmacology, OHSU
	Dept. of Neonatology, OHSU
	Division of Neuroscience, ONPRC
	Dept. of Physiology & Pharmacology, OHSU
	Advanced Imaging Research Center, OHSU
	Dept. Molecular Microbiology and Immun., OHSU
	Dept. of Biomedical Engineering, OHSU
	Dept. Molecular Microbiology and Immun., OHSU

Visiting Scientists:

Excluded by Requester	Private Source

Staff Scientists:

Excluded by Requester	Staff Scientist 2
	Staff Scientist 3
	Senior Staff Scientist
	Staff Scientist 3
	Staff Scientist 2
	Staff Scientist 1
	Senior Staff Scientist
	Staff Scientist 2
	Staff Scientist 1

DIVISION OF NEUROSCIENCE

DESCRIPTION:

The Division of Neuroscience conducts research in the major scientific disciplines of neuroendocrinology, neurodevelopment, neurodegeneration, addiction, aging, obesity & energy utilization, and primate genetics. Each of these areas uses the NHP model to identify, define, and translate to the human condition fundamental and integrative mechanisms underlying nervous system dysfunctions and resultant disease states.

The Division has established itself as a national and international leader in the fields of pubertal development, macular degeneration, healthy aging, alcohol addiction, obesity/diabetes & energy balance and primate genetics. Further, we have emerging expertise in neural stem cells, motor system dysfunctions, epigenetics, primate informatics, *in vivo* MRI/MRS imaging and gene therapy. This research is organized along the lifespan of the organism, from *in utero* to death. Research incorporates over NHP models of human disease processes as well as normative studies of NHP to understand fundamental aspects of brain development, puberty, biological rhythms, immune senescence, and cognitive decline. The Division produces and utilizes specific technologies that optimize the information obtained from our NHP models, including novel methods to acquire *in vivo* imaging data, measure cognitive performance, introduce and assess genetic therapeutics, provide functional neuroanatomical links to behavior, and identify informative phenotypes for genetic analysis of traits. Our longitudinal approaches in our NHP models provides a key translational bridge between animal models and human diseases based in nervous system dysfunction where baseline values or the impact of environmental variables are difficult if not impossible to measure/control. This translational effort involves clinical partners at both our parent institution OHSU and in other national clinical centers. With the numerous high-throughput and repeated phenotypic measures gathered across all laboratories, the Division provides an unprecedented opportunity to provide tissue/data repositories as national resources for primate nervous system disorders. Further, these extensive phenotypic measures provide an opportunity to identify specific and sensitive biomarkers for disease progression or response to treatment.

The Division of Neuroscience also provides specialized training to graduate students, postdoctoral research fellows, and visiting scientists and these activities increase our interactions with the basic science departments at OHSU. Our faculty members hold appointments in, and actively contribute to, the three main OHSU Graduate Programs, namely, the Dept. of Behavioral Neurosciences graduate program and the cross-departmental graduate programs in Neuroscience and in Molecular and Cellular Biosciences. Finally, the Division serves as a regional, national and international resource for integrative neuroscience research because of its unique capabilities to conceptually and experimentally link neural functions of invertebrate and other vertebrate laboratory animal models to those of nonhuman and human primates.

RELEVANCE:

As the fundamental scientific discipline that defines how the nervous system develops, matures and maintains itself throughout life, neuroscience also holds the key to discovering ways to prevent or cure neurological and psychiatric disorders. Our scientists have made significant strides towards unraveling some of the basic mechanisms that govern nervous system function in normalcy and in disease. Collectively we have discovered new targets for intervention in neurodegenerative and demyelinating diseases; new approaches integrating functional brain circuitry with behavior; new technologies for imaging the development as well the loss of physical and functional connectivity in the brain; novel genes and genomic mechanisms contributing to disease risk; and new insights into normative nervous system functions in order to better define diseased states.

DIVISION OF NEUROSCIENCE SPECIFIC AIMS

The Division has established itself as a national and international leader in the fields of pubertal development, nicotine & alcohol addiction, metabolic disease, healthy aging, macular degeneration, neurodegenerative diseases and primate genetics.

Further, we have emerging expertise in therapeutic neural stem cell biology, motor system dysfunctions, epigenetics, primate informatics, *in vivo* MRI/MRS imaging and gene therapy in NHPs. This research is organized within the Division along the lifespan of the organism, from *in utero* to advanced age. Scientists in this Division utilize NHP models of human disease processes as well as normative studies of NHP to understand fundamental aspects of brain development, puberty, biological rhythms, immune senescence, and cognitive decline. The Division produces and utilizes specific technologies that optimize the information obtained from our NHP models, including novel methods to acquire *in vivo* imaging data, measure cognitive performance, introduce and assess genetic therapeutics, provide functional neuroanatomical links to behavior, and identify informative phenotypes for genetic analysis of traits. Our longitudinal approaches in the NHP models provide a key translational bridge between animal models and human diseases based in nervous system dysfunction where baseline values or the impact of environmental variables are difficult if not impossible to measure/control in humans. This translational effort involves clinical partners at both our parent institution OHSU and in other national clinical centers. With the numerous high-throughput and repeated phenotypic measures gathered across all laboratories, the Division provides an unprecedented opportunity to provide tissue/data repositories as national resources for primate nervous system disorders. Further, these extensive phenotypic measures provide an opportunity to identify specific and sensitive biomarkers for disease progression or response to treatment.

The Division of Neuroscience also provides specialized training to graduate students, postdoctoral research fellows, and visiting scientists and these activities increase our interactions with the basic science departments at OHSU. Our faculty members hold appointments in, and actively contribute to, the three main OHSU Graduate Programs, namely, the Department of Behavioral Neuroscience (BNS) graduate program and the cross-departmental graduate programs in Neuroscience (NGP) and in Molecular and Cellular Biosciences (MCB). Finally, the Division serves as a regional, national and international resource for integrative neuroscience research because of its unique capabilities to conceptually and experimentally link neural functions of invertebrate and other vertebrate laboratory animal models to those of nonhuman and human primates.

To advance our knowledge of primate nervous system development, function and disease we propose the following specific aims:

Specific Aim 1: To further our use of interdisciplinary research within the Division, ONPRC and OHSU to provide a deeper understanding of our NHP models of disease.

Specific Aim 2: Promote the further development and implementation of specialized technologies that will uniquely inform NHP research.

Specific Aim 3: Provide tissue and data repositories as national resources for NHP models of nervous system disorders.

Specific Aim 4: Continue to train the next generation of research neuroscientists using NHP models.

DIVISION OF NEUROSCIENCE RESEARCH STRATEGY.

SIGNIFICANCE.

As the fundamental scientific discipline that defines how the nervous system develops, matures and maintains itself throughout life, neuroscience also holds the key to discovering ways to prevent or cure neurological and psychiatric disorders. The evolutionary uniqueness of the primate nervous system is the basis for our advanced cognitive abilities and behavioral flexibility, and involves a complex integration of extensive neuroendocrine and neurophysiological parameters. The Division of Neuroscience at the ONPRC is a premier example of integrated research specifically focused on the primate nervous system to understand and translate disease processes. The success of the Division of Neuroscience is clearly dependent upon the resources and expertise provided by the Division of Comparative Medicine and the Animal Resources Program at the ONPRC. Without the combined effort of clinical and research specialized veterinary care, the expertise of the Surgical and Pathology programs, the behavioral sciences unit, and the specialized resource cores, our outstanding success in translational and integrative neuroscience would not be possible.

The research of the Division addresses some of the fundamental questions in primate neurobiology in the areas of neuroendocrinology, neurodevelopment, neurodegeneration, addiction, aging, and primate genetics. Each of these research areas uses the NHP model to identify, define, and translate to the human condition fundamental and integrative mechanisms underlying nervous system dysfunctions and resultant disease states. Further, with our breadth of expertise, the Division studies co-morbid burdens on disease processes such as drug exposure during brain development, gonadal hormonal status, neurodegeneration, aging and resilience to adverse stress. The ability to study the co-morbidity of disease processes on the overall health of the individual is an important use of NHP models that most other animal research is unable to address due to the longevity of the experimental designs, the ability to acquire multiple repeated measures and the resemblance of neurobiological adaptations of NHPs to human beings' response to disease.

Utilizing all the resources of the ONPRC, our scientists have made significant strides towards unraveling some of the basic mechanisms that govern nervous system function in normalcy and in disease. Collectively we have discovered new targets for intervention in neurodegenerative and demyelinating diseases; new approaches integrating functional brain circuitry with behavior; new technologies for imaging the development as well the loss of physical and functional connectivity in the brain; novel genes and genomic mechanisms contributing to disease risk; and new insights into normative nervous system functions in order to better define diseased states.

As NHPs play a unique role in translational science, the Division also has extensive collaborative efforts with clinical partners in endocrinology, geriatrics, ophthalmology, neurology, pediatrics, psychiatry, and cancer biology. Finally, the Division scientists provide unique and important service to the ONPRC through our stewardship of service and resource cores, participation in governing committees, dissemination of scientific findings to educated and lay audiences and training the next generation of neuroscientists using NHP models.

INNOVATION.

The research in the Division of Neuroscience is organized to address specific mechanisms of disease states and normative processes throughout the lifespan, from *in utero* to advanced age and incorporates NHP models of neuroendocrinology, addiction, neurodegeneration, aging, and primate specific genetic/genomic mechanisms. Although each scientist can be depicted as primarily involved with a single NHP model, the fact is that each Division Scientist is actively engaged in advancing multiple NHP models and therefore contributes cross-disciplinary approaches to many programmatic areas listed in below (and in our organizational chart).

Some key examples of cross-divisional and resource collaborations include: 1) Approaches to immune senescence (involving the division of pathobiology and the aging resource), 2) *In utero* exposure to neurotoxins and brain development (involving time-mated breeding, advanced imaging, the obesity resource, and the endocrinology core), 3) Longitudinal epigenetic changes in prefrontal cortical neurons involved in alcohol addiction using biopsied samples (the advanced imaging core, the genetics research program, the pedigreed rhesus population, and the surgical department), and 4) Several groups of visiting scientists staying for 1-2 weeks to make *ex-vivo* synaptic recordings from monkey brain striatum, brainstem, and amygdala (involving the Division's electrophysiology core, the Advanced imaging service core, the DCM surgical and pathology units). These examples help to illustrate how the Division utilizes all the resources of the ONPRC to conduct innovative research that is not possible anywhere else.

The breadth of the collective knowledge at the ONPRC has contributed immensely to the success of each Scientist and their innovative discoveries over the past 4 years. With the unique set of resources and expertise in NHP clinical science at the ONPRC, the Division has produced novel and innovative approaches to define, prevent and treat human diseases.

Neuroendocrinology: Innovations in Neuroendocrinology were aided by the Endocrinology Service Core, the Imaging service core, the Molecular Biology service core, the Genetics Resource Program, the Time-Mated Breeding Resource, the Obesity Resource, the Aging Resource, the DCM Surgical and Pathology units, and collaborations with the Division of Reproductive and Developmental Biology.

- Excluded by Request Discovered a novel mechanism by which the onset of puberty is controlled at a transcriptional level in the hypothalamus by a set of genes organized hierarchically in functional networks with internal coordination through epigenetic mechanisms Excluded by Requester
- Excluded by Requeste Discovered that ovarian hormones increase excitatory tone to serotonergic neurons in the midbrain by increasing dendritic spine growth. Further discovered that midbrain serotonin determines the sensitivity or resilience to stress, particularly as measured by menstrual cycle quality. Established the first postmenopausal monkey tissue bank (R24).
- Excluded by Reque Developed a therapeutic approach to rescue mutants of the gonadotropin releasing hormone receptor (GnRHR) by pharmacoperone drugs that correct mutant misfolded proteins. This work has developed a high throughput screen for identifying new pharmacoperones and helped identify the underlying basis of constitutive activity in GnRHR mutants. By extension this approach can result in the correction of defective protein in neurodegenerative disorders caused by misfolded molecules, including Alzheimer's disease, hypogonadism, and, most recently, alcoholism.
- Excluded by Reque Discovered new signals involved in the metabolic gating of reproduction, such as the neuropeptide CART in the hypothalamus. This discovery has opened new avenues for developing novel fertility and contraceptive agents. Helped develop the NHP model of maternal obesity and increased our understanding of mechanisms by which maternal high fat diet can confer obesity, diabetes and behavioral abnormalities to the offspring.

Neurodegeneration: Innovations in Neurodegeneration were aided by the Advanced Imaging Core, the Imaging Core, the Genetic Resource Program, the Japanese Macaque Animal Resource, the DCM Surgical and Pathology units, and collaborations with the Division of Pathobiology.

- Excluded by Helped to characterize a unique NHP model of inflammatory demyelinating disease in Japanese macaques that has the potential to unravel the etiology of multiple sclerosis in humans. This NHP model can serve as a translational platform to test novel therapies that prevent demyelination and promote remyelination. Demonstrated that a glycosaminoglycan, hyaluronan, accumulates in the NHP gray matter with normative aging but is elevated in white matter associated with age-related cognitive decline; found that blocking hyaluronidase promotes remyelination and improved axon conduction velocity.
- Excluded by Requester Developing gene therapeutic approaches to treat Huntington's disease with RNAi into the striatum of a NHP. This research relies on the innovative use of MRI imaging guiding surgical placement of the viral vector-based gene to gather preclinical information that is now moving into phase 1 clinical trial in humans. Excluded by Requester
- Excluded by Requester Discovered how to improve the brain response to cerebral ischemia (stroke) by preconditioning with various stimuli such as brief periods of ischemia, and low doses of endotoxin (lipopolysaccharide, LPS) and non-methylated CpG oligodeoxynucleotides (ODNs). Discovered that the brain's response to stroke injury is completely reprogrammed in the setting of prior preconditioning, leading to a novel response dominated by the expression of anti-inflammatory cytokines that are known to be neuroprotective (e.g. TGFβ and IFNβ). With NHPs has begun a translational research program around neuroprotection in stroke using candidate therapeutics.
- Excluded by Designed a method to measure Drusen damage based on fundus photographs of rhesus eyes, an important step in establishing a NHP model of age-related macular degeneration. Established a correlation between microscopically determined changes in dendritic arbor complexity and measurements of MRI *in utero* brain growth. Demonstrated the retention of mutant GnRH receptors in the endoplasmic reticulum and their release by pharmacoperones is associated with transport to plasma membrane and gain of function.

Aging: Innovations in the aging program were aided by the Aging animal resource, the Advanced Imaging service core, the genetics service core, the endocrinology service core, the DCM surgical unit, the behavioral suites in the animal sciences building and collaborations with the Division of Pathobiology.

- Excluded by [redacted] Developed a multidisciplinary approach to help understand how age-related hormonal changes negatively impact the decline of cognitive function and sleep in the elderly. This approach was novel due to the meticulous capturing of circadian gene expression in key brain areas and the adrenal. Also was the co-founder (with Excluded by Requester Director of Geriatrics, OHSU) of the OHSU Healthy Aging Alliance composed of >60 researchers and clinicians to efficiently translate aging innovations from molecular studies to clinical applications.
- Excluded by [redacted] Provides flexible and innovative oversight of the unique NHP aging resource. This resource has been a gateway to our understanding of the effects of aging on the neuroendocrine axis, the efficacy of hormone replacement paradigms on cognition in males and females, the effect of innate immunity manipulation for minimizing ischemia (stroke) damage, the exploration of immune senescence, and the examination of white matter perturbations in the brain.
- Excluded by [redacted] Demonstrated beneficial effects of estrogen replacement therapy on short-term working memory and on visual attention in a rhesus model of menopause. Characterized two macaque models of age-related macular degeneration, the leading cause of blindness in the elderly, and shown their morphological and molecular similarity to the human disease. Defined genetic parallels between rhesus and human age-related macular disease that has led to preclinical studies on stem cell therapy, in collaboration with investigators at the Casey Eye Institute (OHSU). These studies show that retinal transplantation of both neural progenitor cells and stem cell-derived retinal pigment epithelial cells have good survival and did not impair retinal function.

Primate Genetics: Innovations in the primate genetics program were aided by the Molecular Biology Core, the pedigreed rhesus population, the Japanese Macaque Resource, the DCM surgical unit, and collaborations with the Divisions of Pathobiology and Reproductive and Developmental Biology.

- Excluded by [redacted] Identified risk alleles associated with NHP models of age-related macular degeneration, alcohol addiction, multiple sclerosis and infertility. Has also developed a high-throughput approach to screening the rhesus genome for identifying disease risk, parentage and geographic ancestry.
- Excluded by Requester Discovered that chromosomal rearrangement in the gibbon is higher than in other primates and optimized the study of the gibbon genome to discover a transposable element that is a composite of other transposable elements (termed LAVA). The analysis of LAVA will provide insight into how transposable elements are formed and are activated in the genome. This research will have direct application in cancer biology and fundamental evolutionary processes.
- Excluded by Reques Developed a 1,289-member pedigree of Indian-origin rhesus macaques designed for large-scale genomic/genetic analysis of disease phenotypes. This pedigree has a corresponding biobank of blood samples and body measures to enable extensive phenotyping of biomarkers or risk factors for most of the diseases modeled at the ONPRC. These resources have already been used to demonstrate first-ever findings of significant heritability in ONPRC rhesus macaques for multiple phenotypes associated with complex disease, and will be extremely useful for discovering specific genes/genetic pathways that influence these phenotypes.

Addiction: Innovations in the addiction program were aided by the Endocrine service core, the Genetics service core, the Molecular Biology service core, the Advanced Imaging service core, the imaging service core, the Timed-mated Breeding resource core, the DCM surgical and pathology units and collaborations with the Divisions of Pathobiology and Reproductive and Developmental Biology.

- Exclude d by Req Developed the first animal model of an alcoholic drinking phenotype using rhesus and cynomolgus NHPs. This model recapitulates the key aspects of alcoholic drinking including voluntarily drinking to physical dependence and has identified behavioral, physiological and genetic risk factors for heavy drinking as well as documented inflammatory damage to heart, liver, bone and immune systems. An innovative necropsy protocol allows, for the first time in a NHP, the *ex vivo* synaptic recording of key brain areas believed to be involved in addiction. Established the first NHP alcohol tissue bank (R24) to advance translational research. Excluded by Requester

- Excluded by Discovered that vitamin C supplementation to pregnant rhesus monkeys could prevent the effects of prenatal nicotine exposure on lung development and asthma and this discovery has now led to a multicenter clinical trial in pregnant smokers. Is currently testing the hypothesis that a particular SNP found only in NHP and humans in the acetylcholine receptor alpha 5-subunit will increase the addiction to nicotine and co-morbid addiction to alcohol.
- Excluded by *In vivo* imaging of *in utero* brain growth with diffusion weighted MRI. This innovative research has an extremely high potential of translation to *in utero* studies of the human fetus as no surgical or adverse chemical exposure is necessary. This technique is currently being applied to the effects of NHP maternal alcohol on the fetal brain growth, with the promise to better understand critical periods of vulnerability that results in fetal alcohol spectrum disorders. Also innovative is the longitudinal measure of brain function in NHPs with the fMRI procedure known as functional connectivity MRI that reflects the robustness of brain circuitry. These studies are being applied to the NHP model of alcohol self-administration and the NHP model of brain aging, with the objective of translating directly to studies of cognitive decline in human populations ongoing at OHSU. Excluded by Requester

Diabetes, Obesity and Metabolism:

- These notable accomplishments are outlined in detail in the new Division's Scientific Component and are not repeated here. However, it is important to note that the progress and innovation of this group of investigators (Excluded by Requester occurred within the outstanding environment of the Division of Neuroscience and Excluded by Requester etains a cross-appointment in the Division of Neuroscience.

APPROACH

reviewers' comments

Progress Report:

Appointments and Departures: In December 2011, after a national search, Excluded by Requester was appointed as the Head of the Division of Neuroscience. Excluded by Requester took over the responsibilities of Division Head from Excluded by Requester who was founding Head of the Division and served in this capacity for 24 years (1987-2011). Excluded by was recruited to OHSU in 2005, with joint appointments in the Department of Behavioral Neuroscience (Professor with tenure) and the Division of Neuroscience, ONPRC (Senior Scientist) and has extensive experience in overseeing large research programs and serving on key university committees (outlined in Excluded by Narrative). The recruitment of Excluded by Requester included the resources to recruit two additional Core Scientists to the Division, one at the Associate Scientist level with expertise in computational biology/bioinformatics and another at the Assistant Scientist level with expertise in functional synaptic mechanisms of neural circuitry. The strategic planning for these recruits is outlined in the Approach section.

During the last five years two additional Core Scientists were recruited to the ONPRC with appointments in Neuroscience. Each of these Assistant Scientist appointments followed a national search. Excluded by Requester was recruited in 2009 to provide additional expertise in neurodegeneration, gene therapy, and motor system-based dysfunctions. Excluded by background is in Huntington's disease and the motoric function of the striatum in motivated behavior. Excluded by Requester was jointly recruited in 2010 by the Dept. of Behavioral Neuroscience at OHSU with ARRA supplemental funding to a P30 grant to increase translational efforts in NHP genomic research. Excluded by research background is on transposable genetic elements using the gibbon small ape as a model organism. She also brings the Division needed expertise in epigenetic modification and building informatics pipelines for interpreting epigenetic alterations related to disease states. Several affiliate and visiting scientists have been appointed in the Division and these are listed as the end of the Core Scientists narratives and at the end of this component.

The most significant departures actually remain at the ONPRC, and these are Excluded by Requester Excluded by Requester who now comprise the new Division of Diabetes, Obesity and Metabolism (DOM, established September, 2012). This is a well-deserved recognition of their contributions to the ONPRC, the OHSU and the scientific community. The new Division continues to collaborate extensively with the Division of Neuroscience, and Excluded by Requester are cross-appointed in the Division of Neuroscience. Another departure was Excluded by Requester who left the Division in 2010 to pursue a career as an informatics consultant at a local health care network.

Major Accomplishments: The Division of Neuroscience was created 25 years ago with the purpose of bringing to the ONPRC new research programs that would maximize the potential of NHP models for the understanding of human nervous system function. An initial goal of the Division was to build research programs that focused on developmental neuroendocrinology/neurodevelopment and collaborate with the Division of Reproductive Sciences, sharing expertise, specialized reagents, resources, and funding opportunities. Research directions evolved to include the entire lifespan from *in utero* to advanced aging, and incorporate models of fetal drug exposure, aberrant HPA/HPG response, obesity, addictive disorders, stroke, cognitive decline and neurodegeneration. During the past 4 years our scientists have made significant strides towards unraveling some of the basic mechanisms that govern nervous system function in normalcy and in disease. A detailed contribution of each Scientist is provided in their narrative statements. Here we highlight the success in funding, publications, collaborations and service to the core grant in the past 4 years (2009-2012):

Funding: The Division of Neuroscience has been extremely successful in acquiring external funding for our research from the NIH, DOD and NSF as well as from non-governmental foundations and industry (Figure 1). Every one of our Core Scientists primarily appointed in the Division (n=12: 9 primary and 3 cross-appointed) is funded by an external source.

The formation of the new Division of Diabetes, Obesity and Metabolism (DOM) naturally removed their funding from the Neuroscience Division and this decrease is reflected in Figure 1: the difference between January-September 2012, when DOM was within the Division of Neuroscience and the 'present' funding at the time of this submission. Noticeable is the decrease in Industry funding, while foundation and federal funding remain strong. The amount of potential funding in our pending grants is very strong, reflecting the confidence and enthusiasm of our scientists for peer-reviewed acceptance of our novel and innovative NHP models.

Currently, the Division's funding without the Division of DOM includes 41 separate awards, over half (24) of them with a start date in 2011-2012. From the NIH, there are currently 24 grants representing 8 different NIH Institutes and Centers (NINDS, NIAAA, NIHLB, NICHD, NEI, NCI, ORIP, Fogerty). Of the NIH current awards, 18 have a Division Scientist as PI and these include 11 R01s, one R21, one R24, one R00, two U01s, one T32, and one D43; there are five awards where Division Scientists are co-Investigators or subcontract PIs (P51, P30, P60, R21, R24). The remaining six NIH grants are awards to our Affiliate Scientists.
The Division also has nine awards from eight different foundations (e.g. Private Source
Private Source
Private Source
Finally, the Division currently has one award from the DOD, one from the NSF and three from industry Private Source
Private Source

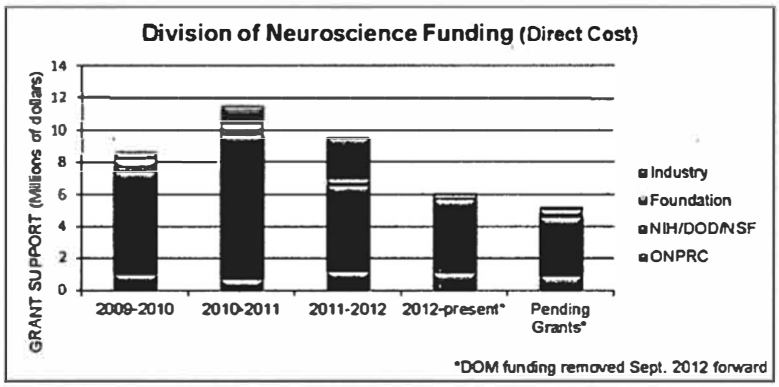


Figure 1. Neuroscience Funding

Thus it is clear that the research programs within the Division of Neuroscience are very well funded with more than half of the awards issued during the past year and with $4 million in pending applications. Our success in funding during the past few years and into the future is based on our unique, innovative and translational NHP models, an increase in the number of awards with cross-disciplinary aims and involving multiple Division Scientists as key personnel, and the outstanding facilities and cores provided by the ONPRC and the P51 core funding.

Publications: To date, the Division has a total of 294 unique publications in the past four years, including 260 peer-reviewed articles, 33 chapters/reviews and one textbook contributed by 12 Core Scientists and four Affiliate Scientists. Abstracts were not counted. The publication rate shows a steady increase over the past 4 years and our trajectory shows that in 2012 we have increased by a third our publications/year from 2010 (Figure 2). Perhaps even more notable is the number of publications in which there are multiple authors from the ONPRC (16/91 to date in 2012) and authorship with member of the OHSU medical school campus (20/91 to date in 2012). Since these are unique (not repeated) counts, over 40% of our current publications (2012) are clearly from collaborative projects at the ONPRC and OHSU (Figure 2A).

Another important feature of our publications is a majority of the publications (156/294) were from NHP studies over the past 4 years (Figure 2B). Finally, our publications appear in the most prestigious journals including Nature Neuroscience, Science Translational Medicine, Journal of Clinical Investigations, Annals of Neurology, Genome Research, Molecular Therapy, Proceeding of the National Academy of Sciences, etc. About 5 publications/year occur in Journals with an impact factor over 10 and the average impact factor the Journals we have published in over the past 4 years is 5.1. This average may be higher as our 2012 articles also occur in new journals that have not yet been ranked, but are highly regarded such as Frontiers in Psychiatry and Frontiers in Neuroinformatics.

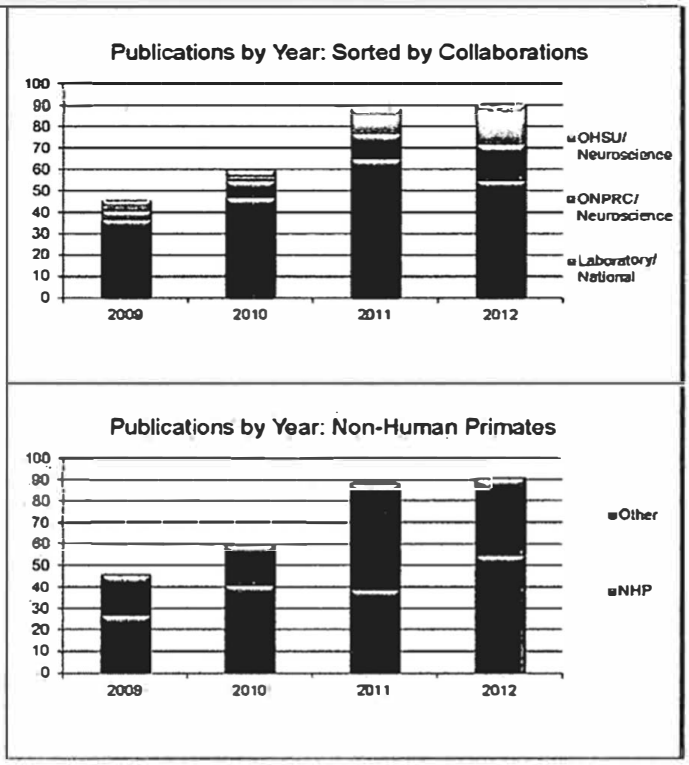


Figure 2. Publications by Division scientists during the last 4 years of Core grant support (2009-2012) A) showing collaborative papers (B) showing the number of publications using NHP models.

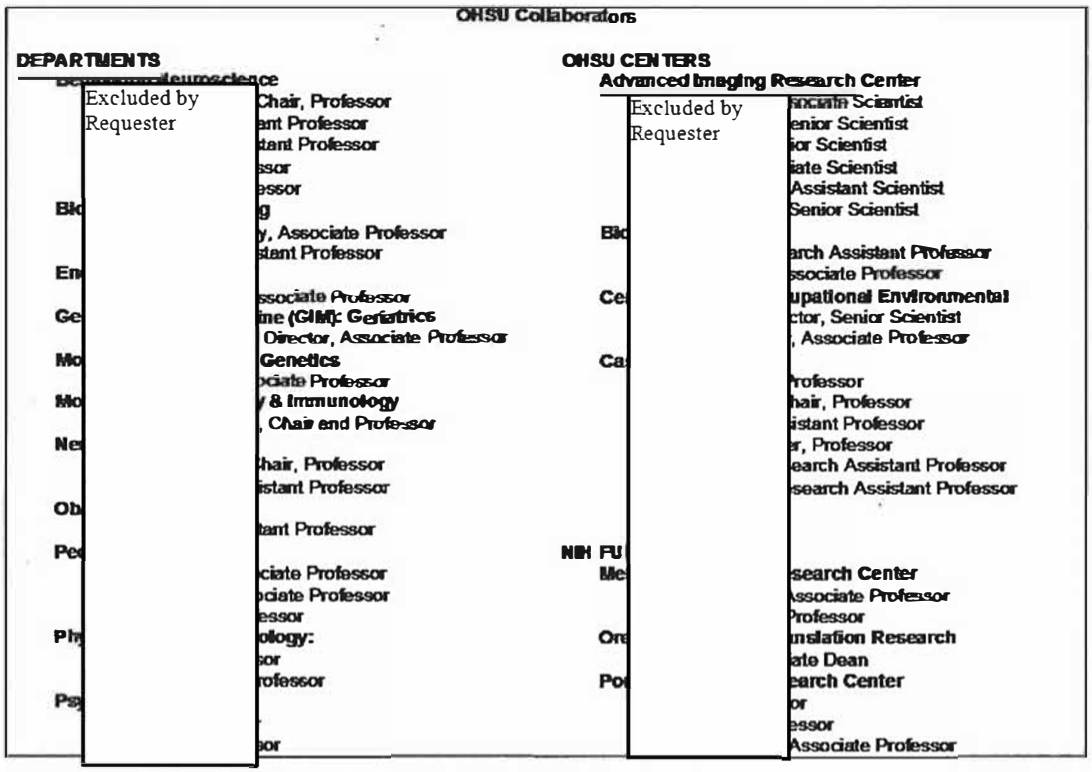


Figure 3. OHSU Collaborators

Collaborations: As shown by our publications, during the last 4 years our collaborations have been extensive and diverse, with scientists at OHSU, elsewhere in the US, and in other countries.

Within OHSU, these collaborations are named in the table. National collaborations involved researchers throughout the United States. International collaborations include institutions in Europe (Germany, England, France, Spain, Italy), Asia (China, South Korea), North America (Mexico and Canada), and South America (Argentina, Chile and Brazil).

In addition to these collaborations, our scientists contribute to the following programmatic (multi-PI) projects:

1. *"White matter damage in age-related cognitive decline"* NIH/NIA AG031892 (PI: Excluded by Requester U. Washington). Co-PIs: Excluded by Requester (ONPRC), Excluded by Requester (ONPRC), Excluded by Requester (OHSU)
2. *Genetics and Genomics Working Group of the Nonhuman Primate Research Consortium* (NHPRC). Co-PIs: Excluded by Requester (ONPRC), Excluded by Requester (ONPRC)
3. *"Portland Alcohol Research Center"*, NIH/NIAAA P60 AA010760 (PI: Excluded by Requester OHSU). Co-PI: Excluded by Requester
4. *"Integrative Neuroscience Initiative on Alcoholism: Stress and Anxiety of Alcohol Abuse"* NIH/NIAAA U01 AA013641(Administrative Core PI and Consortium Coordinator: Excluded by Requester Co-PIs: Excluded by Requester (ONPRC), Excluded by Requester (ONPRC), Excluded by Requester (ONPRC)
5. *"Gibbon Genome Research Consortium"* (PI: Excluded by Requester
6. *"Methamphetamine Abuse Research Center"* (PI: Excluded by Requester OHSU). Co-PI: Excluded by Requester ONPRC)

Awards and Recognitions: As detailed in each of the narratives provided, the Division's scientists have received numerous awards and recognitions in the past 4 years. These include National and International presentations as plenary speakers, grand round speakers and symposia speakers; appointments as Editorial Board members of scientific journals; appointments on national and international peer-review committees and as advisory committee members; awards for scientific achievements from scientific societies; and guests on television & radio news and science shows.

Involvement of Division Scientists in Directing ONPRC Cores and Research Resource Programs: Our scientists serve as directors of several ONPRC service cores and research resources (listed below). A complete description of each of these Core/Programs can be found separate sections of this P51 application.

1. *Molecular Biology and Cell Culture Core* Excluded by Requester
2. *Imaging and Morphology Core* Excluded by Requester

3. *Genetics Core* (Excluded by Requester
4. *Collaborative Research Unit* Excluded by Requester
5. *Obesity Resource* Excluded by Requester
6. *MRI Imaging Resource* Excluded by Requester
7. *Primate Aging Resource* Excluded by Requester

Training in Neuroscience: During the past 4 years of Core Grant support (2009-present) the Division trained 12 high school students, 18 undergraduates, 3 high school teachers, and 36 graduate students in rotations with eight currently conducting their dissertation research with five PhDs earned. Finally, the Division has trained 22 postdoctoral fellows in this time.

The Division Scientists contribute to the Neuroscience Interdisciplinary Graduate Program, the Behavioral Neuroscience Graduate Program, and Molecular and Cellular Biosciences Graduate Program at OHSU. All Core Scientists are members of one or more graduate programs and all of them lecture in courses for medical and graduate students. In addition, several of our scientists serve on key committees important to the graduate programs such as curriculum committees, steering committees; admission committees and awards committees. Division scientists are members of various training grants, including the Reproductive Biology Training grant (Department of Physiology, OHSU), Neuroendocrinology Training Grant (PI: Excluded by Requester M.D., VIABR, OHSU), Molecular Genetic Basis of Human Disease (PI: Excluded by M.D., Dept. Molecular and Medical Genetics, OHSU), the Biological Bases of Drug Seeking Behavior (PI: Excluded by Ph.D., Dept. Behavioral Neuroscience, OHSU), the Biological Bases of Alcoholism (PI: Excluded by Requester Ph.D., Dept. Behavioral Neuroscience, OHSU), and the Multidisciplinary Training in Neuroscience (PI: Excluded by Ph.D., CROET, OHSU). Notably, three of our Scientists are directors of Training grants: Excluded by Requester is P.I. of the Neuroscience of Aging T32, Excluded by Requester is the P.I. of the Reproductive Biology T32 and Excluded by Requester is P.I. of the Fogarty International Training Grant.

Summary: The diverse expertise of our faculty and the special resources of the ONPRC have made the ONPRC a unique research institution for the pursuit of a variety of neuroscience studies. This expertise, initially in neuroendocrinology, now includes the fields of aging, neurodegenerative diseases, developmental neurobiology, addiction and primate genetics. In addition to its comprehensive range of studies across the lifespan, the Division's expertise moves vertically from molecular biology to whole animal physiology and behavior, exploiting both traditional and contemporary approaches to biomedical research. We are a very well-funded Division that is extremely active in disseminating our research findings though our publications, meeting presentations and invited addresses. We are dedicated to the use of NHPs as models of human nervous system disorders and in actively training the next generation of researchers. Finally, we are also very active in providing essential service to the ONPRC and OHSU as core directors, research resource directors, University committee members, peer-review committees, and public outreach.

RESEARCH PLANS FOR THE NEXT FIVE YEARS

Overview: The overall goal for the Division of Neuroscience in this renewal application is to further our use of NHP models to identify, define and translate to the human condition fundamental mechanisms underlying key aspects of primate nervous system dysfunction and resultant disease states.

Our research plan is an outgrowth of our scientific organization, our NHP models and past progress within the Division. This organization is centered on our faculty and their research programs, our NHP models and our opportunities for collaborative research. The Division's faculty now consists of 33 scientists. Of these, 10 are Core Scientists with primary appointments in the Division of Neuroscience and 3 are Core Scientists with joint appointments Excluded by Requester are joint appointed with the Division of Reproductive and Developmental Biology; Smith is primary appointed in DOM). There are 10 are Affiliate Scientists who have primary appointments at OHSU and there are 9 Staff Scientists and 1 Visiting Scientist.

Our research programs (primate genetics, neuroendocrinology, addiction, neurodegeneration, and aging) are dedicated to developing, defining and understanding our animal models (the center of Figure 4). These research programs are not exclusive categories as members of each program are also contributing to another research program. For example, across the entire Division every program incorporates some aspect of neuroendocrinology, primate genetics and stage of life.

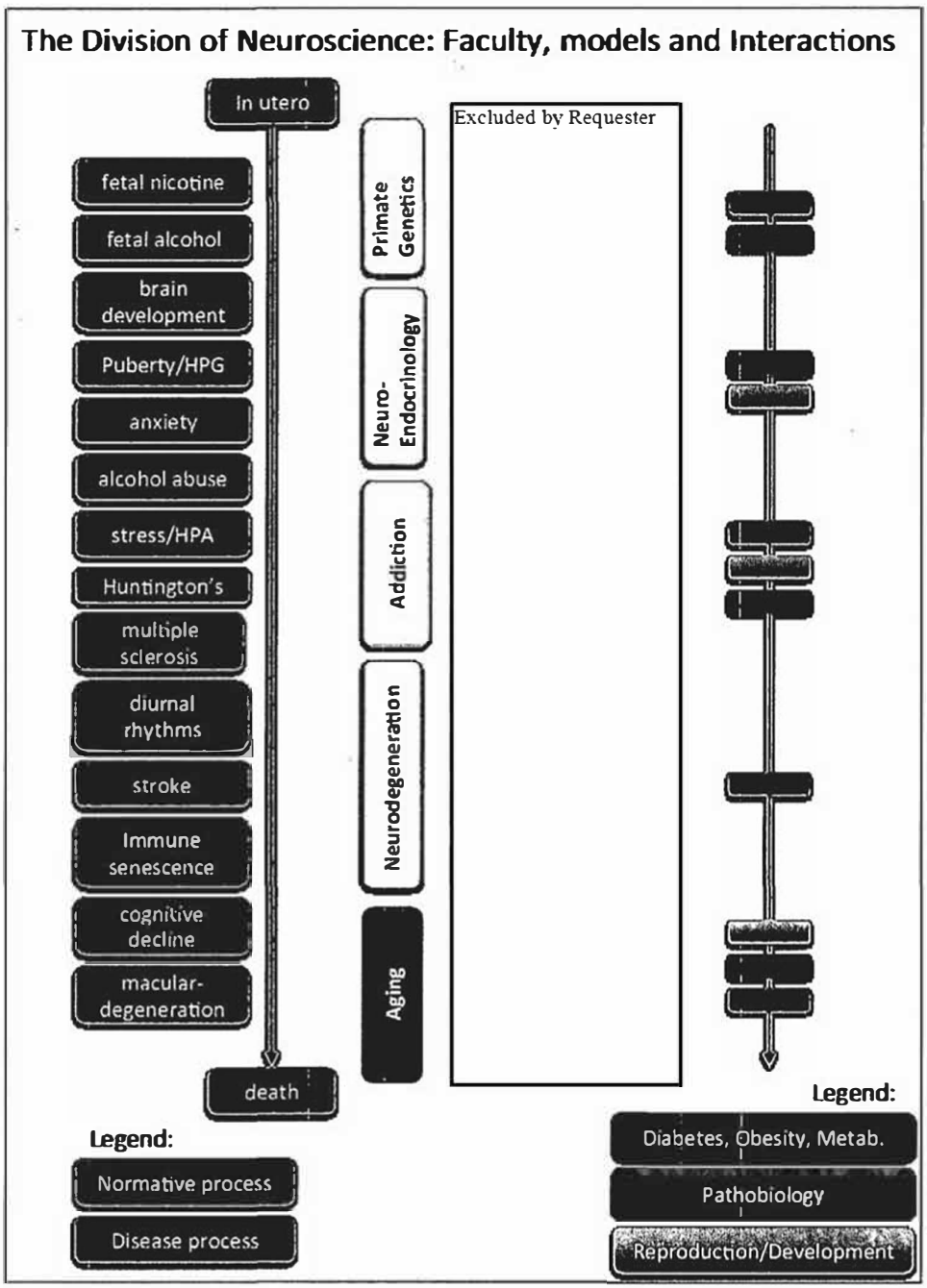


Figure 4. Neuroscience Faculty, Models and Interactions

Our NHP models are the focus of our scientific efforts. Our animal models encompass the lifespan of the primate and include aspects of normal development and aging depicted in green (brain development, onset of puberty and HPG axis function, HPA activity and diurnal rhythms, and immune senescence) as well as dysfunctional nervous system function depicted in blue (fetal nicotine and alcohol exposure, anxiety, alcohol abuse, Huntington's disease, multiple sclerosis, stroke, cognitive decline and macular degeneration). The future goals of each research program are listed below within the approach to Specific Aim 1.

Finally, within this organization, each research program has active collaborations with the other three Scientific Divisions at the ONPRC, color coded on the far right of Figure 3. Thus, every research program is highly integrated, not only in the Division of Neuroscience but also throughout the ONPRC.

Specific Aim 1: To further our use of interdisciplinary research within the Division and the ONPRC to provide a deeper understanding of our NHP models of disease.

Overall, as shown in Figure 3, we have an extensive set of animal models (14) and our collective future plan is not to increase the number of models but to provide a deeper understanding of each model by increasing the number of cross-disciplinary studies, applying new technologies that are uniquely informative for NHP models, and targeting recruitments of expertise in informatics and in functional neural circuitry.

Approach: Each research program in the Division has a collective set of research goals that directly address integrating information on our NHP models. Inherent in all programs is the use of the service cores and animal resources provided by the ONPRC.

Primate Genetics: This is an ONPRC-wide research program with its 'home' in the Division of Neuroscience where it was first established during the previous review cycle. The program has established a diverse portfolio of collaborative genetic and genomic research investigations that directly inform and discover genetic and epigenetic contributions to disease states addressed with our NHP models. In the next 5 years this program will: 1) Identify risk polymorphisms for disease, particularly promoter variants for transcription factors that alter

gene expression as novel genetic risk factors. An example is the investigation of SNPs in hypothalamic oligomenorrhea/amenorrhea, 2) Identify risk polymorphisms in unlinked genes that collectively increase risk for disease (i.e., genetic load). An example is in serotonin and CRH signaling in HPA-axis dysregulation, a key factor in anxiety, depression, post traumatic stress disorder (PTSD), and addiction, 3) Apply family-based gene mapping strategies to an extended pedigree (~1,300 macaques) to discover risk genes for neurodegeneration, neuroendocrine and disorders of inflammation, and 4) Provide longitudinal epigenetic investigation of genome-wide changes in methylation patterns in response to environmental challenges. An example is epigenetic changes in paired blood and brain samples prior to and throughout the course of chronic heavy alcohol consumption.

Addiction: This research program addresses alcohol and nicotine addiction, two of the three leading causes of preventable death in the USA. The program utilizes the propensity of NHPs to self-administer psychoactive substances in a repeated manner that recapitulates addictive disorders in humans. In the next 5 years this program will: 1) Identify key neuroendocrine aspects of the risk for heavy alcohol drinking, particularly as related to HPA-axis response, menstrual cycle quality and immune system regulation of inflammatory cytokines and chemokines, 2) Explore a genetic basis of nicotine and alcohol co-morbidity by focusing on nicotinic receptor SNPs specific to risk for smoking in humans that also occurs in cynomolgus monkeys, 3) Quantify the effects of in utero exposure to alcohol and alcohol-nicotine co-morbidity on fetal brain growth with in vivo MRI imaging, 4) Identify the neural circuitry changes associated with the transition from low and moderate drinking to an alcoholic drinking phenotype and the development of dependence, 5) Test pharmacotherapeutic interventions to decrease addictive alcohol drinking in partnership with pharmaceutical companies.

Neuroendocrinology: This program addresses selected aspects of the neuroendocrine system and examines the consequences that disorders of neuroendocrine regulation have on primate physiology. During the next five years studies will be pursued to: 1) Define the integrative mechanisms linking energy homeostasis, the neuroendocrine brain and the control of puberty. These studies are expected to not only enhance our understanding of how disorders in energy balance influence the timing and progression of puberty, but also provide novel insights into the role of epigenetics in this process, 2) Devise "pharmacoperones" as tools for the treatment of a range of genetic mutations, 3) Define the intracellular pathways that mediate the effects of steroid hormones, stress sensitivity and stress itself on serotonin and norepinephrine neurons, and 4) Gain insights into the role of the maternal environment in development of the NHP offspring, specifically as it relates to the risk of metabolic disorders.

Neurodegeneration: This program addresses the loss of neural function due to normal aging processes as well as disease processes. The program is heavily vested in assessing diagnostic and therapeutic strategies to treat human neurodegenerative diseases. An overall key goal is to deepen the knowledge of our already existing NHP models of neurodegenerative diseases. This will be accomplished in the next 5 years by: 1) Expanding our studies on gray and white matter changes with aging, using our colony of animals as models of normative human brain aging. These studies will be performed in parallel with studies on human age-related cognitive dysfunction, 2) Using targeted breeding of the affected animals in Japanese macaque colony showing symptoms of inflammatory demyelination to develop a stable NHP resource to study the etiology and pathophysiology of MS and related diseases, as well as to provide a platform for developing safe and efficacious pharmacotherapies to block demyelinating attacks and promote remyelination, 3) Continuing to pursue stem cell-based, viral gene therapy-based, and pharmacological approaches to treat neurodegenerative diseases, taking the best candidate reagents in in vitro and murine models to our unique non-human primate models of human conditions, and 4) Improving the brain response to cerebral ischemia (stroke) by further understanding the mechanisms through which 'preconditioning' can completely reprogram the brain's response to stroke injury. These studies will further develop the translational research program in neuroprotection by assessing candidate therapeutics.

Aging: This research program focuses on the neuroendocrine changes that occur in NHPs during aging, especially those associated with the onset of menopause. Using multi-disciplinary approaches, investigators are examining the mechanisms that underlie hormonal changes within the HPG axis and the HPA axis. Moreover, they are examining the physiological, behavioral, and metabolic consequences associated with these changes, and helping with the development of safe and effective alternative therapies to estrogen-based HRT. During the next 5 years this program will: 1) Elucidate the molecular mechanisms that regulate circadian hormonal patterns, and in turn contribute to sleep perturbations in the elderly, 2) Disclose the mechanisms by

which perturbed sleep wake cycles can negatively impact cognitive function and immune response, 3) Investigate if a high-fat Western diet can exacerbate the onset of age-related pathologies, 4) Establish a physiological hormone supplementation paradigm that can alleviate age-associated cognitive decline and attenuated immune response, and 5) Develop novel NHP models for human age-associated disorders, including hot flashes, retinal degeneration, and the impact of alcoholism on age-related declines in physiology and behavior.

Recruitments: We have identified and negotiated two new recruitments that will add key expertise to the Division in our next funding period. One is the recruitment of an Assistant Scientist with expertise in assessing neural circuitry/synaptic function. This position will provide needed expertise in electrophysiological and neurochemical techniques to advance our understanding of the underlying neuropharmacology of our NHP models as well as provide functional information to both the MRI and histological analysis of cellular function. This recruit can have expertise in any scientific area represented in the Division but will be expected to oversee the Division's electrophysiology core and provide training and collaborative efforts as needed. The second recruitment will be in the area of computational biology/bioinformatics. This individual is expected to have a fully developed research program using state-of-the-art computational approaches that will provide needed phenotypic integration within and across all our NHP models to compliment the genomic bioinformatics ongoing in the Genetic Resource of the ONPRC. Both these recruitments are expected to be complete in 2013.

Specific Aim 2: Promote the further development and implementation of specialized technologies.

The Division of Neuroscience has been in the forefront of establishing specialized, often cutting edge, research tools that are uniquely informative of the underlying mechanisms of normal and diseased primate neurobiology. For example, Excluded by Requester helped the ONPRC become a beta testing site for the monkey RNA chip from Affimetrix. Our intention is to continue this vital activity in the next funding period. Although we cannot accurately list all the technologies that may arise for NHPs in the next 5 years, we can provide the following list that is clearly on our horizon:

Resting-state functional connectivity MRI (rs-fcMRI) is based on spontaneous low-frequency (< ~0.1 Hz) signal fluctuations in functionally-related brain regions show strong correlations at rest, and offer the potential to provide a biomarker for brain disturbances in mental disorders that do not cause overt structural or physical abnormalities. Application of rs-fcMRI to NHPs is critical for characterizing the physiological mechanisms responsible for the measured signals, work that cannot be conducted in humans. Excluded by

Structural *in vivo* imaging annotated by *ex vivo* histology is necessary for in vivo development of MRI imaging as a diagnostic tool for abnormal neural development or neurodegeneration in humans. Excluded by Requester

Positron Emission Tomography (PET) is an in vivo imaging technique for brain glucose utilization and neurotransmitter receptor imaging. The OHSU was recently gifted resources to establish a PET center and NHPs will be key in developing diagnostic tools for neural disorders, for example neurodegeneration. Excluded by Requester Excluded by Requester

Advanced stereotaxic devises for intracranial injections are in constant need of improvement and evaluation for accurate placement of gene manipulations, evaluation of neural circuitry, and the neuroanatomical coordinates for biopsy samples. NHPs have the necessary resolution for evaluating these advanced devises. Excluded by Request Excluded by Requester

Advanced genomic resources, include both high-throughput data generation (whole genome sequence, exon-seq, methyl-seq, RNA-seq) and high-throughput data analysis (pipelines for macaque *de novo* and guided sequence assemblies, SNP variant discovery, and DNA methylation analysis). Excluded by Requester

Voltammetry is an approach to electrochemical detection of monoamines with a resolution that compliments electrophysiologcal and microdialysis approaches to studies of synaptic function. Excluded by Requester

Touch screens imbedded in the monkey housing units allows the remote scheduling of cognitive assessments without directly manipulating or disrupting ongoing behavior. Each unit contains a CPU wirelessly connected to a master computer for data collection. (Excluded by Requester

Remote annotation of behavior involves high-speed computing of both visual (video) and auditory (microphone) information from monkeys housed socially. Computer programs are being developed to replace human annotation of behaviors in order for the approach to feasibly impact husbandry practices and behavioral neuroscience protocols. Excluded by Requester

Viral vector delivery of gene for investigative or therapeutic purposes requires continual development. Both adenoviral and lentiviral approaches are being actively pursued. Excluded by Requester

Specific Aim 3: Provide tissue and data repositories as national resources for NHP models of nervous system disorders.

As the depth of knowledge on our NHP models of human normative and diseased processes over the lifespan increases, we are able to provide the larger scientific community with valuable research resources. These resources will go beyond banking and disseminating tissue to include genetic sequence data, pedigree information, longitudinal behavioral, endocrine and physiological data, and the opportunity to align proteomic and genomic data with tissue specific response to disease state or response to treatment.

There are 3 tissue banks in the Division to address this Aim:

1) Aging Tissue Bank Resource: Excluded by Requester

The aging program will continue to collect necropsy samples from male and female rhesus macaques > 10 years of age. The majority of samples are from aged animals (>17 years old), but there are also samples from middle-aged and young adult animals for cross-sectional studies. The primary focus is on brain tissue and banked as unfixed frozen dissections, or perfused-fixed brains to provide sections for immunocytochemistry. In addition there are peripheral tissues that are unfixed then frozen, including all major organs.

2) Monkey Alcohol Tissue Research Resource: Excluded by P.I.; www.MATRR.com): This R24 resource funded through the NIH/NIAAA is a state-of-the-art tissue resource for collecting, archiving and distribution of monkey tissues from an ethanol self-administration SOP. This resource provides novel data for hypothesis testing relating the risk for and consequences of alcohol consumption and serves to bi-directionally bridge the gap between rodent and human studies. This resource contains tissue from > 100 macaques (cynomolgus, rhesus) that chronically drank ethanol and control monkeys matched by age, sex, caloric content of alcohol, and/or laboratory housing. Tissues available at necropsy include viable *ex vivo* slices of informative brain areas (e.g., amgydala, striatum) for electrophysiological and neurochemical analysis of neuroadaptation to chronic ethanol exposure. The concurrently available informatics includes tissue tracking, data management, and a sophisticated integrated analysis of phenotypic information. Currently there are 33 laboratories across the USA and Europe that have utilized tissue from this resource.

3) Postmenopausal Monkey Resource: Excluded by Requester

This R24 funded through the NIH/OD addresses the controversial subject of when best to begin hormonal (estrogen) replacement therapy in postmenopausal women. The loss of ovarian steroids at menopause impacts many physiological systems in women, but the formulation and timing of hormone therapy is controversial. This resource will provide critical information regarding the optimal and safe use of estrogen therapy. This resource utilizes a postmenopausal model of aged ovariectomized rhesus monkeys on a Western diet and treated with placebo, immediate-estrogen or delayed-E replacement. There are longitudinal assessments of social behavior, activity, temperature, cognitive function, brain structure, immune function, fat accumulation, glucose metabolism and bone density. The postmortem tissue will allow assessments of coronary arteries, breast tissue, fat insulin sensitivity, and determine the cellular and molecular function of multiple neural systems.

Specific Aim 4: Continue to train the next generation of research neuroscientists using NHP models.

The Division of Neuroscience will continue to place a high priority on training research scientists. Although we actively engage in summer research opportunities for high school and undergraduate students as well as high school teachers, our main training efforts are focused on doctoral and post-doctoral students and this emphasis will remain in the next funding period. The number of graduate students has risen over the past 5 years, particularly since all of our Scientists have appointments in the academic departments and degree granting programs at OHSU. Each of the current training grants that has a Division Scientist as the PI (Neuroscience of Aging, Reproductive Biology and Fogarty International Training Grant) have plans for renewal in the next 5 year period. In addition, a new training grant in the Neuroscience of Brain Imaging is being planned with Excluded by Requester as the PI. Our capacity to train additional pre- and post-doctoral students is, in part, a reflection of our funding base. The healthy NIH funding that the Division enjoys predicts that we will be able to continue to attract and train outstanding national and international trainees.

Pages 921-936 (Publications) Removed – Excluded by Requester

EXTERNALLY FUNDED RESEARCH PROJECTS - NEUROSCIENCE

Excluded by Requester

Oregon National Primate Research Center
Postmenopausal Monkey Resource
NIH/OD - R24 OD011895
The goal of this project is to establish a postmenopausal monkey resource with aged ovariectomized rhesus monkeys on a Western diet.

Excluded by Requester

Oregon National Primate Research Center/OHSU
Investigating the association between hypomethylation of transposable elements and chromosomal rearrangements in Acute Myeloid Leukemia (AML) using next-generation sequencing
Private Source
This project investigates the relationship between DNA Methylation and chromosomal aberrations in one patient with Acute Myeloid Leukemia.

Excluded by Requester

Oregon National Primate Research Center
International Training & Research in Population & Health Training Grant
NIH/Fogarty International Center - D43 TW000668
Supports fellowships for Mexican and Brazilian nationals at ONPRC/ OHSU who are interested in pursuing an advanced degree or seeking sabbatical or postdoctoral support in the Reproductive Sciences.

Excluded by Requester

Oregon National Primate Research Center
Neuroscience Imaging Center at OHSU
NIH/NINDS P30 NS061800
The Neuroscience Imaging Center at OHSU provides state-of-the-art instrumentation for electron, fluorescent, and confocal microscopy as well as expertise in designing and analyzing imaging experiments, using 3 cores: 1) a Live-cell Imaging Core, 2) a Confocal Core, and 3) an EM Core.

Excluded by Requester

Oregon National Primate Research Center
Laser Capture Microdissection System STIMULUS
NIH/NINDS 1S10 RR027503
The ArcturusXT instrument is being used to procure pure populations of cells out of complex tissues, necessary to isolate RNA and proteins for gene expression analyses.

Excluded by Requester

University of Iowa
Determining the Feasibility of Gene Transfer to Ventricular Lining Cells of Primate Brain for Widespread Distribution of TPP1 Activity by CSF.
Private Source
This project investigates TPP1 expression levels throughout the brain and spinal cord following injection of AAV2-CLN2 into the lateral ventricle of the rhesus macaque.

Excluded by Requester

University of Iowa
Determining the Feasibility of Gene Transfer to Ventricular Lining Cells of Primate Brain for Widespread Distribution of TPP1 Activity by CSF.
Private Source
This project investigates TPP1 expression levels throughout the brain and spinal cord following injection of AAV2-CLN2 into the lateral ventricle of the rhesus macaque.

Excluded by Requester

University of Iowa
Viral delivery of CLN2 to the rodent and non-human primate brain: translational therapeutics for Batten's Disease
Private Source
This project investigates TPP1 expression levels throughout the brain and spinal cord following injection of AAV2-CLN2 into the lateral ventricle of the rhesus macaque.

Excluded by Requester

University of Iowa

Biodistribution and dosing of an AAV expressing RNAi construct for Huntington's disease: a pre-clinical collaboration between CHOP, the University of Iowa and the Oregon National Primate Research Center

Private Source

This project investigates the dosing, biodistribution and safety of HTT suppression in the rhesus macaque using the ClearPoint surgical device to define surgical parameters needed for a Phase I clinical trial investigating RNAi therapeutics in human HD patients.

Excluded by Requester

Oregon National Primate Research Center

Contrast Ultrasound Assessment of Microvascular Function in Insulin Resistant Non-Human Primates

NIH/NIDDK – R01 DK063508

Abnormal microvascular response at the skeletal muscle capillary level, as detected by contrast ultrasound assessment, may play a pathophysiologic role in the development of insulin resistance and type-2 diabetes mellitus.

Excluded by Requester

Oregon National Primate Research Center

The Gene Expression Profile of Neuropeptide Y Neurons in the Dorsomedial Nucleus of the Hypothalamus in Obese Mice

Private Source

Investigate the gene expression profile of Neuropeptide Y neurons in the dorsomedial nucleus of the hypothalamus in obese mice fed a high fat diet.

Excluded by Requester

Oregon National Primate Research Center

Washington NPRC-Collaborative Genetics Resources Unit

NIH P51 RR000166 Subcontract #584669 [University of Washington]

The Genetics Program component of the Washington National Primate Research Center Core grant supports the genetic research needs of individual studies, the animal breeding program and the International Studies Division

Excluded by Requester

Oregon National Primate Research Center

Gene-targeted SNP-discovery in rhesus macaques

NIH P24 RR017444 Subaward 34-5150-2033-006 [University of Nebraska Medical Center]

The objective of this project is to identify gene variations ("SNPs") throughout the rhesus macaque (M. mulatta) genome.

Excluded by Requester

Oregon National Primate Research Center

Washington NPRC-Collaborative Genetics Resources Unit

NIH/ORIP P51 RR000166 Subcontract #722387 [University of Washington]

The Genetics Program component of the Washington National Primate Research Center Core grant supports the genetic research needs of individual studies, the animal breeding program and the International Studies Division.

Excluded by Requester

Oregon National Primate Research Center

Genetic and Epigenetic Analysis of Alcohol Self-Administration in Monkeys

NIH/NIAAA U01 AA020928

This study investigates the effect of chronic alcohol use on DNA and gene expression and represent a novel approach to understanding the epigenetic consequences of alcohol use, and could indicate new directions for the treatment of alcoholism.

Excluded by Requester

Oregon National Primate Research Center

NHP Genome Banking and Genetic Working Group Projects

NIH/ORIP P51-RR000163 Sub-Project ID: 8740

These projects will develop resources for use in characterizing NHPs and sharing genetic material and information across all of the NPRCs.

Excluded by Requester Oregon National Primate Research Center
RC5 Excessive Alcohol Self-Administration in Primates
NIH/NIAAA P60 AA10760 Sub-project ID: 8251
The project will look at the relationships among the acute ethanol response, psychological factors, and ethanol intake at the end of the initiation process.

Excluded by Requester Oregon Health & Science University
Integrative Neuroscience Initiative on Alcoholism: Stress and Anxiety of Alcohol Abuse
NIH/NIAAA U01 AA13541 Excluded by (Consortium Coordinator)
The overall goal of this project is to provide a multidisciplinary battery of experiments designed to explore the neural mechanisms that link stress, anxiety, and excessive alcohol intake.

Excluded by Requester Oregon National Primate Research Center
Integrative Neuroscience Initiative on Alcoholism: Stress and Ethanol Self-Administration in Monkeys
NIH/NIAAA U01 AA13510
The purpose of this study is to characterize hypothalamic-pituitary-adrenal axis and neurosteroid response prior to, during and following heavy alcohol consumption in male cynomolgus monkeys.

Excluded by Requester Oregon National Primate Research Center
NMDA Receptor Modulation of Electrical Synapses in the Primate Brain
NIH/NINDS R21 NS 079110 [subcontract from Seattle Children's Hospital]
The project uses an innovative animal model system in which NMDA receptors are upregulated by voluntary alcohol consumption.

Excluded by Requester Oregon National Primate Research Center
Serum Biomarkers of Alcohol Self-Administration in Non-Human Primates
NIH/NIAAA R24 AA016613 [subcontract from Pennsylvania State University]
The purpose of this grant was to use longitudinal plasma samples from naïve through 12 months of ethanol self-administration to investigate plasma proteomic screens for biomarkers of (1) any use and (2) heavy use of alcohol.

Excluded by Requester Oregon National Primate Research Center
Monkey Alcohol Tissue Research Resource (MATRR)
NIH/NIAAA R24 AA019431
The purpose of this grant is to establish a unique post-mortem tissue bank for alcohol research.

Excluded by Requester Oregon National Primate Research Center
Involvement of the melacortin system in regulation of lipolysis and blood pressure
Private Source
The aim of the project is to examine the involvement of the melanocortin system in the regulation of lipolysis and blood pressure and to characterize possible alternative signaling pathways of MCRs in adipocytes.

Excluded by Requester Oregon National Primate Research Center
Mechanisms for Fetal Hepatic Programming in the Non-human Primate
NIH/NIDDK R01DK078590 [subcontract from University of Colorado]
The purpose of this project is to determine the effect of maternal high fat/calorie diet and metabolic health on the developmental programming of metabolic systems in the liver and muscle focusing on the reprogramming of the insulin signaling, lipogenesis/lipolysis, and gluconeogenesis pathways.

Excluded by Requester Oregon National Primate Research Center
The Impact of Maternal Health and Diet on Development of Fetal Metabolic Systems
NIH/NIDDK R24 DK090964
This project will investigate three dietary interventions designed to limit inflammation, oxidative stress, and substrate availability to the fetus to ultimately reduce the risks of early onset obesity and diabetes.

Excluded by Requester

Oregon National Primate Research Center
Maternal High Fat Diet and the Melanocortin System in Offspring
NIH/NIDDK R01 DK079194
This grant examines the impact of maternal obesity and high fat feeding during pregnancy in a nonhuman primate model on the development of brain circuitry, which controls appetite and energy homeostasis.

Excluded by Requester

Oregon National Primate Research Center
Maternal High Fat Diet and Melanocortin System in Offspring – Administrative Supplement
NIH/NIDDK R01 DK079194-S1
This project investigates the effects maternal health and diet on the development of the hypothalamic melanocortin system in the nonhuman primate.

Excluded by Requester

Oregon National Primate Research Center
Treatment of obesity and insulin resistance in the nonhuman primate
Private Source
The purpose of this study is to determine if treatment with an Ipsen compound could cause weight loss and improvement of glucose homeostasis in high fat diet induced obese nonhuman primates.

Excluded by Requester

Oregon National Primate Research Center
Maternal Diet Modifies the Fetal Primate Epigenome and Circadian Gene Expression
NIH/NIDDK R01 DK080558 [subcontract to University of Utah]
This proposal focuses upon the effects of a maternal high fat/calorie diet and metabolic health upon the fetal and postnatal epigenetic characteristics of circadian genes, which are expressed in fetal liver and hypothalamus.

Excluded by Requester

Oregon National Primate Research Center
Characterization of cardiovascular disease in diet induced obese monkeys
Industry Contract: Private Source
The purpose of this study is to characterize the progression and extent of cardiovascular disease in nonhuman primates fed a high fat diet.

Excluded by Requester

Oregon National Primate Research Center
Effect on serum biomarkers and insulin resistance in high fat and fructose-fed rhesus monkeys
Private Source
The purpose of this study is to investigate changes in serum markers of inflammation, metabolism and pro-coagulant activity during and following treatment with a Genentech compound.

Excluded by Requester

Oregon National Primate Research Center
Effects of humanized antibodies to ANGPTL4 on triglyceride and VLDL-levels in obese Rhesus Macaques
Private Source
This study will test the ability humanized ANGPTL4 antibodies to increase triglyceride clearance through activation of the lipoprotein lipase enzyme to determine whether these antibodies can effectively reduce triglycerides and VLDL and improve glucose homeostasis in obese nonhuman primates.

Excluded by Requester

Oregon National Primate Research Center
Immune therapy of insulin resistance in diet induced obese (DIO) Rhesus macaques with humanized antibody to NKG2D, a natural killer cell activating receptor.
Private Source
The purpose of this study is to investigate whether immune therapy targeting NKG2D can reverse the suppressed immune function and insulin resistance caused by chronic high fat diet (HFD), which would be a novel therapeutic for the treatment of obesity and diabetes.

Excluded by Requester

Oregon National Primate Research Center

Characterization of a GLP-1 receptor antibody in the nonhuman primate brain

Private Source

The purpose of this study is to perform an extensive characterization of the distribution of GLP-1 receptor immunoreactivity in the brain of the Rhesus macaque in order to provide insight into additional functional roles of GLP in the brain.

Excluded by Requester

Oregon National Primate Research Center

Effects of a novel PYY analogue, alone and in combination with a GLP-1 agonist, on food intake and body weight in obese rhesus macaques

Private Source

The experimental protocol will test two anorexigenic peptides in their ability to suppress food intake and decrease body weight: Peptide YY (PYY) and glucagon like peptide (GLP-1) analogs, either as monotherapy, as well as in combination, to determine the most efficacious treatment plan of obesity.

Excluded by Requester

Oregon National Primate Research Center

Characterization of endogenous glucose, cholesterol and fatty acid synthesis in high fat diet fed cynomolgus macaques.

Private Source

To establish baseline metabolic characteristics of cynomolgus macaques on high-fat diet and differentiate the effects of high-fat diet versus metabolic phenotype.

Excluded by Requester

Oregon National Primate Research Center

Effects of an Acceleron locally-acting test article on muscle growth in cynomolgous macaques

Private Source

The current study proposes testing a locally-acting antagonist to the TGFb superfamily ligands, which negatively regulate muscle mass in the cynomolgus macaque, in order selectively increase muscle mass in the treated tissue without being systemically bioavailable.

Excluded by Requester

Oregon National Primate Research Center

Actions of melanocortin agonists in obese primates

Private Source

Study objective is to determine if treatment with a melanocortin agonist that crosses the blood brain barrier can cause hypertension in a primate species.

Excluded by Requester

Oregon National Primate Research Center

Effects of Dopastatin compounds on cardiovascular responses and glycemic control lean Cynomolgus Macaques

Private Source

The purpose of the study is to compare efficacy of several dopastatin compounds on pituitary and pancreatic hormones and to monitor cardiovascular parameters in naïve cynomolgus monkeys.

Excluded by Requester

Oregon National Primate Research Center

Molecular Mechanisms of Human and Murine Beta Cell Proliferation and Regeneration
NIH/NIDDK U01 DK089572 [subcontract from Vanderbilt University]
This project will test the overall hypothesis that key genes and/or environmental stimuli which promote rodent β-cell proliferation can similarly induce the proliferation or regeneration of human or non-human primate (NHP) β-cells.

Excluded by Requester

Oregon National Primate Research Center

Maternal Hyperinsulinemia and fetal programming
NIH/NIDDK R01 DK061518 [subcontract from SUNY]
The purpose of this study is to elucidate the relationship between maternal health and diet on the development of the melanocortin system in the rat.

Excluded by Requester

Oregon National Primate Research Center

Maternofetal Signaling & Lifelong Consequences. Project 1: Gestational diabetes leads to cardiovascular vulnerability in offspring.

NIH/NICHD P01 HD34430 [subcontract to Excluded by Requester OHSU]

This is a project within a program project grant involving a nonhuman primate model of maternal diet induced obesity and insulin resistance/diabetes to determine: 1) if the pathological changes in fetal and infant cardiovascular system and placenta are related to the severity of maternal metabolic status; 2) the degree to which maternal metabolic status influences fetal and infant cardiovascular function, and 3) if infants of diabetic mothers have abnormal blood viscosity, erythrocyte rheology and leukocyte behavior that lead to abnormal microvascular function.

Excluded by Requester

Oregon National Primate Research Center

Neuroendocrine response to gastric bypass in nonhuman primates

NIH/NIDDK RC4 DK090956 Excluded by (MPI)

The overall goal of this project is to use the unique advantages of the NHP model to explore the cellular and molecular mechanisms underlying the effects of RYGB on energy balance and metabolic function.

Excluded by Requester

Oregon National Primate Research Center

NPY Feeding Circuits during Development.

NIH/NIDDK R01 DK060685

The main goal of this proposal is to use a multidisciplinary approach to determine if modification of the endogenous NPY system during postnatal development leads to abnormal body weight management during adulthood.

Excluded by Requester

Oregon Health & Science University

Anti-Thrombogenic Membrane-Mimetic Assemblies

NIH/NHLBI [subcontract thru Emory Univ.]

The goal of this project is to develop and evaluate blood contacting biomaterials that incorporate the bioactive protein, CD39, an enzyme that degrades ADP and therefore may inhibit platelet activation. Candidate biomaterials are being evaluated in the baboon arteriovenous shunt model.

Excluded by Requester

Oregon Health & Science University

Bio-Inspired Small Diameter Vascular Conduits

NIH/NHLBI [subcontract thru Emory Univ.]

The goal of this project is to develop and evaluate vascular substitutes whose mechanical properties will be optimized using biosynthetic and chemically modified collagen and elastin proteins.

Excluded by Requester

Oregon Health & Science University

CTRIP: MMP1-PAR1-based Interventions in Arterial Thrombosis

NIH/NHLBI [subcontract thru Tufts Medical Center]

This project is evaluating the therapeutic potential of a combined PAR1-MMP inhibitor molecule in acute thrombotic diseases.

Excluded by Requester

Oregon Health & Science University

Anti-thrombogenic membrane mimetic assemblies

Thru Beth Israel Deaconess Medical Ctr fr DHHS NIH Natl Heart, Lung, and Blood Inst

The goal of this project is to develop and evaluate blood contacting biomaterials that incorporate the bioactive protein, CD39, an enzyme that degrades ADP and therefore may inhibit platelet activation.

Excluded by Requester Oregon Health & Science University
Vascular tissue engineering: rational design using modeling
NIH/NHLBI – R01 HL095474
This tissue engineering grant seeks to document that cellular preconditioning in vitro can predictably improve outcomes in vivo - a principle that can be extended to other cell types and animal models - these results will validate rational design in general, and encourage studies with other constructs and test beds.

Excluded by Requester Oregon National Primate Research Center
Ethanol Discrimination in Aged Female Monkeys
NIH/NIAAA – F32 AA017040
Funding of this research resulted in data demonstrating that the GABAA receptor mechanisms mediating the discriminative stimulus effects of ethanol are stable across one third of the primate lifespan from young to mature adulthood.

Excluded by Requester Oregon Health & Science University
Genomics Alcohol Research Core
NIH/NIAAA - P30 AA019355
The major goal of the P30 proposal was to recruit a new faculty member (Excluded by Requester expertise in genomics/bioinformatics and non-human primate (NHP) research who would collaborate with investigators from the Primate Genetics Program to establish a research program that focuses on genomics and a macaque model of alcohol abuse.

Excluded by Requester Oregon National Primate Research Center
Signaling mechanisms of retinal bipolar cells
NIH/NEI – R01 EY018625
This project studies the signaling pathway in retinal ON-bipolar originates with a unique metabotropic glutamate receptor, mGluR6, which is found exclusively on the dendrites of ON-bipolar cells

Excluded by Requester Oregon National Primate Research Center
Molecular Mechanisms of Signal Transduction in Retina
NIH/NEI – R01 EY009534
This project hopes to gain a better understanding of the signaling pathway within the inner retina which should provide greater insight into the causes of other visual defects and would pave the way for development of new therapies for previously untreatable visual diseases.

Excluded by Requester Oregon National Primate Research Center
TRP channel expression and function in ON-bipolar cells
NIH/NEI – R01 EY019907
Using a combination of biochemical, immunohistochemical, and electrophysiological approaches, we have found that TRPM1 is necessary for the depolarizing light response of ON-bipolar cells, and further that TRPM1 is a component of the cation channel that generates this light response.

Excluded by Requester Oregon National Primate Research Center
Maternofetal Signaling and Lifelong Consequences/Overall
NIH/NICHD – P01 HD034430
In this project, we will study a model of gestational diabetes in monkeys that eat a high fat diet ad libitum.

Excluded by Requester Oregon Health & Science University
STX: A novel CNS selective estrogen receptor modulator (NeuroSERM)
Dean's Fund for Research Collaboration
The major goal of this project was to examine a rhesus macaque model of estrogen deprivation, mimicking heat flashes.

Excluded by Requester

Oregon National Primate Research Center

Toll-like Receptors: Novel targets of neuroprotection in ischemic brain injury
NIH/NINDS – R01 NS062381
This project examines the reduction of ischemic damage in the brain by pretreatment with toll receptor agonists in a cortical model of stroke.

Excluded by Requester

Oregon National Primate Research Center

Ethanol tolerance: In vivo spectroscopy and drinking in monkeys
NIH/NIAAA R21 AA018039
The goal of this project is to develop a magnetic resonance spectroscopy (MRS) tool to characterize the extent of direct interaction between ethanol molecular constituents of brain tissue.

Excluded by Requester

Oregon National Primate Research Center

Tim Upgrade for Nonhuman-Primate-Dedicated Magnetom Trio STIMULUS
NIH S10 RR027238
This shared instrumentation grant supported the upgrade of the ONPRC's nonhuman-primate-dedicated Siemens magnetom trio 3T MRI instrument with total imaging matrix (Tim) technology.

Excluded by Requester

Oregon National Primate Research Center

Characterizing the FASD cerebral cortex in utero with DTI
NIH/NIAAA R01 AA021981
The objective of these experiments is to develop fetal MRI strategies for characterizing the biological effects associated with the development of subsequent behavioral impairments in fetal alcohol spectrum disorder.

Excluded by Requester

Oregon Health & Science University

Contrast Ultrasound Assessment of Microvascular Function in Insulin Resistant Non-Human Primates
NIH/NIDDK R01 DK063508
In this project, our aim is to determine the contribution of abnormal microvascular responses to during the development of insulin resistance and diabetes mellitus.

Excluded by Requester

Oregon Health & Science University

Molecular Imaging of Inflammation in Atherosclerosis
NIH/NIHL R01-HL0787610
The purpose of this study is to determine whether contrast-enhanced ultrasound (CEU) can detect the earliest stages of artherosclerosis, and then to determine whether targeted CEU can detect early vascular disease in a non-human primate (macaque) model of obesity, insulin resistance, and artherosclerosis that closely resembles the human condition.

Excluded by Requester

Oregon National Primate Research Center

Neural Circuitry Responsible for Metabolic Inhibition of Adaptive Thermogenesis
NIH/NIDDK – R56 DK082558
This project seeks to understand the neural pathways and mechanisms that inhibit sympathetic outflow to brown adipose tissue which will provide a foundation for determining how alterations in these pathways contribute to overweight and obesity, and will represent an important step towards the development of therapeutic approaches to increase energy expenditure even in the face of dietary restriction and thereby combat obesity.

Excluded by Requester

Oregon Health & Science University

A phase-I/II study of IMC-A12 (anti-IGF-I receptor monoclonal antibody) in children with relapsed/refractory solid tumors
NCI/Children's Oncology Group ADVL0712
The goal of this study was to evaluate dose and safety margins for treatment with a therapeutic anti-IGF-IR antibody.

Excluded by Requester

Alterations in Sodium-Potassium ATPase Function: An Underlying Cause of Neurological and Behavioral Deficits in Rett Syndrome

Private Source

This is a one-year grant to study the involvement of a gene termed FXYD1 in the neuropathology of Rett syndrome (RTT).

Excluded by Requester

Oregon National Primate Research Center

RNA interference therapy for Huntington's disease targeting the hypothalamus: thinking outside the basal ganglia.

Private Source

This project investigates the use of RNA interference to prevent neurodegenration in the hypothalamus as well as associated metabolic and hormonal dysregulation in a mouse model of HD.

Excluded by Requester

Oregon National Primate Research Center

Determining the feasibility of gene transfer to ventricular lining cells of non-human primate brain for widespread distribution of TPP1 and SGSH via intrathecal delivery.

Private Source

This project investigates the biodistribution of lysosomal storage enzymes in the non-human primate brain following intra-thecal delivery of AAVs expressing either TPP1 or SGSH.

Excluded by Requester

Oregon National Primate Research Center

Systemic delivery of RNA interference using AAV9: pushing the envelope for a global delivery strategy to treat Huntington's disease.

Private Source

This project investigates the potential reduction of mutant HTT expression in the brain of transgenic HD mice following an injection of AAV9-RNAi constructs into the jugular vein.

Excluded by Requester

Oregon National Primate Research Center

RNAi therapy for Huntington's disease: safety & efficacy in the non-human primate
NIH/NINDS - R00 NS069798
This project investigates the creation of a viral vector-mediated non-human primate model of Huntington's disease and the subsequent assessment of RNA interference to prevent motor and cognitive deficits induced by the model.

Excluded by Requester

Oregon Health & Science University

Vitc to Decrease Effects of Smoking in Pregnancy on Infant Lung Function-CCCLead
NIH/NHLBI R01 HL105460
This project proposes a double blind, placebo-controlled study to determine if vitamin C supplementation (500 mg daily) can decrease the effect of maternal smoking in pregnancy on offspring pulmonary function (VC-SIP).

Excluded by Requester

Oregon Health & Science University

Role of Placental Insufficiency in Preeclampsia, IUGR, and Fetal Programming of Hypertension
R21 HD068896
Our novel approach uses a genetically engineered mouse model and an innovative new microbubble technology to test whether abnormal uteroplacental blood flow may be an underlying cause of preeclampsia and fetal growth restriction, which are common and life-threatening complications of pregnancy, and whether increasing VEGF expression in uterine spiral arteries ameliorates or exacerbates these conditions.

Excluded by Requester

Oregon Health & Science University

Central Regulation of Sympathetic Activity to Brown Fat
NIH/NIDDK – R01 DX057838
The major goal of this project was to understand the neural basis for the regulation of energy metabolism and body weight by neural circuits in the brain and spinal cord.

Excluded by Requester

Oregon Health & Science University

Central Sympathetic Regulation of Thermogenesis in Fever

NIH/NIDDK – R01 NS040987

The major goals of this project are to understand the neural circuits regulating body temperature and how they are engaged during the fever response.

Excluded by Requester

Oregon National Primate Research Center

Oregon Retinal Degeneration Center

Private Source

To establish nonhuman primate models of macular degeneration and to develop gene therapy treatments for retinal degenerative diseases, particularly methods for targeting the macula and cone photoreceptors.

Excluded by Requester

Oregon National Primate Research Center

Pilot Study of TUDCA Dosing and Pharmacokinetics in Nonhuman Primates

Private Source

The goal of this project is to determine the half-life of the neuroprotective bile acid tauroursodeoxycholic acid in rhesus monkey plasma after oral dosing and its accumulation in retina.

Excluded by Requester

Oregon National Primate Research Center

Evaluation of stem cell-derived retinal pigment epithelial cells for retinal disease therapy

NIH/NEI – R01 EY021214

To study the functionality of RPE cells generated from three different stem cell sources in vitro and after transplantation to the subretinal space, and the immune response to these cells in situations that mimic their clinical application.

Excluded by Requester

Oregon National Primate Research Center

Caloric Restriction and Aging in Non-Human Primates

NIH/NEI – R01 EY015293 [subcontract thru Columbia Univ.]

To examine aging changes in the eye, particularly the retina and lens, of rhesus monkeys and to determine if these changes are ameliorated by caloric restriction.

Excluded by Requester

Oregon National Primate Research Center

Retinogeographic Distribution of Secreted Retinoschisin When Delivered by AAV Vectors

Private Source

To conduct a preclinical study of retinal expression and distribution of the AAV-vectored retinoschisin gene in rhesus monkeys in preparation for a human clinical trial for retinoschisis.

Excluded by Requester

Oregon National Primate Research Center

Module II: Nonhuman Primate Models of Retinal Disease

Private Source

To establish nonhuman primate models of macular degeneration and to develop gene therapy treatments for retinal degenerative diseases, particularly methods for targeting the macula and cone photoreceptors.

Excluded by Requester

Oregon National Primate Research Center

Development of a Japanese Macaque Model of Dry Age-Related Macular Degeneration

Private Source

To develop a model of dry macular degeneration for use in preclinical testing of new therapies.

Excluded by Requester

Oregon National Primate Research Center

Leber Hereditary Optic Neruopathy: Gene Therapy Trial

NIH/NEI – R01 EY018600 [subcontract thru University of Miami]

To develop a gene therapy for Leber Hereditary Optic Neuropathy by testing safety and efficacy of AAV-mediated *ND4* gene delivery to the retina in rodent and primate models followed by evaluation in a human clinical trial.

Excluded by Requester — Oregon National Primate Research Center
Novel Mechanisms Underlying the Transsynaptic Control of LHRH Release
NIH/NICHD U54 HD18185 [subproject Excluded by
This project used a combination of genetic and neuroendocrine approaches to define the contribution of $GABA_A$ receptor-mediated inputs to LHRH neurons, and to examine the hypothesis that LHRH secretion is controlled by three novel genes involved in the regulation of excitatory/inhibitory inputs to the LHRH neuronal network.

Excluded by Requester — Oregon National Primate Research Center
Neural Control of the Prepubertal Ovary
NIH/NICHD R01 HD24870
This project is aimed at elucidating the role that neurotrophic factors of the nerve growth factor family play in the control of normal ovarian development in rodents, and the formation of polycystic ovaries in nonhuman primates.

Excluded by Requester — Oregon National Primate Research Center
Neuroendocrinology of Puberty and Sexual Development
NIH/NICHD R01 HD25123
The project was aimed at defining the importance that three newly discovered gene regulatory systems may play in hypothalamic glia-neuronal communication and the impact that they exert on the initiation of female puberty.

Excluded by Requester — Oregon National Primate Research Center
Molecular and Structural Bases of Hypothalamic Puberty
NIH/NICHD R01 HD13254 Excluded by Subproject PI
This project was aimed at understanding the physiological mechanisms responsible for the onset of puberty in humans. Studies proposed in Aim 3 were performed in Excluded by Requester laboratory.

Excluded by Requester — Oregon National Primate Research Center
RNA interference therapy for Huntington's disease: studies in non-human primates
NIH/NINDS RC1NS068280 Excluded by Requester PI Oregon site
This project investigated the short- and long-term safety and tolerability of reducing Huntington expression in the normal non-human primate as a step towards assessing RNA interference as a potential therapy for Huntington's disease.

Excluded by Requester — Oregon National Primate Research Center
The Systems Biology of Mammalian Puberty
NSF IOS-1121691
The goal of this proposal is to use a systems biology strategy to investigate the existence of a layer of repressive gene regulation that may play a fundamental, hitherto unsuspected, role in controlling the timing of mammalian puberty at the transcriptional level.

Excluded by Requester — Oregon National Primate Research Center
Inducing Stable Infertility by RNA Interference
Private Source Excluded by Requester PI Oregon site
This project is testing a newly developed peptide-modified viral vector to target RNA interference to the hypothalamus with the goal of inducing permanent sterilization in dogs and cats.

Excluded by Requester — Oregon National Primate Research Center
Reproductive Biology – Multidisciplinary Training Grant Marie Currie International Outgoing Fellowship_Spain
T32 HD007133
This project investigates the role of epigenetics as a link between nutritional status and the timing of female puberty.

Excluded by Requester

Oregon National Primate Research Center

Altering Energy Balance by Systemic Delivery of RNAi to the Neuroendocrine Brain

NIH/NIDDK R21NS081611

This project is aimed at developing a novel, minimally invasive method to manipulate hypothalamic neuronal function in a temporally defined and cell-specific manner using the melanocortin system of the arcuate nucleus as the prototype.

Excluded by Requester

Oregon National Primate Research Center

Cooperative Research on Infertility in Primates

NIH/NICHD – U54 HD018185

This projects focuses in the role that newly described transcription factors have in the control of GnRH release in non-human primates

Excluded by Requester

Oregon National Primate Research Center

Inducing Stable Infertility by RNA Interference -- Proof-of-Principal Studies

Thru University of Iowa from Private Source

This projects uses RNA interference and a newly developed viral vector to silence genes expressed in the hypothalamus and involved in the control of reproduction

Excluded by Requester

Oregon National Primate Research Center

Reproductive Biology-Multidisciplinary

NIH/NICHD – T32 HD007133

This is a grant that supports training of graduate students and postdoctoral fellows in reproductive sciences

Excluded by Requester

Oregon National Primate Research Center

Abeta Toxicity, ROS and Mitochondrial Dysfunction in Aging/Alzheimer's Disease

NIH/NIA – R01 AG028072

The purpose of this application was to investigate the role of amyloid beta and mitochondria in aging and Alzheimer's disease.

Excluded by Requester

Oregon National Primate Research Center

Neuroprotective Effects of Dimebon in Alzheimer's Disease

Private Source

The overall goal of this application was to study the protective effects of Dimebon in Alzheimer's disease.

Excluded by Requester

Oregon National Primate Research Center

Neuroprotection and Alzheimer's disease

Private Source

The purpose of this application was to study the protective effects of mitochondria-targeted antioxidants in Alzheimer's disease.

Excluded by Requester

Oregon National Primate Research Center

Dynamin-related protein I and neurodegeneration in Alzheimer's disease

Private Source

The purpose of this application is to investigate the role of Dynamin-related protein 1 in Alzheimer's disease pathogenesis.

Excluded by Requester

Oregon National Primate Research Center

Dynamin-Related Protein 1 and Mitochondrial Fragmentation in Alzheimer's Disease

NIH/NIA – R01 AG042178

The purpose of this application is to investigate the role of Dynamin-related protein 1 and amyloid beta in fragmenting mitochondria in Alzheimer's disease.

Excluded by Requester **PhD (MPI)** Oregon National Primate Research Center
Molecular Mechanisms Underlying NHP Pancreatic Beta Cell Failure, and Recovery
NIH/NIDDK R24 DK093437
This project will generate preliminary data on the transcriptional profile of non-human primate islets in preparation for a full R24 proposal.

Excluded by Requester
Molecular Mechanisms of Human and Murine Beta Cell Proliferation and Regeneration
NIH/NIDDK – VUMC 37010 [subcontract thru Vanderbilt Univ.]
This project will test the overall hypothesis that key genes and/or environmental stimuli that promote rodent β-cell proliferation can also induce the proliferation or regeneration of human or non-human primate (NHP) β-cells.

Excluded by Requester Oregon National Primate Research Center
Control of glucagon secretion by native and DPP-4-processed GLP-1
Private Source
The goal of this project is to evaluate the effects of DPP-4 inhibition on glucagon secretion in intact islets and in isolated alpha cells.

Excluded by Requester Oregon National Primate Research Center
Alogliptin effects on pancreatic islet function
Private Source
The goal of this project was to assess the effects of a DPP-4 inhibitor on isolated islet function and response to incretin hormones.

Excluded by Requester Oregon National Primate Research Center
Ex vivo culture of primate islets
ONPRC Pilot research grant
The goal of this project was to investigate the effects of oxygen tension and culture conditions on primate islet viability and function.

Excluded by Requester Oregon National Primate Research Center
High-fat diet-induced alterations in gene expression in the nonhuman primate
NIH/NCRR P51 RR000163-50S4
The goal of this project was to determine hypothalamic gene expression profiles and changes in the CSF proteome in monkeys subjected to a controlled high-fat diet.

Excluded by Requester Oregon National Primate Research Center
Herstatin: a novel cancer therapeutic
Pilot research grant, OHSU BioScience Innovation Program
The goal of this project was the development of a novel HER-2 gene product as a cancer therapy

Excluded by Requester Oregon National Primate Research Center
Collaborative MS Research Center Award
Private Source
The theme of this project is the investigation of mitochondrial dysfunction as a cause of axonal degeneration in MS.

Excluded by Requester Oregon National Primate Research Center
SNF5 mutation leads to intractable pain in schwannomatosis patients
U.S. Army Medical Rsch Acquisi – W81WXH-11-1-0413
The focus of this grant is to elucidate the molecular mechanisms that cause the development of intractable pain in patients with schwannomatosis.

Excluded by Requester

Oregon National Primate Research Center

Role of extracellular matrix in hypoxic-ischemic perinatal white matter injury

NIH/NINDS – R01 NS054044

This grant examined the roles of hyaluronan in perinatal white matter damage caused by hypoxia-ischemia.

Excluded by Requester

Oregon National Primate Research Center

Vascular endothelium-derived factors in Sturge-Weber syndrome hypermyelination

Private Source

This pilot project focused on testing for the presence of oligodendrocyte progenitor cells and myelination disturbances, as well as markers for neovascularizaton, in tissues from patients with Sturge-Weber Syndrome.

Excluded by Requester

Oregon National Primate Research Center

A pilot study to optimize spinal cord surgical procedures

Private Source

This contract was focused on testing the efficacy of a proprietary product on spinal cord injury recovery in non-human primates.

Excluded by Requester

Oregon National Primate Research Center

Therapeutic Remyelination Strategies in a Novel Model of Multiple Sclerosis: Japanese Macaque Encephalomyelitis

U.S. Army Medical Rsch Acquisition Activity – W81XWH-09-1-0276

The goal of this grant is to characterize an encephalomyelitis that resembles multiple sclerosis in Japanese macaques at the ONPRC.

Excluded by Requester

Oregon National Primate Research Center

White Matter Damage in Age-Related Cognitive Decline and Vascular Cognitive Impairment in a Nonhuman Primate STIMULUS

NIH/NIA – R01 AG031892 [subcontract thru Univ. of Washington]

The goal of this multi-PI project is to investigate the hypothesize that hypoxia-ischemia (HI) from VBI produces chronic oxidative stress in white matter that directly damages axons, myelin, and oligodendroglia (OL) progenitors, and that this injury stimulates proliferation of surviving OL progenitors that are impaired from normal maturation and myelination by astrogliosis .with high molecular weight hyaluronic acid (HA) accumulation.

Excluded by Requester

Oregon National Primate Research Center

Targeting Neurotrophic Factor Receptors to Block Pain in Schwannomatosis

Private Source

This project tests how loss of a gene implicated in schwannomatosis, called snf5, influences sensory behaviors in mice and whether agents that block Trk receptors reverse these effects.

Excluded by Requester

Oregon National Primate Research Center

Role of Hyaluronan in Ethanol-Induced Changes in Neurogenesis

Private Source

This grant serves to provide high school teachers with laboratory experience.

Excluded by Requester

Oregon National Primate Research Center

Novel hyaluronidase Inhibitors for the Promotion of Remyelination

Private Source

The goal of this project is to assess the toxicity and efficacy of novel hyaluronidase inhibitors for their ability to promote oligodendrocyte progenitor cell maturation and remyelination in a mouse model of demyelinating disease.

Excluded by Requester Oregon National Primate Research Center
Hyaluronan oligosaccharides for the promotion of remyelination
U.S. Army Medical Rsch Acquisition Activity W81XWH-10-1-0967
The focus of this grant is to examine the patterns of HA degradation products produced by OPC's in vitro, in chemically demyelinated white matter lesions, and within spinal cord lesions of mice with EAE.

Excluded by Requester Oregon National Primate Research Center
Regulation of TRPV1 in sensory neurons by SNF5--null Schwann cells
Private Source
The goal of this project is to identify the genes induced in sensory neurons by factors derived from Schwann cells with mutations in the Snf5 gene.

Excluded by Requester Oregon National Primate Research Center
CD44 and Hyaluronan as Regulators of Adult Neurogenesis
Private Source
The goal of this project is to determine if adult neurogenesis can be regulated by altering PH20 activity in the subgranular zone (SGZ).

Excluded by Requester Oregon National Primate Research Center
White Matter Damage in Age-Related Cognitive Decline
NIH/NIA – R01 AG031892 [subcontract from Univ. of Washington]
This project tests the hypothesis that specific changes linked to oxidative damage in the CNS myelin of humans contributes to age-related cognitive decline.

Excluded by Requester Oregon National Primate Research Center
Control of Gonadotropin Secretion during Lactation
NIH/NICHD R01 HD014643
These studies focus on states of negative energy balance that are associated with a suppression of reproductive function and will identify mechanisms by which a decrease in kisspeptin tone coupled with increased inhibitory input to GnRH cell bodies results in a decrease in GnRH neuronal excitability.

Excluded by Requester Oregon National Primate Research Center
Control of Gonadotropin Secretion during Lactation
NIH/NICHD R01 HD014643-26S1
The major goals of this project are: 1) determine which brainstem and hypothalamic neuronal populations, activated by the suckling stimulus, project to GnRH neurons in the hypothalamus; and 2) identify signals that regulate GnRH neuronal function during lactation, with a focus on signals that convey the status of negative energy balance.

Excluded by Requester Oregon National Primate Research Center
A nonhuman primate model for the link between childhood asthma and obesity
NIH/NHLBI R21 HL094922
To determine the mechanism by which childhood obesity leads to asthma in order to assist in developing new strategies to decrease the incidence of childhood asthma.

Excluded by Requester Oregon National Primate Research Center
Nicotine, nicotinic receptors and lung cancer
NIH/NCI/NIDA R01 CA151601
The purpose of this grant is to develop new therapies for lung cancer based by blocking the ability of nicotine and nicotinic receptors to stimulate lung cancer growth.

Excluded by Requester Oregon National Primate Research Center
Effect of Fetal Nicotine Exposure on Primate Lung
NIH/NICHD – R01 HL087710

The purpose of this project was to characterize the mechanisms underlying the effects of prenatal nicotine on lung development and develop therapies to block those effects.

Excluded by Requester

Oregon National Primate Research Center

Research Proposal for Evaluation of Tiotropium to Inhibit Lung Cancer Growth

Private Source

The purpose of this project is to investigate the potential use of tiotropium as a novel lung cancer therapeutic.

Excluded by Requester

Oregon National Primate Research Center

A Micro-CT Scanner for In Vivo Mouse Imaging and Ex Vivo Monkey Tissue Imaging
NIH/NCRR – S10 RR027499
To obtain funds to purchase a micro-CT scanner for *ex vivo* monkey imaging and *in vivo* mouse imaging.

Excluded by Requester

Oregon National Primate Research Center

Evaluation of Tiotropium to Inhibit Lung Cancer Growth

Private Source

The purpose of this project is to investigate the potential use of tiotropium as a novel lung cancer therapeutic.

Excluded by Requester

Oregon Health & Science University

Development of Toll-like Receptor Agonists as Neuroprotectants in Brain Ischemia
NIH/NINDS – U01 NS064953
The goal of this application is to develop TLR agonists as neuroprotectants in a preclinical model of nonhuman primate stroke. Studies will address optimal dosing and time windows for candidate molecules, as well as gender and age effects on stroke outcome.

Excluded by Requester

Oregon National Primate Research Center

The Consequences of Maternal Obesity and High Fat Diet Consumption on Offspring Energy Balance Regulation

Private Source

Funding for supplies to examine the impact of maternal high fat diet consumption on the development of the central serotonin system in fetal and juvenile nonhuman primates.

Excluded by Requester

Oregon National Primate Research Center

Perinatal Dietary Correlates of Autism Spectrum Disorder

Private Source

We hypothesize that exposure to a high fat diet (HFD) and maternal obesity during development impacts brain development, increasing the risk of the offspring developing autism, and we utilize a nonhuman primate model of HFD-induced maternal obesity to investigate the influence of maternal diet on offspring behavior.

Excluded by Requester

Oregon National Primate Research Center

Oregon Clinical Translational Research Institute (OCTRI) Pilot Project Grant. Project 5: Perinatal Dietary Predictors of Childhood Behavioral Problems and Temperament
NIH/NCRR 5 UL1 RR24140
Mental and physical health problems are related to early temperament. An important example is attention-deficit/hyperactivity disorder (ADHD), which is strongly related to temperament and exacts a heavy toll on children and families, yet has poorly understood etiology, therefore, identifying the early precursors and causal mechanisms for this behavioral problem is of central importance to eventual public health prevention.

Excluded by Requester

Oregon National Primate Research Center

Interacting Impact of Adrenal and Ovarian Aging on the CNS
NIH/NIA – R01 AG029612
The goal of this project is to examine how adrenal and ovarian steroids contribute to the maintenance of cognitive function in primates, and to elucidate the underlying neuroendocrine mechanisms.

Excluded by Requester

Oregon National Primate Research Center

Molecular Neurobiology of Aging

Private Source

This Partners-in Science program grant supports research training for a high-school teacher, Kirsten Thiel, in the field of primate neural aging.

Excluded by Requester

Oregon National Primate Research Center

Circadian Clock Mechanisms in the brain and peripheral organs

Private Source

This Partners-in Science program grant supports research training for a high-school teacher, David Herman, in the field of primate circadian physiology.

Excluded by Requester

Oregon Health & Science University

Neuroscience of Aging Training Grant
NIH/NIA – T32 AG023477
This is a training grant for graduate students and postdoctoral fellows specializing in neuroscience of aging.

Excluded by Requester

Oregon National Primate Research Center

Cognition in Rhesus Macaques in Relation to Age and Endocrine Status
NIH/NIA – R01 AG036670
The goal of this project is to examine how sex steroids contribute to the maintenance of cognitive function in male primates, and to elucidate the underlying neuroendocrine mechanisms.

Excluded by Requester

Oregon National Primate Research Center

Evaluation of novel inflammatory factors as biomarkers of risk for coronary artery calcification in rheumatoid arthritis.

Private Source

This project aims to assess whether two novel markers of inflammation, circulating $CD4^{+}CD28^{-}$ T cell frequencies and Lp-PLA_2 levels, predict coronary artery calcification independently of Framingham risk score in patients with rheumatoid arthritis at the Portland VA Medical Center.

Excluded by Requester

Legacy Health & Research

In vitro and In vivo efficacy of aged native glucagon; lack of cytotoxicity and preservation of hyperglycemic effect

Private Source

The goal of this project is to assess the stability and biological efficacy of glucagon formulations for clinical use in an artificial pancreas.

Excluded by Requester

Oregon Health & Science University

Epigenetics underlies long-term risk of relapse during abstinence
NIH/NIAAA - R01 AA021468
The proposed project will combine genetic, molecular, pharmacological, and behavioral strategy to identify pathways that are altered after a period of abstinence.

Excluded by Requester

Oregon National Primate Research Center

Role of stress in the development of the polycystic ovarian syndrom (PCOS): neuronal mechanisms

Private Source

Using a 3-dimensional culture system for macaque preantral follicles, a role for catecholamines in follicular growth and function, is being evaluated, with relevance to understanding infertility underlying polycystic ovarian syndrome in women.

RESOURCES

Division of Neurocience

Laboratory:

All twelve Core Scientists with a primary appointment in the Division of Neuroscience have between 750- 1,000 sq. ft. of laboratory space assigned to their programs. With the exception of Excluded by Requester the other nine scientists have their research quarters in the Facility Security Excluded by Requester laboratory is in the Facility Security,Excluded by Requester is in the Facility Security,Excluded by Requester research is performed in the MRI Core facility. Additional space for postdoctoral fellows and research technicians is provided in the laboratories.

The CMB building is a 21,000 sq. ft. facility designed for cellular and molecular biology work. As such, it provides about 10,000 sq. ft. of shared core space which includes rooms for tissue culture, darkroom, microscopy, electrophysiology and voltammetry, major shared equipment, radioisotopes, dishwashing and media preparation. A separate room adjacent to the laboratories is available and equipped for small animal surgery. Rooms are also available for the performance of terminal, in vivo experiments such as intracerebral tracking of pharmacological agents.

General equipment available to Division investigators includes:

Alcon Accurus vitrectomy machine for retinal surgery, Autoclaves (2), Beckman scintillation counter, Beckman super-speed centrifuge (2) and rotors, Beckman ultracentrifuges (1) and rotors, Biological Safety Cabinet class II (4), Bio-Rad C1000 Touch-Thermocycler (5), electrophoresis tanks, horizontal and vertical (1), Bioruptor sonicators (Diagenode) (3), Bulldog Bio Thermocycler, CO2 incubator for cell culture (9), Cold room freezer combination unit (2), Cooled benchtop centrifuge LEGEND XTR (Sorvall) (2), cooling bath, Crist non-human primate Stereotaxic Surgical Frame with micromanipulators (2), Custom designed DELL server (1), DELL MD 1200 direct attached storage array (1), dark room equipped w/automatic film developer, DIVA visual evoked potential recording system, Electrocardiograph, Electro-Diagnostic Imaging VERIS system for multifocal electroretinography, electrotransfer apparatus (4), Eppendorf Gradient Mastercycle-Thermocycler, ERG Tool system for electroretinography, Fisher Isotemp incubator, freezers (-20°C) (8), Full set of instruments for retinal surgery, Ganzfeld stimulator for electroretinography, Grass pre-amplifiers for evoked potential electrophysiology (4), Hansen Burian-Allen bipolar electroretinography electrodes (6), Heidelberg Spectralis Ocular Coherence Tomography retinal imaging system, Kopf Rodent Stereotaxic Surgical Frame (2), Laminar airflow working station, laminar flow hood (6), Leica VT1000S Vibrating blade microtome (2), Leica surgical microscope for retinal surgeries, Luminometer auto Lumat LB5593, Med Associates Open Field Chambers for rodent motor, cognitive and anxiety behavioral testing (4), Medicapture surgical video recorder, Mettler balance (2), microfuges (15), microscope-inverted for routine cell culture (4), MJ DNA engine Thermocycler (3), MRI Interventions non-human primate, MRI compatible surgical equipment with ClearPoint Software (allowing for state-of-the are non-human primate neurosurgery that take place in the MRI bore for enhanced precision), NHP automated computer touchscreen cognitive testing chambers (4), Noldus Ethovision videotracking system for motor and behavior analysis, Non-human primate behavioral testing chamber for cognitive (working memory) and fine motor skill tasks (Pick-up task, Lifesaver task), Nutator shaker, Olympus BX51 Fluorescent Microscope, Ophthalmic Imaging Systems digital retinal photography system, ovens (5), pH meter (4), Playroom with foodports for spatial learning testing, power supplies (14), Qubit fluorimeter (Invitrogen) (1), refrigerators (10), slab gel dryers (2), SliceScope Pro 1000 (This rig includes a microscope, faraday cage, computer system and software.), Sorvall centrifuge RT-6000, Sorvall LEGEND MICRO 21 Refrigerated, Sorvall LEGEND MICRO 21, spectrophotometric plate reader (2), Speedotron high-intensity photoflash units for visual stimulation (2), stereomicroscope (2), Stoelting Surgical Infusion Pump (3), Thermo Scientific HM430 Sliding Microtome, Thermo Scientific MaxQ HP Tabletop Orbital Shaker, UDT Instruments photometer, UgoBasile rodent Rotorod behavioral equipment for motor analysis, ultra-low temperature freezer (-85°C) (9), vacuum centrifuges (2), video microscopy system for measurement of calcium mobilization at the single level, vortexes (10), water baths (11), water shaker (3), Wisconsin General Testing Apparati for NHP cognitive testing (2),

Zeiss Axio Imager A2 upright microscope with fluorescence and dark-field capabilities, Zeiss axioskop 40 microscope with transmitted light and epifluorescence, Zeiss axiovert 40CFL cell culture microscope with transmitted light and epifluorescence (1), Zeiss digital retinal fundus camera.

Clinical:
N/A

Animal:
The Addictions program is largely located within a Specific Animal Location where the housing rooms have been outfitted with additional electricity, cable management, and secure anchoring of housing racks to the interior walls Each room can accommodate 4-6 housing racks, and each housing cage is outfitted with a drinking panel as part of the side wall. Each drinking panel is computer operated to capture eating and drinking patterns with 500 msec resolution and 0.1g or 0.1 ml accuracy. In addition, 12 panels have a modern touch screen allowing cognitive assessments, video streaming, and operant scheduling of drug availability upon intitation by the monkey or controlled by the experimenter. All data are streamed to a master computer for data analysis. In addition, the addictions program has 8 operant chambers that accommodate a primate chair and are equipped with response panels and food or fluid reinforcement. The chambers are used for drug discrimination procedures and other cognitive testing.

The Division has equipped 8 behavioral assessment rooms used by the aging, neurodegenerative, neuroendocrinology and addiction programs to measure a variety of cognitive and behavioral endpoints. Cognitive testing is conducted in a suite of 4 rooms in ASB II that are outfitted with sound-attenuating enclosures containing fans for airflow and cameras to unobtrusively monitor animals' performance. Each enclosure contains an automated cognitive testing chamber with a touchscreen and automated feeder system for food rewards. Each chamber is controlled by a Macintosh computer with custom software. In addition, a 4 m x 4 m open-field "playroom" in ASB III has constructed for observing animal behavior in freely moving animals. This space is equipped with a ceiling-mounted video camera linked to a Noldus Ethovision videotracking system, allowing remote monitoring and detailed analysis of behavior and quantification of motor parameters including distance travelled and gait speed. This flexible, multipurpose space has been used for a variety of studies, including measures of anxiety, motor aging and the assessment of spatial memory in a navigational task. Other testing rooms and playrooms with one-way observation windows in ASB III are used for drug discrimination studies, motor skills testing, and assessments of anxiety, temperment and social behavior. In sum, these tools provide quantitative measures of behavioral output, a critical goal of in vivo neuroscience research.

Other suites in ASB are outfitted with equipment for visual system assessments. An electrophysiology lab in ASB II with dedicated, isolated electrical circuits has stimulation and recording equipment for multifocal and full-field electroretinograpy and cortical visual evoked potential recordings. Rooms in ASB III have equipment for retinal imaging including a digital retinal photography system and a Spectralis Ocular Coherence Tomography (OCT) system. The OCT system, acquired in the last year, makes possible high resolution in vivo retinal imaging in infrared and autofluorescence modes and provides a critical endpoint for studies of retinal disease and gene and stem cell therapies.

A blind blood sampling facility is located in ASB I which uses Gilson peristaltic pumps and a swivel-tether system to remotely collect serial blood samples. The importance of this facility to Divison investigators is that it enables them to collect serial blood samples from upto 24 undisturbed animals across the entire 24-hour day, and thereby to monitor the animals' circadian hormone profiles in detail. It also enables them to remotely administer test compounds directly into the vascular circulation without disturbance.

Computer:
All Core and Staff Scientists have PC or Mac computers and full internet and linked printer access.

Office:
Each core scientist has an individual office.

Other:

All scientists have access to ONPRC Research Support Cores and OHSU Shared Resources. Those of particular importance to Division research include:

1. Endocrine Technology Support Core: This service is located in the ONPRC Research Building and performs many non-radioactive, enzyme-linked assays using the Immulite 2000 (Siemens) system for steroid and pituitary hormones.

2. Molecular Virology Support Core: This service performs specialized virology services that are critical for non-human primate (NHP) research, cost-effective, efficient, and state-of-the-art, along with expertise, infrastructure, and training. Key specialty areas are production of virus stocks, viral vectors, and viral antigens, virus identification and quantification in clinical specimens, as well as the provision and development of key reagents and standardized assays.

3. Imaging and Morphology Support Core: This service offers state-of-the-art instruments and technical support for advanced microscopy techniques, including confocal microscopy, Neurolucida and Marianas™ stereology and live cell imaging systems, laser capture microdissection and computers running ImageJ, FIJI, Volocity and Slidebook dedicated to off-line image processing and analysis.

4. Molecular and Cellular Biology Support Core: This core provides non-human primate-focused services in support of molecular biology and cell culture.

5. Magnetic Resonance Imaging Support Core: This service provides assistance in performing MRI exams of sedated NHP subjects. The primary instrument in the MRISC is the ONPRC 3T Siemens Tim Trio. The Core also manages a Caliper Quantum FX Micro computed tomography (microCT) instrument for in vivo rodent and ex vivo nonhuman primate tissue imaging.

6. Primate Genetics Support Core: This core provides services to support the genetic and genomic analysis of NHPs for both colony management and research applications.

NARRATIVE: Excluded by Requester

Division Appointment: Senior Scientist, Division of Neuroscience
Appointment(s): % Effort,Excluded by Requester at ONPRC and joint appointments in the Departments of Physiology & Pharmacology, Behavioral Neuroscience, Obstetrics and Gynecology, OHSU.
Effort on NHP-related studies: % Effort

Research Overview: Excluded by Requester research focuses on the effects of steroid hormones, stress and stress sensitivity on serotonin neurons in the dorsal raphe nucleus and norepinephrine (NE) neurons in the locus ceruleus of male and female NHPs. She employs multiple approaches *in vivo* (behavior, pharmacology challenges) and *in vitro* (immunocytochemistry, golgi staining and in situ hybridization all of which use image analysis, western analysis, genome arrays, PCR expression arrays) to perform basic and translational research on the serotonergic and noradrenergic systems in the midbrain. Due to the similarity of NHP and human midbrain, Excluded by Requester advances are promoting a better understanding of the neurobiology of hormone replacement therapy for menopause, the neurobiology of aggression, and the neurobiology of the stress response in individuals who are stress sensitive or stress resilient. Accomplishments in the past three years include: (1) discovery that ovarian hormones prevent DNA fragmentation in serotonin neurons and promote dendritic spine proliferation on serotonin neurons for increased excitatory glutamate signalling, (2) discovery that serotonin is not regulated by androgens and that serotonin does not regulate aggression in males; rather androgens increase norepinephrine output from the locus ceruleus, which increases aggression, (3) that serotonin function determines the sensitivity or resilience of an individual to stress, but norepinephrine in the locus ceruleus increases with stress. Therefore, the ratio of serotonin/NE function in the midbrain determines whether an individual will ovulate during moderate stress or immediately become anovulatory.

Contribution to Mission: Excluded by Requester provides vision and direction of her laboratory for psychoneuroendocrinology research at ONPRC. She was implemental in the establishment of the U54 NHP Reproductive Tissue Bank. She serves as a facilitator to core, affiliated and visiting scientists to exchange ideas, techniques and NHP models for the purpose of understanding and improving mental health in men and women. She provides very precious NPH brain parts and sections to collaborators outside of ONPRC. She mentors scientists in training, in the beginning, or at mid-level of their careers to foster their professional advancement. Excluded by Requester represents the center as an expert on hormone replacement therapy and the neurbiology of Functional Hypothalamic Amenorrhea (FHA) in women; and in the neurobiology of aggression in men. She has maintained uninterrupted NIH funding since 1981. She currently has an R01 on steroid regulation of serotonin in males; an R01 with Excluded by Requester FHA; an R21 on the regulation of NE in FHA, and she recently established an R24 supported Postmenopausal Monkey Resource with multiple investigator participation. Since May 2009 she has trained 3 postdoctoral fellows, 3 graduate students, 1 clinical fellow and 1 high school intern. In addition, she has served on the thesis committee of 4 graduate students and was invited to present her research at 2 symposiums, 1 medical school department and 2 community gatherings. Since 2009 she has published 17 peer reviewed papers, 2 review chapters and 20 abstracts. Collaborative interactions include:

Affiliate and Visiting Scientist list for Excluded by Requester

Name	Affiliation	Description
Excluded by Requester	PhD Staff Scientist	ONPRC	Behavior of NPHs
	PhD, Professor	OHSU	Neurobiology of aromatase
	PhD, Professor	Univ Pittsburgh	KISS1 expression
	hD, Scientist	WRPRC	Kisspeptin expression
	D, Chair Biology	Idaho State U	Gender, Gene profiling & Prozac
	PhD, Scientist	Univ Mississippi	Gender, Gene profiling & Prozac

NARRATIVE: Excluded by Requester

Division appointment: Assistant Scientist, Division of Neuroscience
Appointment(s): % Effort,Excluded by Requester in the Department of Behavioral Neuroscience at OHSU, and a joint appointment at the ONPRC.
Effort on NHP-related studies: % Effort,Excluded

Research Overview: Excluded by Requester research focuses on genome evolution and epigenetics. Her lab is specialized in gathering high-throughput data on structural variations and epigenetic modifications and studying the interplay between the two in the genome of human and non-human primates. Excluded by has a 10-years track record in comparative genomics and in the last seven years, she has been focusing on investigating the evolution of the gibbon genome. Gibbons display an increased rate of chromosomal rearrangements in comparison to human and most other primates. These species therefore represent a valuable model to study mechanisms underlying genome instability. Specifically, Excluded by is using the gibbon genome to learn about the evolution of human cancer genomes, also characterized by abundant chromosomal rearrangements and altered epigenetic marks. The Excluded by lab is also focusing on investigating transposable elements, sequences that compose a major portion (> 50%) of primate genomes and are able to replicate and move in the genome. Excluded by recently discovered a novel transposable element, called LAVA, which has a composite structure and includes fragments of other transposable elements commonly found in primate genomes. The analysis of the LAVA element promises to give many insights on how new transposable elements generates and become active in the genome.

Contribution to Mission: Excluded by Requester is a member of the ONPRC Extended Executive Committee which meets quarterly to discuss progresses and future directions to be taken by each of the ONPRC programs. She is also on the oversight committee of the Molecular & Cell Biology Core. In 2012 she helped the core to purchase the Illumina MiSeq sequencer, a next-generation sequencer that will be used by researcher at ONPRC/OHSU and will aid MHC-typing at ONPRC. Furthermore, given her deep interest in gibbons, she has been asked to coordinate the international consortium for the analysis of the gibbon draft genome. This opportunity allows her to interact with top scientists from the genomics and mobile DNA fields and achieve great exposure. Finally, Excluded by is part of the INIA stress consortium where she is developing tools to investigate the relationship between changes in DNA methylation and alcohol drinking in non-human primates. In 2012 Excluded by has been an invited speaker in two conferences and two departmental seminars; two of these invitations were at the international level (Japan and Germany).

Excluded by serves the ONPRC mission by developing new computational pipelines and experimental methods to investigate genome instability and epigenetics modifications in non-human primates. She is collaborating with Excluded by Requester at the ONPRC to investigate DNA methylation changes in the rhesus model for alcoholism. Moreover she established several collaborations. For instance, she is collaborating with Excluded by from UCSF to investigate population dynamics in gibbon species. Moreover, she is studying the activity of the LAVA element in collaboration with Private Source,Excluded by Requester

Excluded by Requester was recruited through a P30 core grant from NIAAA with the aim to develop the genomics and bioinformatics effort at both OHSU and ONPRC. She is an Assistant Scientist in the Division of Neuroscience, ONPRC and an Assistant Professor in the Dept. of Behavioral Neuroscience, OHSU. She also holds joint appointments in the Dept. of Molecular and Medical Genetics, the Dept. of Medical Informatics & Clinical Epidemiology and the Private Source Cancer Institute at OHSU. She has been co-mentoring a graduate student from the Behavioral Neuroscience program during his second year project. Moreover, she is advising and is in the thesis committee of a computer science graduate student and she mentored a graduate student from the bioinformatics program from one quarter. Finally, in order to reach out to younger scientists, she became part of the advisory board of the Portland Community College Bioscience Technology Program and she is also in contact with faculty from local collages (e.g. Reed College and Lewis & Clark College).

NARRATIVE: Excluded by Requester

Division appointment: Senior Scientist, Division of Neuroscience
Appointment(s): % Effort Excluded by Requester at ONPRC and joint appointments in Obstetrics & Gynecology and Physiology & Pharmacology, OHSU.
Effort on NHP-related studies: % Effort

Research Overview: Mutants of the gonadotropin releasing hormone (GnRH) receptor (GnRHR) are misfolded proteins that are usually misrouted, typically retained in the endoplasmic reticulum. We have developed a therapeutic approach that allows pharmacoperone drugs, small and target-specific molecules that diffuse into cells and stabilize mutant proteins in a structure that is acceptable to the quality control system (QCS) of the cell, to rescue these mutants and restore them to biological function. We described the molecular mechanism by which many of the mutants are misfolded and basis of the inefficiency of processing of the WT GnRHR in humans and NHPs, (the presence of Lys^{191} in the hGnRHR creates steric interference and decreases probability of the formation of the Cys^{14}-Cys^{200} bridge which is required for trafficking to the PM. We have identified the subtle chemical differences that influence plasma membrane expression in several different NHPs. We have identified 5 chemical classes of pharmacoperones and these act by bridging residues Asp^{98} and Lys^{121}, stabilizing an interaction between transmembrane segments 1 and 2. Among these 5 drug classes, which also interact as other sites on the receptor, are structures within each class that have various serum half-lives and affinity of binding. We have created an *in vivo* proof-of-principle model for this therapeutic approach and high throughput screens for identifying new pharmacoperones with improved characteristics. We have identified the underlying basis of constitutive activity in GnRHR mutants.

Contribution to Mission: Excluded by serves the Center as the Director of Research Advocacy Services with responsibilities defined under the administration Research Strategy, serves on the Policy Committee, Research Advisory Committee, Promotions Committee (Chair), IT Committee, and is PI on the Fogarty Training Grant in Population and Reproduction. He represents the Division Head (when he is unavailable) at Center meetings and participates in seminars. Since May 2009, he has trained a graduate student and 4 postdoctoral (Ph.D.) fellows. In 2009, he received the Media Award of the American College of Neuropsychopharmacology, in 2010 he was elected a fellow of the American Association for the Advancement of Science; in 2012 he was honored as the Distinguished Alumni of Baylor College of Medicine and was asked to give the Presidential Lecture at the Annual Meeting of the American Society for Reproductive Medicine, and in 2013 he will give the James Voogt Annual Lecture at the University of Kansas Medical School. Since 2009, he published 24 peer-reviewed articles, edited 52 books, gave 26 invited lectures and 3 TV/radio Interviews. Out of 27 collaborations, examples include:

Name		Affiliation	Description
Excluded by Requester	.D., Professor	U of TX MD Anderson Cancer Ctr	Design and Use of Mouse Model of Hypergonadotropic Hypogonadism
		ONPRC	Imaging of GnRH Receptor
		Private Source	High Throughput Screens
	,	U of Michigan	Molecular Modeling of the GnRH Receptor
	.,	OTRADI	High Throughput Screens
	MD, D.Sc., Head, Research Unit in Reproductive Medicine	Private Source	GnRH Action and Protein Rescue

NARRATIVE: Excluded by Requester Ph.D.

Division Appointment: Associate Scientist, Division of Neuroscience
Appointment(s): % Effort,Excluded by Requester appointment at the ONPRC.
Effort on NHP-related studies: % Effort

Research Overview: Excluded by Requester is a leader in the genetic characterization of macaques to inform and expand the translational study of non-human primate (NHP) disease models. Leveraging the recent advances in next generation sequencing (NGS) technologies, and in collaboration with other ONPRC investigators, she is analyzing the rhesus, cynomolgus and Japanese macaque genomic sequences to identify risk alleles associated with established disease models, including age-related macular degeneration, alcohol addiction, multiple sclerosis and infertility. She is also exploring the potential for new disease models in Chinese and Indian rhesus macaques, by identifying predicted functional/damaging alleles in genes having significant, replicated associations with human disease. Based upon discovered sequenced variants and their population allele frequencies, she is also developing high-throughput tools to more rapidly and efficiently screen rhesus macaque genomes, providing a consistent platform to survey macaque colonies for disease risk, parentage and geographic ancestry. Finally, Excluded by Requester is establishing new methods for the application of NGS analysis to NHP research. She recently completed a comparison of three commercial human exon-capture designs, to enable the efficient exon-capture and sequencing of macaque DNAs.

Contributions to Mission: Excluded by Requester supports the Mission by serving as the Director of the Primate Genetics Program (PGP) at the ONPRC, which includes three principal investigators, Excluded by Requester Excluded by Requester Their complementary research skills in genetics and genomics provide a platform for collaborative investigations into the genetic and epigenetic contributions to biomedical disease. The PGP also provide service to the ONPRC, supporting colony genetic management, providing bioinformatic/biostatistics research services, and developing and maintaining ONPRC genetic research resources, such as the ONPRC NHP DNA Bank, genetic databases and genotyping services (MHC analysis). Excluded by Requester provides oversight to the ONPRC IT services and the Molecular and Cellular Biology Core. She also serves as ONPRC representative to the Nonhuman Primate Research Consortium (NHPRC) Genetics and Genomics Working Group. She has been an active contributor to this consortium, co-developing SNP based assays that are now used across all 8 NPRCS for colony genetic management. She serves as an NHPRC advisor for the development of bioinformatics databases and analysis pipelines to facilitate sharing of NHP genetic data and standardizing genetic analysis methods to characterize NHP breeding colonies across the NPRCs.

Directly supporting the ONPRC's mission to utilize NHPs as a translational bridge for curing human disease, Excluded by Requester focuses on the genetic characterization of macaque models of human disease. Identifying genetic mechanisms that parallel those in human disease refines and informs the direct relevance of NHP models for translational study. Identifying novel genes and pathway offers opportunity to discover unrecognized pathways in human disease. Excluded by Requester works collaboratively with Excluded by Requester in characterizing the genetic and epigenetic contributions to alcohol addiction using the macaque model, with Excluded by Requester to identify genetic risk factors for macular degeneration in macaques, with Excluded by Requester to explore genetic risk factors for a demyelinating disease in Japanese macaques, and with Excluded by Requester to define the effect of aging on mitochondrial DNA variation.

Excluded by Requester holds a joint faculty appointment in the Departments of Molecular and Medical Genetics (MMG) at OHSU, where she interacts with graduate students and post-doctoral fellows. As a member of the MMG Graduate Program, Excluded by Requester co-directs a graduate course entitled "Genetic Mechanisms." Since 2009 she has served on the thesis committees of three graduate students at OHSU. She served as a co-advisor for a Masters Student in the Dept. of Medical Sciences at Boston University. She also mentored one postdoctoral fellow, one college student and three high school students.

NARRATIVE Excluded by Requester

Division Appointment: Chief, Division of Neuroscience, Senior Scientist
Appointment(s): % Effort, Excluded by Requester appointment at ONPRC and a joint (20%) appointment in the Department Behavioral Neuroscience, OHSU.
Effort on NHP-related studies % Effort

Research Overview: Excluded by Requester is a recognized leader in the field of alcohol research and has focused for over 25 years on the development of animal models to address the behavioral and pharmacological mechanisms in the risk for and consequences of alcohol addiction. These include assessing the neural receptor basis for ethanol's subjective effects (i.e., the cognitive state of intoxication) and how these effects change with chronic stress, menstrual cycle, developmental stage, the aging process and genetic load. Dr. Excluded by Requester has also established the only animal model of alcoholism that captures the phenotype of voluntarily drinking to physical dependence, opening up wide avenues of novel research for discoveries in prevention and treatment of alcoholic drinking. This breakthrough monkey model is informative of key neural circuitry in propagating habitual drinking, novel genetic and epigenetic factors in addictive drinking, translational information on global brain changes with in vivo imaging, and cognitive factors in self-administration. In the past four years Excluded by Requester has established active, funded collaborations with many Division members Excluded by Requester to study the NHP model of alcohol self-administration for genetic, epigenetic, *in vivo* imaging of brain dysfunction, neurogenesis and nicotine co-abuse mechanisms.

Contribution to Mission: Excluded by Requester serves as the Chief of the Neuroscience Division, providing a wide range of opportunities to contribute to Center operations. Excluded by Requester participates in strategic and operational activities as necessary to achieve ONPRC goals. Excluded by Requester also serves as a member of several ONPRC committees, which include Expanded Executive Leadership, Research Advisory Committee, Policy Group, and Animal Utilization subcommittee. Excluded by Requester also holds a joint appointment in the Department of Behavioral Neurosciences at OHSU as serves on the Appointment and Promotions committee and the Awards committee. For University-wide activities Excluded by Requester is a member of the Executive Committee for the Oregon Brain Institute, an organization established to promote neurosciences research from basic to clinical applications. On the National level Excluded by Requester is a member of the Advisory Council for the National Institute on Alcohol Abuse and Alcoholism (2009-2013) and an active member and past President of the Research Society on Alcoholism. Dr. Excluded by Requester also serves on three editorial boards and is an External Advisory Board member to NIH-funded collaborative research or training grants at the University of Colorado, University of North Carolina, Chapel Hill, and Yale University. Internationally, Excluded by Requester is a consultant for the Italian Institute of Medicine and a member of several international research societies on addictive
Excluded by Requester provides oversight of Divisional activities, including personnel, budgetary, and compliance as well as allocations of Divisional resources. These include creating and maintaining shared resources within the Division, such as instrumentation and software used by Division scientists, including a Divisional core electrophysiology facility. Excluded by Requester closely supervises the Administrative assistants assigned to the Division. Excluded by Requester also oversees the weekly Divisional seminar series and the monthly faculty business meetings. Overall, she provides collaborative support and/or mentoring as necessary to individual scientific programs.

Collaborations: Excluded by Requester has a large portfolio of collaborative efforts at the ONPRC, the OHSU, National and International laboratories. Excluded by Requester is a principal investigator in the P60 Portland Alcohol Research Center of OHSU and provides a key link between the mouse and human studies conducted in the center. As the Director of a large consortium on the Integrative Neuroscience of Alcoholism, she has established collaborative efforts with nine other Universities and Institutes to study the monkey model of alcoholism and this has led to the appointment of five visiting scientists to conduct *ex vivo* recordings at the ONPRC and then return to their home Institutions for data analysis and manuscript preparation. As the Director of a R24 Monkey Alcohol Tissue Research Resource (www.MATRR.com), Excluded by Requester provides over 35 national and international labs with tissue, endocrine and behavioral data from the monkey model and this has led high profile, collaborative publications in top tier journals and extended the use of the monkey model beyond neuroscience and into systems biology with hepatic, cardiovascular, and immunological implications.

NARRATIVE: Christopher Excluded by Requester

Division Appointment: Associate Scientist, Division of Neuroscience
Appointment(s): % Effort Excluded by Requester at Advanced Imaging Research Center (OHSU). He has joint appointments in the Department Behavioral Neuroscience, OHSU and the Division of Neuroscience, ONPRC.
Effort on NHP-related studies: Excluded by Request

Research Overview: Research in the Excluded by Requeste laboratory is primarily focused on characterizing the cellular-level anatomical changes that give rise to macroscopic changes associated with brain development and pathology that are observable using magnetic resonance imaging (MRI) techniques. Excluded by [redacted] is a recognized leader in the application of diffusion-weighted MRI (or diffusion tensor imaging, DTI) to the study of fetal and early postnatal brain development. Using several animal model systems, the Kroenke laboratory has established a framework for interpreting DTI changes in the developing cerebral cortex in terms of underlying cellular morphological features of the tissue. Using nonhuman primate research subjects, the DTI measurement and modeling approaches developed in small animal models are currently being translated to *in utero* applications, with the eventual goal of enabling *in utero* studies of human subjects.

Contributions to Mission: Excluded by Requester contributes to the ONPRC mission through his research program, by directing the ONPRC MRI support core, and through educational activities on the ONPRC and OHSU campuses. By using nonhuman primate research subjects to develop non-invasive, MRI-based techniques to characterize brain development and pathology, the Kroenke laboratory research goals are supportive of the ONPRC mission to utilize the nonhuman primate as a translational bridge to understanding and curing human disease.

As director of the MRI support core, Excluded by Requester provides assistance to all scientific and clinical divisions of ONPRC. The fundamental service provided by the MRI support core to ONPRC investigators is assistance performing MRI exams of sedated nonhuman primate subjects. Equipment and supplies for anesthesia and MRI compatible physiological monitoring and regulation are provided by the MRI facility. The support core is a satellite facility of the OHSU Advanced Imaging Research Center (AIRC), and as such, receives services an infrastructure support. These include the construction of radiofrequency (RF) transmitter/receiver and other peripheral electronics instrumentation specialized for NHP MRI experiments, maintenance of computer resources for data access and archiving, quality/assurance oversight for the system, and maintenance of a web-based scheduling system. Additionally, the MRISC is covered by the OHSU research agreement with the MRI system manufacturer, which enables access to system customization tools and "works-in-progress" supplied by the manufacturer. The MRISC also maintains a close relationship with the Division of Animal Resources surgical staff.

Excluded by Requester holds joint faculty appointments in the Advanced Imaging Research Center and the Department of Behavioral Neuroscience at OHSU. In affiliation with OHSU and Portland State University, Excluded by [redacted] teaches magnetic resonance imaging and spectroscopy sections of Biophysics (courses BCMP630 and BCMP631), Biomedical Physics (Ph 405), and Behavioral Neuroscience courses (BEHN 618 and BEHN 616), as well as central nervous system development components to a Behavioral Neuroscience course BEHN 618. He mentored a rotating graduate student in 2009, a Ph.D. one student who completed her dissertation in his laboratory in the spring of 2012, as well as high school and undergraduate students.

NARRATIVE: Excluded by Requester

Division Appointment: Assistant Scientist, Division of Neuroscience
Appointment(s): % Effort, Excluded by Requester appointment at the ONPRC.
Effort on NHP-related studies: % Effort

Research Overview: Excluded by specializes in gene therapy for neurodegenerative disorders. The focus of her laboratory is translational therapeutics for the genetic disorder, Huntington's disease (HD). Excluded by Requester has been directing dosing, biodistribution and safety/toxicity studies assessing RNA interference therapy in the transgenic HD mouse as well as naïve rhesus macaque in addition to planning a Phase 1 clinical trial for evaluation in human HD patients. Excluded by has current NIH funding to create a rhesus macaque model of HD by viral vector delivery of the mutant HD gene to the caudate and putamen, the two most heavily affected brain regions in human HD patients. Her model will allow for both the investigation of HD disease progression as well as serve as an important model in which to screen potential therapeutics, including RNAi. In addition to her research on HD, Excluded by is also currently investigating enzyme replacement in the rhesus macaque for the neurodegenerative, lysosomal storage disorder Batten's disease (BD).

Contributions to Mission: Excluded by serves as the ONPRC representative to the OHSU Faculty Senate wherein she interacts with the Provost and faculty members from each to make decisions on matters such as the development of new academic programs as well as participate in OHSU/ONPRC strategic planning efforts. Additionally, Excluded by serves on the OHSU Research Council, helping to make decisions about academic policy and to ensure that the needs of the research community at the OHSU and ONPRC are met. Due to her expertise in viral vector-based gene therapy, Excluded by Requester serves a member of the ONPRC Virology Support Committee, engaging in decisions about viral vector preparation, production techniques and which viral vectors are engineered at the ONPRC for use in our rodent and non-human primate models of disease.

Towards the ONPRC's mission to utilize the non-human primate as a translational bridge to understanding and curing human disease, Excluded by research focuses heavily on utilizing rhesus macaques to develop novel therapeutics and translational surgical strategies that will help ensure the success of Phase 1 Clinical trials for HD and BD. In doing so, Excluded by has forged important collaborations with both local and national scientists in the fields of neurodegeneration and gene therapeutics to help bring RNAi into the clinic. At the national level, Excluded by is collaborating with Excluded by Requester at the Center for Cellular and Molecular Therapeutics at the Children's Hospital of Phila[illegible] Excluded by Requester at the University of Iowa. Locally, Excluded by is collaborating with Excluded by Requester to investigate HD gene suppression in the basal ganglia, hypothalamus and dorsal raphe nucleus, respectively. When Excluded by was recruited to the ONPRC in the summer of 2010, she brought with her non-human primate surgical expertise that has allowed her to collaborate with Excluded by to biopsy the pre-frontal cortex of habitual drinking macaques as well as establish a current collaboration with Excluded by Requester in the Division of Pathobiology to biopsy regions of association cortex from monkeys infected with simian immunodeficiency virus (SIV).

Excluded by Requester holds joint faculty appointments in the Departments of Neurology and Behavioral Neuroscience at OHSU where she interacts with graduate students and post-doctoral fellows completing their research either at OHSU or at the ONPRC. As a member of the Neuroscience Graduate Program, Excluded by teaches courses in Neurobiology of Disease as well as Topics in Neuroscience. She has recently taken on a graduate student through the Department of Behavioral Neuroscience who will be conducting his dissertation research at the ONPRC in her laboratory. In keeping with the mission of providing training for the next generation of non-human primate research, she has mentored a veterinary student from Oregon State University during a summer externship, two undergraduate trainees from the University of Portland as well as an undergraduate volunteer from Portland State University.

Affiliate and Visiting Scientist list:

Name	Affiliation	Description
Excluded by Requester Visiting Scientist	U of Iowa	AAV2-CLN2 gene therapy for Batten's disease: safety and distribution in non-human primates
Excluded by Requester Affiliate Scientist	U of Portland	Elucidating the source of depressive-like symptoms in transgenic Huntington's disease mice.

NARRATIVE: Excluded by Requester

Division Appointment: Senior Scientist, Division of Neuroscience
Appointment(s): % Effort,Excluded by appointment at the ONPRC.
Effort on NHP-related studies: % Effort

Research Overview: Excluded by Requester is recognized nationally and internationally for his contributions to the field of neuroendocrinology of sexual development. This recognition is evidenced by the numerous invited presentations (more than 300) he has given all over the world, his service to the editorial boards and as an editor of several top journal in his field, and his service to NIH (three study sections, the Advisory Child Health and Human Development [NICHD] and the Council and the Advisory Committee to the NIH Director [Council of Councils]). Excluded by Requester findings have resulted in significant breakthroughs in the field of mammalian puberty, including the demonstration of a fundamental role for prostaglandins in this process, the involvement of glial cells in neuroendocrine communication, and the concept that the onset of puberty is controlled at a transcriptional level by gene networks coordinated by epigenetic mechanisms.

Contribution to Mission Excluded by Requester established the Division of Neuroscience in 1987 and served as Division Head for 24 years (1987-2011). Under his leadership, Division was able to develop unique primate models for the understanding of selected human diseases of the nervous system, and generated tools for therapeutic intervention. He recruited a highly successful and well-funded group of scientists that brought to the ONPRC powerful genetic approaches and genetic models for the understanding of nervous system function. Under his direction, the Division became as a regional, national and international resource for integrative neuroscience research. A major contribution to the overall Mission of NPRCs resulted from Excluded by Requester efforts, along with those of Excluded by Requester to convince Affymetrix to test and produce the first rhesus monkey DNA microarray, which is now being used worldwide to interrogate the rhesus monkey genome. Excluded by has been consistently funded by NIH to carry out NHP-related research. Prominent examples are the R01 grant MH065438 "Molecular Specifiers of Neural Cell Plasticity" (2002-2008) with Excluded by Requester stitute for System Biology), the U54 Program Project HD18185 "Cooperative Research on Infertility in Primates" (1998-2011) with Excluded by , the Challenge grant NS068280 "RNA interference therapy for Huntington's disease: studies in non-human primates" (2009-2011) with Excluded by Requester and the R01 grant "Molecular and Structural Bases of Hypothalamic Puberty" (2005-2011) with Excluded by Excluded by Requester Pending Support,Excluded by Requester Pending In addition, a collaborative grant "Mechanism of AAV-mediated transduction in the nonhuman primate brain" with Excluded by Requester was just funded by OCTRI-ONPRC to develop novel vehicles for gene therapy of the primate brain. During the last 3.5 years he has published 12 papers reporting studies with primates, with In Press,In Preparation . He is mentor for two training grants (Pediatric Endocrinology- T32 HD007497, P.I.: Excluded by Requester and Neuroendocrinology- T32 DK007680, P.I: Excluded by Requester and is the PI of training grant T32HD007133 in Reproductive Biology.

Affiliate and Visiting Scientist list for Excluded by Requester

Name	Affiliation	Description
Excluded by Requester	OHSU	Role of mGluR8 in anxiety. This study explores the role of glutamatergic receptors in the etiology and manifestations of anxiety.
	OHSU	Estrogen Modulation of Bursting Activity in GnRH Neurons. This proposal uses electrophysiological approaches to study the rapid effects of estrogen on the activity of GnRH neurons.
	OHSU	Cross-talk between Estrogen and Leptin Signaling in Hypothalamic Arcuate Neurons. This grant is aimed at elucidating the mechanisms of cell-cell communication that exist between neurons involved in energy balance and reproduction.

NARRATIVE: Excluded by Requester

Division Appointment: Senior Scientist, Division of Neuroscience
Appointment(s): % Effort,Excluded by Requester appointment at the ONPRC.
Effort on NHP-related studies: % Effort

Research Overview: Excluded by Requester is a recognized leader in the field of glial cell biology and remyelination research. His lab has made seminal discoveries in the areas of glial cell and neural stem cell signaling and in identifying mechanisms that influence neural progenitor cell differentiation in development and disease. Through studies in non-human primates, humans, and rodents, the Excluded by lab has discovered that a glycosaminoglycan, called hyaluronan (HA), accumulates in the brain and spinal cord following traumatic and inflammatory insults, and during the course of normal aging. They determined that an enzyme expressed by progenitor cells in areas of damage, the PH20 hyaluronidase, generates digestion products of HA that prevent progenitor cell differentiation and remyelination. Recent findings from the Excluded by R lab indicate that pharmacological inhibition of hyaluronidase activity can promote functional recovery in models of multiple sclerosis. The lab has also found that HA and its receptor, CD44, similarly regulate neural stem cell maturation in the hippocampal denate gyrus and mediate adult neurogenesis. This mechanism may underlie disturbances in neurogenesis that occur in alcoholics and possibly following other chemical insults that affect learning and memory, including drugs used for cancer chemotherapy. Finally, the Excluded by lab has developed a novel transgenic model of a rare form of neurofibromatosis, called schwannomatosis, and identified a novel role for a schwannomatosis-associated gene (Snf5) in the neuropathic pain experienced by schwannomatosis patients.

Contributions to Mission: Through his research program Excluded by Requester is working with other members of the Center to develop a novel model of multiple sclerosis in Japanese macaques. This model will allow Center investigators and others to pursue highly novel studies in the etiology of multiple sclerosis and will serve as a pre-clinical model to test novel therapeutic strategies that prevent disease onset and which promote nervous system repair. The lab is also participating in characterizing changes in neurogenesis in non-human primate models of heavy drinking,, estrogen replacement therapy and aging.

Excluded by Requester has served on numerous committees and is currently a member of the Division of Neuroscience Executive Committee, the ONPRC IACUC, and director of the Center Outreach Committee. He organizes an annual meeting of Oregon neuroscientists that is attended by Center scientists, post-docs and graduate students. He gives frequent presentations to local universities, high schools and middle schools highlighting the accomplishments of Center scientists and the value of non-human primates in biomedical research. Finally, as outlined below, Excluded by Requester is actively involved in teaching. In addition to hosting students in his lab, he consistently lectures in neuroscience graduate program courses and in the medical school neuroscience course at OHSU. He received a Teacher of the Year Award from the Faculty Senate.

Affiliate and Visiting Scientist list for Larry S. Sherman, Ph.D.

Name	Affiliation	Description
Excluded by Requester	OHSU	Studies are focused on mechanisms underlying myelin disturbances in developmental brain injuries.
	Univ of Oklahoma	Studies are focused on understanding how digestion products of hyaluronan influence neural progenitor cell maturation..
	OHSU	Tests the roles of Schwann cell-targeted mutations in the Snf5 gene in altering pain-related genes in sensory neurons
	Univ of Washington	Studies on the mechanisms underluing age-related cognitive decline.

NARRATIVE: Excluded by Requester

Division Appointment: Senior Scientist, Division of Diabetes, Obesity and Metabolism; Senior Scientist, Division of Neuroscience. Senior Scientist
Appointment(s): % Effort, Excluded by appointment at the ONPRC.
Effort on NHP-related studies: % Effort

Research Overview: Excluded by Requester specializes in neuroendocrine regulation of energy balance and reproduction. One specific focus is on the mechanisms involved in the coupling of metabolic status with reproductive function. Excluded by Requester research has resulted in key findings that challenge the current dogma that leptin is the primary signal involved in the metabolic gating of reproduction. New potential signals have been identified, such as CART, a key neuropeptide in the brain that regulates food intake and also has a stimulatory effect on neurons regulating reproduction. These studies are very relevant to humans and could lead to new treatments for restoring fertility or for new contraceptive agents that inhibit fertility. The other area of focus is the role of the maternal environment in development of the offspring, specifically as it relates to the risk of obesity and diabetes. Our NHP model of maternal obesity has resulted in highly important findings relevant to human health. Eating a diet high in fat during pregnancy has long lasting effects on the offspring that likely increase its propensity to develop obesity, diabetes and behavioral abnormalities. This NHP model is being used to examine possible therapeutic interventions during pregnancy that can prevent or reduce the risks of these developmental abnormalities. Excluded by Requester research has been recognized through invited presentations at national and international meetings, service on editorial boards and NIH study sections, and leadership in professional societies (Past President of The Endocrine Society).

Contribution to Mission: Excluded by Requester served as the Director of the ONPRC from 1994-2007 and was responsible for the merger of ONPRC with OHSU. This merger opened up significant research and educational opportunities for ONPRC scientists. Excluded by Requester worked with OHSU to bring the most up-to-date technologies to the center, including DNA microarray, MRI, bioinformatics and genetics expertise. Excluded by Requester also played a key role in forging new collaborative research programs with scientists at OHSU, such as in advanced imaging, addiction, cardiovascular disease, fetal-maternal medicine, metabolic diseases, stroke and stem cell technologies. Excluded by worked with Excluded by Requester to develop the NHP model of maternal obesity and diabetes. This model is now extremely well-funded and is the focus of many collaborative research efforts with scientists at OHSU and throughout the USA. It was also instrumental in the development of the NHP Obese Resource that has provided unique research opportunities for many scientists and pharmaceutical companies.

Excluded by Requester is actively involved in training programs at OHSU and participates in teaching graduate level seminar courses, mentoring graduate students and new clinical faculty, and serving on thesis committees. She serves on the training faculty for 6 NIH-funded training grants: Pre- and Postdoctoral Multidisciplinary Training in Reproductive Biology, T32 HD07133; Pre- and Postdoctoral Multidisciplinary Training in Neuroendocrinology, T32 DK07680; Multidisciplinary Training in Neuroscience, T32 NS07466; Training in Endocrinology, Diabetes, and Clinical Nutrition, T32 DK007674; Oregon Child Health Research Center, K12HD033703; and Building Interdisciplinary Research Careers in Women's Health, K12 HD043488.

Excluded by Requester serves on the OHSU Foundation Board of Trustees. As one of the only active faculty members on the Board, she is in a unique position to inform the lay Board members about research at OHSU, and particularly at the ONPRC. This is particularly important in providing support for translational research in which the NHP is a critical proof of concept step in the process toward developing new biotechnology companies or starting new clinical trials. Under the umbrella of the OHSU Foundation Board, Excluded by chairs the Medical Research Foundation of Oregon Research and Education Committee; this Committee awards up to $1 million in research grants per year to Oregon researchers and presents major awards at its annual awards reception.

NARRATIVE: Excluded by Requester

Division Appointment: Senior Scientist, Division of Neuroscience
Appointment(s): % Effort,Excluded by Requester at the ONPRC.
Effort on NHP-related studies: % Effort

Research Overview: Excluded by Requester is a recognized leader on the effects of nicotine on lung development and lung cancer. Using a rhesus monkey model the Spindel laboratory demonstrated that prenatal nicotine exposure was the primary mediator of the deleterious effects of maternal smoking during pregnancy on infant lung development and critically, that vitamin C supplementation to pregnant rhesus monkeys could prevent some of the effects of prenatal nicotine exposure. This discovery led to a pilot clinical study that demonstrated that supplemental vitamin C given to pregnant smokers who could not be convinced to quit, similarly reversed some of the effects of maternal smoking on offspring lung function. NIH has now funded a multicenter clinical trial that Excluded by is participating in, led by Excluded by Requester of OHSU and an ONPRC affiliate scientist, to further determine the ability of supplemental vitamin C to preserve lung function in offspring of smokers and potentially decrease incidence of asthma. The Excluded by Reque lab also investigates pathways by which nicotine and acetylcholine stimulate lung cancer growth and the potential to use those pathways to develop new therapies for lung cancer. In a new research direction, Excluded by is collaborating with Excluded by to develop a new monkey model to study nicotine and alcohol co-morbidities. This new program is funded by an ONPRC pilot project grant. Excluded by Requester also directs the ONPRC Molecular and Cellular Biology Support Core (MCB Core).

Contributions to Mission: Excluded by and his laboratory make substantial contributions to the mission through his research program, by directing the MCB core, and through participation in essential ONPRC committees. First through his research program the Excluded by Request laboratory has developed key research models for studying the effects of prenatal nicotine exposure in non-human primates. This has involved methods for both invasive and non-invasive methods of pulmonary function testing as well as methods for nicotine delivery that accurately recapitulate nicotine exposure levels of human fetuses. The accuracy of this model has led to translational discoveries that are now being tested in clinical trials. It is the expectation of Excluded by that results of the clinical trials in terms of how genetic polymorphisms affect sensitivity to maternal smoking during pregnancy will be further studied in non-human primates to better understand mechanisms and allow further development of targeted interventions for specific genotypes. In addition to the relatively mature studies on prenatal nicotine Excluded by Requester in collaboration with Excluded by Requester is developing an exciting, new non-human primate model to study the interaction of nicotine and alcohol. Smoking and alcoholism are major public health concerns and are strikingly co-morbid. Smoking increases with alcohol intake and the majority of alcoholics smoke. The nature of this co-morbidity is poorly understood and the expertise of Excluded by with nicotinic receptors and monkey models of nicotine administration and the expertise of Excluded by Requester with monkey models of alcohol self-administration make this an exciting new direction of research.

Excluded by Requester makes a major contribution to the ONPRC by directing the MCB Core. The MCB core provides automated sequencing [both capillary (ABI 3730XL) and NextGen (Illumina MiSeq)], high throughput genotyping and real-time PCR (Life Technologies QuantStudio 12K Flex), and robotic DNA preps among other services to facilitate primate research. Previous work by the MCB Core provided key DNA sequences for development of the first rhesus monkey gene chip produced by Affymetrix. A major focus of the MCB Core will be to work closely with the Primate Genetics Unit to utilize the MiSeq for MHC typing of monkeys to assist in colony management. More detail on the contributions of the MCB Core to the ONPRC mission is provided in the MCB Core Resource Section.

Excluded by Requester also contributes to the ONPRC mission through essential administrative work. Excluded by provides backup direction of the Division of Neuroscience when Excluded by Re uester is away. He serves on the ONPRC IT Advisory Committee, the ONPRC Policy Review Subcommittee and chairs the ONPRC Imaging and Morphology Core Oversight Committee and the ONPRC Primate Genetic Program Advisory Committee.

NARRATIVE: Excluded by Requester

Division Appointment: Assistant Scientist, Division of Diabetes, Obesity, & Metabolism
Appointment(s): % Effort,Excluded by Requester s an Assistant Professor in the Department of Biology at the University of Portland, and % Effort,Excluded by as an Assistant Scientist at the ONPRC.
Effort on NHP-related studies: % Effort

Research Overview: Excluded by specializes in behavioral neuroscience with specific training and expertise in nonhuman primate behavior. A primary focus of the Excluded by aboratory is examining the influence of metabolic and dietary environment on behavioral regulation with an emphasis on behaviors that relate to human mental health and behavioral disorders including anxiety, depression, attention deficit hyperactivity disorder, and autism spectrum disorders. Furthermore Excluded by Requester has expertise in whole animal physiology and measurement of energy balance regulation, feeding behavior and food preference. One specific focus is the impact that exposure to maternal obesity and high fat diet consumption during the perinatal period has on the behavior and physiology of the developing offspring. Key finding of this research to date include an increased risk for anxiety in female offspring and deficits in social behavior in both male and female offspring exposed to maternal high fat diet consumption and obesity Excluded by Requester has demonstrated a suppression of the central serotonin system in offspring exposed to maternal obesity and high fat diet consumption, which likely contributes to the behavioral dysregulation observed in the high fat diet offspring. The working hypothesis is that maternal high fat diet consumption and obesity result in the developing offspring being exposed to increases in circulating inflammatory cytokines. This leads to neural inflammation in the fetus, which modulates the development of neural circuitry regulating physiology and behavior such as the serotonergic, melanocortinergic, and dopaminergic systems. As the majority of women of childbearing age consume a high fat diet and one third are of pregnant women are obese, these studies are fundamental to understanding and identifying behavioral disorders that result from exposure to maternal obesity and HFD consumption.

In order to directly translate her finding in the nonhuman primate model, Excluded by Requester has initiated a translation study to examine the impact of maternal diet on infant temperament in humans. In collaboration with Excluded by from OHSU, the Excluded by Re uest laboratory examines the temperament of infant children from parents diagnosed with ADHD. The relationship between the behavioral data and information on maternal diet during pregnancy, cord blood, and placenta are being examined. Together these studies will further our understanding of how maternal energy status and pre- and early- postnatal nutrition influence susceptibility to obesity and behavioral disorders such as anxiety, depression, attention deficit hyperactivity disorder, and autism spectrum disorders. Excluded by Requester research has been recognized through invited presentations at national and international meetings, serving as a reviewer for a number of scientific publications, and being invited to be part of the National Institute of Health Developmental Biology Subcommittee.

Contribution to Mission: Excluded by has been working with NHP at the ONPRC since 2002. She began as a graduate student with Excluded by Requester examining factors that contribute to individual differences in body weight gain in female nonhuman primates, and then a post-doc fellow and staff scientist under Excluded by mentorship. Excluded by Requester became an Assistant Professor at the Univ. of Portland and an Adjunct Assistant Scientist at ONPRC in 2011. She became a Core Scientist at ONPRC in 2013. Excluded by is actively involved in training future scientists through her teaching and mentoring of University of Portland undergraduate students. Since 2011 Excluded by has mentored 14 students and a post-doctoral fellow. In addition, she has participates in teaching graduate level courses, judging student research presentations at OHSU Research Week, and serving on thesis committees. Out of five collaborations, major examples are listed below:

Name	Affiliation	Description
Excluded by Requester	ONRPC	Maternal High Fat Diet and Melanocortin System in Offspring
	OHSU	Perinatal Dietary Predictors of Childhood Behavioral Problems and Temperament
	Oregon State University	Examining Perinatal Dietary Predictors of Childhood Behavioral Problems and Temperament

NARRATIVE: Excluded by Requester

Division Appointment: Senior Scientist, Division of Neuroscience
Appointment(s): % Effort,Excluded by Requester at the ONPRC.
Effort on NHP-related studies: % Effort

Research Overview: Excluded by Requester 30-year research career as a neuroendocrinologist has focused on the influence of circadian rhythms and reproductive hormones on vertebrate physiology. Key findings from his non-human primate (NHP) studies include: (1) cloning of a novel form of gonadotropin-releasing hormone, which may play a pivotal role in controlling primate ovulation, (2) identification of circadian clock mechanisms in the primate adrenal gland, and other peripheral organs, which help to coordinate 24-hour physiological functions, and (3) identification of genes that are differentially regulated by photoperiod, in a NHP model of Seasonal Affective Disorder. Excluded by Requester current research, which is supported by two NIH R01 grants, uses multidisciplinary approaches to understand how age-associated hormonal changes negatively impact various physiological functions. For example, in collaboration with Excluded by Requester Excluded by Requester he aims to show how physiological hormone supplementation paradigms can improve sleep efficiency and boost cognitive performance in aged rhesus macaques. Furthermore, by making extensive use of gene profiling, his studies are helping with the elucidation of underlying causal mechanisms, and laying the foundation for safe and effective novel therapies for the elderly. Excluded by Requester also lends his expertise to additional collaborative studies, which focus on the development of NHP models of stroke (PI: Excluded by Requester and hot flashes (PI: Excluded by Requester). During the past four years, his research efforts have resulted in the publication of 26 peer-reviewed papers and two book chapters.

Contributions to Mission: Excluded by Requester serves on several committees, including the promotions committees at ONPRC and OHSU, and he is the chair of the Endocrine Core oversight committee. Until recently, he also served on the graduate student admissions committee at OHSU. Nationally Excluded by Requester serves on two editorial boards and has participated as a grant reviewer at many NIH study section meetings.

Excluded by Requester current research focuses exclusively on the use of NHP models for human diseases, especially those associated with aging. He is the co-director of the Biology of Aging Program at ONPRC; this inter-disciplinary research program makes extensive use of the NIA-supported Primate Aging Resource at ONPRC in order to gain insights into healthy and pathological human aging. In addition, Excluded by Requester has been highly instrumental in developing a translational bridge between the basic NHP aging research at ONPRC and clinical aging research and elderly care at OHSU. In collaboration with Excluded by Requester (Director of Geriatrics, OHSU) Excluded by Requester has spearheaded the formation of an OHSU Health Aging Alliance (HAA), which comprises ~60 researchers and clinicians. The goal of the HAA is to establish an international center of excellence for aging research, clinical practice, outreach and education. It builds on the broad spectrum of talent and resources at OHSU, and focuses on translating aging innovations from molecular to clinical applications. The HAA held its inaugural annual conference in late 2011, which was attended by almost 200 delegates and was highlighted by key note presentations by Excluded by Requester (deputy director of the NIA) and Excluded by Requester (director of the Layton Aging and Alzheimer's Disease Center), as well Oregon Sen. Ron Wyden. The conference also provided an important forum for networking; this was followed up by a grant writing retreat, which resulted in Pending Support Although still in its infancy, the HAA (co-directed by Drs. Eckstrom and Urbanski) represents an effective way of integrating the NHP aging research with ongoing aging programs at OHSU. The Alliance has already established a web site and a 5-year business plan.

Excluded by Requester holds affiliated professor positions in the Departments of Physiology & Pharmacology, and Behavioral Neuroscience at OHSU, and is a member of the Neuroscience Graduate Program. His laboratory provides a fertile research training ground for postdoctoral fellows and graduate students (current students: Excluded by Requester as well as high-school teachers via the Partner-in-Science program. Moreover, Excluded by is the program director of the NIH-supported *Neuroscience of Aging* training grant (T32 AG-023477), which is currently in its 8th year of funding.

NARRATIVE: Excluded by Requester

Division Appointment: Division of Neuroscience, Assistant Scientist
Appointment(s): % Effort Excluded by Requester in the Department of Molecular and Medical Genetics at OHSU and a joint appointment at the ONPRC.
Effort on NHP-related studies: % Effort

Research Overview: Excluded by Requester research focuses on the development of ONPRC rhesus macaque pedigrees for multi-center, collaborative gene mapping studies in complex disease. Since 2009, she has developed a single, 1,289-member pedigree of Indian-origin rhesus macaques optimally designed for large-scale genetic/genomic analysis, and a corresponding biobank of samples on >800 of these pedigreed macaques to enable extensive phenotyping. Based on these resources, she has recently demonstrated significant heritability in rhesus macaques for total cholesterol, LDL cholesterol, triglycerides, abdominal circumference, and body mass index (BMI), as well-established risk factors for human cardiovascular disease and obesity. In May 2012, she received ONPRC pilot funding to investigate heritability in this pedigree for 15 additional phenotypes that are biomarkers or risk factors for macaque colitis/human inflammatory bowel disease, cardiovascular disease, diabetes, obesity, osteoporosis, addiction, and behavioral disorders. The pilot study is in collaboration with 14 investigators spanning 7 primate research centers Pending Support
Pending Support

Contributions to Mission: Excluded by Requester provides oversight of the Colony Genetics & Demographics unit, with responsibility for pedigree characterization and population genetic analysis of ~4,500 rhesus macaques at the ONPRC. In this capacity, she works closely with the Div. of Comparative Medicine to design appropriate genetic management strategies at the ONPRC. She has established rigorous decision rules for parentage assignment in order to improve the accuracy of colony pedigree data, and has developed protocols based on sound population genetic principles for the formation of breeding groups, and for the selection of animals for sale or cull. She has instituted a yearly genetic review of the breeding colony, the results of which are presented to the Director and the Head of Comparative Medicine. Excluded by R s also a Co-Investigator who provides genetics expertise on several ONPRC NHP resource grants (i.e., U42, U24), and presents summary results of colony genetic analysis to external Scientific Advisory Boards and others when needed. Finally, Dr. Excluded by Request s an active participant in the NIH/ORIP-supported Genetics and Genomics Working Group, which develops and implements genetic and genomic tools and analytical pipelines for the comparative analysis of non-human primates across the NPRCs. She has recently developed a leading role in this Working Group in the effort currently underway to establish consistent and informative genetic metrics to guide the genetic health and diversity of all national NHP colonies.

The focus of Excluded by research on gene discovery using large pedigrees of rhesus macaques is a highly innovative research direction for the ONPRC, and one that has enormous potential for expansion into multi-center collaborations and consortia that include all the national primate research centers and primate research programs elsewhere. In particular, she is currently exploring the potential for a consortium focused on the genetics of complex diseases in NHPs with leading investigators at the Texas Biomedical Research Institute (baboons) and the Center for Neurobehavioral Genetics at UCLA (vervets). Her initial results demonstrating heritability for several important risk factors for cardiovascular disease and obesity clearly underscore the value of the rhesus macaque pedigree and biobank resources she has developed, and her exploration of many other phenotypes of shared interest across primate research centers will shortly identify additional promising phenotypes for further collaborative pursuit.

In keeping with the ONPRC mission of developing new scientists in NHP genetics, Excluded by Requester olds joint appointments in the Dept. of Molecular and Medical Genetics, and in the Div. of Bioinformatics and Computational Biology at OHSU. She lectures regularly for the graduate Program in Molecular and Cellular Biology (PMCB) and for the Medical School at OHSU on principles of quantitative genetics, genetic linkage and association analysis, and inheritance in complex disease. Excluded by Requester s recently mentored a rotational OHSU graduate student, a Reed College undergraduate summer fellow, a Portland Community College student extern, and will shortly take on an OHSU masters student who will conduct his thesis work in her lab. She additionally serves regularly on the admissions committee of the graduate PMCB program.

Program Director/Principal Investigator (Last, First, Middle): Robertson, Joseph E./Haigwood, Nancy L.

DIVISION OF NEUROSCIENCE DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*

Use Cal, Acad, or Summer to Enter Months Devoted to Project

Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Excluded by Requester	Div Chief/Sr. Scientist	% Effort			Institutional Base Salary	53,910	13,478	67,388
	Asst Scientist					5,186	1,297	6,482
	Sr. Scientist					8,985	2,246	11,231
	Admin Asst					3,044	1,066	4,110
	Assoc Scientist					11,750	2,938	14,688
	Assoc Scientist					13,059	3,265	16,324
	Admin Coordinator					2,369	734	3,103
	Asst Scientist					10,322	2,580	12,902
	Sr. Scientist					17,970	4,493	22,463
	Admin Asst					6,234	2,182	8,416
	Sr. Scientist					14,119	3,530	17,648
	Sr. Scientist					17,970	4,493	22,463
	Sr. Scientist					17,348	4,337	21,685
	Asst Scientist					5,111	1,278	6,388
To Be Named	Admin Coordinator	1.80				8,036	2,813	10,849
To Be Named	Asst Scientist	1.20				8,500	2,635	11,135
To Be Named	Assoc Scientist	1.20				16,000	4,000	20,000
	SUBTOTALS →					219,914	57,363	277,276

CONSULTANT COSTS		
None Requested	0	0
EQUIPMENT *(Itemize)*		
None Requested	0	0
SUPPLIES *(Itemize by category)*		
Office & Admin Supplies	398	
		398
TRAVEL		
None Requested	0	0
INPATIENT CARE COSTS		0
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		
None Requested	0	0
OTHER EXPENSES *(Itemize by category)*		
Maintenance - Equipment	398	
Biohazard Waste Disposal	397	
		795
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 278,468
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 278,468

DIVISION OF NEUROSCIENCE
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	277,276	285,594	294,162	302,987	312,077
CONSULTANT COSTS	0	0	0	0	0
EQUIPMENT	0	0	0	0	0
SUPPLIES	398	409	422	434	447
TRAVEL	0	0	0	0	0
INPATIENTS CARE COSTS	0	0	0	0	0
OUTPATIENTS CARE COSTS	0	0	0	0	0
ALTERATIONS AND RENOVATIONS	0	0	0	0	0
OTHER EXPENSES	795	819	843	869	895
DIRECT CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	278,469	286,823	295,427	304,290	313,419
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	278,469	286,823	295,427	304,290	313,419
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					1,478,427

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

PERSONNEL

Division Chief, Senior Scientist - Excluded by Requester % Effort (12 calendar months effort: 1.8 ORIP, 10.2 Program Income). As Division Chief, Excluded by s responsible for all Divisional administrative activities and provides the overall scientific direction of the Division; oversees the submission of grant proposals, recruitment and personnel matters, represents the Division at the level of ONPRC Administration including as a member of the Executive Leadership Committee, the Policy Committee, the Research Advisory Committee and the Animal Utilization Committee; encourages scientific interactions between Division members and researchers at other institutions, encourages faculty participation in the Graduate Programs at OHSU. Excluded by Requester primary research interest is in behavioral pharmacology of alcohol abuse and alcoholism using NHP models to understand the factors that establish and maintain the addictive properties of alcohol and other substances of abuse.

Assistant Scientist - Excluded by Requester % Effort Dr. Excluded by Requester research focuses on genome evolution and epigenetics, using high-throughput data on structural variations and epigenetic modifications in NHPs, including the gibbon genome. This work is relevant to chromosomal rearrangements and altered epigenetic marks in cancer, aging and addiction.

Senior Scientist - Excluded by Requester % Effort Dr. Excluded by Reques ill continue his world-renown research on neuroendocrine (GnRH) hormone action and the ability of pharmacoperones to overcome hormone receptor defects and resulting diseases (e.g., hypogonadotropic hypogonadism). He provides unique service in monitoring and responding to animal extremists/organizations targeting primate centers (Director, Office of Research Advocacy).

Administrative Assistant - Excluded by Requester % Effort Excluded by Requester provides administrative services to the scientists in the Division of Neuroscience on a 50% basis, shared with the Division of Reproductive and Developmental Biology. He assists with the preparation of grant applications and progress reports and provides the scientists with basic office support.

Administrative Coordinator – To Be Named (12 calendar months effort: 1.8 ORIP, 10.2 Program Income). This position provides administrative services to the scientists in the Division of Neuroscience, and will assist with the preparation of grant applications and progress reports and provide the scientists with basic office support. In addition, this position serves had the Division Chief's main administrative coordinator providing assistance with matters on the Division level.

Associate Scientist - Excluded by Requester % Effort Excluded by Requester Excluded by is a leader in the genetic characterization of macaques to inform and expand the translational study of NHP disease models. Leveraging the recent advances in next generation sequencing (NGS) technologies, and in collaboration with other investigators, she is analyzing the rhesus, cynomolgus and Japanese macaque genomic sequences to identify risk alleles associated with established disease models, including age-related macular degeneration, alcohol addiction, multiple sclerosis and infertility. Excluded by Requester also directs the Primate Genetics Services program.

Associate Scientist - Excluded by Requester % Effort Excluded by is a biophysicist primarily interested in generating and applying advanced MRI/MRS techniques to brain development, brain alterations in disease states and brain neurochemistry using NHP models. Dr. Excluded by Requester s also the Director of the MRI Support Core (a satellite facility to the OHSU Advanced Imaging Research Center).

Administrative Coordinator - Excluded by Requester % Effort Excluded by Requester Excluded by provides administrative services to the scientists in the Division of Neuroscience. She assists with the preparation of grant applications and progress reports and provides the scientists with basic office support.

Assistant Scientist - Excluded by Requester % Effort Excluded by Requester Excluded by Requester specializes in gene therapy for neurodegenerative disorders. Her current focus is translational

therapeutics using RNAi for the fatal, genetic disorder, Huntington's disease (HD). Excluded by Requester is also currently investigating gene delivery strategies (enzyme replacement) in NHPs for the neurodegenerative disorder Batten's disease (BD).

Senior Scientist - Excluded by Requester % Effort,Excluded by Requester Excluded by Reque will continue to study the neuroendocrine control of female sexual development, expanding his research further into the involvement of glial cells in neuroendocrine communication and the concept that the onset of puberty is controlled at a transcriptional level by gene networks coordinated by epigenetic mechanisms.

Administrative Assistant - Excluded by % Effort,Excluded by Requester provides administrative services to the scientists in the Division of Neuroscience. She assists with the preparation of grant applications and progress reports and provides the scientists with basic office support.

Senior Scientist - Excluded by Requester % Effort,Excluded by Requester Excluded by Requester will continue to inflammatory processes and neural stem cell function. Dr. Sherman is working with other members of the ONPRC to develop a novel model of multiple sclerosis in Japanese macaques. This model will allow investigators and others to pursue highly novel studies in the etiology of multiple sclerosis and will serve as a pre-clinical model to test novel therapeutic strategies that prevent disease onset and which promote nervous system repair. The lab is also participating in characterizing changes in neurogenesis in non-human primate models of heavy drinking, estrogen replacement therapy and aging.

Senior Scientist - Excluded by Requester % Effort Excluded by Requester research program is directed towards understanding the role of nicotinic acetylcholine receptors in normal lung development and how that role is affected by prenatal exposure to nicotine, how cholinergic signaling by lung cancer may affect cancer growth and the co-morbidity between nicotine and alcohol addiction. Excluded by Requester also directs the MCB Support Core.

Senior Scientist - Excluded by Requester % Effort Income). Primary interest is in examining how various neuroendocrine circuits of NHPs change during development and aging, and also in response to changing environmental conditions. Excluded by Requester current research uses multidisciplinary approaches to understand how age-associated hormonal changes negatively impact various physiological functions. Excluded by Requester also lends his expertise to additional collaborative studies, which focus on the development of NHP models of stroke and hot flashes.

Assistant Scientist - Excluded by Requester % Effort Excluded by research focuses on the development of rhesus macaque pedigrees for multi-center, collaborative gene mapping studies in complex disease. Based on these resources, she has recently demonstrated significant heritability in rhesus macaques for total cholesterol, LDL cholesterol, triglycerides, abdominal circumference, and body mass index (BMI), as well-established risk factors for human cardiovascular disease and obesity.

Assistant Scientist, To be named. (4.8 calendar months effort: 1.2 ORIP, 3.6 Program Income). Scientific position at the assistant level, we plan to recruit a scientist with expertise in neurophysiology and integrative neurobiology to address neuroendocrine, neurodevelopmental and neurodegenerative processes. This applicant will be expected to establish a nationally visible research program complementing existing strengths in genomics and phenotypic characterizations of disease processes involving the non-human primate nervous system. We currently are recruiting and anticipate filling this position in early 2013.

Associate Scientist, To be named. (4.8 calendar months effort: 1.2 ORIP, 3.6 Program Income). Scientific position at the associate level, we plan to recruit a scientist with expertise in Bioinformatics or Computational Biology with an emphasis in systems biology. The successful applicant must make a commitment to establish a nationally visible research program complementing existing strengths in genomics and phenotypic characterizations of disease processes involving the NHP nervous system. We currently are recruiting and anticipate filling this position in mid 2013.

SUPPLIES

Office & Admin Supplies: Funding is requested for standard office supplies (paper, pens, folders, printer cartridges etc.) for the Division administrative activities.

OTHER EXPENSES

Maintenance – Equipment: These funds would be used to partially cover the maintenance and repair costs for multi-user Division equipment, replacement of Division minor equipment.

Biohazard Waste Disposal: These funds would be used to pay for disposal of biological and chemical waste generated by the division laboratories that cannot be practically attributed to specific grants. Charges are per the standard OHSU Radiation Safety schedule.

Division of Neuroscience Income Table

Last Funded Year (53)

Source	Funding (direct costs)
P51 base grant support	$489,721.36
Program income derived from P51 base grant	611,812.22
Other Sources	0
Total	$1,101,533.58

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$278,468.57
Program income derived from P51 base grant	652,287.85
Other Sources	100,000.00
Total	$1,030,756.42

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

The Division of Neuroscience receives salary support and support for other expenditures from program income. Other sources represents recruitment funding from the VP for Research.

TITLE: DIVISION OF REPRODUCTIVE & DEVELOPMENTAL SCIENCES

CORE-SUPPORTED PERSONNEL:

Core Scientists (See Biographical Sketches listed in the Overview of the ONPRC)

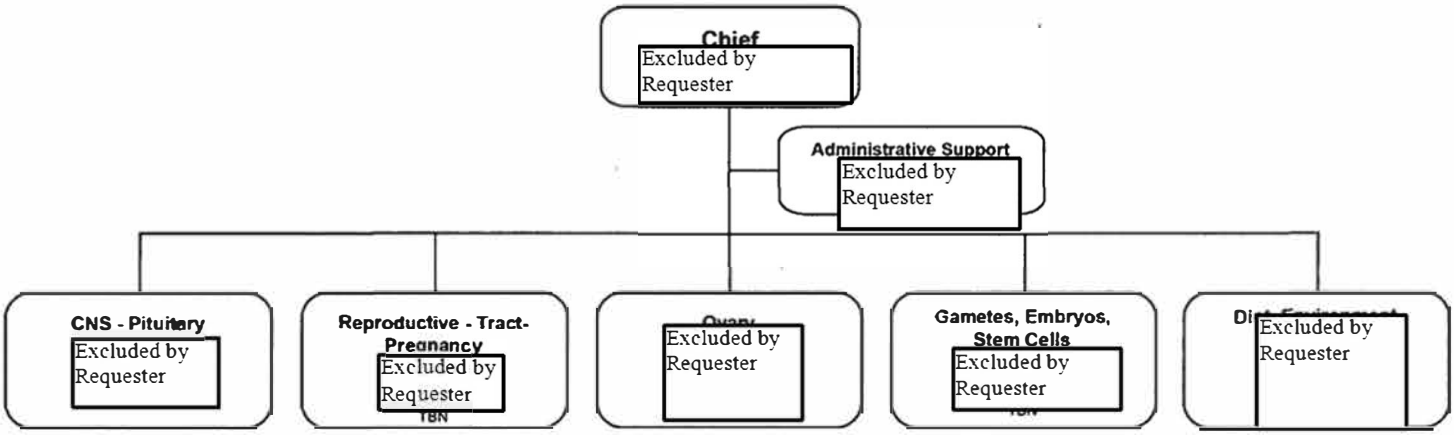
Excluded by Requester	Division Chief/Senior Scientist
	Senior Scientist
	Senior Scientist
	Assistant Scientist
	Assistant Scientist
	Associate Scientist
	Senior Scientist
	Senior Scientist
	Associate Scientist
TBN	Senior Scientist
TBN	Associate Scientist
TBN	Assistant Scientist

* Indicates a partial core appointment

Administrative Support:

Excluded by Requester	Administrative Assistant
	Administrative Coordinator
	Administrative Coordinator

Division of Reproductive & Developmental Sciences (DRDS)
Organizational Chart



DIVISION OF REPRODUCTIVE & DEVELOPMENTAL SCIENCES (DRDS)

DESCRIPTION:

The mission of the Division of Reproductive & Developmental Sciences is to conduct basic and applied research on aspects of reproductive and developmental biology that are relevant to promoting human health and to controlling reproductive disorders and fertility. The Division's research focuses on understanding the central (neural), peripheral (endocrine, paracrine and autocrine) and environmental (e.g., diet, stressors) factors controlling reproductive success, particularly in females. Research projects span the continuum of reproductive processes from gamete (egg) and embryo development, to intrauterine pregnancy and maternal-fetal development, to delivery and neonatal development. A theme in all laboratories is the use of Old World monkeys (macaque species) as models for whole animal, cellular and molecular studies of direct relevance to women's and child health. Division scientists have world-renowned expertise in nonhuman primate applications to: (a) understand the causes and treatment of infertility; (b) develop the next generation of contraceptives; (c) unravel and prevent premature delivery and maternal causes of childhood morbidity; (d) comprehend the effects of reproductive aging; and (e) characterize stem cell populations and in the use in regenerative medicine. The high level of scientific activity and innovation is exemplified by our primary researchers (seven core, four affiliate, and one visiting scientist) who averaged $5.6 million (direct costs) in annual research support during 2009-2012. All scientists have joint appointments in departments at OHSU (particularly Ob-Gyn, Center for Women's Health), and are involved in graduate (Ph.D./M.D.) and postdoctoral training (NICHD-supported training grant in reproduction), as well as clinical research training. Division scientists are also committed to raising scientific awareness among young (K-12) students, their teachers and the general public. As such, the Division's goals for 2014-2019 are to: (1) promote research opportunities in existing fields of nonhuman primate reproductive and developmental science; (2) expand opportunities in emerging fields of research; (3) ensure availability of primate resources for reproductive research; and (4) promote efforts to train scientists that focus on primate and human reproductive health.

RELEVANCE:

A better understanding of the processes controlling human reproduction and development would greatly impact society; currently two of 10 women are infertile, four of 10 pregnancies spontaneously abort and one of 10 children have a birth defect. Conversely, five of 10 pregnancies are unintended and human population growth threatens the quality of life in many areas of the world. Division scientists are using nonhuman primate models to understand the environmental, genetic/molecular, cellular and organismal influences that impact women's and neonatal health.

DIVISION OF REPRODUCTIVE AND DEVELOPMENTAL SCIENCES PERSONNEL AFFILIATION & ROLE

Core Scientists

Excluded by Requester	Division Chief and Senior Scientist
	Senior Scientist
	Senior Scientist
	Senior Scientist
	Senior Scientist
	Senior Scientist
	Senior Scientist
	Senior Scientist
	Associate Scientist
	Associate Scientist
	Assistant Scientist
	Assistant Scientist

[1] Joint appointment in the Division of Neuroscience, ONPRC
[2] Joint appointment in the Division of Diabetes, Obesity & Metabolism, ONPRC
[3] Joint appointment in the Division of Neuroscience, ONPRC
[4] Joint appointment in the Department of Obstetrics & Gynecology, OHSU

Affiliate Scientists

Excluded by Requester	Department of Obstetrics & Gynecology, OHSU
	Department of Obstetrics & Gynecology, OHSU
	University of California, Riverside
	Div. Reproductive & Developmental Sciences, ONPRC
	Div. Reproductive & Developmental Sciences, ONPRC
	Div. Reproductive & Developmental Sciences, ONPRC

Visiting Scientists

Excluded by Requester	Department of Psychiatry, University of Pittsburgh

Staff Scientists

Excluded by Requester	Staff Scientist 1
	Senior Staff Scientist
	Staff Scientist 1
	Staff Scientist 2
	Staff Scientist 3

DIVISION OF REPRODUCTIVE & DEVELOPMENTAL SCIENCES SPECIFIC AIMS

A better understanding of the processes and factors influencing human reproduction and development would greatly impact human health and quality of life. Currently it is estimated that 2 of 10 adult women are infertile, 4 of 10 pregnancies are "spontaneously" lost, and 1 of 10 children are born with a birth defect. It is also increasingly clear that environmental contaminants, lifestyle (e.g., the western-style diet), and clinical therapies (e.g., the chemo- and radiation therapy for cancer) can profoundly and negatively impact fertility, Conversely, 5 of 10 pregnancies are unintended and human population growth (to over 7 billion people) threatens our quality of life, if not life itself for many species, and threatens global resources. Thus, the rationale remains as great as ever to use advances in our knowledge of reproductive biology and fetal/neonatal development to better understand the causes of infertility and prevent its occurrence, as well as to develop the next generation of contraceptives to prevent fertility. Likewise, as our knowledge of gametes and early embryonic development expands, the use of these reproductive cells/tissues offers sources of pluripotent cells than have unparalleled potential for applications to regenerative medicine.

Nonhuman primates are a valuable model for research advances pertaining to human reproductive and fetal/neonatal health. It's been established that many of the factors and mechanisms controlling reproductive processes (notably within the hypothalamic-pituitary-gonadal axis, plus maternal recognition of pregnancy and term delivery) are more similar between monkeys, apes and man, than with typical laboratory rodent models. For logistical and ethical reasons, studies on humans and apes are very limited; consequently Old World monkeys (macaque species) are a preferred nonhuman primate (NHP) model for basic and applied studies on reproductive processes that portend translational applications to humans.

The Division of Reproductive & Developmental Sciences at ONPRC has a long and rich history in contributing significant advances in primate reproductive biology and its applications to women's health. Research and training activities span the continuum of reproductive processes from gamete (egg) and embryo development, to intrauterine pregnancy and maternal-fetal development, to delivery and neonatal health. A general theme of all laboratories is the use of NHP models for whole animal, cellular and molecular studies of direct relevance to women's reproductive and child health. The core, affiliate and visiting scientists embrace the objectives of the NPRC program in performing research on NHPs, developing NHP models of reproductive diseases, providing training opportunities in primatology, and disseminating our scientific advances. As such, our specific aims for the next 5-year grant interval are to:

Specific Aim 1: Promote research opportunities in existing fields of primate reproductive and developmental science.

Specific Aim 2: Expand opportunities in emerging fields of research.

Specific Aim 3: Ensure availability of primate resources for reproductive research.

Specific Aim 4: Promote efforts to train scientists that focus on primate and human reproductive health.

DIVISION OF REPRODUCTIVE & DEVELOPMENTAL SCIENCES (DRDS) – RESEARCH STRATEGY

SIGNIFICANCE

As summarized in the Specific Aims section, the rationale has never been stronger for advancing our knowledge of human reproductive processes and fetal/neonatal development, in order to improve or control fertility, and to ensure maternal-fetal and neonatal health. Growing recognition of the deleterious effects of environmental factors and clinical therapies for other diseases, combined with intrinsic (genetic or post transcription) defects in cellular mechanisms, broadens the interdisciplinary research needed to understand reproductive processes, and to improve the diagnosis and treatment of reproductive disorders. At the same time, couples continue to experience unintended pregnancies (with many choosing contragestational methods with significant health risk), due in part to lack of access (cost-related or otherwise), non-compliance and non-use due to perceived risks of side-effects. The effects of reproductive health "disorders" on quality of life are personal, but the significant costs on the health care system are societal. It is estimated that the cost of diagnosing and treating infertility in the U.S.A. alone exceeds $5 billion per year; this is an underestimate as it only includes those requesting treatment – which is limited by lack of insurance coverage in many states. If pregnancy occurs, the costs of premature delivery and the lifelong health problems associated with "premie babies" are astronomical - $26 billion annually! Conversely, unintended pregnancies accounting for 51% (> 1 million) of publicly funded births in the U.S., cost over $11 billion annually. Clearly, further advances through state-of-the-art research are needed to improve women's and child health. For example, there is a renewed effort by both federal (NICHD) and private [Private Source] agencies to promote development of the next generation of contraceptives for men and women. Likewise, with the development of embryonic stem cells (ESCs) derived from pre-implantation embryos, detailed investigations are needed to characterize and compare ESCs to adult stem cells isolated or derived (induced pluripotent SCs, iPSCs) from various tissues, and to evaluate their use in regenerative medicine to maintain tissue function.

Due to the evolutionary theme of species developing scenarios that optimize reproduction for their environmental niche, differences abound in the structure-function and regulation of reproductive organs between mammals. Notably, many characteristics of and mechanisms controlling reproduction are more comparable in Old World Monkeys, apes and man, and less similar to those in typical laboratory animal models, such as rats and mice. For example, many primates experience long (28 day) ovarian-uterine cycles ending with menstruation, whereas rodents have short (3-4 day) cycles characterized by an estrus interval promoting mating. Likewise, signals for maternal recognition (placental chorionic gonadotropin versus coital neural activity) of pregnancy, maternal-fetal-placental development and function, plus term delivery are much more similar between NHPs and women than rodents. Also, with longer lifespans (including menopause) and metabolisms similar to humans, NHPs are more likely to respond to environmental factors (e.g., dietary restriction or the Western-style, high-fat, high-sugar, diet) in a manner comparable to humans.

Therefore, the mission of the DRDS is to perform basic and applied research on NHPs (primarily macaque species) to increase our understanding of primate reproduction and embryonic/fetal development, and to use this knowledge to control reproductive disorders, fertility and neonatal health. In addition, the Division, as part of the OHSU system and in partnership with other local programs, provides research training for individuals entering science-oriented careers (e.g., pre-and post-doctoral fellows) and a research-oriented knowledge base in primate reproduction and development for others (e.g., K-12, high school teachers, college undergraduates, and the local public). Finally, the Division serves as a regional, national and international resource, especially as it relates to NHP models and research.

The research of the Division focuses on understanding the environmental (e.g., diet, stressors), central (neural) and peripheral (endocrine, paracrine and autocrine) factors controlling NHP reproduction and development, primarily in the female (Fig. 1). Research projects span the continuum of reproductive processes from gamete and embryo development, through pregnancy initiation and maternal-fetal development, to delivery and neonatal health. Research groups utilize rhesus, cynomolgus and Japanese macaques (in order of prevalence) for whole animal, cellular and molecular studies of direct relevance to women's and child health. Researchers are creating and using NHP models to investigate reproduction and its disorders, with the goal of considering the etiology, diagnosis and treatment of reproductive disorders, as well as developing novel approaches to contraception. Figure 1, summarizes the core, affiliate and visiting scientists (n=18) comprising the Division. Some have primarily appointments in other ONPRC divisions or the Department of Obstetrics & Gynecology, OHSU, but include the reproductive system as a major part of their research. While fostering the

individuality of investigator's research (Fig. 1), a theme that emerged in recent years is the formation of interdisciplinary groups performing translational research on key issues in women's reproductive health. The interdisciplinary groups bringing their expertise to clinical problems include:

1) Infertility disorders and their treatment (e.g., polycystic ovarian syndrome, endometriosis, menstrual irregularities, oocyte quality and oncofertility) – Excluded by Requester Excluded by Requester
2) Fertility control and contraceptive development (reversible and irreversible methods, specifically targeting the oocyte, follicle or gamete transport prior to fertilization) – Excluded by Requester Excluded by Requester
3) Pregnancy disorders and their treatment (including metabolic and environmental disruptors, intrauterine infection and effects on maternal-fetal/neonatal health) – Excluded by Requester
4) Reproductive aging and its effects (neural-behavioral, ovary-oocyte quality, immune system) Excluded by Requester Excluded by Requester

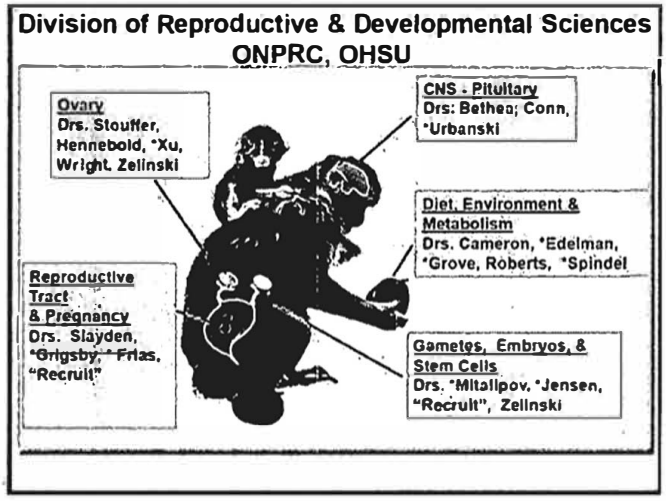


Figure 1. *Current core and affiliate scientists in the DRDS, with those having their primary appointment in the Division highlighted in blue, and those with joint appointments from Ob-Gyn, OHSU, or the Neuroscience and DOM divisions, ONPRC, highlighted in green or red, respectively. An asterisk notes those added since 2011, when the division reviewed and expanded its focus to include developmental biology. Two open positions are noted as a "recruit" under their proposed areas of selection.*

In addition, a number of Staff Scientists (typically senior postdoctoral associates serving as laboratory managers for scientists or working independently in laboratories to develop their own future research) and Collaborative Scientists (**both nationally and internationally, see division members' Narratives**) with a history of substantial interactions with ONPRC researchers contributed to the advances accrued over the past five years. The Division foot print includes space and services of five service cores (Assisted Reproductive Technologies or ART Core; Excluded by Requester Director until 2012 Excluded by Requester since July 2012; Endocrine Technology Core; Excluded by Director; Imaging & Morphology Core, Excluded by Director; Molecular & Cellular Biology Core; Excluded by Reques Director; Research Histology Unit of DCM Pathology, Excluded Excluded by Reques Director) that were critical in Division research projects. The core directors actively participate in the NHP research and model development in the Division.

INNOVATION

During the past grant interval, division scientists contributed a number of NHP models for reproductive and developmental research, plus key discoveries that advanced our understanding of the basic biology and its application to reproductive health:

- In the area of assisted reproductive technologies (ART) and gene therapy, Excluded by Requester and colleagues developed the novel technique called **"spindle transfer"**, whereby the condensed chromosomes/spindle complex in the mature, metaphase II oocyte is isolated by micromanipulation and introduced into an enucleated oocyte from another monkey. The newly constructed oocyte, consisting of the nuclear genome from one female and the cytoplasmic components (including mitochondria and their DNA) from another female, was capable of fertilization, early embryonic development and yielding healthy offspring (1). Translational studies are ongoing to apply the "spindle transfer" technique to human oocytes (Dept. of Ob-Gyn, OHSU) as a potential therapy to prevent transmission of mitochondrial gene defects from mother to offspring, while retaining the mother's genomic contribution.
- A number of macaque **embryonic stem cell (ESC) lines** were derived from naturally occurring and somatic cell nuclear transfer (SCNT)–derived blastocysts, with increasing efficacy of derivation indicating that individual ESC lines could be derived from patients for therapeutic purposes. However, the "gold standard" for confirming their pluripotency, as confirmed with mouse ESCs, i.e., their ability to incorporate into embryos and form chimeric animals, had not been attempted. Excluded by Requester and his ART Core

associates demonstrated the totipotency of cells from early (four-cell) embryos by producing the first primate **chimeras** (2), but neither macaque ESCs nor cells from the inner cell mass (early fetus) incorporated into host embryos or developed into chimeras. These results provide insight into the species–specific nature of primate embryos and suggest that cell-cell interactions or differentiated state of primate ESCs differs from those from mice.

- Excluded by Requester developed a novel protocol of ovariectomy combined with short- or long-term steroid hormone replacement in macaques to investigate the effects of **reproductive aging and menopause** on women's health. Detailed studies at the systems, cellular and molecular levels provided numerous insights, including (a) increased anxiety and food intake, plus decreased socializing and physical activity in the steroid-depleted state, but (b) increased dendritic spines on serotonergic neurons in the dorsal raphe nucleus of the brain, which correlated with increased expression of glutamate receptors and pivotal proteins involved in cytoskeletal remodeling, by female sex steroids. Such findings (3) supported the award of a R24 Resource Grant (2012-16) to provide this NHP model for investigators to examine the effects of reproductive aging and steroid hormone replacement on various tissues, organs and systems.
- Excluded by Requester identified a novel class of therapeutics, termed **pharmacoperones**, which can correct defects in misfoldings of cellular proteins and their movement to plasma membranes (4). Their potential in preventing numerous diseases associated with protein misfolding was established by proof-of-principle studies on hypogonadotropic hypogonadism, a significant disorder of the reproductive system in humans.
- Previous research established the importance of cholesterol uptake, as the primary source of steroid precursors, in the development of the functional corpus luteum in the primate ovary. However, Excluded by Requester discovered a **reverse cholesterol transport system** that depletes intracellular stores and whose expression increases during luteal regression at the end of the menstrual cycle (5). Thus, the balance between cholesterol uptake and release may control luteal function, and be altered in cases of luteal dysfunction associated with infertility or recurrent loss of pregnancy.
- Excluded by Requester and colleagues provided "proof-of-concept" for the use of **macrolide antibiotics** to eradicate a bacterial (U. parvum) infection in the macaque placenta-fetus, resulting in prevention of early labor while reducing fetal lung injury and fetal brain inflammation (6). In addition, she designed and established a **specialized intensive care nursery** to support prematurely born macaque infants and allow neonatal studies on the effects of intrauterine infection and their prevention in NHP newborns.
- A collaborative effort between Excluded by Requester supported by both NIH and industry Private Source identified the genome-wide changes in the **transcriptome (mRNAs) in the primate ovary at precise intervals:** (a) leading up to ovulation and luteinization of the mature follicle at midcycle (7), and (b) during the functional lifespan of the corpus luteum in the menstrual cycle and simulated (hCG-treated) early pregnancy. These public databases (GEO GSE22776, GSE12807, GSE25335) are now being mined for basic and applied research, including the identification of gene products that are selectively expressed in the ovary and hence are potential targets for novel ovary-based contraceptives.
- Excluded by Requester identified molecules in the primate oocyte, such as WEE2 (a kinase regulating the reinitiation of meiosis), which could be novel targets for an **oocyte-based contraceptive** in women (8). In addition, Excluded by Requester identified a potential **nonsurgical approach to female contraception**, whereby a sclerosing agent approved by the FDA to treat varicose veins can occlude the oviducts when delivered transcervically to NHPs without adverse effects.
- Using small groups of macaques for contraceptive trials, Excluded by Requester discovered that **an antagonist to the prostaglandin E receptor 2 (EP2) significantly reduced fertility during five months of treatment, without altering ovarian/menstrual cyclicity. Moreover, the contraceptive effect was reversible in two months (unpublished).** Thus, an EP2 antagonist has promise as a novel nonhormonal contraceptive for women.
- Methods were validated for gentle removal of the surface epithelium of the macaque ovary (OSE), plus characterization of proliferation and cell death in the OSE. Studies led by Excluded by Requester discovered that **OSE removal does not impair ovarian or menstrual cyclicity** nor lead to intra-abdominal adhesions (9). The very slow regrowth of the OSE, perhaps from the attached oviductal fimbria, suggests that OSE/OFE removal may be novel therapy to prevent ovarian cancers in women at risk (based on genetic, other markers).
- In a collaboration between bioengineers at Northwestern University, reproductive biologists at ONPRC Excluded by Requester and clinical scientists at OHSU, UC-San Diego and Univ. of Pennsylvania within the

Oncofertility Consortium, techniques were designed that permitted the **growth and maturation of primate (macaque) follicles from the earliest (primary, secondary) growing stages to the antral, steroidogenic stage during long-term, 3-D culture** (10). This novel methodology allows, for the first time, detailed studies on individual follicles to understand the processes and regulation of primate follicular development, and the application of this knowledge to growing human follicles and the enclosed oocytes as a new assisted reproductive technology for infertility treatment in women, including cancer patients.

- Advances in **cryopreservation of ovarian biopsies** (11) by [Excluded by Requester] established that, unlike "slow-freezing", vitrification provided ovarian tissue with (a) viable secondary (preantral) follicles that will grow in vitro, and (b) cortical strips that can be transplanted into macaques to restore menstrual cyclicity (i.e., cyclic ovarian hormone production) and to provide mature oocytes for ART procedures.
- Heavy and irregular menstruation is a common problem affecting women's reproductive health and quality of life. [Excluded by Requester] developed a NHP model to mimic **contraception-associated menstrual disorders** (employing IUDs inserted in the macaque uterus), and techniques for quantitating the duration and volume of blood loss (using "mini-tampons"). This model (unpublished) will be valuable for basic and applied studies by pharmaceutical companies aimed at therapies to prevent menstrual disorders.

APPROACH

reviewers' comments

Progress Report

Division Faculty Departures and Appointments. Although the leadership of DRDS has remained stable (Dr. [Excluded by Requester] Division Chief, 1996-present), a number of changes in the faculty occurred since the last renewal. Departures include [Excluded by Requester] Senior Scientist [Excluded by Requester] moved to University of Pittsburgh, but remains a Visiting Scientist) and [Excluded by Requester] Assistant Scientist (returned to clinical pathology; with M.D.). Two national searches were performed, with [Excluded by Requester], Assistant Scientist (and K99/R00 awardee) hired to replace [Excluded by Requester] (see Maternal-Fetal Medicine, Aim 2). A senior investigator was selected to increase our expertise in gamete/stem cell biology, but his recruitment failed due to family issues. Thus, the department has two open slots for scientists.

In addition, following a visioning process (and the recommendation of the ONPRC Advisory Board), the Division expanded its name (DRDS) and focus to emphasize developmental as well as reproductive biology. Consequently, three core scientists from other programs at ONPRC [Excluded by Requester] [Excluded by Requester] accepted the invitation to participate in the Division's activities as joint faculty appointees, while keeping their primary appointment elsewhere (Fig. 1). Also, three scientists were added either from Ob-Gyn, OHSU [Excluded by Requester] or as a BIRCWH scholar [Excluded by Requester] who are committed to research programs within the scope of DRDS. Thus, the Division includes 11 scientists (core and affiliate) who have their primary appointment at ONPRC within DRDS, plus six others who with primary/dual appointment in other divisions (n=3 Diabetes, Obesity & Metabolism; n=2 Neuroscience; n=1 Pathology & Immunology).

Scientific Impact – Research Funding. Core and Affiliate Scientists, with their primary appointment at ONPRC in this Division, continued to enjoy remarkable success in competing for grant support for their research program. ONPRC has a long, productive history of performing reproductive research which, until the past decade, relied primarily on investigator-initiated R01 grants. Two decades ago (1993), the level of direct costs awarded for division research totaled less that $2 million. Over the next decade, with the addition of several core and affiliate scientists, plus the conversion of an NICHD-supported Research Core (P30) grant to an Infertility Center (SCCPIR, U54 HD018185, 1999 and renewed in 2004), the amount awarded increased to over $4.4 million. For the first 3.5 years of the current grant interval (May 2009-December 2012), the direct costs awarded averaged $5.71 million per year. There were fluctuations due to transient ARRA funding, the end (SCCPIR Infertility grant), beginning (Oncofertility Consortium) and delay in renewal (CDRC Contraceptive grant) of center programs, and one-year major contracts from industry (notably [Private Source]). Nevertheless, it is anticipated that the fourth year (2012-13) will generate over $6 million, with the potential for $7+ million if the new SCCPIR Center or the Gates Contraceptive Center (see Future Plans) is funded. To date, the total grant funds awarded to the Division (June 2009-December 2012) is $33.3 million. This averages just over $3.3 million per investigator for the 10 core and affiliate scientists with their primary appointment in DRDS.

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) remains the major provider of research support; up to 76% of Division funding in 2009-11. However, reliance has declined since the 1990's, as scientists successfully competed for awards from other sources within the NIH and other federal agencies (11% in 2010). In addition, substantial support (25% of 2010 monies) was received from non-federal sources, including research foundations [Private Source] and pharmaceutical or biotech companies [Private Source]. The latter component reflects investigators' efforts to move into more targeted translational (clinically relevant) research and to diversify their research support.

Examples of Division scientists' success in attracting individual (R21, R01, pharma contracts) and multi-investigators center awards include:

- [Excluded by Requester] added as an Assistant Scientist in 2011, competed successfully for a K99/R00 Award (HD 055503, 2008-12) and received her first R01 grant (HD 069610, 2012-17)
- [Excluded by Requester] three current R01s (HD 057121, 2009-14 Histocompatible Primate ESCs; HD 059946, 2010-15 Altered Nuclear Transfer; HD 063276, 2010-15 Mitochondrial Gene Therapy
- [Excluded by Requester, Private Source] (2011-12, Preclinical Study on NHP Endometrial Xenografts); R21 OD 012377 (2013-15, A Macaque Model for Endometriosis-Induced Pelvic Pain and Infertility)
- [Excluded by Requester] as Co-PIs, renewed a NICHD-funded Contraceptive Development and Research Center (U54 HD 055744, 2012-17) which, with [Excluded by Requester] [Excluded by Requester] aims to develop contraceptives that selectively block oocyte maturation, ovulation or gamete transport.

- Excluded by Requester serve as PIs of individual R01s (HD 020869 and HD 050356, respectively) within the Oncofertility Consortium (RL1A-HD 058293) a NIH Roadmap Initiative uber-grant directed by Excluded by Requester at Northwestern University. The research uses NHP models to perfect methods that can be applied to female cancer patients to restore fertility after chemo-or radiation therapy.
- Excluded by Requester R01 (MH 086542, 2010-15 Steroid Regulation of Serotonin in Male Macaques); R21 (HD 062864, 2010-12 Norepinephrine in Stress-Induced Amenorrhea of Macaques); R24 (OD 011895, 2012-16, Postmenopausal Monkey Resource)

Scientific Impact – Research publications. The numbers and journal sites of publications from the Division scientists illustrate the continue productivity and impact in basic and applied reproductive and developmental biology. Annually averaging in the low 60s in the 1990s, the total number of publications reached the low 70s in the first decade of the millennium (2000-9). Over the interval of this progress report (2009- Dec, 2012), core, affiliate and visiting scientists with their primary appointment in the Division were listed as authors 219 times on research articles in peer-reviewed journals, 47 on reviews or chapters in books or symposium monographs, and over 200 on abstracts of research presented at national or international meetings. This equates to 64 research articles, 13 chapters/reviews and 57 abstracts per investigator over a 3 1/2 year interval. Since 2009, division scientists published their peer-reviewed research in a variety of scientific journals. These include the highest rated (*Science Citation Index*) journals in reproductive biology (*Biol of Reprod, Hum Reprod, Mol Hum Reprod*), developmental biology (*Develop Biol, J Develop Biol*), endocrinology and neuroendocrinology (*Endocrinol, Mol Endocrinol, Am J Endocrinol Metab, Mol Neurobiol, Mol Brain Res*) and clinical reproduction (*J Clin Endocrinol Metab, Obstet Gynecol, A, J Obstet Gynecol, J Clin Invest*). Researchers are also publishing landmark papers in high-profile journals, such as *Nature, Cell* (Fig. 2) and *Stem Cell*. In addition, investigators are publishing more in on-line (*PLoS One*) and specialized journals (*J Biol Chem, Contraception, Placenta, Age, Cryobiology*) that are gaining recognition in emerging fields.

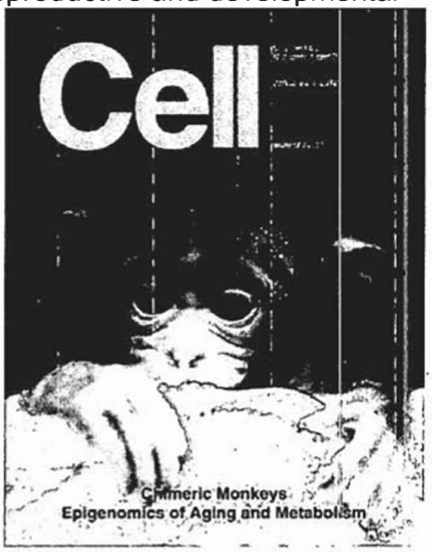


Figure 2. *Cover page highlighting one of three chimeric monkeys from Dr. Mitalipov's landmark research advancing our understanding of early embryonic development in primates. Cell 148:285-295, 2012; plus editorial "Leading Edge Commentary".*

Examples of important publications (2009-present; many cited in the Innovation section) from various laboratory groups are included in the Reference section.

Scientific Impact-Trainees. Since 2009, Division scientists have trained 22 graduate students in their research programs. Six were from other countries, performing their research as sponsored by **international programs** (e.g. the Fogarty Program in International Training and Research in Population & Health, D43 TW00688, 2007-12) with co-mentors at ONPRC, OHSU. The others were students in programs within the Graduate College, OHSU, performed laboratory rotations, and often remained to complete their dissertation research in division laboratories. These students originated from several degree-granting programs, including the Program in Molecular & Cellular Biosciences, Molecular & Medical Genetics, and Neurosciences. A recent example is Excluded by who received her Ph.D. in Behavioral Neurosciences after completing landmark research with Excluded by Requester on the chronic effects of hyperandrogenemia and high-fat diet on adolescent female macaques, and the similarities to neuroendocrine, ovarian and metabolic defects observed in young women with polycystic ovarian syndrome. Notably, 10 of the graduate students were female and five were Hispanic minorities.

The Division also trained 26 postdoctoral (Ph.D.) and 10 clinical (M.D.) fellows in the current grant interval. All laboratories except one (the recently appointed Excluded by were sites of postdoctoral training. Again, female fellows (n=16) are well represented and seven are minorities. While several fellows competed successfully for independent support (e.g., a Lalor Fellowship) or received **international funding** (via the Fogarty program listed earlier), many individuals were initially supported through the NICHD-sponsored training grant T32-HD07133 in Reproductive Biology. Following its renewal for its 31st - 36th years (2010-2015) Excluded by departure required the appointment of a new P.I. In discussions with the NICHD program director, the faculty

decided to appoint Co-directors: (a) Excluded by Requester then Chief, Division of Neuroscience and a internationally renown reproductive neuroendocrinologist at ONPRC, and (b) Excluded by Requester Professor, Department of Physiology & Pharmacology, OHSU, who trained as a postdoctoral fellow at ONPRC and has an active research program in reproductive biology, toxicology and behavior. As an OHSU-wide training program, it provides 1-2 years of support for one graduate student ant two postdoctoral fellows per year. By the second year, trainees and their mentors are expected to pursue other funding sources (e.g., NRSA).

Division trainees historically are recruited into professional positions in academic institutions or industry and develop stellar research-oriented careers. Notably, two postdoctoral fellows competed successfully for NICHD K99/R00 Pathway to Independence Awards one Excluded by Requester was retained as faculty at ONPRC, OHSU after a national search, and one Excluded by Requester was recruited to a tenure-track position at the University of Arizona. One trainee Excluded by Requester recently competed with 11 other applicants and was awarded a BIRCWH scholar position on the ONPRC, OHSU faculty. Our clinical trainees also benefit from their research experience and successfully compete for research fellow positions in infertility, family planning or maternal-fetal-medicine at institutions such as University of Michigan, Columbia University and University of Washington, Seattle. Likewise, our foreign trainees typically return to their home country after being recruited for faculty positions, e.g., Excluded by Requester to Federal University of Santa Catarina, Brazil Excluded by Requester to CEDIE-CONICET, Argentina. Examples of division trainees who became leaders in the field of primate reproductive and developmental sciences include: (1) Excluded by Requester Director, Wisconsin National Primate Research Center, (2) Excluded by Requester DVM, leader in NHP and human stem cell biology, University of Wisconsin, and (3) Excluded by Requester Ph.D., Co-director of Reproductive Sciences Program and Consortium for Stem Cell Therapies, University of Michigan.

Scientific Impact – Service to Profession and Public. Division scientists were very active in promoting the activities of scientific societies and research groups, including organizing and hosting meetings in Oregon and elsewhere. Notably, members served on the Local Arrangements Committee Excluded by Requester chair) for the 44th Annual Meeting of the Society for the Study of Reproduction (SSR), held in Portland, August 2011 Excluded by Requester Excluded by Requester also organized the annual meeting of the NICHD-supported U01 (Program Projects)/U54 (Centers) Contraceptive Development researchers, held in Portland, September 2010. Division investigators and scientists remain active in the annual Northwest Reproductive Sciences Symposium, whose aim is to promote collaborations among researchers in Oregon, Washington, and Idaho, as well as northern California and British Columbia, Canada. The meeting was held at ONPRC, Beaverton, OR, in April 2012, and featured Excluded by Requester Univ. of California-San Francisco, as the keynote speaker. Most recently, Dr. Excluded by Requester organized in International Meeting on Animal Extremism, held June 2012 in Washington, D.C., through the Federation of American Societies for Experimental Biology (FASEB). The Division's senior scientists are leaders in various societies (e.g., Excluded by Requester SSR past-president and active committee member; Excluded by Requester committee member for the Society of Biological Psychiatry, American College of Neuropsychopharmacology; Excluded by Requester past-president of the Endocrine Society and active committee member), and its associate scientists are performing activities of major importance (e.g., Excluded by Requester SSR Board of Directors, and Chair, Program Committee for 2012 meeting; Excluded by Requester Co-chair, SSR Program Committee for 2014 meeting). Also, our OHSU affiliates are internationally known leaders, especially in family planning and contraceptive research (notably Excluded by Requester Board Member of the International Committee for Contraception Research, Program Committee for 2013 meeting of the European Society for Contraception and Reproductive Health). All of the senior and associate scientists have or are serving on federal review boards [e.g., Excluded by Requester member of ICER Study Section 2012-2016; Excluded by Requester FIRCA (2011) and Loan Repayment (2012) Special Emphasis Panels]. Further activities are listed in the scientist's narrative pages.

Division members were also very active in efforts to promote scientific awareness and understanding of reproductive health issues to the public, from younger school-age children to adults. For example, twelve scientists and trainees volunteered to help Excluded by Requester (Director of Education Outreach, ONPRC) to organize and host an all-day activity for over 70 middle school children, called "Camp Monkey", prior to the 2011 SSR meeting in Portland in August. Co-sponsored by SSR and ONPRC, the day included activities to learn about monkeys and their value in research, primate reproduction and development, and issues related to reproductive health. Efforts succeeded in attracting male and female students from several different school systems, including disadvantaged children with little science background. Its resounding success (as documented from students, parents and volunteers), led to plans to provide this "camp" on an annual basis

(August, 2012). Division members also participate in other educational opportunities, including presentations to science classes; [Excluded by Requester] is most active as organizer of Saturday Academy classes for 10-12 high school students/year that offers hands-on laboratory exercises and lectures on "Oncofertility" [Excluded by Requester] also helped organize and teach classes and laboratories in "Advanced Biology: Oncofertility" as the Health & Science School, Beaverton, OR.

Future plans

The DRDS has a remarkable opportunity to sustain and broaden its impact in NHP research and training. With the vision in 2011 to expand its mission to include select aspects of primate developmental biology, especially related to basic and applied aspects of macaque embryonic and adult (iP) stem cell biology and fetal/neonatal health, the expanded division has even greater potential at a local, national and international level. The expansion is timely as federal and international entities recognize the lack of improvements in many aspects of women's health over the past decade. The NICHD acquired a new director ([Excluded by Requester] who is spearheading a re-evaluation of priorities in reproductive research and women's/child health. And private agencies (e.g., [Private Source] are targeting areas of women's reproductive health (including family planning and contraception) critical to controlling the ever growing human population and consequent depletion of world resources. Moreover, the emergence of centers for health research at our home institution at OHSU, including: (1) The Center for Women's Health [Excluded by Requester] director), (2) The Reproductive Endocrinology & Infertility (REI), Family Planning, and Maternal-Fetal Medicine (MFM) units of the Department of Obstetrics & Gynecology [Excluded by Requester] head, recruited 2011), (4) The [Private Source] Cancer Center [Excluded by Requester], director), (5) The Heart Institute [Excluded by Requester], director), (6) The Diabetes Center [Excluded by Requester] director and division member), and (7) The Moore Nutrition Center, [Excluded by Requester] interim director), provide emerging and new avenues for interdisciplinary research in primate reproductive and development science, with direct relevance to human health. Also, other expanding research programs at ONPRC, including the stem cell, aging and child development programs, as well as the newly formed Division of Diabetes, Obesity & Metabolism, provide key opportunities. Finally, expanded use of core facilities at ONPRC/OHSU including: (1) The Virology Core [Excluded by Requester] director), (2) the MRI facility at ONPRC [Excluded by Requester] director) as part of the OHSU Advanced Imaging Core, and (3) the Genetics unit [Excluded by Requester] director), offering second-generation sequencing, provides additional sophisticated techniques that can be applied to systems, cellular and molecular studies on primate reproduction and development. Finally, the value of primate research for "pre-clinical" research bridging the knowledge gap between traditional laboratory animal models and humans is receiving increasing attention as valuable components in portfolios of NIH institutes and pharmaceutical/biotechnology companies with research agendas in reproductive and childhood health.

Within this context, the Division will focus its activities:

Aim 1: To promote research opportunities in existing areas of excellence at ONPRC in primate reproductive & developmental sciences. One area of excellence, that includes core and affiliate scientists at ONPRC, plus collaborators around the world, is contraceptive research and development. In 2012, the NICHD-funded Contraceptive Development & Research Center (CDRC, [Excluded by Requester] at ONPRC, OHSU was renewed for 5 years (2012-2017). This center focuses on use of the macaque model to discover novel methods for blocking fertility in females by preventing oocyte maturation (Project I, [Excluded by Requester], [Excluded by Requester]), ovulation or cumulus-oocyte activity in the mature follicle (Project II, [Excluded by Requester], [Excluded by Requester]) or gamete transport in the female reproductive tract (Project III, [Excluded by Requester]). The CDRC also includes critical collaborations with **international and national investigators** at [Private Source], [Private Source] (notably [Excluded by Requester]) for drug prototypes and pharmacokinetic studies (Projects I-III), and at the University of Minnesota [Excluded by Requester] and Moffitt Cancer Center [Excluded by Requester] for novel drug design and delivery (Project I). However, a 50% cut in the proposed (maximum allowed) budget to $864,000 direct costs per year will significantly impair the rate of progress. Therefore, efforts are beginning to find alternate sources of funding to promote NHP studies as a crucial step in developing the next generation of nonhormonal contraceptives for women.

One likely possibility is the [Private Source]. One of the major goals announced for the [Private Source] "Grand Challenges Program" is to create new technologies for contraception. Notably [Excluded by Requester] has become an ardent and highly visible spokesperson for family planning and

women's rights throughout the world. In 2011, Excluded by received an initial grant, which provided promising data leading a major ($1,000,000) grant in 2012 to explore a novel approach to irreversibly block fertility in female macaques. In July, 2012, Excluded by Requester visited the Private Source campus, made presentations on the current contraceptive program at ONPRC/OHSU, and proposed to establish a Private Source Center for Contraceptive Development that complements federally supported efforts. As a result, we were invited to

Pending Support

Another possibility for significant funding for contraceptive R& D is from pharmaceutical programs. Drs. Excluded by Requester have active ties with companies, such as Private Source Private Source In late 2011, Excluded by Requester participated in an "Expert Meeting on Contraception-on-Demand" sponsored by Private Source Since then discussions have occurred with Excluded by Requester Excluded by about ovary- and reproductive tract-based approaches for "ConD."

As envisioned, the next 5-year interval will expand our international, interdisciplinary program on contraceptive R&D for controlling women's fertility that leverages federal (NICHD), foundation Private Source and pharmaceutical Private Source support. When the NHP research is combined with contraceptive studies on women at OHSU through the NICHD-funded Contraceptive Clinical Trials Center, Excluded by Requester P.I.), our group will be in a unique situation to facilitate rapid translation of drug discovery and validation to novel, nonhormonal contraceptives for family planning and population control.

A second area of excellence at ONPRC is infertility research and its treatment. At the beginning of the previous grant interval (2009), the ONPRC had an active NICHD-funded Specialized Cooperative Center Program in Reproduction Research (SCCPRR) that included three NHP-related research projects on women's infertility. However, NICHD's vision of the composition and activities of SCCPIRRs (now merged with Infertility Centers) changed such that a primarily clinical project is required, and thematic research that synergized to address a single topic is encouraged. Hence, a novel SCCPIRR application was prepared that includes interdisciplinary, translational research to discern the effects of elevated androgen levels with and without a Western-style (high fat and fructose content) diet on: (1) the hypothalamus-pituitary-ovarian axis, as well as adipose tissue, (2) the impact on fertility, and (3) if the treatment effects are reversible. The proposed center includes several scientists from ONPRC Excluded by Requester as well as clinical scientists at UCLA Excluded by Requester and a visiting researcher (and prior ONPRC core scientist, Excluded by Requester three research projects use the NHP macaque model and will likely provide new information on the actions of androgens and diet/obesity-related factors on reproductive function in peri-pubertal to young adult females, with relevance to the etiology and treatment of fertility disorders such as polycystic ovarian syndrome (PCOS). One project involves translational research on a unique subpopulation of PCOS women who are "lean", to dissect the effects of androgen from those of obesity-related factors and to explore therapies to prevent androgen action. With additional strong preliminary data, demonstrating neuroendocrine, ovarian, uterine and adipose dysfunction in treated macaques, we are optimistic that our revised SCCPIRR application (2012) will receive an outstanding score. We hope to finish in the top 2 for funding in 2013; but we are also exploring alternative sources of funding.

Thus, the next 5-year interval will reorient our focus on infertility in women to include a multi-institutional, interdisciplinary program addressing the environmental (notably diet) as well as intrinsic (e.g., androgen) causes of reproductive dysfunction in a NHP model, with direct translation to collaborative clinical studies. This focus includes the emerging topic of the effects of adipose tissue (through adipokines and cytokines) on the reproductive system and fertility. As such, the program will expand collaborative efforts with new members of the Division of Diabetes, Obesity and Metabolism Excluded by Requester Excluded by Requester who have joint appointments in this Division and interests in women's health research. In addition, efforts will continue to provide avenues for research by investigators in other important areas of infertility, such as endometriosis and aberrant menstruation Excluded by Requester and oncofertility Excluded by Requester Excluded by Requester Unfortunately, the NIH's Roadmap Directive, which funded the Oncofertility Consortium (2007-12, no-cost extension to 2013), ended with the appointment of a new NIH Director. However, five grant submissions already include advances in techniques (3-D culture of individual follicles;

novel cryoprotection protocols), plus remarkable preliminary data, that portend major advances in our understanding of the processes and factors controlling development of the mature follicle (and its enclosed oocytes) in macaques, and the translation of our finding to human follicles to provide additional ARTs for preserving or restoring fertility in women after treatments that destroy ovarian function (e.g., radiation or chemotherapy in females).

In support of these programs, the Division will continue to foster productive researchers in contraception and infertility research. In 2011, Excluded by Requester were reviewed by the ONPRC Promotions Committee and promoted to Associate Scientist positions, on their current trajectory they will be eligible for promotion to Scientist positions in 2017. Also, active involvement of affiliate scientists located primarily at ONPRC Excluded by Requester and OHSU Excluded by Requester support these programs. With the renewal of the BIRCWH program at OHSU in late 2012, an outstanding beginning researcher Excluded by competed successfully for a position as BIRCWH scholar and Assistant Scientist, Division of Reproductive & Developmental Sciences. She has already Pending Support

Pending Support

Aim 2: To Expand opportunities in emerging fields of research. Current and recruited scientists in the Division of Reproductive & Developmental Sciences have unique opportunities to contribute to emerging areas of research at the local and national level. These areas focus on priorities developed between ONPRC and its collaborators at OHSU, and from the fledgling "focus groups" proposed 5 years ago which have developed into bonafide research programs:

1) Maternal-Fetal Medicine (MFM). The NHP remains the optimal model for unraveling the mechanisms controlling pregnancy in women from implantation and establishment of the fetal-placental-maternal unit, through intrauterine fetal development, to onset of labor and delivery of the infant. Macaque species have proven valuable in manipulative studies addressing the causes and treatments of pregnancy disorders. While having a presence in this field, recent developments at OHSU and ONPRC provide unique opportunities to become leaders in this field. First, Excluded by Requester was recruited to OHSU in 2010 as Chair, Department of Ob-Gyn and Director, Center for Women's Health (CWH). As an accomplished educator and clinical researcher in MFM from the University of California, San Francisco, Excluded by s committed to fostering collaborative efforts in basic and translational research between ONPRC and Ob-Gyn/CWH. A member of the MFM Division, and former WRHR fellow, Excluded by Requester cently received a joint appointment in DRDS and DOM. Studies will take advantage of expertise in cardiovascular research and non-invasive imaging to study the vascular dynamics of the placenta Excluded by through contrast-enhanced ultrasonography and MRI. Second, after a national search Excluded by Requester was hired as an Assistant Scientist in the Division in 2011 to replace the Excluded by Requester Her plans to use the NHP model to study the causes and prevention of preterm labor, plus the effects on neonatal health, generated strong support for her recruitment as a core scientist. Excluded by Requester has already attracted R01 funding (2012-2017) and initiated new collaborations with researchers in Pediatrics at OHSU Excluded by Requester and elsewhere (including the Washington National Primate Center Excluded by Requester to study effects of intrauterine infection and its treatment on early delivery and neonatal defects.

An important aim in the next 5 years will be to foster integration and collaborations between interested scientists at ONPRC, OHSU and their use of various pregnancy models in NHPs. Excluded by as mentioned above, is already developing ties with OHSU researchers and working with Excluded by Requester to promote a program in Child Health & Development. Importantly, the newly created Division of Diabetes, Obesity and Metabolism also contains members Excluded by and colleagues) interested in the effects of maternal nutrition and obesity on maternal-placental-fetal development and function. An interdisciplinary program involving members of two ONPRC divisions, two OHSU departments (Ob-Gyn, Pediatrics) and two primate centers (ONPRC, WNPRC) is envisioned to improve our understanding of primate pregnancy, its disorders and the effects on the neonate. Likewise, research will utilize expertise in pediatric neuroscience and behavior to evaluate the effects of pregnancy disorders on the fetal/neonatal brain and behavior and possible treatment. **It is proposed that an open position in the Division of Reproductive & Developmental Sciences be leveraged with that from the Division of Diabetes, Obesity & Metabolism to strengthen interactions in this area. Alternatively, a similar option could occur to recruit an outstanding clinical scientist between ONPRC and the MFM Division, Ob-Gyn, OHSU that is interested in NHP research.**

2) Gamete/Embryo/Stem Cell Biology. The ONPRC research program is unique in its ability to provide adequate quantities of primate gametes (oocytes, as well as sperm) and preimplantation embryos for research through the ART Core program. In the past five years, the pioneering efforts of Excluded by Requester and colleagues established the feasibility of generating NHP embryonic stem cell (ESC) lines, not only from natural embryos but from cloned embryos produced by somatic cell (typically fibroblast cells) nuclear transfer (SCNT), as well as pluripotent cells from genetically-engineered somatic cells (iPSCs). **It is proposed to recruit another scientist (potentially leveraged to recruit two with joint support from OHSU programs, such as the Reproductive Endocrinology & Infertility Division, Ob-Gyn) to perform basic and translational research that expands the division's programs in developmental biology and regenerative medicine.** This person would replace Excluded by Requester who departed in 2011 and complement the interests of Excluded by Requester who recently assumed the supervision of the ART Core and is studying the factors/markers that are requisites for generating a healthy (developmentally viable) egg and early embryo. Likewise, the individual could expand efforts employing primate models to regenerate cell types from pluripotent cells for the purpose of restoring tissue function. It is recognized that competition for established researchers in the field of stem cell biology and regenerative medicine is fierce; in the past year, efforts to recruit a senior-scientist-level researcher with interests in translational ties to OHSU programs (notably the Urology program, and Private Source Cancer Center) almost succeeded but were ultimately stymied by family issues. Success may be more likely if we focus on recruiting and mentoring a more junior or beginning scientist.

Finally, in the next two years, it is anticipated that Excluded by Requester s division chief but remain active in the research arena. The ONPRC Director's approach is to select experts from the OHSU community to perform a national search for his replacement. **Based on recent searches, there should be viable candidates for the next Division Chief from within, as well as outside, OHSU. But considering the expertise in ovarian biology provided by other core Excluded by and affiliate scientists Excluded by Excluded by outside candidates in other areas of reproductive and developmental sciences such as MFM or gamete/stem cell biology, or other interdisciplinary programs such as reproductive immunology or aging, would broaden the research scope of the division.**

Aim 3: To ensure availability of primate resources for reproductive and developmental research. As programs continue to grow and mature, considerable oversight and vision is required by ONPRC to anticipate and meet the NHP needs of researchers, including those in the Division of Reproductive & Developmental Sciences. This is particularly relevant for division scientists, since our needs for adult female macaques for studies related to women's health, derive from the same population required to sustain the breeding program at ONPRC. The Division will assist the ONPRC leadership and DCM in efforts to ensure the availability of optimal NHP resources for reproductive and developmental research, including:

1. Participation on the ONPRC Animal Utilization Committee (AUC). This committee, which includes Division Chiefs, reviews all Animal Planning Forms (APF) and Animal Allocation Requests from investigators when submitting and activating a grant, respectively. These documents are reviewed monthly by DCM members and scientists on the AUC for availability of animals and space for the research program. In addition, semi-annual reviews provide a summary of animal needs for pending and active research programs. Also, the AUC requires regular reviews of each animal resource (e.g., the Primate Aging colony, the Timed-Mating Program, the Obese Primate Resource), as well as the breeding colony. The combination of these data helps to develop a realistic perspective on researcher's current and future needs.
2. Work with the DCM leadership for efficient use and management of NHP resources. With ONPRC approaching limitations in space and colony population, divisions can provide feedback on the suitability of animals for protocols, their re-use in other programs, or sale as unneeded NHPs. During the current 5-year interval, consultation with Excluded by generated a user-friendly software program to evaluate the reproductive history of monkeys (e.g., chronologic presentation of menstrual periods, interval of menstruation, number of menstrual cycles, intervals of pregnancy and characteristics of offspring) that aids in selection of reproductively competent females. Likewise, it can be used to identify "irregular or noncycling" females for assignment to other studies or removal (sale) from the colony. Recently (late 2012), DCM and division representatives began working with Excluded by Requester nd colleagues at Portland State University to develop a computer simulation program to provide real-time information on the NHP colony at ONPRC and to project effects of manipulations (e.g., removing 80 adult females/year for research) over time. This tool will provide valuable insight regarding colony management and use. The

division chief and other representative animal users will help in the validation and use of this tool, as well as conversion from the antiquated IRIS program to LabKey (see IS section) for modern acquisition and utilization of NHP data as relevant to research protocols.

3. Research growth in areas that do not require large numbers of female rhesus macaques. First, expansion of areas in maternal-fetal-medicine and stem cell biology would potentially require few (~10) animals per project. For example, Excluded by Requester recent R01 requires 6 pregnant females/year from the Timed Mated Breeding Colony. Characterization of NHP stem cell lines would only require a few monkeys for their generation (or perhaps none if using cryopreserved lines), and ultimately for their testing in vivo for tissue regeneration. Second, alternatives to rhesus macaques can be considered. The cynomolgus macaque displays characteristics similar to those of rhesus females, with some advantages, such as their year-round retention of ovarian cyclicity and more docile nature. For these reasons, ONPRC investigators are using these animals in contraceptive trials within the NICHD-funded CDRC. We plan to expand the use of cynomolgus macaques within Pending Support

Aim 4: To promote efforts to train scientists that focus on primate and human reproductive health. Part of the Division's mission is to train the next generation of researchers dedicated to using NHP models to produce advances in understanding and improving women's reproductive health and human (fetal and neonatal) development. To that end:

1. Undergraduate training will be offered primarily as 8-week summer internships. Applications are submitted through the Education Outreach Coordinator Excluded by at ONPRC. Those indicating interest in reproductive and development sciences will be reviewed by division scientists; 4-5 summer interns are typically selected per summer. For many interns, this is their first in-depth laboratory experience with exposure to the scientific method, modern research techniques and ethical issues of animal research.
2. Graduate training will continue primarily through programs offered within the Graduate College, OHSU. Newly recruited scientists (e.g., Excluded by Requester will be encouraged to develop joint faculty appointments in OHSU that provide teaching opportunities and visibility to entering students. Attention will again focus on the renewal of the NICHD-funded T32 Training Grant in Reproduction. It is anticipated that Excluded by Requester (Co-P.I.) will retire prior to its renewal in 2015, and another ONPRC scientist, preferably within the division, will assume the directorship of this program with Excluded by Requester Co-P.I.). Over the past decade, division involvement in his department (Physiology & Pharmacology) diminished, due to the primary focus of the department chair on chemical biology. Efforts to re-invigorate involvement will be a goal as the current chair Excluded by Requester sumes more responsibility for training grant activities.
3. Postdoctoral training. Postdoctoral fellows and their career development will be a continued focus of divisional research laboratories. Fellows (Ph.D., M.D., D.V.M.) will be recruited into slots on the Reproduction Training Grant, and encouraged to submit applications for individual awards (e.g., NIH NRSA, Lalor Foundation). Clinical fellows and residents will be recruited through Ob-Gyn programs (e.g., Family Planning) and Medicine to pursue research related to women's reproductive health. Unfortunately, a key program that contributed to the international character and research training experience, the Fogarty Program in Population & Health, is ending, in part because of the success of the program. As a result, Fogarty applications for training (D43) programs can no longer include G20 countries, which excludes our connections with Mexico, Argentina and Brazil. One option is to develop a program related to other emerging countries, particularly in Africa Pending Support

Pending Support

Based on the current economic and professional climate, it is critical that our selection and mentoring committees accept only high-potential trainees and provide them with non-traditional training outside of reproductive and developmental biology. Notably, OHSU and the Oregon Center for Translational Research (OCTRI) offer a variety of programs ranging from Ethics in Research, to Grant Writing, and Clinical-based Research. Advanced postdoctoral fellows motivated to research-oriented careers in reproduction and development in NHP models and women's/child health, will be encouraged to pursue NIH K-type awards (e.g., K99/R00 Pathway to Independence) to facilitate their transition to independent positions at quality institutions.

Pages 994-1010 (Publications) Removed – Excluded by Requester

Externally Funded Research Projects – Developmental and Reproductive Sciences

Excluded by Requester

Oregon National Primate Research Center
Norepinephrine in Stress-Induced Amenorrhea of Macaques
NICHD - R21 HD062864
Determine whether the brain stem norepinephrine system plays a role in the mechanisms by which common life stresses (i.e., dieting, moderate exercise and psychological stress) impair activity of the reproductive axis.

Excluded by Requester

Oregon National Primate Research Center
Ovarian Steroid Regulation of Serotonin in Primates
NIH/NIMH - R01 MH62677
Determine the cellular and molecular actions of estrogen and progesterone in serotonin neurons of nonhuman primates.

Excluded by Requester

Oregon National Primate Research Center
Postmenopausal Monkey Resource
NIH/OD - R24 OD000895
The goal of this project is to establish a postmenopausal monkey resource with aged ovariectomized rhesus monkeys on a Western diet.

Excluded by Requester

Oregon National Primate Research Center
Role of Serotonin in Mediating Stress-Induced Infertility
NIH/NICHD - Subcontract w/University of Pittsburgh - R01 HD062618
Examine the ability of a serotonin reuptake inhibitor to therapeutically treat stress induced infertility in women and in female monkeys.

Excluded by Requester

Oregon National Primate Research Center
Specialized Cooperative Centers Program in Reproductive & Infertility Research (SCCPRR):
NIH/NICHD - U54 HD018185
Project I: Determine effect of mild stress on pregnancy rate in primates and IVF success in patients. Primate Reproductive Tissue Bank: Collect and distribute monkey reproductive tissues to U54 investigators.

Excluded by Requester

Oregon National Primate Research Center
Steroid Regulation of Serotonin in Male Macaques
NIMH - R01 MH086542
The purpose of this project is to determine how androgens regulate the serotonin neural system in male nonhuman primates.

Excluded by Requester

Oregon National Primate Research Center
The Primate Corpus Luteum: Functional Regression and Cardiovascular Impacts
DHHS NIH/NICHD - K99 HD067678
Contribute to better management of cardiovascular disease (CVD) risk in women by determining how reproductive processes influence CVD risk factors.

Excluded by Requester

Oregon National Primate Research Center
Behavioral Genomics of Alcohol Neuroadaptation
DHHS NIH/NIAAA - P60 AA010760
Address the causes vs. effects of androgen as related to reproductive dysfunction. Mechanistic studies in primates and lean PCOS women will discern between the roles of peripubertal androgen exposure and diet, and offer insight into improving therapy for infertility.

Excluded by Requester

Oregon National Primate Research Center
CDI-Type I: Computational Models for the Automatic Recognition of Non-Human Primate Social Behaviors
NSF – BCS-1027834

The goal of this project is to create and develop remote monitoring tools for measuring and understanding behavior of monkeys in a social group.

Excluded by Requester

Oregon National Primate Research Center

Factors Underlying Alopecia in Rhesus Macaques

Private Source

The goal of this project is to examine the various factors that may be associated with alopecia in rhesus macaques, including self-epilating behavior, temperament, and stress levels.

Excluded by Requester

Oregon National Primate Research Center

Self-Injurious Behavior and Primate Well Being
DHHS/NIH – R24 RR011122
Investigate potential correlates self-injurious behavior (SIB) and alopecia in captive rhesus monkeys

Excluded by Requester

Oregon National Primate Research Center

Gonadotropin-Releasing Hormone Action
NIH/NICHD - R01 HD019899
The long-term goal of these studies is centered on the molecular mechanisms by which gonadotropin releasing hormone (GnRH) regulates the pituitary gonadotrope.

Excluded by Requester

Oregon National Primate Research Center

High Throughput Screening Assay Development for Pharmacoperones
NIH/NIDDK - R01 DK085040
This is a 3 year project to develop a high-throughput screen for pharmacoperone drugs from chemical libraries

Excluded by Requester

Oregon National Primate Research Center

High Throughput Screening for Pharmacoperones: A New Class of Therapeutics

Private Source

Development of High-throughput Screens for Pharmacoperone Drugs

Excluded by Requester

Oregon National Primate Research Center

International Training & Research in Population & Health Training Grant
DHHS NIH Fogarty International Center - D43 TW000668
Supports fellowships for Mexican and Brazilian nationals at ONPRC/ OHSU who are interested in pursuing an advanced degree or seeking sabbatical or postdoctoral support in the Reproductive Sciences.

Excluded by Requester

Oregon National Primate Research Center

Mouse Model for Diseases of Protein Misfolding
NIH/OD - R21 OD012220
The goal of this project is to develop and characterize two animal models for human (and animal) diseases of misfolded proteins.

Excluded by Requester

Oregon National Primate Research Center

Compartmental Analysis of Proteomics Biomarkers during Intra-uterine Infections
NIH/NICHD - R00 HD055053
Expand understanding of the pathophysiology of choriodecidual inflammation/infection with U.parvum in a nonhuman primate model.

Excluded by Requester

Oregon National Primate Research Center

Primate Model of Ureaplasma In Utero Infection: Prevention of Neurologic Sequelae

Private Source

Establish a special care nursery (SCN) that will support postnatal survival of prematurely born rhesus monkeys exposed to Ureaplasma and antibiotic treatments in utero.

Excluded by Requester

Oregon National Primate Research Center

Primate Model of Mid-gestation Ureaplasma in utero Infection: Prevention of Neurologic Sequelae

NICHD/NINDS - R01 HD069610

Determine the extent of cerebral white matter inflammation and neuronal injury caused by prolonged Ureaplasma intra-amniotic infection (IAI) and to assess the efficacy of antenatal therapy to prevent neurologic damage in the fetus and adverse neurobehavioral consequences in the neonate.

Excluded by Requester

Oregon National Primate Research Center

Studies of Ureaplasma Invasion of Epithelial Cells

Private Source

Summer employment of a high school teacher to extend and complement the in vivo data obtained from experimental choriodecidual model and to learn modern scientific techniques and concepts that can influence their teaching and encourage students to consider science careers.

Excluded by Requester

Oregon National Primate Research Center

Studies of Ureaplasma Invasion of Epithelial Cells

Private Source

Summer employment of a high school teacher to extend and complement the in vivo data obtained from experimental choriodecidual model and to learn modern scientific techniques and concepts that can influence their teaching and encourage students to consider science careers.

Excluded by Requester

Oregon National Primate Research Center

Characterization of Transcriptome in Primate Ovarian Function

Private Source

Summer employment of a high school teacher to learn modern scientific techniques and concepts that can influence their teaching and encourage students to consider science careers.

Excluded by Requester

Oregon National Primate Research Center

Contraceptive Development Research Center (CDRC) - Contraception by Blockade of Periovulatory Events in Primates: Control of Follicular and Cumulus-Oocyte Activity

NIH/NICHD - U54 HD055744

The objectives of this project include the characterization of factors responsible for the expansion of the cumulus granulosa cell complex surrounding the oocyte and its release from the ovulatory follicle, and (2) whether antagonists to these factors could serve as novel, nonhormonal contraceptive targets.

Excluded by Requester

Oregon National Primate Research Center

Identification and Characterization of Kev Proteases Necessary for Ovulation

Private Source

Summer employment of a high school teacher to learn modern scientific techniques and concepts that can influence their teaching and encourage students to consider science careers.

Excluded by Requester

Oregon National Primate Research Center

Leukemia Inhibitory Factor as a mediator of Primate Ovulation & Oocyte Maturation

NIH - R21 HD072528

The goal of this project is to determine the role leukemia inhibitory factor (LIF) plays in regulating key events in primates that are necessary for the release of an oocyte that is capable of undergoing fertilization, implantation and embryonic development.

Excluded by Requester

Oregon National Primate Research Center

Prostaglandin Synthesis and Action in the Primate Corpus Luteum

NIH/NICHD - R01 HD42000-07 and ARRA (Stimulus Funding)

The major goal of this project will be to understand the role of prostaglandin-E2 in macaque luteal development and function, as well as the role of prostaglandin-F2α in its regression during non-fertile cycles.

Excluded by Requester

Oregon Health and Science University

Contraceptive Development Research Center (CDRC) - Contraception by Blockade of Periovulatory Events in Primates: Control of Oocyte Maturation

NIH/NICHD - U54 HD055744

Project I addresses the hypothesis that novel follicle cell- and oocyte-derived proteins control nuclear and cytoplasmic maturation of the oocyte, and can be exploited to prevent timely egg maturation and hence fertility during the menstrual cycle.

Excluded by Requester

Oregon Health and Science University

PDE3 Inhibitors: Selective Blockers of Oocyte Maturation

DHHS NICHD - R01 HD042710

Explores molecular biology of the phosphodiesterase system of the primate ovary, and feasibility of PDE3 blockade as a novel contraceptive strategy.

Excluded by Requester

Oregon Health and Science University

Transcervical Polidocanol as a novel method of nonsurgical female sterilization: initial studies in the nonhuman primate

Private Source

This project addresses the feasibility of using the local administration of a schlerosing agent to block gamete transport in the oviduct.

Excluded by Requester

Oregon Health and Science University

Polidocanol Foam for Permanent Female Contraception

Private Source

This project continues the exploration of using the local administration of a schlerosing agent to block gamete transport in the oviduct.

Excluded by Requester

Oregon National Primate Research Center

Altered Nuclear Transfer

NIH/NICHD - R01 HD059946

The goal of this project is to explore modifications in SCNT in macaques that dramatically improve the efficiency of reprogramming and the derivation of patient-specific pluripotent cells for cell replacement therapy while avoiding the creation and destruction of totipotent embryos.

Excluded by Requester

Oregon National Primate Research Center

Evaluation of Stem Cell-derived RPE Cells

NIH/NIE - EY021214-0

The goal of this proposal is to study the functionality of retinal pigment epithelium cells generated from three macaque stem cell sources and investigate the immune response to these cells in various situations that mimic their clinical application.

Excluded by Requester

Oregon National Primate Research Center

Genetic Analysis of Germ Cell Formation

NIH Subcontract with Stanford University - R01 HD047721

The major goal of this project was to use human embryonic stem cells (hESCs) to specifically probe the genetics of germ cell formation in vitro and in vivo using federally approved hESC lines and a primate model.

Excluded by Requester

Oregon National Primate Research Center

Genetically Modified Rhesus Monkeys

NS/NINDS NIH - R01 NS044330

The objective was to create the infrastructure necessary to produce genetically modified somatic cells in culture and to use those cells as donors for nuclear transfer.

Excluded by Requester

Oregon National Primate Research Center

Histocompatible Primate Embryonic Stem Cells
NIH/NICHD - R01 HD057121
The goal of this project is to generate important new insights concerning reprogramming of primate somatic cells to the pluripotent state employing somatic cell nuclear transfer (SCNT) and direct reprogramming approaches.

Excluded by Requester

Oregon National Primate Research Center

Mitochondrial Gene Therapy
NIH/NICHD - R01 HD063276
The goal of this project is to explore the feasibility, efficiency and safety of mitochondrial gene replacement in eggs prior to fertilization in a clinically relevant nonhuman primate model.

Excluded by Requester

Oregon National Primate Research Center

Pluripotent Stem Cells in Development and Disease
NIH/NICHD - Subcontract 26-3301-6570
Magee-Women's Research Institute & Foundation
The goal of this project is to investigate the potential of rhesus monkey pluripotent cells experimentally induced by reprogramming of adult somatic cells using two different approaches: somatic cell nuclear transfer (SCNT) and direct reprogramming for translational therapeutic application in humans.

Excluded by Requester

Oregon National Primate Research Center

Propagation of Monkey Models of Human Disease
NIH - R01 RR016030
Major goal was to propagate MHC type Mamu A-01 rhesus macaques through application of the Assisted Reproductive Technologies (ART).

Excluded by Requester

Oregon National Primate Research Center

Specialized Cooperative Centers Program in Reproductive & Infertility Research (SCCPRR)
NIH/NICHD - U54 HD018185
To increase our understanding of the causes and to improve treatment of infertility in women, by using macaque models to investigate the mechanisms whereby various stressors cause infertility.

Excluded by Requester

Oregon National Primate Research Center

Translating Human Pluripotent Stem Cells from Heart Disease Models to Cardiac Repair
Transatlantic Networks of Excellence in Cardiovascular Research Program Private Source
This transatlantic alliance, consisting of several PI's in the UA and Europe, focuses on the potential of human iPSCs and ESCs to study cardiac diseases and as a source of cells for regenerative therapy.

Excluded by Requester

Oregon National Primate Research Center

Regulation of Cumulus-Oocyte Expansion in Primates
Private Source
Postdoctoral training to develop an in vitro system for studying macaque cumulus-oocyte expansion and its control by hormonal and intrafollicular factors.

Excluded by Requester

Oregon National Primate Research Center

Alogliptin Effects on Pancreatic Islet Function
Private Source
The goal of this project was to assess the effects of a DPP-4 inhibitor on isolated islet function and response to incretin hormones.

Excluded by Requester

Oregon National Primate Research Center

Control of Glucagon Secretion by Native and DPP-4-Processed GLP-1
Private Source

The goal of this project is to evaluate the effects of DPP-4 inhibition on glucagon secretion in intact islets and in isolated alpha cells.

Excluded by Requester Oregon National Primate Research Center
Herstatin: A Novel Cancer Therapeutic
OHSU BioScience Innovation Program - Pilot research grant
The goal of this project was the development of a novel HER-2 gene product as a cancer therapy.

Excluded by Requester Oregon National Primate Research Center
Molecular Mechanisms of Human and Murine Beta Cell Proliferation And Regeneration
NIH/NIDDK subcontract w/Vanderbilt U - U01 DK089572
This project will test the hypothesis that key genes and/or environmental stimuli that promote rodent β-cell proliferation can induce the proliferation or regeneration of human or non-human primate (NHP) β-cells.

Excluded by Requester Oregon National Primate Research Center
Molecular Mechanisms Underlying NHP Pancreatic Beta Cell Failure and Recovery
NIH/NIDDK - R24 DK093437
The goal of this project is to characterize the NHP as a model for beta cell response to bariatric surgery.

Excluded by Requester Oregon National Primate Research Center
Optimized receptor binding profile in an ultra-stable, ultra-rapid-acting insulin
NIH/NIDDK Subcontract - R34 DK09204
The goal of this project is to characterize novel insulin analogs with respect to insulin receptor activation and cross-reaction with IGF-I receptor and tumorigenicity.

Excluded by Requester Oregon National Primate Research Center
An Ultra Fast-Acting, Ultra Stable Insulin Analog
DHHS/NIH NIDDKD, SRA-11-088
This project will assess the efficacy in vitro and in vivo of a novel insulin analog.

Excluded by Requester Oregon National Primate Research Center
Progestin releasing intra-uterine systems (IUS) and vaginal rings
Private Source
Goal is to develop new progestin-releasing intrauterine systems and vaginal rings that have fewer uterine bleeding-related side effects than those currently available.

Excluded by Requester Oregon National Primate Research Center
Characterization of Retinoid Receptors in the Nonhuman Primate Endometrium during the Menstrual Cycle
Private Source
Summer employment of a high school teacher to learn modern scientific techniques and concepts that can influence their teaching and encourage students to consider science careers.

Excluded by Requester (PI, Project III) Oregon National Primate Research Center
Contraception by Blockade of Periovulatory Events in Primates - Control of Gamete Transport and Fertilization
NIH/NICHD - U54 HD055744
Project III investigates a novel strategy for female contraception that utilizes a new class of drugs, the Selective Estrogen Receptor Modulators (SERMs).

Excluded by Requester Oregon National Primate Research Center
Effect of Novel Androgens on Ectopic Endometrium in Rhesus Macaques
Private Source
Effect of novel androgens on ectopic endometrium in rhesus macaques: Use of androgen-releasing intrauterine devices.

Excluded by Requester

Oregon National Primate Research Center

Effect of Novel Androgens on Ectopic Endometrium in Rhesus Macaques

Private Source

Continue stuy on the effect of novel androgens on ectopic endometrium in rhesus macaques: Use of androgen-releasing intrauterine devices.

Excluded by Requester

Oregon National Primate Research Center

Intra-Uterine Administration of a Selective Glucocorticoid Receptor Agonist in Cynomolgus Monkeys

Private Source

Our goal is to investigate new androgen-based therapies for endometriosis

Excluded by Requester

Oregon National Primate Research Center

Microarray Analysis of RNA from Ectopic Endometrium in Rhesus Macaques

Private Source

The goal of this study was to analyze gene expression in archived samples of eutopic and ectopic endometrium by Affymetrix GeneChip® Rhesus Macaque Genome Array.

Excluded by Requester

Oregon National Primate Research Center

Molecular Analysis of Estrogen Action in the Rhesus Macaque Fallopian Tube

Private Source

Summer employment of a high school teacher to learn modern scientific techniques and concepts that can influence their teaching and encourage students to consider science careers.

Excluded by Requester

Oregon National Primate Research Center

Preclinical Studies on Human Fibroids in Immunodeficient Mice

Private Source

The goal of this study was to develop a new model for studies of uterine fibroids where human fibroid explants are engrafted into immunodeficient mice.

Excluded by Requester

Oregon National Primate Research Center

Preclinical Studies on NHP Endometrial Xenografts

Private Source

The goal of this study is to assess the action of estrogen receptor beta agonists in rhesus macaques.

Excluded by Requester

Oregon National Primate Research Center

Studies on Menstrual Bleeding in Artificially-Cycled Rhesus Macaques

Private Source

The goal of this study is to investigate gynecological indications of dysfunctional uterine bleeding.

Excluded by Requester

Oregon National Primate Research Center

Suppression of Menstrual Bleeding in Rhesus Macaques with Chemokine Inhibitors

Private Source

We tested two proprietary compounds that specifically block the receptors for IL8 and MCP-1 and that could provide a therapy for excessive menstrual bleeding.

Excluded by Requester

Oregon National Primate Research Center

Androgen Exposure in Female Prepubertal Monkeys Relevance to PCOS?

NIH/NICHD Subcontract with University of Virginia - GC11822-134177

Collaborative effort between SCCPIR centers to develop a NHP model for polycystic ovarian syndrome by treating peripubertal macaques with testosterone and a Western-style diet.

Excluded by Requester

Oregon National Primate Research Center
Contraception by Blockade of Periovulatory Events in Primates
NIH/NICHD - U54 HD055744
To develop the next generation of reversible or nonreversible nonhormonal contraceptives for women that specifically block oocyte maturation (Project I), ovulation and/or cumulus-oocyte interactions (Project II) or gamete transport in the reproductive tract (Project III).

Excluded by Requester

Oregon National Primate Research Center
Contraception by Blockade of Periovulatory Events in Primates
Administrative Supplement (ARRA Funding)
NIH/NICHD - HD055744-03W1
The goal of the ARRA supplement was to accelerate scientific research that is ongoing within the Oregon National Primate Research Center and Contraceptive Development Research Center.

Excluded by Requester

Oregon National Primate Research Center
Contraceptive Trial Testing a PGE2 Receptor Antagonist in Female Monkeys
Private Source
Test in group-housed macaques to determine the efficacy and reversibility of a PGE2 receptor antagonist in blocking fertility without altering menstrual cyclicity

Excluded by Requester

Oregon National Primate Research Center
Gene Expression in the Primate Corpus Luteum during Early Pregnancy
Private Source
Summer employment of a high school teacher, to learn modern scientific techniques and concepts that can influence their teaching and encourage students to consider science careers.

Excluded by Requester

Oregon National Primate Research Center
Prepubertal Exposure to Testosterone Monkey
NIH/NICHD Subcontract with U of California at San Diego - 10303850-SUB
Collaborative effort between SCCPIR centers to develop a NHP model for polycystic ovarian syndrome by treating peripubertal macaques with testosterone and a Western-styled diet.

Excluded by Requester

Oregon National Primate Research Center
Polycystic Ovarian Syndrome Model: Androgen-treated Pubertal Monkeys
NCRR/NIH Subcontract with Univ. of Pittsburgh - R21 RR030276
To determine if exposure of prepubertal monkeys to chronically elevated testosterone levels, combined with a high fat, high fructose diet, led to symptoms comparable to those in young women developing polycystic ovarian syndrome.

Excluded by Requester

Oregon National Primate Research Center
Progesterone Receptor and Action in the Primate Ovary
NIH/NICHD - R01 HD020869
Investigate the local actions of steroid hormones, notably progesterone, via either genomic or non-genomic receptor-mediated signaling pathways, to control events in the primate (macaque) ovulatory follicle and in the corpus luteum of the menstrual cycle or early pregnancy.

Excluded by Requester

Oregon National Primate Research Center
R01B – The Oncofertility Consortium: Bioengineering Primate Follicles - From Immature Eggs to Live Births - From Immature Eggs to Live Births
NIH/NCRR/NICHD - RL1 HD058294
Interdisciplinary, collaborative effort with multiple investigators to develop procedures for preventing fertility loss in female cancer patients, with R01B targeted at techniques that (a) grow macaque preantral follicles in 3-D culture to the stage that their enclosed oocytes are capable of fertilization and embryo development, and (b)

promote the restoration of ovarian cyclicity and function after removal, cryopreservation, thawing, and autotransplantation of macaque ovarian cortex.

Excluded by Requester

Oregon National Primate Research Center
Specialized Cooperative Centers Program in Reproductive & Infertility Research (SCCPRR)
NIH/NICHD - U54 HD018185
To increase our understanding of the causes and to improve treatment of infertility in women, by using macaque models to investigate the mechanisms whereby various stressors cause infertility (Project I), neuroendocrine dysfunction prevents timely puberty (Project II), and controlled ovarian stimulation in IVF protocols cause ovarian hyperstimulation syndrome (OHSS; Project III).

Excluded by Requester

Oregon National Primate Research Center
Pursuit of Novel Strategies to Prevent Ovarian Cancer
NIH/NCRR Supplement - P51 RR00163
This is a collaborative project between ONPRC and Ob-Gyn (OHSU). Determine whether clinical trials may begin immediately, and to determine if pharmacological and surgical alternatives will be effective in patients.

Excluded by Requester

Oregon National Primate Research Center
Biology of the Ovarian Surface Epithelium
NICHD - R01 HD050356
Investigate the nonhuman primate ovarian surface epithelium and its potential regulation of ovarian cyclicity and ovulation; in addition study the complementary influence of the ovary on this population of cells, in the context of ovarian cancer.

Excluded by Requester

Oregon National Primate Research Center
R01A - The Oncofertility Consortium: Fertility Preservation in Women - Assessment of Ovarian Tissue Cryopreservation Methods in Non-Human Primates
NIH/NCRR/NICHD - RL1 HD058293
Compare the vitrification freeze-thaw method to the slow freeze method using ovarian cortex from rhesus monkey and to test novel cryopreservation options

Excluded by Requester

Oregon National Primate Research Center
Contraception by Blockade of Periovulatory Events in Primates: Control of Oocyte Maturation
NIH/NICHD - U54 HD055744
Project I: Investigate a novel strategy for female contraception that utilizes PDE and WEE2 inhibitors to disrupt timely meiotic maturation of the macaque oocyte, thereby preventing fertilization and pregnancy. The NPC: Maintain a breeding colony of cynomolgus macaques to provide cost-effective contraceptive trials of ovary/reproductive tract-specific agents as reversible contraceptive agents in a nonhuman primate model.

Excluded by Requester

Oregon National Primate Research Center
Role of stress in the development of the polycystic ovarian syndrome (PCOS): neuronal mechanisms

Private Source

The goal of this project is to investigate the effects of neurotransmitters, e.g. norepinephrine, on the function of macaque preantral follicles during 3-dimensional culture.

Excluded by Requester

Oregon National Primate Research Center
Pre-Clinical Trials for Female Fertility Preservation
NIH/NICHD Subcontract U. of Massachusetts - R01 HD045787
Investigate the efficacy of sphingosine-1-phosphate as a protective agent against radiation-induced follicle and oocyte loss in the nonhuman primate ovary.

Excluded by Requester

Oregon National Primate Research Center

Study of Models for Preserving Ovarian Function from Anti-Cancer Therapy

Private Source

Summer employment of a high school teacher, to learn modern scientific techniques and concepts that can influence their teaching and encourage students to consider science careers.

Excluded by Requester

Oregon National Primate Research Center

Studies of Cryopreservation of Ovarian Function from Anti-Cancer Therapy

Private Source

Summer employment of a high school teacher, to learn modern scientific techniques and concepts that can influence their teaching and encourage students to consider science careers.

Excluded by Requester

Oregon National Primate Research Center

Gene Expressions in 3D Follicles Pilot Project

Northwestern University Subaward - UL1 DE019587

Examine difference in gene expression between small antral follicles cultured in the 3D system and those developed in vivo during the spontaneous menstrual cycle in nonhuman primates.

RESOURCES

Follow the 398 application instructions in Part I, 4.7 Resources.

Division of Reproductive and Developmental Sciences

Laboratory:

The majority of Core Scientists with their primary appointments in the Division moved from the original Research Building to the Facility Security Five Core Scientists Excluded by Requester Excluded by Requester plus two Affiliate Scientists with major research programs Excluded by Requester occupy 900 sq. ft. research laboratories on the Facility Security Facility Security This location also contains newly renovated space for the Assisted Reproductive Technologies (ART) Core directed by Excluded by Requester plus facilities of the Imaging Core directed by Excluded Excluded by Requester One Core Scientist Excluded by Requester occupies a 1200 sq. ft. research laboratory in the Facility Security Facility Security One Core Scientist Excluded by Requester occupies a 1200 sq. ft. laboratory in the Facility Security Other Affiliate Scientists Excluded by Requester have smaller (≤ 500 sq. ft.) laboratories, typically adjacent to or merged with areas of established scientists that provide mentoring and collaborative opportunities. All Staff Scientists perform their research in space assigned to Core Scientists. Open 900 sq. ft. laboratories exist on the first and second floor of the VGTI/ONPRC Building for two scientists to be recruited in the next grant interval.

Each scientist with an independent research program has a well-equipped laboratory with general (e.g., low-speed centrifuges, refrigerators, freezers, pH meters, shaker baths) and specialized (e.g., ultracentrifuges, -80° freezers, thermal cyclers, electrophoresis systems, spectrophotometers, microplate readers, bright-field, Nomarski, and fluorescence microscopes, cell culture hoods and incubators) for molecular, cellular, and systems approaches to experiments. Equipment varies per laboratory based on the research focus.

Clinical:

N/A

Animal:

All animal protocols are performed in separate areas from investigators' laboratories, either in the rodent area Facility Security Facilities for nonhuman primates and animal care programs are accredited by the AAALAC. Health care and husbandry are expertly provided by the veterinary scientists and colony staff in the DCM. The ONPRC core grant provides outstanding facilities and infrastructure for nonhuman primate (NHP) husbandry and research support (animal care technicians, and twelve veterinarians including Excluded by Requester Head, DCM, three pathologists and two surgical veterinarians). Pair-housed cages for approximately 1,500 nonhuman primates, including those assigned to Division projects, are located in the Specific Animal Location Animals receive a physical examination by a veterinarian before assignment to any project. All surgery on nonhuman primates is performed in dedicated aseptic operating rooms Facility Security The surgery facilities, supervised by the surgical veterinarian, Excluded by Requester are used daily by his staff to perform various procedures for the DRDS, including biopsies, subcutaneous implants of hormones, hysterotomies, organ biopsies, ovariohysterectomies, maternal-fetal monitoring, vascular catheter implants and exploratory laparotomies and laparoscopies. Major surgical support equipment includes steam and ETO sterilizers, gas anesthetic machines with gas scavengers, surgical tables, surgical lights, electrocautery, monitors for ECG, temperature, pulse oximetry, blood pressure and end-expired CO2. The Facility Security Facility Security Post-operatively, animals are observed by the Surgery Staff, DCM Area Supervisor and animal technicians, and are reviewed daily by the veterinary staff. For further details, refer to the DCM section.

In addition, the DCM provides specialized animal resources to assist investigators in their research fields, e.g., the Timed-Mating Breeding (TMB) Program and Obese Nonhuman Primate Resource. The TMB Program provides investigators with macaques at known stages of pregnancy, particularly for investigation of maternal-fetal interactions and effects of agents on fetal development and delivery. The Obese NHP Resource maintains colonies of Japanese, rhesus and cynomolgus macaques to support investigations on the effects of

maternal diet and metabolic health on prenatal and neonatal development. These resources are expanding our effort to understand the complications and progression of diseases (e.g., cardiovascular disease, metabolic dysfunction) associated with obesity.

Computer:
All Core and Staff Scientists have PC or Mac computers and full internet and linked printer access.

Office:
Each Core Scientist and many Affiliate Scientists [Excluded by Requester] have 200 sq. ft. offices in close proximity to the research areas. Other Affiliate [Excluded by Requester] Visiting [Excluded by] and Staff Scientists share smaller offices. In general, trainees (graduate students, postdoctoral fellows) and technicians have desk areas within the laboratory.

Other:
The ONPRC supports in full, or partially with OHSU, research support core laboratories that facilitate research projects in the Division (See CORE SCIENCE SERVICES). Those of particular relevance to the Division's research include:

1. Endocrine Technologies. This core enables analysis of multiple hormones and endocrine factors using ELISA, RIA and Luminex assays optimized for NHP samples.

2. Assisted Reproductive Technologies. This core provides a number of services critical to division projects including: (a) samples of sperm, and (b) performance of in vitro fertilization, preimplantation embryo culture, and single embryo transfers for pregnancy. The core also provides oversight of the research ultrasonography systems (GE Voluson; Siemens) used for analysis of ovarian follicular populations and ovarian plus uterine vascular parameters.

3. Magnetic Resonance Imaging. This core contains a Siemens 3T Trio MRI instrument dedicated to nonhuman primate imaging. It is located in its own 2500 ft2 building, adjacent to the Animal Services Building surgical area, and includes animal preparation areas and offices. Several division programs use this facility, in tandem with ultrasonography in the surgical area, to quantitate adipose sites and vascular parameters in the primate reproductive tract and maternal-fetal-placental unit.

4. Flow Cytometry. This core contains four analyzers, two Becton Dickinson FACS Calibur analyzers and computers, plus 2 LSR 2 systems. These systems offer the opportunity for 4-18 color (parameter) analysis of cell populations using 2-3 lasers. The facility contains an Aria II FACS for 3 laser, 14-color rapid sorting (usually 5-10,000 cells/sec at 25 psi) of cells. This facility is used to characterize and sort cell types in reproductive tissues, such as the corpus luteum.

5. Molecular Virology. This core offers production of standardized virus stocks, assays for quantifying viruses and virus-specific antibodies, plus derivation and maintenance of cell systems needed to propagate viruses. This unit has become a valuable resource in efforts to produce adenoviral vector systems for reproductive studies.

Scientific Environment
The ONPRC and OHSU provide an exceptionally supportive environment for studies on primate reproductive and developmental sciences. Major strengths of the institution that directly impact our ability to successfully conduct studies related to women's and child health include: (1) the magnitude and scope of the nonhuman primate resource, notably adult, regularly cycling female macaques, but also special, unique resources including time-mated females offering pregnancies at well-defined stages of pregnancy, females before (pre-pubertal) and after (peri-to-post menopausal) reproductive age, and females receiving health-varying treatments such a Western-style (high fat/fructose) diet, (2) a broad array of clinical (e.g., surgery, pathology) and research technical (e.g., hormone assays, assisted reproductive technologies) cores that provide valuable, efficient assistance for in vivo protocols, and cellular and molecular experiments, (3) a number of highly qualified investigators with diverse yet complementary expertise with long-standing interest in reproductive or developmental biology, and (4) established interactions with joint appointees within ONPRC divisions, plus

basic (e.g., Private Source,Excluded by Requester) and clinical scientists at OHSU (e.g., Excluded by Requester Ob-Gyn) or elsewhere (e.g., Excluded by Ob-Gyn, UCLA) to translate advances to areas related to fertility control (contraception) or overcoming infertility (premature ovarian failure in cancer patients; polycystic ovarian syndrome) in women.

NARRATIVE: Excluded by Requester

Division Appointment: Senior Scientist, Division of Reproductive & Developmental Sciences
Appointment(s): % Effort Excluded by Requester at ONPRC and joint appointments in the Departments of Physiology & Pharmacology, Behavioral Neuroscience, Obstetrics and Gynecology, OHSU.
Effort on NHP-related studies: % Effort

Research Overview: Excluded by Requester research focuses on the effects of steroid hormones, stress and stress sensitivity on serotonin neurons in the dorsal raphe nucleus and norepinephrine (NE) neurons in the locus ceruleus of male and female NHPs. She employs multiple approaches *in vivo* (behavior, pharmacology challenges) and *in vitro* (immunocytochemistry, golgi staining and in situ hybridization all of which use image analysis, western analysis, genome arrays, PCR expression arrays) to perform basic and translational research on the serotoninergic and noradrenergic systems in the midbrain. Due to the similarity of NHP and human midbrain, Excluded by advances are promoting a better understanding of the neurobiology of hormone replacement therapy for menopause, the neurobiology of aggression, and the neurobiology of the stress response in individuals who are stress sensitive or stress resilient. Accomplishments in the past three years include: (1) discovery that ovarian hormones prevent DNA fragmentation in serotonin neurons and promote dendritic spine proliferation on serotonin neurons for increased excitatory glutamate signaling, (2) discovery that serotonin is not regulated by androgens and that serotonin does not regulate aggression in males; rather androgens increase norepinephrine output from the locus ceruleus, which increases aggression, (3) that serotonin function determines the sensitivity or resilience of an individual to stress, but norepinephrine in the locus ceruleus increases with stress. Therefore, the ratio of serotonin/NE function in the midbrain determines whether an individual will ovulate during moderate stress or immediately become anovulatory.

Contribution to Mission: Excluded by Requester provides vision and direction of her laboratory for psychoneuroendocrinology research at ONPRC. She was implemental in the establishment of the U54 NHP Reproductive Tissue Bank. She serves as a facilitator to core, affiliated and visiting scientists to exchange ideas, techniques and NHP models for the purpose of understanding and improving mental health in men and women. She provides very precious NHP brain regions and sections to collaborators outside of ONPRC. She mentors scientists in training, in the beginning, or at mid-level of their careers to foster their professional advancement. Excluded by represents the center as an expert on hormone replacement therapy and the neurobiology of Functional Hypothalamic Amenorrhea (FHA) in women; and in the neurobiology of aggression in men. She has maintained uninterrupted NIH funding since 1981. She currently has an R01 on steroid regulation of serotonin in males; an R01 with Excluded by Requester on FHA; an R21 on the regulation of NE in FHA, and she recently established an R24 supported Postmenopausal Monkey Resource with multiple investigator participation. Since May 2009 she has trained three postdoctoral fellows, 3 graduate students, 1 clinical fellow and 1 high school intern. In addition, she has served on the thesis committee of 4 graduate students and was invited to present her research at 2 symposiums, 1 medical school department and 2 community gatherings. Since 2009 she has published 17 peer reviewed papers, 2 review chapters and 20 abstracts. Collaborative interactions include:

Name		Affiliation	Description
Excluded by Requester	hD, Staff Scientist	ONPRC	Behavior of NHPs
	PhD, Professor	OHSU	Neurobiology of aromatase
	hD, Professor	Univ Pittsburgh	KISS1 expression
	D, Affiliate Scientist	WRPRC	Kisspeptin expression
	D, Chair Biology	Idaho State U	Gender, Gene profiling & Prozac
	PhD, Affiliate Scientist	Univ Mississippi	Gender, Gene profiling & Prozac

NARRATIVE: Excluded by Requester

Division Appointment: Senior Scientist, Division of Reproductive & Developmental Sciences
Appointment(s): % Effort Excluded by Requester at ONPRC and joint appointments in Obstetrics & Gynecology and Physiology & Pharmacology, OHSU.
Effort on NHP-related studies: % Effort Exc

Research Overview: Mutants of the gonadotropin releasing hormone (GnRH) receptor (GnRHR) are misfolded proteins that are usually misrouted, typically retained in the endoplasmic reticulum. We have developed a therapeutic approach that allows pharmacoperone drugs, small and target-specific molecules that diffuse into cells and stabilize mutant proteins in a structure that is acceptable to the quality control system (QCS) of the cell, to rescue these mutants and restore them to biological function. We described the molecular mechanism by which many of the mutants are misfolded and basis of the inefficiency of processing of the WT GnRHR in humans and NHPs, (the presence of Lys191 in the hGnRHR creates steric interference and decreases probability of the formation of the Cys14-Cys200 bridge which is required for trafficking to the plasma membrane. We have identified the subtle chemical differences that influence plasma membrane expression in several different NHPs. We have identified 5 chemical classes of pharmacoperones and these act by bridging residues Asp98 and Lys121, stabilizing an interaction between transmembrane segments 1 and 2. Among these 5 drug classes, which also interact as other sites on the receptor, are structures within each class that have various serum half-lives and affinity of binding. We have created an in vivo proof-of-principle model for this therapeutic approach and high throughput screens for identifying new pharmacoperones with improved characteristics. We have identified the underlying basis of constitutive activity in GnRHR mutants.

Contribution to Mission: Excluded by Requester serves the Center as the Director of Research Advocacy Services with responsibilities defined under the administration Research Strategy, serves on the Policy Committee, Research Advisory Committee, Promotions Committee (Chair), IT Committee, and is PI on the Fogarty Training Grant in Population and Reproduction. He represents the Division Head (when he is unavailable) at Center meetings and participates in seminars. Since May 2009, he has trained a graduate student and 4 postdoctoral (Ph.D.) fellows. In 2009, he received the Media Award of the American College of Neuropsychopharmacology, in 2010 he was elected a fellow of the American Association for the Advancement of Science; in 2012 he was honored as the Distinguished Alumni of Baylor College of Medicine and was asked to give the Presidential Lecture at the Annual Meeting of the American Society for Reproductive Medicine, and in 2013 he will give the James Voogt Annual Lecture at the University of Kansas Medical School. Since 2009, he published 24 peer-reviewed articles, edited 52 books, gave 26 invited lectures and 3 TV/radio interviews.

Out of 27 collaborations, examples include:

Name	Affiliation	Description
Excluded by Requester .D., Professor	U of TX MD Anderson Cancer Ctr	Design and Use of Mouse Model of Hypergonadotropic Hypogonadism
Senior Staff	ONPRC	Imaging of GnRH Receptor
Assoc Professor	Private Source	High Throughput Screens
, Professor	U of Michigan	Molecular Modeling of the GnRH Receptor
., Scientist	OTRADI, Oregon	High Throughput Screens
MD, D.Sc., Head, Research Unit in Reproductive Medicine	Private Source	GnRH Action and Protein Rescue

NARRATIVE: Excluded by Requester

Division Appointment: Assistant Scientist, Division of Reproductive & Developmental Sciences (DRDS)
Appointment(s): % Effort Excluded by Requester n Obstetrics & Gynecology, OHSU and a joint appointment at the ONPRC.
Effort on NHP-related studies: % Effort

Research Overview: Excluded by Requester specializes in using advanced imaging of the placenta to understand factors that affect placental development and nutrient transport. A specific focus is the impact of maternal nutrition and obesity on placental function, reproductive outcomes, and fetal programming in our NHP model of excess nutrition during pregnancy. The adverse obstetric outcomes attributed to both obesity and diabetes in humans are confounded by an inability to separate the contributions of maternal diet. Excluded by Requester research resulted in the first report of placental hemodynamic abnormalities in a primate placenta that are secondary to a high fat diet, suggesting that a Western style diet has an independent impact on the adverse obstetric and neonatal consequences reported in the obese human population. Because the placenta regulates nutrient flow from mother to fetus, it likely occupies a central role in mediating the adverse obstetric/neonatal risks associated with obese and/or diabetic pregnancies. Current assessments of placental function (both clinical and research) are limited by an inability to link *in vivo* placental perfusion with functional outcomes, such as histopathology and nutrient transport. Excluded by and his collaborators developed a novel dynamic contrast enhanced-MRI (DCE-MRI) protocol that quantifies placental blood flow creating a placental perfusion map that can be correlated with placental histopathology and nutrient transport. These novel studies will set the framework for understanding how the placental develops and adapts to adverse conditions and will lead to exciting future studies of blood flow on nutrient transfer, and perhaps improved imaging techniques to identify placental dysfunction in humans. Another area of focus is the use of advanced imaging including ultrasound, contrast-enhanced ultrasound, and MRI to investigate placental/fetal development in other NHP models of placental dysfunction, including chronic exposure to nicotine and intraamniotic infection. Excluded by research has been recognized through invited presentations at national and international meetings and awards of research excellence.

Contribution to Mission: Excluded by Request has been working with NHPs since 2007 as a WRHR scholar under Dr. Excluded by Request mentorship and became an associate scientist in 2013. Excluded by directs the placental biology group of the NHP Obese Resource responsible for designing and executing both the *in vivo* and *in vitro* studies of placental function in this important model. Given the central focus of the placenta on fetal nutrient transport, Excluded by Requester collaborates with scientists and clinicians at OHSU from the divisions of pathology, cardiology, endocrinology, the Heart Research Institute, and the Advanced Imaging Research Center. As the primary ultrasound diagnostic imager based at the ONPRC, Excluded by Request also supports the NHP work at ONPRC by providing imaging capabilities to scientists in DRDS and the Division of Neuroscience. Excluded by Requester is one of the founding members of the new ONPRC division called the Division of Diabetes, Obesity, & Metabolism. As a Maternal Fetal Medicine (MFM) subspecialist and Director of the Diabetes and Pregnancy Program at OHSU, Excluded by Request is actively involved in providing clinical care for pregnant mothers with diabetes and obesity. This clinical care involves the development and implementation of institutional guidelines for the management of diabetes and nutrition during pregnancy. As a clinician-investigator, Excluded by is poised to translate insights from the NHP into clinical studies; as well as provide mentorship to young clinician-investigators embarking on an academic career. Excluded by is actively involved in training programs at OHSU. He teaches medical students, obstetric residents, and MFM fellows. In the past three years, he has mentored or co-mentored two fellows and three residents for their required research projects. Excluded by also serves on the OHSU IRB. He is a reviewer for OHSU clinical research grants funded by the Center for Women's Health Circle of Giving and the Moore Institute for Nutrition and Wellness. Out of 10 collaborations, major examples are listed below:

Name	Affiliation	Description
Excluded by Requester	ONPRC	The effects of nicotine on placental growth and fetal cardiovascular development
	ONPRC,OHSU,AIRC	The use of DCE-MRI to quantify uteroplacental blood flow

NARRATIVE: Excluded by Requester

Division Appointment: Assistant Scientist, Division of Reproductive & Developmental Sciences (DRDS)
Appointment(s): % Effort Excluded by Requester at the ONPRC and a joint appointment in Obstetrics & Gynecology, OHSU
Effort on NHP-related studies: % Effort

Research Overview: Excluded by Requester current research program and future objectives incorporate studies directed at the fundamental mechanisms of parturition, with emphasis on novel diagnostic biomarkers and therapeutic interventions for preterm labor associated with reproductive tract infections (i.e., *Ureaplasma* spp.), and for the prevention of subsequent fetal and neonatal sequelae (i.e., lung and cerebral white matter injury). Her field of research has expanded from preterm birth studies to include the regulation of fetal growth and placental plasticity utilizing a unique NHP model of growth restriction model. This research seeks to understand the ability of the developing placenta to adapt to a reduced umbilical placental blood flow as simulated by fetal interplacental vessel ligation.

Excluded by Requester independent research program has evolved through expanded interdisciplinary collaboration among clinician scientists with neonatal-pediatric specialties and basic scientists with expertise in microbiology, reproductive immunology, cardiovascular physiology and clinical/veterinary pathology. Together, with her collaborators, they have expanded the infant care facilities at the ONPRC with the addition of a specialized intensive care nursery (SCN); this has enabled new research initiatives to expand beyond the maternal-fetal environment to a critical translation point between prenatal and postnatal life. This unique resource and nursery is designed to support postnatal survival of prematurely born rhesus monkeys exposed to *Ureaplasma* chorioamnionitis (with and without antimicrobial therapy) in order to delineate the cognitive and neurobehavioral consequences of *in utero* infection and antenatal treatments. Future plans are to expand these studies to determine neonatal pulmonary function sequelae because it is increasingly clear that fetal lung infection is an important precursor of asthma and chronic lung disease in childhood. Excluded by Requester continuing research will strengthen the collaborative relationships among the obstetrical, neonatal and pediatric communities within OHSU and ONPRC, and enable translation of *"proof-of-concept"* data collected from our non-human primate model to the clinical setting.

Contribution to Mission: A remarkable accomplishment during Excluded by Requester tenure at the ONPRC is the development of a special care nursery (SCN) for prematurely born rhesus monkeys. The SCN has the look and feel of a human neonatal intensive care unit. She has developed the facility to support the cardiopulmonary, (including mechanical ventilation), thermoregulatory, and nutritional needs of prematurely born infants. Dr. Excluded by Reques was recently awarded a 5 year grant from NICHD (1R01 HD069610) in support of this research. This synchronicity of translational research centered around Excluded by research program is a harbinger of meaningful interdisciplinary and interdepartmental collaboration at the ONPRC and OHSU. It also paves the way for developing a clinical Prematurity Prevention Program at OHSU, and will open the door to countless basic and translational research collaborations from across the country. Since 2009, she published 5 peer reviewed articles, 1 reviews/book chapters and 13 abstracts at national or international meetings. Out of 14 collaborations, major examples are listed below:

Name	Affiliation	Description
Excluded by Requester	ONPRC	Primate model of mid-gestation *Ureaplasma* in utero infection: Prevention of Neurologic Sequelae.
	OHSU	Primate model of mid-gestation *Ureaplasma* in utero infection: Prevention of Neurologic Sequelae. Compartmental analysis of proteomic biomarkers during intra-uterine infections.
	University of Alabama	Primate model of mid-gestation *Ureaplasma* in utero infection: Prevention of Neurologic Sequelae. Compartmental analysis of proteomic biomarkers during intra-uterine infections.
	WaNPRC	Primate model of mid-gestation *Ureaplasma* in utero infection: Prevention of Neurologic Sequelae.

NARRATIVE: Excluded by Requester

Division Appointment: Interim Chief and Senior Scientist, Div. Diabetes, Obesity and Metabolism. Senior Scientist, Division of Developmental and Reproductive Sciences.
Appointment(s): % Effort,Excluded by Requester at the ONPRC.
Effort on NHP-related studies: % Effort

Research Overview: Excluded by Requester specializes in investigations on the development of metabolic disorders. His group focuses on the impact of poor maternal metabolic health and diet on the development of metabolic systems. The primary concept is that abnormalities in the development of these systems will predispose the offspring to a wide variety of health complications later in life. Furthermore he is investigating different dietary and nutritional interventions that may reverse or prevent the development of health complications in the offspring. A parallel to these developmental programming studies is the investigation of metabolic adaptations in females in different reproductive states, including during the menstrual cycle, pregnancy, and lactation. These studies are part of a long and highly-productive collaboration with Excluded by Requester Recently, he joined a consortium with members of DRDS to investigate the combined effect of mild hyperandrogenemia and chronic high-fat diet consumption on the development of polycystic ovarian syndrome (PCOS)-like symptoms. Another area of focus is the treatment of metabolic diseases. 1) Through collaborations with several groups, he developed a Roux-en-Y Gastric Bypass (RYGB) model in the obese and diabetic rhesus macaque. These important studies use an integrated biology approach with sophisticated diagnostics to understand how RYGB can reverse diabetes symptoms. 2) He also developed a NHP model of diet-induced obesity (DIO) to investigate pharmacotherapies for the treatment of obesity, diabetes and cardiovascular disease. For these studies, he partnered with several world-wide pharmaceutical companies. These studies were not only important for the science, but also in diversifying research funding. This funding approach helped stabilize research resources and benefited the academic studies. These Private-Public Partnerships also resulted in access to powerful diagnostic tools and several recent publications. Since 2009, Excluded by Requester has published 36 peer-reviewed articles and made 31 presentations at national or international meetings.
Contribution to Mission: Excluded by became a core scientist in the Division of Neuroscience in 2003. During his tenure at ONPRC, Excluded by has developed two key NHP models that made a significant impact on the research community: 1) In collaboration with Excluded by Requester developed the NHP model in which female macaques are chronically fed a diet high in fats. This model has been essential for determining the relative contribution of a poor nutritional diet versus poor maternal metabolic health on the developing fetus. 2) Dr. Excluded by Reque also developed a NHP model of diet-induced obesity. This model is critical for how it mimics the progression of metabolic diseases observed in humans. In 2007, ONPRC established the NHP Obese Resource (directed by Excluded by providing access to these models to the scientific community. Investigators at more than 10 U.S. universities have active funding using this resource. In the past year, six different pharmaceutical companies used animals and/or tissue/blood samples generated in this resource. Due to success of this program, and because OHSU has identified metabolic diseases as a key area of focus, ONPRC recently made the decision to establish a new scientific division, the Division of Diabetes, Obesity, & Metabolism. Excluded by is serving as the founding and Interim Division Chief until a formal open search can be performed for a permanent chief. In the past 5 years Excluded by Requester has obtained $12M in research funding (direct costs).

Excluded by Requester is actively involved in training programs at OHSU. In the past 3 years, he has mentored 4 graduate students that successfully defended their Ph.D. thesis, as well as 7 postdoctoral fellows, including 3 that recently advanced to independent positions. Excluded by serves as training faculty for 2 NIH-funded training grants: T32 HD07133, Pre- and Postdoctoral Multidisciplinary Training in Neuroendocrinology; and T32 NS07466, Training in Endocrinology, Diabetes, and Clinical Nutrition. Excluded by also provides service as an Editor and editorial board member for several journals, and is involved in reviewing grants for NIH.

Name	Affiliation	Description
Excluded by Requester	Obesity Res. Ctr., Monash Univ., Melbourne Australia	Investigation of therapeutics for the treatment of diabetes and obesity in DIO NHP.
	Dept Pediatrics, Univ. of Colorado at Denver	Relative contribution of poor maternal health and diet on the development of metabolic systems in the NHP.
	Dept. Cardiology, OHSU	Develop. of vascular inflammation & atherosclerosis in obese NHP.

NARRATIVE: Excluded by Requester

Division Appointment: Associate Scientist, Division of Reproductive & Developmental Sciences (DRDS)
Appointment(s): % Effort Excluded by Requester in the ONPRC and a joint appointment in the Department of Obstetrics & Gynecology, OHSU.
Effort on NHP-related studies: % Effort

Research Overview: Excluded by research focuses on characterizing the cellular and molecular pathways responsible for the release of a fertilizable oocyte as well as the development, function, and regression of the corpus luteum. Using a genomic approach, he has identified genes within the macaque naturally-selected follicle whose products are critical for ovulation of an egg that is capable of being fertilized. The product of these genes represent novel contraceptives targets whereby inhibitors of their activities are evaluated in vitro and then tested in contraceptive trials using NHPs to validate their efficacy in vivo. Additional analysis of the macaque periovulatory follicle transcriptome led to the discovery of cytokines/growth factors, including amphiregulin and leukemia inhibitor factor, that coordinate the cellular events necessary for follicle rupture and the continued maturation of the oocyte. Such factors represent important determinants of oocyte competency in terms of subsequent embryonic development following fertilization. Lastly, in depth characterization of the CL transcriptome at distinct stages of the luteal phase revealed molecular events involved in CL development and regression. Luteal development and function was found to associate with increased sensitivity to prostaglandin E2, whereas primate luteal regression corresponded with an increased sensitivity to prostaglandin F2α. Additional analysis of the macaque CL transcriptome during its regression also revealed an increase in the expression of the reverse cholesterol transport system. Induction of reverse cholesterol transport in macaque luteal cells depleted the intracellular stores of cholesterol, thereby limiting their steroidogenic capacity. Thus, the characterization of the rhesus macaque CL transcriptome through the luteal phase provided insight into the cellular mechanisms responsible for its development from the remnants of the ruptured ovulatory follicle and its demise in the absence of fertilization. Insight gained into the mechanisms responsible for NHP luteal development and regression have implications in understanding early pregnancy loss in women due to luteal dysfunction.

Contribution to Mission: Excluded by Requester brings significant molecular and cellular biology expertise to the DRDS. In addition to his independent research projects, he has collaborated with ONPRC and Ob/Gyn investigators to utilize the NHP model to develop and test novel contraceptives. He serves as Director of the Assisted Reproductive Technologies (ART) Support Core, which provides interested scientists with gametes and embryos, ovarian follicular cells and fluid, as well as pregnancies and fetal tissues in support of investigations on gamete and ovarian follicle function, contraception, fertilization, early embryogenesis, implantation, fetal development, and the creation of disease models in NHPs. Since May 2009, he trained two postdoctoral (Ph.D.) fellows, and two clinical (M.D.) fellows Excluded by served on 4 different NIH and 4 international grant review panels. Since 2009, he has published 17-peer reviewed articles and 16 abstracts at national or international meetings.

Out of 7 Collaborators, examples include:

Name	Affiliation	Description
Excluded by Requester	OHSU	The discovery of novel emergency contraceptives and increasing efficacy of existing forms.
	OHSU/ONPRC	The discovery of novel, nonhormonal female contraceptives.
	ONPRC	Identifying novel, nonhormonal female contraceptives as well as the mechanisms involved in luteal development, function and regression.
	Private Source	The utilization of genomic approaches to identify follicular determinants of oocyte quality.
		Developing molecular tools for the efficient manipulation of the NHP genome.

NARRATIVE: Excluded by Requester

Division Appointment: Senior Scientist, Division of Reproductive & Developmental Sciences (DRDS)
Appointment(s): % Effort Excluded by Requester at the ONPRC. He is a Research Associate Professor in the Department of Obstetrics & Gynecology and Pediatrics, OHSU, and has a joint appointment in Molecular & Medical Genetics and Oregon Stem Cell Center, OHSU.
Effort on NHP-related studies: % Effort

Research Overview: Excluded by Requester overall research goal is to use molecular and cellular approaches to answer scientifically and clinically pertinent questions regarding primate gamete, embryo and stem cell biology. The main focus of several ongoing projects is to understand the mechanisms of genetic and epigenetic reprogramming of aged somatic cells to the totipotent and pluripotent states following somatic cell nuclear transfer (SCNT). Specifically, we are interested in the role of mitochondria and mitochondrial (mt)DNA in reprogramming and re-setting the developmental program in experimental pluripotent stem cells derived from aged somatic cells. Another objective is to develop efficient protocols for deriving primate pluripotent stem cells via SCNT from somatic cells carrying mtDNA mutations. Several other projects in the lab are focused on the assessment of the safety and efficacy of stem cell based therapies by transplantation studies in a clinically relevant nonhuman primate model. The overall goal of these studies is to take advantage of recent developments in Excluded by Requester laboratory that allowed for the first time derivation of immuno-matched pluripotent cells by SCNT or iPS approaches, suitable for autologous transplantation into existing monkeys.

Contribution to Mission: As a Senior Scientist, Excluded by Requester conducts publicly visible research and provides expertise, training and services related to the Assisted Reproductive Technologies (ART) and Pluripotent Stem Cells to division, ONPRC and OHSU members. He was head of the Stem Cell & Developmental Biology Working Group and served as ART Core director from 2006 to 2012. He mentors postdoctoral fellows, research associates and staff scientists in their careers to foster their professional advancement. He serves on several committees including the ART Core oversight committee, Oregon Embryonic Stem Cell Research Oversight (OSCRO) committee, OHSU MD/PhD Committee, and others as needed, including the recent Search Committee for a faculty in Stem Cell and Developmental Biology for the Division. Excluded by Requester bridges his basic research in NHPs with OHSU clinical programs at the Depts. of Ob-Gyn and Pediatrics, Molecular & Medical Genetics and Oregon Stem Cell Center. He recently launched a satellite human embryo and stem cell research laboratory at the South Water Front campus of the OHSU to translate advances made in a NHP model.

Excluded by Requester represents the Center as an expert and resource in NHP ARTs, embryo and stem cell biology, and its relevance to human development and disease. He currently serves as Principal Investigator on 3 NIH/NICHD R01 grants (2009–2014; 2010-2015; 2010-2015), as Co-PI on another NEI R01 (2011-2016) and as Principal Investigator on the grant from the Private Source Private Source (2012-2017). Pending Support Since May 2009, he trained 7 graduate students, eleven postdoctoral (PhD and MD) fellows, and several summer (undergraduate or high school teacher) students. Excluded by Requester is the recipient of the 2010 Discovery Award, from the Private Source and the 2010 Women's Health Research Award, the Center for Women's Health, OHSU. Since 2009, he published 16-peer reviewed articles, 2 book chapters and 21 abstracts at national or international meetings. Examples of collaborative Interactions:

Name	Affiliation	Description
Excluded by Requester	OHSU	Human gamete and embryo biology, Assisted Reproductive Technologies, Prevention of inherited mtDNA mutations
	Private Source	Translating Human Pluripotent Stem Cells from Heart Disease Models to Cardiac Repair
		Translating Human Pluripotent Stem Cells from Heart Disease Models to Cardiac Repair
		Study rhesus gene function by altering and removing individual genes using TALENs

NARRATIVE: Excluded by Requester

Division Appointment: Senior Scientist, Division of Reproductive & Developmental Sciences
Appointment(s): % Effort Excluded by Requester at the ONPRC, and joint appointment as Professor of Medicine, Pediatrics and Cell and Developmental Biology, OHSU
Effort on NHP-related studies: % Effort

Research Overview: Excluded by Requester principal research focus is the action of the insulin/IGF signaling system in metabolic disease. His group has developed techniques for the isolation and analysis of function of NHP islets and adipose tissue, including the effects of incretin action. This expertise supports current studies on islet function, including analyses of incretin-based therapeutics, funded by the NIH and pharma, as well a number of pending NIH and pharma-funded projects. Excluded by Requester studies of adipose function are the basis for pending NIH and pharma projects examining androgen and incretin action in NHP adipose explants using novel fluorescent imaging approaches. Previous expertise in cellular analyses of insulin and IGF action supports NIH and Private Source funded research on the action of novel insulin and glucagon analogs and formulations for clinical use.

Contribution to Mission: Excluded by [illegible] is the Associate Director for Research and is responsible for: 1) oversight of externally funded research; 2) specific oversight of research involving for-profit entities; 3) interactions with the OHSU Technology Transfer and Business Development Office and their engagement with pharma entities interested in research at ONPRC; 4) liason with the OHSU Center for Diabetes and Obesity Research; 5) liason with the OHSU Foundation; 6) liason with OHSU clinical departments collaborating with ONPRC investigators; and 7) oversight of ONPRC research support cores. Out of >10 collaborations, examples include:

Name	Affiliation	Description
Excluded by Requester	Private Source	NIDDK-funded SBIR to analyze biochemistry and biological activity of novel insulin analogs for clinical use. This project includes studies on the effect of insulin analogs on nonhuman primate adipose tissue explants.
	ONPRC Private Source	NIDDK-funded R24 grant to assess the effects of gastric bypass surgery on metabolism in a nonhuman primate model.
	ONPRC U. of Mass Med. Center	NIDDK-funded R24 seed grant to establish nonhuman primate model of islet biology.
	Private Source	NIDDK-funded U grant to determine effect of mouse islet development genes on nonhuman primate islet biology.
	OHSU and Legacy Health Indiana U.	Private Source -funded research project designing a stable, bioactive glucagon formulation for use in an artificial pancreas.
	OHSU (Surgery) OHSU (Pediatrics)	Analysis of immune cell function in human adipose tissue.
	OHSU (Oregon Stem Cell Center)	Generation of antibodies and aptamers for isolation of islet cell types.
	ONPRC	Effects of second-generation antipsychotics on central and peripheral insulin action.
	ONPRC ONPRC ONPRC/U. of Pittsburg	Effects of peripubertal androgen on female endocrine function.

NARRATIVE: Excluded by Requester

Division Appointment: Associate Scientist, Division of Reproductive & Developmental Sciences
Appointment(s): % Effort,Excluded by Requester at the ONPRC and a joint appointment in the Department of Obstetrics & Gynecology, OHSU.
Effort on NHP-related studies % Effort

Research Overview: Excluded by Requester research involves endocrine and paracrine regulation of the primate reproductive tract of nonhuman primates. Excluded by conducts translational studies in macaques that contribute to improving women's health. His studies focus on excessive menstrual bleeding, endometriosis, and novel contraceptives that act by interfering with the movement of gametes through the reproductive tract. Excluded by Requester laboratory utilizes in vivo therapies in rhesus and cynomolgus macaques, noninvasive imaging such as contrast-enhanced ultrasound, immunohistochemistry and real-time PCR to assess the action of steroid receptor targets in the reproductive tract. Over the last 3 years, Excluded by has evaluated the use of Selective Estrogen Receptor Modulators (SERMs) for the purpose of contraception, and anti-inflammatory glucocorticoids for the purpose of controlling heavy menstrual bleeding and novel androgens for the treatment of endometriosis. Excluded by also developed a new "induced endometriosis" model in rhesus macaques that will permit assessment of pain and infertility during early stages of the disease. In this model, macaque endometriosis is created by inoculating the peritoneal cavity with menstrual debris to initiate the disease. Pelvic ultrasound and contrast enhanced ultrasound imaging are used characterize the effects of induced endometriosis on uterine function. The effects of induced endometriosis on uterine receptivity to embryo implantation are evaluated in embryo transfer studies, in collaboration with the ONPRC Assisted Reproductive Technologies Core.

Contribution to Mission: Excluded by research utilizes nonhuman primates in translational studies to promote women's health. In the last 3 years Excluded by has been active in training one Postdoctoral Fellow, one Fogarty Fellow, and two Partners in Science High School Teachers. Excluded by serves on six regular committees including: the West Campus Institutional Animal Care and Use Committee; the Radiation Safety Committee; the Endocrine Technology Support Core Oversight Committee; and was the head of the recent search committee for Core Scientist (Maternal-Fetal Biology), and the Equipment Committee of the Division of Reproductive & Developmental Sciences.

Excluded by Requester represents the Center as a resource in NHP uterine biology, and its relevance of the nonhuman primate to women's reproductive health. He has maintained funding through the NICHD U54 Contraceptive Development & Research Center (2007–17). Excluded by has served as PI on 6 collaborative research projects with Private Source is slated to serve as the nonhuman primate core supervisor on a new proposed NICHD Specialized Cooperative Center in Infertility and Reproduction Research (SCCPIR (2013–18). Since 2009 Excluded by published 7 peer reviewed articles, 2 reviews/book chapters and 24 abstracts at national or international meetings. Collaborative interactions include:

Name	Affiliation	Description
Excluded by Requester	Private Source	Studies involve novel therapies for endometriosis and unwanted uterine bleeding
		Studies assessing physiological mechanisms associated with postmenstrual repair.
	Cardiology OHSU	Noninvasive imaging of embryo implantation in the nonhuman primate with contrast-enhanced ultrasound.

NARRATIVE: Excluded by Requester

Division Appointment: Senior Scientist, Division of Reproductive & Developmental Sciences (DRDS)
Appointment(s): % Effort Excluded by Requester at the ONPRC.
Effort on NHP-related studies: % Effort

Research Overview: Excluded by Requester is a recognized leader on the effects of nicotine on lung development and lung cancer. Using a rhesus monkey model the Excluded by Requester laboratory demonstrated that prenatal nicotine exposure was the primary mediator of the deleterious effects of maternal smoking during pregnancy on infant lung development and critically, that vitamin C supplementation to pregnant rhesus monkeys could prevent some of the effects of prenatal nicotine exposure. This discovery led to a pilot clinical study that demonstrated that supplemental vitamin C given to pregnant smokers who could not be convinced to quit, similarly reversed some of the effects of maternal smoking on offspring lung function. NIH has now funded a multicenter clinical trial that Excluded by Requester is participating in, led by Excluded by Requester of OHSU and an ONPRC affiliate scientist, to further determine the ability of supplemental vitamin C to preserve lung function in offspring of smokers and potentially decrease incidence of asthma. The Excluded by Requester lab also investigates pathways by which nicotine and acetylcholine stimulate lung cancer growth and the potential to use those pathways to develop new therapies for lung cancer. In a new research direction, Excluded by Requester is collaborating with Excluded by to develop a new monkey model to study nicotine and alcohol co-morbidities. This new program is funded by an ONPRC pilot project grant.

Contributions to Mission: Excluded by Requester and his laboratory make substantial contributions to the mission through his research program, by directing the Molecular & Cell Biology (MCB) core, and through participation in essential ONPRC committees. First through his research program the Excluded by Requester laboratory has developed key research models for studying the effects of prenatal nicotine exposure in NHP. This has involved methods for both invasive and non-invasive methods of pulmonary function testing as well as methods for nicotine delivery that accurately recapitulate nicotine exposure levels of human fetuses. The accuracy of this model has led to translational discoveries that are being tested in clinical trials. It is the expectation of Excluded by Requester that results of the clinical trials in terms of how genetic polymorphisms affect sensitivity to maternal smoking during pregnancy will be further studied NHP to better understand mechanisms and allow further development of targeted interventions for specific genotypes. In addition to the relatively mature studies on prenatal nicotine, Excluded by in collaboration with Excluded by is developing an exciting, new NHP model to study the interaction of nicotine and alcohol. Smoking and alcoholism are major public health concerns and are strikingly co-morbid. Smoking increases with alcohol intake and the majority of alcoholics smoke. The nature of this co-morbidity is poorly understood and the expertise of Excluded by with nicotinic receptors and monkey models of nicotine administration and the expertise of Excluded by Requester with monkey models of alcohol self-administration make this an exciting new direction of research.

Excluded by makes a major contribution to the ONPRC by directing the MCB Core. The MCB core provides automated sequencing [both capillary (ABI 3730XL) and NextGen (Illumina MiSeq)], high throughput genotyping and realtime PCR (Life Technologies QuantStudio 12K Flex), and robotic DNA preps among other services to facilitate primate research. Previous work by the MCB Core provided key DNA sequences for development of the first rhesus monkey gene chip produced by Affymetrix. A major focus of the MCB Core will be to work closely with the Primate Genetics Unit to utilize the MiSeq for MHC typing of monkeys to assist in colony management. More detail on the contributions of the MCB Core to the ONPRC mission is provided in the MCB Core Resource Section.

Excluded by Requester also contributes to the ONPRC mission through essential administrative work. He serves on the ONPRC IT Advisory Committee, the ONPRC Policy Review Subcommittee and chairs the ONPRC Imaging and Morphology Core Oversight Committee and the ONPRC Primate Genetic Program Advisory Committee.

Name	Affiliation	Description
Excluded by Requester	OHSU	Effect of Fetal Nicotine Exposure on Primate Lung
	Private Source	Effect of Fetal Nicotine Exposure on Primate Lung

NARRATIVE: Excluded by Requester

Division Appointment: Chief and Senior Scientist
Appointment(s): % Effort,Excluded by Requester at the ONPRC and joint appointments in the Obstetrics & Gynecology, and Physiology & Pharmacology, OHSU.
Effort on NHP-related studies: % Effort

Research Overview: Excluded by Requester research focuses on the structure-function of the NHP ovary, with emphasis on the regulation of follicle selection, the development, ovulation and luteinization of the mature follicle and the functional lifespan of the corpus luteum. He employs multiple approaches both in vivo (e.g., intrafollicular injection, contrast-enhanced ultrasonography and molecular resonance imaging) and in vitro (3-dimensional culture, genome arrays) to perform basic and translational research on the ovary during the menstrual cycle and early pregnancy. Due to similarities to ovarian function in women, Excluded by Requester advances are promoting applications of NHP protocols to understanding and treating ovary-based infertility and to designing ovary-targeted contraceptives for women. Accomplishments in the past three years include: (1) reporting the dynamics of the transcriptome (mRNAs) in the monkey periovulatory follicle, and its application to test novel methods to block cumulus-oocyte activity and follicle rupture, and hence fertility, (2) use of 3-D culture techniques to grow primate follicles individually from the early preantral to antral stage, and its application to study early folliculogenesis in primates and to restore fertility in female patients after cancer therapy, and (3) development of a NHP model for polycystic ovarian syndrome, by combining chronic testosterone treatment and western-style diet in peri-pubertal female monkeys, to discern the actions of hyperandrogenemia and/or obesity in this infertility disorder, as well as possible treatments.

Contribution to Mission: As Division Chief, Excluded by Requester provides direction and vision to promote the research, training and resource goals of division members. He serves as a facilitator to core, affiliated and visiting scientists to exchange ideas, techniques and NHP models for the purpose of understanding and improving reproductive health in women. He mentors scientists in training, in the beginning, or at mid-level of their careers to foster their professional advancement. Excluded by regularly meets with the ONPRC leadership to represent Reproductive & Developmental Sciences in day-to-day activities, oversight and planning of research programs, animal resources and research services. He serves on six regular committees including the Executive Leadership Team, Policy Committee and Animal Utilization Committee, and others as needed, including the most recent Search Committees for Division Chiefs. Excluded by liaises with basic and clinical programs at OHSU, including the Depts. of Ob-Gyn and Pediatrics, the Center for Women's' Health (CWH), and recently served on the Search Committee for Chair, Ob-Gyn. He serves on the Board of Directors of the BIRCWH program at OHSU, and is an ambassador to the CWH, OHSU Foundation.
Excluded by Requester represents the Center as an expert and resource in NHP ovarian biology, and its relevance to women's reproductive health. He has sustained his principal NIH R01 grant (1983–2016), served as Director/PI of a funded NICHD Specialized Cooperative Center in Infertility and Reproduction Research (SCCPIR U54; 2004–12) Pending Support and served as co-director/Co-PI of a NICHD U54 Contraceptive Development & Research Center (2007–17). Recently, he has served as PI for an R01 grant (2007-13) within the NIH Director's Roadmap Grant, The Oncofertility Consortium; a multi-institutional program directed by Private Source,Excluded by Requester He has also been an investigator on collaborative research with Private Source Since May 2009, he trained four graduate students, four postdoctoral (Ph.D.) fellows, four clinical (M.D.) fellows or residents, and four summer (undergraduate or high school teacher) students. He received the 2010 Distinguished Researcher Award from the American Society for the Study of Reproduction. Since 2009, he published 23 peer reviewed articles, 5 reviews/book chapters and 39 abstracts at national or international meetings. Collaborative interactions include:

Name	Affiliation	Description
Excluded by Requester	ONPRC	Biology of the NHP Ovarian Surface Epithelium, Oncofertility: 3-D Culture of NHP Follicles
	OHSU	Development of Ovary-based Nonhormonal Contraceptives
	Univ. of Pittsburgh	Development of NHP Model for PCOS
	Private Source	Oncofertility Consortium; 3-D Culture of NHP Follicles
		Development of Ovary-based Nonhormonal Contraceptives
		Biology of the Primate Ovary

NARRATIVE: Excluded by Requester

Division Appointment: Senior Scientist, Divisions of Neuroscience and Reproductive & Developmental Sciences
Appointment(s): % Effort,Excluded by Requester at the ONPRC.
Effort on NHP-related studies: % Effort

Research Overview: Excluded by Requester 30-year research career as a neuroendocrinologist has focused on the influence of circadian rhythms and reproductive hormones on vertebrate physiology. Key findings from his non-human primate (NHP) studies include: (1) cloning of a novel form of gonadotropin-releasing hormone, which may play a pivotal role in controlling primate ovulation, (2) identification of circadian clock mechanisms in the primate adrenal gland, and other peripheral organs, which help to coordinate 24-hour physiological functions, and (3) identification of genes that are differentially regulated by photoperiod, in a NHP model of Seasonal Affective Disorder. Excluded by Requester current research, which is supported by two NIH R01 grants, uses multidisciplinary approaches to understand how age-associated hormonal changes negatively impact various physiological functions. For example, in collaboration with Excluded by Requester Excluded by Requester he aims to show how physiological hormone supplementation paradigms can improve sleep efficiency and boost cognitive performance in aged rhesus macaques. Furthermore, by making extensive use of gene profiling, his studies are helping with the elucidation of underlying causal mechanisms, and laying the foundation for safe and effective novel therapies for the elderly. Excluded by Requester also lends his expertise to additional collaborative studies at OHSU, which focus on the development of NHP models of stroke (PI: Dr. Excluded by Requester and hot flashes (PI: Excluded by Requester During the past 4 years, his research efforts have resulted in the publication of 26 peer-reviewed papers and 2 book chapters.
Contributions to Mission: Excluded by Requester serves on several committees, including the promotions committees at ONPRC and OHSU, and he is the chair of the Endocrine Technology (ETSL) Core oversight committee. Until recently, he also served on the graduate student admissions committee at OHSU. Nationally, Dr. Excluded by Requester serves on two editorial boards and has participated as a grant reviewer at many NIH study section meetings.

Excluded by Requester current research focuses exclusively on the use of NHP models for human diseases, especially those associated with aging. He is the co-director of the Biology of Aging Program at ONPRC; this inter-disciplinary research program makes extensive use of the NIA-supported Primate Aging Resource at ONPRC in order to gain insights into healthy and pathological human aging. In addition, Excluded by Requester has been highly instrumental in developing a translational bridge between the basic NHP aging research at ONPRC and clinical aging research and elderly care at OHSU. In collaboration with Excluded by Requester Director of Geriatrics, OHSU), Excluded by Requester spearheaded the formation of an OHSU Health Aging Alliance (HAA), which comprises ~60 researchers and clinicians. The goal of the HAA is to establish an international center of excellence for aging research, clinical practice, outreach and education. It builds on the broad spectrum of talent and resources at OHSU, and focuses on translating aging innovations from molecular to clinical applications. The HAA held its inaugural annual conference in late 2011, which was attended by almost 200 delegates and was highlighted by key note presentations by Dr. Marie Bernard (deputy director of the NIA) and Excluded by Requester (director of the Layton Aging and Alzheimer's Disease Center), as well Oregon Sen. Ron Wyden. The conference also provided an important forum for networking; this was followed by a grant writing retreat, which resulted in the submission of Pending Support Pending Support Although still in its infancy, the HAA (co-directed by Drs. Eckstrom and Excluded by Requester represents an effective way of integrating the NHP aging research with ongoing aging programs at OHSU. The Alliance has already established a web site and a 5-year business plan.

Excluded by Requester holds affiliated professor positions in the Departments of Physiology & Pharmacology, and Behavioral Neuroscience at OHSU, and is a member of the Neuroscience Graduate Program. His laboratory provides a fertile research training ground for postdoctoral fellows and graduate students (current students: Excluded by Requester as well as high-school teachers via the Partner-in-Science program. Moreover, Excluded by Requester is the program director of the NIH-supported *Neuroscience of Aging* training grant (T32 AG-02347?), which is currently in its 8th year of funding. Collaborative interactions are numerous, as noted above, particularly in the area of primate aging and age-associated hormonal events.

Program Director/Principal Investigator (Last, First, Middle): Robertson, Joseph E./Haigwood, Nancy L.

DIVISION OF REPRODUCTIVE & DEVELOPMENTAL SCIENCES DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Excluded by Requester	Div Chief/Sr. Scientist	% Effort			Institutional Base Salary	53,910	13,478	67,388
	Sr. Scientist					17,970	4,493	22,463
	Sr. Scientist					8,985	2,246	11,231
	Admin Asst					3,044	1,066	4,110
	Asst Scientist					17,970	4,493	22,463
	Asst Scientist					10,314	2,578	12,892
	Assoc Scientist					12,793	3,198	15,990
	Admin Coord					8,036	2,813	10,849
	Admin Coord					7,233	2,531	9,764
	Sr. Scientist					8,985	2,246	11,231
	Sr. Scientist					17,970	4,493	22,463
	Assoc Scientist					12,793	3,198	15,991
To Be Named	Sr. Scientist	1.20				17,970	4,493	22,463
To Be Named	Asst Scientist	1.20				10,600	2,650	13,250
To Be Named	Assoc Scientist	1.20				13,250	3,313	16,563
	SUBTOTALS →					221,823	57,287	279,110

CONSULTANT COSTS		
None Requested		0
EQUIPMENT *(Itemize)*		
None Requested		0
SUPPLIES *(Itemize by category)*		
Office & Admin Supplies	600	
		600
TRAVEL		
None Requested	0	0
INPATIENT CARE COSTS		0
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		
None Requested		0
OTHER EXPENSES *(Itemize by category)*		
Maintenance - Equipment	300	
Biohazard Waste Disposal	300	
		600
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 280,310
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 280,310

PHS 398 (Rev. 6/09) **Form Page 4**

DIVISION OF REPRODUCTIVE & DEVELOPMENTAL SCIENCES
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	279,110	287,484	296,108	304,991	314,141
CONSULTANT COSTS	0	0	0	0	0
EQUIPMENT	0	0	0	0	0
SUPPLIES	600	618	637	656	675
TRAVEL	0	0	0	0	0
INPATIENTS CARE COSTS	0	0	0	0	0
OUTPATIENTS CARE COSTS	0	0	0	0	0
ALTERATIONS AND RENOVATIONS	0	0	0	0	0
OTHER EXPENSES	600	618	637	656	675
DIRECT CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	280,310	288,720	297,381	306,303	315,492
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	280,310	288,720	297,381	306,303	315,492
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					1,488,205

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

PERSONNEL

Division Chief, Senior Scientist – Excluded by Requester % Effort Income). As Division Chief, responsible for all Divisional administrative activities and provides the overall scientific direction of the Division; oversees the submission of grant proposals, recruitment and personnel matters, represents the Division at the level of ONPRC Administration including as a member of the Expanded Executive Leadership Committee, the Policy Committee, the Research Advisory Committee and the Animal Utilization Committee; encourages scientific interactions between Division members and researchers at other institutions, encourages participation in Interdisciplinary Research Programs, encourages faculty participation in the Graduate Programs at OHSU. Excluded by Requester primary research interest is in primate ovarian biology to provide basic and translational advances related to female contraception and prevention of infertility.

Senior Scientist – Excluded by Requester % Effort,Excluded by Requester will continue her internationally-renown research program in primate neuroendocrinology and aging to provide basic and translational advances related to steroid hormone action and menopausal changes in women. She served as chair of the ONPRC Promotions Committee during the 5-year interval, and is PI of the R24 Postmenopausal Monkey Resource.

Senior Scientist – Excluded by Requester % Effort,Excluded by Requester will continue his world-renown research on neuroendocrine (GnRH) hormone action and the ability of pharmacoperones to overcome hormone receptor defects and resulting diseases (e.g., hypogonadotropic hypogonadism). He provides unique service in monitoring and responding to animal extremists/organizations targeting primate centers (Director, Office of Research Advocacy), and provides division perspective at committee meetings in Excluded by Requester absence.

Administrative Assistant – Excluded by Requester % Effort Provides administrative support for the laboratory programs of Excluded by Requester This remaining % Effort is shared with the Neuroscience Division and its scientists. With two open core positions to be filled, it is anticipated Excluded by Requester will become a full-time employee in DRDS.

Assistant Scientist – Excluded by Requester % Effort Support is matched with that from Division of Metabolic Diseases to promote the development of this beginning investigator interested in primate placental function and vasculature in health and disease.

Assistant Scientist – Excluded by Requester % Effort,Excluded by Requester Excluded by Requester became a Core faculty member in late 2011. She will continue to develop an independent program in NHP maternal-fetal-placental function, particularly as related to the causes and treatment of premature labor/delivery and its effects on the fetus and newborn. She became the division's IACUC representative in 2013.

Associate Scientist – Excluded by Requester % Effort,Excluded by Requester Excluded by Requester will continue to develop and expand his nationally-known program on the molecular aspects of NHP ovary and oocyte biology, particularly as related to developing ovary-based contraceptives and understanding the causes and treatment of polycystic ovarian syndrome in women. He serves on numerous committees, provides needed expertise in reproductive immunology, and became supervisor of the ART Core in 2012.

Administrative Coordinator – Excluded by Requester % Effort,Excluded by Requester Excluded by Excluded by Requester provides administrative support for the laboratory programs of Excluded by Requester as well as the ART Core.

Administrative Coordinator – Excluded by Requester % Effort serves as division coordinator, supervising the activities of Excluded by Requester as well as providing

support for all duties of the division chief. In addition, she provides administrative support for the laboratory programs of Excluded by Requester

Senior Scientist – Excluded by Requester % Effort,Excluded by Requester Excluded by will continue his highly-visible, frontier-expanding research on NHP gamete and pre-implantation embryo development, including the characterization of macaque stem cells and their application to models of regenerative medicine. He served as director of the ART Core for several years, and continues to provide NHP stem cell lines, training and consultation to research groups around the world.

Senior Scientist – Excluded by Requester % Effort,Excluded by Requester will expand his novel research on the regulation of adipose tissue and fat metabolism by sex steroids. He is PI of a project in the SCCPIR (Infertility) Center evaluating the effects of elevated androgen levels and high-fat diet on the reproductive and metabolic axes in female macaques, and its relevance to polycystic ovarian syndrome in women.

Associate Scientist – Excluded by Requester % Effort,Excluded by Requester will continue to develop and expand his nationally-known program on basic and translational research on the primate reproductive tract (oviduct, uterus and cervix). During the last grant interval, Excluded by Requester was the division representative on the ONPRC IACUC.

Senior Scientist – To be named (4.8 calendar months: 1.2 ORIP, 3.6 Program Income). Funds are requested to support the recruitment of a renowned scientist in one of the major research areas within the field of reproductive and developmental sciences, who will serve as Division Chief when Excluded by Requester Personal Info Personal Info Because Excluded by Requester anticipates remaining in the Division as a Senior Scientist, there is opportunity to recruit a Senior Scientist to complement one of the existing or emerging areas at the time of this recruitment.

Scientist (2) To Be Named – Funds are requested for the following positions: The positions exist due to:

- Assistant Scientist – To Be Named (4.8 calendar months effort: 1.2 ORIP, 3.6 Program Income). Departure of Excluded by Requester (Assistant Scientist) to a medical pathology position. A rationale is provided in the Division plans for hiring a beginning scientist in the area of gamete/stem cell developmental biology to replace the expertise Excluded by Requester and to complement that of Excluded by Requester plus use the unique resources of the ART Core.
- Associate Scientist – To Be Named (4.8 calendar months effort: 1.2 ORIP, 3.6 Program Income). Departure of Excluded by Requester Associate Scientist) to a full-time position at the University of Pittsburgh. There is no plan to replace the neuroendocrine expertise of Dr. Cameron since she continues as a visiting scientist and other investigators (e.g., Excluded by Requester Neuroscience scientist) share this interest. Rather, it is proposed that a mid-level (Associate) scientist be hired in the area of maternal-fetal-placental biology to synergize with the laboratory of Excluded by and build further ties with the Maternal-Fetal Medicine Division, Ob-Gyn, OHSU, as well as the DOM Division, ONPRC.

SUPPLIES

Office & Admin Supplies: Standard office supplies (paper, pens, folders, computer software, etc.) are requested for the four offices of Excluded by Requester

OTHER EXPENSES

Maintenance –Equipment: including computers, printers, shredder, plus software upgrades .

Biohazard Waste Disposal: These funds would be used to pay for disposal of biological and chemical waste generated by the division laboratories that cannot be practically attributed to specific grants. Charges are per the standard OHSU Radiation Safety schedule.

Division of Reproductive & Developmental Sciences Income Table

Last Funded Year (53)

Source	Funding (direct costs)
P51 base grant support	$339,879.78
Program income derived from P51 base grant	895,181.04
Other Sources	0
Total	$1,235,060.82

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$280,310.21
Program income derived from P51 base grant	574,050.93
Other Sources	250,000.00
Total	$1,104,361.15

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

The Division of Reproductive & Developmental Sciences receives salary support and support for other expenditures from program income. Other sources represents recruitment funding from the VP for Research.

TITLE: DIVISION OF PATHOBIOLOGY AND IMMUNOLOGY

CORE-SUPPORTED PERSONNEL:

Core Scientists (See Biographical Sketches, listed alphabetically in the Overview of the ONPRC)

Excluded by Requester	Interim Division Chief, Senior Scientist
	Associate Scientist
	Senior Scientist
	Senior Scientist
	Associate Scientist
	Senior Scientist
	Senior Scientist
	Assistant Scientist
	Senior Scientist
TBN	Assistant Scientist
TBN	Division Chief, Senior Scientist

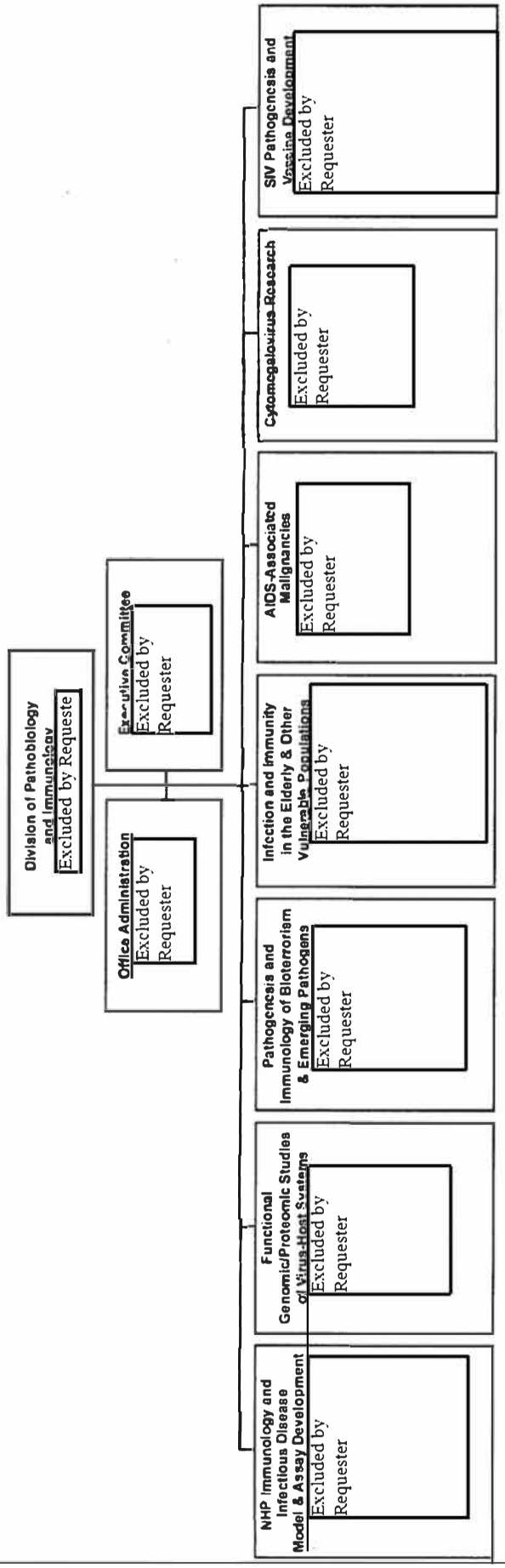
Research Support:

Excluded by Requester	Staff Scientist III
	Staff Scientist III

Administrative Support:

Excluded by Requester	Administrative Coordinator
	Administrative Coordinator
	Administrative Assistant

Division of Pathobiology & Immunology
Organizational Chart



DIVISION OF PATHOBIOLOGY AND IMMUNOLOGY PERSONNEL AFFILIATION AND ROLE

Core Scientists:

Excluded by Requester	Interim Division Chief, Senior Scientist
	Senior Scientist
	Senior Scientist
	Senior Scientist
	Senior Scientist
	Senior Scientist
	Associate Scientist
	Associate Scientist
	Assistant Scientist

[1] Primary appointment Vaccine and Gene Therapy Institute, OHSU
[2] Joint appointment Vaccine and Gene Therapy Institute, OHSU
[3] Joint appointment Department of Pathology, OHSU
[4] Joint appointment Department of Molecular Microbiology & Immunology, OHSU

Affiliate Scientists:

Excluded by Requester	Vaccine and Gene Therapy Institute, OHSU
	Vaccine and Gene Therapy Institute, OHSU
	Division of Pathobiology and Immunology, OHSU
	University of California, Riverside
	University of Arizona, Tucson, AZ
	Division of Pathobiology and Immunology, OHSU
	Vaccine and Gene Therapy Institute, FL
	Vaccine and Gene Therapy Institute, OHSU

Staff Scientists:

Excluded by Requester	Staff Scientist I
	Staff Scientist I
	Senior Staff Scientist
	Staff Scientist I
	Staff Scientist II
	Staff Scientist III

DIVISION OF PATHOBIOLOGY AND IMMUNOLOGY

DESCRIPTION:

The mission of the Division of Pathobiology and Immunology is to conduct basic and applied research on infectious diseases that account for more than 25% of all deaths worldwide. This number is likely to be even larger if certain cancers, and cardiovascular and respiratory/digestive deaths, which can also be attributed to infection, are included. The Division's research focuses on understanding host-pathogen interactions and how these interactions can shift from a controlled and balanced equilibrium to an uncontrolled state that leads to morbidity and mortality. Research projects include dissecting the host immune response to infection and identifying the components of the innate and adaptive immune response that are necessary to protect against infection and disease progression, to molecular virological approaches to identify viral determinants of pathogenesis. All of this research involves the use of animal models, with a major emphasis on nonhuman primate (NHP) models, specifically macaque species, which are relevant for human studies given that NHPs share developmental, physiological and evolutionary relationships with humans, and are susceptible to the same or closely related infectious agents with similar, if not identical, sequelae. Division scientists have internationally recognized expertise in NHP applications in: (a) immunology; (b) model development for infectious microorganisms that are relevant to humans; (c) novel vaccine development and evaluation; and (d) molecular techniques to identify pathogenic determinants associated with disease. The high level of scientific activity and innovation is exemplified by our primary researchers (nine core and four affiliate scientists) who averaged $21.1 million (direct costs) in annual research support during the 2009-2012 period. All scientists have joint appointments in departments at OHSU (particularly Molecular Microbiology and Immunology, and Pathology) and most have appointments in the Vaccine and Gene Therapy Institute, and are actively involved in graduate (Ph.D./M.D.) and post-doctoral training (NIAID-supported training grants in virology, microbial pathogenesis and immunology), as well as clinical research training. Going forward, the Division's goals for the next five-year funding cycle of the P51 will focus on: (1) expanding its research portfolio by building upon our existing strengths to develop new NHP models of infectious and chronic disease; (2) ensure availability of NHP resources for infectious disease research; and (3) continue to train the next generation of scientists dedicated to the diligent use of NHP models to combat primate and human health concerns.

RELEVANCE:

Elucidating the host-pathogen interactions that lead to infection and disease are paramount to protecting human health, as the World Health Organization (WHO) estimates that infectious diseases are responsible for 25% of all deaths worldwide. Interestingly, six diseases account for 90% of infectious disease deaths, and include acute respiratory infections (including pneumonia and influenza), AIDS and AIDS-associated disease, diarrheal diseases, tuberculosis, malaria and measles. Division scientists are utilizing NHP models to better understand the complex host-pathogen interactions to maintain a synergistic balance or shift to a protective and healthy interaction.

DIVISION OF PATHOBIOLOGY & IMMUNOLOGY SPECIFIC AIMS

The World Health Organization (WHO) estimates that infectious disease is responsible for 25% of all deaths worldwide and that this number is likely to be even larger if certain cancers, cardiovascular and respiratory/digestive deaths, which can also be attributed to infection are included. Interestingly, six diseases account for 90% of infectious disease deaths, and include acute respiratory infections (including pneumonia and influenza), AIDS and AIDS-associated disease, diarrheal diseases, tuberculosis, malaria and measles. To curb this growing global problem further elucidation of host-pathogen interactions is absolutely needed to better design therapeutics and vaccines to prevent morbidity and mortality from existing and newly emerging infectious agents. Commensurate with this need is the absolute requirement for an animal model that parallels and shares developmental, physiological and evolutionary relationships with humans, and are susceptible to the same or closely related infectious agents with similar, if not identical sequelae. Addressing this challenge is the goal for the scientists within the Division of Pathobiology and Immunology (DPI), which is home to a team of outstanding virologists, immunologists and pathologists, many of whom are also scientists within the Vaccine and Gene Therapy Institute (VGTI), who are imbued with a team ethic and a commitment to nonhuman primate (NHP) models. The fundamental theme is that progress in these areas of investigation requires high level expertise and experience in virology, immunology and pathology, a combination that is rarely found in a single investigator, but that would be provided by a close-knit collaborative environment in which scientists encompassing these disciplines could interact on a daily basis. Furthermore, it was felt that NHP models would be an essential element of any truly clinically relevant investigations in these areas.

Within the next 5 year funding cycle of the P51 the Division will focus on expanding its' research portfolio by building upon our existing strengths to develop new NHP models of infectious and chronic disease, and simultaneously, train a new crop of scientists dedicated to the diligent use of NHP models to combat primate and human health concerns. Accomplishing these goals will be a challenge and we plan to tackle this by recruiting an established scientist, who utilizes NHPs for both infectious and chronic disease research to lead the Division within the next two years. and recruit immunologists (senior and junior investigators) to fill the gaps generated by the departure of Excluded by Requester within three years. The specific aims for the Division are:

Specific Aim 1: To promote and expand research opportunities in existing areas of NHP Immunology and Infectious Disease Science

Specific Aim 2: Develop new NHP models of emerging infectious and chronic disease

Specific Aim 3: Train new era of scientists to expand NHP models of infectious disease

DIVISION OF PATHOBIOLOGY & IMMUNOLOGY – RESEARCH STRATEGY

SIGNIFICANCE

The global morbidity and mortality associated with infectious diseases represents a significant economic and public health concern that is unlikely to be eliminated, especially as humans encroach poorly characterized areas and travel from one region of the globe to another, carrying novel pathogens to distant populations that represent naïve hosts. Similarly, some infectious agents that have been present for millennia continue to plaque humankind, and are in dire need of new approaches to curb their spread and stop the related increase in healthcare costs. To address these growing concerns, scientists utilize animal models that recapitulate disease in humans to dissect how pathogens invade, replicate and induce disease, and, at the same time, elucidate how the host immune system combats the incoming pathogen to eliminate or control the infection. Murine models are particularly helpful, specifically genetic knockouts, as they provide insights into which components of the immune system are important [reviewed in (1)]. Unfortunately, as valuable as murine models are, they do not always represent how pathogens behave in humans. Additionally, the pathogens that naturally infect mice may not closely resemble those pathogens that cause disease in humans. As such, scientists need a more relevant animal model such as nonhuman primates (NHP). Old World monkey species have the closest evolutionary relationship to humans of any approachable animal model, and as such comprise the most appropriate, if not the only, model system for a variety of infectious diseases, particularly including AIDS and diseases caused by select agents (4, 7, 8, 17). Importantly, the organization and function of the immune system in NHP closely resembles that of humans, and thus, these animals provide an invaluable resource for the study of pathogenesis and immunity of infectious disease, the development of vaccines and other immuno-therapeutics to such agents and, just as importantly, investigation of fundamental questions in basic primate immunology that due to ethical or practical constraints are not amenable to study in the human system (4). To this end, division scientists in the previous funding period utilized NHP models to define the host immune responses involved in protective immunity and identify pathogenic mechanisms utilized by viruses to induce disease. These advances led to new insights into vaccine design that demonstrated persistent immune stimulation with cytomegalovirus (CMV) vectors can induce long-lived CD4+ and CD8+ effector memory T cells (T_{EM} cells) that can control SIV viremia and protect rhesus macaques (RM) from disease. These findings led to a substantial increase in funding to bolster further development in AIDS pathogenesis and vaccine studies, and to develop novel NHP models of emerging and re-emerging pathogens. Although development of these models often involves an initial discovery of a new NHP agent or disease that mimics a human condition, such initial discovery is but a very small fraction of the overall effort required to create a model that is at the same time a useful surrogate of human disease and an experimentally approachable system amenable to incisive mechanistic dissection. This effort involves both an iterative process of refining the actual model and the creation of tools that turn a veterinary disease into a scientifically exploitable model system.

For the upcoming funding period, Core Scientists intend to expand into novel areas of research that build upon their existing strengths. For example, extent the use of CMV vectors to provide persistent immune stimulation to other pathogens, such as *Mycobacterium tuberculosis* (Mtb) and malaria. Simultaneously, Division scientists will continue to train new infectious disease researchers and immunologists to utilize and build upon NHP models of infectious diseases in order to obtain the data necessary elucidate mechanisms of microbial pathogenesis in models that closely recapitulate aspects of the human disease (4). Considerable efforts are still required to perfect some of the models, and the Division is uniquely positioned to address these needs.

INNOVATION

The mission of scientists in Pathobiology & Immunology is to maximize the research value of NHPs, which represents a unique animal resource to address unmet needs in infectious and chronic disease research that closely parallel disease in humans. Importantly, the ONPRC has outstanding resources to facilitate NHP research, which include the U24 resource that provides expanded Specific Pathogen Free (eSPF) rhesus macaques (RM) of Indian origin, the U42 resource to provide SPF RM of Indian origin for AIDS-related research, and a Japanese macaque resource (JMR) to breed JM for the Japanese macaque encephalomyelitis (JME) model of multiple sclerosis (MS)-like disease and the macular degeneration model or Drusen, and the requisite infrastructure [Animal Biosafety Level 3 (aBSL-3) containment] to house and study animals infected with highly pathogenic agents and biostatisticians to assist in statistical analysis. Additionally, several

immunological reagents, surgical techniques and advanced imaging approaches have been created and validated in NHP and these tools help dissect host-pathogen interactions in an outbred animal that before now were only accessible in inbred rodent models through genetic knockouts. Contributing to this innovation is the ability of Division virologists to manipulate viral genomes via molecular genetic techniques to engineer defined mutations in viral pathogens to further interrogate the complex role specific viral open reading frames or viral encoded macromolecules play in the host-pathogen interaction. The translation of these integrated studies in NHP will increase our understanding of host-pathogen interactions to develop more rational approaches to prevent and treat infectious disease in humans. Some of the Division's innovations since the last renewal include:

- Excluded by Requester laboratory reported that cytomegalovirus (CMV) vectors encoding SIV antigens can elicit high frequency, persistent and mucosal-oriented CD4+ and CD8+ effector memory T cell responses to SIV proteins, and these T_{EM} cell responses in the mucosa of RM were protective against pathogenic SIV challenge in a percentage of animals.
- Excluded by Requester reported that for CMV to successfully re-infect a CMV-positive host the newly infectious virus must evade the host's CD8+ T cells. This study helps define how CMV vectors must be constructed to enable the virus to serve as a vaccine vector in previously CMV-exposed hosts. CMV infection is widespread with some regions of the globe having greater than 90% seropositivity.
- Excluded by Requester reported the development of a simian varicella virus (SVV) infection model of RM that closely resembles varicella zoster virus (VZV)-associated chicken pox in humans. This is an important animal model that will allow scientists to improve their understanding of the immune response to VZV and to develop and test better vaccines to reduce the incidence of shingles and its attendant neurological complications.
- Excluded by long-standing research program designed to unravel the virologic and immunologic determinants of mother-to-child transmission (MTCT) reported the importance of maternal neutralizing antibodies to control HIV infection in newborns. In a seminal publication Excluded by and colleagues reported that infusion of neutralizing antibodies at levels incapable of blocking infection before oral challenge was capable of inducing a rapid B cell response in the animals, which significantly reduced plasma viremia and limited CD4 decline.
- Excluded by laboratory investigates the function of viral encoded miRNAs and found that one of human CMV's viral microRNAs down-regulates multiple cell cycle genes through mRNA 5'UTRs, which differs from the conventional targeting of 3'UTRs. Importantly, for the Division's goals, his laboratory was the first to report that rhesus CMV encodes seventeen microRNAs.
- Excluded by Requester reported that Japanese macaques (JM) housed at the ONPRC have developed a spontaneous demyelinating disease, referred to as Japanese macaque encephalomyelitis (JME) that possesses clinical and histopathological similarities to multiple sclerosis (MS). This finding represents the first natural occurring nonhuman primate model of MS.
- Excluded by Requester and his colleagues have developed a novel vaccine platform that utilizes hydrogen peroxide (H_2O_2) to inactivate viruses for vaccine production. His team reported H_2O_2 inactivated lymphocytic choriomeningitis virus (LCMV), vaccinia virus and West Nile virus were highly immunogenic and provided a range of protection against these pathogens in a small animal model of viral pathogenesis.
- Excluded by Requester and his colleagues reported the isolation of a novel simian herpesvirus from a spontaneous demyelinating lesion of a JM that developed JME. The genomic sequence of the virus was recently accepted and the virus is closely related to rhesus macaque rhadinovirus and human Kaposi's sarcoma-associated herpesvirus. Interestingly, the virus referred to as Japanese macaque rhadinovirus (JMRV) encodes additional open reading frames that may be associated with pathogenesis.

APPROACH.

reviewers' comments

reviewers' comments

Progress Report

As mentioned above, the research of the Division scientists (core and affiliates) focuses on increasing our understanding in host-pathogen interaction and how changes in this interaction can lead to acute and chronic disease, or prevention of disease. Much has been gained in our understanding since the last program renewal and Division scientists have made substantial contribution in achieving our research goals. The primary areas

of our research are represented in the Pathobiology and Immunology organization chart, and include the Division Core and Affiliate scientists who are associated with each area. The diagram indicates that a number of Division scientists participate in more than one area, which we consider to be a significant strength of the Division's research program as each individual's knowledge and expertise contributes to the area of focus. Additionally, several of these areas of research overlap which also increases our knowledge base. For example, the AIDS Pathogenesis and Vaccine Development, and Cytomegalovirus (CMV) programs have considerable interactions as elucidating aspects of the immunology and pathobiology of CMV is absolutely essential, because CMV is being utilized as a vaccine vector for SIV and other pathogens. Likewise, the Kaposi's sarcoma-associated herpesvirus (KSHV)/Rhesus macaque rhadinovirus (RRV) program interacts closely with the AIDS Pathogenesis research program as KSHV and RRV infection are associated with malignancies in the context of AIDS, and there is considerable research being conducted in this area.

Progress and Major Accomplishments – Research Funding

The progress of Division scientists is best illustrated in **Figure 1** where the efforts of core scientists have resulted in a truly meteoric rise in grant funding since the Division was re-structured in 2001 with the addition of scientists from the Vaccine and Gene Therapy Institute (VGTI). More importantly, since the last renewal in 2008, the Division has more than doubled the amount of direct research dollars from $10 million to approximately $25 million in 2012. This funding represents federal and foundation grants possessing components involving the use of NHPs. Additionally, Division research funding has diversified, including funding support for biodefense-related studies, aging studies and other areas including cancer and autoimmune-related diseases. Each of the primary areas of research will be summarized below with a description of research, and impact of research based on select publications. Some publications will be listed in more than one area as they represent the close interaction between related areas of research.

A. B.

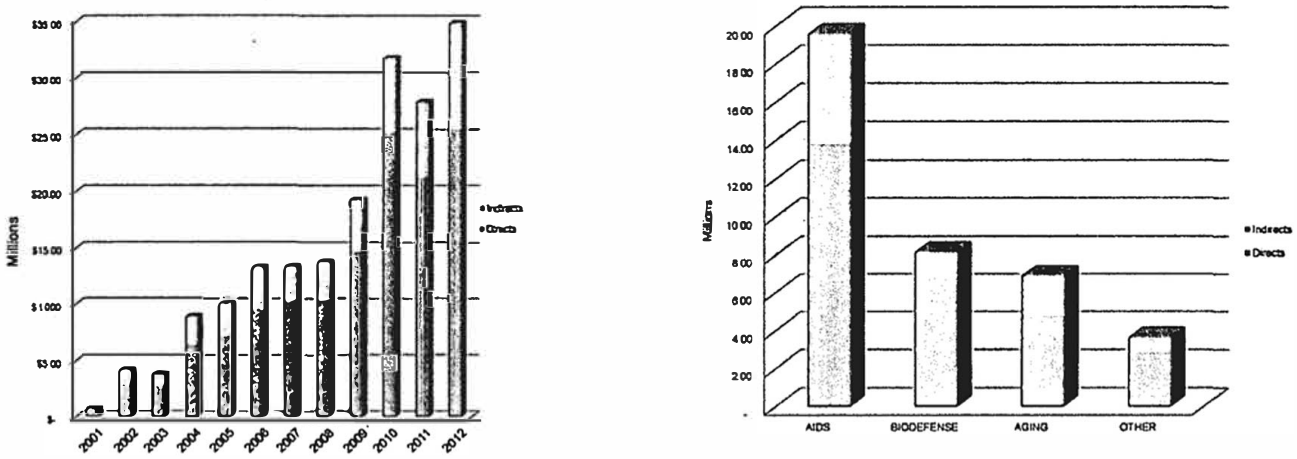


Figure 1: Current Division of Pathobiology & Immunology Grant Funding. A. External grant funding involving the use of nonhuman primates for each year is shown with direct costs in blue and indirect costs in red. B. Funding in primary areas of research are shown. Funding in the "other" category includes cancer and autoimmune disease.

A. NHP Immunology and Infectious Disease Model and Assay Development: NHP model development is not limited to identification of viruses and associated diseases; it also involves development of tools and protocols that enables fundamental dissection of immunity and immunopathogenesis. This area of research is directed by Excluded by Requester former Division Head and the developer of Ag-specific T cell cytokine flow cytometry (ICS) in humans in the mid-1990s. Excluded by has successfully adapted this technique to NHP work and has disseminated these assays widely. In addition to this technique, Excluded by group has also 1) definitively established the phenotypic signatures of naïve and memory T cell subsets (central memory, T_{CM} and effector memory, T_{EM}) in RM and the fundamental physiology of these subsets; 2) optimized approaches for systemic assessment of T cell dynamics in RM; 3) developed bronchopulmonary lavage as a repeatedly accessible site of the NHP mucosal immune system, and thoracic duct drainage as a means to obtain larger quantity (>10^9) lymphocyte harvests in NHP (in collaboration with Excluded by Requester 4) developed multiple intestinal mucosal biopsies to assess gut-associated lymphoid tissue (GALT) for T cell subsets and effector function; 5) developed techniques for characterization of T cell receptor-defined clonotypes within Ag-specific NHP T cell populations; 6) developed new, more predictive immunologic monitoring protocols for SIV pathogenesis; 7)

developed the tools for comprehensive assessment of RhCMV-, SIV-, RRV-, SVV- and foamy virus-specific T cells; 8) adapted phospho-protein flow cytometry for the analysis of intracellular signaling in NHP T cells; 9) worked with external collaborators to develop approaches for high efficiency transduction of primary RM T cells; and 10) contributed as part of a larger consortium seeking to develop and/or refine the use of mAbs, particularly "monkeyized" mAbs, to experimentally manipulate NHP immunity *in vivo*. In keeping with Dr. Excluded by Requester focus on memory T cell dynamics, a top priority is the development of reagents capable of long-term neutralization of the common gamma-chain cytokines IL-15 and IL-7. The fruits of these developments are coming to completion and are widely utilized by NHP immunologists and virologists, including outside investigators through the Division's Collaborative Research Unit that is led by Excluded by Requester and managed by Excluded by Requester

Scientific Impact – Select Research Publications (ONPRC Core faculty are in bold and Affiliate are underlined.)

Excluded by Requester

B. AIDS Pathogenesis and Vaccine Development: The AIDS epidemic represents one of medicine's most pressing challenges, and as such, has emerged as a major focus of the Division's research effort. Indeed, AIDS-related research is a dominant focus of the Excluded by Requester laboratories. This effort includes research in the following areas: 1) basic SIV/HIV virology; 2) immunopathogenesis of SIV/HIV infection; 3) biology of opportunistic infections and AIDS-associated malignancies; and 4) SIV/HIV vaccine development.

The most extensive aspect of the Division's AIDS program is the multi-lab effort to develop an effective AIDS vaccine using the SIV/rhesus macaque (RM) model(s). Two approaches are being pursued by Division scientists: cell-mediated immunity and humoral immunity. Until recently, the field's extensive efforts to achieve this goal have not yielded a truly effective vaccine in rigorous challenge models, indicating the need for innovative, novel and perhaps unconventional approaches. With the exception of attenuated SIV vaccines, which, though effective, have proved too dangerous for human development, most previous T cell-targeted approaches have focused on non- or minimally persistent vectors. We have rationalized that efficacy of a T cell-targeted vaccine might require the long-term immunostimulatory capabilities of a persistent vector. Our experience with both human and rhCMV has demonstrated qualities that make this virus an ideal candidate for such a persistent T cell-targeted vector. In this regard, it is well established that CMV elicits one of the highest frequency T cell responses of any microbe studied to date. In humans, the pan-CMV proteome-specific T cell response averages ~10% of circulating memory cells, both CD4+ and CD8+. RhCMV-specific responses are analogously high in rhCMV-exposed RM, and the representation of rhCMV-specific T cells is even higher at mucosal effector sites. Based on these and other considerations, Excluded by Requester have constructed and *in vivo*-tested rhCMV vectors encoding SIV proteins and have found that not only are these vectors capable of eliciting high frequency, persistent and mucosal-oriented CD4+ and CD8+ T cell responses to SIV inserts, but that these vectors are capable of sub-clinically infecting RM and eliciting such immune responses without regard to the animal's CMV status or the number of times it has previously seen the vector. This group subsequently found that CMV vector elicited SIV-specific T cell responses in the mucosa of RM and

the responses were protective against pathogenic SIV challenge in a percentage of animals. Importantly, the investigators identified the mechanisms responsible for the unique immunobiologic properties of these vectors(6). This work was published in Nature Medicine (**Figure 2**). Subsequent to this finding, this same group reported that CMV vectors are capable of inducing strong SIV-specific CD4+ and CD8+ T_{EM}, and these cell types were responsible for protecting against repeated rectal challenges. These remarkable findings provide evidence that CMV vectors have enormous potential to deliver protective T cell immunity to HIV infection and potentially other pathogens. These remarkable findings provide evidence that CMV vectors have enormous potential to deliver protective T cell immunity to HIV infection and potentially other pathogens.

***Figure 2**: Cover page highlighting the remarkable ability of novel RhCMV vectors encoding SIV-antigens to protect vaccinated RM against pathogenic SIV challenge. Nat Med 15: 293-299, 2009; plus editorial "News and Views" by Franchini 15: 244-246.*

The second approach to developing an AIDS vaccine is dedicated to humoral immunity and is a major focus of Excluded by Requester laboratory. Her long-standing research program is designed to unravel the virologic and immunologic determinants of mother-to-child transmission. Her recent work in this area has focused on the role that maternal antibodies play in facilitating development of antiviral immunity in the infected newborn. In a seminal publication Excluded by and colleagues reported that infusion of neutralizing antibodies at levels incapable of blocking infection before oral challenge was capable of inducing a rapid B cell response in the animals, which substantially reduced plasma viremia

Excluded by Requester

C. Kaposi's Sarcoma-associated herpesvirus (KSHV)/Rhesus Macaque Rhadinovirus (RRV) Program: As indicated above, the biology and pathogenesis of the gamma herpesviruses, KSHV and its closely related simian gamma herpesvirus, RRV, has emerged as a major research focus of Excluded by Requester KSHV is the etiologic agent of Kaposi's sarcoma (KS), a multifocal vascular tumor of the skin and mucosa, and two B cell lympho-proliferative diseases (LPD), primary effusion lymphoma (PEL) and multi-centric Castleman's disease (MCD) (2, 3, 16). KSHV is necessary but not sufficient for the development of these diseases. HIV co-infection, immunosuppression, and other ill-defined factors all increase the risk of disease. RRV infection of RM co-infected with SIV leads to the development of LPD resembling those associated with KSHV, demonstrating the RM/SIV/RRV model is a valuable model for KSHV-associated pathologies(18).

Advances made by Division faculty and their collaborators include: 1) the use of functional genomic and proteomic technologies to obtain transcriptional and proteomic profiles of KSHV and RRV-infected cells; 2) the identification of several viral and cellular genes that contribute to KSHV/RRV pathogenesis(13); 3) the development of novel animal- and cell-based systems to elucidate gene function(12); 4) the identification and characterization of viral and immune modulators of disease and their host cell targets(11); and 5) the identification and validation of known and novel cancer targets for the treatment of KS and PEL/MCD(14). Collaborations with clinicians to enhance the translational component of the program include evaluating expression of KSHV and host proteins in KS biopsies pre- and post-therapeutic intervention.

Excluded by Requester

D. Cytomegalovirus (CMV) Research Program: A common theme for the majority of the faculty in the Division is an interest in the immunology and pathobiology of CMV. The research topics of the PIs vary from the development of CMV as a new vaccine platform to mechanisms of CMV immune evasion and CMV pathogenesis. CMV is a species-specific virus and although the chimpanzee CMV genome shares the closest homology to human CMV (HCMV), rhesus CMV (rhCMV) also encodes the majority of the HCMV ORFs and provides a much better model with the RM. A major accomplishment in the previous funding period has been the establishment of the rhCMV vaccine vector system. Already many of the studies that have been performed in the rhCMV/macaque model have elucidated many questions that have not been approachable in humans, including the ability of rhCMV to re-infect immuno-competent macaques, the inability of rhCMV lacking the genes that down-regulate MHC I to efficiently re-infect primates, and the utility of rhCMV as a platform vector to induce a significant response to antigens cassetted into the viral BAC(5). In addition to these accomplishments, Excluded by and his colleagues have established the first humanized mouse model in which we can establish HCMV latency as well as reactivate virus in infected mice(15). Currently, Excluded by Requester and his colleagues are identifying the viral and cellular targets of the viral miRNAs that potentially impacts the establishment of a persistent infection. These studies are being evaluated in the humanized mouse model and will be translated to rhCMV to help design new rhCMV vector systems to improve safety.

Excluded by Requester

E. Pathogenesis and Immunology of Bioterrorism and Emerging Pathogens: The increasing threat of bioterrorism and the increasing realization of the dangers posed by emerging infectious diseases have placed a national priority on understanding the diseases caused by these agents, and the development of vaccines by

which vulnerable populations can be protected. The VGTI and Division faculty's expertise in virology, immunology, pathology and NHP models is tailor made for rapidly responding to this priority, and over the past five years the Division and the VGTI have aggressively pursued research programs in Biodefense and Emerging Diseases. This effort was rewarded when Excluded by Requester received NIAID support to create the Pacific Northwest Regional Center of Excellence for Biodefense and Emerging Infectious Disease Research (PNWRCE) centered here at OHSU. The research activities of the program are aimed at providing a deeper understanding of pathogen-host interactions; how these interactions impact innate and adaptive immune responses; and the age-related defects in immunity that lead to immunosenescence and an increased vulnerability to infectious disease. The information generated from these activities will facilitate the development of next-generation therapeutics, diagnostics, and vaccines against Category A-C pathogens.

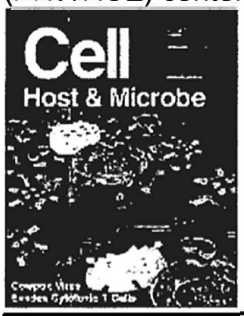


Figure 3: *Cover page highlighting how poxvirus evasion is due to two proteins encoded by cowpox virus—one that blocks peptide acquisition by MHC class I and one that retains empty MHC class I in the endoplasmic reticulum—and that viruses lacking both proteins have reduced virulence in vivo and resemble vaccinia virus in being unable to prevent activation of CD8$^+$ T cells. Cell Host & Microbe 2009, 6(5):433-445.*

Excluded by Requester

F. Infection and Immunity in the Elderly and Other Vulnerable Populations: Populations especially vulnerable to infection, including emerging infections and the agents of bioterrorism, encompass up to one-third of the U.S. population, and include the elderly, the immunosuppressed (those with congenital, acquired and iatrogenic immune deficiencies) and individuals under stress. These individuals face two problems: increased morbidity and mortality in the face of numerous infectious pathogens, and poor responsiveness to many vaccines that effectively protect the immunocompetent population. The aim of this program, initially led by Excluded by Requester is to integrate rodent and NHP models to gain insight into the underlying immune deficiencies that face vulnerable populations, to verify the obtained results in humans and to devise new vaccine and treatment approaches to protect these populations from infectious disease. The vast majority of the efforts in the past period were focused upon the elderly.

Excluded by Requester

Excluded by Requester

G. Functional Genomic/Proteomic Studies of Virus-Host Systems: Viruses are master manipulators of their host environment. At the cellular level, viruses counteract the innate host immune response and usurp host cell metabolic pathways for their entry, replication and exit. At the organism level, viruses stimulate, but also deflect and circumvent the host's innate and adaptive cellular immune response. Both traditional and new, global approaches are needed to understand these complex virus-host interactions. Excluded by Requester established functional genomics techniques at the VGTI, in particular DNA microarrays and mass-spectrometry and these techniques are now used by several investigators Excluded by Requester to study virus-host interaction at a global level. Additionally, outside collaborations with expertise in functional genomics, proteomics and systems biology Excluded by Requester Excluded by Requester expand the capabilities and research scope of this program. These projects encompass both *in vitro* and *in vivo* studies of a number of viruses in human, NHP and small animal models. Viruses studied include: HIV/SIV; CMV of human, mouse, rat and rhesus; cowpox and monkeypox viruses; Flaviviruses including West Nile Virus, Dengue Virus, Yellow Fever and Japanese Encephalitis virus; and KSHV and RRV.

Excluded by Requester

H. Scientific Impact – Trainees: The primary focus of Division scientists to date has been the development of a robust, externally funded portfolio of new research programs, which involves training the next generation of researchers to continue to build this program. All core scientists except Excluded by Requester are faculty of the Department of Molecular Microbiology and Immunology at OHSU, and the Division currently houses 7 graduate students and 11 post-doctoral fellows. Over the past 5 years, Division core and affiliate scientists have trained 14 graduate students and 14 post-doctoral fellows. The Division also supports a seminar series in which outside scientists are brought into the Division each year for formal lectures and informal discussion with Division scientists and students. The Division recognizes the critical need for future scientists with specific expertise in NHP models of immunity and infectious disease, and has sought NIH funding for a formal training program focused on NHP immunology and virology Excluded by This program was funded in 2010 and we will continue our effort to develop and build this program during the next Core grant cycle.

I. Scientific Impact – professional service: Division scientists serve on a plethora of prestigious panels, scientific advisory boards, study sections and editorial boards. The details of these activities can be found in each investigator's individual scientific activity forms, and highlights include the following: Excluded by Requester presently serves on the Board of Scientific Counselors for the Vaccine Research Center and the Council of Councils at NIH, and formerly as Chair, AIDS Vaccine Research Subcommittee in the Division of AIDS at NIH and member on the Scientific Advisory Committee for the International AIDS Vaccine Initiative (IAVI). Dr. Excluded by Reque is a former member of the NIAID Council (DAIDS subcommittee) and the AIDS Vaccine Research Subcommittee. He serves as a scientific advisor to the Comprehensive T Cell Vaccine Monitoring Consortium (CTCV) of the Collaboration for AIDS Vaccine Discovery (CAVD) Program sponsored by the Private Source Private Source Excluded by Requester is a former Editor of the Journal of Virology and current Associate Editor of PLoS Pathogens. Excluded by Requester is a permanent member of the NIH Virology B (VirB) Study Section. Excluded by Requester is an Editor for the Journal of Virology and Section Editor for PLoS Pathogen. Excluded by Requester Excluded by Requester are members of the Editorial Board of the Journal of Virology.

Future Plans

SPECIFIC AIM 1: To promote and expand research opportunities in existing areas of NHP Immunology and Infectious Disease. We expect to continue and thoughtfully expand the current scientific programs described above for which Division scientists have been extremely successful in garnering federal and foundation support. New scientific programs will be evaluated on the basis of national health research

priorities, expertise of Division scientists and ONPRC infrastructure to accommodate the animal containment and support.

a. *Mycobacterium tuberculosis:* Taking the aforementioned comments into consideration, Excluded by Requester have started a new scientific program involving tuberculosis pathobiology and vaccine research. This program was actually initiated more than 8 years ago by OHSU-based affiliate investigators, Excluded by Requester but progress was stalled due to a lack of an appropriate animal biosafety level 3 (aBSL-3) facility to support NHP research with this agent. Although these investigators successfully piloted a new approach to tuberculosis research in RM at that time Excluded by Requester the 4 animal aBSL-3 facility used for this study was deemed inadequate for serious investigation and was not pursued for more than 4 years (10). Now, with the new aBSL-3 facility and portable CT scan capable of supporting *M. tuberculosis*-infected NHP, we can resume this research. This scientific program complements Divisional expertise in the immunobiology of persistent agents, T cell memory, and the waning of cellular immunity with age, and broadens our programmatic focus from an exclusive focus of viral diseases to a high priority bacterial pathogen. Taken together, these efforts will maintain and enhance the ONPRC Pathobiology & Immunology Division's reputation as a center for exciting, cutting-edge NHP research, and at the same time meet national health research priorities. The timeline for these studies to initiate has just begun and we envision this program will be up and running within the next year and that further expansion in this targeted area will occur over the next five years. Full expansion into Mtb will likely require the hiring or close collaboration with a card carrying Mtb expert to become fully immersed.

b. *Malaria research:* Another scientific program that will begin soon involves malaria research. Excluded by Requester who has past experience in malaria research, recently received an R21 from NIAID to start malaria studies in RM with an emphasis on developing a CMV vaccine vector encoding specific malaria antigens. The goal for these studies is to identify immunodominant antigens and engineer these target antigens into CMV vectors for vaccine evaluation for this high priority protozoan pathogen. The timeline for these studies to start is within the next year. Given the importance of malaria as international health priorities, we envision this program will garner considerable support from NIH and other private foundations.

c. *Potential outcomes:* We anticipate that we will be able to move forward with these two research programs, despite not having card-carrying experts in either area. The fact that Excluded by Requester has garnered support for the Mtb studies from Aeras is confirmation that the expertise of our Division scientists is viewed positively to move studies forward without an Mtb expert in house. In the event an Mtb expert is needed to assist with interpretation of results, the PIs have established collaboration with Excluded by Requester (University of Pittsburgh), who has extensive experience with Mtb-infection in RM. Locally, Excluded by Requester who is an Assistant Professor in the Molecular Microbiology and Immunology (MMI) Department at OHSU and an expert in Mtb pathobiology, can provide guidance and insight if needed. With regard to the malaria research program, we expect a similar situation, but believe the past training of Excluded by Requester supports this high risk funding mechanism. Recruitment of a malaria expert may be less important as Excluded by Requester is a malaria expert and a member of MMI and can provide guidance if needed.

SPECIFIC AIM 2: Develop new NHP models of emerging infectious and chronic disease. We are currently seeking to expand this program, which was largely supported by the Pacific Northwest Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research (RCE) (U54 RFA-AI-08-002) in Region 10. Our application was a joint program between OHSU and the University of Washington (UW) in which Excluded by was the PI and Excluded by at UW, the co-PI. Our goals for the coming funding cycle are to build on the strengths and preliminary data that we developed through the RCE program. The two major themes of the RCE are the development of vaccines for vulnerable populations and the use of functional genomics and genetics to understand pathogen-host response for biodefense organisms and emerging disease. The application focused on multiple viral pathogens and all involved NHP components.

a. *Emerging infectious disease*: One project that successfully translated into an R44 award involved the development of a new Yellow Fever vaccine for vulnerable populations. This funded work was awarded to Excluded by Requester and his colleagues and has been ongoing for two years and will lead to further studies, as the novel vaccine is capable of protecting RM from developing disease. The ability to successfully and reproducibly induce disease in RM and define the host immune response to infection was essential for the award.

Flaviviruses (FV) were also a primary focus of the RCE, as FV infections are becoming more prevalent around the globe as the Aedes aegypti and albopictus mosquitoes, which serve as the vectors for dissemination, have been found in different regions of the globe, including here in the United States. This is a growing public health concern and new approaches are desperately needed to stem FV infections. Division scientists supported by the RCE program have devoted efforts to better understand the immunopathogenesis associated with West Nile virus (WNV), Dengue virus (DV) and Japanese encephalomyelitis virus (JEV) infection and replication. The result of these efforts has translated to an NIH U01 and R01 to Excluded by Requester to develop a WNV vaccine and tetravalent DV vaccine, respectively. The R01 supporting DV vaccine development was awarded and will bolster the Division's emphasis on new infectious disease models over the next five years.

Support for the RCEs is scheduled to end within the next two years and Division scientists are planning on migrating to new funding mechanisms to further research in many of the pathogens that were studied through the RCE. These include viral pathogenesis and system biology approaches to study DV, influenza virus and Ebola virus infections in vitro and in vivo. Additional efforts will be focused on building upon our Chikungunya virus (CHIKV) program, which was partially funded by the RCE and an ONPRC pilot project award to Drs. Excluded by Requester CHIKV is an alphavirus that is transmitted to humans by virus-carrying Aedes mosquitoes was originally isolated to the Indian Ocean region, but has since begun to spread into the Mediterranean region and further north into Europe. Infection is frequently accompanied with arthralgia that can be persistent and debilitating, which was observed in the LeUnion outbreak. Preliminary studies in RM demonstrate that subcutaneous CHIKV infection can lead to inflamed joints with high viral loads, accompanied with histopathology consistent with joint injury. As the ONPRC and VGTI have the necessary infrastructure to pursue these studies, we envision that within the next 5-year interval we will expand further into this program, supported by federal funds.

b. Chronic disease model in NHP: The JME model of inflammatory demyelinating disease closely resembles clinical and histopathological aspects of MS. This unique model was identified here at the ONPRC and appears to be associated with a novel rhadinovirus. In the coming year, Excluded by and his colleagues in the Division of Neuroscience and others at OHSU intend to further develop and characterize this valuable model by applying for external support from multiple funding agencies and societies including the Private Source Private Source Department of Defense, NINDS and Office of the NIH Director (R24). Their goal is to secure program project support from NINDS to make this model available to other investigators. A concern these Center scientists will face is the limited number of animals in this troop. The Center is aware of this and has utilized computer models to predict the availability of animals in this troop for research purposes. These models confirm that with careful management, the research programs utilizing this resource can be maintained.

With Personal Info,Excluded by Requester Division Head to undertake a greater leadership role in the VGTI and focus on his research programs, we plan to take this opportunity to recruit a senior scientist to lead the Division and expand research in new directions that complement our current expertise. Although, Excluded by has the experience and foresight to lead the Division, he is spearheading the efforts to establish the JME model, which is receiving support from the Center. During this interval, Excluded by Requester has formulated an executive team comprised of Excluded by Requester to help provide guidance as the Division goes through this transition. With regards to the recruitment, we anticipate the individual will be an outstanding scientist with a strong program involving NHP, who has extensive experience in immunopathology, and has a strong track record of NIH support. We anticipate this recruitment, based on a national search, will be completed within the next year, as we have contacted individuals who may be interested in this position. We plan to contact other NPRCs to determine if they have contacts who may be interested, network at immunology meetings or utilize a professional recruitment consultant. Support for this recruitment will be provided jointly by the VGTI (primary appointment) and the ONPRC to leverage our ability to attract an outstanding candidate.

c. Potential Outcomes: Given the current funding climate, we anticipate that we may have to submit multiple proposals to funding agencies to garner support for the FV and JME program. Every effort will be made to ensure the strongest proposal is submitted. This will involve extensive preparation and vetting with our senior scientific staff to make each application as bulletproof as possible and targets health research priorities.

SPECIFIC AIM 3: Train scientists to focus and improve on NHP models of infectious disease. As stated above, NHP provide an outstanding animal model to investigate important health priorities in humans. This essential resource needs to be meticulously managed and utilized to ensure the model remains accessible. Accomplishing this involves extensive training, diligence and foresight to all who intend to utilize this valuable

model. The goal of this aim is to ensure Division scientists are stewards in the utilization and training associated with this model.

a. Participation on ONPRC committees that oversee NHP utilization: Utilizing NHP in research is a privilege that is governed by federal regulations that must be adhered to; otherwise dire consequences will be imposed, potentially eliminating access to this model. To ensure this model remains available for current and future needs, Division scientists will participate on committees that focus on NHP usage, including the Animal Utilization Committee (AUC), which is reviews programmatic needs and is associated with the allocation of NHPs for research. Another important committee is the Institutional Animal Care and Use Committee (IACUC), which is relevant to address animal research and animal welfare, and the Institutional Biosafety Committee (IBC) to evaluate human and animal biosafety. Division scientists who have actively participated on these committees in the past include Excluded by Requester and Excluded by Requester and will continue to provide representatives who will receive the appropriate training (national training seminars, webinars or one-on-one training) for informed participation and contribution.

b. Train the next generation of scientists: As discussed above, training the next generation of scientists is a high priority of Division scientists. We are fortunate to have received a T32 training grant in virology to support and guide budding virologists, and to be associated with an immunology training grant awarded to the MMI Department at OHSU. These funding mechanisms to support their training are instrumental; however, actual training is more relevant and must be directed by scientific principles that necessitate the appropriate use of animals to address questions and hypotheses that are best evaluated in NHPs. Our senior scientists in the Division have extensive experience training pre- and post-doctoral researchers, and will continue to identify and train those young scientists who have an innate interest and desire to investigate questions in an animal model. A summary of our pre- and post-doctoral training was provided in section H. Additionally, our senior scientists will mentor our junior faculty to ensure they are adequately prepared to undertaken NHP studies and possess the necessary mentoring skills to train students. Over the next funding period, our Senior Scientists will continue to mentor our junior faculty. This will be accomplished by assigning a Senior Scientist with similar interests to work with the junior members and help them craft successful grant applications and discuss their research strategies and objectives. These practices are currently ongoing in the Division.

c. Work closely with the NHP Infectious Disease Resource and Division of Comparative Medicine (DCM) for efficient use and management of NHP resources: The Infectious Disease Resource led by Excluded by was created to ensure efficient utilization of NHP for infectious disease studies by providing highly trained and experienced animal care technicians devoted solely to ID studies. The unit provides careful handling and acquisition of samples for all Division scientists, and eliminates the variation in animal handling and sample acquisition that could impact sensitive studies. Additionally, the Unit works closely with DCM to ensure all animal needs are addressed for future NHP needs, including management of the ONPRC's U24 and U42 resources. In the coming years as use of NHP models for ID studies grow we anticipate the recruitment of another veterinarian for this Resource dedicated to infectious disease studies. Additionally, Division scientists will work closely with DCM to evaluate new animal management software programs to ensure compatibility with current and future scientific programs.

d. Provide access to NHP infectious disease-related studies to outside investigators: During the last funding period, the Division's Collaborative Research Unit (CRU), led by Excluded by Requester has been highly successful at providing outside investigators access to the NHP to address novel scientific questions (9). Examples of the success associated with the CRU and several Division Scientists with outside investigators can be found in the PI narratives. A novel study, in particular, is the recently accepted *Neisseria* infection study, which was a collaborative effort with investigators from the University of Arizona. The Division possesses the expertise in viral pathogenesis, immunology and animal management to attract and assist investigators in NHP studies. In the coming funding period, the Division will continue to evolve and utilize state-of-the-art surgical and animal manipulation techniques to address relevant questions associated with microbial pathogenesis, vaccine development and evaluation. We have combined immunology expertise provided by Excluded by Requester in the Infectious Disease Resource to assure that external investigators will have access to the very best advice in designing and completing studies with him and Excluded by Requester and the new To-be-named Staff Scientist.

Potential Outcomes: The importance of the NHP model to infectious disease research cannot be overstated. All efforts will be made to ensure the outcomes are positive and will require buy-in from all Division scientists. This has already been an accepted practice and we do not foresee problems ensuring this success.

Pages 1058-1068 (Publications) Removed – Excluded by Requester

Division of Pathobiology and Immunology - Externally Funded Research Projects

Excluded by Requester Oregon National Primate Research Center, OHSU
Establishment of Specific Pathogen Free Rhesus Macaque Colonies
NIH - U42RR16025
The major goal of this project is to expand and characterize a rhesus macaque breeding colony for production of genetically defined SPF rhesus macaques for AIDS-related research.

Excluded by Requester Oregon National Primate Research Center, OHSU
Establishment of Specific Pathogen Free Rhesus and Pigtail Macaque Colonies
NIH – U24OD010850
The major goal of this project is to develop an expanded definition Indian specific pathogen free (SPF) rhesus macaque breeding colony to support research focused on AIDS-related opportunistic infections.

Excluded by Requester Oregon National Primate Research Center, OHSU
Vaccination and Immune Senescence in Primates: Core B – Animal Core
NIH – P01AG0236644
The goal of this project is to provide research support and veterinary services for nonhuman primates enrolled in this Program Project Grant.

Excluded by Requester Oregon National Primate Research Center, OHSU
Pacific Northwest Regional Center of Excellence: Core B – Nonhuman Primate Core
NIH – U54AI081680
The first goal of the PNWRCE is to identify age-related immune system defects to develop new vaccines and supplemental therapies to enhance protection of individuals to NIAID Category A-C pathogens and a second goal of this center is to use systems genetic, chemical, and proteomics approaches to identify therapeutic targets for biodefense and emerging diseases.

Excluded by Requester Oregon National Primate Research Center, OHSU
Development of Effector-Memory T Cell AIDS Vaccine: Nonhuman Primate Core
NIH – U19AI094417
In this Program, we will modify CMV vectors and/or use complementary heterologous vaccines with CMV vectors to both increase the potency of CMV/SIV vectors so as to achieve rates of protection closer to 100% of vaccines, and reduce the pathogenicity and shedding potential of CMV vectors

Excluded by Requester Oregon National Primate Research Center, OHSU
Consortium for AIDS Vaccine Research in Nonhuman Primates. Nonhuman Primate Core NIH – P01AI095985
The Nonhuman Primate (NHP) Core seeks to consolidate the NHP experimental objectives of the Consortia for AIDS Vaccine Research (CAVR) in Nonhuman Primates proposal into a single Core composed of highly experienced research personnel.

Excluded by Requester Oregon National Primate Research Center, OHSU
Oral Mucosal Vaccination against HIV Infection (Subcontract)
NIH - R01DE019063
The major goal of this subcontract is to evaluate the innate, adaptive cellular and humoral immune responses to SIV elicited by a DNA prime/replication-incompetent Ad5 vaccine given to rhesus macaques at two oral mucosal sites.

Excluded by Requester Oregon National Primate Research Center, OHSU
Genetically Defined Attenuated Living Vaccine for Francisella
NIH - R41AI072906
The goals of this project are to develop and virulence test attenuated, non-reverting deletion mutants of Francisella tularensis strain SchuS4 as candidate attenuated vaccines and efficacy test them in mouse and rhesus macaque lethal challenge models using prototype virulent SchuS4.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU

Pacific NorthWest Regional Center of Excellence: Developmental Research Project - Role of cytokines in Chikungunya virus-associated disease
NIH/NIAID - U54 AI081680
The goal is an understanding of the contribution of these host-virus interactions to CHIKV-associated disease. CHIKV is a re-emerging arthritogenic mosquito-borne RNA Alphavirus.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU

Intratypic variation of oncogenic HPV types as a risk factor for cervical neoplasia
NIH/NCI - R01 CA133569 (Subcontract)
The goal of this project is the examination of the molecular evolution and population genetics of oncogenic papillomavirus types collected from clinical cervical swabs.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU

Pacific NorthWest Regional Center of Excellence: Career Development Project: Induction and Evasion of the Innate Immune Response by Chikungunya Virus
NIH/NIAID - U54 AI081680
The goal of this project is a characterization of the viral and cellular factors involved in Chikungunya virus-associated stimulation of innate immunity in infected cells and the mechanisms used by the virus to tolerate these responses.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU

Evasion of Innate Immunity by Cytomegalovirus
Private Source
The goal was characterization of the molecular basis of innate immune induction by human cytomegalovirus in an in vitro model.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU

Immune Evasion by Gamma 2 Herpesviruses.
NIH R01CA/AI094011
To understand the molecular mechanisms by which gamma 2 herpesviruses, particularly Kaposi's sarcoma associated herpesviruses (KSHV), interfere with MHC class I antigen presentation and the implication of these mechanisms for viral pathology.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU

Modulation of Innate Immune Responses by Cytomegalovirus.
NIH R01AI070890
The goal of this study is to identify how HCMV activates the interferon-response and how RhCMV inhibits this activation.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU

Competitive supplement to parent grant to study the role of RhCMV lacking innate immune modulators in vivo.
NIH R01AI070890-03S1
The goal of this study was to test the role of the major tegument protein pp65 in a rhesus macaque model of cytomegalovirus infection.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU

Evasion of antigen presentation by Rhesus Cytomegalovirus.
NIH R01AI059457
The goal of this study is to identify and characterize RhCMV genes preventing MHC I antigen presentation and to examine the importance of these genes in vivo using a Rhesus Macaque model.

Excluded by Requester

Vaccine and Gene Therapy Institute, OHSU

Mechanisms of T Cell Escape by Orthopoxviruses.
NIH R21AI077048
The goal of this project is to identify the mechanisms and viral genes that prevent T cell recognition of monkeypoxvirus- and cowpoxvirus-infected antigen presenting cells.

Excluded by Requester

Vaccine and Gene Therapy Institute, OHSU

Development of an Attenuated CMV Vector for an HIV/AIDS Vaccine: CMV Vector Design
Private Source
Collaboration for AIDS Vaccine Discovery (CAVD)
The major goal of this project is to develop an effective and safe HIV/AIDS vaccine based upon spread-impaired (pp71-deleted) CMV vaccine vectors that will fully exploit the vulnerability of early mucosal HIV/SIV infection to effector-memory T cell responses.

Excluded by Requester

Vaccine and Gene Therapy Institute, OHSU

Development of an Effector-Memory T Cell AIDS Vaccine. Project 1: Development and Analysis of Replication-Deficient CMV Vectors
NIH P01AI094417
Development and Analysis of Replication-Deficient CMV Vectors.

Excluded by Requester

Vaccine and Gene Therapy Institute, OHSU

Pacific Northwest Regional Center of Excellence: Project RP008 - Kinase Networks Controlling Flavivirus Replication
NIH U54AI081680
To use a high-throughput chemogenomics approach to identify and characterize kinase networks regulating flavivirus replication and innate immune responses to flaviviruses.

Excluded by Requester

Vaccine and Gene Therapy Institute, OHSU

Development of a Thienopyradine Compound as an Anti-dengue Virus Therapeutic
Private Source

Synthesis of A3 analogs that maintain efficacy against DENV, remain non-cytotoxic, and show improved solubility will be considered the first milestone for completion of this project.

Excluded by Requester

Oregon National Primate Research Center, OHSU

NIH - P01AI087064
Programming HIV Immunity for Broadly Neutralizing Antibodies by Vaccination
The overall goal is to design novel vaccines based on env genes derived from virions (plasma RNA) from HIV-infected subjects who develop broad Nabs in an accelerated fashion (<3 years).

Excluded by Requester

Oregon National Primate Research Center, OHSU

Programming Neutralizing Antibodies for HIV Vaccines
Private Source
The hypothesis we are testing is that the administration of gradually changing envelope genes during infection is "programming" the immune response to focus on conserved regions of the HIV Envelope protein.

Excluded by Requester

Oregon National Primate Research Center, OHSU

Proof of Concept for Card-based CD4 Cell Counting
NIH - SBIR R44MH079695 (subcontract)
This grant is a Phase II application. The role of the Haigwood laboratory will be to provide expertise for flow cytometry and HIV biology to the EI Spectra team to develop a low-cost point of care CD4 counter.

Excluded by Requester Oregon National Primate Research Center, OHSU
Role of Neutralizing Antibodies in Transmission of SHIV
NIH - R01HD038653
This grant examines the role of maternal IgG and neutralizing antibodies (NAbs) in limiting post-partum transmission (or disease) in infants exposed orally to SHIV-SF162P3. .

Excluded by Requester Oregon National Primate Research Center, OHSU
Combination Approach to Broadly Protective AIDS Vaccines (no cost extension)
NIH - P01AI054564
Project 2: Dual Subtype Quasispecies Envelope SHIV Vaccines
The project seeks to develop quasispecies vaccines based on viral variants arising in the course of SHIV or HIV infection.

Excluded by Requester Oregon National Primate Research Center, OHSU
Novel antigen display system to present multiple antigens as HIV vaccines
NIH - R01AI074379
This R01 focuses on the construction and testing of vaccines based on a novel antigen display system from G. stearothermophilus that forms 60-mer particles similar in size to VLPs displaying HIV peptides and proteins at the N-terminus of each subunit.

Excluded by Requester Oregon National Primate Research Center, OHSU
Analyzing the HIV-Specific Neutralizing Antibody Response and Repertoire in Newborn Macaques
Private Source
The goal of this grant is to develop methods to clone macaque monoclonal antibodies from B cells in SHIV-infected macaques and to map the early neutralizing antibody response.

Excluded by Requester Oregon National Primate Research Center, OHSU
NIH/NIAID R21AI096977
Induction of HIV neutralizing antibodies by targeting macaque B cell receptors
The role of the Haigwood laboratory is to develop novel proteins based on the mimotopes, to vaccinate macaques with these plus DNA, and to determine the immunogenicity of these novel immunogens, followed by collection of blood and tissue samples for antibody cloning and characterization.

Excluded by Requester Oregon National Primate Research Center, OHSU
NIH 2R44AI091546
Oral, replicating Ad4-HIV vaccine development & evaluation in NHP challenge model
This Phase II SBIR grant will test the efficacy of Adenovirus-4 based vaccines in rhesus macaques, challenged with SHIV.

Excluded by Requester Oregon National Primate Research Center, OHSU
Antibody Effector Function in Protection Against HIV-1
NIH - 2 R01 AI55332
The purpose of this project is to explore the importance of effector function in antibody-mediated protection against HIV.

Excluded by Requester Oregon National Primate Research Center, OHSU
Role of Fc Receptor polymorphisms in antibody-mediated protection
NIH - 1 R01 AI097315
The objective of this project is to determine whether genetic factors, in particular Fcγ receptor polymorphisms, influence the efficacy of a low-dose broadly neutralizing antibody passive immunization strategy against low-dose mucosal virus challenges.

Excluded by Requester

Vaccine and Gene Therapy Institute, OHSU

Characterization of VZV Infection in Rhesus Macaques and Evaluation of VZV Vaccines

Private Source

The goal of this project is to characterize disease progression and the development of anti-VZV immune response following VZV infection in rhesus macaque.

Excluded by Requester

Vaccine and Gene Therapy Institute, OHSU

The Modulation of Immune Senescence by Menopause and Estrogen Replacement Therapy

Private Source

The goal of this project is to elucidate the impact of menopause on immune senescence and immune response to vaccination in older women.

Excluded by Requester

Vaccine and Gene Therapy Institute, OHSU

Impact of Immune Senescence on Herpes Zoster in a Nonhuman Primate Model

NIH - R01AG037042

The goal of this proposal is to use our nonhuman primate model of VZV to: 1) identify age-related differences in the VZV-specific T cell responses and 2) determine how these differences in immune responses affect the aged ability to control VZV replication and to maintain latency.

Excluded by Requester

Vaccine and Gene Therapy Institute, OHSU

Pacific Northwest Regional Center of Excellence: Project 3 - Yellow Fever Vaccination of the Aged and Immunocompromised

NIH - U54AI081680

The goal of this project is to determine the immunogenicity and efficacy of a novel inactivated vaccine against yellow fever using a nonhuman primate model of viscerotropic yellow fever.

Excluded by Requester

Vaccine and Gene Therapy Institute, OHSU

Genetic and Functional Approach to Prevent VZV-induced Vasculopathy

Private Source

The major goal of this study is to identify highly immunogenic antigens in SVV, a simian homologue of VZV that can be used as a subunit vaccine in a nonhuman primate model of shingles.

Excluded by Requester

Vaccine and Gene Therapy Institute, OHSU

Pacific Northwest Regional Center of Excellence: Project 5 – Mechanisms of Ebola virus pathogenesis and innate and adaptive immunity

NIH - U54AI081680

The goal of this project is to develop and to assess the immunogenicity and efficacy of new vaccination strategies against EBOV.

Excluded by Requester

Vaccine and Gene Therapy Institute, OHSU

Molecular and Biological Characterization of Pandemic Flu

NIH - P01AI058113 (Mount Sinai Subcontract)

The goals of this project are to define the contribution of viral and host genes to the global host response and characterize age-related differences in disease progression and host immune response to pathogenic influenza infection.

Excluded by Requester

Vaccine and Gene Therapy Institute, OHSU

Impact of ovarian steroids loss on immune senescence in female macaques

Private Source

Major goals: the goal of this study is to dissect the impact of age versus that of menopause on T cell function and response to vaccination using rhesus macaques

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU
Postmenopausal Monkey Resource
NIH - R24OD011895.
The goal of this proposal is to establish a postmenopausal monkey resource with aged Ovx rhesus monkeys on a Western diet and treated with placebo, immediate-E or delayed-E replacement.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU
Mechanisms of KSHV-Induced Cellular Transformation
NIH - R01 CA099906
The goal of this project is to understand how KSHV-induction of the proto-oncogene c-Kit contributes to the development of Kaposi's sarcoma, with consideration of c-Kit as a therapeutic target for KS.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU
The role of HIV-1 Vpu in the regulation of CD40
NIH - R01 AI063938
The goal of this project is to understand the mechanism and significance of HIV-1 Vpu induction of the cytokine receptor CD40 on endothelial cells and macrophages.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU
Characterization of Vpu-mediated degradation of BST-2
NIH - R01 AI090490
The goal of this project is to understand how the HIV-1 protein Vpu antagonizes the expression and function of the host virus restriction factor BST-2/tetherin.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU
Pacific Northwest Regional Center of Excellence in Biodefense and Emerging Infectious Diseases
NIH - U54AI081680
The first goal of the PNWRCE is to identify age-related immune system defects to develop new vaccines and supplemental therapies to enhance protection of individuals to NIAID Category A-C pathogens.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU
Molecular Aspects of Cytomegalovirus Latency
NIH - R01AI021640
The long-term goal of this project is to develop an understanding of the cellular and molecular mechanisms involved in HCMV latency and reactivation, and, specifically, to identify the viral genes responsible for these viral phenotypes and to characterize the mechanisms and products encoded by these genes that promote growth in MDM and EC.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU
Training Program in Virology
NIH - T32AI074494
The proposal is for training of graduate students and postdoctoral fellows in virology.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU
The Role of the Cytomegalovirus Secretome in the Acceleration of Transplant Vascular Sclerosis
NIH - R01HL088603
In this project we propose the use of viral genetics to unravel the wound healing and angiogenesis mechanisms involved in CMV acceleration of TVS and CR.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU
33rd International Herpesvirus Workshop
NIH - R13CA102553
The proposal is for travel funds for students and postdoctoral fellows to attend and give presentations at the 33rd International Herpesvirus Workshop.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU
Protective Immunity in Special Populations: Interface between Innate and Adaptive Immunity
NIH - BAA-NIAID-DAIT-HIHAI2010085
This contract is a renewal of ongoing studies of our group with Dr Nikolich-Zugich to characterize defects in the aged immune system.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU
Development of Effector-Memory T Cell AIDS Vaccine. Project 2: Attenuation of CMV Vector Pathogenicity and Transmission by Altering Viral Tropism
NIH - P01AI094417
The goal of this project is to determine whether genetically modifying CMV to limit its ability to replicate in cell types associated with disease and transmission, while retaining its ability to persist in cells important for eliciting immunity, will lead to a safe and effective vector for an HIV/AIDS vaccine.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU
Development of an Attenuated CMV Vector for an HIV/AIDS Vaccine. Objective 2 – Assessment of HCMV Vectors in Humanized Mouse Models
Private Source
The goal of this project is to construct HCMV/HIV vector homologues of the interim and optimized designs in Objective 2 and to determine whether these homologues exhibit analogous replication, tropism characteristics and level of insert expression compared to the *in vivo*-validated RhCMV/SIV version.

Excluded by Requester University of Arizona
Immunological basis of age-related susceptibility to West Nile virus
NIH - BAA 05-11 HHSN266200500027C ADB Contract N01 50027
The goal is to use a succession of rodent, primate and human models to elucidate critical age-related defects in innate and adaptive responses to WNV.

Excluded by Requester University of Arizona
Critical parameters of CD8+ T-cell mediated protection
NIH - 5R01 AI066096-03
The goal is to elucidate the role of different CD8 T-cell in vivo properties, their diversity and their quantitative variation in immune defense against viruses.

Excluded by Requester University of Arizona
Vaccination and Immune Senescence in Primates
NIH - 5 P01 AG023664
The goal is to dissect primary defects in the immune response of old primates to vaccination and to improve outcomes of vaccination in this vulnerable population of primates.

Excluded by Requester University of Arizona
Immune protection in Special Populations
BAA NIHAI20100085 ADB Contract HHSN 272201100017C NIH/NIAID N01-AI-00017
To use a combination of rodent and human models to elucidate critical age-related defects in innate and adaptive responses to WNV.

Excluded by Requester University of Arizona
T Cell Homeostasis and Function in Immune Senescence
NIH - 8R01 AG020719
To understand T cell dysregulation in immune senescence.

Excluded by Requester University of Arizona
Mechanisms of reduced T-cell immunity in older adults
NIH - 1R01 AG35309
To elucidate why older humans exhibit impaired immunity in certain regions of their bodies.

Excluded by Requester University of Arizona
Studies of Immunosenescence and Other Late Effects of Acute Ionizing Radiation Exposure in Atomic Bomb Survivors: Project: Effects of Radiation and Aging on T Cell Homeostasis and Function
BAA-NIAID-DAIT-NIHAI2008023 Radiation Effects Research Foundation
To elucidate whether and how radiation may precipitate or accelerate manifestations of aging in the immune system.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU
DARE: Delaney AIDS Research Enterprise to Find a Cure. Project 3: "Targeting the PD-1 Pathway to Eradicate SIV/HIV"
NIH - U19 AI096109
In this project we will explore the role of negative regulators including PD-1 in maintaining latency in vitro and in vivo.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU
Development and Function of the B Cell Response to SIV/HIV in NHP. Project: Role of NK Cells in Antibody Mediated Protection Following SHIV Challenge (Subcontract)
NIH - U19 AI067854
NIH/Center for HIV/AIDS Vaccine Immunology (CHAVI)
In this study, we propose to elucidate the role of natural killer (NK) cells in HIV vaccine development and, in particular, their function in Ab mediated protection against a mucosal SHIV challenge in RM.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU
Vaccination and Immune Senescence in Primates, Project 4: Immune senescence and CMV immunity in primates
NIH - P01AG023664
Excluded by Requester project within this PPG (#4) examined the effect of aging on the rhesus macaque T cell response to the persistent herpesvirus RhCMV, and conversely the contribution of RhCMV immunity to global immune senescence.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU
Development of an Attenuated CMV Vector for an HIV/AIDS Vaccine
Private Source
The major goal of this project is to develop an effective and safe HIV/AIDS vaccine based upon spread-impaired (pp71-deleted) CMV vaccine vectors that will fully exploit the vulnerability of early mucosal HIV/SIV infection to effector-memory T cell responses.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU
Development of an Effector-Memory T Cell AIDS Vaccine
NIH - P01AI094417
In this Program, we will modify CMV vectors and/or use complementary heterologous vaccines with CMV vectors to both increase the potency of CMV/SIV vectors so as to achieve rates of protection closer to 100% of vaccines, and reduce the pathogenicity and shedding potential of CMV vectors (while retaining immunogenicity), so as to achieve an effective vaccine that is safe enough for use in a general human population.

Excluded by Requester

Vaccine and Gene Therapy Institute, OHSU

Development and In Vivo Characterization of Safety-Enhanced RhCMV/SIV Vectors
NIH - R01AI095113
The primary objective of this grant is to use the RM model to design and test CMV vectors with genetically engineered restrictions in replication/spread (single or low cycle; only exploring designs that are equally applicable to rhesus and human CMV), so as to develop a CMV vector with a safety profile compatible with clinical translation and that retains, to the greatest extent possible, the immunogenicity and protective capacity of WT vectors.

Excluded by Requester

Vaccine and Gene Therapy Institute, OHSU

Efficacy of Oral CMV/SIV Vectors
NIH - R01DE021291
In this project, we will compare in detail the phenotypic, migratory, functional and gene expression properties and protective capacity of SIV-specific CD8+ T cells elicited by RhCMV/SIV vectors given via a subcutaneous vs. oral route.

Excluded by Requester

Vaccine and Gene Therapy Institute, OHSU

Role of Memory T Cell Dynamics in SIV Infection
NIH - R37AI054292
The major goal of this project is to study the relationship between memory T cell turnover, immunity and disease progression in the SIV rhesus macaque model of AIDS.

Excluded by Requester

Vaccine and Gene Therapy Institute, OHSU

Rejuvenation of the T-cell Compartment in Aging Primates
NIH – R01AI082529
The major goal of this project is to assess the ability of immuno-therapeutics such as IL-7 and KGF to rejuvenate the naïve T cell compartment of immuno-senescent rhesus macaques.

Excluded by Requester

Vaccine and Gene Therapy Institute, OHSU

Consortium for AIDS Vaccine Research in Nonhuman Primates: CMV Vectors and Early Control of Mucosal SIV Challenge
NIH – U19AI095985
The primary goal of this project is to understand the biologic basis for the efficacy of RhCMV/SIV vector-elicited T cell responses (in comparison to T cell responses elicited by other vaccine modalities – adenovirus vectors, pox virus vectors and live attenuated SIV – in Projects 1 and 3) by direct visualization and characterization (at necropsy) of the intercept of these responses with SIV in early infection after both intra-rectal challenge and intra-vaginal challenge.

Excluded by Requester

Vaccine and Gene Therapy Institute, OHSU

Immune Correlates of Protection against HIV and SIV Infection
Private Source
The goal of this project is to identify and understand the specific characteristics of immune responses that protect against pathogenic SIV infection in rhesus macaques and HIV-1 in humans.

Excluded by Requester

Vaccine and Gene Therapy Institute, OHSU

Development of RhCMV Vectors for SIV Infection
NIH - R01AI060392
The major goal of this project was to develop and assess RhCMV as a vaccine vector for SIV infection, and to investigate the hypothesis that a persistent vector engenders superior anti-SIV immunity than current strategies using disabled or acute vectors.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU

IAVI HIV T Cell Vaccine Research & Development Program

Private Source

Excluded by Requester role in this large multi-center project is to compare the ability of SIV vaccine approaches using different viral vectors to provide immunologic protection against pathogenic SIV challenge in rhesus macaques and to provide flow cytometry expertise to the overall program.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU

Harnessing Innate Immunity to Enhance the Immunogenicity of T Cell-Inducing HIV Vaccines

Private Source

Excluded by Requester ole in this project is to test the ability of selected adjuvants (primarily toll-like receptor agonists) vectors, alone or in combination, to activate the innate immune system and generate cellular immune responses in the rhesus macaque.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU

CMV Vector Design & Development

Private Source

The major goal of this project was to compare the efficacy of CMV/SIV vectors, CMV/SIV vectors + Ad5/SIV vectors and DNA/SIV vectors + Ad5/SIV vectors against intra-rectal challenge with highly pathogenic SIVmac239, to determine correlates of immune protection, and to explore the effect of strategic gene deletion on CMV vector immunogenicity.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU

DARE: Delaney AIDS Research Enterprise to Find a Cure, Project 2: Investigating the Impact of Homeostatic Proliferation on HIV Persistence

NIH - U19AI096109

The long-term objective of this project is to define *in vivo* the immunologic factors that are altered by HIV infection and that contribute to T cell homeostasis.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU

Challenge of rCMV(TB)-Vaccinated Rhesus Macaques with Virulent Mycobacterium Tuberculosis

Private Source

The major goal of this project is to determine an appropriate challenge dose for young, male Indian-origin Rhesus Macaques.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU

Endogenous Retrovirus-Specific Antibodies to Block AIDS Virus Infection

Private Source

The primary goal of this Phase II project is to determine whether ERV-specific antibodies can mediate protection from acquisition of the AIDS virus.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU

An Endogenous Retrovirus-based Vaccine for HIV

Private Source

This project seeks to determine the contribution of endogenous retrovirus specific CD8+ T cells to control of SIV infection.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU

Novel Melanoma Antigen Targets for Cellular Immunotherapy

Private Source

This project aims to identify endogenous retroviruses activated in malignant melanocytes and thus represent potential targets for cellular immunotherapy in melanoma patients.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU
A Novel APOBEC-based Vaccine Approach for HIV
NIH – R21/R33AI93179
This project aims to determine if Vif-induced degradation of APOBEC can be harnessed as a target for the immune response against HIV.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU
Identifying endogenous retrovirus T cell targets in SIV-infected macaques
NIH - R21AI087474
This project aims to identify endogenous retrovirus-derived CD8+ and CD4+ T cell epitopes utilizing a cohort of MHC-defined rhesus macaques.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU
Endogenous Retroelement Vaccines
Private Source
This project seeks to determine the safety and immunogenicity of vaccines encoding retroelements present in germline DNA.

Excluded by Requester Vaccine and Gene Therapy Institute, OHSU
Characterizing AIDS virus-protective CMV-induced T cell responses in an MHC simplified model
Private Source
The goal of this proposal is to begin characterizing these unique CMV-induced, SIV-specific CD8+ T cells by defining their restricting Major Histocompatibility Complex (MHC) molecules in an MHC simplified nonhuman primate model, the Mauritian cynomolgus macaque.

Excluded by Requester Vaccine and Gene Therapy Institute, Florida
Novel Concepts for the Eradication of HIV
Private Source
The major project of this goal is to identify mechanisms that lead to HIV latency and also to develop immune based strategies aimed at the eradication of HIV.

Excluded by Requester Vaccine and Gene Therapy Institute, Florida
PD-1 Function, Signaling, and Regulation
NIH - P01 AI080192
The major objective of this proposal is to define the molecular mechanisms that are downstream of PD-1 /PDL-1 interaction and that lead to T cell dysfunction and exhaustion;

Excluded by Requester Vaccine and Gene Therapy Institute, Florida
Role of PD-1/PDL-1 in chronic immune activation induced dysfunction in HIV Infection
NIH - AI076174
This project will aim at investigating the mechanisms that lead to disruption of T cell homeostasis in subjects undergoing hyperimmune activation in HIV infection and to define the role of PD-1 and PDL-1/PDL-2 in the perturbations of T cell homeostasis.

Excluded by Requester Vaccine and Gene Therapy Institute, Florida
Enhancing Vaccine Induced T&B Cell Memory through DC Targeting
NIH - 2U19A1057234
The major objective of this proposal is to define how the manipulation of DCs through targeting of specific receptors on DC will enhance self-renewal and differentiation of memory T cells specific for Influenza Ags in the context of Flu vaccine trials.

Excluded by Requester

Vaccine and Gene Therapy Institute, Florida

Comprehensive T-Cell Vaccine Immune Monitoring Consortium

Private Source

The major objective of this proposal is to develop system biology approaches involving transcriptomics and single cell assays the HIV specific response in T cells from the blood and mucosal tissues.

Excluded by Requester

Vaccine and Gene Therapy Institute, Florida

Follow-Up Correlate Analysis RV144 and Related Studies

Fred M Hutchinson Cancer Research Center 5 U02 AI068618

The major objective of this proposal is to define, using systems biology approaches at the population and single cell levels the transcriptional profiles of Ag specific T cells in response to the RV144 HIV vaccine that has showed partial protection from infection (30% of vaccinated subjects).

Excluded by Requester

Vaccine and Gene Therapy Institute, Florida

Consortia for AIDS Vaccine Research in Nonhuman Primates

NIH - RFA-AI-10-004

The major objective of this proposal is to perform a systems biology analysis of several well-developed vaccine modalities and provide a comprehensive analysis of early immune events following SIV/SHIV challenge of macaques in the presence or absence of vaccine-induced responses

Excluded by Requester

Vaccine and Gene Therapy Institute, Florida

Investigating the impact of homeostatic proliferation on HIV, persistence

NIH - RFA-AI-10-009

The major objective of this proposal is to define the role of cytokines such as IL-7 and IL-15 both known to play a major role in the homeostatic proliferation of memory T cells on the persistence of the HIV reservoir; the Sekaly lab will be involved in quantifying the HIV reservoir and in defining the impact of addition of IL-7 and IL-15 in ex vivo models and in vivo models on the persistence of HIV

Excluded by Requester

Vaccine and Gene Therapy Institute, Florida

The role of negative regulators of T cell activation in the maintenance of the HIV reservoir

NIH - RFA-AI-10-009 U19

The major objective of this proposal is to define the role of cell surface molecules such as PD-1, CTLA-4 and other molecules known to impact on T cell activation on HIV persistence and the maintenance of the HIV reservoir in latently infected cells.

Excluded by Requester

Vaccine and Gene Therapy Institute, Florida

Dissecting Immunological Interplay between Poverty Related Diseases and Helminth Infections: an African-

Private Source

We will conduct a systems biology approach to evaluate whole blood gene expression signatures as a novel means of assessing transcriptional signatures associated with HIV immunity in the context of other microbe:host intercepts (e.g. helminthes, malaria).

Excluded by Requester

Vaccine and Gene Therapy Institute, Florida

CURE project

Private Source

The goal of this project is to i) characterize novel HIV latency activator compounds ii) Identify novel drugable targets leading to HIV reactivation iii) Identify biomarkers predictive of HIV eradication.

Excluded by Requester

Vaccine and Gene Therapy Institute, Florida

DARE: Delaney AIDS Research Enterprise to Find a Cure

NIH - U19AI096109

The long-term objective of this project is to define in vivo the immunologic factors that are altered by HIV infection and that contribute to T cell homeostasis.

Excluded by Requester — Oregon National Primate Research Center, OHSU
Rapid Diagnosis of Monkeypox and Smallpox Infections
NIH - 5R43AI063675
The goal of this research is to develop sensitive and specific serological tests for rapid diagnosis of virulent orthopoxvirus infections including monkeypox and smallpox.

Excluded by Requester — Oregon National Primate Research Center, OHSU
The Alternative NFkB Pathway in Survival and Function of Anti-viral T Cells
NIH - R21 AI077032
The goal of this research is to determine the role of NFkB pathways (traditional and alternative pathways) in survival and function of CD4 and CD8 T cell memory.

Excluded by Requester — Oregon National Primate Research Center, OHSU
Development of a Yellow Fever Vaccine for Vulnerable Populations
NIH - R43AI079898
The goal of this Phase I proposal is to demonstrate feasibility in the development of a new yellow fever virus vaccine by optimizing vaccine formulation and demonstrating immunogenicity in mice.

Excluded by Requester — Oregon National Primate Research Center, OHSU
Development of a Safe and Effective Vaccine against West Nile Virus
NIH - UO1AI082196
The goal of this proposal is to optimize a WNV vaccine and produce clinical-grade vaccine under cGMP conditions for later Phase I clinical trials.

Excluded by Requester — Oregon National Primate Research Center, OHSU
Vaccine-induced CD8+ T Cell Memory
NIH - R56AI076506
The goal of this proposal is to measure T cell responses following immunization with a non-replicating inactivated vaccine.

Excluded by Requester — Oregon National Primate Research Center, OHSU
Cytokine-mediated T Cell Activation
NIH - 5 RO1 AI 054458-05
The goal of this research is to determine how virus-specific T cells respond to signals from innate cytokines such as IL-12 and IL-18 and to determine what cytokines or other effector functions are upregulated by this type of non-antigen-specific stimulation.

Excluded by Requester — Oregon National Primate Research Center, OHSU
Vaccinia and Atopic Dermatitis Network
NIH - N01 AI 40029/HHSN266200400029C
The goal of this research is to determine the underlying mechanisms that result in a higher incidence of adverse events in vaccinia-infected subjects with current or previous history of atopic dermatitis (eczema).

Excluded by Requester — Vaccine and Gene Therapy Institute, OHSU
Pacific Northwest Regional Center of Excellence: Yellow Fever Project
NIH - U54AI081680
The first goal of this proposal is to develop and characterize a yellow fever virus challenge model in non-human primates and to test the efficacy of a H2O2-based yellow fever vaccine.

Excluded by Requester

Oregon National Primate Research Center

Development of an H2O2-Inactivated Dengue Virus Vaccine

NIH - R01AI098723

In this proposal, we provide preliminary data demonstrating the antigenicity, immunogenicity, and protective efficacy of a proprietary new H_2O_2-based vaccine platform that can be used to develop a safe and effective tetravalent dengue virus vaccine.

Excluded by Requester

Vaccine and Gene Therapy Institute, OHSU

Mechanisms of CMV Latency in Accelerated Vascular Disease

NIH - R01 HL83194

The goal of this project is to determine the viral latency mechanisms involved in rat cytomegalovirus (RCMV)-accelerated transplant vascular sclerosis (TVS), which is the hallmark vascular disease associated with chronic rejection of solid organ grafts.

Excluded by Requester

Vaccine and Gene Therapy Institute, OHSU

Chemokine Receptors in Vascular Disease

NIH - R01 HL65754

The long-term goal of this project is to determine the role of viral pathogens in the development of vascular diseases such as atherosclerosis, restenosis, and transplant vascular sclerosis (TVS).

Excluded by Requester

Vaccine and Gene Therapy Institute, OHSU

NIH - R01 HL085451

Cytomegalovirus Chemokine Receptors in Transplant Vascular Sclerosis

The long-term goal of this project is to determine the role of viral pathogens in the development of vascular diseases such as atherosclerosis, restenosis, and transplant vascular sclerosis (TVS).

Excluded by Requester

Vaccine and Gene Therapy Institute, OHSU

Pacific Northwest Regional Center of Excellence - New Opportunity:Determination of Age-related Defects in Chikungunya Virus Infections

NIH - U54 AI081680

The goal of this project is to develop a non-human primate model of chikungunya virus infection and determine the effects of aging on immunity towards the virus.

Excluded by Requester

Vaccine and Gene Therapy Institute, OHSU

NIH/NIAID Pacific Northwest Regional Center of Excellence: Developmental Research Project - Identification of Age-Related Defects to CHIKV Infections in a NHP Model

NIH - U54 AI081680

This project seeks to uncover the immunological and virological basis underlying increased Chikungunya virus (CHIKV) disease severity in the elderly.

Excluded by Requester

Vaccine and Gene Therapy Institute, OHSU

Rhesus HHV-8 Homologue in AIDS-related Malignancies

NIH - R01CA075922

The major goals of this study are to identify viral determinants that contribute with the development of RRV-associated disease in the SIV-infected rhesus macaque.

Excluded by Requester

Vaccine and Gene Therapy Institute, OHSU

Anti-viral IL-6 Approach to Mitigate KSHV-related Diseases

NIH - R01CA132638

The major goals of this study are to evaluate whether vaccination with a novel vIL-6/Fc fusion protein is capable of inducing host responses that can mitigate RRV-associated disease.

Excluded by Requester

Vaccine and Gene Therapy Institute, OHSU

Biodefense Proteomics Research Programs: Identifying Targets for Therapeutic Interventions using Proteomic Technology

NIH - AID325645-A-N4; from NIH Contract DMID-BAA-03-3

The major goals of this study are to utilize proteomic techniques to identify novel monkeypox virus targets.

RESOURCES

Follow the 398 application instructions in Part I, 4.7 Resources.

Division of Pathobiology & Immunology:

Laboratory:

The Division is housed in three locations on the OHSU west campus: the Facility Security Building is a 34,040 gross square feet facility consisting of three floors. The total laboratory space is 16,025 sq ft, which includes four 1200 sq ft labs, four 900 sq ft labs and each of these labs additionally contains a 200 sq ft BSL-2 lab. There are two 1,250 sq ft BSL-3 suites, which include four 800 sq ft tissue culture labs. There are six common equipment rooms in addition to a dark room, four cold-rooms, and two radioactive hot labs. In the basement there is a secured Gammacell 40 Irradiator. The basement level of the Facility Security also has small laboratory animal housing of approximately Facility Security including an ABSL-3 level containment facility suitable for rodent studies. There are shower-in/shower-out facilities as well as pass-through autoclaves. Facility Security houses twelve laboratories and four cores. There is one BSL-3 suite on each floor. The first floor of the Facility Security is comprised of the laboratories of Excluded by Requester The second floor of the VGTI/ONPRC contains the laboratories of Excluded by Requester The third floor of the Facility Security building contains the laboratories of Excluded by Requester The ONPRC Facility Security contains Excluded by Requester boratory, and the ONPRC Research Annex 2 contains Excluded by Requester

The Core Scientists' laboratory space in the Facility Security houses fume hoods plus additional dedicated BSL-2 tissue culture labs of 200 sq ft with class II A/B3 biosafety cabinets. Though laboratory equipment is often specific to the research within the individual scientist's lab, the total equipment available to the Facility Security esearch team follows: 1 Thermo Finnagan Mass Spectrometer, 1 Molecular Dynamics Typhoon 8600 Phosphorimager, 1 MDS Nordion Gammacell-40 Irradiator, 3 ABI Taqman , 2 BD FACSCaliburs, 3 BD LSRII's, 1 Zeiss Axioskop 2 Plus Imaging Microscope with Axiocam, 1 Zeiss Axiovert 200 Inverted Imaging Microscope with Axiocam, 3 Zeiss Inverted Fluorescent Microscopes, 3 Beckman Ultracentrifuges, 2 Beckman High Speed Centrifuges, 4 large New Brunswick Environmental Shakers, 44 (3 not installed) Baker Biosafety Cabinets, 54 Thermo Forma CO2 Incubators, 2 Bellco Roller Bottle Apparatuses and Incubators, 2 large Heraeus Biological Incubators, 15 Thermo Forma Ultralow Freezers, 5 Thermo Forma Liquid Nitrogen Storage Units, 19 Centrifuges (Beckman, Sorval, Eppendorf and Jouan), 4 PCR Clean Work Stations, 2 Spectrophotometers (Beckman and Pharmacia), 2 Thermo Cryomed Controlled Rate Freezers, 1 Leica Cryostat, 3 Speed Vac Concentrators (Thermo Savant and Labconco), 3 Thermo Savant Gel Dryers, 2 Fisher Scientific Plate Washers, 1 Molecular Devices Plate Reader, 31 Thermocyclers (MJ Research, Perkin Elmer and BioRad), 1 Thermo Shadon Cytospin, 9 Olympus Inverted Microscopes, 7 Olympus Upright Microscopes, 3 Dissecting Microscopes, 22 Eppendorf Microcentrifuges, Balances, Hybridization Ovens, -20(C Freezers, 4(C Refrigerators, Water Baths, Power Supplies, Gel Apparatuses and more. Dr. Picker's lab includes an additional FACSCalibur and a third LSR II analyzer. This equipment as well as other equipment at the VGTI/ONPRC is protected with an Uninterrupted Power System in case of a power outage.

The Facility Security contains 2 BSL-3 suites comprising 4 BSL-3 tissue culture laboratories of 800 sq ft each. Entrance to these BLS-3 labs is contingent upon successful in-house training. These labs contain class II A/B3 biosafety cabinets, pass-through autoclaves, CO2 incubators, centrifuges and light, inverted and fluorescent microscopes. The first floor suite houses the FACSVantage cell sorter, a cryostat and a Coulter counter. The second floor suite contains an ultracentrifuge.

The Facility Security houses Excluded by Requester lab and office. It includes 1,000 sq ft of Biosafety Level 2 (BSL-2) laboratory space that contains a tissue culture room with 2 class II A/B3 biosafety cabinets, laboratory bench space, and a LSR II analyzer.

The Facility Security Building houses Excluded by Requester lab and office. It includes 1,642 sq ft of Biosafety Level 2 (BSL-2) laboratory space that contains 2 tissue culture rooms, laboratory bench space, a cell counter,

dark room, cold room and support space. Adjacent to the BSL-2 laboratory is a 462 sq ft Biosafety Level 3 (BSL-3) laboratory, equipped with shower-in/shower-out facilities, biosafety cabinets and pass-through autoclave. A laboratory appropriately equipped to provide clinical diagnostic virology is also available in the Research Annex.

Clinical:
N/A

Animal:
The ONPRC and OHSU Laboratory Animal Care and Use programs are fully accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC) and supervised by veterinarians who are certified as Diplomates of the American College of Laboratory Animal Medicine (ACLAM). Animal care is provided by a sufficient number of trained veterinarians and technicians. Nonhuman primate housing facilities include eight group-housing units of approximately Specific Animal Locati and outdoor breeding corrals of approximately Specific Animal Specific pathogen-free rhesus macaque breeding colonies supporting infectious disease research are housed in a Specific Animal harem breeding facility and ten shelter group housing units comprising Specific Animal The Center has an Specific BSL-3 containment animal housing facility supporting AIDS and other infectious disease research. This facility has a capacity of 240 Class III macaques housed in 15 rooms of 16 animals each. Support facilities include dedicated necropsy and clinical treatment/surgical rooms and decontamination (autoclave) for caging.

Computer:
Equipment consists of 30 G4 Macintosh computers, 28 IBM-compatible PC's, 4 color printers, 2 copy machines and 2 facsimile machines. The computers are fully loaded with Adobe Workshop, Photoshop, Powerpoint, Excel, FileMakerPro and network capabilities.

Office:
Each Core Scientist has individual offices available to them. Office space is allotted at 2,650 sq ft. A conference room/library consisting of 535 sq ft is equipped with videoconferencing capabilities for viewing seminars presented at locations other than the West Campus. The conference room is also available for meetings and presentations.

NARRATIVE: Excluded by Requester

Division Appointment: Associate Scientist, Pathobiology and Immunology
Appointment(s): % Effort,Excluded by Requester at ONPRC
Percent effort directed towards NHP studies: % Effort

Current Research: Excluded by Requester research is focused on improving nonhuman primates (NHP) for use as models for human infectious diseases, developing new NHP models for human infectious diseases, and NHP virology. His laboratory is developing an expanded specific pathogen free rhesus macaque breeding resource to support development of polyoma, gamma herpesvirus and beta herpesvirus infection models in the rhesus macaque The overall goal is to enhance the rhesus macaque as a model for investigating viral pathobiology and immunobiology, and vaccine development relevant to human HIV infection and AIDS-related opportunistic infections. Current research projects include 1) vaccine and immunologic interventions that will attenuate the early events of mucosal simian immunodeficiency virus (SIV) infection, 2) T cell dynamics in SIV infection, and delineation of viral mechanisms of pathogenesis that target them, 3) development of rhesus cytomegalovirus-vectored vaccines for SIV and other diseases, 4) identification of sites of SIV persistence/latency in the optimally-treated host and therapeutic strategies to clear these reservoirs of infection, 5) vaccine strategies for NIAID category A-C pathogens, and 6) gamma-2 herpesvirus-associated AIDS-related malignancies and multiple sclerosis-like demyelinating encephalomyelitis.

Contribution to Mission: Excluded by Requester heads the Center's Nonhuman Primate Infectious Disease Resource (IDR). His IDR team provides professional and technical expertise for managing and conducting infectious disease studies using NHPs to achieve to the highest level possible the goals of the studies in an environment that is safety for both personnel and study animals. The IDR provides comprehensive management and specialized technical services necessary for conducting complex NHP infectious disease protocols using large cohorts of animals for multi-investigator program projects investigating several hypotheses in parallel, hosts and conducts NHP infectious disease studies for off-site collaborating investigators, assists new investigators in their transition from research focused on small animals or humans to NHPs, develops NHP infectious disease models to support new research projects, and provides access to state-of-the-art immunological assays and analysis and anatomic pathology required for infectious disease studies using NHP models.

Division and Center activities: Excluded by Requester is an active participant on the OHSU West Campus. He serves on the OHSU Institutional Biosafety Committee, the VGTI-ONPRC Leadership Committee, and several ONPRC committees. These include Animal Utilization Committee, Virology Core and Flow Cytometry oversight committees, and the ABSL-3 oversight committee.

Collaborative Interactions:
ONPRC: Excluded by Requester
Excluded by Requester

Outside:
1. Excluded by Requester (OHSU)
2. Excluded by Requester (Providence Portland Medical Center)
3. Excluded by Requester (Univ Arizona)
4. Excluded by Requester (Univ Arizona)
5. Excluded by Requester Private Source
6. Excluded by Re UC,Davis)
7. Excluded by Requ (NEPRC)
8. Excluded by Private Source
9. Excluded by (
10. Excluded by Requ (UCSF)
11. Excluded by Nationwide Children's Hospital, The Ohio State Univ)
12. Excluded by (UCLA)
13. Excluded by Requester (University of California, Riverside)

NARRATIVE: Excluded by Requester

Division Appointment: Senior Scientist, Pathobiology and Immunology
Appointment(s): % Effort,Excluded by Requester at VGTI and a joint appointment to ONPRC
Percent effort directed towards NHP studies: % Effort

Description of independent research program: Excluded by Requester research is focused on host/pathogen interaction with a particular focus on the identification and characterization of viral gene products that modulate the innate and adaptive immune response. Among other accomplishments, he demonstrated the functional conservation of HCMV immune evasion mechanism in rhesus CMV and, in collaboration with Excluded by Requester Excluded laboratory, he then demonstrated that escape from CD8+ T cells enables CMV to overcome pre-existing immunity and establish secondary persistent infections. Together with the induction of high levels of effector memory T cells, the ability to super-infect is a key feature of CMV as a new vaccine vector platform. His current research is focused on increasing the immunogenicity as well as safety of CMV vectors in collaboration with Excluded by Requester In addition, he directs research in the immune evasion mechanisms of Simian Varicella virus, Kaposi's sarcoma-associated herpesvirus, rhesus cytomegalovirus, monkeypox virus and cowpox virus. He also studies the host/pathogen interaction of Dengue and West Nile virus using small molecule and small interfering RNA screens as well as interactome experiments.

Contribution to Mission: Excluded by Requester has served as the Director of the Shared Microarray Core on the West Campus, ONPRC Promotion committee, and ONPRC Seminar committee. His scholarly contributions are several and include Section Editor of PLoS Pathogens, Editorial Board of the Journal of Virology, and he is currently the Editor of the Journal of Virology.

Collaborative interactions:
ONPRC: Excluded by Requester

Outside:
1. Excluded by Requester (Univ Arizona, Tucson, AZ) - West Nile virus infection in aged animals
2. Excluded by Requester Private Source - West Nile Virus and Dengue virus induction of innate immune responses
3. Excluded by Requester (Univ Washington, Seattle, WA) - transcriptome analysis of Dengue virus-infected cells
4. Private Source,Excluded by Requester - single cycle cytomegalovirus vectors
5. Excluded by Requester (Univ Maryland, Baltimore, MD) - cytomegalovirus vectored prostate cancer vaccines
6. Private Source,Excluded by Requester - development of a synthetic cytomegalovirus vector
7. Excluded by Requester (Univ Florida, Gainesville, FL) - immune evasion of monkeypox virus
8. Private Source,Excluded by Requester - immune evasion of monkeypox virus
9. Excluded by Requester (Univ San Francisco) - interactomics of Dengue virus
10. Private Source,Excluded by Requester immune evasion of mousepox virus
11. Excluded by Requester PhD (Univ Colorado – Denver, CO) - immune evasion of simian varicella virus
12. Private Source,Excluded by Requester - T cell inhibition by monkeypoxvirus
13. Private Source,Excluded by Requester - small molecule screening for Dengue virus inhibitors
14. Excluded by Requester (Pacific Northwest National Laboratory, Richland, WA) - proteomics of rhesus cytomegalovirus infection
15. Private Source,Excluded by Requester - in vivo model for dengue virus
16. Excluded by Requester (Medical College Wisconsin, Milwaukee) - NK cell evasion of rhesus cytomegalovirus
17. Excluded by Requester (Naval Medical Research Center, Silver Spring, MD) - cytomegalovirus-vectored malaria vaccine
18. Excluded by Requester (Univ Washington, Seattle, WA) - single cycle rhesus cytomegalovirus
19. Excluded by Requester (University of California, Riverside, CA)

NARRATIVE: Excluded by Requester

Division Appointment: Senior Scientist, Division of Pathobiology & Immunology
Appointment(s): % Effort Excluded by Requester at the ONPRC and a joint appointments in the Department of Molecular Microbiology & Immunology, OHSU, and Vaccine & Gene Therapy Institute, OHSU.
Effort on NHP-related studies: % Effort

Research Overview: Excluded by 's principal research focus is the role of antibodies in limiting infection and pathogenesis in HIV infection. Her group has developed models for SHIV pathogenesis in newborn pigtail and rhesus macaques and uses passive transfer of polyclonal IgG and human monoclonal antibodies to determine their effects on disease in vivo. Excluded by group regularly produces multiple gram lots of endotoxin-free preparations of polyclonal IgG from HIV infected human subjects for collaborating groups. Excluded by Requester is an expert in glycoprotein expression, with a focus on HIV-1 and SIV Envelope proteins produced in mammalian cells. Previous work in the development and purification of HIV Envelope proteins for the clinic led to writing the IND and to clinical testing of HIV gp120 vaccines. These gp120 proteins have been shown recently to be partially effective in reducing viral acquisition in a Phase III trial when used in combination with attenuated poxvirus vectors. The lab currently has four funded projects and Pending Support to develop novel vaccines for HIV that are effective in eliciting neutralizing or other protective antibodies in vivo in rabbits and macaques.

Contribution to Mission: Excluded by Requester is the Director of the Center and is responsible for: 1) overall leadership through managing the senior leadership of the Center and oversight of the activities of the Associate Directors and Division Heads; 2) management and renewal of the P51 grant as a whole, including liason with the external Scientific Advisory Board; 3) setting the scientific priorities and leading the strategic planning activities of the center via formal workshops and scientific retreats; 4) oversight of the standing committees of the ONPRC, including Research Advisory, Animal Utilization, and Policy Group; 5) interactions with the host institution OHSU via the office of the Vice President for Research; 6) liason with the OHSU Foundation with Associate Director Charles Roberts; 7) liason with the Vaccine & Gene Therapy Institute.

Key collaborations include:

Name	Affiliation	Description
Excluded by Requester	Private Source	NIAID-funded P01 to develop novel HIV vaccines that are based on natural HIV Envelope sequences derived from human subjects who developed broadly neutralizing antibodies with 3 years of infection. Excluded by is the PI of the P01 and leads a Project and two Cores. Vaccines are tested in rabbits and macaques.
		NIAID-funded R01 to develop novel vaccines for HIV using scaffold proteins to display conserved epitopes, involving testing in rabbits and mice.
	ONPRC Private Source	Pending Support
		SBIR Phase II grant from NIAID to study the role of oral, replicating Ad4-HIV vaccines in macaque challenge studies performed at ONPRC.
	ONPRC ONPRC	
	NIAID, NIH NIAID, NIH	Purification of polyclonal IgG from HIV-positive subjects to test for the ability to protect macaques from infection.
	VRC, NIH VRC, NIH VRC, NIH ONPRC	Analysis of human monoclonal antibodies derived from elite neutralizer subjects for their ability to protect newborn macaques from infection.
	Private Source	NIAID-funded R21 to determine if peptide mimetopes can induce HIV neutralizing antibodies by targeting macaque B cell receptors.
		Role of B cells in HIV and SHIV pathogenesis and the cloning of macaque B cells and monoclonal antibodies, follow-up to an NIAID-funded grant.

NARRATIVE: Excluded by Requester

Division Appointment: Core and Associate Scientist, Pathobiology and Immunology
Appointment(s): % Effort Excluded by Requester at VGTI and a joint appointment to ONPRC
Percent effort directed towards NHP studies: % Effort

Current Research: The overall goal of Excluded by Requester laboratory is to understand how viruses cause infectious disease and cancer, with the aim of identifying novel anti-viral or anti-tumor therapies. Her laboratory devotes most of their current effort towards human immunodeficiency virus type 1 (HIV), the infectious cause of AIDS, and Kaposi's sarcoma herpesvirus (KSHV), the etiologic agent of Kaposi's sarcoma (KS) and rare B cell tumors. Immunocompromised rhesus macaques develop disease symptoms that resemble those seen in KSHV-infected humans following inoculation with rhesus macaque rhadinovirus (RRV), a closely related herpesvirus. Excluded by Requester is currently using the RRV-macaque model to test a potential KS therapeutic that targets heme-oxygenase-1 (HO-1), an enzyme that is implicated in both KSHV replication and tumorigenesis. Excluded by Requester HIV research focuses on viral antagonism of the host innate immune response. Her current studies address viral antagonism of BST-2, a host protein that inhibits infectious virus release but is effectively neutralized by the HIV protein Vpu. While SIV does not express Vpu, it encodes other strategies to overcome BST-2. Excluded by Requester laboratory is currently exploring ways to transition their expertise with BST-2 into the SIV-macaque model of AIDS. Most recently, Excluded by Requester has begun research with the newly characterized Japanese macaque rhadinovirus (JMRV) that is associated with a spontaneous MS-like disease in genetically susceptible JM. Using her expertise with brain endothelial cells (BEC) and the blood brain barrier (BBB) she has begun to examine the interaction of JMRV with JM-derived BEC *in vitro*, and the effects of JMRV on BBB function. She also plans to examine JM plasma for circulating biomarkers of BBB dysfunction. Overall, Excluded by Requester research is evolving to effectively use non-human primate models of human disease to understand viral pathogenic mechanisms and validate novel diseases targets.

Contribution to Mission: Excluded by Requester laboratory performs basic and translational research to elucidate virus/host interactions that contribute to disease and to identify and test novel therapeutic targets. This work involves the use of research cores and fosters collaborations with other core scientists to promote multi-disciplinary research. To foster inter-institutional collaborations, Excluded by Requester presents research data at national and international meetings and provides reagents and protocols to colleagues upon request.

Division and Center activities: Excluded by Requester is the Chair of the OHSU Institutional Biosafety Committee and previously served a full term as a member of the West Campus Institutional Animal Care and Use Committee. She is also a member of the ONPRC Library Committee and serves on several graduate student committees to promote student education and training.

Collaborative Interactions:

ONPRC:
1. Excluded by Requester ovel therapeutics for KSHV/RRV; JMRV-BBB interaction and disease consequence.
2. gamma-herpesvirus pathogenesis and immune evasion.
3. erpesviral microRNA targetomes.
4. herpesviruses and pathogenic angiogenesis.

Outside:
1. Excluded by Requester (OHSU): endothelial cell physiology and acute disease responses.
2. Excluded by Requester (OHSU): detection of endothelial microvesicles in plasma.
3. Excluded by Requester (OHSU): leukocyte-endothelial interaction models.
4. Excluded by Requester Private Source KSHV epidemiology and therapeutics.
5. Excluded by Requester (Univ. Pittsburgh Medical Center, Pittsburgh, PA): histopathology of KS.
6. Excluded by Requester (Univ. Florida, Gainesville, FL): recombinant herpesvirus technology.

NARRATIVE: Excluded by Requester

Division Appointment: Senior Scientist, Division of Pathobiology and Immunology
Appointment(s): % Effort,Excluded by Requester t VGTI and a joint appointment to ONPRC
Percent effort directed towards NHP studies: % Effort

Current Research: Excluded by Requester expertise in human cytomegalovirus (HCMV) biology spans more than twenty-seven years and his laboratory continues to study HCMV to understand how CMV manifests disease. Research findings from his laboratory have led to a better understanding of HCMV tropism and persistence, identifying both the viral and host factors that contribute. Currently, his lab is focused on elucidating the role of the viral microRNAs that are expressed during infection and how these microRNAs impact viral persistence and the infected cells' response to infection. His laboratory is also developing small animal models to translate the in vitro findings of his HCMV research into an in vivo model to elucidate the biological implications.

Contribution to Mission: Excluded by Requester past and current research efforts on HCMV are instrumental in the development of tropism-modified RhCMV vectors to serve as effective AIDS vaccines for evaluation in the well-characterized simian immunodeficiency virus (SIV)-infected rhesus macaque (RM) model. Specifically, one component of his research is to create RhCMV vectors which define deletion of viral genes associated with epithelial cell tropism to minimize shedding of recombinant virus, but do not reduce the vector's ability to engender an immune response in the vaccinated host. Another component of this research program is to generate tropism-deficient RhCMV/SIV vectors with specific and stringent growth restriction in neuronal and myeloid cells, respectively.

Division Activities: Excluded by Requester is the Director of the Vaccine and Gene Therapy Institute (VGTI) whose research facilities are co-incident with the Division of Pathobiology and Immunology. Additionally, he is co-Director of the Pacific Northwest Regional Center of Excellence (PNWRCE) for Biodefense and Emerging Infectious Diseases Research. The PNWRCE brings together a consortium of investigators with extensive expertise and basic and translational research capacity directed at a broad range of the National Institutes of Health's National Institute of Allergy and Infectious Diseases (NIAID) Category A–C Priority Pathogens. Several of these investigators are Core and Affiliate Scientists in the Division. The research activities are aimed at providing a deeper understanding of pathogen-host interactions; how these interactions impact innate and adaptive immune responses; and the age-related defects in immunity that lead to immunosenescence and an increased vulnerability to infectious disease. The information generated from these activities will facilitate the development of next-generation therapeutics, diagnostics, and vaccines against Category A–C Pathogens. His leadership is instrumental as he mentors junior faculty in their research efforts related to viral pathogenesis and animal model design. Excluded by also provides oversight and input regarding design of rhesus CMV vector construction for SIV vaccine studies.

Collaborative Interactions:

ONPRC: Excluded by Requester

Outside:

1. Excluded by Requester (OHSU) - HCMV
2. Excluded by Requester (Univ Arizona, Tucson, AZ) - PNWRCE and host pathogens
3. Excluded by Requester Univ Washington, Seattle, WA) - PNWRCE, research in emerging infectious diseases
4. Private Source,Excluded by Requester - PNWRCE, research in emerging infectious
5. Private Source,Excluded by Requester - DENV markers
6. Excluded by Requester (University of California, Riverside)

NARRATIVE: Excluded by Requester

Division Appointment: Division Head (through 9/12) and Senior Scientist, Pathobiology and Immunology
Appointment(s): % Effort,Excluded by Requester t VGTI and a joint appointment to ONPRC
Percent effort directed towards NHP studies: % Effort

Research Overview: The primary focus of Excluded by Requester laboratory is the development of therapeutic approaches to prevent, treat, and potentially cure HIV/AIDS using the SIV/SHIV rhesus macaque (RM) model. This effort includes research aimed at detailed understanding of the immunopathogenesis of AIDS in untreated progressive SIV infection, the effect of anti-retroviral treatment on these infections, including immune regeneration and the biology of the residual (latent or active) SIV reservoir in optimally treated RM, immune vulnerabilities of SIV, early acute infection (relevant to a prophylactic vaccine) and in established, treated infection (relative to a therapeutic vaccine), and the necessary stimuli need to generate immune responses that exploit these immune vulnerabilities. Key contributions include 1) definition of the intimate relationship between SIV and CD4+ memory T cell differentiation and homeostasis, in particular, showing that the host mechanisms, rather than only the virus itself, play a key role in the development of immune deficiency, and 2) delineation of the vulnerability of early high pathogenic SIV infection to effector memory T cells elicited by SIV protein expression Cytomegalovirus (CMV) vectors. Recently, this later work has revealed that immune responses elicited by CMV/SIV vectors appear to functionally cure unequivocal infection with the highly pathogenic SIVmac239, and Excluded by has established a large research and development program to develop safe and effective CMV vectors for clinical translation. At the time of this writing (10/2012), this work is funded by an R37 grant, 3 RO1 grants, 1 P01 grant, 2 U19 project grants from NIH and a grant from the Private Source Private Source

Contribution to Mission: From 2000 to September 2012, Excluded by Requester was the head of the Division of Pathobiology and Immunology, responsible for the scientific direction and coordination of NHP resources for all infectious disease and immunology research at the center. This included participation in executive management of the center, service on the animal utilization committee and the research advisory committee, as well as oversight of core scientist recruitment to the division (two core scientists, Excluded by Requester Excluded by were recruited during the last reporting period). In addition, during the last reporting period, Excluded by managed both the Pathobiology and Immunology Division's Collaborative Research Unit (coordinating and performing NHP infectious disease research for outside investigators) and SIV-infected RM resource, as well as chaired the ABSL3 oversight committee, and served as a member on the oversight committees for the Virology and Flow Cytometry Cores at the center. In September 2012, Excluded by Requester stepped down as Division Head to focus on his large research and vaccine development program, but continues to serve ONPRC in the other managerial and committee roles described above.

Collaborative Interactions:

ONPRC: Excluded by Requester

Outside *(all HIV pathogenesis and vaccine development)*:

1. Excluded by Requester (NCI-Frederick, Frederick, MD)
2. Private Source,Excluded by Requester
3. Excluded by Requester (UC Davis, Davis, CA)
4. Excluded by Requester (NEPRC, Southborough, MA)
5. Private Source,Excluded by Requester
6. Private Source,Excluded by Requester
7. Excluded by Requester (VRC, NIH)
8. Excluded by Requester (Univ Minnesota, Minneapolic, MN)
9. Private Source,Excluded by Requester
10. Private Source,Excluded by Requester
11. Excluded by Requester (Univ Arizona, Tucson, AZ)
12. Private Source,Excluded by Requester

NARRATIVE: Excluded by Requester

Division Appointment: Assistant Scientist, Pathobiology and Immunology
Appointment(s): % Effort,Excluded by Requester at VGTI and a joint appointment to ONPRC
Percent effort directed towards NHP studies: % Effort

Current Research: The Excluded by Req laboratory aims to determine which antigens should be targeted to overcome the formidable obstacle of pathogen sequence diversity. Viral sequence diversity is the Achilles' heel of traditional vaccine approaches and poses one of the greatest hurdles to vaccine development. Thus, the Sacha laboratory is actively exploring four distinct, but related areas of immunity to highly variable pathogens such as HIV: the role of virus-specific CD4+ T cells, non-pathogen targets for vaccination, spontaneous elite control of SIV, and the role of macrophages as pathogen reservoirs.

Contribution to Mission: Excluded by Requester serves on the West Campus Institutional Animal Care and Use Committee, which reviews and approves all study protocols involving animals for biomedical research. This is vital to ensuring that the research performed at the ONPRC and VGTI conforms to the high standards set by the Office of Laboratory Animal Welfare. Excluded by also serves on the ONPRC Information Technology (IT) Advisory Committee, which advises the IT director on how IT services and resources should be deployed to maximally support the ONPRC.

Collaborative Interactions:

ONPRC: Excluded by Requester

Outside:
1. Excluded by Requester (Univ California, San Francisco) – Alternate antigens for HIV vaccine development
2. Excluded by Requester Univ Hawaii, Manoa) - Markers of T cell exhaustion
3. Private Source,Excluded by Requester - Liposomal drug delivery to immune system cells
4. Excluded by Requester Univ Wisconsin, Madison) - Deep sequencing of viral quasispecies

NARRATIVE: Excluded by Requester

Division Appointment: Senior Scientist, Pathobiology and Immunology
Appointment(s): % Effort,Excluded by Requester at ONPRC
Percent effort directed towards NHP studies: % Effort

Current Research: Excluded by Requester is investigating the underlying mechanisms of humoral and cell-mediated immunity against acute viral infections. This work has included developing several models of acute viral infection and/or vaccination in order to address basic immunological questions related to the development and maintenance of long-term protective immunity. He has also developed a series of clinical studies in which he studies immunological memory directly in human subjects. During the course of this work, he studies a number of viruses including arenaviruses (lymphocytic choriomeningitis virus, LCMV), flaviviruses (West Nile virus, yellow fever, and dengue), and orthopoxviruses (vaccinia, cowpox, and monkeypox). The combination of basic research in animal models and applied research in clinical studies involving both healthy and immunocompromised populations has provided the opportunity to better define the requirements for immunological memory and to learn how to develop more effective diagnostics and vaccine candidates. These experiments lay the foundation for future studies in which Excluded by Requester and team members will develop new antiviral vaccines and determine the mechanisms involved with building strong vaccine-induced immunity. For instance, these scientists have recently discovered a new hydrogen peroxide-based approach to vaccine production that results in a safer, more effective vaccine preparation that can be used to create better human and animal vaccines.

Contribution to Mission: Excluded by Requester laboratory performs state-of-the art research on vaccine development and studies antiviral immunity and pathology. In addition to performing basic and applied research, Excluded by Requester also presents research data at several national and international meetings each year and this functions to foster inter-institutional collaborations as well as engage the broader scientific community. Excluded by Requester teaches and directs an advanced immunology course at OHSU and participates with the ONPRC Outreach Coordinator by providing lectures to local schools and/or service on discussion panels.

Division and Center activities: Excluded by Requester serves on several committees at the ONPRC and OHSU. These include Radiation Safety Committee (Chair), Virology Core oversight committee, Aging Resource oversight committee, Immunology oversight committee, ONPRC Library oversight committee, OHSU Institutional Animal Care & Use Committee and West Campus IACUC (alternate), and West Campus ABSL-3 oversight committee.

Collaborative Interactions:

ONPRC: Excluded by Requester collaborations on monkeypox and cowpox immune evasion

Outside:

1. Private Source,Excluded by Requester development of vaccines against West Nile virus, yellow fever, and dengue
2. Excluded by Requester (OHSU, MMI department): role of pre-formed CD40L in antiviral immunity
3. Excluded by Requester (OHSU, MMI department): analysis of immunity against herpes simplex virus
4. Excluded by Requester (OHSU, Dermatology department): eczema vaccinatum, Phase I clinical trial on yellow fever, immunity following smallpox vaccination
5. Excluded by Requester MD (OHSU, Surgery department): immune responses in adipose tissue
6. Private Source,Excluded by Requester orthopoxvirus epitope detection following smallpox vaccination
7. Private Source,Excluded by Requester clinical studies involving eczema herpeticum
8. Private Source,Excluded by Requester analysis of DNA vaccination to prevent monkeypox infection
9. Excluded by Requester (University of California, Riverside) pathogenesis and vaccine development for yellow fever and dengue

NARRATIVE: Excluded by Requester

Division Appointment: Senior Scientist, Pathobiology and Immunology
Appointment(s): % Effort,Excluded by Requester at VGTI and a joint appointment to ONPRC
Percent effort directed towards NHP studies: % Effort

Current Research: The overall goal of Excluded by Requester laboratory is to understand how viruses cause disease, using viral infection of nonhuman primates (NHP) as models for analogous human disease. His laboratory focuses on understanding how simian herpesviruses, rhesus macaque rhadinovirus (RRV) and Japanese macaque rhadinovirus (JMRV), and an orthopoxvirus, monkeypox virus, cause disease in macaques. Utilizing molecular, genetic and virological techniques, his group examines how these viruses infect and replicate in cell culture, and how they cause illnesses in animals. He has shown that inoculation of immunocompromised monkeys with RRV results in disease symptoms that closely resemble those observed in humans infected with the human immunodeficiency virus (HIV) and Kaposi's sarcoma-associated herpesvirus (KSHV). More recently, he and his collaborators are investigating how JMRV is associated with the development of Japanese macaque encephalomyelitis, a spontaneous disease that closely resembles multiple sclerosis. Utilizing this two-pronged approach, his laboratory is identifying the viral determinants that contribute to disease. The information that is generated from this research will be essential in the development of new vaccine strategies for preventing virus infection and disease.

Contribution to Mission: Excluded by Requester laboratory performs research to identify host/pathogen interactions that lead to disease. In addition to performing basic and applied research, Excluded by Requester also presents research data at several national and international meetings each year and this functions to foster inter-institutional collaborations as well as engage the broader scientific community. Excluded by also provides reagents to others that his laboratory has generated to ensure the animal model(s) that he is developing are made available.

Division and Center activities: Excluded by Requester is an active participant on the OHSU West Campus. Previously, he served as Chair of the OHSU Institutional Biosafety Committee and more recently was Chair of the West Campus Institutional Animal Care and Use Committee, before stepping down to serve as the Interim Division Head for Pathobiology and Immunology. In addition to these Center activities, he serves on several committees at the ONPRC. These include the Virology Core oversight committee, Imaging Resource oversight committee and the West Campus ABSL-3 oversight committee.

Collaborative Interactions:

ONPRC:
1. Excluded by Requester investigate how monkeypox virus causes disease
2. Excluded by Requester underlying cause(s) of JME
3. Excluded by Requester inhibition of gamma-herpesvirus infection with novel compounds

Outside:
1. Excluded by Requester (OHSU): underlying cause(s) of JME
2. Private Source,Excluded by Requester role of RRV miRNAs in viral-associated disease
3. Excluded by Requester (Univ Virginia, Charlottesville, VA): structure of RRV virions
4. Excluded by Requester Pacific Northwest National Laboratories, Richland, WA): biomarker discovery in JME
5. Excluded by Requester Georgia State Univ., Atlanta, GA): simian hemorrhagic fever virus pathogenesis
6. Excluded by Requester Univ Arizona, Tucson, AZ): Neisseria colonization in rhesus macaques
7. Excluded by Requester Univ Arizona, Tucson, AZ): monkeypox virus pathogenesis
8. Excluded by Requester Univ California, Riverside): host response to RRV infection

Program Director/Principal Investigator (Last, First, Middle): Robertson, Joseph E./Haigwood, Nancy L.

DIVISION OF PATHOBIOLOGY & IMMUNOLOGY DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Excluded by Requester	Interim Div Chief/Sr. Sci	% Effort			Institutional Base Salary	8,985	2,246	11,231
	Assoc Scientist					13,478	3,369	16,847
	Admin Coord					2,207	773	2,980
	Admin Coord					8,278	2,897	11,175
	Sr. Scientist					8,985	2,246	11,231
	Sr. Scientist					8,985	2,246	11,231
	Assoc Scientist					6,404	1,601	8,005
	Sr. Scientist					8,985	2,246	11,231
	Sr. Scientist					8,985	2,246	11,231
	Asst Scientist					5,732	1,433	7,165
	Sr. Scientist					12,659	3,165	15,824
	Admin Asst					2,077	831	2,908
To Be Named	Asst Scientist	0.60				5,159	1,290	6,448
To Be Named	Div Chief/Sr Scientist	1.80				26,955	6,739	33,694
	SUBTOTALS →					127,874	33,328	161,202
CONSULTANT COSTS								
None Requested							0	0
EQUIPMENT *(Itemize)*								
None Requested								0
SUPPLIES *(Itemize by category)*								
Office & Admin Supplies							398	
								398
TRAVEL								
Domestic							0	0
INPATIENT CARE COSTS								
OUTPATIENT CARE COSTS								0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*								
None Requested								0
OTHER EXPENSES *(Itemize by category)*								
Maintenance - Equipment							398	
Biohazard Waste Disposal							398	
								795
CONSORTIUM/CONTRACTUAL COSTS						DIRECT COSTS		0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*								$ 162,395
CONSORTIUM/CONTRACTUAL COSTS						FACILITIES AND ADMINISTRATIVE COSTS		0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD								$ 162,395

DIVISION OF PATHOBIOLOGY & IMMUNOLOGY
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	161,202	166,038	171,019	176,150	181,434
CONSULTANT COSTS	0	0	0	0	0
EQUIPMENT	0	0	0	0	0
SUPPLIES	398	409	422	434	447
TRAVEL	0	0	0	0	0
INPATIENTS CARE COSTS	0	0	0	0	0
OUTPATIENTS CARE COSTS	0	0	0	0	0
ALTERATIONS AND RENOVATIONS	0	0	0	0	0
OTHER EXPENSES	795	819	843	869	895
DIRECT CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	162,395	167,266	172,284	177,453	182,777
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	162,395	167,266	172,284	177,453	182,777
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					862,175

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

PERSONNEL

Interim Division Chief, Senior Scientist – Excluded by Requester % Effort Program Income)..As Division Chief, Excluded by Requester is responsible for all Divisional administrative activities and provides the overall scientific direction of the Division; oversees the submission of grant proposals, recruitment and personnel matters, represents the Division at the level of ONPRC Administration including as a member of the Executive Leadership Committee, the Policy Committee, the Research Advisory Committee and the Animal Utilization Committee; encourages scientific interactions between Division members and researchers at other institutions, encourages faculty participation in the Graduate Programs at OHSU. Excluded by Requester will continue his internationally-renown research program in AIDS-associated malignancies and viral-mediated inflammatory demyelination. He has served as Interim Division Chief since September 2012 and prior to this, served three years as Chair of the OHSU West Campus Institutional Animal Care and Use Committee.

Associate Scientist – Excluded by Requester % Effort Income). Excluded by Requester will continue his nationally recognized research program in viral pathogenesis utilizing NHP models, where he has led the ONPRC Nonhuman Primate Infectious Disease Unit for the last three years.

Administrative Coordinator – Excluded by Requester % Effort,Excluded by Requester Excluded supports the Division of Pathobiology and Immunology by providing administrative support associated with manuscript preparation.

Administrative Coordinator – Excluded by Requester % Effort,Excluded by Requester Excluded supports the Division of Pathobiology and Immunology and assists the Division Chief in all ONPRC-related activities.

Senior Scientist – % Effort,Excluded by Requester will continue his internationally-renown research program on viral mechanisms of immune evasion on both RNA and DNA viruses, and further his research on vaccine development utilizing rhesus cytomegalovirus as vaccine vector.

Senior Scientist – % Effort,Excluded by Requester will continue her internationally-renown research program on the creation and characterization on neutralizing antibodies against SIV, as a model for HIV vaccine development. She has served as Director of the ONPRC since 2007.

Associate Scientist – % Effort,Excluded by Requester Excluded will continue her nationally recognized research program in AIDS-associated malignancies and HIV molecular virology. In addition to her research, Excluded by Requester serves as the Chair of the OHSU Institutional Biosafety Committee, a position she has held for the last four years.

Senior Scientist – % Effort,Excluded by Requester will continue his internationally-renown research program on cytomegalovirus persistence and pathogenicity, which has led to new insights to the role of viral microRNAs in viral persistence. He will also continue with his work developing a dengue virus research program.

Senior Scientist – % Effort,Excluded by Requester will continue his internationally-renown research program on developing a HIV vaccine to prevent AIDS, utilizing the SIV/rhesus macaque model. He served as Chief of the Division from 2000 - 2012.

Assistant Scientist – % Effort,Excluded by Requester will continue to develop his research program on NHP immunology in the context of SIV infection and how the virus is capable of circumventing the host response. Additionally, he will continue to develop new in vivo techniques to elucidate the role of monocytes/macrophages in virus infections.

Senior Scientist – % Effort Excluded by Requester will continue his nationally recognized research program on viral immunology and vaccine development. His studies have led to a new vaccine production platform that can be evaluated in the NHP.

Administrative Assistant – % Effort Excluded by Requester Excluded supports the Division of Pathobiology and Immunology by providing administrative support associated with manuscript preparation, and purchasing supplies for office and research.

Assistant Scientist – To Be Named (3 calendar months effort: 6 ORIP, 2.4 Program Income). A junior scientist will be recruited to the Division to fill the vacancy created when Excluded by Requester left the ONPRC. This recruitment will be a national search to fill an ORIP-supported core grant position.

Division Chief, Senior Scientist – To be named (3.6 calendar months effort: 1.8 ORIP, 1.8 Program Income). A senior scientist with an established and recognized excellence in NHP immunology or model development will be recruited as new Division Head to complement the existing research team. This individual will have administrative skills commensurate with the position.

SUPPLIES

Office & Admin Supplies: Funding is requested for standard office supplies (paper, pens, folders etc.) for the offices of the PIs, and administrative coordinators and assistant.

OTHER EXPENSES

Equipment Maint & Repair: Funds are requested to cover maintenance and repair of division laboratory equipment that cannot be practically attributed to specific grants.

Biohazard Waste Disposal: Funds are requested to pay for disposal of biological and chemical waste generated by the division laboratories that cannot be practically attributed to specific grants. Charges are per the standard OHSU Radiation Safety schedule.

Division of Pathobiology & Immunology Income Table

Last Funded Year (53)

Source	Funding (direct costs)
P51 base grant support	$156,933.34
Program income derived from P51 base grant	316,241.16
Other Sources	0
Total	$473,174.50

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$168,010.23
Program income derived from P51 base grant	523,432.39
Other Sources	100,000.00
Total	$791,442.62

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

The Division of Pathobiology & Immunology receives salary support and support for other expenditures from program income. Other sources represents recruitment funding from the VP for Research.

TITLE: DIVISION OF DIABETES, OBESITY, & METABOLISM

CORE-SUPPORTED PERSONNEL:

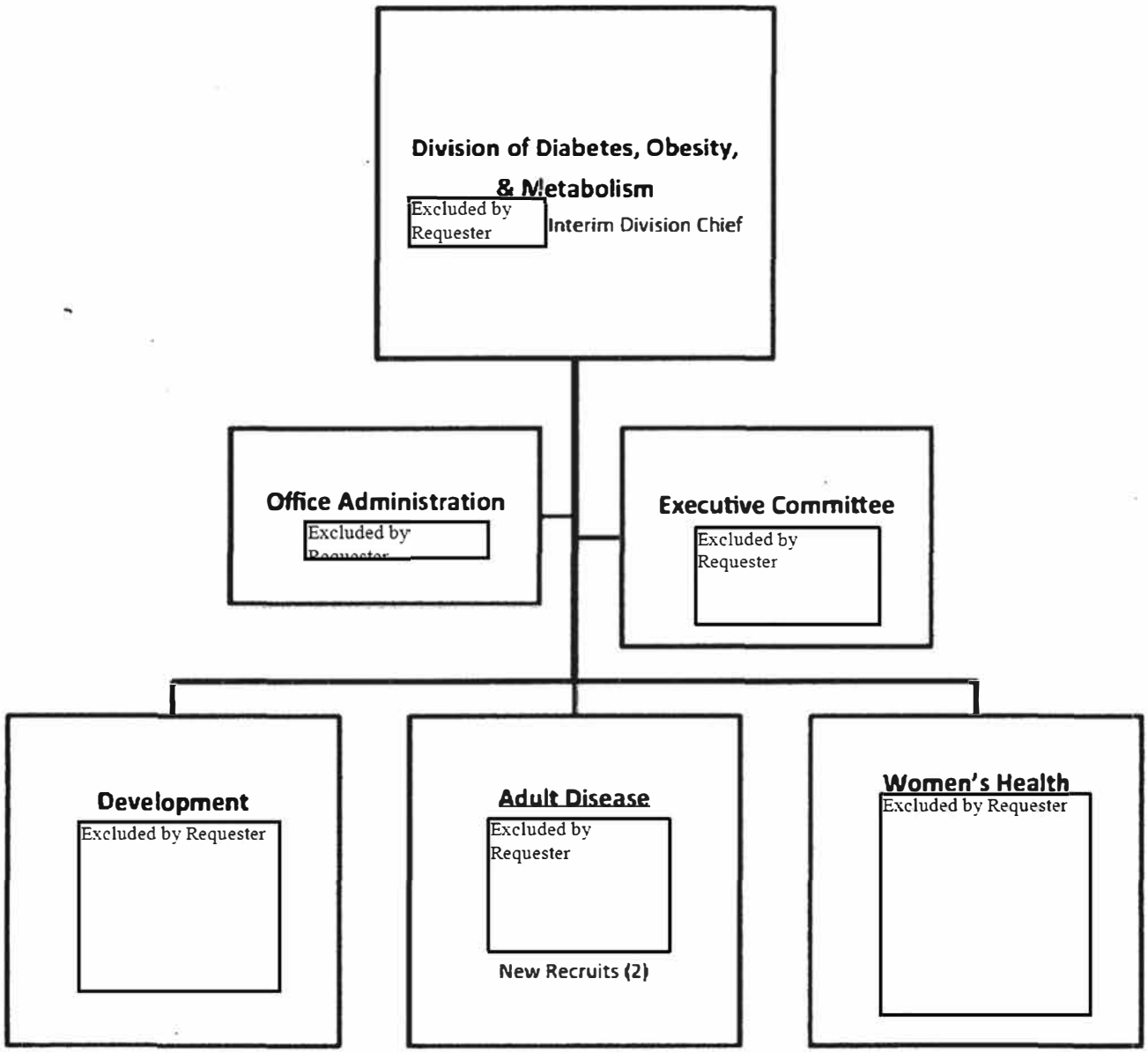
Core Scientists (See Biographical Sketches, listed alphabetically in the Overview of the ONPRC)

Excluded by Requester	Interim Division Chief, Senior Scientist
	Assistant Scientist
	Senior Scientist
	Senior Scientist
	Assistant Scientist
TBN	Senior Scientist
TBN	Assistant Scientist

Administrative Support

Excluded by Requester	Administrative Coordinator
TBN	Administrative Coordinator

Division of Diabetes, Obesity, & Metabolism
Organizational Chart



DIVISION OF DIABETES, OBESITY, & METABOLISM PERSONNEL AFFILIATION AND ROLE

Core Scientists:

Excluded by Requester	Interim Division Chief, Senior Scientist
	Senior Scientist
	Senior Scientist
	Assistant Scientist
	Assistant Scientist

[1] Joint appointment with the Division of Neuroscience, ONPRC
[2] Joint appointment with the Division of Reproductive & Developmental Sciences, ONPRC
[3] Joint appointment with the Department of Obstetrics and Gynecology, OHSU
[4] Primary appointment with the University of Portland

Affiliate Scientists:

Excluded by Requester	Private Source
	University of Texas Southwestern
	Private Source
	University of Colorado Denver
	Molecular & Medical Genetics, OHSU
	University of Massachusetts
	Private Source
	& Pharmacology, OHSU
	Cardiology, OHSU
	Pediatrics, OHSU
	University of Colorado, Denver
	Private Source
	Physiology & Pharmacology, OHSU
	University of Cincinnati

Visiting Scientists:

Excluded by Requester	Instructor, University of Colorado Denver

Staff Scientists:

Excluded by Requester	Staff Scientist II
	Staff Scientist II
	Staff Scientist II
	Staff Scientist I

DIVISION OF DIABETES, OBESITY & METABOLISM

DESCRIPTION:

The Division of Diabetes, Obesity, & Metabolism was established in 2012 to focus research efforts on what has been cumulatively referred to as metabolic diseases, which includes diabetes, obesity and cardiovascular diseases. Together these diseases afflict more than 2/3rd of the population in the U.S. and are the number one cause of preventable death. Financially, these diseases are responsible for more than 30% of health care costs. The scientific goal of this division is to understand the underlying causes and pathophysiology of obesity, diabetes, and associated metabolic diseases, as well as pursuing effective and safe interventions and therapeutics. Investigators in this division also have a special emphasis on women's health and on the developmental programming of metabolic diseases. This includes expertise in the central nervous system that controls appetite and energy expenditure, pancreas function, and adipose tissue function. Our investigators utilize a broad array of research tools including noninvasive imaging, complex whole animal studies on physiology and behavior, and *in vitro* and *ex vivo* techniques. The nonhuman primate model of diet induced obesity has proven to be a critical in the understanding of the complex mechanism underlying the disease process, and, in many cases provides the only preclinical animal species that truly models the pathophysiology of these diseases in humans. Thus the NHP models has provided an important competitive advantage for our investigators in obtaining funding from both the NIH and through industry sponsored collaborations. Even though we are a small division at this time (two full time core scientist, and three part-time core scientist) we have $4.7 million (direct costs) of funding during 2011/12, with 60% coming from NIH and the rest from Industry collaborations. Furthermore, our external collaborators have almost $2.5 million in support during that time directly related to research using our Obese NHP Resource. Our scientists have strong connection with both academic and clinical departments at OHSU supporting the dedication to true translational science. Our scientists also actively participate in the training and mentoring of scientists at all levels and are involved in several postdoctoral and clinical training grants. The goals of our new Division for the 2012-2019 are to: 1) to develop a cohesive and integrated Division focused on the integrated investigation of metabolic diseases, 2) to recruit both new and established investigators to our Division to compliment our existing faculty to provide a more integrated investigation of metabolic diseases, and 3) to develop a supportive and constructive training environment for our next generation of scientists.

RELEVANCE:

Approximately 1/3rd of Americans are classified clinically as obese, with twice that number being overweight and at a high risk of associated complications such as diabetes and cardiovascular disease. While there has been intense focus on understanding the pathogenesis and treatment of these metabolic diseases over the last decade, progress has been limited by appropriate preclinical models that represent the full human disease complications. Our new Division brings together internationally renowned scientist with access to critical nonhuman primate models and state-of-the-art research tools to address this worldwide health epidemic.

DIVISION OF DIABETES, OBESITY & METABOLISM SPECIFIC AIMS

It is well publicized that obesity, diabetes and cardiovascular diseases (commonly referred to as metabolic diseases) have become the principal preventable cause of death in the United States. While there are many contributing factors to these diseases, it is recognized that sedentary life styles and the overconsumption of calorically dense and highly palatable foods are primary contributors of this world-wide health epidemic. More importantly, and more costly in regards to the long-term health of Americans, quality of life and for the economical impact on the health care system, is the devastating increase in childhood metabolic diseases. Over the past decade ONPRC has fostered the development of a small but internationally recognized and well-funded group of investigators focused on various aspects of metabolic diseases, including both adult and early onset obesity, diabetes and cardiovascular diseases. This group has developed several powerful nonhuman primate (NHP) models that uniquely mimic the complexities of the development and pathogenesis of metabolic diseases in humans. Using these models, and the unique tools available at ONPRC, this group has established strong and productive collaborations with renowned investigators at OHSU, throughout the United States and Internationally. In recognition of this evolving strength at ONPRC, the previous core grant renewal established a focused working group to continue to develop this area of expertise. The establishment of this working group was enthusiastically supported in the previous critique of the P51 grant and by the ONPRC Scientific Advisory Board. Over the past five years, ONPRC has invested in the establishment and expansion of the Obese NHP Resource, which supports the development and maintenance of these powerful animal models and research tools, and has made them available to the national research community. Because of the continued success of this research program and the recognized importance to improving human health, ONPRC has now formally established a new research division dedicated to the investigation of metabolic diseases, the Division of Diabetes, Obesity and Metabolism. Leading the development of this new division will be senior scientists 1) Excluded by - Interim Division Head (formerly of the Division of Neuroscience); 2) Dr. Excluded by Requester – ONPRC Associate Director for Research; 3) and Excluded by Requester (Formerly Director of ONPRC and member of the Division of Neuroscience) along with a talented group of young and affiliated scientists. Our scientists have set some fundamental goals for the coming five years that will be key for the continued development and long-term success of this division.

Specific Aim 1: To develop a fully integrated and collaborative Division focused on the understanding of the biology and pathophysiology of metabolic diseases, with a collective group of scientists focused on the diverse aspects of this health epidemic as a foundation. There will be a strong focus on increasing our understanding of the molecular and pathophysiological complications that develop during the progression of these diseases, as well as the investigation of therapeutics and interventions to prevent or reverse complications associated with these diseases.

Specific Aim 2: To recruit new investigators to provide new expertise and technical approaches to allow a more diverse and integrated approach to the investigation of these complex diseases. These diverse approaches and areas of expertise will allow a more efficient use of these valuable research models, as well as providing a rich intellectual environment. Currently the Division consists of 3 senior core scientists, two junior core scientists and 4 staff scientists. The goal over the next five years would be to expand the Division with the recruitment of two additional assistant core scientists in areas that compliment our current faculty, but expand into areas where we lack expertise, like adipose biology, cardiology or immunology.

Specific Aim 3: To develop a supportive and constructive environment for training the next generation of scientists in the use of complex and highly translatable NHP models of metabolic diseases. The NHP model has been identified nationally as a critical translational research tool. This is especially important in the areas of metabolic diseases since the NHP model so closely mimics the human disease. However, only a small number of national investigators that regularly use this valuable model. Thus, it is key to provide a rich training environment and resources to expand this research community.

DIVISION OF DIABETES, OBESITY & METABOLISM RESEARCH STRATEGY

SIGNIFICANCE

Obesity, diabetes, and cardiovascular diseases (commonly referred to as "metabolic diseases") have emerged over the past two decades as a worldwide health epidemic, and collectively are considered the primary cause of preventable death [1]. Being obese or overweight impacts 2/3 of Americans. More disturbing is the dramatic increase in metabolic disease among children and infants [2]. Being obese predisposes children to a lifetime of health problems and medical costs [3, 4]. It is clear that availability of highly palatable and calorically dense foods, as well as decreased activity, and early life programming events are major contributors to this epidemic. Besides the impact on human health and quality of life, these diseases also have a serious impact on our economy. Being obese raises a person's average annual medical costs by $2741. The total direct health care costs of obesity are estimated at $260 billion per year [5]. The total annual costs of diabetes and obesity together in the U.S. exceeds $500 billion, 30% of all medical costs. This is without addition in the costs of the 3rd major metabolic disease (cardiovascular disease). In addition to these consequences of metabolic diseases, a new area is emerging, a link between diabetes and cognitive decline, including Alzheimer's and other neurodegenerative diseases. Because of the broad health implications, the impact on the quality of life, and the financial costs, it is imperative that we gain a better understanding of the pathogenesis, treatment, and prevention of metabolic diseases.

OHSU has made several strategic moves over the past 10 years to expanded their expertise in the clinical treatment of metabolic diseases through: 1) the establishment of the Harold Schnitzer Diabetes Health Center; 2) recruitment of internationally recognized bariatric surgeons; 3) expansion of clinical cardiovascular research; and 4) the establishment of the Moore Institute for Nutrition and Wellness, which has a focus on metabolic diseases in children. In parallel, ONPRC has also emphasized and supported diabetes and obesity research; most recently through the establishment a Metabolic Disease Working Group (MDWG), which primarily consisted of faculty from the Div. of Neuroscience. To support this program, ONPRC established the Obese NHP Resource, which has developed and validated key NHP models. In the past 5 years, investigators in this group established research collaborations with investigators in all ONPRC divisions, several OHSU departments, and with outside universities. In recognition of this success, ONPRC established the Division of Diabetes, Obesity, & Metabolism in August of 2012, to be initially led by Excluded by [redacted]. Finally, in August 2012, there was an amazing $125 million donation to establish a Cardiovascular Research Institute. This donation will allow an expansion of clinical care and research; as well as imaging and animal resources, and faculty recruitment at the ONPRC.

Nonhuman Primates are an important research model for metabolic diseases:

Basic research using rodent models has identified key mechanisms leading to the pathogenesis and complications of metabolic diseases; however, there are key differences in the physiology and pathology of these diseases between rodents and humans. This has been highlighted by a series of failures of drugs during clinical development: drugs that were successful in rodent models. There are distinct differences between rodents and humans in: 1) the ontogeny of the development of metabolic systems; 2) the cytoarchitecture of the pancreas, liver, gastrointestinal tract, and brain; 3) the regulation of energy expenditure; and 4) the progression of complications of metabolic diseases. Investigators in our new Division have a history of taking advantage of the strengths of both the rodent and NHP models to make significant contributions to our understanding of the pathogenesis of these metabolic diseases, as well as working towards the development of therapeutics and interventions. *Below is a summary of selected research highlights by Division investigators.*

Developmental Programming of Metabolic Systems:

As a whole, OHSU is exceptionally strong and internationally renown[redacted] Excluded by Requester [redacted]d on the developmental origins of adult diseases. As members of this group, [redacted]ave used rodent models to investigate the impact of nutrition on the development and reprogramming of metabolic systems. To understand how this may translate into human health, these investigators developed a NHP model using female Japanese macaques chronically consuming a Western style diet (WSD, high in fats and calories and highly palatable). Using this model, and with expanded collaborations with Excluded by Requester [redacted] Excluded by Requester [redacted] (Heart Research Center, OHSU), and Excluded by Requester [redacted] these investigators have made critical observations in regards to the relative contribution of poor maternal diet and metabolic health on pregnancy complications and on the development of metabolic systems in offspring. A fundamentally important

observation from these studies has been that many of the health complications in the offspring are independent of maternal obesity/diabetes, and are primarily due to the chronic consumption of the WSD. Importantly, a primary underlying mechanism appears to be placenta dysfunction and inflammation, which results in an inflammatory response and lipotoxicity in the developing fetus [6-9]. An important advancement of our studies in recent years has been the utilization of innovative techniques, through collaborations with Private Source,Excluded by Requester and Exclude Univ. of Utah), to evaluate the epigenetic modifications of gene systems [10-12]. Importantly, these studies have demonstrated that epigenetic modifications in long-lived species are different than what is common in short-lived species.

The metabolic outcomes of developmental programming that we have reported in the NHP model are consistent with clinical reports. For instance, recent studies have demonstrated that maternal obesity, or gestational diabetes, leads to significant inflammation of the placenta in human pregnancies [13-15]; however, these investigations are limited in their ability to collect appropriate samples, and the control of the maternal environment (e.g., health and nutrition). Our ongoing collaborative studies of this serious health issue have identified a key link between diet and fetal development and health in a well-controlled and characterized model that has important similarities to humans. Furthermore, these studies have begun to identify safe and viable interventions that may have a long-term impact on human health and significant reductions in health care costs. We believe that these studies have a direct, relevant translation to human health, and that our close association with OHSU clinical departments and the Moore Institute will allow for the rapid translation of targeted clinical investigations. More importantly, we believe that the key findings of our studies provide hope for millions of obese women that proper nutrition during pregnancy alone can significantly reduce the risk of pregnancy complications and improve the life-long health of their children.

Neuropsychiatric complications associated with developmental programming: It is certain that poor metabolic health can impact the quality of life; however, neuropsychiatric complications, such as depression, anxiety, ADHD, learning disabilities, and autism can have a devastating impact on the quality of life throughout the life span. Recent evidence in epidemiological studies have demonstrated a disturbing trend between obesity and psychiatric disorders. Obesity is associated with a significant increase in the diagnosis of anxiety and depressive disorders, especially in young women [16]. This increased risk has been presumed to be related to the peer pressures experienced by these young women. Maternal obesity is also associated with a significant increase in the risk of children developing autism [17, 18]; how and why this occurs is unknown. Ongoing studies led by Excluded by Requester and collaborators have shown that chronic consumption of a WSD during pregnancy, independent of maternal obesity, increases anxiety-like behavior in infant female macaques [9, 19]. Importantly, the results of these studies, while consistent with what has been observed in humans, is in contrast to results in rodent models. Furthermore, she has identified decreases in the critical neurotransmitter serotonin as a likely culprit for causing the anxiety disorder in these animals [9]; studies that could not be performed in humans. This suggests that the increased occurrence of anxiety/depressive disorders in young obese women may not be simply due to peer pressure issues, but may be related to an underlying neurochemical imbalance caused by poor maternal nutrition. In collaboration with clinical psychiatrists at OHSU and advanced imaging experts, Excluded by Requester is now investigating possible social behaviors displayed by our infant and juvenile offspring that may also be caused by poor maternal diet. Considering the prevalence of the consumption of the WSD within the U.S. and the prevalence of maternal obesity, these may be the highest risk factors for psychiatric disorders in the nation. Furthermore, we believe that these studies are already changing the perspective of diagnosing, understanding the cause, and therapeutics/interventions for these psychiatric disorders.

Specialized Metabolic Consequences in Women: Excluded by has long history of investigating metabolic adaptations in females, as they relate to the different stages of the reproductive life. Initially these studies used rodent models in which she investigated the neural circuitry by which nutritional and metabolic signals are integrated into the reproductive neuroendocrine axis. Recently this led to the recruitment of Excluded by Requester (an electrophysiologist), and expanded collaborations with Excluded by Requester (Univ. of Washington) and Excluded by Requester Excluded by (OHSU) to investigate the molecular and cellular changes in the neuroendocrine axis. The key finding of these studies is the redefining of how peripheral metabolic signals, in physiologically relevant settings, indirectly modulate the reproductive neuroendocrine axis through a defined network of neurons in the hypothalamus [20-22]. These studies in rodents are relevant to human health issues: 1) the declining age in the onset of puberty. Precocious puberty has been linked to early onset weight gain and obesity. Thus, it is critical to understand the underlying mechanisms and long-term consequences of this condition.

2) Poly-cystic ovarian syndrome (PCOS) in women is also linked to obesity and insulin resistance. With the expertise of our investigators and collaborators in the integration of metabolic signals into the reproductive neuroendocrine axis, we are uniquely positioned to study these health issues in the NHP model, which more closely resembles the human. To this goal, we [Excluded by Requester,Pending Support]

[Pending Support]

therapeutics of the treatment of metabolic diseases.

[Excluded by Requester,Private Source] have had a long and productive collaboration investigating both the pathogenesis of obesity and diabetes,and the development of therapeutics for the treatment of these important diseases. [Excluded by] was originally an investigator in the Division of Neuroscience, but left to direct an obesity research institute in Australia. However, this collaboration has been maintained. In summary, these investigators have been involved in development of several therapeutic areas in a series of studies that started in rodent models, advanced through the NHP models, and have entered into clinical development. A prime example of this success has been the development of drugs targeting the melanocortin system, which is recognized as a potent regulator of food intake, energy expenditure, and glucose homeostasis in rodents, NHPs, and humans [23-28]. [Excluded by Requester] using an obese NHP model, recently demonstrated that selective analogs of the melanocortin system could stimulate significant weight loss and improved glucose homeostasis in animals being maintained on a WSD, with no evidence of side effects [29]. Analogs of melanocortin have been in clinical development for the treatment of obesity in humans for the past 5 years. However, several of these compounds caused significant side effects and clinical trials were stopped. Importantly, our investigators were able to recapitulate the negative side effects of some melanocortin analogs, but identify other analogs that lack any negative effects [29]; these safe analogs are now in clinical development.

In a more recent collaboration, [Excluded by Requester] [Private] [Private Source] [Excluded by Reque] (Univ. Cincinnati), and [Excluded by Request] (UT Southwestern) are investigating the underlying mechanism by which Roux-en-Y gastric bypass (RYGB) causes weight loss and remission of diabetes. To date, these studies have confirmed that the surgery in the obese/diabetic macaque has very similar effects as in the human; however, these studies are able to more closely monitor metabolic endpoints and behaviors over an extended period of time, which is difficult in clinical studies. The primary question of this study is how RYGB affects the brain and pancreas in a primate species; which have significant cytoarchitecture differences between rodents and primates.

Cumulatively, these ongoing studies using the obese NHP models give our investigators a powerful and unique perspective to investigate novel therapeutics. These studies are clinically relevant and provide important training for young scientists in translational research. It is important to note that the interaction with industry partners is a major strength of our Division, allowing access to important new technologies and tools in which to advance our studies into the clinic. Furthermore, these interactions provide alternative career paths for students and fellows and expanded funding opportunities for faculty. Finally, these ongoing studies have the potential to generate more patents and intellectual property for ONPRC/OHSU.

INNOVATION

In the past 5 years, the faculty brought together to form the Division of Diabetes, Obesity, & Metabolism have developed numerous innovative tools. These tools give our investigators a competitive advantage for diversified funding from NIH, foundations, as well as with industry partners.

Animal Models: Our investigators have developed important NHP models in which to investigate several aspects of metabolic diseases. These models include different cohorts of diet-induced obese (DIO) monkeys (including rhesus, cynomolgus, and Japanese macaques), which are managed by the Obese NHP Resource. For this DIO model, young adult male and female animals are maintained on a WSD (primarily saturated fat) for numerous years. These animals can also be supplemented with fructose sweetened drinks to further model soda consumption, which is a significant contributor to the complications in metabolic diseases. The value of this model is that they develop the full spectrum of the complications of metabolic disease in a similar fashion to humans. However, unlike clinical studies, the metabolic phenotype can be carefully characterized over many years, through the development of obesity, insulin resistance, to full

diabetes and cardiovascular disease. These models have been essential for: 1) our funded research consortium investigating the relative effects of poor maternal diet and metabolic health on developmental programming in offspring; 2) our newly funded research consortium investigating RYGB; and 3) the broad array of industry partnership studies investigating novel therapeutics. Furthermore, we are now expanding these dietary challenges to investigate, in collaboration with investigators in the Division of Reproductive & Developmental Sciences, the interaction of mild hyperandrogenemia and a WSD during the peripubertal period.

Metabolic phenotyping core: We are unique in our access to a metabolic phenotyping facility for both rodents and NHPs. This includes the ability to determine energy expenditure/metabolic rate (metabolic chambers), various tolerance tests, euglycemic/hyperinsulinemic clamps, automated feeding systems, videography (for monitoring behavior), cardiovascular/thermosensing telemetry, and a vast array of noninvasive imaging technology. An important component to the success of our programs and training is the ability to perform head-to-head comparisons between the extensively characterized and broadly utilized rodent models and the more limitedly utilized NHP model.

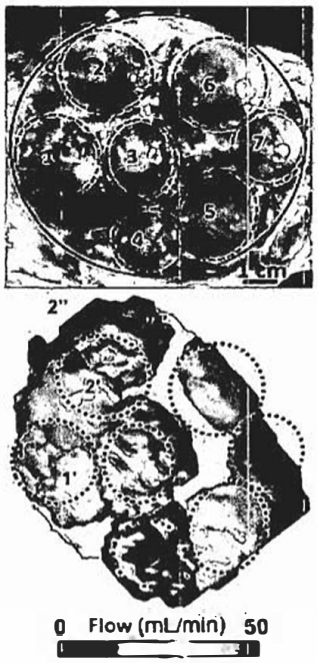


Figure 1 *Top*: photograph of NHP placenta with identified cotyledons. *Bottom*: heat map of blood flow in the same placenta using ceMRI. Note the variable flow rate between cotyledons.

Noninvasive Imaging: ONPRC has a broad array of noninvasive imaging technologies available directly on campus, including ultrasound, MRI and CT, as well as access to technologies at OHSU. The use of these imaging techniques, along with our ability to perform serial laproscopic biopsies of tissues or with subsequent necropsy of the whole animal allows for the validation of the imaging techniques and can push the diagnostics for early detection of abnormalities. These techniques may then be more valuable in the clinical setting. Below is a summary of some of the innovative applications of these techniques by investigators in our division.

1) Ultrasound: Several variations of this technique being used, including i) standard Doppler ultrasound - to investigate the effects of maternal diet on placental function [6], ii) contrast microbubble enhanced ultrasound – to investigate microvascular reperfusion [30], and iii) VCAM and P Selectin labeled microbubbles – Excluded by (Dept. Cardiology) has been developing this technique to characterize vascular inflammation and plaque formation in the DIO macaque. The analysis of placental function and vascular inflammation are two techniques that we believe have direct clinical relevance and will improve clinical diagnosis.
2) MRI: The 3T MRI is used for structural imaging of the brain, muscle, and liver. However, more advanced techniques are also being used: i) MR spectroscopy for analysis of liver and muscle fat deposition, ii) contrast enhanced MR (ceMRI) for investigation of placental function by Excluded by Requester in collaboration with investigators in the Advance Imaging Center (OHSU). This technique has a much higher resolution than ultrasound and can be used to investigate individual cotyledon function (Fig. 1).

Pending Support,Excluded by Requester

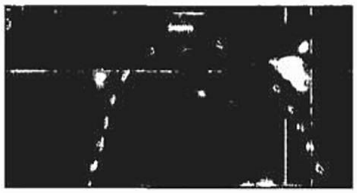


Figure 2. PET imaging in the cold-exposed cynomolgus mac. The bright yellow pixels, indicates active BAT. Image provided by Dr. Cameron.

3) PET: While OHSU currently does not have a PET facility, Excluded by is collaborating with Excluded by Requester (Univ. of Pittsburgh) to characterize BAT function in NHPs. This technique has been used in humans to characterize the distribution of BAT; however, little is known about BAT regulation in humans. Preliminary data show that BAT distribution in the NHP is similar to humans (Fig. 2). Furthermore, the molecular characterization of the BAT has been confirmed through gene expression and histological analysis. Through the recent generous donation by the Private Source family, OHSU and ONPRC are developing a PET imaging facility, with a planned PET/CT at ONPRC. This facility will provide a competitive advantage in many research areas, including cardiovascular and neurochemical characterizations.

Pancreatic Islet isolation and function: It has been established that the rodent and human have distinctly different pancreatic cytoarchitecture, and that the NHP is similar to humans [31]. Excluded by Requester is

successfully isolating islets from the NHP. These islets are being distributed to laboratories in the U.S., including to [Private Source,Excluded by Requester] Univ. Massachusetts). These investigators have been characterizing the function of NHP islets in comparison to rodents and humans. Furthermore, [Excluded by Requester] has developed membrane electrical signatures of pancreatic beta cells using electrophysiology, which will be important for understanding the complex and intricate cell-to-cell interactions within the islets.

In vitro imaging and cell culture techniques: A significant advancement that our group has accomplished is the development of an array of ex vivo and primary cell culture techniques for the NHP. This includes the use of primary cell cultures for adipocytes, hepatocytes, and myocytes. These techniques are important as they allow for application of molecular tools to study specific molecular mechanisms, i.e., siRNA knock down of specific genes. An example of the value of these studies is the technique developed by Drs. [Excluded by Requester] for using fluorescent label substrates (glucose and fatty acids), coupled with confocal microscopy, to perform dual uptake studies in ex vivo adipose tissue explants. Using this technique, they were able to demonstrate a surprising mosaic whereby different adipocyte populations preferentially transported glucose or fatty acids in response to insulin stimulation (Fig. 3). To date, they have used this technique to investigate the direct impact of gonadal steroids on insulin signaling in adipose tissue [32, 33]. [Excluded by Requester,Pending Support]

[Excluded by Requester,Pending Support]

Utilization of Cores and Resources: Our investigators are grateful for all of the animal resources and exceptional support staff within the DCM. One of the great strengths of our Center is the access to exceptional core facilities and specialized animal resources. These facilities are important to the current faculty and the training of their students and fellows, as well as for our ability to recruit new faculty (Aim 2). For obvious reasons, the Obese NHP Resource is the most important special animal resource to our investigators. Furthermore, since [Excluded by Requester] all share funding that utilizes the Japanese macaques, this special animal resource is also pivotal to the continued success of their program. However, we believe that there will be increasing use of the Primate Aging Resource (PAR), and the Time Mated Breeding (TMB) program as well. Aging is associated with metabolic diseases due to the natural decrease in metabolism that occurs during old age, resulting in spontaneous obesity and diabetes. Furthermore, the risk of metabolic diseases dramatically increases in women following menopause. Thus, access to the PAR, as well as collaborations with members of the Biology of Aging Research Program, will provide some important research opportunities and expanded funding. While division faculty have not utilized the TMB program in the past [Pending Support,Excluded by Requester]

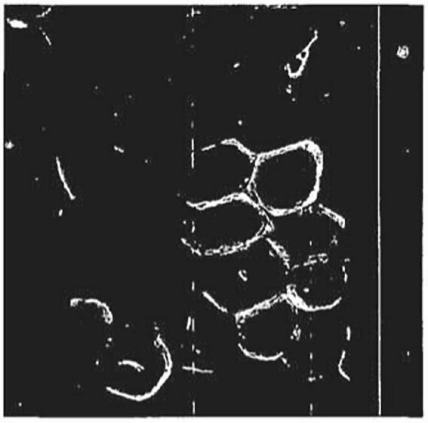


Figure 3. Labeled fatty acid (red) and glucose (green) uptake in NHP adipose explants in response to insulin stimulation. Note that most adipocytes take up fatty acids, but only a subset take up glucose in response to insulin.

[Pending Support]

Our Division members also make heavy use of several cores within ONPRC and OHSU. The expertise and equipment of the Molecular and Cell Biology Core and the Imaging Core are used daily by our investigators and their students and fellows. The training and protocol development provided by Dr. [Excluded by Request] of the Imaging core, has been especially important. Because of the constant metabolic phenotyping being performed by the Obese Resource and our investigators for hormones such as insulin and leptin, the Endocrine Service core also provides a critical service. The Virology (for production of AAV delivery systems) and the Flow Cytometry (for immune cell analysis) cores also provide important services to our investigators. Finally, the Microarray and Proteomics services at OHSU have also been utilized and are considered important to our faculty.

APPROACH

reviewers' comments

AIM 1: To develop a cohesive, integrated and well-funded division focused on the understanding of the pathophysiology of metabolic diseases. This new Division was developed from the MDWG established during the last Core grant cycle. The original participants in this working group were Drs. Excluded by Requester and Staff scientists Excluded by Requester Over the past five years, this group developed strong collaborations with other investigators at ONPRC, OHSU, nationally, and internationally. This program was supported by the expansion of the Obese Resource, and strong funding from both federal sources and from Industry collaborations. More recently, additional young investigators were recruited including Excluded by Requester (Dept. OB/GYN, OHSU), Excluded by Requester (Neuroscience), Excluded by Requester (DRDS), and Excluded by Requester (Neuroscience) that diversified our expertise and provided a more integrated approach to the study of metabolic diseases. While we are a diverse group, we have identified key strengths and common interests that will be the foundation for our division, which include: 1) developmental programming of metabolic systems, and 2) the pathogenesis and treatment of adult diet-induced metabolic diseases. However, our investigators have identified Women's Health as an overall unifying focus. Females have complex changes in their metabolic systems throughout their lifespan that correspond with puberty, the menstrual cycle, pregnancy, lactation, and menopause. Furthermore, their metabolic health and nutrition during pregnancy and lactation have a significant impact on the development of metabolic systems and behavior in their offspring. Because approximately 2/3rd of women of reproductive age are overweight or obese, this area of research is of critical health importance for the next generation. However, the progression of metabolic complications in females is a grossly understudied area. We believe that developing a metabolic research program focused on Women's Health gives this new division a relatively unique focus. This focus also fits well with our strong collaborative relationship with investigators in the DRDS, and with clinical departments at OHSU.

Overview: We recognize that a key component to the long-term success of this division is to develop strong external collaborations and to have a diversified funding portfolio. Currently, our division investigators have approximately $5.2 million in funding (direct costs, 2012/2013), with 70% of that coming from federal sources (NIH) and the rest from industry collaborations (Fig. 4). We feel this is an exceptional level of funding taking into consideration that this funding is distributed between only 2 full time core scientists (Drs. Excluded by Requester and 3 part-time investigators % Effort Excluded by Requester % Effort Currently, our investigators have active collaborations (as defined by funding and publications) with investigators in all three of the other ONPRC scientific divisions, as well as 15 investigators at OHSU, and 20 investigators at other institutions. Below is a more specific outline of the ongoing collaborations and

funding of investigators in our division, as well as collaborations and interactions that will be our focus over the next five years.

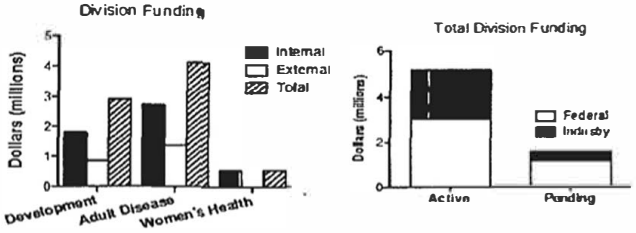


Figure 4. Division Funding (Direct costs). Left Panel summarizes the funding of division investigators (internal) by research area, as well as funding of external collaborators using ONPRC resources. Right Panel summaries total active and pending funding from NIH grants and industry collaborations.

Developmental programming of metabolic systems:
The program established by Excluded by (brain and pancreas) and Exclude d by Req brain) focused on developmental programming of metabolic systems has become internationally renown. The investigators involved in this research focus now also include Excluded by Requester (brain and behavior), Exclude d by Re (placental function), Excluded by Requester (placental biology), and Excluded b Requ brain, electrophysiology). Importantly, this group also has an exceptional list of internationally recognized affiliate scientists, including Excluded by (OHSU – placental function/ cardiovascular disease), Exclude d by Req (OHSU – Inflammation), Excluded by (OHSU, lipid biology), Excluded by (Univ. Colorado at Denver – muscle and liver physiology), and Excluded by Epigenetics). In the past core grant cycle (< 4 yrs), our investigators have published 20 manuscripts/reviews on this topic, and made 55 national and international presentations. Furthermore, in the current year, our investigators have over $1.8 million in funding related to this topic, while affiliated investigators (External) have $0.9 million in funding. The main funding in this program is through a multi-PI consortium grant (R24) led by Excluded by

It should be noted that Excluded by Requester were key members in the OHSU team that developed the Moore Institute for Nutrition & Wellness at OHSU. Members of our division also participate in the Early Childhood Health multidisciplinary group being led by Excluded by Requester

Future Goals: Areas that this program are expected to grow over the next five years:

1) Psychiatric disorders: There is a disturbing rise in early onset psychiatric disorders in children, including Autism-like disorders, anxiety, depression, and ADHD. These disorders greatly impact the quality of life of those affected. Excluded by Requester have identified disturbing behavioral outcomes while investigating the impact of poor maternal metabolic health and diet on the brain development in offspring. A key finding of these studies was consumption of a WSD during pregnancy, independent of maternal obesity, greatly increased the occurrence of abnormalities in social behavior in the offspring, which is consistent with Autism-like behavior. This has led to the development of collaborations with Excluded by Requester from the Dept. of Psychiatry at OHSU. These studies will be greatly aided by the MRI expertise at ONPRC and the new PET facility being built. Pending Support

2) Pancreas development. Excluded by Requester through the Multi-PI R24 g ran (2011-2016), has funding to investigate pancreas development in the NHP model to determine the relative impact of poor maternal health and diet. This study has already identified some distinct differences between the development of the pancreas in the rodent and NHP. Excluded by Requester These exciting findings have led to a new collaboration with Private Source,Excluded by Requester With use of animals from the Obese NHP Resource, they will investigate pancreas development at several different stages.

Women's Health: While we have separated out the Developmental programming studies from the Women's Health program, there is obvious overlap between the programs. However, our investigators also have a strong expertise in the more general area of Women's Health. Excluded by has been the key contributor to this area of research and was instrumental in the establishment of the Women's Health Center at OHSU. Her main focus of research is on hypothalamic circuits that integrate metabolic signals to the reproductive neuroendocrine axis. This program has been consistently funded by R01 funding for 28 years. These studies have been expanded through the recruitment of Excluded by and through collaborations with Excluded by Requester from OHSU, and Excluded by Requester from the Univ. of Washington.

Another area of Women's Health research is being led by Excluded who has an expertise in fetal maternal health. Clinically, Excluded runs a high-risk pregnancy clinic at OHSU focused on maternal obesity and gestational diabetes, and is an expert in ultrasound imaging. This expertise has led to several

collaborations at ONPRC, in addition to the maternal HFD/obesity program described above, including with Excluded by (Effects of maternal nicotine exposure on placental growth and function), Excluded (OHSU; The use of contrast enhanced [ce] ultrasound to measure uteroplacental perfusion), Excluded by Request (The use of ceMRI to identify regional abnormalities in placental health and function). An obvious key focus of Excluded by Requester group is the development of more powerful imaging techniques for the earlier detection of pregnancy complications. To help build his program, Excluded has recruited a junior faculty, Excluded by Re uester to his group. Excluded by Requester has an expertise in placental biology and pathology.

Future Goals: While this program currently has a relatively modest level of funding (approximately $0.6 million per year in funding), several investigators from this division are involved in a new collaborative effort with investigators in DRDS, as well as with Excluded by (Univ. of Pittsburgh). This new program, to be supported by Pending Support
Pending Support

Pathogenesis and therapeutics for adult metabolic diseases: In the past 5 years, there has been impressive growth in the program focused on adult metabolic diseases led by Excluded by Requester Excluded by Requester. In the current year, there are approximately $2.7M in funds coming into ONPRC in this research area, and approximately $1.4M to investigators at other Institutes that are directly related to collaborations using the ONPRC Obese NHP Resource. The primary sources of these funds are from: 1) A multi-PI grant that includes Excluded by Requester from ONPRC; and Private Source, Excluded by Excluded by Requester (UT Southwestern), and Exclude d by Req (Univ. Cincinnati), which is focused on the discovery of the underlying mechanisms by which RYGB causes weight loss and improved diabetes outcomes in the DIO macaque. 2) Excluded by Requester from the Dept. of Cardiology at OHSU has two funded R01s using DIO macaques to investigate the progression of vascular complications.

The importance of the NHP research models has also led to intense interest by Industry groups and has resulted in consistent funding over the past year 5+ years, with over $2.1M of direct costs to our division investigators in the current 2012/2013 year, and over Pending Support. These industry-sponsored studies are not only important to diversify funding in the face of challenges in NIH funding, but are also important translational research. These studies are peer reviewed by a scientific panel within ONPRC, result in publications, and, to date, have accelerated two novel therapeutics into clinical trials.

Future Goals: Because of the overall expertise in this area of our investigators at ONPRC and OHSU, and because of the emerging recognition of the importance of the NHP model, we anticipate significant growth in our division around adult metabolic diseases in several different areas.

1) Excluded by Requester have already established collaborations with Excluded by Univ. of Mass.) and Excluded by Requester that will focus on pancreas function and complications that lead to diabetes. A driving force behind this collaboration has been the optimization of islet isolation technique for the NHP by Excluded by group. This initial collaboration has already resulted in a Multi-PI (R24) seed grant from NIDDK to further develop common interests and develop more tools to aid in future research. This group expects to Pending Support
Pending Support
2) As mentioned above, a portion of the the generous $125M gift from the Private Source will allow us to expand animal facilities for the study of metabolic diseases, and for the expansion of the imaging capabilities, including PET/CT, ultrasound capabilities, and a Cath. Lab for vascular imaging. This will give ONPRC imaging capabilities that parallel the best clinical facilities. In addition, it is expected that there will be funds for new recruitments of a senior investigator focused on cardiovascular diseases. Excluded by Requester is leading the establishment of a Diabetes Research Center (DRC) at OHSU. OHSU currently has the Schnitzer Diabetes Health Center, which focuses on clinical care; however, the Private Source is now initiating fundraising to support the research component. Furthermore, Excluded by Requester has established a link with the DRC at the Univ. of Washington (UW). The investigators at UW are also interested in access to the Obese NHP Resource, and the UW has some core facilities and expertise, in pancreas function, brain circuitry, and lipid metabolism that will complement our expertise.
3) Neurodegenerative Diseases: There is a well-established link between diabetes and neuropathies, especially retinopathies. ONPRC has a leading expert on retinopathies in Excluded by who has been characterizing the progression of retinopathies in obese/diabetic animals. Furthermore, she has been

working with investigators at OHSU in the Casey Eye Institute to develop more sophisticated noninvasive imaging techniques to quantify changes in eye health. Other neurological diseases also have an link with diabetes, such as Alzheimer's disease. The Div. of Neuroscience has a strength in neurodegenerative diseases. As the animals in the Obese NHP Resource become older they will become a powerful tool to study neurodegenerative diseases as well as pathological aging. Dr. Excluded by Request (Neuroscience) is already collaborating with Excluded by to characterize metabolic complications in her animal models. Furthermore, ONPRC also has a strong Biology of Aging Research Program that will utilize the aging Obese NHP Resource animals in comparison to their healthy aging cohort.

4) Adipose tissue biology/lipid metabolism: **To be discussed in AIM 2.**
5) Immunological/inflammation: **To be discussed in AIM 2.**

AIM 2: To recruit new investigators to provide expanded expertise and technical approaches to allow a more diverse and integrated approach to the investigation of these complex diseases. These diverse approaches and areas of expertise will allow a more efficient use of this research model, as well as providing a rich intellectual environment. Currently our new division only has two full time core scientists and three part time core scientists. However Excluded by Requester has also put in notice that she will be Personal Info To have a critical mass for this new division, we are proposing to have 6 core scientist positions; thus, it will be necessary to recruit at least three new investigators over the next three years to establish a critical mass, and to diversify our areas of expertise.

Division Strengths: Our Division currently has strength in whole animal physiology in both rodent and NHP models. We also have significant strength in our direct collaborations with clinician scientists, both within our group Excluded by as well as investigators at OHSU. Below is a summary of specific areas of expertise.

1) Neuroscience: This division originated from members of the Div. of Neuroscience, thus, it is not surprising that this would be one of our strengths. Excluded by Requester are experts on hypothalamic and brainstem circuits involved in the regulation of food intake and energy expenditure. Excluded by Requester is an expert on the serotonin system, as well as complex behaviors. Excluded by is an electrophysiologist focused on hypothalamic circuits. Our group also has strong affiliate scientists with expertise in hypothalamic circuits Excluded by Requester
2) Pancreas: Excluded by Requester both have funding to investigate pancreas development, function, and pathogenesis. These investigators also have funded collaborations with internationally renowned experts in this field in Excluded by Univ. Mass.) and Excluded by Requester
3) Muscle/liver physiology: Although we do not have the expertise directly here at ONPRC, this division has Affiliate scientists who are funded to investigate muscle and liver physiology and pathology, including Excluded by Requester (UC Denver).
4) Cardiology: This division has an Affiliate scientist from OHSU who is an expert in preclinical and clinical research on cardiovascular disease. Excluded by Requester (OHSU) is a renowned expert in cardiovascular imaging and utilizes the obese NHP to develop novel imaging techniques.

Future AIMs: Recruitment: While we recognize there are several areas of expertise that would augment our research environment, our division investigators have developed a consensus about what expertise would have the greatest impact and allow our group to move forward to address important health concerns associated with metabolic diseases. The salary support for the three new positions have been included in the Division budget, but the recruitment packages will come from the Vice Provost's office. Furthermore, a complete renovation plan has been developed for the Divisional laboratory space within the Research Building that will provide high caliber research space for the new recruits. The renovations for updating the infrastructure of the building (seismic stability) were finished this year, along with renovation of offices and conferences rooms. Funding for the renovation of the laboratories will come from the Private Source and ongoing fundraising from the OHSU Foundation. These new facilities will certainly add to our competitiveness in recruiting premier young and established investigators. Finally, our current supportive mentoring environment (see Aim 3), along with the successful funding of our investigators, and the guaranteed salary support, will make these positions very desirable for young investigators.

1) Division Chief: Currently, Excluded by Requester is serving as the Interim Division Chief. However, our Division investigators, as well as the Administration, feel it is important to have an open competitive recruitment for this position. Excluded by will compete for this position, but it may also be an opportunity to recruit an additional senior investigator and a leader; possibly in one of the areas of expertise listed below.

2) Cardiovascular Disease: We have discussed above the [Private Source] ($125 million) and the establishment of the Cardiovascular Research Institute (CRI) at OHSU. To support the expansion of research in this important area, we also plan to have a co-recruitment, with the CRI, of a senior core scientist in this area. We are confident that, with the combined intellectual environment of our Division and the CRI, along with the expansion of the Obese NHP Resource, and the exceptional imaging capabilities that are planned, will make us very competitive in recruiting a preeminent senior investigator for this position. A search is planned for early 2013.
3) Adipose biology: While [Excluded by Requester] do have active programs in adipose tissue biology, this has still been identified as a key area for recruitment. While there are many areas of adipose tissue biology that are interesting and important, an expertise in brown adipose tissue (BAT) biology would likely have the greatest impact on the program. Historically, BAT was believed to be important in rodent species, but not in humans. However, recently it has been made clear that humans do have BAT and that it is involved in thermogenesis; however, it is not known how or if BAT is an important component in energy homeostasis or the pathogenesis of metabolic disease. There is now evidence that NHP have a similar distribution of BAT to humans (Fig. 2), and preliminary studies between [Excluded by Requester] (Univ. of Pittsburgh) have utilized PET imaging to demonstrate that BAT in the NHP responds to cold exposure. Once PET imaging is established at OHSU and ONPRC, we will be uniquely positioned with the necessary research tools and animal resources to investigate the importance of BAT in a primate. This recruit would likely be at the level of assistant scientist. A recruit in this area would have potential collaborations with investigators at ONPRC and OHSU interested in: a) neurocircuits, which regulate energy expenditure through activation/suppress of BAT function; b) weight loss surgeries, interventions, and therapeutics; and c) *in vitro* imaging of adipose tissue. We believe this is also a highly fundable area. [Excluded by Requester] would be good candidates to serve as faculty mentors for this young scientist. We plan to initiate this recruitment in 2014.
4) Immunology/Inflammation: It is well recognized that obesity and diabetes are inflammatory diseases. The activation of the inflammatory response is hypothesized to be a key driver for other associated complications, such as atherosclerosis. Furthermore, there is emerging evidence that obesity and diabetes are also associated with immune dysfunction. Indeed, ongoing studies in collaboration with Dr. [Excluded by Requester] (Div. Pathobiology and Immunology) have demonstrated that a similar activation of inflammatory response and dysfunction in the immune system occurs in the NHP during the progression of DIO. This makes the NHP an important model to understand immune complications that occur in metabolic diseases. This position would also build collaborations between our Division and the Div. of Pathobiology and Immunology. This recruit would be at the level of assistant scientist. There are subspecialties in immunology that would benefit the program: a) A neuroimmunologist would help address key questions about the inflammation and immune response in the brain that occur in chronic metabolic diseases. Such a recruit would also bridge collaborations with investigators in the Div. of Neuroscience. b) A gastrointestinal (GI) immunologist would help address key questions about the importance of the GI immune system in the pathogenesis of obesity and diabetes. There is emerging evidence that one mechanism by which bariatric surgery improves diabetes outcomes is through modification of the GI immune system, which then impacts the systemic immune system and peripheral insulin sensitivity. The GI microbiota has also become key player in energy homeostasis and disease progression. We plan to initiate this recruitment in 2015.

AIM 3: To develop a supportive and constructive environment for training of the next generation of scientists in the use of the complex and highly translatable NHP models of metabolic diseases.
It is well recognized that the NHP is an important research tool that better models the disease progression than any other preclinical species. However, there is only a small community of investigators that regularly uses this valuable model. It is key to provide a rich training environment and resources to train and expand this research community. This will be especially important for ensuring that our new recruits (Aim 2) have all the support necessary to establish a successful NHP program. We believe that we have all the tools and resources necessary to provide a rich training environment for investigators at all levels and for making the trainee competitive at the next level. Although we are a new Division, our investigators have the experience (Table 1), dedication, and the resources to provide a rich training environment.

Table 1. Mentoring Experience: Our faculty are actively involved in training scientists from all levels. Below is a list of training from our faculty since 2009 and currently (#).

Faculty	High School Undergrad.	Grad. Students	Thesis Comm.	Postdoc./ Clin. Fellows	Faculty/resident Mentoring
Excluded by Requester Sen. Sci	4 (1)	4 (0)	6 (0)	6 (3)	2 (1)
Sen. Sci	1 (0)	2 (0)	5 (0)	2 (1)	4 (3)
, Sen. Sci	0	0	2(0)	2(1)	1(1)
ssoc. Sci	1(1)	0	0	0	6 (4)
, Assist Sci.	16 (5)	0	1(1)	1 (1)	0

Highlighted mentoring successes:

1) Excluded by Requester – was a postdoctoral mentor of Excluded by [illegible] in 2011. Excluded by Requester is now an independent faculty at the University of Portland, with a % Effort esearch position at ONPRC.
2) Excluded by [illegible] – served as a faculty mentor for Excluded who received independent funding in 2011 as part of an R24 Multi-PI grant.
3) Excluded by R – was the postdoctoral mentor for Excluded by [illegible] In 2011, Excluded by Reque was recruited by Private Source as a Senior Scientist.
4) Excluded by [illegible] serves as the faculty mentor for Excluded by [illegible] (Staff Scientist II), who recently Priority Score and is now independently funded.
5) Excluded by Requester has served as the faculty advisor for Excluded by [illegible] (DRDS), who recently received her first R01 award.

Table 2. Our faculty are involved in several ONPRC, OHSU and Foundation Training Grants.

Training Grant	Grant Number	Mentors
Women's Reproductive Health Research (WRHR) Career Development Award	K12 HD001243	Excluded by Requester
Pre- and Postdoctoral Multidisciplinary Training in Reproductive Biology	T32 HD07133	
Pre- and Postdoctoral Multidisciplinary Training in Neuroendocrinology	T32 DK07680	
Training in Endocrinology, Diabetes, and Clinical Nutrition	T32 DK007674	
Oregon Child Health Research Center	K12 HD033703	
Building Interdisciplinary Research Careers in Women's Health	K12 HD043488	
National Research Service (NRSA) Award, Institutional Predoctoral Training Program in Systems Biology of Developmental Biology	T32 HD46420	
Multidisciplinary Training in Neuroscience	T32 NS07466	
Private Source		

Resources

1) *Funding* – our investigators are well funded (Fig. 4), providing the students and fellows the financial support to be productive and creative in their studies. Furthermore, our senior scientists are dedicated to mentoring new investigators (current and those to be recruited) on successfully developing an independent program and for obtaining their own funding. Finally, our faculty are involved in numerous training grants (Table 2).
2) *Animal Resources*: This division is supported by the Obese NHP Resource, which provides access to powerful animal models, as well as technical support to both train investigators in techniques, and also provides assistance in performing studies. Our facility also supports both NHP and rodent models that provide trainees the important experience of using the NHP model, but also access to more traditional

models (rats and mice) that are more broadly used by the research community. We are also unique in the access to a full metabolic phenotyping core for both NHPs and rodent models, which allow for an integrated and comparative approach to projects – learning the value and limitation of all research models. The ability to utilize both NHP and rodent models makes our investigators competitive for a broader range of independent positions.

3) *Core facilities* – As described above, our investigators and their trainees have access to a broad array of core facilities that have developed specific research tools for studies in the NHP; including, the Molecular and Cell Biology Core, Hormone Core, Imaging Core, Genetics, Microarray Core (OHSU) and the MRI facility.

Training Strategies: Our faculty are involved in mentoring trainees at several different levels, and have developed programs to provide experience in key areas for the development of independence. Our faculty members recognize that there are ever increasing challenges in obtaining independent funding and faculty positions; therefore, we must provide broad training experience that will allow our trainees to be competitive for a wide range of positions, both in academia and within Industry.

1) Journal Club – Being up to date with the latest literature is a critical component of sustaining a successful research program. Learning to critically evaluate published studies is also an important research tool. Excluded by Requester has organized a weekly journal club for 10+ years that is focused on critically evaluating the latest research, while putting the new studies in the perspective of the historical literature. With the initiation the new Division, Excluded by Requester has expanded the covered topics to include all aspects of metabolic diseases. This journal club involves all students and faculty, with each taking turns discussing recent published studies from their chosen topic. This open discussion provides a historical perspective from the senior investigators, a clinical perspective from the clinicians, and allows for an open discussion of the strengths and limitations of each manuscript.
2) Division Seminar – Being comfortable speaking in front of a group of peers and concisely and clearly communicating scientific studies is key to a successful scientific career. The Staff Scientists in the Division will take turns organizing our weekly seminar series. All students, fellows, and Staff scientists will present 1-2 times per year in this seminar series. We will also have invited speakers from other research divisions or other local institutes that allow the students to hone their communication skills, as well as to learn different scientific perspectives and strategies. The core faculty members also provide an overview of their program every other year at the ONPRC Work-in-Progress Seminar Series run by the Director. All students, fellows, and faculty also participate in the ONPRC seminar series, which hosts internationally renowned investigators once a month.
3) Visiting Scientists – several investigators in our Division also participate in hosting visiting scientists, which provide training and access to the use of NHP models to external investigators. We believe this type of training is part of our mandate as a National Resource, and technical support is provided by the Obese NHP Resource. In the past year, our division members have hosted: 1) Excluded by Requester (Univ. of Colorado at Denver) – to learn to make NHP primary liver and skeletal muscle cell cultures; and 2) Private Source,Excluded by Requester to perform pilot studies in isolated NHP macrophages in culture. In the coming year, there are already plans to host: 1) Private Source,Excluded by Requester to work with NHP adipocyte cultures; and 2) Private Source,Excluded by Requester to obtain technical training in measuring appetite, glucose homeostasis, and energy expenditure in the NHP model.
4) Teaching – although ONPRC is a research institute with little teaching duties for faculty, we do recognize that trainees may have teaching duties in their future positions. While there are limited teaching opportunities at OHSU, there are opportunities at other local Universities to gain this experience. For example, Excluded by Requester during her postdoctoral fellowship, taught classes a Portland Community College; she is now a faculty member at the Univ. of Portland where she teaches Physiology. Excluded by Requester (a student in Excluded by Requester laboratory) taught classes at Portland State University; she is now a faculty member at Corban University teaching Biology to PreMed students.

In summary, while proposing to have a supportive and constructive training environment may seem modest and overly obvious, we feel that with the establishment of a new Division that it is important to ensure the fundamental training environment is developed. As additional investigators are recruited, we believe we will be able expand our training environment, providing a rich, diverse, and complete experience for our trainees; making them exceptionally competitive for subsequent positions both within academia and industry.

Pages 1117-1123 (Publications) Removed – Excluded by Requester

Externally Funded Research Projects – Diabetes, Obesity, & Metabolism

Excluded by Requester — Oregon Health and Science University
Women's Reproductive Health Research (WRHR) Career Development Award
K12 HD001243
The goal of this project was to investigate placental development in a non-human primate model of excess nutrition.

Excluded by Requester (PI of sub) — Thermalin Diabetes, LLC / Oregon National Primate Research Center
Optimized receptor binding profile in an ultra-stable, ultra-rapid-acting insulin
NIH/NIDDK R34 DK092041
The goal of this project is to characterize novel insulin analogs with respect to insulin receptor activation and cross-reaction with IGF-I receptor and tumorigenecity.

Excluded by Requester (PI of sub) — University of Colorado (Denver) / Oregon National Primate Research Center
Mechanisms for Fetal Hepatic Programming in the Non-human Primate
NIH/NIDDK R01DK078590
The purpose of this project is to determine the effect of maternal high fat/calorie diet and metabolic health on the developmental programming of metabolic systems in the liver and muscle focusing on the reprogramming of the insulin signaling, lipogenesis/lipolysis, and gluconeogenesis pathways.

Excluded by Requester — Oregon National Primate Research Center
Primate model of mid-gestation Ureaplasma in utero infection: Prevention of neurologic sequelae
NIH/NICHD R01 HD069610
The objectives of this research proposal are to assess the therapeutic effect of antenatal maternal antibiotic therapy in preventing or mollifying cerebral white matter damage in the neonate (as a consequence of prolonged *U.parvum* intra-amniotic infection, IAI) and to correlate neurobehavioral outcomes with neuropathologic findings of neonatal brain injury.

Excluded by Requester — Oregon National Primate Research Center
Compartmental analysis of proteomic biomarkers during intra-uterine infections
NIH/NICHD R00 HD055053
Our specific research aims focus upon defining the temporal and compartmental relationships among specific biomarkers and the biologic and clinical manifestations of early and late stages of ascending infection studies (from choriodecidual to intra-amniotic models)..

Excluded by Requester — Oregon National Primate Research Center
Treatment of Obesity and Insulin Resistance in the Non-Human Primate
Private Source
The purpose of this study is to determine if treatment with a propietary compound could cause weight loss and improvement of glucose homeostasis in high fat diet induced obese nonhuman primates.

Excluded by Requester — Oregon National Primate Research Center
Involvement of the melanocortin system in regulation of lipolysis and blood pressure
Private Source
The aim of the project is to examine the involvement of the melanocortin system in the regulation of lipolysis and blood pressure and to characterize possible alternative signaling pathways of MCRs in adipocytes.

Excluded by Requester) Oregon National Primate Research Center
The Impact of Maternal Health and Diet on Development of Fetal Metabolic Systems
NIH/NIDDK R24 DK090964
This project will investigate three dietary interventions designed to limit inflammation, oxidative stress, and substrate availability to the fetus to ultimately reduce the risks of early onset obesity and diabetes.

Excluded by Requester Oregon National Primate Research Center
Maternal High Fat Diet and the Melanocortin System in Offspring
NIH/NIDDK R01 DK079194
This grant examines the impact of maternal obesity and high fat feeding during pregnancy in a nonhuman primate model on the development of brain circuitry, which controls appetite and energy homeostasis.

Excluded by Requester Oregon National Primate Research Center
NIH/NIDDK R01 DK079194
Maternal High Fat Diet and Melanocortin System in Offspring – Administrative Supplement
This project investigates the effects maternal health and diet on the development of the hypothalamic melanocortin system in the nonhuman primate.

Excluded by Requester Oregon National Primate Research Center
Effect on serum biomarkers and insulin resistance in high fat and fructose-fed rhesus monkeys
Private Source
The purpose of this study is to investigate changes in serum markers of inflammation, metabolism and pro-coagulant activity during and following treatment with a Genentech compound.

Excluded by Requester Oregon National Primate Research Center
Effects of humanized antibodies to ANGPTL4 on triglyceride and VLDL-levels in obese Rhesus Macaques
Private Source
This study will test the ability humanized ANGPTL4 antibodies to increase triglyceride clearance through activation of the lipoprotein lipase enzyme to determine whether these antibodies can effectively reduce triglycerides and VLDL and improve glucose homeostasis in obese nonhuman primates.

Excluded by Requester Oregon National Primate Research Center
Immune therapy of insulin resistance in diet induced obese (DIO) Rhesus macaques with humanized antibody to NKG2D, a natural killer cell activating receptor.
Private Source
The purpose of this study is to investigate whether immune therapy targeting NKG2D can reverse the suppressed immune function and insulin resistance caused by chronic high fat diet (HFD), which would be a novel therapeutic for the treatment of obesity and diabetes.

Excluded by Requester Oregon National Primate Research Center
Characterization of a GLP-1 receptor antibody in the nonhuman primate brain
Private Source
The purpose of this study is to perform an extensive characterization of the distribution of GLP-1 receptor immunoreactivity in the brain of the Rhesus macaque in order to provide insight into additional functional roles of GLP in the brain.

Excluded by Requester Oregon National Primate Research Center
Effects of a novel PYY analogue, alone and in combination with a GLP-1 agonist, on food intake and body weight in obese rhesus macaques
Private Source
The experimental protocol will test two anorexigenic peptides in their ability to suppress food intake and decrease body weight: Peptide YY (PYY) and glucagon like peptide (GLP-1) analogs, either as monotherapy, as well as in combination, to determine the most efficacious treatment plan of obesity.

Excluded by Requester — Oregon National Primate Research Center

Characterization of endogenous glucose, cholesterol and fatty acid synthesis in high fat diet fed cynomolgus macaques

Private Source

To establish baseline metabolic characteristics of cynomolgus macaques on high-fat diet and differentiate the effects of high-fat diet versus metabolic phenotype.

Excluded by Requester — Oregon National Primate Research Center

Effects of an Acceleron locally-acting test article on muscle growth in cynomolgous macaques

Private Source

The current study proposes testing a locally-acting antagonist to the TGFb superfamily ligands, which negatively regulate muscle mass in the cynomolgus macaque, in order selectively increase muscle mass in the treated tissue without being systemically bioavailable.

Excluded by Requester — Oregon National Primate Research Center

Actions of melanocortin agonists in obese primates

Private Source

Study objective is to determine if treatment with a melanocortin agonist that crosses the blood brain barrier can cause hypertension in a primate species.

Excluded by Requester — Oregon National Primate Research Center

(Co-PI) Oregon National Primate Research Center

Effects of Dopastatin compounds on cardiovascular responses and glycemic control lean Cynomolgus Macaques

Private Source

The purpose of the study is to compare efficacy of several dopastatin compounds on pituitary and pancreatic hormones and to monitor cardiovascular parameters in naïve cynomolgus monkeys.

Excluded by Requester — (MPI) Massachusetts General Hospital

PI) Oregon National Primate Research Center

Neuroendocrine response to gastric bypass in nonhuman primates

NIH/NIDDK RC4 DK090956

The overall goal of this project is to use the unique advantages of the NHP model to explore the cellular and molecular mechanisms underlying the effects of RYGB on energy balance and metabolic function.

Excluded by Requester — University of Utah

(PI sub) Oregon National Primate Research Center

Maternal Diet Modifies the Fetal Primate Epigenome and Circadian Gene Expression

NIH/NIDDK R01 DK080558

This proposal focuses upon the effects of a maternal high fat/calorie diet and metabolic health upon the fetal and postnatal epigenetic characteristics of circadian genes, which are expressed in fetal liver and hypothalamus.

Excluded by Requester — Oregon Health and Science University

Contrast Ultrasound Assessment of Microvascular Function in Insulin-Resistant Non-Human Primates

NIH/NIDDK R01 DK063508

This proposal will study the temporal relation between the development of insulin-resistance and skeletal muscle capillary responses to insulin and exercise in a non-human primate model of insulin resistance produced by high fat diet and activity restriction in adult rhesus macaques.

Excluded by Requester — Oregon Health and Science University
Molecular Imaging of Inflammation in Atherosclerosis
NIH/NIHL R01-HL0787610
The purpose of this study is to determine whether contrast-enhanced ultrasound (CEU) can detect the earliest stages of artherosclerosis, and then to determine whether targeted CEU can detect early vascular disease in a non-human primate (macaque) model of obesity, insulin resistance, and artherosclerosis that closely resembles the human condition.

Exclu ded by Requester — Oregon Health and Science University
NCI/Children's Oncology Group ADVL0712
A phase-I/II study of IMC-A12 (anti-IGF-I receptor monoclonal antibody) in children with relapsed/refractory solid tumors
The goal of this study was to evaluate dose and safety margins for treatment with a therapeutic anti-IGF-IR antibody.

Excluded by Requester — Oregon Health and Science University
Role of Placental Insufficiency in Preeclampsia, IUGR, and Fetal Programming of Hypertension
R21 HD068896
Our novel approach uses a genetically engineered mouse model and an innovative new microbubble technology to test whether abnormal uteroplacental blood flow may be an underlying cause of preeclampsia and fetal growth restriction, which are common and life-threatening complications of pregnancy, and whether increasing VEGF expression in uterine spiral arteries ameliorates or exacerbates these conditions.

Excluded by Requester **PhD** — SUNY Buffalo
(PI sub) — Oregon National Primate Research Center
Maternal Hyperinsulinemia and fetal programming
NIH/NIDDK R01 DK061518
The purpose of this study is to elucidate the relationship between maternal health and diet on the development of the melanocortin system in the rat.

Excluded by Requester — Vanderbilt University
(PI sub) — Oregon National Primate Research Center
PI sub) — Oregon National Primate Research Center
Molecular Mechanisms of Human and Murine Beta Cell Proliferation and Regeneration
NIH/NIDDK U01 DK089572
This project will test the overall hypothesis that key genes and/or environmental stimuli which promote rodent β-cell proliferation can similarly induce the proliferation or regeneration of human or non-human primate (NHP) β-cells.

Excluded by Requester — Xeris Pharmaceuticals
Private Source
Non-Aqueous Glucagon to Enable Outpatient Studies with a Bi-Hormonal Pump
The goal of this project is to assess the suitability of novel glucagon formulations for therapeutic use in an artificial pancreas.

Excluded by Requester **(MPI)** — Oregon National Primate Research Center
Oregon National Primate Research Center
NIH/NIDDK R24 DK093437
Molecular Mechanisms Underlying NHP Pancreatic Beta Cell Failure, and Recovery
This project will generate preliminary data on the transcriptional profile of non-human primate islets in preparation for a full R24 proposal.

Excluded by Requester
Oregon National Primate Research Center
Private Source
Control of glucagon secretion by native and DPP-4-processed GLP-1
The goal of this project is to evaluate the effects of DPP-4 inhibition on glucagon secretion in intact islets and in isolated alpha cells.

Excluded by Requester
Oregon National Primate Research Center
Private Source
Alogliptin effects on pancreatic islet function
The goal of this project was to assess the effects of a DPP-4 inhibitor on isolated islet function and response to incretin hormones.

Excluded by Requester
Oregon Health and Science University
Oregon National Primate Research Center
ONPRC Pilot research grant
Ex vivo culture of primate islets
The goal of this project was to investigate the effects of oxygen tension and culture conditions on primate islet viability and function.

Excluded by Requester
Oregon Health and Science University
Oregon National Primate Research Center
NIH/NCRR P51 RR000163-50S4
High-fat diet-induced alterations in gene expression in the nonhuman primate
The goal of this project was to determine hypothalamic gene expression profiles and changes in the CSF proteome in monkeys subjected to a controlled high-fat diet.

Excluded by Requester
Oregon National Primate Research Center
Herstatin: a novel cancer therapeutic
Pilot research grant, OHSU BioScience Innovation Program
The goal of this project was the development of a novel HER-2 gene product as a cancer therapy

Excluded by Requester
Oregon National Primate Research Center
Control of Gonadotropin Secretion during Lactation
NIH/NICHD R01 HD014643
These studies focus on states of negative energy balance that are associated with a suppression of reproductive function and will identify mechanisms by which a decrease in kisspeptin tone coupled with increased inhibitory input to GnRH cell bodies results in a decrease in GnRH neuronal excitability.

Excluded by Requester
Oregon National Primate Research Center
Control of Gonadotropin Secretion during Lactation Supplement (American Recovery & Reinvestment Act).
NIH/NICHD R01 HD014643-26S1
The goal of this administrative supplement is to create and staff a fully functional electrophysiology setup in the lab, enabling us to complete and expand Specific Aim 1 of the parent grant--determine the direct effects of various neuropeptides related to regulation of energy homeostasis (NPY, orexin, MCH, NKB) on GnRH neurons, using electrophysiology and the GnRH GFP rat.

Excluded by Requester
Oregon National Primate Research Center
A nonhuman primate model for the link between childhood asthma and obesity
NIH/NHLBI R21 HL094922
To determine the mechanism by which childhood obesity leads to asthma in order to assist in developing new strategies to decrease the incidence of childhood asthma.

Excluded by Requester

Oregon National Primate Research Center

NIH/NHLBI R01 HL087710.

Effect of Fetal Nicotine Exposure on Primate Lung

The purpose of this project is to characterize the mechanisms underlying the effects of prenatal nicotine on lung development and develop therapies to block those effects.

Excluded by Requester

Oregon National Primate Research Center

Perinatal Dietary Correlates of Autism Spectrum Disorder

Private Source

We hypothesize that exposure to a high fat diet (HFD) and maternal obesity during development impacts brain development, increasing the risk of the offspring developing autism, and we utilize a nonhuman primate model of HFD-induced maternal obesity to investigate the influence of maternal diet on offspring behavior.

Excluded by Requester

Oregon National Primate Research Center

Oregon Clinical Translational Research Institute (OCTRI) Pilot Project Grant. Project 5: Perinatal Dietary Predictors of Childhood Behavioral Problems and Temperament

NIH/NCRR 5 UL1 RR24140-05

Mental and physical health problems are related to early temperament. An important example is attention-deficit/hyperactivity disorder (ADHD), which is strongly related to temperament and exacts a heavy toll on children and families, yet has poorly understood etiology, therefore, identifying the early precursors and causal mechanisms for this behavioral problem is of central importance to eventual public health prevention.

Excluded by Requester

Oregon National Primate Research Center

Private Source

The Consequences of Maternal Obesity and High Fat Diet Consumption on Offspring Energy Balance Regulation: *An Emphasis on the Serotonin System*

This grant provides funding for supplies to being the initial examination of the impact of maternal high fat diet consumption on the development of the central serotonin system in fetal and juvenile nonhuman primates.

Excluded by Requester

Oregon Health and Science University

The Impact of Maternal Health and Diet on Development of Fetal Metabolic Systems

NIH/NIDDK R24 DK090964

This grant examines the impact of maternal obesity and high fat diet (HFD) during pregnancy on the development of metabolic systems (pancreas, liver and muscle) in fetal and juvenile offspring.

Excluded by Requester

Oregon Health and Science University

PI of sub) Oregon National Primate Research Center

Maternofetal Signaling & Lifelong Consequences. Project 1: Gestational diabetes leads to cardiovascular vulnerability in offspring.

NIH/NICHD P01 HD34430

This is a project within a program project grant involving a nonhuman primate model of maternal diet induced obesity and insulin resistance/diabetes to determine: 1) if the pathological changes in fetal and infant cardiovascular system and placenta are related to the severity of maternal metabolic status; 2) the degree to which maternal metabolic status influences fetal and infant cardiovascular function, and 3) if infants of diabetic mothers have abnormal blood viscosity, erythrocyte rheology and leukocyte behavior that lead to abnormal microvascular function.

Excluded by Requester

Legacy Health & Research

In vitro and In vivo efficacy of aged native glucagon; lack of cytotoxicity and preservation of hyperglycemic effect

Private Source

The goal of this project is to assess the stability and biological efficacy of glucagon formulations for clinical use in an artificial pancreas.

RESOURCES

Follow the 398 application instructions in Part I, 4.7 Resources.

Division of Diabetes, Obesity, and Metabolism:

Laboratory:

The Faculty and Staff for the Division of Diabetes, Obesity, and Metabolism are housed within the ONPRC [Facility Security] Within this building, there is currently over 16,000 sq. ft. of office space and 4,400 sq. ft. of total laboratory space. Within the [Facility Security] is a large open lab space of 2,000 sq. ft. that is shared by PIs [Excluded by Requester] This space has been recently renovated for their purpose. This space includes a large open generalized space with 8 work-benches, 3 fume hoods, a shared chemical cabinet, and 2 shared flammable cabinets. This lab is well equipped with all of the tools for performing molecular, cellular, and histological procedures. In addition, there are separate rooms for a shared cell culture hood (with two biological incubators), a shared microscope room (with two bright field/fluorescence scopes, each with digital cameras connected to computers), and a room with electrophysiology equipment (used by Dr. [Excluded by Requester] a staff scientist in [Excluded by] group). This laboratory is also equipped with a water filtration system that is shared by all Division laboratories. Finally, there are eight -80° C freezers and several -20°C freezers and refrigerators that are shared among these investigators.

[Excluded by Requester] has a neighboring laboratory that is over 700 sq. ft. This laboratory is equipped with 4 workbenches, a fume hood, chemical and flammable safety cabinets. This laboratory also has a new cell culture hood and 2 incubators. His laboratory also has the necessary refrigerators and freezers, as well as other general equipment. Finally, there is a shared chemiluminescence gel doc station and a florescence micro-plate reader located in this laboratory.

There is a third laboratory space available on the same floor that occupies approximately 400 sq. ft. This laboratory is currently vacant and will be remodeled for the next recruitment to the Division. As mentioned above, the funds to renovate this space are proposed as part the $125 million gift from the [Private Source] for the development of a Cardiovascular Research Institute. This complete renovation and modernization would also result in addition laboratory space that would be available for additional recruits.

On the same floor as the laboratories are several shared laboratory spaces: 1) There is a 300 sq. ft. space that houses shared equipment, including the ABI real-time PCR machine, a large liquid nitrogen tissue/cell storage tank, and shared refrigerators and freezers with supplies; 2) A 115 sq. ft. dark room with automated developer system and light-sealed cabinets; 3) There is a 385 sq. ft. dedicated radioactivity room. This room is used by all laboratories for any experiment using radioisotopes, including in situ hybridization for P^{33}-labeled riboprobes, as well as labeled glucose or fatty acids for tissue/cell uptake studies; 4) The Obese Resource also has a 385 sq. ft. tissue and blood sample-processing laboratory. This space is used by all of the laboratories as a site for the primary processing of tissue and blood samples. This room has a couple of different types of centrifuges for this purpose. The value of this space is that it limits exposure of the main laboratories to NHP biological waste; and 5) There is a 90 sq. ft. small animal procedure room, which has the appropriate environmental and light controllers for housing rodents for short periods of time.

Below is a summary of some specialized equipment shared by Division investigators.

1) COBE 2991 Cell Processor – this is a tissue centrifuge for the processing of isolated islets. Dr. [Excluded by Request] laboratory has become a National resource for the supply of NHP pancreatic islets.
2) 3-Dimensional Cell Culture – [Excluded by] has a cell culture incubator with a revolving chamber. This equipment is especially important for pancreatic islet cultures, as it allows for the retention of natural 3-D shape of the islets.
3) Metabolic chambers for NHPs– [Excluded by Requester] group has 3 indirect calorimetry chambers for measuring metabolic rate, as well as resting quotient (for determine carbohydrate or fat metabolism) in NHPs. This includes a custom built extra-large cage for adult obese animals.
4) CLAMS – [Excluded by Requester] also has a Comprehensive Lab Animal Monitoring System (CLAMS, Columbus Instruments) for monitoring food intake and energy expenditure in rodents. This is one of the few groups in the world that have a full metabolic phenotyping facility for both rodents and NHPs.

5) Automated feeding system – Excluded by Requester group has an automated feeding system with microchip reader that allows for the measurement of food intake and food preference in group-housed animals. With this system, microchips are placed into the hands of the NHPs and when they pull the lever for a food pellet, it electronically records that animal's number.
6) Video scoring systems – Excluded by Requester each have extensive video monitoring and behavior scoring equipment.
7) Olympus Slide Scanner – Excluded by Requester (Pathologist from DCM) have shared the purchase of a slide scanner that allows for the high-resolution scanning of histological and histochemistry slides, including for fluorescence. This scanning equipment is especially important for the large format slides needed for histochemical analysis of NHP tissues (brain, pancreas, etc). This equipment is also coupled to an imaging software system that allows for the stereological analysis of the tissues. This equipment also allows for the archiving and sharing of digital images with colleagues.
8) Electrophsyiology – Excluded by Requester have an extensive electrophysiology set up for performing electrical recordings in the brain and pancreas of both rodents and NHPs.

Clinical:
N/A

Animal:
All approved animal protocols and procedures are performed within procedure space under the management of the Division of Comparative Medicine (DCM), which is directed by Excluded by Requester This includes small animal space in the basement of the Specific Animal Location as well as the numerous NHP buildings. The Animal Care and Use program at ONPRC is fully accredited by the American Association for Accreditation of Laboratory Animals Care (AAALAC) and supervised by a group of highly experienced and qualified veterinarians certified by the American College of Laboratory Animal Medicine (ACLAM). A full description of the extensive NHP and small animal facilities and support staff is provided elsewhere. However, there are several animal resources and facilities that are especially important to the success of investigators in this Division.

1) Specific Animal Location provides 10 indoor/outdoor small group housing that is used as a breeding facility for Japanese macaques that are maintained either on a standard chow diet or a Western style diet. Each of these groups contains 10-12 animals and provides important offspring for several grants from Division faculty, as well as investigators at other Universities. Currently, there are a total of 71 breeding females in this groups (of various treatments) that provide approximately 35 pregnancies per year. The long-term maintenance of this resource is dependent on careful planning of the larger Japanese macaque Resource that is housed in the outdoor corral. These animals are also maintained by the Obese NHP Resource.
2) Specific Animal Location for the purpose of studying the behavior of group-housed juveniles (produced from the above Japanese macaque breeding facility), there are two dedicated group housing rooms fitted with automated feedings systems and cameras. These rooms allow our investigators to monitor various types of social and feeding behavior of juvenile animals. In addition, ONPRC has started construction on two new group-behavioral suites that will be fitted with these same automated feeding systems and viewing cameras. The advantage of these new behavioral suites is that they will have one-way glass along one wall that will allow better visual advantage for taping and observing animal behaviors.

Obese NHP Resource – In addition to the Japanese macaques mentioned above, the Obese NHP Resource houses 65 adult rhesus and 32 adult cynomolgus macaques maintained chronically on a high-fat Western style diet. These animals are maintained in individual and paired housing (depending on the experimental need) in the Specific Animal Location This allows close proximity to the surgical suites, imaging equipment, as well as the metabolic phenotyping equipment. These animals are an essential component to the long-term success of investigators in our Division.

Computer:
Each investigator has their own computers, connected to the internet, and access to shared color printers and copy machines. Furthermore, the Research Building has wireless internet available throughout the building.

Research staff (Research Associates and Assistants) has access to shared desks and computers within the laboratories.

Office:

Excluded by Requester each have individual offices within the Facility Security Building, and Excluded by Requester has an office in the Facility Security Building. There is additional office space available for new investigators being recruited in the coming years. The other Division staff scientists, postdoctoral/clinical fellows, and graduate students have desks in shared office space. The Divisional administrative coordinator has a small individual office, with a computer and printer/copier, next to the Division Chief's office.

Division faculty have access to two conference rooms within the Research Building; a small conference room with a video projector that can comfortably house up to 10 people, and a large conference room with dual video projectors and electronic white board. This large conference room holds 40 plus people and is used for the weekly Division meeting and Journal club. There are also additional conference rooms of various sizes in the Cooley, VGTI/ONPRC, and Administration Buildings that are also available to faculty members.

Other:

Our Division investigators use most of the ONPRC Research Support Cores, including the Molecular and Cell Biology Core, Imaging and Morphology Core (Directed by Excluded by Requester Endocrine Technology core, Flow Cytometry core, Molecular Virology Core, and MRI Core. These are more completely in the Core Science Services section.

NARRATIVE: Excluded by Requester

Division Appointment: Associate Scientist, Division of Diabetes, Obesity, and Metabolism (DOM)
Appointment(s): % Effort,Excluded by Requester n Obstetrics & Gynecology, OHSU and a joint appointment at the ONPRC.
Effort on NHP-related studies: % Effort

Research Overview: Excluded by Requester specializes in using advanced imaging of the placenta to understand factors that affect placental development and nutrient transport. A specific focus is the impact of maternal nutrition and obesity on placental function, reproductive outcomes, and fetal programming in our NHP of excess nutrition during pregnancy. Adverse obstetric outcomes attributed to both obesity and diabetes in humans are confounded by an inability to separate the contributions of maternal diet. Excluded by Requester esearch resulted in the first report of placental hemodynamic abnormalities in a primate placenta that are secondary to a high fat diet, suggesting that a Western style diet may have an independent impact on the adverse obstetric and neonatal consequences reported in the obese human population. Because the placenta regulates nutrient flow from mother to fetus, it likely occupies a central role in mediating the adverse obstetric/neonatal risks associated obese and/or diabetic pregnancies. Current assessments of placental function (clinical and research) are limited by an inability to link *in vivo* placental perfusion with functional outcomes, such as histopathology and nutrient transport. Excluded by and collaborators have developed a novel dynamic contrast enhanced-MRI (DCE-MRI) protocol that quantifies placental blood flow creating a placental perfusion map that can be correlated with placental histopathology and nutrient transport. These novel studies will set the framework for understanding how the placenta develops and adapts to adverse conditions and will lead to future studies of blood flow on nutrient transfer, and perhaps improved imaging techniques to identify placental dysfunction in humans. Another area of focus is the use of advanced imaging including ultrasound, contrast-enhanced ultrasound, and MRI to investigate placental/fetal development in other NHP models of placental dysfunction, including chronic exposure to nicotine and intraamniotic infection. Excluded by Requester research has been recognized through invited presentations at national and international meetings and awards of research excellence.

Contribution to Mission: Excluded by Requester has been working with NHPs since 2007 as a WRHR scholar under Dr. Excluded by Request mentorship and became an associate scientist in 2013. Excluded by Requester directs the placental biology group of the NHP Obese Resource responsible for designing and executing both the *in vivo* and *in vitro* studies of placental function in this important model. Given the central focus of the placenta on fetal nutrient transport, Dr. Frias collaborates with scientists and clinicians at OHSU from the divisions of pathology, cardiology, endocrinology, the Heart Research Institute, and the Advanced Imaging Research Center. As the primary ultrasound diagnostic imager based at the ONPRC, Excluded by also supports the NHP work at ONPRC by providing imaging capabilities to scientists in DRDS and the Division of Neuroscience. Excluded by Requeste is one of the founding members of the new ONPRC division called the Division of Diabetes, Obesity, & Metabolism. As a Maternal Fetal Medicine (MFM) subspecialist and Director of the Diabetes and Pregnancy Program at OHSU, Excluded by Request is actively involved in providing clinical care for pregnant mothers with diabetes and obesity. This clinical care involves the development and implementation of institutional guidelines for the management of diabetes and nutrition during pregnancy. As a clinician-investigator, Excluded by Requester is poised to translate insights from the NHP into clinical studies; as well as provide mentorship to young clinician-investigators embarking on an academic career. Excluded by Requester s actively involved in training programs at OHSU. He teaches medical students, obstetric residents, and MFM fellows. In the past three years, he has mentored or co-mentored two fellows and three residents for their required research projects. Excluded by Requester also serves on the OHSU IRB. He is a reviewer for OHSU clinical research grants funded by the Center for Women's Health Circle of Giving and the Moore Institute for Nutrition and Wellness. Out of 10 collaborations, major examples are listed below:

Name	Affiliation	Description
Excluded by Requester	ONPRC	The effects of nicotine on placental growth and fetal cardiovascular development
	ONPRC,OHSU,AIRC	The use of DCE-MRI to quantify uteroplacental blood flow
	Private Source	The role of liver and visceral fat in glucose and lipid metabolism during pregnancy

NARRATIVE: Excluded by Requester

Division Appointment: Interim Division Chief and Senior Scientist, Div. of Diabetes, Obesity, and Metabolism
Appointment(s): % Effort Excluded by Requester at the ONPRC.
Effort on NHP-related studies: % Effort

Research Overview: Excluded by Requester specializes in the development of metabolic systems. More specifically, his group is focused on the impact of poor maternal metabolic health and diet on the development of metabolic systems. The primary concept is that abnormalities in the development of these systems will predispose the offspring to a wide variety of health complications later in life. Furthermore, we have been investigating different dietary and nutritional interventions that may reverse or prevent the development of health complications in the offspring. As a parallel to these developmental programming studies is the investigation of metabolic adaptations in females in different reproductive states, including during the menstrual cycle, pregnancy, and lactation. These studies are part of a long and highly productive collaboration with Excluded by Requester. More recently, we have established a consortium with members of the Division of Reproductive & Developmental Sciences to investigate the combined effect of mild hyperandrogenemia and chronic Western style diet consumption on the development of polycystic ovarian syndrome (PCOS)-like symptoms.

Another area of focus is the treatment of metabolic diseases: 1) We have developed a Roux-en-Y Gastric Bypass (RYGB) model in the obese and diabetic Rhesus macaque. The primary goal of these studies it to understand how RYGB can diabetes remission. 2) We have also developed a NHP model of diet-induced obesity (DIO) to investigate pharmacotherapies for the treatment of obesity, diabetes, and cardiovascular disease. These models are also used in multi-PI research consortiums.

Contribution to Mission: Related to the Division of Diabetes, Obesity, and Metabolism: Excluded by Requester became a core scientist in the Division of Neuroscience in 2003. During his tenure at ONPRC, Excluded by Requester has worked extensively in both rodent and NHP models to investigate the development and regulation of metabolic systems and how they contribute to the pathogenesis of metabolic diseases. More specifically, he has developed several novel NHP models that are used broadly by the research community, including investigators at 10 different universities. His group has 30 peer-reviewed manuscripts (out of a total of 36) since 2009 focused on broad areas of metabolic disease using NHPs; and has given 32 invited presentations on the topic. In the past 4 years Excluded by Requester has obtained $14.25 million in research funding (total cost). In recognition of the success of this program, and because OHSU has identified metabolic diseases as an key area of focus, ONPRC recently established a new scientific division called the Division of Diabetes, Obesity, & Metabolism. Excluded by Requester is serving as the founding and Interim Division Chief until a formal open search can be performed for a permanent Division Chief. Excluded by Requester will compete for that open position.

Excluded by Requester is actively involved in training programs at OHSU, for graduate students, postdoctoral fellows and young faculty. In the past three years, he has mentored four graduate students that have successfully defended their Ph.D. thesis; three of which had projects related to metabolic systems. He has several postdoctoral fellows, including three that have recently advanced to independent positions. Excluded by Requester serves as training faculty for 2 NIH-funded training grants: T32 HD07133, Pre- and Postdoctoral Multidisciplinary Training in Neuroendocrinology; and T32 NS07466, Training in Endocrinology, Diabetes, and Clinical Nutrition. Excluded by Requester also serves the mission through his service as an Editor and editorial board member for several journals, and through his involvement in in reviewing grants for NIH. Sample collaborations related to DOM:

Name	Affiliation	Description
Excluded by Requester	Private Source	Investigation of therapeutics for the treatment of diabetes and obesity in DIO NHP.
	Dept. Pediatrics, Univ. of Colorado at Denver	Determine the relative contribution of poor maternal health and diet on the development of metabolic systems in NHP.
	Metabolism Research Institute, Univ. Cincinnati	Investigation of the impact of RYGB on diabetes in the DIO macaque.
	Dpt. Cardiology, OHSU	Investigation of vascular inflammation and atherosclerosis in the obese NHP.

NARRATIVE: Excluded by Requester

Division Appointment: Senior Scientist, Division of Diabetes, Obesity and Metabolism
Appointment(s): % Effort,Excluded by Requester at the ONPRC, and a joint appointment as Professor of Medicine, Pediatrics and Cell and Developmental Biology, OHSU
Effort on NHP-related studies: % Effort

Research Overview: Excluded by Requester principal research focus is the action of the insulin/IGF signaling system in metabolic disease. His group has developed techniques for the isolation and analysis of function of NHP islets and adipose tissue, including the effects of incretin action. This expertise supports current studies on islet function, including analyses of incretin-based therapeutics, funded by the NIH and pharma, as well a number of pending NIH and pharma-funded projects. Excluded by studies of adipose function are the basis for pending NIH and pharma projects examining androgen and incretin action in NHP adipose explants using novel fluorescent imaging approaches. Previous expertise in cellular analyses of insulin and IGF action supports NIH and JDRF-funded research on the action of novel insulin and glucagon analogs and formulations for clinical use.

Contribution to Mission: Excluded by Requester is the Associate Director for Research and is responsible for: 1) oversight of externally funded research; 2) specific oversight of research involving for-profit entities; 3) interactions with the OHSU Technology Transfer and Business Development Office and their engagement with pharma entities interested in research at ONPRC; 4) liason with the OHSU Center for Diabetes and Obesity Research; 5) liason with the OHSU Foundation; 6) liason with OHSU clinical departments collaborating with ONPRC investigators; and 7) oversight of ONPRC research support cores. Out of >10 collaborations, examples include:

Name	Affiliation	Description
Excluded by Requester	Private Source	NIDDK-funded SBIR to analyze biochemistry and biological activity of novel insulin analogs for clinical use. This project includes studies on the effect of insulin analogs on nonhuman primate adipose tissue explants.
	ONPRC Private Source	NIDDK-funded R24 grant to assess the effects of gastric bypass surgery on metabolism in a nonhuman primate model.
	ONPRC Private Source	NIDDK-funded R24 seed grant to establish nonhuman primate model of islet biology.
		NIDDK-funded U grant to determine effect of mouse islet development genes on nonhuman primate islet biology.
	OHSU and Legacy Health Indiana U.	Private Source unded research project designing a stable, bioactive glucagon formulation for use in an artificial pancreas.
	OHSU (Surgery) OHSU (Pediatrics)	Analysis of immune cell function in human adipose tissue.
	OHSU (Oregon Stem Cell Center)	Generation of antibodies and aptamers for isolation of islet cell types.
	ONPRC	Effects of second-generation antipsychotics on central and peripheral insulin action.
	ONPRC ONPRC ONPRC/U. of Pittsburg	Effects of peripubertal androgen on female endocrine function.

NARRATIVE: Excluded by Requester

Division Appointment: Senior Scientist, Division of Diabetes, Obesity and Metabolism
Appointment(s): % Effort Excluded by Requester t the ONPRC.
Effort on NHP-related studies: % Effort

Research Overview: Excluded by Requester specializes in neuroendocrine regulation of energy balance and reproduction. One specific focus is on the mechanisms involved in the coupling of metabolic status with reproductive function. Excluded by research has resulted in key findings that challenge the current dogma that leptin is the primary signal involved in the metabolic gating of reproduction. New potential signals have been identified, such as CART, a key neuropeptide in the brain that regulates food intake and also has a stimulatory effect on neurons regulating reproduction. These studies are very relevant to humans and could lead to new treatments for restoring fertility or for new contraceptive agents that inhibit fertility. The other area of focus is the role of the maternal environment in development of the offspring, specifically as it relates to the risk of obesity and diabetes. Our NHP model of maternal obesity has resulted in highly important findings relevant to human health. Eating a diet high in fat during pregnancy has long lasting effects on the offspring that likely increase its propensity to develop obesity, diabetes and behavioral abnormalities. This NHP model is being used to examine possible therapeutic interventions during pregnancy that can prevent or reduce the risks of these developmental abnormalities. Excluded by Requester research has been recognized through invited presentations at national and international meetings, service on editorial boards and NIH study sections, and leadership in professional societies (Past President of The Endocrine Society).

Contribution to Mission: Excluded by Requester served as the Director of the ONPRC from 1994-2007 and was responsible for the merger of ONPRC with OHSU. This merger opened up significant research and educational opportunities for ONPRC scientists. Excluded by worked with OHSU to bring the most up-to-date- technologies to the center, including DNA microarray, MRI, bioinformatics and genetics expertise. Excluded by Requester also played a key role in forging new collaborative research programs with scientists at OHSU, such as in advanced imaging, addiction, cardiovascular disease, fetal-maternal medicine, metabolic diseases, stroke and stem cell technologies. Excluded by worked with Excluded by Requester to develop the NHP model of maternal obesity and diabetes. This model is now extremely well funded and is the focus of many collaborative research efforts with scientists at OHSU and throughout the USA. It was also instrumental in the development of the NHP Obese Resource that has provided unique research opportunities for many scientists and pharmaceutical companies.

Excluded by Requester is actively involved in training programs at OHSU and participates in teaching graduate level seminar courses, mentoring graduate students and new clinical faculty, and serving on thesis committees. She serves on the training faculty for 6 NIH-funded training grants: Pre- and Postdoctoral Multidisciplinary Training in Reproductive Biology, T32 HD07133; Pre- and Postdoctoral Multidisciplinary Training in Neuroendocrinology, T32 DK07680; Multidisciplinary Training in Neuroscience, T32 NS07466; Training in Endocrinology, Diabetes, and Clinical Nutrition, T32 DK007674; Oregon Child Health Research Center, K12HD033703; and Building Interdisciplinary Research Careers in Women's Health, K12 HD043488.

Excluded by Requester serves on the OHSU Foundation Board of Trustees. As one of the only active faculty members on the Board, she is in a unique position to inform the lay Board members about research at OHSU, and particularly at the ONPRC. This is particularly important in providing support for translational research in which the NHP is a critical proof of concept step in the process toward developing new biotechnology companies or starting new clinical trials. Under the umbrella of the OHSU Foundation Board, Excluded by Requester chairs the Medical Research Foundation of Oregon Research and Education Committee; this Committee awards up to $1 million in research grants per year to Oregon researchers and presents major awards at its annual awards reception.

NARRATIVE: Excluded by Requester

Division Appointment: Assistant Scientist, Division of Diabetes, Obesity, & Metabolism
Appointment(s): % Effort Excluded by Requester as an Assistant Professor in the Department of Biology at the University of Portland, and a % Effort as an Assistant Scientist at the ONPRC.
Effort on NHP-related studies: % Effort

Research Overview: Excluded by Requester specializes in behavioral neuroscience with specific training and expertise in nonhuman primate behavior. A primary focus of the Excluded by Request laboratory is examining the influence of metabolic and dietary environment on behavioral regulation with an emphasis on behaviors that relate to human mental health and behavioral disorders including anxiety, depression, attention deficit hyperactivity disorder, and autism spectrum disorders. Furthermore, Excluded by has expertise in whole animal physiology and measurement of energy balance regulation, feeding behavior and food preference. One specific focus is the impact that exposure to maternal obesity and high fat diet consumption during the perinatal period has on the behavior and physiology of the developing offspring. Key finding of this research to date include an increased risk for anxiety in female offspring and deficits in social behavior in both male and female offspring exposed to maternal high fat diet consumption and obesity. Excluded by has demonstrated a suppression of the central serotonin system in offspring exposed to maternal obesity and high fat diet consumption, which likely contributes to the behavioral dysregulation observed in the high fat diet offspring. The working hypothesis is that maternal high fat diet consumption and obesity result in the developing offspring being exposed to increases in circulating inflammatory cytokines. This leads to neural inflammation in the fetus, which modulates the development of neural circuitry regulating physiology and behavior such as the serotonergic, melanocortinergic, and dopaminergic systems. As the majority of women of childbearing age consume a high fat diet and one third are of pregnant women are obese, these studies are fundamental to understanding and identifying behavioral disorders that result from exposure to maternal obesity and HFD consumption.

In order to directly translate her finding in the nonhuman primate model, Excluded by Requester has initiated a translation study to examine the impact of maternal diet on infant temperament in humans. In collaboration with Excluded by Requester from OHSU, the Excluded by Request laboratory examines the temperament of infant children from parents diagnosed with ADHD. The relationship between the behavioral data and information on maternal diet during pregnancy, cord blood, and placenta are being examined. Together these studies will further our understanding of how maternal energy status and pre- and early- postnatal nutrition influence susceptibility to obesity and behavioral disorders such as anxiety, depression, attention deficit hyperactivity disorder, and autism spectrum disorders. Excluded by research has been recognized through invited presentations at national and international meetings, serving as a reviewer for a number of scientific publications, and being invited to be part of the National Institute of Health Developmental Biology Subcommittee.

Contribution to Mission: Excluded by has been working with NHP at the ONPRC since 2002. She began as a graduate student with Excluded by Requester examining factors that contribute to individual differences in body weight gain in female nonhuman primates, and then a post-doc fellow and staff scientist under Excluded by Requester mentorship. Excluded by became an Assistant Professor at the Univ. of Portland and an Adjunct Assistant Scientist at ONPRC in 2011. She became a Core Scientist at ONPRC in 2013. Excluded by is actively involved in training future scientists through her teaching and mentoring of University of Portland undergraduate students. Since 2011, Excluded by Requester has mentored 14 students and a post-doctoral fellow. In addition, she has participates in teaching graduate level courses, judging student research presentations at OHSU Research Week, and serving on thesis committees. Out of five collaborations, major examples are listed below:

Name	Affiliation	Description
Excluded by Requester	ONRPC	Maternal High Fat Diet and Melanocortin System in Offspring
	OHSU	Perinatal Dietary Predictors of Childhood Behavioral Problems and Temperament
	Oregon State University	Examining Perinatal Dietary Predictors of Childhood Behavioral Problems and Temperament

Program Director/Principal Investigator (Last, First, Middle): Robertson, Joseph E./Haigwood, Nancy L.

DIVISION OF METABOLIC DISEASES DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*

Use Cal, Acad, or Summer to Enter Months Devoted to Project

Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Excluded by Requester	Interim Div Chief/Sr. Scie	% Effort			Institutional Base Salary	53,910	13,478	67,388
	Asst Scientist					4,493	1,123	5,616
	Admin Coord					8,745	2,711	11,455
	Sr. Scientist					8,985	2,246	11,231
	Sr. Scientist					8,985	2,246	11,230
	Asst Scientist					1,988	616	2,604
To Be Named	Asst Scientist	1.20				10,070	2,518	12,588
To Be Named	Admin Coord	1.80				7,950	2,783	10,733
To Be Named	Sr. Scientist	1.20				16,000	4,000	20,000
	→							
	SUBTOTALS					121,125	31,721	152,845

CONSULTANT COSTS		
None Requested	0	0
EQUIPMENT *(Itemize)*		
None Requested	0	0
SUPPLIES *(Itemize by category)*		
Office & Admin Supplies	159	
		159
TRAVEL		
None Requested	0	0
INPATIENT CARE COSTS		0
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		
None Requested	0	0
OTHER EXPENSES *(Itemize by category)*		
Maintenance - Equipment	150	
Biohazard Waste Disposal	150	
		300
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 153,304
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 153,304

DIVISION OF METABOLIC DISEASES
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	152,845	157,431	162,153	167,018	172,029
CONSULTANT COSTS	0	0	0	0	0
EQUIPMENT	0	0	0	0	0
SUPPLIES	159	164	169	174	179
TRAVEL	0	0	0	0	0
INPATIENTS CARE COSTS	0	0	0	0	0
OUTPATIENTS CARE COSTS	0	0	0	0	0
ALTERATIONS AND RENOVATIONS	0	0	0	0	0
OTHER EXPENSES	300	309	318	328	338
DIRECT CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	153,304	157,903	162,640	167,520	172,545
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	153,304	157,903	162,640	167,520	172,545
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					813,913

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

BUDGET JUSTIFICATION

Interim Division Chief, Senior Scientist - Excluded by Requester % Effort Program Income). Excluded by Requester is highly recognized in the field of obesity and diabetes, and is an expert in NHP metabolic physiology and the principal architect of the NHP model of diet-induced obesity and pre-diabetes. Dr. Excluded by Requester s expected to continue to maintain his NHP program and to participate in Division and ONPRC-wide activities (e.g., weekly seminars, Division and Center meetings, journal club). As Interim Division Chief, Dr. Exclude d by Re will ensure that Division investigators have the necessary access to NHP and core support facilities. He will also participate in the Expanded Executive Leadership Committee, and ensure that this information is made accessible to the Division scientists, and will represent the Division views within the committee.

Assistant Scientist - Excluded by Requester % Effort,Excluded by Requester has a % Effort appointment within this Division and a joint appointment with the Division of Reproductive & Developmental Sciences % Effort appointment in the Department of Obstetrics/Gynecology at OHSU. Within this Division, Excluded by Request is expected to continue to develop his independently funded research program; which uses the diet induced obese NHP model to investigate the impact of maternal diet and health on placental function. He is also expected to participate in all Division and ONPRC activities (e.g., weekly seminars, Division and Center meetings, journal club). In addition, Excluded by has been tasked with mentoring clinical fellows or junior faculty that are working on projects at ONPRC

Administrative Coordinator – Excluded by Requester % Effort Responsible for providing administrative services to the scientists in the Division of Metabolism and will assist with the preparation of grant applications and progress reports and provide the scientists with basic office support.

Associate Director, Senior Scientist - Excluded by Requester % Effort Income). Excluded by has a joint appointment with the Division of Reproductive & Developmental Sciences, as well as being a member of the Administrative team. Within the Division, Excluded by Requester is expected to continue his strong funding history, related to his work investigating the function of isolated pancreatic islets and adipose tissue in the diet induced obese NHP model. He is also expected to continue his participation in Division and ONPRC-wide activities (e.g., weekly seminars, Division and Center meetings, journal club).

Senior Scientist - M Excluded by Requester % Effort,Excluded by Requester Excluded by Re uester has a % Effort appointment as a core scientist. She is expected to continue her long-stand funding, as well as participating in Division and ONPRC-wide activities (i.e., weekly seminars, Division and Center meetings, journal club). Excluded by Re uester will continue to direct the Division journal club, which trains young investigators at all levels to critical evaluate research literature. She is a member of the OHSU Foundation board where she advocates for philanthropic contributions to ONPRC. Excluded by Requester will also continue to be the Divisions representative to the IACUC committee. As Excluded by Re uester has indicated the possibility of retiring within the next two years, this position would be filled through a recruitment of an assistant/associate level scientist (see Research Strategies).

Assistant Scientist - % Effort,Excluded by Requester % Effort,Excluded by Requester Core appointment in this Division. Excluded by Requester has a teaching position at the University of Portland, but all of her research will be conducted through ONPRC. Within this Division, she will be expected to continue to develop her independent research program focused on the impact of poor maternal health and diet on the development of psychological disorders (i.e., Autism), which exclusively utilizes NHPs. She is also expected to participate in all Division and ONPRC activities (e.g., weekly seminars, Division and Center meetings, journal club).

Assistant/Associate Scientist - To Be Named (4.8 calendar months effort, 1.2 ORIP, 3.6 Program Income). This investigator would constitute a new recruitment to the department. This investigator would be expected to develop and/or maintain a research program utilizing NHPs. Our Division has identified two potential areas of recruitment for either the assistant/associate scientist level (outlined in the Research Strategy), including

adipose/lipid biology and immunology/inflammation. This investigator would also be expected to participate in all Division and ONPRC activities (e.g., weekly seminars, Division and Center meetings, journal club). Recruitment funds for this Scientist would come from Senior Vice President for Research.

Administrative Coordinator – To Be Named (6 calendar months effort: 1.8 ORIP, 4.2 Program Income) This position provides administrative services to the scientists in the Division of Met and will assist with the preparation of grant applications and progress reports and provide the scientists with basic office support. In addition, this position serves had the Division Chief's main administrative coordinator providing assistance with matters on the Division level.

Senior Scientist – To Be Named: (4.8 calendar months effort, 1.2 ORIP, 3.6 Program Income). This investigator would constitute a new recruit with a research program focused on cardiovascular research. This position would be recruited in conjunction with the Private Source Cardiovascular Institute and would be expected to develop a program, using NHPs, focused on some aspect of cardiovascular disease. This investigator would also be expected to participate in all Division and ONPRC activities (e.g., weekly seminars, Division and Center meetings, journal club). Furthermore, because this would be a senior investigator, we would expect this faculty member to participate in mentoring of young faculty and students/fellows at ONPRC. We also expect this investigator to participate in various committees, such as IACUC and/or the Obese Resource oversight committee.

SUPPLIES

Office & Admin Supplies: Funds are requested for general office and administrative supplies, including paper and supplies for printers and copiers for the Division Chief, Core Division scientists, and Division Administrative Coordinator.

OTHER EXPENSES

Maintenance – Equipment: Funds are requested to pay for the maintenance contracts on large shared equipment for the Division. Examples of the equipment include the qPCR machine and the Olympus Slide scanner, each of which are used by several Division investigators. These costs cannot be covered by NIH grants.

Biohazard Waste Disposal: These funds would be used to pay for disposal of biological and chemical waste generated by the division laboratories that cannot be practically attributed to specific grants. Charges are per the standard OHSU Radiation Safety schedule.

Division of Metabolic Diseases Administration Income Table

Last Funded Year (53)

Source	Funding (direct costs)
P51 base grant support	$117,238.20
Program income derived from P51 base grant	82,599.68
Other Sources	0
Total	$199,837.88

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$153,304.15
Program income derived from P51 base grant	247,181.64
Other Sources	100,000.00
Total	$500,485.79

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

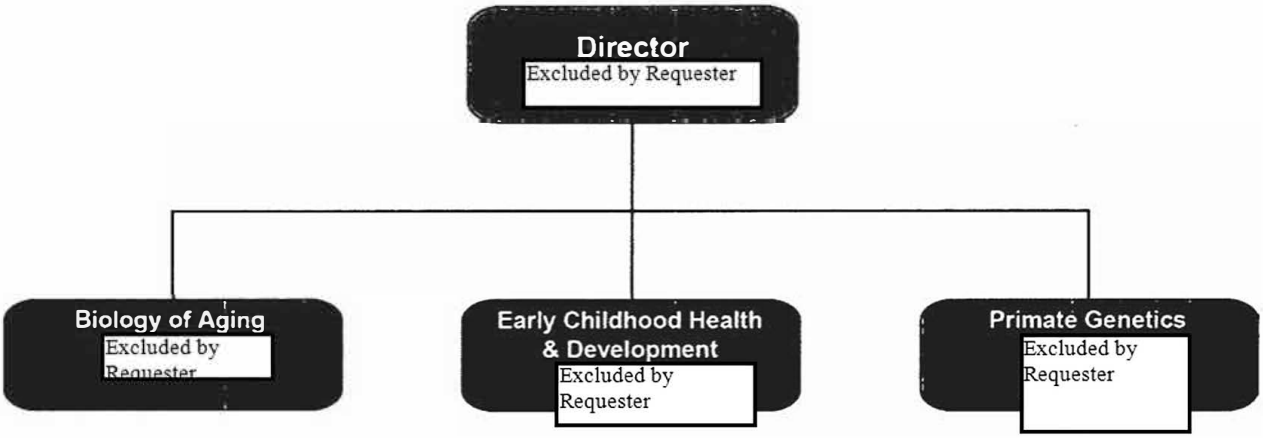
The Division of Metabolic Diseases Administration receives salary support and support for other expenditures from program income. Other sources represents recruitment funding from the VP for Research.

TITLE: INTERDISCIPLINARY RESEARCH PROGRAMS

PERSONNEL:

Personnel are not supported by the Interdisciplinary Research Programs.

INTERDISCIPLINARY RESEARCH PROGRAMS
Organizational Chart



INTERDISCIPLINARY RESEARCH PROGRAMS PERSONNEL AFFILIATION AND ROLE

FACULTY:

Core Scientists

Excluded by Requester	Senior Scientist
	Senior Scientist
	Associate Scientist
	Assistant Scientist
	Assistant Scientist
	Assistant Scientist

Affiliate Scientists

Excluded by Requester	Dept. of Physiology & Pharmacology, OHSU
	University of California, Riverside
	Division of Neuroscience, ONPRC
	University of Arizona
	Vaccine & Gene Therapy Institute, OHSU
	Dept. Molecular Microbiology and Immun., OHSU
	Dept. of Physiology & Pharmacology, OHSU
	Advanced Imaging Research Center, OHSU
	Dept. Molecular Microbiology and Immun., OHSU
	Div. Reproductive & Developmental Sciences, ONPRC

INTERDISCIPLINARY RESEARCH PROGRAMS (IDRP) - DESCRIPTION

During the last funding period, we established three Working Groups to foster areas that were represented in the existing Research Divisions and that had extensive opportunities for external collaborative work. These groups were the: (1) Biology of Aging; (2) Metabolic Diseases; and (3) Stem Cells and Developmental Biology. The Working groups were developed following the ONPRC Scientific Retreat in 2007 and the review by the National Scientific Advisory Board in 2008. The explicit goal of these programs was to explore and to expand research programs that fostered interdivisional and inter- and intra-institutional collaborations.

As expected, during the past funding period, each of these has been highly successful in the original goals, with each evolving along different paths. As described below and in the research strategy section, the Biology of Aging Working Group has continued to mature and is now designated an Interdisciplinary Research Program (IDRP) in Healthy Aging at the Center. The Metabolic Disease Working Group has matured to become the new Research Division of Diabetes, Obesity & Metabolism, as detailed in its designated section. The Stem Cell & Developmental Biology Working Group has been integrated into the original Division of Reproductive Sciences with its change in focus to the Division of Reproductive & Developmental Sciences. A new IDRP in Addiction is a central focus in the Neuroscience Division. Two new IDRPs have been established based on recommendations from the 2011 Scientific Retreat. The Early Childhood Health & Development program represents the increasing interactions between the Center and the Departments of Ob-Gyn and Pediatrics at OHSU. The Primate Genetics Program, with growing importance at ONPRC in all aspects of our colony and research, represents the growing importance of genetic and genomic aspects of the NHP model and the unique pedigreed NHP colonies at the Center.

As with the Working Groups, these programs are supported minimally by the P51, to provide funds to enhance communication and interaction by supporting seminar speakers and symposia. These groups meet regularly to exchange ideas, to develop new avenues of research, and to discuss potential funding opportunities.

INTERDISCIPLINARY RESEARCH PROGRAMS (IDRP) SPECIFIC AIMS

In the previous P51 renewal, three Working Groups were established to foster areas that were not adequately represented by the existing Research Divisions. These included Biology of Aging, Metabolic Disease, and Stem Cells and Developmental Biology. The explicit goal of these was to establish interdisciplinary research programs that fostered interdivisional and inter- and intra-institutional collaborations. As expected, during the past funding period, each of these has evolved along different paths. As described below and in the research strategy section, the Biology of Aging Working Group has continued to mature and is now designated an IDRP at the Center. The Metabolic Disease Working Group has matured to become a new Research Division, as detailed in its designated section. The Stem Cell & Developmental Biology Working Group has been integrated into the original Division of Reproductive Sciences with its change in focus to the Division of Reproductive & Developmental Sciences. Two new Interdisciplinary Research Programs have been established based on recommendations from the 2011 Scientific Retreat. The Early Childhood Health & Development program represents the increasing interactions between the Center and the Departments of Ob-Gyn and Pediatrics at OHSU, and the Primate Genetics Program represents the growing importance of genetic and genomic aspects of the NHP model and the unique pedigreed NHP colonies at the Center. As with the Working Groups, these programs are supported minimally by the P51, to provide funds to enhance communication and interaction by supporting seminar speakers and symposia. The Specific Aims are:

Specific Aim 1: Biology of Aging. The Biology of Aging Program is a multi-disciplinary research program involving Core and Affiliate investigators from each of the four research Divisions, and it draws strength from the broad spectrum of scientific and technical expertise afforded by its members. Since nearly 20% of the US population will be 65+ years old by 2030, a universal goal is to find safe and effective ways of enhancing the health and quality of life in the elderly, and to find ways of reducing premature senescence. Unfortunately, the mechanisms that underlie normal and pathological human aging are still poorly understood, and this significantly hampers the development of effective therapies. NHPs are long-lived and show age-related physiological changes that more closely resemble those of humans. The associated Primate Aging Resource provides Center investigators an unique opportunity to study the etiology of normal and pathological human aging. The goals for the next funding period include: 1) strengthening existing NHP aging disease models and to developing new models; and 2) strengthen inter-disciplinary collaborations and increase their translational potential.

Specific Aim 2: Early Childhood Health & Development. The overall goal of the newly established Early Childhood Health & Development Program is to develop and utilize NHP models that encompass key developmental stages (i.e., prenatal and postnatal life) that have been demonstrated to strongly influence the risk of developing cardiovascular, pulmonary, metabolic and psychological disease during early childhood and throughout life. Specifically, program investigators collectively study events that occur during pregnancy (i.e., intra-amniotic infection, hypoxia, growth restriction, maternal nutrition, placental abnormalities and preterm birth), as well as broad aspects of human development (i.e., cardio-pulmonary physiology, neurodevelopment, immune function and vaccine development) as a means of understanding factors and/or events during prenatal and postnatal life that can have profound effect on the overall health of an individual and as an adult. The near-term goals of the program during the next funding period are to: 1) identify and develop key areas of research within the program to increase collaborative interactions and the scope of research in this area; 2) seek an array of funding opportunities to take advantage of the integrated interests of the program, in particular collaborative, team-science mechanisms; and 3) develop a strategic plan for longevity of the program.

Specific Aim 3: Primate Genetics Research. The goal of the Primate Genetics Program is to leverage the complementary genetics expertise of program investigators, unique ONPRC capabilities such as the Japanese Macaque Resource, and state-of-the-art technologies such as those available through the Molecular & Cellular Biology Research Support Core, to characterize the contribution of genetic and epigenetic variation to complex disease phenotypes in non-human primates, and to translate these findings to human disease. The goals of the program include :1) ongoing genetic studies in macular degereration and neuropsychiatric disorders, obesity, cardiovascular disease and obesity; 2) characterization of rhesus genome variation; 3) epigenetic studies in alcohol abuse and adiposity; and 4) NHP genomic analysis method development.

INTERDISCIPLINARY RESEARCH PROGRAMS (IDRP) RESEARCH STRATEGY

1. BIOLOGY OF AGING

SIGNIFICANCE

Based on the latest Census Bureau data, one in five US residents is expected to be 65+ years old by 2030. This change in population dynamics will have a significant impact on society and on the health care system, but the important question directed at biomedical researchers is *"What, if anything, can you do about it?"* The ONPRC has stepped up to this challenge by establishing an interdisciplinary Biology of Aging (BoA) Program, co-directed by Excluded by Requester This Program comprises investigators from ONPRC's four research divisions, as well as affiliated scientists from the OHSU School of Medicine. The collaborative spirit of these investigators and their wide breath of expertise provide unique multidisciplinary approaches to studying the mechanisms that underlying normal aging as well as aging-associated pathologies. The strength of the program stems from the special resources and expertise at OHSU, and also from the ONPRC's well-established Primate Aging Resource (PAR; funded by the National Institute on Aging independently from the P51 Core grant). Moreover, the integration of the BoA Program within the OHSU Healthy Aging Alliance (HAA) significantly increases the translational potential of non-human primate (NHP) research and will accelerate the development of safe and effective therapies for the elderly.

INNOVATION

Primate Aging Resource. Rhesus macaques show many of the same physiological changes as elderly humans, including increased sleep perturbations, cognitive decline, immune senescence, and attenuation of circulating sex-steroid hormone levels. They thus provide a unique translational platform to examine the etiology of aging-associated physiological changes and pathology. The ONPRC PAR comprises more than 100 rhesus macaques aged 18+ years and maintains animals under carefully controlled environmental conditions (e.g., photoperiod, temperature, and diet). This enables NHP studies to be performed with fewer variables than is possible with human studies, and without the self-selection bias that commonly confounds clinical trials. Another important attribute of the NHP aging model is the availability of suitable post-mortem brain tissue, especially for gene-profiling studies- something that is very difficult to achieve in humans because RNA quality is generally degraded by excessively long port-mortem tissue-collection intervals (1).

The importance of having a carefully managed NIA-supported PAR at the ONPRC cannot be over-emphasized. Excluded by Requester (director of the PAR), works closely with the BoA investigators and with the Division of Comparative Medicine to ensure that steady supply of aged NHPs for model development and multi-disciplinary studies. Regular meetings and e-mail exchanges between BoA investigators ensures that research activities are highly coordinated and that this valuable, but limited, resource is used efficiently.

Support cores and facilities. The BoA Program also benefits from several ONPRC Support Cores and from on-campus diagnostic equipment similar to that used in human clinical studies. Ongoing studies make extensive use of the Endocrine Technologies Support Core for hormone determination, and the Imaging and Morphology and Molecular and Cellular Biology Support Cores for help with histology and gene-expression profiling using Affymetrix rhesus macaque gene arrays. In addition, support from the Bioinformatics Unit of the Primate Genetics Support Core is used for analysis and interpretation of the complex data, and is considered indispensible. The BoA Program also benefits tremendously from expert veterinarian care, which ensures that aged monkeys remain in good health while assigned to various studies, and from the expert assistance provided by Pathology Services during necropsy and post-mortem tissue evaluation. The MRI Support Core's 3-T magnet is especially valuable for ongoing aging studies, as it enables morphological and functional changes to be monitored non-invasively in the brain and peripheral organs. Similarly, whole-body DEXA scans and Actiwatch actigraphy enable longitudinal, non-invasive monitoring of body composition and locomotor activity cycles, respectively.

Many hormones that show age-related changes, and which play a key role in the etiology of age-associated pathologies, are secreted in a circadian manner. Consequently, the study of subtle endocrine changes cannot rely on single blood sample collections; instead, samples often need to be collected serially at different times of the day in order to establish accurate and meaningful plasma hormone profiles. For this purpose, the ONPRC has special blind-sampling rooms, which enable 24-hour serial blood samples to be collected remotely from un-sedated monkeys, using an indwelling vascular catheter and swivel-tether assembly (2). In addition to remote blood sampling from unstressed animals, this system enables hormones and pharmacological agents to be administered intravenously without disturbing the animals. Consequently, this innovative facility represents an important component of both ongoing and pending aging research grants.

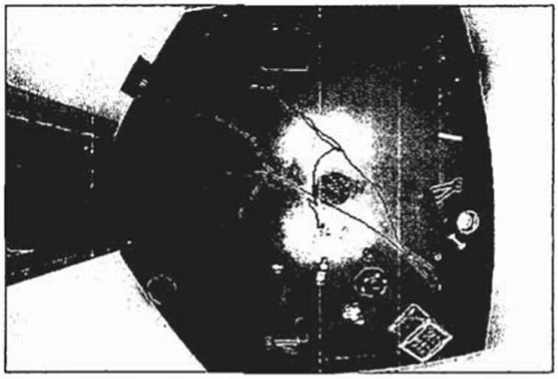


Figure 1. Overhead view of the playroom equipped with a Noldus video-tracking system. The image was taken using a ceiling-mounted, PC-linked CCD camera that analyzes center-point movement. The computer-generated trace depicts movement of an animal that entered through a port (*upper-left*) and moved around for 1 minute. Total distance traveled and average speed are calculated using EthoVision Color-Pro 3.1 software. This setup provides information about overall activity level and also enables assessment of spatial learning and memory using a navigational maze.

For monitoring age-associated cognitive changes, the ONPRC has several custom-built testing booths equipped with computer touch-screens. Ongoing studies are making extensive use of these booths in evaluating the efficacy of sex-steroid supplementation on performance in Delayed Response (DR) and Delayed-Matching Sample (DMS) cognitive tasks. In addition, the ONPRC now also has a custom-built dedicated "playroom" for video monitoring of monkeys using a Noldus EthoVision system (Figure 1), and has recently developed a novel spatial learning and memory test that involves navigation in this playroom (Figure 1). Animals learn to find a single baited food port among several ports, and are tested until they learn an initial baited position and then additional new (shift) positions. This task has been used to examine correlations between cognitive performance and indices of activity and sleep quality. For example, performance in the maze correlated significantly with activity parameters, including sleep latency and number of wake bouts. Total activity levels also were correlated with performance in a Delayed Non-Matching Sample (DNMS) task, including both trials to acquisition and percent correct at longer delays. These data support the hypothesis that an age-associated decline in sleep quality is associated with poor cognitive performance. Interestingly, we have also found correlations between cognitive performance in this spatial maze and immune function, as well as correlations with biochemical markers in the hippocampus, such as M_1 muscarinic receptors. These data emphasize the value of our innovative spatial maze and the value of the NHP model of aging.

OHSU Healthy Aging Alliance (HAA). To improve the translational potential of the NHP aging model, the ONPRC BoA Program has become a cornerstone for the OHSU HAA; indeed, [Excluded by Requester] co-directs both the ONPRC BoA Program and the OHSU HAA. The HAA was formed in 2009 with a mission to address gaps that currently exist between innovative aging research related to understanding the biology of aging and healthcare delivery, including the scientific and technological innovations that are necessary to improve quality of life. The Alliance involves ~60 other researchers, clinicians, policy makers, and older adults, and draws its strength from OHSU's Schools of Dentistry, Medicine, and Nursing, and benefits from the basic science research performed by BoA investigators and the unique technological developments of the Oregon Center for Technology and Aging. In addition, the Oregon Geriatrics Education Center plays a key role in improving the care of the elderly through education and training of health care providers. As depicted in Figure 2 on the following page, this network of investigators and shared resources can speed the translation of new scientific discoveries into safe and effective therapies. The model also represents a cost-effective use of valuable resources and a framework for inter-professional training in aging.

APPROACH

reviewers' comments

reviewers' comments

Future plans/goals for the next funding period.

Goal 1. To strengthen existing NHP aging disease models and to develop new models.

Hormone replacement therapy. Ongoing R01 and R24-funded BoA research involves the collaborative efforts of several investigators, and focuses on age-related sleep disruption, cognitive decline, and immune senescence. These highly integrated studies involve [Excluded by Requ] (*molecular mechanisms*), [Excluded by Request] (*brain imaging*), [Excluded by Requester] (*immune system*), [Excluded by Requester] (*learning and memory*), [Excluded] (*spatial cognition*), [Excluded] (*bioinformatics*), and [Excluded by Requester] (*neuroendocrine and circadian rhythms*), and are designed to elucidate common mechanisms and to develop safer and more effective hormonal therapies for the elderly.

Pending Support

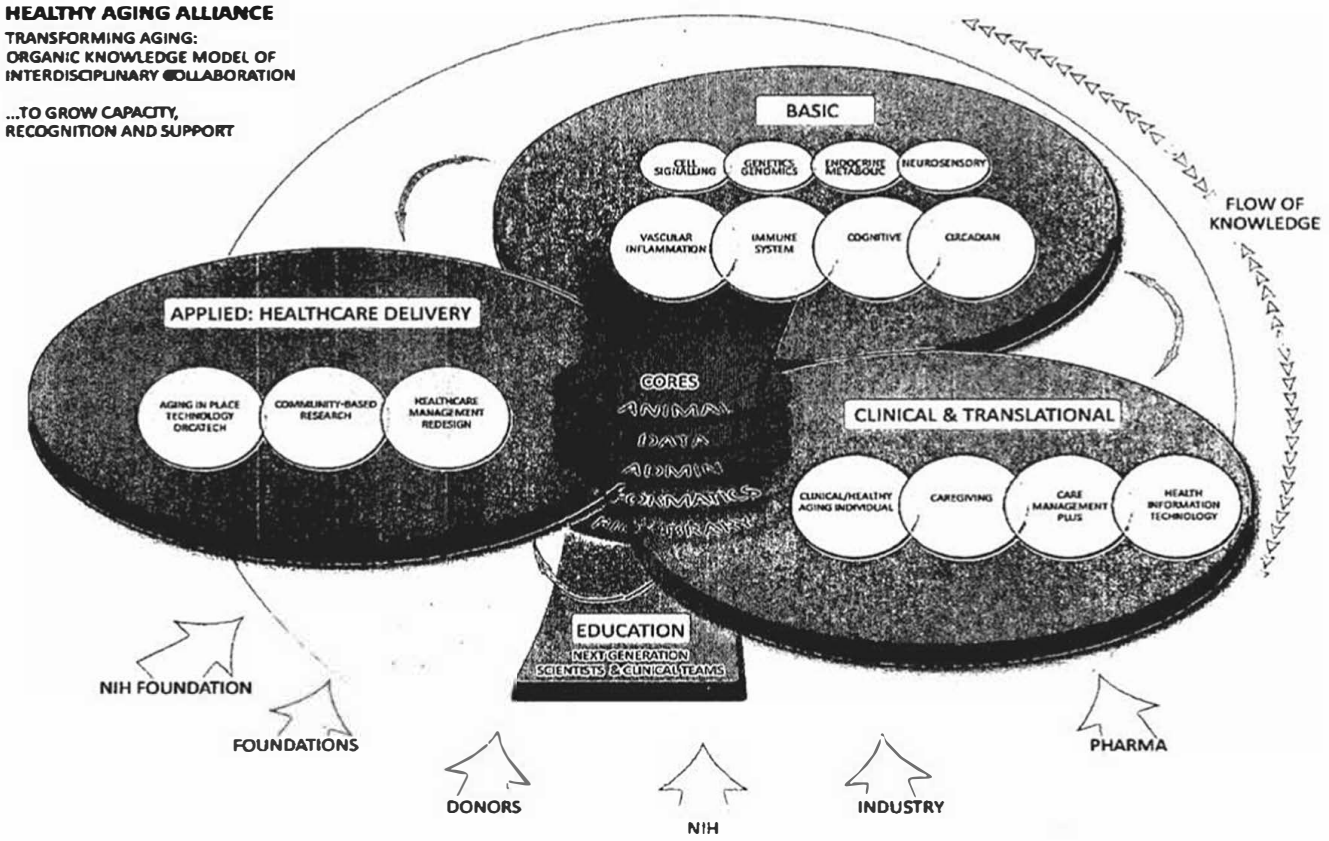


Figure 2. Graphic representation of the mission of the OHSU Healthy Aging Alliance and the critical contribution of the ONPRC BoA Program, especially to the basic science component.

Neurodegeneration. Although neurodegenerative diseases are often studied separately from aging, they nevertheless often contain a strong aging component. Therefore, under the umbrella of the BoA Program, several neurodegenerative models are in development; our goal is to develop these models further. Some of these, such as [Excluded by Requester] NHP *stroke* model (supported by a U54 grant), already involve several collaborative investigators (e.g., [Excluded by Requester]). Other neurodegenerative models include [Excluded by] (*multiple sclerosis*), [Excluded by Requ] (*Alzheimer's disease*), [Excluded by Requester] *retinal degeneration*), and [Excluded by Request] (*Huntington's disease*).

Hot flashes. One of the most common complaints by women associated with the onset of menopause is the occurrence of hot flashes. On the other hand, our understanding of what causes the thermoregulatory system is hampered by the lack of suitable animal models in which to study the menopause-associated vasomotor thermoregulatory changes. Excluded by Requester in collaboration with Excluded by Requester Excluded by R are developing a monkey hot flash model to test the efficacy and safety of potential therapies, including novel centrally-acting selective estrogen receptor modulators (SERMs).

Substance abuse. Alcoholism is a common human addiction, with severe physiological consequences. However, the impact of alcohol abuse on long-term aging processes is unclear. Alcoholism represents a major research focus area of Excluded by Requester and she has an opportunity to acquire unique aged rhesus monkeys for the BoA Program. These animals have been regularly consuming alcohol for a significant portion of their lives, and have already been characterized from the perspective of several behavioral characteristics. We expect these animals to be shipped to the ONPRC and form the basis of a multidisciplinary PPG proposal, involving Excluded by Requester and others.

Regenerative medicine. OHSU has recently established a new Center for Regenerative Medicine, headed by Excluded by Requester This Center has extensive expertise in the area of functional regeneration of tissue after trauma (e.g., using stem cells), and we intend to collaborate on ways of adapting such therapies for the treatment of aging-associated disorders.

Sleep and circadian rhythm disorders. Perturbed sleep-wake cycles negatively impact several biological systems (e.g., cognition, mood, immune function, and metabolism), and are a major health complaint in the elderly. The Center for Research on Occupational and Environmental Toxicology at OHSU has recently appointed a new director Excluded by Requester who is an expert in human circadian rhythm disorders. In collaboration with Excluded by Requester (director of OHSU Sleep and Mood Disorder Laboratory), we intend to expand translational circadian rhythm research at OHSU, by studying aging circadian mechanisms in the NHP aging animal model.

Goal 2. To strengthen interdisciplinary collaborations and increase their translational potential. During the previous funding period, several BoA investigators began to collaborate on studies using the PAR and to submit severalal inter-disciplinary grants. These included R21 and R01 grants to study the impact of hormonal supplementation on sleep-wake cycles and cognition in aged male and female monkeys, and a U54 grant to develop an NHP model of stroke. In addition, a multi-disciplinary R24 resource grant, to study menopause in female monkeys was recently funded. Pending Support

Pending Support

During the next funding period, our goal is to increase collaborative interactions between BoA researchers and other members of the OHSU Healthy Aging Alliance (HAA). This will be achieved through meetings, journal clubs, communal seminars, regular e-mail exchange, and shared training/education. Progress has already been made in each of these areas. For example, in 2012, the local chapter of the Society for Neuroscience included a special Aging symposium, with Excluded by Requester as the keynote speaker, while other aging-related seminars at the ONPRC included presentations by Excluded by Requester Excluded by Requester The 2012 HAA conference will include Excluded by Requester as the keynote speaker and will offer opportunities for networking. Many BoA investigators are involved in local outreach and education, and have presented seminars in the Portland Area Geriatric Seminar Series, and regularly train high-school teachers as part of the Partners-in-Science Program (Private Source Furthermore, many BoA investigators contribute to training graduate students and postdoctoral fellows though a T32 *Neuroscience of Aging* training grant (directed by Excluded by which also involves a monthly journal club. The HAA has recently established a website (maintained by Excluded by to keep OHSU Aging investigators informed of upcoming special aging-related events and funding opportunities.

The long-term goal of these interdisciplinary efforts is to develop more extensive collaborative research projects involving NHPs, such as a P01 Program Project Grant, and to secure funds from industry to help develop therapies for human aging-related disorders, especially hot flashes, stroke, immune senescence, and cognitive decline. By examining multiple systems, the BoA Program will be making the most effective use of the valuable PAR. Furthermore, because of extensive archiving of post-mortem tissue by Excluded by additional investigators will also be given an opportunity for subsequent investigation of other organ systems. With the concomitant development of the OHSU HAA, and the closer integration of basic and clinical research aging programs, we envisage the development of a solid platform for the future establishment of either a Nathan Shock or Claude Pepper Aging Center at OHSU.

2. EARLY CHILDHOOD HEALTH & DEVELOPMENT

SIGNIFICANCE

The early childhood period is now being recognized as one of the most important developmental phase throughout the lifespan. The intrauterine milieu, gestational length, and size at birth can have profound impact on the individual's mental and physical health and development, both in childhood and adult life. Early Childhood Health & Development (ECHD) investigators collectively study events that occur during pregnancy (i.e., intra-amniotic infection, hypoxia, growth restriction, maternal nutrition, placental abnormalities, and preterm birth), as well as broad aspects of human development (i.e., cardio-pulmonary physiology, neurodevelopment, immune function, and vaccine development) as a means of understanding factors and/or events during prenatal and postnatal life that can have profound effect on the overall health of an individual and as an adult.

Preterm labor resulting in premature birth is arguably the most important unresolved public health issue in obstetric medicine today and remains the leading cause of neonatal morbidity and mortality. A major strength of the pregnant rhesus macaque non-human primate (NHP) as a model lies in the opportunity to study the interconnectedness of maternal and perinatal health, particularly as the incipient underlying cause of so many obstetrical and neonatal adverse outcomes resides within the maternal-fetal environment. The NHP is unsurpassed in its potential to define the pathogenesis of many adult-onset disease states (i.e., asthma/COPD, cardiovascular disease, hypertension, obesity, diabetes, and AIDS), and is an invaluable tool through which to validate novel diagnostic and therapeutic strategies prior to introduction into obstetric and/or pediatric medicine (i.e., antibiotic, pharmaceutical, and vaccine development).

The most vexing problem facing infants born prematurely is the preponderance of survivors with chronic lung disease and neurodevelopmental disabilities, including cerebral palsy. These negative health and developmental effects of prematurity often extend to later life, resulting in enormous medical, educational, psychological and social costs (estimated to exceed $26 billion annually). In turn, these adverse events have considerable impact on maternal psychological well-being and quality-of-life outcomes for mother-infant dyads. Mothers of preterm infants are at a higher risk of postpartum depression, anxiety, recurrent preterm birth, impaired maternal-infant bonding, diminished physical health, finanical burden, and restrictions on social or employment activities. Most studies of premature infants show continued sequelae such as cognitive deficits, academic underachievement, and the need for increased remedial assistance during childhood, which can result in enormous negative psychological and emotional effects on the family.

The ability to investigate the temporal sequence of events from conception and beyond the maternal-fetal environment to a critical translation point between prenatal and postnatal life marks the beginning of a new era of research initiatives for the ONPRC. The NHP provides unparalleled opportunities for direct comparison with human fetuses/neonates for several reasons; 1) rhesus monkeys display the same susceptibility to microorganism associated with preterm birth (i.e., *U. parvum*) as human infants; 2) the hormonal control of parturition and hemochorial placentation with a discrete chorioamnion and amniotic cavity all simulate human pregnancy; 3) unlike rodents, who are born immature in terms of comparable brain maturation, the rhesus neonate has significantly more white matter at birth, making the monkey a far better model for assessing the developing white matter and pre-myelination of oligodendrocytes; 4) optimum frequency of neurobehavioral and cognitive testing in neonates and children is not always achievable in humans, and the correlation of important translational measures such as advanced imaging techniques (ultrasound and MRI), pulmonary function, neurodevelopment assessments and neuropathology would be virtually impossible to achieve; 5) the developmental ontogeny of NHP metabolic systems is similar to humans; and 6) the NHP has a similar immune function and is recognized as a critical model for vaccine development, particularly in the newborn in the presence of maternal transplacental IgG. Given the confluence of resources and expertise in developmental biology, pathoimmunology, maternal-fetal medicine, and pediatric research, we believe our integrative scientific approach has a high probability of success and will readily translate to clinical application.

INNOVATION

The ONPRC is internationally recognized for its translational research in pregnancy and reproductive sciences and is one of few primate centers in the US that has developed the infrastructure and technical expertise to sustain an outstanding rhesus macaque time-mated breeding program (TMB). The TMB program continues to be an intergral component of the animal resources provided to investigators by the ONPRC, in particular the ECHD working group. The rationale for use of pregnant rhesus monkeys as experimental

models is based upon their biological similarities to humans. Features that make the rhesus macaque particularly useful for studies related to human parturition and developmental biology include: i) physiology of the menstrual cycle and implantation; ii) the structural features of the uterus and cervix, placenta and fetal membranes; iii) the mechanism of labor and myometrial responses to prostaglandins and oxytocin and their inhibitors/antagonists; and iv) the regulation of the feto-placental steroidogenesis is qualitatively similar in humans and NHPs. Examples of innovative models developed that are utilized by this program include:

Long-term catheterized pregnant NHP model. The catheterized pregnant rhesus model permits studying maternal and fetal interactions in a relatively inaccessible intra-uterine space. This mobile system allows matched samples of maternal plasma and amniotic fluid to be obtained at any time of the day or night and to continuously monitor uterine contractions without disturbing the animals. Excluded by Requester current research incorporates studies directed at the fundamental mechanisms of parturition, with emphasis on novel diagnostic biomarkers and therapeutic interventions for preterm labor associated with reproductive tract infections. She and her colleagues recently reported a seminal study demonstrating that early identification of intraamniotic infection with *Ureaplasma* spp (the most frequent bacteria found in intra-amniotic infection in human beings) can be successfully eradicated with a specific macrolide antibiotic, Azithromycin, resulting in prolonged gestation and a reduction of the fetal inflammatory response syndrome (3).

Preterm neonatal NHP model. The ONPRC has developed a special-care nursery (SCN) for prematurely born rhesus monkeys (established by Excluded by similar to a human neonatal intensive care unit. Excluded by Requester and collaborating OHSU Neonatologists developed the facility to support the cardiopulmonary, (including mechanical ventilation, CPAP), thermoregulatory, and nutritional needs of prematurely born rhesus macaques. The SCN will facilitate studies of the pathogenesis of neurologic impairment and diseases of prematurity (supported by 1R01 HD069610). These studies will be expanded to determine neonatal pulmonary function sequelae since fetal lung infection is an important precursor of asthma and chronic lung disease in childhood. This research will strengthen collaborative relationships among the obstetrical, neonatal, and pediatric communities within OHSU and ONPRC, and enable translation of *"proof-of-concept"* data collected from these unique NHP maternal-fetal and neonatal models to the clinical setting. It also paves the way for developing a clinical Prematurity Prevention Program at OHSU in collaboration with Excluded by Requester OHSU OB/GYN. The SCN will also support investigation into an important area of perinatal research through a new collaboration with Excluded by Chief, Division of Pediatric Anesthesia and Director of the OHSU Pediatric Pain Management Center). The administration of appropriate analgesia in children varies by age, with neonates being the group at highest risk of receiving inadequate analgesia. The goal of this collaboration will be to optimize the comfort and minimize the distress of premature infants as they are cared for in the intensive care units and/or emergency medical setting.

Prenatal nicotine exposure and fetal lung development. The Excluded by Reques laboratory focuses on the role of acetylcholine, nicotinic, and muscarinic receptors in lung development and lung cancer, including the development of therapeutic approaches to block the effects of prenatal nicotine exposure on lung development. This is being pursued in clinical studies in conjunction with the OHSU pediatrics and maternal-fetal medicine departments (4), in studies in monkeys and transgenic mice and by electrophysiology of lung cells (5-7). The expression of multiple neurotransmitters by airway epithelium also suggests new targets for developing novel lung therapeutics (8, 9).

Infant NHP model of isoflurane-induced neuroapoptosis. Recent studies suggest that anesthesia exposure in infancy induces long-term neurobehavioral deficits. This NHP model is aimed at clarifying whether anesthetic drugs commonly used in pediatric medicine can trigger neuroapoptosis in the neonatal brain. Excluded by Requester an OHSU physician-scientist at OHSU, is investigating the effects of modified immune response following severe trauma, techniques for regional anesthesia, and innovative airway devices in pediatric anesthesia. His project "Long-term outcome of single vs triple anesthesia exposure of infant monkeys" was selected for the 2012 *Frontiers in Anesthesia Research Award* (10-12). This award recognizes his originality, scientific excellence, and leadership in the anesthesiology field, and exemplifies the success of the collaborative efforts between OHSU's department of Anesthesiology and ONPRC.

Prevention or modulation of infectious disease. HIV infection in newborns leading to AIDS is one of the most intransigent problems in the developing world due to lack of widespread and affordable availability of antiretroviral treatment (ART) to limit mother-to-child transmission. Most transmission occurs at parturition by the oral or conjunctival route. In the presence of ART, that risk can be reduced to 2-5%, but there is another 25% risk of acquisition for newborns that breastfeed. ART also selects for drug-resistant virus that persists in

the mother and can be transmitted to subsequent infants during birth. Thus, vaccines and treatments are needed to limit transmission, both at parturition and during the breastfeeding period. [Excluded by Requester] laboratory has a long-standing interest in structure-function studies of protective antibodies that has led to a current focus in three overlapping areas of research: 1) neutralizing antibodies (NAbs) directed to the HIV and SIV Envelope (Env) glycoproteins; 2) limiting mother-to-child transmission (MTCT) of HIV/SIV; and 3) HIV vaccine development. [Excluded by] and her group have shown for the first time that passive antibodies given at the time of oral exposure to the pathogenic chimeric virus SHIV (13), which causes rapid disease and death in newborn macaques, has a profound effect on viral control and prevents rapid death (14). She and her colleagues are working to further this utilize this model to examine how human monoclonal antibodies and vaccines may limit transmission and enhance the development of antiviral immunity during breastfeeding.

APPROACH

reviewers' comments

Goal 1. Identify and develop key areas of research within the ECHD Program. The focus of the ECHD Program, headed by [Excluded by Requester] Pathobiology & Immunology) and [Excluded by Requester] (Reproductive & Developmental Sciences) is to develop and utilize NHP models that encompass key developmental stages (i.e., prenatal and postnatal life) known to strongly influence the risk of developing cardiovascular, pulmonary, metabolic and psychological disease during early childhood and throughout life (Figure 3).

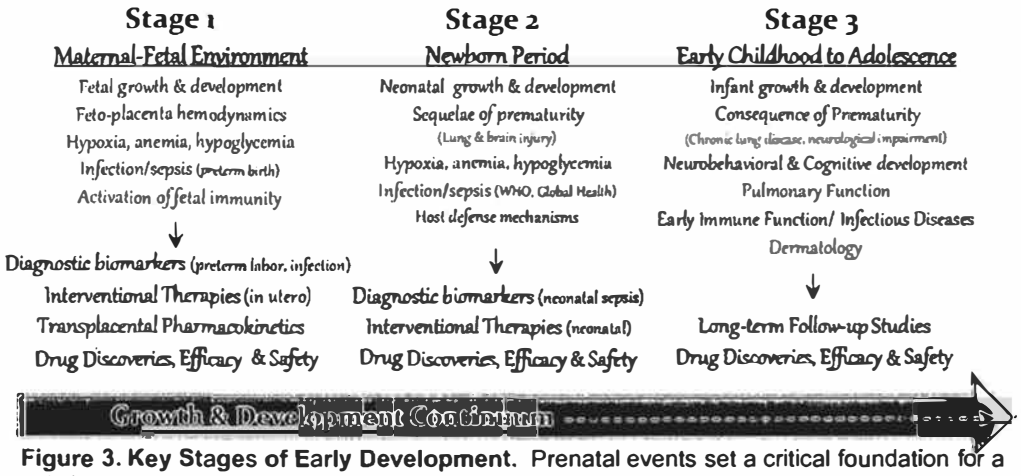


Figure 3. Key Stages of Early Development. Prenatal events set a critical foundation for a child's developmental trajectory and entire life course (Stage 1). The newborn period is a critical translation point between prenatal and postnatal life (Stage 2), and early childhood to adolesence continues the growth and development continum (Stage 3).

Our initial goal is to establish a more formal basis to bring together the diverse expertise of scientists at ONPRC, OHSU, and beyond (national and international level) who are already actively using pregnant/neonatal NHP models. The number of scientists at ONPRC and OHSU (as well as from outside universities) that currently work on different aspects of pregnancy and maternal-fetal medicine or early childhood and development is quickly growing. The field of epigenetic modification of life-term health requires that investigators who wish to make a meaningful contribution understand perinatal biology from the gene to whole animal phenotype. The ECHD Program seeks to assemble an armamentarium required to study both whole-animal physiology and molecular biology as it pertains to pregnancy and perinatal research. Current invesigators working within the framework of the ECHD span multiple departments/divisions and include areas such as pregnancy and perinatal research, neonatology/pediatrics, cardiovascular physiology and ultrasonography, neurobehavior and cognitive development, neuroscience and advanced imaging, immunology and vaccine development, and nutrition and metabolism. We will utilize these initial areas of integration as a basis for the ECHD program. We envisage this will improve communication, foster collaborative efforts, and strengthen our ability to understand the etiology and pathogenesis of disease states originating prenatal and/or postnatally, and to investigate the efficacy and safety of interventional therapies.

Goal 2. Seek funding opportunities to take advantage of the integrated interests. The establishment of the ECHD Program will facilitate the organization of interested researchers into a cohesive collaborative, interdisciplinary group, strengthen interactions between the OPNRC and OHSU and provide a forum for periodic evaluation of research progress and strategic planning. The latter will be implemented by an annual conference involving ONPRC, OHSU, and external collaborators; the first of these meetings is scheduled for May 13th, 2013 at Doernbeceher Children's Hospital, OHSU. Table 1 on the following page summarizes the

investigators working in this area now. We plan to utilize this conference as a starting point for continuing quarterly meetings of subgroups that form after this initial conference. Other activities will include journal clubs, shared training and educational days designed to promote network development amoung investigators (established PIs and new investigators).

Table 1. Scientists and clinicians currently working on early childhood health and development.

Excluded by Requester	Affiliation	Stage 1	Stage 2	Stage 3
	ONPRC-Reproductive & Dev Biol	X	X	X
	OHSU-Pediatrics	X	X	X
	OHSU-Pediatrics	X	X	X
	ONPRC-Comparative Medicine		X	X
	OHSU-Ob/Gyn	X	X	
	OHSU/DOM-Ob/Gyn	X	X	
	OHSU/ONPRC-Ob/Gyn	X	X	
	ONPRC-Neuroscience	X	X	X
	OHSU-Pediatrics	X	X	X
	OHSU-Pediatrics	X	X	X
	ONPRC-Neuroscience	X	X	X
	ONPRC- Neuroscience	X	X	X
	OHSU-Anesthesiology		X	X
	ONPRC- Pathobiology & Immunology		X	X
	OHSU-Pediatrics		X	X
	OHSU-Pediatrics		X	X
	ONPRC-Diabetes, Obesity & Metabolism	X	X	X
	ONPRC- Pathobiology & Immunology		X	X
	ONPRC-Neuroscience		X	X
	Washington NPRC		X	X

Goal 3. Continue to build and foster education and training opportunities for clinical fellows, postdoctoral fellows, graduate students and veterinary residents interested in perinatal research areas. Several ECHD investigators already contribute to training graduate and postdoctoral fellows through a T32 training grant in Reproductive Biology. Excluded by Requester are actively involved in joint mentorship of 2 neonataologists during their clinical/research fellowship. Likewise, Excluded by Requester contribute to the training of current Maternal-Fetal-Medicine clinical/research fellows in the OHSU Department of Obstetrics and Gynecology. Furthermore, we will partner closely with the Oregon's Clinical and Translational Research Institute (OCTRI). OCTRI's commitment to child health research extends from pilot project funding to representation on the national CTSA Child Health Oversight Committee. OCTRI provides unique support to child health and pediatric research through the Pediatric Clinical and Translational Research Center in Doernbecher Children's Hospital. The PCTRC offers a dedicated inpatient and outpatient unit in Doernbecher Children's Hospital, RN study coordinators, and Bionutrition Unit services. Additionally, all of OCTRI's resources are available to child health & pediatric researchers.

The ONPRC has a ACLAM-approved laboratory animal medicine residency program for D.V.M.s. The ECHD Program will collaborate with this training program to integrate specialized training modules that are currently in place for the SCN. These were developed and implemented by the combined efforts of OHSU Neonatologists Excluded by Requester and ONPRC Clinical Veterinarian Excluded by Requester. This highlights the unique potential and outstanding facilities, expertise, and educational opportunities made available through the ECHD platform. Many ECHD investigators are also involved in local outreach and educational programs, and have presented seminars to students/general public, and regularly train high-school teachers as part of the Partners-in-Science program (funded through the Private Source

3. PRIMATE GENETICS

SIGNIFICANCE

The primary mission of the Primate Genetics Program (PGP) is to describe the relationship between genotype and disease phenotype in non-human primates (NHP), and to translate these findings to human disease. The rhesus macaque is already a well-established model for numerous complex human diseases that challenge public health systems world-wide, including addiction and other neuropsychiatric disorders, cardiovascular disease, obesity, diabetes, macular degeneration, and immune senescence, among others. Susceptibility to these complex human diseases is caused by multiple genes, epigenetic phenomena, the environment, and interaction between these contributing factors. The use of NHPs as genetic and genomic

models for human disease capitalizes on the significant advantages of using this model over similar studies in humans, including close genetic similarity to humans, extensive pedigrees that provide substantial analytical power, a rigorously controlled environment (e.g., diet, housing) that enhances genetic signal over noise, and substantially greater ability to conduct large-scale studies at lower cost.

The PGP will capitalize on ONPRC-specific resources and investment in new ONPRC faculty to implement cutting-edge genetic and genomic approaches to studying the multifactorial basis of human disease in the NHP. ONPRC resources that are being leveraged for these purposes include the rhesus macaque colony pedigree, comprising ~6,250 individuals and spanning 6 generations, accompanying medical health records that provide a wealth of data for exploring the genetic contribution to complex traits, and sample biobanks representing thousands of ONPRC animals. Additional resources include analytical pipelines designed for next-generation genetic data in NHPs, including those developed for analysis of data from exome sequencing, genome-wide methylation analysis, and whole-genome sequencing.

State-of-the-art genetic and genomic research requires combining skills across closely related genetic disciplines in order to generate and interpret the massive amounts of data common to genetic and genomic studies. In recognition of this, our recent investment in talented junior faculty with a complimentary range of genetic and genomic expertise will be critical to the future goals of the PGP. The three primary PGP investigators include: 1) Excluded by Requester Director of the PGP, who has a substantial history in next-generation genomic and molecular genetic approaches to characterize NHP disease models; 2) Excluded by Excluded by Reques providing outstanding expertise in quantitative trait analysis and gene mapping using pedigree-based approaches; and 3) Excluded by Requester who contributes state-of-the-art expertise in epigenetic and structural variant analysis. This unique combination of resources and expertise provides a critical knowledge base that can be applied to collaborative genetic research with the PGP, across the ONPRC, and beyond.

The PGP has emphasized the development of exciting new collaborations and research directions within the program and at the ONPRC, and with other investigators at the national and international level. Within the PGP, several new proposals will leverage the pedigreed rhesus population to investigate the role of rare variants (Excluded by Requester epigenetic variation Excluded by Requester and variation in transcript levels Excluded by Requester to risk factors for cardiovascular disease and obesity. A new study, in collaboration with Excluded by Chief, ONPRC Div. of Neuroscience), and based on the NHP model of alcohol self-administration she developed, also investigates the contribution of single nucleotide variants and epigenetic methylation to alcohol abuse Excluded by Requester

All PGP investigators are also actively engaged in both national and international consortia activity aimed at facilitating collaborative genetic research in NHPs and enabling the translation of these findings to humans. Excluded by is a member of the NHP transcriptome project, which is sequencing and characterizing expressed genes in 11 NHP species, and optimizing approaches for the comparative transcriptional study of NHPs. Excluded by Requester conduct genomic research within the NIH/NIAAA-funded INIA stress Consortium, which facilitates sharing of research resources and also expedites the translation of NHP genetic findings to human studies. Excluded by Requester are members of the NIH/ORIP-supported Genetics and Genomics Working Group of the NHP Research Consortium (NHPRC), which focuses on developing genetic research tools for use across the NPRCs. Towards this goal, Excluded by Requester partnered with investigators at the California NPRC in designing two rhesus macaque SNP panels, a genetic management (GM) panel that supports parentage determination of offspring, and an ancestry-informative markers (AIMs) panel used to distinguish Indian and Chinese-origin rhesus macaques (Excluded by Requester These SNP arrays has been adopted by all 8 NPRCs, allowing for the first time the ability to directly compare rhesus macaque genetic variation at each of NPRCs. Excluded by leads and coordinates the international consortium for the analysis of the gibbon draft genome. This tremendous opportunity allows her to be at the forefront of genomic research, interacting with top scientists from the genomics field and gaining access to new resources as they are produced. In summary, PGP investigators work closely with each other and with additional investigators at the ONPRC and at the national and international levels to expand the use and application of genetic research in NHPs to important human diseases.

INNOVATION

The PGP leverages unique ONPRC NHP pedigree information, associated sample biobanks, and cutting-edge next-generation sequencing (NGS) technology to enable genetic, epigenetic, transcriptomic, and phenotypic analysis of disease. These unique resources include a single, extended pedigree of ONPRC

rhesus macaques (1,289 macaques spanning 6 generations) developed recently by Excluded by Requester specifically for gene-mapping studies of complex disease phenotypes, together with corresponding banked samples on >1,200 of these pedigreed macaques to support extensive phenotyping. Excluded by also heads a comprehensive ONPRC DNA bank containing samples from over 10,000 NHPs, including 22,872 individual samples from 9 NHP species. Complementing these unique biological resources, state-of-the-art instrumentation is available to support -omics studies in NHPs, including Illumina HiSeq and miSeq next-generation sequencers, a QuantStudio high-throughput genotyping and real-time PCR platform (LifeTech, Inc.), and OHSU core facilities that include both ABI/LifeTech and Illumina high-throughput genotyping platforms. Highly skilled bioinformatics and biostatistical support, as well as advanced computing resources are also available to PGP investigators, their collaborators, and other ONPRC investigators.

APPROACH

reviewers' comments

Future plans/goals for the next funding period

Goal 1. Genetic studies at the ONPRC.

Continued research in age-related macular degeneration, neuropsychiatric disorders. The genetic characterization of well-established NHP disease models can advance our understanding of the relevance and translational value of NHPs in the study of complex human disease. Three recent investigations illustrate this point. First, our study of age-related macular degeneration (ARMD) in rhesus macaques identified risk polymorphisms that mirror those discovered in human studies, namely promoter variants in the *HTRA1* and *ARMS2* genes that are associated with altered gene expression and risk for drusen accumulation, the hallmark of ARMD (16). This study provided one of the first published examples of parallel genetic mechanisms contributing risk for both human and NHP complex disease. Its discovery highlighted the value of the rhesus macaque ARMD model, attracting the attention of pharmaceutical companies and financial support for additional research. In a separate investigation, we identified a promoter variant in the *EAP1* gene that disrupted a transcription factor binding site (SMAD3/4), altered gene expression, and was significantly associated with hypothalamic oligomenorrhea/ammenorrhea in rhesus macaques (17). Moreover, this study suggested a previously unrecognized genetic risk factor that may contribute to human hypothalamic oligomenorrhea/amenorrhea. Lastly, in a genetic study of HPA axis pathway dysregulation, a condition associated with several neuropsychiatric disorders, we identified polymorphisms in three unlinked genes contributing to serotonin and cortisol signaling in rhesus macaques. Importantly, we also demonstrated an additive effect of the three variants on the degree of HPA axis dysfunction (18). This finding has critical implications for evaluating similar risk in human populations, particularly since HPA axis dysfunction has been linked to anxiety, major depressive disorder, post-traumatic stress disorder, schizophrenia and alcohol abuse (19-24), among others. These studies have not only been successful in discovering genetic variants and potential molecular mechanisms associated with complex NHP traits, but have also reinforced the relevance and translational value of these NHP models for the study of human disease.

New genetic research in cardiovascular disease, inflammation, obesity, and macaque colitis. Underscoring the value of the pedigree and biobank resources she developed, Excluded by R ecently reported a series of first-ever findings describing substantial sex-specific heritability in rhesus macaques for multiple risk factors for cardiovascular disease and obesity, including total, HDL, LDL, and VLDL cholesterol, triglycerides, waist circumference, and body-mass index. Based on these results, Excluded by Requester was recently awarded an ONPRC pilot project to assess heritability for levels of insulin, sVCAM-1, IL-6, TNFα, IFNγ, IL12p40, IL-2, cortisol, ghrelin, and osteocalcin in 300 pedigreed macaques. Excluded by Requester are also collaborating on a R24 proposal to conduct exome sequencing and genome-wide genetic linkage and association analysis of these and other important biomedical traits in 600 pedigreed macaques. Pending Support

Pending Support

In addition to the large pedigree-based studies described above, Excluded by Requester are also collaborating on an additional novel project aimed at identifying genes and biological pathways that are differentially expressed in PBMCs between male rhesus macaques with extreme high and low values of LDL cholesterol. This project will use next-generation RNAseq methods to elucidate genes and pathways involved in susceptibility to atherosclerosis, and will provide preliminary data for an R01 proposal to map expression QTLs (eQTLs) influencing LDL cholesterol levels in larger sample sizes.

Excluded by Requester is also actively collaborating with Excluded by Requester head veterinarians in the ONPRC Dept. of Comparative Medicine, to characterize specific pedigrees developed around macaques affected by chronic colitis. The goal of this effort is to test the hypothesis of a genetic basis for macaque colitis, and to provide preliminary data supporting future grant proposals to identify causative genetic and environmental contributions to this disease. They have already identified a focal set of 233 animals with chronic colitis, and are currently characterizing a ~900-member pedigree containing these affected animals and their relatives for genetic analysis. This analysis will be supported by peripheral biomarker and histological analysis of ~200 matching blood and gut tissue samples already collected on affected animals at necropsy by Excluded by and Excluded by Requester These collaborative studies leverage the opportunities afforded by the large pedigreed rhesus macaque population, a wealth of expertise in macaque disease models, genomic research expertise in the PGP, and Excluded by Requester experience in quantitative trait analysis.

Goal 2. Genomic studies at the ONPRC.

Discovery of rhesus macaque genome variation. Excluded by Requester is actively engaged in the discovery and characterization of rhesus macaque genome variation, both to establish resources for the study of NHP disease models and to identify potential unrecognized models of disease suggested by identified functional variants. In one study, the transcriptome and H3K4me3-marked DNA regions in hippocampus from 14 rhesus macaques were sequenced using NGS approaches. A total of 462,802 high-quality macaque SNPs were identified, most of which were novel and disproportionately located in gene-linked regions. At least one SNP was identified in each of 16,797 annotated macaque genes. Although there were more coding SNPs (cSNPs) per individual in macaques than in humans, the number of damaging nonsynonymous cSNPs in the macaque was nearly equivalent to that of humans (25).

A whole-genome variant discovery study was also undertaken with 12 unrelated Indian and Chinese-origin rhesus macaques. Using 30-45x coverage, Excluded by Requester group identified over 33 million high quality SNPs, which have been deposited for public access in dbSNP (http://www.ncbi.nlm.nih.gov/projects/SNP/), expanding the number of publically available rhesus SNPs by more than 6-fold. Among the variants, a subset predicted to truncate or damage protein function were identified in Indian and Chinese-origin rhesus macaques. This rhesus macaque variant catalog serves as a valuable resource for evaluating candidate SNPs associations with characterized NHP disease models. In addition, predicted functional SNPs in disease associated genes, suggest additional, currently unrecognized disease susceptibilities to explore in the rhesus macaque.

The gibbon as model for genome evolution. Excluded by Requester is investigating mechanisms of large-scale chromosomal rearrangements in gibbons, which are exceptional among primates because they have experienced an unusually high rate of chromosomal rearrangement. Recent observations suggest that reduced methylation of transposable elements (TEs) may have increased the rate of chromosomal rearrangements during the evolution of gibbon species (26). Excluded by work investigates a model where *the weakening of epigenetic control* over TEs accounts for the accelerated rate of chromosome evolution. This issue is relevant to other systems, like cancer cells, in which both genome instability and disruption of DNA methylation occur. Moreover, Excluded by has recently discovered a novel TE, a composite element termed LAVA based on its composition of L1, *Alu*, VNTR (variable number of tandem repeats), and *Alu*-like sequences (27). LAVA represents an exceptional model to study how new TEs arise in the genome and impact chromosome evolution. For instance, LAVA is expanded in the centromere of one gibbon genus (*Hoolock*). This natural phenomenon represents an excellent model to investigate the role of repetitive DNA in the centromere, which is a highly debated issue. Excluded by is exploiting this phenomenon by taking advantage of applications of NGS such as ChIP-seq. By joining genomic and epigenetic approaches to investigate these fundamental biological phenomena, we anticipate that Excluded by will make significant contributions to the understanding of chromosomal rearrangements and centromeric function and evolution.

Goal 3. Epigenetic studies at the ONPRC.

DNA methylation, alcohol, and interaction with phenotype. A new research project led by Excluded by Requester and Excluded studies the effects of chronic alcohol consumption on DNA methylation in rhesus macaques. This NIH-funded study is part of the INIA stress consortium that focuses on the interplay between stress and alcohol use. The study makes use of a unique opportunity made feasible by the established alcohol self-administration macaque model developed by Excluded by Requester This model allow us to perform a longitudinal study, comparing levels of DNA methylation in macaques before and after 12 months of alcohol consumption, using genomic

samples obtained from both the blood and brain samples. This project heavily leverages NGS technology, and its applications to the study of DNA methylation. Although we are gathering genome-wide data, which enables us to identify global changes in DNA methylation, we are also evaluating a set of candidate genes known to be involved in alcohol addiction or the endocrine stress response. Our preliminary data show differential methylation in a subset of these target genes after 12 months of drinking, providing promise for identifying epigenetic-linked changes that may associate with the transition from alcohol use to alcohol addiction.

Such findings could suggest novel mechanisms and treatments for alcohol addiction in humans. This study will also determine whether the methylation signature detected in blood can suggest the state of DNA methylation changes in the brain of alcoholics, providing a potentially tractable approach for clinical evaluation. Finally, this study also builds upon previous work identifying genetic risk factors in the same animals, allowing us to investigate the interactions between genetic and epigenetic effects. This novel study is possible thanks to the unique and complementary expertise in the fields of genomics, epigenetics, and behavioral neuroscience currently available at the ONPRC.

DNA methylation and adiposity. A project involving Excluded by Requester explores the extent of DNA methylation variability and its correlation with variation in measures of adiposity in the ONPRC rhesus macaque pedigreed population. Very little is known about inter-individual variability of methylation and how much this is influenced by genes, or to what extent methylation is responsible for phenotypic variation. In this project, we are using adiposity as the phenotype of choice, given the health-related implications and the potential to translate this finding to the human population. Our long-term goal is to describe levels of inter-individual variation for DNA methylation, and investigate their heritability and correlation with adiposity in rhesus macaques. We are particularly interested in disease-relevant phenotypes, like adiposity, as we aim to identify some "epigenetics signature" which could serve as biomarkers for susceptibility to disease phenotypes like obesity and cardiovascular disease. The same study would be extremely difficult in human populations given the confounding environmental factors (diet, smoke, pollution, different stress levels, etc.), but the conclusions that we will derive from this study will be applied to humans more directly than is possible with more distantly related animal models. This project capitalizes on the NHP resources at the ONPRC, the complementary expertise of the core scientists of the ONPRC Primate Genetics Program (Drs. Carbone, Vinson), and builds on the expertise and reputation of the ONPRC in obesity research.

Goal 4. Developing methods for genomic analysis of NHPs: a research resource for the ONPRC. We are also optimizing a variety of technical approaches for NHP genome analysis, where possible leveraging existing human-based genomic resources and approaches for cross species use. For example, to enable efficient use of exon-seq approaches for NHP research, we recently completed a comparison of the on-target recovery rate of macaque exons, using three established human-based designs developed by Illumina, Roche-Nimblegen, and Aglient. Exon recovery was efficient with all three systems, and between 92-95% as measured by the HumanRefSeq database, but Illumina underperformed the other two when compared against the RhesusOrthoMeta database. Off-target sequence recovery was highest with the Roche-Nimblegen system at 20% vs 5% for the other two designs. Considering the relative breadth of exon coverage, we conclude that the Agilent human-exon design system has the highest recovery efficiency for macaque exon enrichment. Together with our now established bioinformatics analysis pipeline, we are poised to leverage exon-seq for the efficient analysis of macaque variation at the ONPRC.

In a separate study,we compared different approaches for genome-wide analysis of methylation levels in the rhesus macaque. Comparison of equivalent Illumina HiSeq sequencing, using whole-genome bisulfite sequencing (WGBS), reduced-representation bisulfite sequencing (RRBS), Methylation-sensitive Restriction Enzyme analysis (MRE), and methyl-cap enrichment (MeCAP), revealed that MeCAP achieved the broadest genome representation of 10X read coverage and higher of the four methods, using a single lane of Illumina HiSeq sequencing. Though WGBS is the undisputable gold standard for genome-wide CpG methylation analysis, for larger studies limited by funding, the MeCAP approach, either alone or in combination with RRBS, offers opportunity to achieve reproducible measures and deep coverage. In addition, the bioinformatic pipelines for use with each of these approaches to methylation analysis are now in place and available for use at the ONPRC. These NGS method-development studies benefit PGP investigators as well as other ONPRC colleagues whose studies can be advanced by NGS approaches.

Pages 1160-1168 (Publications) Removed – Excluded by Requester

INTERDISCIPLINARY RESEARCH PROGRAMS: EXTERNALLY FUNDED RESEARCH PROJECTS

Excluded by Requester — Oregon National Primate Research Center
Postmenopausal Monkey Resource
NIH/OD - R24 OD011895
The goal of this project is to establish a postmenopausal monkey resource with aged ovariectomized rhesus monkeys on a Western diet.

Excluded by Requester — Oregon National Primate Research Center/OHSU
Investigating the association between hypomethylation of transposable elements and chromosomal rearrangements in Acute Myeloid Leukemia (AML) using next-generation sequencing
Private Source
This project investigates the relationship between DNA Methylation and chromosomal aberrations in one patient with Acute Myeloid Leukemia.

Excluded by Requester — Oregon National Primate Research Center
Washington NPRC-Collaborative Genetics Resources Unit
NIH P51 RR000166 Subcontract #584669 [University of Washington]
The Genetics Program component of the Washington National Primate Research Center Core grant supports the genetic research needs of individual studies, the animal breeding program and the International Studies Division.

Excluded by Requester — Oregon National Primate Research Center
Gene-targeted SNP-discovery in rhesus macaques
NIH P24 RR017444 Subaward 34-5150-2033-006 [University of Nebraska Medical Center]
The objective of this project is to identify gene variations ("SNPs") throughout the rhesus macaque (M. mulatta) genome using Next Generation Approaches.

Excluded by Requester — Oregon National Primate Research Center
Washington NPRC-Collaborative Genetics Resources Unit
NIH/ORIP P51 RR000166 Subcontract #722387 [University of Washington]
The Genetics Program component of the Washington National Primate Research Center Core grant supports the genetic research needs of individual studies, the animal breeding program and the International Studies Division.

Excluded by Requester — Oregon National Primate Research Center
Genetic and Epigenetic Analysis of Alcohol Self-Administration in Monkeys
NIH/NIAAA U01 AA020928
This study investigates the effect of chronic alcohol use on DNA and gene expression and represent a novel approach to understanding the epigenetic consequences of alcohol use, and could indicate new directions for the treatment of alcoholism.

Excluded by Requester — Oregon National Primate Research Center
Integrative Neuroscience Initiative on Alcoholism: Stress and Ethanol Self-Administration in Monkeys
NIH/NIAAA U01 AA13510
The purpose of this study is to characterize hypothalamic-pituitary-adrenal axis and neurosteroid response prior to, during and following heavy alcohol consumption in male cynomolgus monkeys.

Excluded by Requester — Oregon National Primate Research Center
Compartmental Analysis of Proteomics Biomarkers during Intra-uterine Infections
NIH/NICHD - R00 HD055053
Expand understanding of the pathophysiology of choriodecidual inflammation/infection with U.parvum in a nonhuman primate model.

Excluded by Requester Oregon National Primate Research Center
Primate Model of Ureaplasma In Utero Infection: Prevention of Neurologic Sequelae
Private Source
Establish a special care nursery (SCN) that will support postnatal survival of prematurely born rhesus monkeys exposed to Ureaplasma and antibiotic treatments in utero.

Excluded by Requester Oregon National Primate Research Center
Primate Model of Mid-gestation Ureaplasma in utero Infection: Prevention of Neurologic Sequelae
NICHD/NINDS - R01 HD069610
Determine the extent of cerebral white matter inflammation and neuronal injury caused by prolonged Ureaplasma intra-amniotic infection (IAI) and to assess the efficacy of antenatal therapy to prevent neurologic damage in the fetus and adverse neurobehavioral consequences in the neonate.

Excluded by Requester Oregon National Primate Research Center
Studies of Ureaplasma Invasion of Epithelial Cells
Private Source
Summer employment of a high school teacher to extend and complement the in vivo data obtained from experimental choriodecidual model and to learn modern scientific techniques and concepts that can influence their teaching and encourage students to consider science careers.

Excluded by Requester Oregon National Primate Research Center
Studies of Ureaplasma Invasion of Epithelial Cells
Private Source
Summer employment of a high school teacher to extend and complement the in vivo data obtained from experimental choriodecidual model and to learn modern scientific techniques and concepts that can influence their teaching and encourage students to consider science careers.

Excluded by Requester Oregon Health & Science University
STX: A novel CNS selective estrogen receptor modulator (NeuroSERM)
Dean's Fund for Research Collaboration
The major goal of this project was to examine a rhesus macaque model of estrogen deprivation, mimicking heat flashes.

Excluded by Requester Oregon National Primate Research Center
The Modulation of Immune Senescence by Menopause and Estrogen Replacement Therapy
Private Source
The goal of this project is to elucidate the impact of menopause on immune senescence and immune response to vaccination in older women.

Excluded by Requester Oregon National Primate Research Center
Impact of Immune Senescence on Herpes Zoster in a Nonhuman Primate Model
NIH - R01AG037042
The goal of this proposal is to use our nonhuman primate model of VZV to: 1) identify age-related differences in the VZV-specific T cell responses and 2) determine how these differences in immune responses affect the aged ability to control VZV replication and to maintain latency.

Excluded by Requester Oregon National Primate Research Center
Pacific Northwest Regional Center of Excellence – Project 3 - Yellow Fever Vaccination of the Aged and Immunocompromised
NIH - U54AI081680
The goal of this project is to determine the immunogenicity and efficacy of a novel inactivated vaccine against yellow fever using a nonhuman primate model of viscerotropic yellow fever.

Excluded by Requester Oregon National Primate Research Center

Pacific Northwest Regional Center of Excellence - New Opportunity – Determination of Age-related Defects in Chikungunya Virus Infections
NIH - U54AI081680
The goal of this project is to develop a nonhuman primate model of CHIKV infection to characterize the immune response and develop vaccines against this re-emerging virus.

Excluded by Requester Oregon National Primate Research Center
Impact of ovarian steroids loss on immune senescence in female macaques
Private Source
Major goals: the goal of this study is to dissect the impact of age versus that of menopause on T cell function and response to vaccination using rhesus macaques.

Excluded by Requester Department of Immunobiology, University of Arizona
Immunological basis of age-related susceptibility to West Nile virus
NIH - BAA 05-11 HHSN266200500027C ADB Contract N01 50027
The goal is to use a succession of rodent, primate and human models to elucidate critical age-related defects in innate and adaptive responses to WNV.

Excluded by Requester Department of Immunobiology, University of Arizona
T Cell Homeostasis and Function in Immune Senescence
NIH - 8R01 AG020719
To understand T cell dysregulation in immune senescence.

Excluded by Requester Department of Immunobiology, University of Arizona
Studies of Immunosenescence and Other Late Effects of Acute Ionizing Radiation Exposure in Atomic Bomb Survivors: Project: Effects of Radiation and Aging on T Cell Homeostasis and Function
BAA-NIAID-DAIT-NIHAI2008023 Radiation Effects Research Foundation
To elucidate whether and how radiation may precipitate or accelerate manifestations of aging in the immune system.

Excluded by Requester Department of Immunobiology, University of Arizona
Vaccination and Immune Senescence in Primates
NIH - 5 P01 AG023664-04
The goal is to dissect primary defects in the immune response of old primates to vaccination and to improve outcomes of vaccination in this vulnerable population of primates.

Excluded by Requester Oregon National Primate Research Center
Vaccination and Immune Senescence in Primates
NIH - P01AG023664
Excluded by Requester project within this PPG (#4) was entitled "Immune senescence and CMV immunity in primates" and examined the effect of aging on the rhesus macaque T cell response to the persistent herpesvirus RhCMV, and conversely the contribution of RhCMV immunity to global immune senescence.

Excluded by Requester Oregon National Primate Research Center
Rejuvenation of the T-cell Compartment in Aging Primates
NIH – R01AI082529
The major goal of this project is to assess the ability of immuno-therapeutics such as IL-7 and KGF to rejuvenate the naïve T cell compartment of immuno-senescent rhesus macaques.

Excluded by Requester Oregon National Primate Research Center
Vaccination and immune Senescence in Primates
NIH – 5P01AG023664
The goal of my research within this program project is to analyze the antibody responses of young and aged primates in order to better understand the defects in immune responsiveness that are associated with aging.

Excluded by Requester Oregon Health & Science University
Development of Toll-like Receptor Agonists as Neuroprotectants in Brain Ischemia
NIH/NINDS – U01 NS064953
The goal of this application is to develop TLR agonists as neuroprotectants in a preclinical model of nonhuman primate stroke. Studies will address optimal dosing and time windows for candidate molecules, as well as gender and age effects on stroke outcome.

Excluded by Requester Oregon National Primate Research Center
Interacting Impact of Adrenal and Ovarian Aging on the CNS
NIH/NIA – R01 AG029612
The goal of this project is to examine how adrenal and ovarian steroids contribute to the maintenance of cognitive function in primates, and to elucidate the underlying neuroendocrine mechanisms.

Excluded by Requester Oregon National Primate Research Center
Molecular Neurobiology of Aging
Private Source
This Partners-in Science program grant supports research training for a high-school teacher, Kirsten Thiel, in the field of primate neural aging.

Excluded by Requester Oregon National Primate Research Center
Circadian Clock Mechanisms in the brain and peripheral organs
Private Source
This Partners-in Science program grant supports research training for a high-school teacher, David Herman, in the field of primate circadian physiology.

Excluded by Requester Oregon Health & Science University
Neuroscience of Aging Training Grant
NIH/NIA – T32 AG023477
This is a training grant for graduate students and postdoctoral fellows specializing in neuroscience of aging.

Excluded by Requester Oregon National Primate Research Center
Cognition in Rhesus Macaques in Relation to Age and Endocrine Status
NIH/NIA – R01 AG036670
The goal of this project is to examine how sex steroids contribute to the maintenance of cognitive function in male primates, and to elucidate the underlying neuroendocrine mechanisms.

RESOURCES

Follow the 398 application instructions in Part I, 4.7 Resources.

Resources are not applicable to the Interdisciplinary Research Programs. Resources are those available to the individual investigator(s) and Center-wide.

NARRATIVE: Excluded by Requester

Division appointment: Assistant Scientist, Division of Neuroscience
Appointment(s): % Effort in the Department of Behavioral Neuroscience at OHSU, and a joint appointment at the ONPRC.
Effort on NHP-related studies: % Effort

Research Overview: Excluded by Requester research focuses on genome evolution and epigenetics. Her lab is specialized in gathering high-throughput data on structural variations and epigenetic modifications and studying the interplay between the two in the genome of human and non-human primates. Excluded by Requester has a 10-years track record in comparative genomics and in the last seven years, she has been focusing on investigating the evolution of the gibbon genome. Gibbons display an increased rate of chromosomal rearrangements in comparison to human and most other primates. These species therefore represent a valuable model to study mechanisms underlying genome instability. Specifically, Excluded by is using the gibbon genome to learn about the evolution of human cancer genomes. also characterized by abundant chromosomal rearrangements and altered epigenetic marks. Excluded by Requester Lab is also focusing on investigating transposable elements, sequences that compose a major portion (> 50%) of primate genomes and are able to replicate and move in the genome Excluded by recently discovered a novel transposable element, called LAVA, which has a composite structure and includes fragments of other transposable elements commonly found in primate genomes. The analysis of the LAVA element promises to give many insights on how new transposable elements generates and become active in the genome.

Contribution to Mission: Excluded by Requester is a member of the ONPRC Extended Executive Committee which meets quarterly to discuss progresses and future directions to be taken by each of the ONPRC programs. She is also on the oversight committee of the Molecular & Cell Biology Core. In 2012 she helped the core to purchase the Illumina MiSeq sequencer, a next-generation sequencer that will be used by researcher at ONPRC/OHSU and will aid MHC-typing at ONPRC. Furthermore, given her deep interest in gibbons, she has been asked to coordinate the international consortium for the analysis of the gibbon draft genome. This opportunity allows her to interact with top scientists from the genomics and mobile DNA fields and achieve great exposure. Within the IDRP she has been contributing to the development of cutting edge approaches and analyses to study epigenetic modifications in the NHP model. Finally, Excluded by is part of the INIA stress consortium where she is developing tools to investigate the relationship between changes in DNA methylation and alcohol drinking in non-human primates. In 2012 Excluded by has been an invited speaker in two conferences and two departmental seminars; two of these invitations were at the international level (Japan and Germany).

Excluded by Requester serves the ONPRC mission by developing new computational pipelines and experimental methods to investigate genome instability and epigenetics modifications in non-human primates. She is collaborating with Excluded by Requester at the ONPRC to investigate DNA methylation changes in the rhesus model for alcoholism. Moreover she established several collaborations. For instance, she is collaborating with Excluded by Request from UCSF to investigate population dynamics in gibbon species. Moreover, she is studying the activity of the LAVA element in collaboration with Private Source,Excluded by Requester

Excluded by Requester was recruited through a P30 core grant from NIAAA with the aim to develop the genomics and bioinformatics effort at both OHSU and ONPRC. She is an Assistant Scientist in the Division of Neuroscience, ONPRC and an Assistant Professor in the Dept. of Behavioral Neuroscience, OHSU. She also holds joint appointments in the Dept. of Molecular and Medical Genetics, the Dept. of Medical Informatics & Clinical Epidemiology and the Private Source Cancer Institute at OHSU. She has been co-mentoring a graduate student from the Behavioral Neuroscience program during his second year project. Moreover, she is advising and is in the thesis committee of a computer science graduate student and she mentored a graduate student from the bioinformatics program from one quarter. Finally, in order to reach out to younger scientists, she became part of the advisory board of the Portland Community College Bioscience Technology Program and she is also in contact with faculty from local collages (e.g. Reed College and Lewis & Clark College).

NARRATIVE: Excluded by Requester

Division Appointment: Associate Scientist, Division of Neuroscience
Appointment(s): % Effort,Excluded by Requester at the ONPRC.
Effort on NHP-related studies: % Effort

Research Overview: Excluded by is a leader in the genetic characterization of macaques to inform and expand the translational study of non-human primate (NHP) disease models. Leveraging the recent advances in next generation sequencing (NGS) technologies, and in collaboration with other ONPRC investigators, she is analyzing the rhesus, cynomolgus and Japanese macaque genomic sequences to identify risk alleles associated with established disease models, including age-related macular degeneration, alcohol addiction, multiple sclerosis and infertility. She is also exploring the potential for new disease models in Chinese and Indian rhesus macaques, by identifying predicted functional/damaging alleles in genes having significant, replicated associations with human disease. Based upon discovered sequenced variants and their population allele frequencies, she is also developing high-throughput tools to more rapidly and efficiently screen rhesus macaque genomes, providing a consistent platform to survey macaque colonies for disease risk, parentage and geographic ancestry. Finally, Excluded by is establishing new methods for the application of NGS analysis to NHP research. She recently completed a comparison of three commercial human exon-capture designs, to enable the efficient exon-capture and sequencing of macaque DNAs.

Contributions to Mission: Excluded by supports the Mission by serving as the Director of the Primate Genetics Program (PGP) at the ONPRC, which includes three principal investigators, Excluded by Requester, Excluded by Requester. Their complementary research skills in genetics and genomics provide a platform for collaborative investigations into the genetic and epigenetic contributions to biomedical disease. The PGP also provide service to the ONPRC, supporting colony genetic management, providing bioinformatic/biostatistics research services, and developing and maintaining ONPRC genetic research resources, such as the ONPRC NHP DNA Bank, genetic databases and genotyping services (MHC analysis). Excluded by provides oversight to the ONPRC IT services and the Molecular and Cellular Biology Core. She also serves as ONPRC representative to the Nonhuman Primate Research Consortium (NHPRC) Genetics and Genomics Working Group. She has been an active contributor to this consortium, co-developing SNP based assays that are now used across all 8 NPRCS for colony genetic management. She serves as an NHPRC advisor for the development of bioinformatics databases and analysis pipelines to facilitate sharing of NHP genetic data and standardizing genetic analysis methods to characterize NHP breeding colonies across the NPRCs.

Directly supporting the ONPRC's mission to utilize NHPs as a translational bridge for curing human disease, Excluded by focuses on the genetic characterization of macaque models of human disease. Identifying genetic mechanisms that parallel those in human disease refines and informs the direct relevance of NHP models for translational study. Identifying novel genes and pathway offers opportunity to discover unrecognized pathways in human disease. Excluded by works collaboratively with Excluded by in characterizing the genetic and epigenetic contributions to alcohol addiction using the macaque model, with Excluded by to identify genetic risk factors for macular degeneration in macaques, with Excluded by Requester to explore genetic risk factors for a demyelinating disease in Japanese macaques, and with Excluded by Requester to define the effect of aging on mitochondrial DNA variation.

Excluded by Requester holds a joint faculty appointment in the Departments of Molecular and Medical Genetics (MMG) at OHSU, where she interacts with graduate students and post-doctoral fellows. As a member of the MMG Graduate Program, Excluded by co-directs a graduate course entitled "Genetic Mechanisms." Since 2009 she has served on the thesis committees of three graduate students at OHSU. She served as a co-advisor for a Masters Student in the Dept. of Medical Sciences at Boston University. She also mentored one postdoctoral fellow, one college student and three high school students.

NARRATIVE: Excluded by Requester

Division Appointment: Assistant Scientist, Division of Reproductive & Developmental Sciences (DRDS)
Appointment(s): % Effort,Excluded by Requester at the ONPRC and a joint appointment in Obstetrics & Gynecology, OHSU
Effort on NHP-related studies: % Effort

Research Overview: Excluded by Requester current research program and future objectives incorporate studies directed at the fundamental mechanisms of parturition, with emphasis on novel diagnostic biomarkers and therapeutic interventions for preterm labor associated with reproductive tract infections (i.e., *Ureaplasma* spp.), and for the prevention of subsequent fetal and neonatal sequelae (i.e., lung and cerebral white matter injury). Since the inception of Dr. Excluded by NICHD K99/R00 Career Development Award (The first awarded for ONPRC), her field of research has expanded from preterm birth studies to also include the regulation of fetal growth and placental plasticity. This research seeks to understand the ability of the developing placenta to adapt to a reduced umbilical placental blood flow as simulated by fetal interplacental vessel ligation. Excluded by Requester independent research program has evolved through expanded interdisciplinary collaboration among clinician scientists with neonatal-pediatric specialties and basic scientists with expertise in microbiology, reproductive immunology, cardiovascular physiology and clinical/veterinary pathology. Together, with her collaborators, they have expanded the infant care facilities at the ONPRC with the addition of a specialized intensive care nursery (SCN); this has enabled new research initiatives to expand beyond the maternal-fetal environment to a critical translation point between prenatal and postnatal life. This unique resource and nursery is designed to support postnatal survival of prematurely born rhesus monkeys exposed to *Ureaplasma* chorioamnionitis (with and without antimicrobial therapy) in order to delineate the cognitive and neurobehavioral consequences of *in utero* infection and antenatal treatments. Future plans are to expand these studies to determine neonatal pulmonary function sequelae because it is increasingly clear that fetal lung infection is an important precursor of asthma and chronic lung disease in childhood. Excluded by continuing research will strengthen the collaborative relationships among the obstetrical, neonatal and pediatric communities within OHSU and ONPRC, and enable translation of *"proof-of-concept"* data collected from our non-human primate model to the clinical setting.

Contribution to Mission: A remarkable accomplishment during Excluded by Requester tenure at the ONPRC is the development of a special care nursery (SCN) for prematurely born rhesus monkeys. The SCN has the look and feel of a human neonatal intensive care unit. She has developed the facility to support the cardiopulmonary, (including mechanical ventilation), thermoregulatory, and nutritional needs of prematurely born infants. Dr. Excluded by Request was recently awarded a 5 year grant from NICHD (1R01 HD069610) in support of this research. This synchronicity of translational research centered around Excluded by Requester research program is a harbinger of meaningful interdisciplinary and interdepartmental collaboration at the ONPRC and OHSU. It also paves the way for developing a clinical Prematurity Prevention Program at OHSU, and will open the door to countless basic and translational research collaborations from across the country. Since 2009, she published 5 peer reviewed articles, 1 reviews/book chapters and 13 abstracts at national or international meetings. Out of 14 collaborations, major examples are listed below:

Name	Affiliation	Description
Excluded by Requester	ONPRC	Primate model of mid-gestation *Ureaplasma* in utero infection: Prevention of Neurologic Sequelae.
	OHSU	Primate model of mid-gestation *Ureaplasma* in utero infection: Prevention of Neurologic Sequelae. Compartmental analysis of proteomic biomarkers during intra-uterine infections.
	University of Alabama	Primate model of mid-gestation *Ureaplasma* in utero infection: Prevention of Neurologic Sequelae. Compartmental analysis of proteomic biomarkers during intra-uterine infections.
	WaNPRC	Primate model of mid-gestation *Ureaplasma* in utero infection: Prevention of Neurologic Sequelae.

NARRATIVE: Excluded by Requester

Division Appointment: Senior Scientist, Division of Pathobiology & Immunology
Appointment(s): % Effort,Excluded by Requester at the ONPRC and a joint appointments in the Department of Molecular Microbiology & Immunology, OHSU, and Vaccine & Gene Therapy Institute, OHSU.
Effort on NHP-related studies: % Effort

Research Overview: Excluded by Requester principal research focus is the role of antibodies in limiting infection and pathogenesis in HIV infection. Her group has developed models for SHIV pathogenesis in newborn pigtail and rhesus macaques and uses passive transfer of polyclonal IgG and human monoclonal antibodies to determine their effects on disease in vivo. Excluded by group regularly produces multiple gram lots of endotoxin-free preparations of polyclonal IgG from HIV infected human subjects for collaborating groups. Excluded by is an expert in glycoprotein expression, with a focus on HIV-1 and SIV Envelope proteins produced in mammalian cells. Previous work in the development and purification of HIV Envelope proteins for the clinic led to writing the IND and to clinical testing of HIV gp120 vaccines. These gp120 proteins have been shown recently to be partially effective in reducing viral acquisition in a Phase III trial when used in combination with attenuated poxvirus vectors. The lab currently has four funded projects and one pending project to develop novel vaccines for HIV that are effective in eliciting neutralizing or other protective antibodies in vivo in rabbits and macaques.

Contribution to Mission: Excluded by Requester is the Director of the Center and is responsible for: 1) overall leadership through managing the senior leadership of the Center and oversight of the activities of the Associate Directors and Division Heads; 2) management and renewal of the P51 grant as a whole, including liason with the external Scientific Advisory Board; 3) setting the scientific priorities and leading the strategic planning activities of the center via formal workshops and scientific retreats; 4) oversight of the standing committees of the ONPRC, including Research Advisory, Animal Utilization, and Policy Group; 5) interactions with the host institution OHSU via the office of the Vice President for Research; 6) liason with the OHSU Foundation with Associate Director Charles Roberts; 7) liason with the Vaccine & Gene Therapy Institute. She co-leads the Early Childhood Health & Development IDRP program with Excluded by Requester

Key collaborations include:

Name	Affiliation	Description
Excluded by Requester	Private Source	NIAID-funded P01 to develop novel HIV vaccines that are based on natural HIV Envelope sequences derived from human subjects who developed broadly neutralizing antibodies with 3 years of infection. Excluded by is the PI of the P01 and leads a Project and two Cores. Vaccines are tested in rabbits and macaques.
		NIAID-funded R01 to develop novel vaccines for HIV using scaffold proteins to display conserved epitopes, involving testing in rabbits and mice.
	ONPRC Private Source	Pending Support SBIR Phase II grant from NIAID to study the role of oral, replicating Ad4-HIV vaccines in macaque challenge studies performed at ONPRC.
	ONPRC ONPRC	
	NIAID, NIH NIAID, NIH	Purification of polyclonal IgG from HIV-positive subjects to test for the ability to protect macaques from infection.
	VRC, NIH VRC, NIH VRC, NIH ONPRC	Analysis of human monoclonal antibodies derived from elite neutralizer subjects for their ability to protect newborn macaques from infection.
	Private Source	NIAID-funded R21 to determine if peptide mimetopes can induce HIV neutralizing antibodies by targeting macaque B cell receptors.
		Role of B cells in HIV and SHIV pathogenesis and the cloning of macaque B cells and monoclonal antibodies, follow-up to an NIAID-funded grant.

NARRATIVE: Excluded by Requester

Division Appointments: Senior Scientist, Divisions of Neuroscience and Reproductive & Developmental Sciences
Appointment(s): % Effort Excluded by Requester at the ONPRC.
Effort on NHP-related studies: % Effort

Research Overview: Excluded by Requester 30-year research career as a neuroendocrinologist has focused on the influence of circadian rhythms and reproductive hormones on vertebrate physiology. Key findings from his non-human primate (NHP) studies include: (1) cloning of a novel form of gonadotropin-releasing hormone, which may play a pivotal role in controlling primate ovulation, (2) identification of circadian clock mechanisms in the primate adrenal gland, and other peripheral organs, which help to coordinate 24-hour physiological functions, and (3) identification of genes that are differentially regulated by photoperiod, in a NHP model of Seasonal Affective Disorder. Excluded by current research, which is supported by two NIH R01 grants, uses multidisciplinary approaches to understand how age-associated hormonal changes negatively impact various physiological functions in NHPs. For example, in collaboration with Excluded by Requester Excluded by Requester he aims to show how physiological hormone supplementation paradigms can improve sleep efficiency and boost cognitive performance in aged rhesus macaques. Furthermore, by making extensive use of gene profiling, his studies are helping with the elucidation of underlying causal mechanisms, and laying the foundation for safe and effective novel therapies for the elderly. Excluded by Requester also lends his expertise to additional collaborative studies, which focus on the development of NHP models of stroke (PI Excluded by Requester and hot flashes (PI: Excluded by During the past four years, his research efforts have resulted in the publication of ~30 peer-reviewed papers and two book chapters.

Contributions to Mission: Excluded by Requester serves on several committees, including the promotions committees at ONPRC and OHSU, and he is the chair of the Endocrine Core oversight committee. Until recently, he also served on the graduate student admissions committee at OHSU. Nationally, Excluded by serves on two editorial boards and has participated as a grant reviewer at many NIH study section meetings. Excluded by current research focuses exclusively on the use of NHP models for human diseases, especially those associated with aging. He is the co-director of the Biology of Aging Program at ONPRC; this inter-disciplinary research program makes extensive use of the NIA-supported Primate Aging Resource at ONPRC in order to gain insights into healthy and pathological human aging. In addition, Excluded by has been highly instrumental in developing a translational bridge between the basic NHP aging research at ONPRC and clinical aging research and elderly care at OHSU. In collaboration with Excluded by Requester (Director of Geriatrics, OHSU), Excluded by has spearheaded the formation of an OHSU Health Aging Alliance (HAA), which comprises ~60 researchers and clinicians. The goal of the HAA is to establish an international center of excellence for aging research, clinical practice, outreach and education. It builds on the broad spectrum of talent and resources at OHSU, and focuses on translating aging innovations from molecular to clinical applications. The HAA held its inaugural annual conference in late 2011, which was attended by almost 200 individuals and was highlighted by key note presentations by Dr. Marie Bernard (deputy director of the NIA), as well Oregon Sen. Ron Wyden. The conference also provided an important forum for networking; this was followed up by a grant writing retreat, which resulted in the Pending Support Pending Support one of which has already been funded. The second annual HA conference was held in 2012 at the Portland Arts Center, and was attended by >300 individuals. Its main mission was to showcase to the public the aging research that is being performed at the ONPRC and OHSU; Private Source Excluded by Requester provided the keynote address. Although it is still in its infancy, the HAA (co-directed by Drs. Eckstrom and Excluded by represents an effective way of integrating the NHP aging research with ongoing aging programs at OHSU. The Alliance has already established a web site and a 5-year business plan.
Excluded by Requester holds affiliated professor positions in the Departments of Physiology & Pharmacology, and Behavioral Neuroscience at OHSU, and is a member of the Neuroscience Graduate Program. His laboratory provides a fertile research training ground for postdoctoral fellows and graduate students (current students: Excluded by Requester and Excluded by Requester, as well as high-school teachers via the Partner-in-Science program. Moreover, Dr. Urbanski is the program director of the NIH-supported *Neuroscience of Aging* training grant (T32 AG-023477), which is currently in its 8th year of funding.

NARRATIVE: Excluded by Requester

Division Appointment: Division of Neuroscience, Assistant Scientist
Appointment(s): % Effort Excluded by Requester in the Department of Molecular and Medical Genetics at OHSU and a joint appointment at the ONPRC.
Effort on NHP-related studies: % Effort

Research Overview: Excluded by Requester research focuses on the development of ONPRC rhesus macaque pedigrees for multi-center, collaborative gene mapping studies in complex disease. Since 2009, she has developed a single, 1,289-member pedigree of Indian-origin rhesus macaques optimally designed for large-scale genetic/genomic analysis, and a corresponding biobank of samples on >1,200 of these macaques to enable extensive phenotyping and analysis. With these resources, she has recently demonstrated first-ever findings of significant heritability in rhesus macaques for levels of total-, HDL- , LDL-, and VLDL cholesterol, and for triglycerides, abdominal circumference, weight, and body mass index (BMI), all well-established risk factors for human cardiovascular disease and obesity. In May 2012, she received ONPRC pilot funding to investigate heritability for 10 additional phenotypes that are biomarkers or risk factors for macaque colitis/human inflammatory bowel disease, cardiovascular disease, diabetes, obesity, osteoporosis, addiction, and behavioral disorders. The pilot study is in collaboration with 14 investigators spanning 7 primate research

Pending Support

Contributions to Mission: Excluded by Requester provides oversight of the Colony Genetics & Demographics unit, with responsibility for pedigree characterization and population genetic analysis of ~4,500 rhesus macaques at the ONPRC. In this capacity, she works closely with the Div. of Comparative Medicine to design appropriate genetic management strategies at the ONPRC. She has established rigorous decision rules for parentage assignment in order to improve the accuracy of colony pedigree data, and protocols based on sound population genetic principles for the formation of breeding groups. She has instituted a yearly genetic review of the breeding colony, the results of which are presented to the Director and the Head of Comparative Medicine. Excluded by Requester is also a Co-Investigator who provides genetics expertise on several ONPRC NHP resource grants (i.e., U42, U24), and presents summary results of colony genetic analysis to external Scientific Advisory Boards and others when needed. Finally, Excluded by is an active participant in the NIH/ORIP-supported Genetics and Genomics Working Group, which develops and implements genetic tools and analytical pipelines for the comparative analysis of non-human primates across the NPRCs. She has recently developed a leading role in this Working Group in the effort currently underway to establish consistent and informative genetic metrics to guide the genetic health and diversity of all national NHP colonies.

The focus of Excluded by Requester research on gene discovery using large pedigrees of rhesus macaques is a highly innovative research direction for the new Primate Genetics Program IDRP, and one that has enormous potential for expansion into multi-center collaborations and consortia that include all the national primate research centers and primate research programs elsewhere. In particular, she is currently exploring the potential for a consortium focused on the genetics of complex diseases in NHPs with leading investigators at the Texas Biomedical Research Institute (baboons) and the Center for Neurobehavioral Genetics at UCLA (vervets). Her initial results demonstrating heritability for several important risk factors for cardiovascular disease and obesity clearly underscore the value of the rhesus macaque pedigree and biobank resources she has developed, and her exploration of many other phenotypes of shared interest across primate research centers will shortly identify additional promising phenotypes for further collaborative pursuit.

In keeping with the ONPRC mission of developing new scientists in NHP genetics, Excluded by holds joint appointments in the Dept. of Molecular and Medical Genetics, and in the Div. of Bioinformatics and Computational Biology at OHSU. She lectures regularly for the graduate Program in Molecular and Cellular Biology (PMCB) and for the Medical School at OHSU on principles of quantitative genetics, genetic linkage and association analysis, and inheritance in complex disease. Excluded by has recently mentored a rotational OHSU graduate student, a Reed College undergraduate summer fellow, a Portland Community College student extern, and will shortly take on an OHSU masters student who will conduct his thesis work in her lab. She additionally serves regularly on the admissions committee of the graduate PMCB program.

Program Director/Principal Investigator (Last, First, Middle): Robertson, Joseph E./Haigwood, Nancy L.

INTERDISCIPLINARY RESEARCH PROGRAM DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*

Use Cal, Acad, or Summer to Enter Months Devoted to Project

Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
SUBTOTALS →						0	0	0

CONSULTANT COSTS		
None Requested	0	0
EQUIPMENT *(Itemize)*		
None Requested	0	0
SUPPLIES *(Itemize by category)*		
None Requested	0	
		0
TRAVEL		
None Requested	0	0
INPATIENT CARE COSTS		0
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		
None Requested	0	0
OTHER EXPENSES *(Itemize by category)*		
Interdisciplinary Program	3,600	
		3,600
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 3,600
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 3,600

PHS 398 (Rev. 6/09) **Form Page 4**

INTERDISCIPLINARY RESEARCH PROGRAM
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	0	0	0	0	0
CONSULTANT COSTS	0	0	0	0	0
EQUIPMENT	0	0	0	0	0
SUPPLIES	0	0	0	0	0
TRAVEL	0	0	0	0	0
INPATIENTS CARE COSTS	0	0	0	0	0
OUTPATIENTS CARE COSTS	0	0	0	0	0
ALTERATIONS AND RENOVATIONS	0	0	0	0	0
OTHER EXPENSES	3,600	3,708	3,819	3,934	4,052
DIRECT CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	3,600	3,708	3,819	3,934	4,052
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	3,600	3,708	3,819	3,934	4,052
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					19,113

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

PERSONNEL
None

SUPPLIES
None

TRAVEL
None

OTHER EXPENSES
Funds in the amount of $3600 are requested to pay honoraria and related meeting expenses for outside speakers to participate in scientific symposia and seminars to support the goals of the IDRP. These funds will be shared by the three programs.

Interdisciplinary Research Program Income Table

Last Funded Year (53)

Source	Funding (direct costs)
P51 base grant support	$3,000.00
Program income derived from P51 base grant	17,000.00
Other Sources	0
Total	$20,000.00

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$3,600.00
Program income derived from P51 base grant	20,400.00
Other Sources	0
Total	$24,000.00

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

The Interdisciplinary Research Program receives support for other expenditures from program income.

TITLE: PILOT RESEARCH PROGRAM

CORE-SUPPORTED PERSONNEL:

Personnel are not supported by the Pilot Research Program, except as specified by individual pilot project proposals.

PILOT RESEARCH PROGRAM PERSONNEL AFFILIATION AND ROLE

Core Scientists:

Excluded by Requester	Associate Director for Research, Senior Scientist Director, Office of Research Advocacy, Senior Scientist Chief and Senior Scientist, Division of Neuroscience Interim Chief and Senior Scientist, Division of Diabetes, Obesity, & Metabolism Director and Senior Scientist Chief and Senior Scientist, Division of Reproductive & Developmental Biology Interim Chief and Senior Scientist, Division of Immunology & Pathobiology Alternate, Senior Scientist, Division of Neuroscience

Affiliate Scientists:

Excluded by Requester	Pediatric Endocrinology, OHSU

PILOT RESEARCH PROGRAM

DESCRIPTION:

The ONPRC has had an extensive program for center support of Pilot Projects during the past four years; 21 projects were funded on the core base grant or from grant-related income. The Pilot Project program has played a critical role in allowing investigators to develop research projects using NHPs; this has been particularly true for new investigators recruited to the ONPRC who had no prior experience using NHPs. The program also provides funds to develop new NHP models and preliminary data that are absolutely essential if new external grant funding is to be obtained. It is still early for grant submissions to result from many of the Center-funded projects. However, the success of the program is evident from the significant number of publications and grant applications resulting from the completed projects.

There is a Center-wide process for soliciting, reviewing, approving and monitoring all Pilot Projects. The program announcement is sent out by email to the campus and contacts at the other NPRCs and posted on the ONPRC public website. Letters of Intent are reviewed by the ONPRC Research Advisory Committee (RAC) for scientific merit and for assessment of the impact on animal availability and housing requirements and appropriate full proposals are requested. The full proposals are reviewed by the RAC, appropriate NSAB members, and ad hoc experts as needed. Each proposal is scored 1-9 in the areas of significance, innovation, approach, investigator, environment, and overall. The proposal can be approved, returned with suggestions for revision, or rejected. Once approved, projects involving animals then must obtain IACUC approval before funding is initiated. Progress reports are submitted and reviewed on a yearly basis.

PILOT RESEARCH PROGRAM SPECIFIC AIMS

The goal of the ONPRC Pilot Project program is to encourage new avenues of investigation using appropriate nonhuman primate (NHP) models through the provision of funds for generation of preliminary data that can serve as the foundation for follow-up support from the NIH and other agencies and sources. This will be achieved through pursuit of the following Specific Aims:

Specific Aim 1. Solicit proposals from a wide spectrum of potential applicants through effective outreach at the institutional, local, and national levels. Annual announcements are circulated through e-mail and the ONPRC website to Center, OHSU, and NPRC consortium members to attract a robust response from interested parties.

Specific Aim 2. Employ a strong, credible, and transparent review process to select the most meritorious proposals. Proposals are evaluated through a two-step process that includes an initial assessment of letters of intent by the ONPRC Research Advisory Committee (RAC), followed by a request for full proposals from the highest-ranked preliminary proposals. These are then reviewed in depth by the ONPRC RAC and external *ad hoc* reviewers chosen from the ONPRC National Scientific Advisory Board (NSAB) and other entities as necessary for appropriate expertise.

Specific Aim 3. Monitor progress and outcomes to determine return on investment of allocated funds. Productivity in terms of manuscripts and grants submitted and awarded based on Pilot Program support are assessed through final reports and follow-up monitoring by the Associate Director for Research.

The ONPRC Pilot Project program plays a critical role in allowing investigators to develop research projects using NHPs, and is especially important for new investigators recruited to the ONPRC who lack significant prior NHP research experience. The program also provides funds for established investigators to develop new NHP models and preliminary data that are absolutely essential if new external grant funding is to be obtained.

PILOT RESEARCH PROGRAM RESEARCH STRATEGY

SIGNIFICANCE

The ability to generate preliminary data to demonstrate relevance and feasibility is crucial to the justification for funding for new research directions. Apart from start-up packages typically provided to newly-hired investigators, there are few other sources of funds available to initiate new projects. In addition, the inherently greater expense of NHP studies increases the need for access to adequate levels of pilot funding. Thus, a strong Pilot Program is crucial to the success of newly independent, NHP-focused investigators, the development of new directions for current NHP investigators, and for facilitating the entry of investigators with experience with other animal or clinical research areas into NHP research.

INNOVATION

The principal innovative aspect of the Pilot Project program is the nature of the projects supported. In addition, in the previous funding period, ONPRC partnered with the OHSU Clinical and Translational Science Award (CTSA) program-supported Oregon Clinical and Translational Research Institute (OCTRI) to fund a novel NPRC-CTSA joint pilot project program that is described below. A specific innovation to be pursued in the next funding period will be the development and deployment of a web-based pilot application through the ONPRC general website based on a similar program being developed by our OCTRI colleagues.

APPROACH

reviewers' comments

Progress Report.

In years 1 and 2 of the current funding period (P51 years 50-53), Pilot Program funds were used to support the 4 demonstration projects described in the P51 application for 2 years each. In year 3, 21 LOIs were submitted in response to the solicitation, of which 11 were requested to submit full proposals. Of these, 5 were funded. In year 4, 17 LOIs were submitted in response to the solicitation, of which 7 were requested to submit full proposals. Ten WaNPRC Ignition Award applications were considered for funding as well. Of these 17 full proposals reviewed, 4 were funded. A summary of the submitted LOIs and applications is provided in **Table 1**. The reviewers of proposals evaluated in the previous funding period are listed in **Table 2**. The awarded proposals and their funding amount is shown in **Table 3**. The return on investment in terms of publications and grants awarded, pending, or unfunded, is summarized in **Table 4**.

Table 1

	2009- Year 50	2011- Year 52	2012- Year 53	ONPRC/OCTRI- Year 3	Totals
# of letter of intents	17	21	17	9	
# of applications received	17	11	17	4	
# of applications funded.	4	5	4	2	2
# of internal funded PIs	4	2	4	Joint applications	2
# of external funded PIs	0	3	0	Joint applications	2
total amount of pilot funding	$ 600,000	$ 271,101	$ 200,000	$ 113,637	$ 113,637

Table 2

Pilot Reviewers	Department/Institution	Years Reviewed
Excluded by Requester	Professor and Director University of California, San Diego Department of Reproductive Medicine, SOM	2012- Year 53 2011- Year 52 2009- Year 50
	Director of Research Advovacy; OHSU Cell & Developmental Biology, Physiol & Pharmacology, Ob/Gyn	2012- Year 53 2011- Year 52 2009- Year 50
	Excluded by Requester, Professor University of Iowa Department of Molecular Physiology and Biophysics	2012- Year 53 2009- Year 50
	OHSU Oregon Clinical & Translational Research Institute	ONPRC/OCTRI 2012- Year 3
	Division of Neuroscience	2012- Year 53
	Division of Pathobiology & Immunology	2012- Year 53 2011- Year 52 2009- Year 50
	Radioimmunoassay Lab	2009- Year 50
	NIAID/NIH	2012- Year 53 2009- Year 50
	OHSU Department of Behavioral Neuroscience	ONPRC/OCTRI 2012- Year 3
	Virology Core	ONPRC/OCTRI 2012- Year 3
	NCI-Frederick, SAIC-Frederick	2012- Year 53 2009- Year 50
	Department of Neurobiology and Physiology Institute for Neuroscience Center for Reproductive Science Northwestern University	2009- Year 50
	Private Source	2012- Year 53 2009- Year 50
	OHSU Pediatrics; Vaccine & Gene Therapy Institute	ONPRC/OCTRI 2012- Year 3
	OHSU Pediatrics	ONPRC/OCTRI 2012- Year 3 2012- Year 53 2011- Year 52
	Department of Molecular Genetics & Microbiology University of Florida, College of Medicine	2012- Year 53 2009- Year 50
	Division of Neuroscience	2011- Year 52 2009- Year 50
	OHSU Department of Molecular Microbiology & Immunology	ONPRC/OCTRI 2012- Year 3
	Division of Pathobiology & Immunology	2012- Year 53 2011- Year 52 2009- Year 50
	OHSU Department of Medicine: Endocrinology, Diabetes & Clinical Nutrition	ONPRC/OCTRI 2012- Year 3

Excluded by Requester	Private Source	2012- Year 53 2009- Year 50
		2009- Year 50
	Division of Diabetes, Obesity, and Metabolism; Division of Reproductive & Developmental Sciences; OHSU Pediatrics	ONPRC/OCTRI 2012- Year 3 2012- Year 53 2011- Year 52 2009- Year 50
	Chief, Perinatology Research Branch Program Director for Obstetrics and Perinatology NICHD/NIH	2009- Year 50
	OHSU Department of Medicine: Endocrinology, Diabetes & Clinical Nutrition	ONPRC/OCTRI 2012- Year 3
	Division of Reproductive & Developmental Sciences	ONPRC/OCTRI 2012- Year 3 2012- Year 53 2011- Year 52 2009- Year 50
	Associate Director Division of Pathology, Yerkes National Primate Research Center	2011- Year 52
	Division of Pathobiology & Immunology	2012- Year 53 2011- Year 52 2009- Year 50

TABLE 3
Pilot Projects- year 50-53

PI	Title	2009- Year 50	2011- Year 52	2012- Year 53	ONPRC/OCTRI- Year 3
Excluded by Requester	Ex vivo analysis of primate islet function	$ 150,000			
	Deriving oocytes from ESCs	$ 150,000			
	Evaluation of normal and ectopic implantation with contrast-enhanced ultrasound.	$ 150,000			
	Determination of Immune Correlates of Protection for Chikungunya Virus Infections in a Nonhuman Primate Model	$ 150,000			
	T Cell responses during respiratory synctial virus infection in non-human primates.		$ 20,980		
	Does Leukemia Inhibiroty Factor serve as a Critical Regulator of Primate Oocyte Maturation and Ovulation?		$ 58,532		
	Development of Genome Editing Technology in NHP		$ 67,475		
	Development and Validation of a Novel MRI Biomarker of Myelin in a Non-Human Primate Model of MS		$ 55,888		
	Novel Method to Broaden Adaptive Immunity Against Variable Pathogens		$ 68,226		
	Multi-center Study of Genetic Influences on a wide range of Novel Disease Phenotypes in ONPRC Rhesus Macaques			$ 30,000	
	Development of a model to study the co-morbidity of nicotine and alcohol addiction and role of clinically relevant genetic polymorphisms			$ 70,000	
	Monkey OX40L development as a new potential therapy for AIDS			$ 30,000	
	Impact of the T cell modulator ORF 193 on monkeypox virulence.			$ 70,000	
	High resolution mapping of the AAV capsid amino acids responsible for neuronal and glial cell transduction in the nonhuman primate brain				$58,750 ONPRC, $8,750 OCTRI
	Inducing donor-specific tolerance through clonal deletion				$54,887 ONPRC, $5,757 OCTRI
	Totals per Year	$ 600,000	$ 271,101	$ 200,000	$113,637 ONPRC
		*Proposals were awarded $150,000 total over 2 years. ($75,000 per year)			

As illustrated in **Table 4**, all 4 of the initial 2-year Pilot Projects have contributed to a significant return on investment (ROI) with respect to funded and pending grant applications and publications. These four Pilot Projects have resulted in 12 publications to date and $4,711,278 in funded direct costs and

Pending Support

Pending Support,Evaluative Info,Unfunded Info

funding. Year 4 (P51 year 53) awards are not included in this analysis as they are still ongoing and no outcomes are available at this time. Thus, the Pilot Program has been very successful in terms of stimulating new research funding and publications, particularly with respect to the year 50 demonstration projects that were initially viewed as modestly competitive.

TABLE 4

Award Year	PI	Title	# of Publications	# of Grant Applications submitted	Total Direct Costs-Funded	Total Direct Costs-Pending	Total Direct Costs-Unfunded	Amount Awarded
ONPRC/OCTRI-Year 3	Excluded by Requester	High resolution mapping of the AAV capsid amino acids responsible for neuronal and glial cell transduction in the nonhuman primate brain						$ 67,500
ONPRC/OCTRI-Year 3		Inducing donor-specific tolerance through clonal deletion		1	$ 5,000	$ 210,000		$ 60,644
2012- Year 53		Impact of the T cell modulator ORF 193 on monkeypox virulence.						$ 70,000
2012- Year 53		Monkey OX40L development as a new potential therapy for AIDS						$ 30,000
2012-Year 53		Development of a model to study the co-morbidity of nicotine and alcohol addiction and role of clinically relevant genetic polymorphisms						$ 70,000
2012-Year 53		Multi-center Study of Genetic Influences on a wide range of Novel Disease Phenotypes in ONPRC Rhesus Macaques						$ 30,000
2011- Year 52		T Cell responses during respiratory synctial virus infection in non-human primates.						$ 20,980
2011- Year 52		Does Leukemia Inhibiroty Factor serve as a Critical Regulator of Primate Oocyte Maturation and Ovulation?		1	$ 275,000			$ 58,532
2011- Year 52		Development of Genome Editing Technology in NHP		1			$ 275,000	$ 67,475
2011- Year 52		Development and Validation of a Novel MRI Biomarker of Myelin in a Non-Human Primate Model of MS		1	$ 1,476,000			$ 55,888
2011- Year 52		Novel Method to Broaden Adaptive Immunity Against Variable Pathogens						$ 68,226
2009- Year 50		Deriving oocytes from ESCs	8	1		$ 1,986,500		$ 150,000
2009-Year 50		Ex vivo analysis of primate islet function	2	9	$ 3,595,002	$ 320,637		$ 150,000
2009- Year 50		Evaluation of normal and ectopic implantation with contrast-enhanced ultrasound.	1	3	$ 959,490	$ 1,372,742		$ 150,000
2009- Year 50		Determination of Immune Correlates of Protection for Chikungunya Virus Infections in a Nonhuman Primate Model	3	2	$ 156,786			$ 150,000
Totals			14	19	$ 6,467,278	$ 3,889,879	$ 275,000	$ 1,199,245

In addition to the regular ONPRC Pilot Project program, ONPRC and OCTRI established a novel joint pilot program in 2010 in reponse to a mandate from the NCRR encouraging increased interaction between the NCRR-supported NPRC and CTSA programs. This program requires the participation of two co-PIs, one

ONPRC investigator and one from the OHSU main campus representing OCTRI. The solicitation process, review of LOIs, and review of full proposals is similar to the process described in Specific Aim 2 below for regular ONPRC pilot projects, except that the management of this joint program was the responsibility of OCTRI for the initial 2 years (2010 and 2011), with the next two years (2012 and 2013) being managed by ONPRC. The review of LOIs is done by a committee comprised of representatives from the ONPRC RAC and the OCTRI Review Committee, and full proposals are reviewed by this committee as well as by two additional ONPRC/OCTRI investigators chosen for their expertise in the appropriate area.

In 2012 (P51 year 53), the first year of ONPRC funding of this joint program, 9 LOIs were submitted in response to the solicitation, of which 4 were requested to submit full proposals. Two were awarded. The reviewers for these joint pilot proposals are also included in **Table 2**. The final year of this joint program will be 2013, the last budget year before the new funding period, and $100,000 will be allocated for this program. These peojects are still ongoing, so no specific outcomes are available at this time. In light of the dissolution of the NCRR and the transfer of the CTSA and NPRC programs to different components of NIH (i.e., NCATS and OD/ORIP, respectively), this joint program will not be continued in the next funding period.

Specific Aims/Plans for the Next Funding Period.

Specific Aim 1. Solicit proposals from a wide spectrum of potential applicants through effective outreach at the institutional, local, and national levels.
Program announcements describing the ONPRC Pilot Project program, its funding levels, application procedures, and regulatory requirements are sent out on an annual basis by email to all ONPRC core and affliliate scientists, OHSU faculty (including all OCTRI-affiliated investigators), to all of the members of the NPRC consortium, and also posted on the ONPRC website. Prospective applicants are directed to submit initial letters of intent (LOI), which are evaluated through the process detailed in the following section. In the next funding period, we plan on introducing a web-enabled application process through the ONPRC website. A program is currently being developed at OHSU for the OCTRI pilot program, and we will adapt this mechanism for the ONPRC program with appropriate modifications.

Specific Aim 2. Employ a strong, credible, and transparent review process to select the most meritorious proposals.
LOIs submitted by the posted deadline are reviewed by the ONPRC Research Advisory Committee (RAC) for scientific merit and for assessment of the impact on animal availability and housing requirements. Approximately 8-10 of the top-ranked LOIs are selected for submission of full proposals, which are then evaluated using a 9-point scale based on standard NIH research project criteria of significance, innovation, approach, investigator, environment, and overall impact. Full proposals are reviewed by the RAC, and each proposal is also reviewed by two members of the SAB and/or other external reviewers with appropriate expertise. Feedback is not provided on LOIs, but reviews are provided to applicants asked to submit full proposals. Generally, 4-5 proposals are approved for funding (up to a maximum level of $75,000/yr), and are initiated following IACUC and other necessary approvals (i.e., IBC, etc.).

Specific Aim 3. Monitor progress and outcomes to determine return on investment of allocated funds.
All funded Pilot Projects are required to submit a progress report at the end of the funding period (typically 1 year). Requests for a 1-year no-cost extension may be granted based on appropriate justification and submission of the progress report. A final report is required at the end of any no-cost extension period. Ongoing tracking of submitted grants and publications resulting from Pilot Program funding is done by the Associate Director for Research office.

PILOT PROGRAM PUBLICATIONS

Excluded by Requester

PILOT PROJECT TITLE: Deriving Oocytes from Embryonic Stem Cells
Name, Title, & Affiliation of the Principal Investigator: Excluded by Requester Senior Scientist, ONPRC
Year(s) funded: 2009-2011

Abstract, including Specific Aims.
Embryonic Stem Cells (ESCs) can proliferate indefinitely while maintaining an undifferentiated pluripotent state and when allowed, differentiate into any cell type of an adult body and, ultimately, these cells can be utilized for the treatment of a wide range of human conditions that can be attributed to the loss or malfunction of specific cell types. The PI has demonstrated for the first time that adult primate skin cells can be reprogrammed to ESCs by somatic cell nuclear transfer (SCNT), thus completely abrogating immune rejection concerns. Recent advances indicate that ESCs support formation of the earliest stages of germ lineage in vitro. However, in vitro differentiation of ESCs into functional haploid oocytes and sperm is challenging, making clinical applications in infertility untenable at this time. The goal of this proposal is to evaluate the potential of monkey ESCs to contribute to the female germ cell lineage, and to explore the feasibility of deriving functional oocytes suitable for use in ARTs. Our main hypothesis is that primate ESCs derived by fertilization, SCNT, or parthenogenesis are capable of forming female germ cells and gametes upon spontaneous or directed differentiation. To achieve our goal, we propose to accomplish two Specific Aims: 1) To evaluate the potential of monkey ESCs to contribute to female germ cells upon spontaneous in vivo and in vitro differentiation; and 2) To develop optimal culture conditions for directed differentiation of monkey ESCs to oogonia and oocytes. Successful completion of the proposed studies will result in significant advances in stem cell and developmental biology in general and promote utilization of therapeutic cloning and assisted reproductive technologies for deriving patient-related oocytes and embryos for treatment of female infertility.

Excluded by Requester

Grant applications and funded grants resulting from the pilot project

Pending Support

PILOT PROJECT TITLE: Ex Vivo Analysis of Primate Islet Function
Name, Title, & affiliation of the Principal Investigator: Excluded by Requester Senior Scientist, ONPRC
Year(s) funded: 2009-2011

Abstract, including Specific Aims.
Type-1 diabetes mellitus (T1DM) is characterized by autoimmune-mediated β-cell destruction, while T2DM is characterized by progressive β-cell insufficiency. The transition from pre-diabetes to frank T2DM occurs when β-cell function becomes inadequate to maintain insulin levels high enough to overcome peripheral insulin resistance. Thus, β-cell failure is the critical defect in both T1 and T2DM. The successful treatment of T1DM and comprehensive therapy for T2DM will involve the propagation, maintenance, or restoration of β-cell/islet function, which requires an understanding of the requirements for the survival, function, and potential expansion of intact islets ex vivo. We hypothesize that novel culture techniques will increase ex vivo primate islet survival and function and amenability to molecular analyses. We will address this hypothesis through the following specific aims: 1) Determine the effects of physiological O_2 and microgravity/3-D culture on islet survival, integrity, and function; 2) Assess the effect of current diabetes therapies on the function of isolated primate islets. 3) Assess potential factors stimulating β-cell replication.

This proposal will employ non-human primate islets that closely approximate human islets in order to examine both basic and translational aspects of islet function, treatment response, and potential for islet cell propagation.

Excluded by Requester

Grant applications and funded grants resulting from the pilot project.

Funded

1. Private Source investigator-initiated sponsored research program proposal 08-009ALO, "Effects of alogliptin on primate islet function," 2009-2010, $103,750 DC (PI).
2. P51 RR000163-50S4 Excluded by R "High-fat diet-induced alterations in gene expression in the nonhuman primate," 2009, $350,000 DC (co-investigator).
3. 1U01 DK089572 Excluded by "Molecular mechanisms of human and murine beta cell proliferation and regeneration," 2010-2015, $1,500,000/yr (co-investigator on ONPRC subcontract).
4. RC4 DK090956 Excluded b "Neuroendocrine response to gastric bypass in nonhuman primates," 2010-2012, $488,170/yr (co-investigator on Excluded b ONPRC subcontract).
5. R24 DK093437 Excluded by Molecular mechanisms underlying NHP pancreatic beta cell failure and recovery, 2011-2012, $300,000 DC (MPI).
6. Private Source investigator-initiated studies program proposal #39570, "Control of glucagon secretion by native and DPP-4-processed GLP-1," 2011-2012, $120,994 DC (PI).
7. Private Source research grant Excluded by Reque "In vitro and in vivo evaluation of aged native glucagon: lack of cytotoxicity and preservation of hyperglycemic effect," 2012-2013, $732088 DC (co-investigator).

Pending Support

PILOT PROJECT TITLE: Evaluation of Normal and Ectopic Implantation with Contrast-Enhanced Ultrasound

Name, Title, & affiliation of the Principal Investigator: Excluded by Requester PhD Associate Scientist, ONPRC
Year(s) funded: 2009-2011

Abstract, including Specific Aims.
Our goal was to perform studies on early intrauterine pregnancy (IUP) in rhesus macaques. During pregnancy, the vessels of the endometrium are extensively modified to provide blood flow to the growing conceptus. Contrast-enhanced ultrasound (CEU) is a new technique capable of high-resolution imaging of the microvasculature within organs. The method relies on the detection of gas-filled microbubbles that are injected intravenously while imaging by ultrasound. Our hypothesis was that CEU imaging could permit earlier visualization of embryo implantation and, for the first time, a detailed evaluation of the growing endometrial vessels at the fetal-maternal interface. Our Specific Aim was to develop microbubble CEU for visualization of early pregnancy and assessment of intrauterine vascular parameters during embryo implantation in rhesus macaques. We demonstrated that CEU can identify the primary placental lobe and underlying vessels ~2 days earlier than the conventional method, Doppler Ultrasound (DUS), which only detected pregnancy-associated endometrial thickening. CEU revealed changes in vascular perfusion between the endometrium, myometrium, and the endometrial-myometrial junctional zone. In addition to the high rate of blood flow to the growing conceptus, CEU identified a high rate of blood flow to the myometrium (>10 mL/min/g tissue), with less flow in the endometrium and endometrial-myometrial zone (<3 mL/min/g) distant from the site of implantation. We concluded that CEU provides a sensitive, non-invasive method to assess vascular perfusion of the macaque uterus during embryo implantation. We propose CEU as a new diagnostic tool to monitor vascular changes associated with early pregnancy in women.

Excluded by Requester

Grant applications and funded grants resulting from the pilot project

1. Pending Support
2.
3. Competitive renewal for CDRC U54 HD 055744-01Project 3; Excluded by Requester (coPI) Direct Costs $959,490 (5 years; funded)

PILOT PROJECT TITLE: Determination of Immune Correlates of Protection for Chikungunya Virus Injections in a Nonhuman Primate Model

Name, Title, & affiliation of the Principal Investigator: Excluded by Requester PhD, Asst. Professor, VGTI/OHSU
Year(s) funded: 2009-2011

Abstract, including Specific Aims.
The goal of this study is to elucidate the immunological basis of increased susceptibility of aged individuals to Chikungunya virus (CHIKV) infection using a non-human primate (NHP) model. CHIKV, a NIAID Category C Biological Agent, is a re-emerging arbovirus that caused massive recent outbreaks in the Indian Ocean. To date, infections have been limited to Africa and the Indian Ocean Region; however, recent outbreaks in Europe have increased worldwide awareness of this debilitating and potentially lethal viral infection. Importantly, the mosquitoes that transmit CHIKV are now found in much of the United States making CHIKV spread possible in the US. While CHIK is not considered to be life-threatening, over 200 fatalities were associated with the disease on the French island of Reunion in the Indian Ocean in 2005-6. Additionally, virus-induced arthritis can be extremely debilitating and last for weeks to years in the aged. Severe cases involving infections of the central nervous system have also been described in immune compromised individuals, including the elderly. We propose to compare the pathophysiology of CHIKV infection and identify age-related differences in adaptive immunity that underlie increased disease severity in the elderly using a NHP model of CHIKV infection.

Specific Aims:

1) To determine the clinical progression of disease and characterize the immune responses to CHIKV in adult vs. aged RM. We will determine the effect of age on CHIKV pathogenesis by measuring: 1) T & B cell proliferation and activation in response to infection; 2) the magnitude and kinetics of antigen-specific responses; 3) viral load kinetics, tissue specificity and cellular tropism; and 4) physiological parameters associated with disease.
2) To determine the immune correlates of protection to CHIKV infection. In this aim, we will determine the correlates of immune protection to CHIKV infection and disease in RM by depleting CD4 or CD8 T cells or B cells and by following virus dissemination and disease parameters.

Full bibliographic material on each paper published, in press or submitted, resulting from pilot project.
Excluded by Requester

Grant applications and funded grants resulting from the pilot project.
Identification of Age-Related Defects to CHIKV Infections in a NHP Model
NIH/NIAID Pacific NorthWest Regional Center of Excellence Developmental Research Project
U54 AI081680 Excluded by Requester (PI) 03/01/11 – 02/28/14

Antibody-Based Therapy of Chikungunya Virus
NIH/NIAID
R01AI089591-03 Sub Award: WU-13-152 Excluded by Requester (PI) 12/1/2012 - 12/31/2013

PILOT PROJECT TITLE: Analysis of the host response to simian hemorrhagic fever infection in rhesus macaques.

Name, Title, & affiliation of the Principal Investigator: Excluded by Requester PhD, Regents' Professor, Department of Biology, Georgia State University, Atlanta, GA
Year(s) funded: 2010

Abstract, including Specific Aims.
Innate cellular responses allow a host to restrict the replication/spread of a pathogen until the adaptive immune mechanisms can be mobilized. Occasionally, a pathogen that is new to a host, such as simian hemorrhagic fever virus (SHFV) in macaques, can both evoke an inflammatory response as well as overcome the innate barriers that normally restrict pathogen dissemination resulting in a massive systemic release of inflammatory mediators and the death of the host. Such a scenario is common to all viral hemorrhagic fevers and to bacterial septic shock (Bray, 2005). BSL4-level hemorrhagic fever viruses, such as Ebola and Marburg, could be exploited in the future by terrorists as biological weapons. To date, there are no effective therapies available for prophylaxis or treatment of viral hemorrhagic disease in humans. The major challenge for the development of "generic" countermeasures for viral hemorrhagic fevers and septic shock is to block harmful host responses without impairing the ability of the host to eliminate the pathogen. Many aspects of the disease observed in SHFV-infected macaques are similar to those observed in Ebola Zaire virus-infected macaques. The main advantage of the SHFV-macaque hemorrhagic fever model is that it is safe for humans and only requires BSL2 level containment. However, infected macaques must be isolated from uninfected macaques because of the possibility of aerosol transmission between infected macaques. The successful development of an SHFV-macaque hemorrhagic disease model would provide significant advantages for the testing of new therapies for hemorrhagic disease. As a first step toward the further development of an SHFV hemorrhagic fever model, additional preliminary data about host cell-virus interactions must be obtained. Recent technical advances in the construction of infectious clones of large RNA viruses and in the analysis of cellular and cytokine responses in non-human primates as well as in the detection of SHFV and virus-infected cells now provide the means of further investigating virus-host interactions during the development of SHFV-induced hemorrhagic fever disease in macaques.

Specific Aims.
Aim 1: To validate the virulence of the SHFV stock used to make an SHFV infectious clone in macaques.
Aim 2: To analyze the kinetics of viremia and cytokine production after SHFV infection in macaques.
Aim 3: To analyze the cellular immune responses in SHFV-infected macaques.
Aim 4: To document the symptoms and pathology induced by an SHFV infection.

Full bibliographic material on each paper published, in press or submitted, resulting from pilot project.
In Preparation

Grant applications and funded grants resulting from the pilot project.
Pending Support

PILOT PROJECT TITLE: Time-course of gene expression changes in response to acute ethanol: epigenetic mechanisms

Name, Title, & affiliation of the Principal Investigator: Excluded by Requester PhD, ONPRC
Year(s) funded: 2010-2012

Abstract, including Specific Aims.
Alcoholism can be a life-long struggle, implying persistent neural adaptations. Recent work using human blood samples (i.e., alcoholics versus controls) suggests that alcohol can induce epigenetic modifications of DNA [i.e., cytosine methylation at cytosine-phosphate-guanine (CpG) dinucleotides]. However, this could relate to the diagnosis, co-morbidities or pre-disposing factors rather than exposure to ethanol. It is unknown whether ethanol can affect CpG methylation. The proposed studies will fill this gap in knowledge by testing the hypothesis that acute ethanol increases CpG methylation in blood and brain in rhesus macaques.

The proposed studies are unique, and distinct from any previous work conducted in the Excluded by Requester Lab, which is primarily behavioral. The proposed studies in epigenetics are not just a minor change in standard procedures in the Excluded by Requester Lab - they are completely new. Furthermore, no studies in any lab have studied epigenetic effects of ethanol in primates. This is not just a specialized interest. Of course, ethanol is the most widely abused substance among humans. Importantly, many of the endogenous substrates for the receptors mediating the effects of ethanol are steroids or neurotransmitters with key roles in regulating physiological systems that respond to stress [hypothalamic-pituitary-adrenal (HPA) axis]. Thus, studying the epigenetic effects of ethanol is a translationally relevant gateway toward studying how DNA modifications affect function of the HPA axis, which is affected in many neuropsychiatric diseases. Epigenetic modifications could be an important mechanism underlying physiological homeostasis following stress, including ethanol.

Specific Aim: Determine whether a single large dose of ethanol induces epigenetic modification of DNA. The time-course of these studies (0, 2 h, 24 h) will maximize the utility of an existing data set generated by a procedure conducted by the Excluded by Requester Lab. Specifically, Excluded by Requester administered 2.0 g/kg ethanol (i.v.; 8-drink equivalent) or saline to 1.0-1.5-y old macaques for a behavioral study about three years ago. By chance, 2-3 d before the test, blood was collected from these subjects for extraction of DNA. No samples were collected from these subjects until Excluded by Requester completed the longitudinal data set by extracting DNA from blood samples she collected in spring-fall 2010 (N = 90). This aim will add important early time-points to this longitudinal data set for analysis of epigenetic modifications of ethanol in genome-wide and in candidate genes. Two of the candidate genes are involved in monoamine metabolism (monoamine oxidase A, MAOA; dopamine transporter, DAT) and are reported to be hypermethylated in alcoholics compared to controls. The third candidate gene (aldehyde dehydrogenase 2, ALDH2) regulates levels of aldehyde intermediates produced by monoamine and ethanol metabolism, has been suggested to mediate the behavioral effects of ethanol, and contains one of the strongest genetic associations with alcoholism.

Full bibliographic material on each paper published, in press or submitted, resulting from pilot project.
None.

Grant applications and funded grants resulting from the pilot project.
1. Unfunded Info
2.

PILOT PROJECT TITLE: Transudation characteristics of passively administered IgG (binding and neutralizing antibodies purified from SIV-infected rhesus macaques) in oral and esophageal mucosal and lymphatic tissues of uninfected and SIV-infected rhesus macaques

Name, Title, & affiliation of the Principal Investigator: Excluded by Requester MD, Post-Doc Researcher, ONPRC
Year(s) funded: 2010

Abstract, including Specific Aims.
Passively transferred neutralizing antibodies (NAbs) protect against mucosal virus challenge in non-human primate (NHP) models of HIV-1 infection. Although the protection afforded by the presence of the NAbs can be correlated to an easily quantifiable concentration in serum or plasma of treated animals, reported concentrations of transferred NAbs in mucosal secretions at the site of virus challenge have been varied and inconsistent. Consequently, there is limited understanding of the amount and timing of the appearance of transferred NAbs in mucosal and lymphoid tissue. It is generally accepted, however, that only a narrow window of opportunity exists for NAbs to intercept virus in the mucosa and regional lymphatics prior to systemic virus spread. A practical and reliable process to detect and quantify the amounts of functional NAbs distributed to the relevant tissues at sites of potential virus exposure is needed. Therefore, we describe here a simple technique to extract and measure passively transferred NAbs in mucosal and lymphatic tissues of rhesus macaques. In a timed serial sacrifice experiment, we pre-treated four macaques with 200 mg/kg of SIVIG, a polyclonal NAb IgG preparation specific for SIV gp130 glycoprotein. We collected blood and mucosal secretions beginning 3 hours after NAb subcutaneous delivery continuing at specified time points until necropsy. Lymph node and mucosal biopsies were performed at selected sites and time points. The 4 animals were serially necropsied at 9 hours, 48 hours, 1 week, and 2 weeks after NAb treatment. Mucosal and lymphatic tissue specimens were collected at 14 different sites relevant to oral, rectal, and vaginal mucosal transmission. We detected and quantified the passively transferred NAb in all tissue types and determined the anatomic distribution and kinetics of the NAb *in vivo*. Further, we demonstrate that our tissue preparations provide a more reliable and consistent source for evaluating the distribution and kinetics of infused antibody preparations in the mucosal compartment compared to secretions. This approach can enhance future evaluations of newly isolated monoclonal antibodies and engineered antibodies in their efficacy as therapeutics and in the assessment of antigen-specific antibody responses elicited in vaccine studies for a range of pathogens transmitted across mucosal surfaces.

Specific Aims. The overall project goal is to develop protocols to detect and determine kinetics of passively administered IgG neutralizing antibodies in oral mucosal secretions and tissues, tonsils, esophageal and duodenal mucosal tissue, and regional lymph node tissues in macaques receiving passive neutralizing antibody treatment via subcutaneous administration.

1. Measure localization and kinetics of passively administered SIVIG treatment in 2 uninfected macaques to determine baseline detection, levels and rates of decay.

2. Measure presence and levels of specific anti-SIVgp130 antibody as well as SIV antigen in plasma and tissues at 24h and approximately 2 weeks post virus challenge in 2 additional animals. Immunohistochemistry for evaluation of co-localization of anti-SIVgp130 antibody with SIV antigens will also be performed on tissue specimens from the animal infected for 2 weeks.

Full bibliographic material on each paper published, in press or submitted, resulting from pilot project.
None

Grant applications and funded grants resulting from the pilot project.
None

PILOT PROJECT TITLE: Characterization of Host and Viral Factors that contribute to Herpes Zoster

Name, Title, & affiliation of the Principal Investigator: Excluded by Requester PhD, Assistant Scientist, ONPRC.
Year(s) funded: 2010

Abstract, including Specific Aims.
Reactivation of latent varicella zoster virus (VZV) leads to herpes zoster (HZ, also known as shingles), a disease that causes major morbidity and occasionally mortality in older individuals. Advanced age is the primary risk factor not only for developing HZ, but also complications such as post herpetic neuralgia. Current estimates predict that by 2020 more than 70 million Americans will be over the age of 65; therefore, the incidence of HZ and associated complications will certainly increase. Furthermore, the currently approved vaccine against HZ reduces the incidence of shingles by only 51%. Thus, a significant portion of the vaccine recipients still remains susceptible to VZV reactivation. Unfortunately, our understanding of the host and viral factors that result in VZV reactivation remains very limited. We have recently developed a nonhuman primate model wherein young rhesus macaques infected with a the highly homologous simian varicella virus (SVV), display the hallmarks of VZV infection in humans; i.e., the appearance of generalized varicella rash, the development of cellular and humoral immunity, and the establishment of latency with limited transcriptional activity in sensory ganglia. This is the only animal model that recapitulates both immunological and virological hallmarks of VZV infection. In this application, we propose to enhance this model by characterization virological and immunological factors that lead to reactivation by completing the three aims below:

Specific aim 1: Developing a protocol to induce SVV reactivation in rhesus macaques
Specific aim 2: characterize viral transcriptional program associated with reactivation
Specific aim 3: Characterize the role of ORF 61 in the establishment of latency and reactivation

Full bibliographic material on each paper published, in press or submitted, resulting from pilot project.
Excluded by Requester

Grant applications and funded grants resulting from the pilot project.
Supplement to 1 R01 AG037042-01 ($90K) 09/1/2012-3/31/2013 NIH/NIA
Impact of immune senescence on herpes zoster in a nonhuman primate model
Role: PI

PILOT PROJECT TITLE: Assessment of the role of IL-15 in acute Simian Immunodeficiency Virus (SIV) infection.

Name, Title, & affiliation of the Principal Investigator: Excluded by Requester PhD, Staff Scientist I, VGTI/OHSU
Year(s) funded: 2010

Abstract, including Specific Aims.
HIV and pathogenic SIV infection is characterized by a state of hyper immune activation, which is thought to play a major role in the dysregulation and ultimate failure of CD4+ memory T cell homeostasis. IL-15 a proinflammatory cytokine produced by cells of the innate immune system upon ligation of toll-like receptors with their ligands and induction of type I interferons. Recent studies have suggested that IL-15 may play a significant role in acute HIV/SIV infection. Plasma isolated from women during acute HIV infection revealed that the level of certain plasma cytokines including IL-15 predicted 66% of variation in viral loads. In particular, the level of IL-15 was significantly associated with higher plasma viral load set points. In nonhuman primates, IL-15 production is increased during acute SIV infection leading to an upregulation of CD4 expression on CD4+ memory T cells, increasing their susceptibility to SIV infection. Our goal is to use the rhesus anti-IL-15 monoclonal antibody (rhM111) to neutralize IL-15 signaling during acute SIV infection to delineate the contribution of IL-15 to immune activation, target cell availability and virus replication set points.

Specific Aims
1. To determine whether anti-IL-15 treatment during acute SIV infection affects T cell activation, proliferation and functionality.
2. To determine whether anti-IL-15 treatment during acute SIV infection results in lower peak and plateau phase plasma viral load set points.
3. To determine whether anti-IL-15 treatment leads to a reduction in the levels of pro-inflammatory cytokines and lower levels of immune activation.

Full bibliographic material on each paper published, in press or submitted, resulting from pilot project.
None

Grant applications and funded grants resulting from the pilot project.
None

PILOT PROJECT TITLE: Characterization of *Neisseria* colonization and genetic exchange in rhesus macaques.

Name, Title, & affiliation of the Principal Investigator: Excluded by Requester PhD, Research Assistant Professor, BIO5 Institute, University of Arizona
Year(s) funded: 2010

Abstract, including Specific Aims.
The genus *Neisseria* contains at least 19 species of Gram-negative β-proteobacteria. They colonize mucosal surfaces of a range of animals, including humans and nonhuman primates. Two species of *Neisseria* are associated with disease in humans, *Neisseria meningitidis* and *Neisseria gonorrhoeae*. *N. meningitidis*, a significant cause of morbidity and mortality, results in over 500,000 cases of invasive disease annually, often resulting in meningococcal meningitis and septicemia. Polysaccharide-based meningococcal vaccines are available for some serotypes but are not efficacious in the most at risk population, the very young. *N. gonorrhoeae* causes gonorrhea, a sexually transmitted disease that results in >62 million cases worldwide each year. While not life-threatening, *N. gonorrhoeae* promotes HIV transmission and results in high health care costs associated with multiple sequelae that lead to infertility. The development of antibiotic resistance in *N. gonorrhoeae* has limited effective treatment to a single antibiotic, there is no vaccine available and infection does not promote lasting immunity. Both pathogenic species are carried asymptomatically in 10% to >60% of the population depending on the study group analyzed. Animal models that allow characterization of how *Neisseria* species colonize and persist are greatly needed. One avenue that has not been explored is the development of animal models for *Neisseria* species isolated from their native host. We have isolated *Neisseria* species from rhesus macaques (RM). In this pilot, we aim specifically to establish the following:

Specific Aim 1: Establish a colonization model for *Neisseria* species in rhesus macaques.
Specific Aim 2: Detect genetic exchange between *Neisseria* strains over time as they persist in their host.

Full bibliographic material on each paper published, in press or submitted, resulting from pilot project.

In Press

Grant applications and funded grants resulting from the pilot project.

Pending Support

PILOT PROJECT TITLE: T Cell responses during respiratory syncytial virus infection in non-human primates.

Name, Title, & affiliation of the Principal Investigator: Excluded by Requester PhD, Associate Professor of Pediatrics, Ohio State University
Year(s) funded: 2011-2012

Abstract, including Specific Aims.
Purpose: To define mechanisms of T cell immunity in young rhesus macaques during primary RSV infection. Hypothesis: Different functional populations of CD4 and CD8 T cells will cooperate to confer optimal protective immunity to RSV.

Rationale: The precise mechanisms by which T cells protect from pathogenic RSV infection or contribute to disease are not yet fully understood. Studies in mice have shown that T cells are critical for RSV clearance, but whether or not this happens in humans or non-human primates remains to be demonstrated. Severe human lower respiratory tract disease caused by RSV correlates with the absence of pulmonary CD8 T cell responses, but the mechanisms by which T cells control RSV infection remain unknown. Preliminary results from our laboratory show that protection from RSV challenge correlated with a robust anti-RSV F protein CD8 T cell response. Based on these findings, we hypothesized that induction of T cell immunity is critical for the control of RSV infection. To test this hypothesis we need to develop a non-human primate model of RSV infection. Although macaque models of RSV infection have been used to test the safety and immunogenicity of vaccine candidates, the antigen-specific T cell response against RSV has not been characterized. Thus, in this pilot study we propose to develop an experimental model of RSV infection in young rhesus macaques to characterize T cell responses. The rationale for our proposed research is that, once we have a non-human primate model where the role and functional characteristics of RSV-specific T cells can be understood, we will be able to design strategies to manipulate the outcome of T lymphocyte responses that may results in the development of new approaches to induce immunity or to prevent inflammation.

Specific Aims.
1. To determine clinical, viral and immune parameters of RSV infection in rhesus macaques.
2. To define the kinetic relationship between RSV-specific T cell responses and the clinical course of infection.
3. To determine the functional characteristics of RSV-specific T lymphocytes during primary infection.

Full bibliographic material on each paper published, in press or submitted, resulting from pilot project.
None. Animals have just become available for project.

Grant applications and funded grants resulting from the pilot project.
None.

PILOT PROJECT TITLE: Development of Genome Editing Technology in Nonhuman Primates

Name, Title, & Affiliation of the Principal Investigator: Excluded by Requester PhD, Staff Scientist I, ONPRC
Year(s) funded: 2011-2012

Abstract, including Specific Aims.
Not every human genetic disease can be modeled in mice. There are two main reasons for this: First, the mouse ortholog to a human gene of interest may not exist, as illustrated by the absence in rodents of DIRAS3, a tumor suppressor gene that encodes the signaling protein GTP-binding RAS-like 3. Second, if the mouse ortholog gene does exist, its deletion may not recreate the phenotype described in humans. An example of this situation is provided by the hypoxanthine phosphoribosyltransferase 1 (HPRT) gene, which is mutated in Leisch-Nyhan disease. The vast majority of genetic models of human disease have utilized the mouse as an experimental animal due to the relative ease with which genetically modified animals can be produced by engineering embryonic stem (ES) cells and creating chimeric animals able to transmit the desired mutations via the germline. Generating nonhuman primate mutants (NHPs) using ES cells would be prohibitively expensive and inefficient, since producing homozygote animals with the desired genetic modification would take at least 10 years.

It appears now clear that this difficulty could be potentially overcome by the use of "genome-editing technology" (GET), a technique initially developed using Drosophila melanogaster. GET has been applied to mammalian species and promises to extend our genomic engineering capabilities to cells and entire organisms from any species. GET enables efficient and precise genetic modification via the induction of a double-strand break (DSB) in a specific genomic target sequence, followed by the generation of desired modifications during subsequent DNA break repair. The DSB is induced by a 'zinc finger nuclease' (ZFN), which is a designed, sequence-specific endonuclease that can be customized to cleave a user-chosen DNA target. *Because many genetic diseases are caused by mutations or deletions of single genes, we propose to use the ZFN technology to rapidly and specifically create targeted mutations of endogenous NHP genes, thus mimicking all the molecular and pathological events seen in human disease.*

Specific Aim. To develop the ZFN technology for the targeted disruption of rhesus macaque DIRAS3 and HPRT1 genes. Bioinformatics analysis of the rhesus DIRAS3 and HPRT1 genes show potential target sites for the development of ZFN with high binding activity and low off-target effects. To generate ZFNs, we first need to develop two new methodologies: A) The construction of combinatorial zinc-finger libraries for the creation of multi-finger arrays that recognize the 9 bp target site at the gene of interest, and B) A bacterial two-hybrid assay (B2H) to identify which one of the multi-finger arrays possesses high affinity and high specificity. We estimate that setting up these methodologies will require about a year of work.

Full bibliographic material on each paper published, in press or submitted, resulting from pilot project.
None

Grant applications and funded grants resulting from the pilot project.
Application number: 1 R21 RR033307-01
Unfunded Info

PILOT PROJECT TITLE: Development and Validation of a Novel MRI Biomarker of Myelin in a Non-Human Primate Model of MS

Name, Title, & Affiliation of the Principal Investigator: Excluded by Requester, Senior Scientist, OHSU
Year(s) funded: 2011-2012

Abstract, including Specific Aims.
Disorders of the myelin sheath are numerous; multiple sclerosis is perhaps the best-known disease, but there are many other including transverse myelitis, acute disseminated encephalomyelitis and the leukodystrophies. Subtle developmental abnormalities of myelin have been implicated in attention deficit hyperactivity disorder, autism, and schizophrenia. Age-related loss of myelin and its compactness may be a risk factor or contributor to senile dementias. The overall aim of this project is to develop and validate a non-invasive MRI measure that will serve as a robust in vivo biomarker of myelin. It is expected that this biomarker will be capable to provide information on both the quantity and quality of myelin throughout the CNS. This project is developmental in nature and proposes the leverage of an ongoing Department of Defense (DoD) funded project, "Therapeutic Remyelination Strategies in a Novel Model of Multiple Sclerosis: Japanese Macaque Encephalomyelitis" Excluded by Requester PIs) to more efficiently achieve the study aims.

The following specific aims are proposed:
Aim 1: To develop quantitative relaxographic MRI techniques that provide precise and reproducible measurement of myelin-associated water in the Japanese macaque central nervous system (CNS).
Aim 2: To investigate longitudinal changes of myelin content in JME lesions.

Full bibliographic material on each paper published, in press or submitted, resulting from pilot project.
None. Work in progress.

Grant applications resulting from the pilot project.
NIH/NINDS P01 (Overall PI Excluded by Requester Project 3 PI: Rooney) 07/01/12-06/30/17
"Japanese macaque encephalomyelitis: a spontaneous nonhuman primate model of multiple sclerosis."
Project 3:" MRI Biomarkers of Neuroinflammation and Angiogenesis in JME." Total (Project 3 only): $1,476,000

Pending Support

PILOT PROJECT TITLE: Novel Method to Broaden Adaptive Immunity Against Variable Pathogens

Name, Title, & Affiliation of the Principal Investigator: Excluded by Requester Assistant Scientist, VGTI/OHSU
Year(s) funded: 2011-2012

Abstract, including Specific Aims.
Addressing the extreme antigenic diversity of HIV-1 is one of the top challenges facing the scientific community. While considerable work has been done over the past decade in vector development, relatively little progress has been made towards understanding what an optimal HIV-1 vaccine insert would be. The goal of this proposal is to test the hypothesis that a novel vaccine design, which increases the diversity of the vaccine antigen with no a priori knowledge of variant pathogen sequences, will broaden the cellular immune response. To this end, we will characterize the diversity of both antigenic sequences generated *in vitro* and the breadth and depth of CD8+ T cell responses engendered *in vivo* using the SIV-infected macaque model of HIV. We hope these studies will provide preliminary data for a R01 submission and lay the foundation for future experiments to test if increased CD8+ T cell breadth and depth engendered by our vaccine construct will protect against a heterologous, low dose mucosal SIV challenge.

Specific Aim 1. Characterize the full diversity of antigen produced from the CURVE vaccine construct. Clone SIVsmE543-3 *gag* and *env* into our diversity-engendering vaccine construct, named CURVE, and use ultradeep 454 pyrosequencing to assess the full diversity of the antigenic sequences produced.

Specific Aim 2. Characterize the breadth and depth of the CD8+ T cell response in CURVE-E543-3-Gag/Env-vaccinated Indian rhesus macaques. Vaccinate 4 Mamu-A*01 positive Indian rhesus macaques with CURVE-E543-3-Gag and -Env. Measure the breadth and depth of the CD8+ T cell response engendered.

Full bibliographic material on each paper published, in press or submitted, resulting from pilot project.
None.

Grant applications and funded grants resulting from the pilot project.
none

PILOT PROJECT TITLE: The Role of ORF197 for Virulence of Monkeypox Virus

Name, Title, & Affiliation of the Principal Investigator Excluded by Requester PhD, Senior Scientist, VGTI/OHSU
Year(s) funded: 2012

Abstract, including Specific Aims.
In contrast to vaccinia virus (VACV), which strongly stimulates T cells, monkeypox virus (MPXV) inhibits T cell stimulation by an unprecedented molecular mechanism. Specifically, we demonstrated that human T cells become unresponsive in the presence of MPXV-infected cells even when strong external stimuli such as anti-CD3 antibodies are used. This novel type of immune evasion mechanism raised the question how MPXV achieves this inhibition and how this T cell stunning affects MPXV virulence as well as the ability of MPXV to evade vaccine-induced T cell immunity. We hypothesize a) that open reading frame (ORF) 197 contributes in a significant way to MPXV virulence and b) that ORF197 helps MPXV to escape vaccine-induced T cells. In this pilot project, we propose to test the first part of this hypothesis. Our preliminary data suggest that MPXV lacking ORF197 no longer inhibits the stimulation of poxvirus-specific T cells or stimulation of T cells by anti-CD3. Thus, ORF197 seems to be the only gene in MPXV mediating T-cell evasion. Importantly, this gene is conserved in Variola major virus (VARV), the causative agent of smallpox. The only other homologue is found in cowpox virus, a related orthopoxvirus (OPXV) that contains at least two additional T cell evasion genes. In contrast, VACV does not encode this gene. To test the hypothesis that ORF197 is a key virulence factor we propose the following specific aim.

Specific Aim 1: To compare the virulence of recombinant MPXV lacking ORF197 to parental wild type MPXV. Eight age and sex-matched rhesus macaques (RM) will be intra-bronchially (*ib*) inoculated with MPXV. The animals will be divided into two groups of 4 animals each. Group 1 will be experimentally inoculated with 2 x 10^5 plaque forming units (PFU) of parental wild type MPXV strain US2003 and serve as controls. Group 2 will be inoculated with 2 x 10^5 PFU of recombinant MPXV-strain US2003 lacking ORF197. The animals will be followed on a daily basis to document changes in their clinical status, including temperature, activity and overall health and enumeration of the number of pox lesions. Additional measures will include measure of peripheral viral load, kinetics and magnitude of the host adaptive immune response, and comparative histopathological examination.

Full bibliographic material on each paper published, in press or submitted, resulting from pilot project.
None.

Grant applications and funded grants resulting from the pilot project.
None.

PILOT PROJECT TITLE: Mechanism of AAV-Mediated Transduction in the Nonhuman Primate Brain

Name, Title, & Affiliation of the Principal Investigator: Excluded by Requester MD, PhD, Associate Professor, OHSU; Gregory Dissen, PhD, Staff Scientist III, ONPRC.
Year(s) funded: 2012

Abstract, including Specific Aims.
The long-term goal of this new collaborative project is to understand the mechanism of adeno-associated virus (AAV) vector transduction in the nonhuman primate (NHP) central nervous system (CNS) and establish more effective and safer AAV-mediated CNS gene therapy approaches that have broader clinical applications. In this pilot project, we will a) test the feasibility of using AAV Barcode-Seq, a novel approach we developed, to study functional significance of each of the amino acids in the AAV capsid protein, and b) generate preliminary data that address the mechanism of neuronal and glial cell transduction for future extramural grant applications. To this end, we propose the following specific aims:

Specific Aim 1: To establish proof-of-principle for the use of AAV Barcode-Seq to study the AAV biology in the NHP CNS. We will generate an AAV library comprising 10 AAV serotypes and 118 AAV9 capsid mutants. These mutants derive from a group of 191 AAV9 capsid mutants we already engineered to assess functional and structural significance of all 381 amino acids in the entire C-terminal half of the viral capsid. The library will contain only 118 mutants, because 73 of the original 191 mutants exhibited significant impairment of intact particle formation, and therefore, need to be excluded. Each of the serotypes and mutants in the library is composed of 2 viral clones whose viral genomes are tagged with clone-specific DNA barcodes. The AAV library will be injected into the cisterna magna of 3 adult rhesus macaques, and various CNS and peripheral samples will be collected. Then the biological properties of each serotype and mutant in various samples will be determined by massively parallel Illumina sequencing. We have named this approach "AAV Barcode-Seq". The results will not only establish proof-of-principle for the approach but also elucidate in a high-throughput manner the capsid amino acids responsible for manifesting each targeting phenotype.

Specific Aim 2: To create a high-resolution map of the AAV capsid amino acids responsible for neuronal and/or glial cell transduction in the NHP CNS. We will create an AAV library containing 118 AAV9 mutants, each of which composed of 4 viral clones tagged with clone-specific DNA barcodes. Of the 4 clones in each mutant, 2 clones are designed to express clone-specific RNA barcodes on in neurons and the other 2 are designed to express clone-specific RNA barcodes in glial cells. Synapsin 1 and glial fibrillary acidic protein promoters will be used to drive neuron and glial cell-specific expression, respectively. The library will be injected into 3 adult rhesus macaques as described above. The transduction in neurons and glial cells with each viral clone will be assessed in various CNS regions by AAV Barcod-Seq of the viral RNA barcodes. The results will allow high resolution mapping of the AAV capsid amino acids responsible for neuronal and/or glial cell transduction in the NHP CNS.

Full bibliographic material on each paper published, in press or submitted, resulting from pilot project.
None

Grant applications and funded grants resulting from the pilot project.
None

PILOT PROJECT TITLE: Inducing Donor-Specific Tolerance Through Clonal Deletion

Name, Title, & Affiliation of the Principal Investigator Excluded by Requester PhD, Assistant Scientist, VGTI/ONPRC; Excluded by Requester MD, Professor, OHSU
Year(s) funded: 2012

Abstract, including Specific Aims.
Each year there are ~16,000 kidney transplants performed in the U.S. Transplant recipients rely on immunosuppressive drugs, which must be taken for life. The long-term complications of immunosuppression include increased susceptibility to infections and cancers as well as specific side effects of the drugs, including nephrotoxicity. Therefore, there is an urgent need to discover novel approaches to induce donor-specific tolerance in transplant recipients, thus eliminating the need for long-term immunosuppression. Our long-term goal is to induce donor-specific tolerance in a rhesus monkey model of kidney transplantation using a novel approach to specifically eliminate allospecific lymphocytes. Our working hypothesis is that performing donor specific lymphocyte transfusion (DST) will induce the activation of alloreactive lymphocytes that can subsequently be removed using specific depletion reagents. This approach presents a highly innovative way to prevent solid organ transplant rejection by both immunodepleting and immunomodulatory mechanisms.

This proposal has two aims that will support the overall goals of this pilot project:

Aim 1: To define the appropriate dose of donor lymphocytes necessary to provoke an alloresponse.
Prior studies using DST in humans used variable methods and doses of donor blood cell preparations to induce tolerance. The most promising studies used peripheral blood mononuclear cells (PBMC) only, but the appropriate dose was never defined. We will use an adaptive study design starting with 1 x 10^8 cells followed by dose escalation or de-escalation as needed. The development of the alloresponse will be monitored by measuring: 1) upregulation of activation markers on recipient T and B cells; 2) increased proliferation of T and B cells; 3) T cell cytokine production in response to stimulation with donor PBMC; and 4) generation of donor-specific alloantibodies.

Aim 2: To optimize dose of new immune-modulating drugs to deplete alloreactive lymphocytes.
We will optimize the dose and timing of Brentuximab vedotin, an immune-modulating drug that has recently been approved by the FDA to treat CD30+ B cell lymphomas. This drug also targets activated T and B cells, which upregulate CD30. We propose to use Brentuximab vedotin to eliminate alloreactive T and B cells activated by DST. The success of this approach will be evaluated by repeating the DST 3 weeks after the last Brentuximab vedotin administration and assessing alloreactive T and B cell activation using the same methods described in specific aim 1.

Full bibliographic material on each paper published, in press or submitted, resulting from pilot project.
None.

Grant applications and funded grants resulting from the pilot project.
Pending SRA with Seattle Genetics

PILOT PROJECT TITLE: Monkey OX40L Development as a New Potential Therapy for AIDS

Name, Title, & Affiliation of the Principal Investigator: [Excluded by Requester] PhD, Assistant Professor, VGTI/OHSU

Year(s) funded: 2012

Abstract, including Specific Aims.

A variety of pathogenic mechanisms have been proposed to be responsible for AIDS pathogenesis in humans and AIDS-susceptible nonhuman primates (NHPs). We, and others, have previously shown that disease progression in pathogenic simian immunodeficiency virus (SIV) infection of rhesus macaques (RM) is associated with the irreversible loss of central memory CD4+ T cells caused by both direct virus infection and chronic immune activation. OX40 (CD134) is a member of the tumor necrosis factor (TNF) receptor family molecules expressed primarily on activated CD4+ and CD8+ T cells. The ligand for OX40 (OX40L, CD252) belongs to the TNF superfamily, and is expressed on professional antigen-presenting cells (APC) such as mature dendritic cells, activated B cells and macrophages. The interaction between OX40 and OX40L provides an important co-stimulatory signal to activated T cells, leading to the expansion and survival of antigen-specific activated T cells. Therefore, it has been an attractive target to modulate immune responses. We hypothesize that the cellular activation pathway OX40/OX40L *in vivo* could enhance T cell activation, proliferation, and function resulting in improved overall T cell function and homeostasis without significant triggering of unbalanced immune activation. Our plan in this Pilot study includes the following Specific Aims:

Specific Aim 1: To determine in vivo activity of a novel monkey OX40L for T cell proliferation, activation, and function in normal healthy macaques.

Specific Aim 2: To assess whether the expected enhanced activation of T cells seen in Aim #1 restores T cell homeostasis in persistent SIV infection.

Full bibliographic material on each paper published, in press or submitted, resulting from pilot project.

None.

Grant applications and funded grants resulting from the pilot project.

None.

PILOT PROJECT TITLE: Development of a Model to Study the Co-Morbidity of Nicotine and Alcohol Addiction and Role of Clinically Relevant Genetic Polymorphisms

Name, Title, & Affiliation of the Principal Investigator: Excluded by Requester PhD, Senior Scientist, ONPRC
Year(s) funded: 2012

Abstract, including Specific Aims.
This is a pilot project to develop a model to study nicotine and alcohol co-morbidities. As such, it falls within the interest of the new addiction working group and represents a completely new collaboration between the investigators named above and a new area of research. It also represents support for a junior investigator, Dr. Excluded by to transition to monkey research from a strong background in alcohol/nicotine interactions in mice. Nicotine and alcohol addictions are major public health issues and clearly interact. The majority of alcoholics smoke, but not all smokers drink, and the rate of smoking increases as alcohol consumption increases. The purpose of this project is to develop a nicotine self-administration paradigm to complement Dr. Grant's existing alcohol self-administration paradigm, then determine how prior nicotine use affects alcohol self-administration and vice versa. In addition, we will study how the predisposition to excessive nicotine consumption, excessive alcohol consumption, and the interaction of the two are affected by the single-nucleotide polymorphism (SNP) rs16969968, in which amino acid 398 of the α5 nicotinic acetylcholine receptor (nAChR) is mutated from an Asp to Asn (α5 D398N). This common polymorphism has been shown in genome-wide association studies (GWAS) and targeted studies to increase risk of nicotine, alcohol, and polydrug addictions, and is an area of intense investigation of addictive mechanisms. Remarkably, we have discovered that cynomolgus monkeys also express this polymorphism, allowing us to assess the role and mechanisms of his polymorphism for addictions in a non-human primate model. Thus, the specific aims of this application are:

1. To develop an oral nicotine self-administration model in cynomolgus monkeys and determine how the α5 D398N SNP affects nicotine consumption.
2. To combine this model with the existing Grant alcohol self-administration model;
3. To determine how prior nicotine addiction affects alcohol addiction and
4. To determine how the α5 nAChR SNP modifies these addictions.

Full bibliographic material on each paper published, in press or submitted, resulting from pilot project.
None

Grant applications and funded grants resulting from the pilot project.
None.

PILOT PROJECT TITLE: A Multi-Center Study of Genetic Contributions to a Wide Range of Novel Disease Phenotypes in Rhesus Macaques

Name, Title, & Affiliation of the Principal Investigator: Excluded by Requester PhD, Assistant Professor, ONPRC.
Year(s) funded: 2012

Abstract, including Specific Aims.
The ONPRC has unparalleled resources for genetic studies of complex disease, in which the primary goal is to characterize the contribution of genes (i.e., heritability) relative to environmental influences, and ultimately to identify functional genetic variants (i.e., gene mapping) across the genome that influence susceptibility to disease. Accordingly, we have developed a large, powerful pedigree of ONPRC rhesus macaques designed for this research purpose, and have additionally collected blood samples and measures of morphometry and adiposity on the majority of these animals to date, to support extensive phenotyping. We have already demonstrated the power of these resources by finding significant heritability for a number of established risk factors for human cardiovascular disease and obesity. These initial results have led to significant interest among investigators at this and other institutions in characterizing heritability for complex traits relevant to their own research, in order to support future proposals aimed at identifying influential genetic variants. Here, we propose to investigate the feasibility of exponentially expanding genetic analysis in this pedigree by assaying 300 animals for 15 risk factors for complex diseases of shared interest among 7 primate research centers. The specific aims of this project are to:

1) Characterize the distribution of normal baseline variation in multiple phenotypes that are established risk factors for human disease in 300 healthy, unchallenged rhesus macaques.

2) Assess genetic contributions to these risk factors, which have never before been investigated for heritability in rhesus macaques. We will test hypotheses of a significant genetic contribution to normal variation in multiple risk factors for complex disease in pedigreed rhesus macaques.
This project is important because the demonstration of heritability is a critical prerequisite for obtaining future funding to identify functional genetic variants using this pedigree. Results from this pilot project will: 1) provide a first-ever description of heritability of important risk factors for human disease in rhesus macaques; 2) establish a model for future multi-center collaboration in genetic studies of complex disease in ONPRC macaques; and 3) enhance the success of future grant proposals by identifying promising phenotypes for further pursuit.

Full bibliographic material on each paper published, in press or submitted, resulting from pilot project.
None

Grant applications and funded grants resulting from the pilot project.
none

Program Director/Principal Investigator (Last, First, Middle): Robertson, Joseph E./Haigwood, Nancy L.

PILOT RESEARCH PROGRAM DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
SUBTOTALS →						0	0	0
CONSULTANT COSTS								
None Requested							0	0
EQUIPMENT *(Itemize)*								
None Requested							0	0
SUPPLIES *(Itemize by category)*								
None Requested							0	
								0
TRAVEL								
None Requested							0	0
INPATIENT CARE COSTS								0
OUTPATIENT CARE COSTS								0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*								
None Requested							0	0
OTHER EXPENSES *(Itemize by category)*								
Pilot Research Program							300,000	
								300,000
CONSORTIUM/CONTRACTUAL COSTS						DIRECT COSTS		0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*								$ 300,000
CONSORTIUM/CONTRACTUAL COSTS						FACILITIES AND ADMINISTRATIVE COSTS		0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD								$ 300,000

PHS 398 (Rev. 6/09) **Form Page 4**

PILOT RESEARCH PROGRAM
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	0	0	0	0	0
CONSULTANT COSTS	0	0	0	0	0
EQUIPMENT	0	0	0	0	0
SUPPLIES	0	0	0	0	0
TRAVEL	0	0	0	0	0
INPATIENTS CARE COSTS	0	0	0	0	0
OUTPATIENTS CARE COSTS	0	0	0	0	0
ALTERATIONS AND RENOVATIONS	0	0	0	0	0
OTHER EXPENSES	300,000	300,000	300,000	300,000	300,000
DIRECT CONSORTIUM/CONTRACTUAL COSTS					
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	300,000	300,000	300,000	300,000	300,000
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	300,000	300,000	300,000	300,000	300,000
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					1,500,000

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

PERSONNEL
None requested

CONSULTANT COSTS
None requested

SUPPLIES
None requested

TRAVEL
None requested

OTHER EXPENSES
Funds are requested in the amount of $300,000 per year (per FOA guidelines) to allow investigators to develop pilot projects using NHPs. Providing funds to develop new NHP models and preliminary data are absolutely essential if new external grant funding is to be obtained. Proposed projects must be submitted to, and approved by, ONPRC Research Advisory Committee (RAC). Each project will be limited to $100,000 per year, with a limit of two years of funding, per ORIP guidelines.

Pilot Research Program Income Table

Last Funded Year (53)

Source	Funding (direct costs)
P51 base grant support	$300,000.00
Program income derived from P51 base grant	0
Other Sources	0
Total	$300,000.00

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$300,000.00
Program income derived from P51 base grant	0
Other Sources	0
Total	$300,000.00

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

TITLE: IMPROVEMENT & MODERNIZATION

CORE-SUPPORTED PERSONNEL:

Personnel are not supported by Improvement & Modernization.

IMPROVEMENT AND MODERNIZATION

DESCRIPTION:

Improvement and Modernization (I&M) funds are provided up to a maximum of $600,000 per year. These funds can be used to upgrade the physical plant (repairs and renovation of facilities) and to replace obsolete shared resources and equipment (FOA, IV. G.). At ONPRC, Facilities, the Division of Comparative Medicine (DCM), Information Systems (IS), and the Research Support Cores provide shared resources to support the NHP research mission of ONPRC. Items are requested by each of these areas, individually justified, and then a committee works with the requestors to prioritize the requests to insure the continued improvement and modernization of these shared resources, and that the requests contribute to the fulfillment of the goals of the ONPRC as described in the P51 award application.

IMPROVEMENT AND MODERNIZATION: SPECIFIC AIMS

Improvement and Modernization (I&M) funds are provided up to a maximum of $600,000 per year. These funds can be used to upgrade the physical plant (repairs and renovation of facilities) and to replace obsolete shared resources and equipment (FOA, IV. G.). At ONPRC, Facilities, the Division of Comparative Medicine (DCM), Information Systems (IS), and the Research Support Cores provide shared resources to support the NHP research mission of ONPRC. Items are requested by each of these areas, individually justified, and then a committee works with the requestors to prioritize the requests to insure the continued improvement and modernization of these shared resources and that the requests contribute to the fulfillment of the goals of the ONPRC. A distinction is made between routine maintenance items provided by Facilities and specialized improvement/maintenance programs aimed toward the long-term preservation of the integrity and functionality of our facilities. Routine maintenance is included in the Facilities operations budget; specialized improvement/maintenance is included in the I&M budget. The amount provided through this mechanism is an integral part of a larger effort to provide for the comprehensive upkeep and improvement of the ONPRC facilities and resources that are used for NHP research and support.

Through these funds I&M supports:

- Improvement and modernization of buildings and equipment used in support of the NHP resources and research through Facilities requests.
- Improvement and modernization of Research Support Core equipment used in support of NHP Research through requests from the individual Research Support Cores.
- Improvement and modernization of Information Systems specific to the NHP related work of the ONPRC such as the PRIMe system and NHP research related bioinformatics through requests from the ONPRC Information Systems.
- Improvement and modernization of the DCM resources that provide for the care of our NHP colony through requests from DCM.

Specific Aim 1: To appropriately identify, justify, and prioritize requests for the improvement and modernization of ONPRC resulting in improved equipment and facilities specifically related to NHP research and support.

Specific Aim 2: To provide for the timely implementation of the approved requests through skilled professionals resulting in efficient and effective use of the improved resources.

IMPROVEMENTS AND MODERNIZATION RESEARCH STRATEGY.

SIGNIFICANCE.

Improvement and Modernization (I&M) funds are provided up to a maximum of $600,000 per year. These funds can be used to upgrade the physical plant (repairs and renovation of facilities) and to replace obsolete shared resources and equipment (FOA, IV. G.). At ONPRC, Facilities, the Division of Comparative Medicine (DCM), Information Systems (IS), and the Research Support Cores provide shared resources to support the NHP research mission of ONPRC. Items are requested by each of these areas, individually justified, and then a committee works with the requestors to prioritize the requests to insure the continued improvement and modernization of these shared resources and that the requests contribute to the fulfillment of the goals of the ONPRC. A distinction is made between routine maintenance items provided by Facilities and specialized improvement/maintenance programs aimed toward the long-term preservation of the integrity and functionality of our facilities. Routine maintenance is included in the Facilities operations budget; specialized improvement/maintenance is included in the I&M budget. The amount provided through this mechanism is an integral part of a larger effort to provide for the comprehensive upkeep and improvement of the ONPRC facilities and resources that are used for NHP research and support. This larger effort makes use of the OHSU capital request process and ONPRC program income if available for this purpose, along with the I&M funds to address the long-term needs of facility and resource improvement and modernization.

The ONPRC Facilities group uses a number of methods to develop comprehensive maintenance plans for the campus buildings and its supporting infrastructure: 1) Information pertaining to all mechanical and electrical components on the campus are recorded in a Computerized Maintenance Management System (CMMS) database. Along with the nameplate data for all of this equipment, this database also includes the manufacturers recommended maintenance schedules, including frequency and types of maintenance that should be performed on a yearly basis. This information is used to produce Preventative Maintenance work orders on a monthly basis, which are issued to the facilities staff and then recorded in the database after completion, thereby providing an ongoing status of each piece of equipment. The database also includes the commissioning date for each piece of equipment which allows the establishment of projected useful life, which is turn will allow for a predicted or recommended replacement date that can be used in developing our five year preventive and predicted maintenance plan. 2) Use of industry standards, such as those produced by IFMA, the International Facility Management Association, and BOMA, the Building Owners and Managers association. These standards are based on many years of actual industry data and are updated on a regular basis by soliciting input from members around the world. As an example, the industry standard for office painting is every 8-10 years, the industry standard for replacement of water heaters is every 10-12 years, the industry standard for re-lamping of buildings is every 3-4 years, etc. Using these types of standards allows us to predict when various components will require replacement or component rebuild, such as the internal rebuild of our boilers and chillers. Along with actual staff observations of needed maintenance, repairs, or replacements, we can utilize the combination of these two methods to accurately predict and develop a comprehensive plan for maintaining the campus infrastructure and building components. 3) Strategic planning and assessments by management of needs to modernize our resources are also employed. This is the case in the strategic decision to replace the aging IRIS electronic health record system with PRIMe which is based on LabKey.

INNOVATION

Historically Information Systems has not been included in the I&M budgeting process. Because the Electronic Health Records system is a key component to the infrastructure support at the ONPRC, that historical pattern is being changed in this application.

A strategic review of our Information Systems department in 2010 and 2011 by the Ad Hoc IT Advisory Committee showed that the IS department had suffered from a lack of a strong, comprehensive managerial vision. The committee report included the following bullet points outlining the effect of this.

- The absence of strong, comprehensive managerial vision for IS has at least the following effects:
  - There is no comprehensive effort to assess the current and future campus IS needs and therefore the means to solve those needs.
    - Problems are identified organically as they arise and are solved as time and resources allow.
    - Overall managerial consideration of campus IS needs is reactive.
    - Existing aspects of the system reflect historical needs. IRIS deals with clinical care of animals. Desktop Support deals mainly with desktop computers. IS and bioinformatics partnership initiatives that support the operational and research needs of ONPRC science largely do not exist.
      - The operational needs of science include aspects such as complex local area network support, database set up and management, access control, lab data backup, and complex server needs.
      - The research needs of science include aspects such as data mining and next-gen sequencing.
  - The lack of strategic planning in the ONPRC IS department results in the following departmental modus operandi:
    - Making things work on a day to day basis with limited resources to meet user needs. When daily demands do not occupy time fully, employees will work on upgrading and expanding systems based on user requests.
  - No identifiable formal structure exists to facilitate planning for major improvements and identifying future needs.

The results of the committee's evaluation and recommendation resulted in the hiring of a new IS manager to lead the process of creating a comprehensive managerial vision for IS. This vision has resulted in the replacement of an aging IRIS system with the PRIMe system based on LabKey. Another change that appropriately follows is to insure that the IS infrastructure resources have sufficient funding and are included IS in the annual I&M allocation. This change from prior applications is reflected in the budget being submitted with this core application and is focused primarily on the continued development of the PRIMe system to meet the needs of a state-of-the-art electronic health records system for NHP care.

APPROACH

reviewers' comments

Progress Report and Major Accomplishments.

I&M expenditures over the past five-year period are summarized in the following table.

I/M Expenditures Yr 50 - 54

	Yr 50	Yr 51	Yr 52	Yr 53*	Yr 54**
Alterations and Renovations	309,429	232,851	259,391	153,560	255,000
Equipment	331,413	231,241	502,670	95,591	345,000
Total* **	640,842	464,092	762,061	249,151	600,000

*Yr 53 represents expenditures through 12/31/12

** Yr 54 represents the I&M budget plan

***Total includes approved carryforward amounts causing average spending to exceed $600,000 per year during years 50 through 53.

Accomplishments of this five-year period are highlighted below.

Significant equipment (> $10,000) purchases through I&M funding for the period of May 1, 2009 through December 31, 2012 are as follows:

NHP Racks with Cages (DCM)	$264,600
Endoscopy Unit (DCM)	$25,922
Microscope (DCM)	$20,908
Sedecal 32 KW Frequency X-Ray Generator (DCM)	$19,983
55 Britz Rack Modifications for ASA operation (DCM)	$121,044
Forklift (DCM)	$18,727
Bronchoscope (DCM)	$11,022
Real-time PCR System (Molecular & Cell Biology)	$58,302
Type A2 Biological Safety Cabinet (Endocrine)	$10,198
Tissue Tek Embedding Center (DCM)	$10,948
NHP Racks with Cages (DCM)	$122,006
VS2 & HM2 Machine (DCM)	$22,495
Transfer/Jump Boxes (DCM)	$15,000
Pentra 60 C+ with work station (DCM)	$34,493
Integrated syst. for generation of DNA clonal clusters (Genetics)	$45,450
Promega Maxell Extraction System (Virology)	$11,056
Cages repair & maintenance (DCM)	$106,650
One over One Socialization Racks (DCM)	$123,750
Analyzer (Pentra 400) (DCM)	$48,849
Polycom HD (IS)	$12,742
Vehicles - 2 (Facilities and DCM)	$19,500
Animal Resources Simulation Software Deveopment (DCM)	$14,500

The Facilities and Property Management unit managed and completed the following I&M projects to specific buildings during the past five years:

Administration Building

- Siesmic upgrades ($62,823)
- Renovation of IS Office areas ($25,765)

Facility Security

- Reinsulate piping around the boiler ($10,317)

Cellular & Molecular Biology (Cooley)
- Generator Upgrade with PENS Tie-in Capability ($41,636)
- Replace vacuum pump ($25,940)

Central Stores Building
- Replace siding ($12,392)

Facility Security
- Water Heater Replacement ($13,511)

Corrals
- Extended pavement to Specific Animal Locati ($40,037)
- Specific Animal Loc Upgrades ($57,029)

KROC
- Water Heater Replacement ($13,512)

Montagna Auditorium
- Replace hardie siding ($56,990)

MRI Building
- Upgrades to electrical and other aspects of building to accommodate MRI upgrades ($67,265)

Physical Plant
- Replace the roof of the Physical Plant Office ($76,770)
- HVAC Replacement ($14,777)
- Chiller #1 Rebuild ($96,096)
- Water Heater Replacement ($19,471)

Research Building
- Endocrine Core Lab Move and Renovation ($23,666)

Facilities General
- Pressure wash, paint and seal/coat building exteriors (surface maintenance program)
- Epoxy floors in animal areas
- Paint interiors of animal rooms, corridors and labs
- Re-lamping of campus buildings
- Replacement/Upgrade of Fire Alarm Dialers
- Parking lot resurfacing
- Installation of Water Quality Treatment Swale B

PLANS FOR THE NEXT 5 YEARS

In the next five-year period, funds are requested for areas outlined in the following table to fulfill the specific aims for Improvements and Modernization (all items are individually itemized within the budget justification).

Improvement & Modernization
Request Summary Next Five Years

	Support Cores	Facilities	Info. Systems	DCM	Total
YEAR 55	$131,100	$169,000	$44,000	$255,900	$600,000
YEAR 56	98,500	220,000	44,000	237,500	600,000
YEAR 57	76,300	196,500	50,800	276,400	600,000
YEAR 58	100,200	251,000	37,500	211,300	600,000
YEAR 59	39,000	239,000	76,500	245,500	600,000
Total	$445,100	$1,075,500	$252,800	$1,226,600	$3,000,000

Specific Aim 1 – To appropriately identify, justify, and prioritize requests for the improvement and modernization of ONPRC resulting in improved equipment and facilities specifically related to NHP research and support. Each major infrastructure area works to identify equipment and alteration and renovation needs that have a significant impact on the NHP research and support work of the ONPRC.

In the case of the Support Cores, the Director of those cores will meet with its oversight committee and discuss the status of the core's work and volume, technological changes, and whether it makes sense to replace equipment or adopt new technologies. The core Director will then propose I&M equipment purchases that are supported by the committee to the Associate Director for Research with a justification of the need. With his approval, these items are assigned for review by the I&M review committee.

Facilities uses the standards described in the introduction (like BOMA and IFMA) and the expertise of their staff members to prioritize requests for equipment and for alterations and renovations. These are discussed by the Facilities Manager with the Associate Director for Administration and then if agreed upon, submitted to I&M committee for review.

Information Systems uses ONPRC staff expertise and expertise of members of OHSU ITG (such as expertise of employees in the Advanced Computing Center) to make recommendations for equipment purchases that are taken by the Manager, Information Services to the Associate Director for Administration for review of justifications and prioritization. If agreed upon, items are submitted to the I&M Committee for review.

DCM makes use of their staff expertise in their respective areas to evaluate the needs for the care and support of the NHP colony. The managers and veterinarian staff meet to discuss needs with the Associate Director for DCM and the justification for the items are reviewed then items are prioritized for submission to the I&M committee.

Each area is responsible to get quotes for proposed equipment purchases, and Facilities makes use of both internal pricing expertise and contractors to provide accurate price estimates for alterations and renovations. These quotes and estimates are used to support the amount being requested. It should be noted that some equipment, especially IS equipment, can be configured with a variable number of components. A good example is the Powervault MD 1200 storage arrays plus hard drives for Biostatistics. These units are quoted with all the hard drives purchased, however that may not be needed depending on storage requirements at the time. Another example is that in the alternation and renovation industry a contractor will typically only guarantee a quote for 90 days. It is understood that there are both escalation and changes in technology which may increase, keep constant, or decrease the future price. Therefore the amount allocated in the I&M request is an estimate at today's rates and may occasionally even be different than the quote.

Currently the I&M Committee membership is composed of four members the Associate Director for DCM, the Associate Director for Administration, the Chief, Division of Reproductive and Developmental Sciences, and the Manager, Business Services. Each member takes responsibility for one of the four areas to make sure that justifications are clear, and if they are not clear they will contact the manager of the appropriate area to ask for clarification of the justification.

The committee then meets as needed to present the items on their list to the other members for review and questions. This normally results in an iterative process in which certain questions are taken by the members back to the manager of the particular area for further clarification and updates. Once the committee has clarity on the requests and their priority, they create a master list from which items of high priority and close match to the NHP aims and goals of the P51 award are selected for funding through the I&M funds.

Items not selected are kept on the master list and the Associate Director for Administration along with the Director work on other sources of funding. One common source is the OHSU capital request process. Alteration and Renovation items are considered annually for funding beginning January by the OHSU Space Committee. Equipment requests are submitted into the University equipment budgeting process in March. Through an allocation and prioritization process, some funding is provided annually to institutes like the ONPRC for requested items.

This continuing annual process provides the means to identify, justify, and prioritize the improvements and modernization needs for the NHP research and support work at the ONPRC and meet the Specific Aim 1.

Specific Aim 2 – To provide for the timely implementation of the approved requests through skilled professionals resulting in efficient and effective use of the improved resources. The timely implementation of improvements and modernization is a very important aspect of an efficient and effective program. One waste of resources that must continually be identified and avoided is the purchase of equipment or alteration and renovation of a building simply because it was scheduled.

One recent example of this was the scheduled replacement of a chiller at the Facilities Building. A review of the chiller by our staff and outside experts at the expected time of replacement showed that the chiller could be rebuilt at a substantial cost savings and because of excellent maintenance over the years, would still have an appropriate lifespan. At the same time, social housing requirements were being given increased priority and used primate caging became available at a substantially reduced price. Through a review of priorities and this opportunity, a decision was made to rebuild, rather than replace, the chiller freeing up funding that could be put toward the purchase of improved caging for NHPs.

This continual assessment takes place throughout the year at meetings between the Associate Director of Administration and Facilities and IS, between the Associate Director for Research and the Support Cores, and between the Associate Director for DCM and his staff. The assessment assumes the I&M plan, but uses the expertise of internal staff and outside resources to review the constantly changing environment and needs of the ONPRC. The Associate Directors and the I&M Committee have the commitment that any changes in the I&M plan must comply with the aims and goals of the P51 award and be clearly in support of the NHP research and care at the ONPRC.

Another matter that affects the timely implementation of the I&M plan is that other sources of funding may be identified during the five-year grant period for particular approved and planned projects. A replacement of the HVAC system in the Colony Annex was planned for year 53, however a request to change an awarded G20 to remodel the Colony Annex was approved and within this project's total funding was sufficient funding for an HVAC system upgrade. This Colony Annex project does not yet have final approval at the writing of this grant, but as soon as approval is granted, the Facilities Manager, the Associate Director for Administration, and the I&M Committee will work on repurposing these funds.

In these decisions, both for the five-year plan as presented in this document, and for any adjustments to the plan on an annual basis, it is extremely important to the ONPRC leadership that the appropriately skilled individuals and teams work on these decisions.

Weekly meetings take place between the Facilities Manager and the Associate Director for Administration in which the qualifications and performance of professional consultants and contractors are evaluated for our continued use of their skills. Although OHSU has lists of pre-approved contractors for various purposes such as architectural services and general contractor services, not all of these contractors have the requisite skills to perform alterations and renovations for primate housing. There is a continual effort to identify the appropriate teams of individuals that can advise and perform to excellent standards.

In the same way, DCM, IT, and Research Support Cores work to make sure that decisions to upgrade or change technology have a sufficient base of expert input to make an informed decision. In the case of IS, along with the expert advice of staff within the ONPRC, consultation with individuals at other NPRCs with experience in ARMS and LabKey, an outside consulting firm was hired to do an evaluation of the main choices for our Electronic Health Records system. Those choices were primarily upgrading the current system, building a new system, converting to ARMS, or converting to LabKey. The consulting firm was part of the decision making process that lead to the adoption of LabKey as the basis for our new PRIMe system, a system that is also installed at the Wisconsin National Primate Research Center.

Efforts such as the above are the result of constant work to evaluate our I&M decisions in order to make the most effective and efficient use of these funds as is reasonably possible. It is our goal that the identification, justification, prioritization, and implementation of I&M purchases would reflect the highest standards of quality decision making and provide for the continual improvement and modernization of the ONPRC facilities and equipment.

Program Director/Principal Investigator (Last, First, Middle): Robertson, Joseph E./Haigwood, Nancy L.

MODERNIZATION AND IMPROVEMENT DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*

Use Cal, Acad, or Summer to Enter Months Devoted to Project

Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
None Requested								0
SUBTOTALS →								0

CONSULTANT COSTS		
None Requested		0
EQUIPMENT *(Itemize)*		
10 Channel Perkin Elmer gamma counter	54,000	
ViiA 7 Real-Time PCR System	40,000	
Inverted flourescence microscope	37,800	
Install new autoclave in the Research Building	38,700	
Vehicle replacement	10,000	
Development of PRIMe software through Labkey	25,000	
Bioinformatics server	10,100	
Powervault MD 1200 storage arrays with hard drives	11,200	
Istat1 blood gas units (2)	15,000	
Squeeze boxes (2)	5,500	
Specific Animal Location tall squeeze double cages for use in animal rooms with hanging cages (30)	126,000	
tall squeeze doubles to replace the Specific Animal Locati tall Nursery cages (16)	69,600	
Vaporized Hydrogen Peroxide Decontamination unit	110,000	
Mobile satelite indoor racks (2)	5,000	
Transfer box replacement	10,800	
Golf cart with P/U bed	4,000	
Endoscope refurbishment/replacement	10,000	
Digital Dental Radiography	7,300	
		590,000
TRAVEL		0
None Requested		0
INPATIENT CARE COSTS		0
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		
Lighting efficiency upgrades throughout campus	10,000	
		10,000
OTHER EXPENSES *(Itemize by category)*		
None Requested		0

CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 600,000
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 600,000

MODERNIZATION AND IMPROVEMENT
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	0	0	0	0	0
CONSULTANT COSTS	0	0	0	0	0
EQUIPMENT	590,000	397,000	335,000	423,000	360,600
SUPPLIES	0	0	0	0	0
TRAVEL	0	0	0	0	0
INPATIENTS CARE COSTS	0	0	0	0	0
OUTPATIENTS CARE COSTS	0	0	0	0	0
ALTERATIONS AND RENOVATIONS	10,000	203,000	265,000	177,000	239,400
OTHER EXPENSES	0	0	0	0	0
DIRECT CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	600,000	600,000	600,000	600,000	600,000
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	600,000	600,000	600,000	600,000	600,000
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					3,000,000

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

YEAR 55
EQUIPMENT

(Note that every item is given a potential quote reference number to help with the quote identification (indicated as Q.1, Q. 2 etc.). Not all reference numbers will have quotes for two possible reasons. 1) A quote was not available at the time of award submission and may be available at the site visit, 2) a quote is not possible for this item. Note also that not all sequential numbers will be represented as quote numbers were assigned during the prioritization process to help with reference and decision making, but before final determinations were made. Some quote numbers were therefore dropped.)

- **Ten – channel Perkin Elmer (model 2470-0100) gamma counter (Endocrine) - $54,000 (Q. 1)**
  This instrument detects the radioactivity of I^{125}, the isotope that is essential for many in-house and commercial radioimmunoassays, including NHP (macaque) LH, FSH, glucagon and leptin. These assays, which remain irreplaceable by non-radioactive assays in terms of sensitivity and precision, are critical for the NHP research community and constitutes approx. 25% of the ETSL Core's annual income. Following the e=demise of the Core's gamma counter, an out-of-production 25-year old counter was donated by the Neuroscience Division. However, its annual maintenance by LPS, Inc. has become problematic, with parts for this model becoming rare – faulty detector channels are already irreplaceable. A similar, 25-year old counter is available on-site, but suffers the same problems, and would require the undesirable transport of radioactive materials through busy hallways and corridors.
  Therefore, a new Perkin Elmer (which acquired Packard) unit is requested for reliable performance and warrantied service. A 10-channel, instead of the current 5-channel, unit is warranted to reduce the assay time and improve data output. Assays frequently include 200 samples, which currently require 7-8 hours of counting time. Due to radioactive decay, the time lapse between counting the beginning standard curve and last experimental sample can be significant, especially when differences in sample valves are small. Moreover, the modest difference between a 5- and 10-channel unit (approx. $5000) argues for investment in the latter capability

- **ViiA 7 Real-Time PCR System** Specific Private Vendor **(Virology) - $40,000 (Q. 2)**
  The ViiA7 is a current-generation realtime qPCR system. The Virology Core routinely assays NHP diagnostic samples for viral load by quantitative PCR. Our current system (ABI 7500 – price includes an anticipated $12,000 trade-in) is an older generation entry-level machine that is limited to 96-well plate throughput and uses a "slow qPCR" run format. The most important reason for upgrading to the ViiA7 is that it can run both 96 and 384-well plates using interchangeable blocks, which allows assaying significantly more samples at a time and more replicates per sample. The ViiA7 can also run "fast qPCR" protocols that decrease run times compared to the 7500, which will help increase service turnaround. The ViiA7 also has up to 10-fold better sensitivity (down to 1 copy) and better multiplexing capabilities than our current 7500 system. These capabilities will be necessary to keep the Virology Core technologically up-to-date and to address increased NHP viral sample throughput and higher sensitivity requirements.

- **Inverted fluorescence microscope** Specific Private Vendor **(Molecular & Cell Biology) - $37,800 (Q. 3)**
  The Molecular and Cellular Biology Service Core (MCBSC) is in major need of a new inverted microscope for visualization of cell cultures. The Core's present scope is over 20 years old and dates back to the origin of the ONPRC Tissue Culture Core that existed prior to the MCBSC. More importantly the present, aged microscope lacks fluorescence and a camera. The lack of the camera means none of the work of the core, such as establishment of monkey primary cell lines, can be photographed for documentation, without going to another room which increases sterility and biohazard risks. An important new function of the MCBSC is preparation of lentiviral vectors for expression or knockdown of nonhuman primate mRNAs. Typically the lentiviral vectors express fluorescent proteins for monitoring viral titer, infection efficiency, cell sorting and evaluating expression in cell lines or in animal tissue if used *in vivo*. The lack of fluorescent capabilities in the Core's present microscope means, that as for analyses, lentiviral cultures must be taken to different room to examine fluorescent expression with

attendant sterility and biohazard risks. Thus there is significant need for a new inverted microscope for the MCBSC to allow efficient and safe documentation and image analysis of cell cultures and lentivirus preparations essential for nonhuman primate research.

- **Purchase and install a new autoclave in the Research Building (Facilties) - $38,700 (Q. 5)**
  Funds are requested for replacement of this autoclave which is the oldest and most frequently used on campus. Recent lab moves into the building has placed a greater demand on this unit. Because it has outlived its useful life, it should be replaced at this time.

- **Vehicle replacements (Yr. 1 of 5) (Facilites and DCM) - $10,000 (Q. 6)**
  To keep the Facilities transportation fleet in good shape and replace older vehicles as needed, funds are requested to replace one per year in the next three years. These vehicles are used by the technicians to support maintenance and repair activities associated with research, administrative and NHP housing areas.

- **Development of PRIMe software through LabKey (Yr. 1 of 4) (IS) - $25,000 (Q. 8)**
  It is critical to have a contract in the software's initial years with LabKey Software for the purposes of: 1) continue enhancing the product for ONPRC in the "core" areas that will affect all users of the LabKey software, most notably the Electronic Health Records System for NHP's (PRIMe) and where it requires LabKey's assistance in making "core" area modifications; and 2) enhance the product wherever necessary as a supplement to internal staff as part of collaborating with other NHPRCs in a leveraged, synergistic effect. Software development rates are estimated in the $175-$185 per hour range.

- **Bioinformatics Server (IS) - $10,100 (Q. 9)**
  We request funds to purchase a Dell PowerEdge R510 server to meet the support the increasing computational needs for NGS genomic and transcriptomic analyses for ONPRC investigators. The selected server is equipped with 96GB of RAM, and 8 3TB hot-swappable HDDs, configured in a RAID6 format, resulting in 18TB of usable data storage for in process analyses. By configuring with two-hex-core multithreaded processors, this machine will be able to run 24 parallel instantiations.

- **Powervault MD 1200 storage arrays plus hard drives or equivalent for Bioinformatics (IS) - $11,200 (Q. 10)**
  We request funds to purchase a PowerVault MD1200 direct attached storage disk array, with 12 X 2TB 7200RPM SAS disk drives to store raw and intermediate files for NGS data received for bioinformatics analysis. One MD1200 is requested in Year 1 to expand present capacity, and another in Year 5 to further expand or replace data storage resources.

- **Istat1 blood gas units, 2 @ $7,500 (DCM) - $15,000 (Q. 11)**
  We currently perform ~1500 blood gas tests annually campus wide using independent hand held units. These units have a useful life of ~7 years. We currently have multiple units past their useful life and the company has announced they will no longer service the older units. These new units would allow us to continue our satellite analysis campus wide.

- **Squeeze boxes, 2 @ $2,750 (DCM) - $5,500 (Q. 12)**
  Squeeze boxes are needed when NHP cages do not have squeeze mechanisms. The animal is transferred from the cage to the squeeze box, then sedated or manipulated. The ONPRC has many hanging cage areas that have cages without squeeze backs, especially the Catch Areas Specific Animal During processing of corrals the animals occupy two catch areas. Getting more squeeze boxes will improve efficiency.

- **Sets of Specific Animal tall squeeze double cages for use in animal rooms with hanging cages, 30 @ $4,200 (DCM) - $126,000 (Q.13)**
  These cages will be used to phase out the single, non-squeeze hanging caging. The ONPRC has

multiple areas were hanging caging is still used [Specific Animal Location] [Specific Animal] This will allow for pair housing of larger animals.

- **Sets of [Square Footage] tall squeeze doubles to replace the [Specific Animal Location] tall Nursery cages, 16 @ $4,350 (DCM) - $69,600 (Q. 14)**
  This caging [Specific Animal Loc] replaces smaller caging [Specific Animal Loc] that creates compliance challenges in the NHP nursery in ASB.

- **Vaporized Hydrogen Peroxide Decontamination Unit (DCM) - $110,000 (Q. 86)**
  Vaporized hydrogen peroxide decontamination is needed to decontaminate animal areas such as the ABSL3 and quarantine. VHP can be safely used next to occupied areas. Equipment such as computerized tomography (CT) can also be safely decontaminated with VHP. We currently use chlorine dioxide gas to decontaminate the ABSL3. Chlorine dioxide can be caustic to equipment and can not be used near occupied space.

- **Mobile satellite indoor racks, 2 @ $2,500 (DCM) - $5,000 (Q. 15)**
  Indoor satellite cages are used to house and treat animals near their natal group. The RFO needs to regularly phase out older satellite racks that are outdated and showing wear.

- **Transfer box replacement each year, 12 @ $900 (DCM) - $10,800 (Q. 17)**
  Transfer boxes are needed to safely transfer awake or sedated animals from one area to another. The RFO needs to replace older broken transfer boxes.

- **Golf cart with P/U bed (DCM) – $4,000 (Q. 16)**
  Electric golf carts are needed in new animal areas (PENS) and to replace existing well used equipment. Golf carts are used to move staff and light equipment in an environmentally friendly way reducing the need for standard vehicles. Lifespan of a golf cart is approximately four to six years.

- **Endoscope refurbishment/replacement (Yr. 1 of 5) (DCM) - $10,000 (Q. 18)**
  With the emphasis on minimally invasive surgery, the endoscopy equipment gets heavy usage and requires continual repair or replacement. Although careful cleaning and maintenance is practiced, the heavy usage, especially of bronchoscopes, requires a consistent source of funding to keep scopes in proper working order.

- **Digital Dental Radiography, Bio-Ray SDX DuraSoft Digital Intraoral Sensor with USB interface and imaging software (DCM) - $7,300 (Q. 19)**
  We are currently using a hand tank for dental radiography developing. This unit would increase efficiency as well as greatly improve the quality of the product we are attempting to capture and thereby improve NHP care.

ALTERATIONS AND RENOVATIONS

- **Lighting efficiency upgrades throughout campus (Yr. 1 of 5) (Facilities) - $10,000 (Q. 7)**
  Funds are requested to install a variety of energy saving devices like occupancy sensors and light timers, as well as fluorescent lamps and ballasts, to enable Facilities & Property to be proactive in maintaining energy efficient lighting throughout campus.

YEAR 56
EQUIPMENT

- **Hamilton automatic sample handler Model 600-Series (Endocrine) - $6,000 (Q. 20)**
  Most of the NHP and non-NHP samples handled by the ETSL Core are accomplished with a Hamilton

automatic sample handler for precision and accuracy. Currently, we have two in use; one is new and the other one has been used for 4 years. The average "bench life" of a unit in our hands is estimated at 3 years. Before the new unit, we were using an old unit for about 5 years that required a replacement of the driving motor for $2,000, and then the motor broke down again in less than 2 years,. In hindsight, we should probably have replaced the broken unit with a new one instead of sending it to the company for repair; a new unit costs $6,000. We propose to replace our older unit during year 56 of the Core grant period, and the second unit (at 6 years of age) in year 59.

- **Tissue-Tek Tissue processor (VIP6, #TN6030) (DCM/Pathology) - $52,900 (Q. 21)**

  Consistent dehydration, clearing and infiltration of paraffin – embedded tissues is a prime prerequisite for production of high-quality tissue sections in the Research Histology Unit – Pathology. Failure to perform these tasks prevents consistent sectioning, and hence loss, of valuable NHP tissue samples and/or inability to generate thin (3 micron) sections for analyses. Thus a reliable tissue processor is vital to a histology laboratory.

  The current Tissue-Tek processor is very old, such that parts and service have become problematic. Should lengthy repair time occur, laboratory function would be disrupted. A new VIP6 has the capacity to process up to 300 cassettes, with the option to lower reagent amounts if a smaller load is anticipated. It is a versatile, closed system that allows xylene to be used without a fume hood. Although Tissue-Tek offers excellent units, demonstrations will include the Thermo Scientific brand as well.

- **Upgrade to MicroBrightfield Bioscience (MBF) system (Imaging) - $54,200 (Q. 22)**

  The MBF system was built on an older Zeis Axioscope microscope with financing shared by several PIs, the Neuroscience and Reproductive Sciences divisions and ONPRC. The system uses a motorized stage and several software packages: StereoInvestigator, Neurolucida, solid module to image and analyze microscope images of large areas. It is particularly useful for NHP studies as it allows obtaining images of whole sections of various large organs such as brain, ovaries, etc. Images are then used to analyze numbers of cell regions that show pathology associated lesions, anatomical changes with addiction or targeted viral infections for gene therapy, numbers, classes and sizes of ovarian follicles, patterns of gene expression, etc. Neurolucida may be used to trace and analyze the complexity of dendritic arbors or neurons. The system generates very large image files that are limited by the top of the line 64-bit Windows-based computer acquired in 2009. We plan to acquire the largest memory, fastest processor that will be supported by the MBF in 2014. In addition, the high resolution, very sensitive motorized stage shows signs of fatigue and intermittently does not perform properly , requires service and downtime that interferes with our work. A 40x oil objective will be needed for neuronal tracing that requires frequent change between 40x and 100x, and back and where the only 40x objective we have, a dry one, is an impediment in designing a smooth workflow. Computer with all required cards $10,000, stage $20,000, objective $5,000, software upgrade $5,000.

- **Vehicle replacements (Yr. 2 of 5) (Facilities and DCM) - $10,000 (Q. 6)**

  To keep the Facilities transportation fleet in good shape and replace older vehicles as needed, funds are requested to replace one per year in the next three years. These vehicles are used by the technicians to support maintenance and repair activities associated with research, administrative and NHP housing areas.

- **Development of PRIMe software through LabKey (Yr. 2 of 4) (IS) - $25,000 (Q. 8)**

  It is critical to have a contract in the software's initial years with LabKey Software for the purposes of: 1) continue enhancing the product for ONPRC in the "core" areas that will affect all users of the LabKey software, most notably the Electronic Health Records System for NHP's (PRIMe) and where it requires LabKey's assistance in making "core" area modifications; and 2) enhance the product wherever necessary as a supplement to internal staff as part of collaborating with other NHPRCs in a leveraged, synergistic effect. Software development rates are estimated in the $175-$185 per hour range.

- **Storage Area Network (SAN) Expansion (IS) - $27,000 (Q. 27)**

  The ONPRC SAN supports the VMware virtualized cluster and hosts all servers and services supporting

PRIMe, IRIS and other ONPRC applications. Data requirements will continue to grow. The expansion of the existing system with more disk space is in anticipation of needing more storage to supplement what exists today.

- **PAM unit w/ ventilator, stand (DCM) - $8,800 (Q. 28)**
  The unit currently being used in hospital was purchased in 2002 and the warranty expires this year. The manufacturer confirmed that the useful life is 10 years. This unit will need to be replaced.

- **Leica Autostainer XL (replacement for original stainer) (DCM) - $32,000 (Q. 29)**
  The autostainer is an integral component for the efficient production of correctly stained slides for pathologists and investigators. Our original autostainer was purchased as a used model in 2002. It provided excellent service for several years but had to be replaced in 2009. At that time there was minimal money available in I&M to replace this essential piece of equipment. A lower capacity demo model was purchased to replace it. It is difficult to use and is more prone to failure than the original piece of equipment. In 2016, the second stainer will have been used for 7 years which is its expected serviceable life.

- **Transfer box replacement each year, 12 @ $900 (DCM) - $10,800 (Q. 17)**
  Transfer boxes are needed to safely transfer awake or sedated animals from one area to another. The RFO needs to replace older broken transfer boxes.

- **Two over Two NHP racks with** Specific Animal Location **tall, 10 @ $11,650 (DCM) - $116,500 (Q. 31)**
  These NHP housing racks are needed to add to existing inventory and to make rack change out more efficient. These allow for pair housing. These racks will hold up to a 15 kg animal/cage.

- **Endoscope refurbishment/replacement (Yr. 2 of 5) (DCM) $10,000 (Q. 18)**
  With the emphasis on minimally invasive surgery, the endoscopy equipment gets heavy usage and requires continual repair or replacement. Although careful cleaning and maintenance is practiced, the heavy usage, especially of bronchoscopes, requires a consistent source of funding to keep scopes in proper working order.

- **Mobile tunnels between Corrals** Specific Animal Lo **4 @ $4,700 (DCM) - $18,800 (Q. 33)**
  Mobile tunnels are used to transfer, or herd, awake animals from Corra Specific Animal Location and to move animals from Corral Specific Animal The existing equipment is aging and of a poor design and therefore potentially unsafe to animals and staff in the future.

- **Surgical Anesthesia cart + ventilator (DCM) - $20,000 (Q. 34)**
  Current surgical anesthesia carts are over 20 years old and no longer serviceable, anesthesia circuits are corroding and replacement parts are not available, ventilators are antiquated and imprecise.

- **Light Source for endoscope tower (DCM) - $5,000 (Q. 35)**
  Current light source has a bulb that is no longer manufactured. Once the bulb currently in use bums out, the light source will no longer be operational or repairable.

ALTERATIONS AND RENOVATIONS

- **Tunnel Cage Washer Replacement in the Cage Wash Building (** Specific Animal Location **DCM) - $193,000 (Q. 87)**
  The tunnel cage washer facility is a Specific Animal Locati semi-enclosed building located in the Facility Security Facility of the ONPRC Specific Animal Every ONPRC NHP is provided sanitized caging, jump boxes and tunnels processed via the central tunnel cage washer: 1) washing cages used in the corral catch areas for animal processing, 2) washing jump boxes and tunnels used for processing animals in the group housing areas, and 3) washing hanging cages used in quarantine and selected holding facilities. In addition, the central tunnel washer is the only machine capable of processing the 879 large hanging cages. Finally, the tunnel washer facility has been in service for approximately 40 years and has

exceeded its mechanical life expectancy.

- **Lighting efficiency upgrades (2nd yr. of 5) (Facilities) - $10,000 (Q. 7)**
  Funds are requested to install a variety of energy saving devices like occupancy sensors and light timers, as well as fluorescent lamps and ballasts, to enable Facilities & Property to be proactive in maintaining energy efficient lighting throughout campus.

YEAR 57
EQUIPMENT

- **Promega semi-automated robot (Maxwell 16, PRAS 2000) (Virology) - $16,600 (Q. 36)**
  The Virology Core requests a semi- automated robot for purification of nucleic acids (DNA, RNA) from various samples sources (blood, plasma, cells, etc.). In the current P51 grant period, a used Maxwell unit was purchased to establish this technology in the laboratory. The Maxwell was chosen as it was previously shown to outperform other entry-level robots in viral RNA extraction from diagnostic samples. This Maxwell unit allowed the Virology Core to establish a new sensitive and state-of-the-art NHP SIV viral load service for routine clinical determinations and also for fast-turnaround samples for research studies. It is also now being used in other viral diagnostics services, such as for various CMV assays. We now need a second Maxwell, unit (this is not a trade-in) to a) address increased sample throughput (due to the rather limited sample capacity of the Maxwell up to two separate purification runs are required per qPCR assay run, which impedes fast-turnaround processing) and to b) increase flexibility and prevent loss of service capacity in the event one unit fails.

- **Quiagen PCR assay robot** Specific Private **Virology) - $54,750 (Q. 37)**
  Currently, the Virology Core sets up all PCR assays manually, which requires significant labor time. The QIAgility is an assay set up robot to aid in PCR and qPCR set up. In order to effectively address increasing sample throughput for NHP viral diagnostics and improve sample turnaround times, the Virology Core needs an automated PCR set up to speed up this tedious bottleneck step and become more efficient. The QIAgility is a programmable high precision robot that can set up plates in all common formats and carry out dilutions. The multi-format capability is particularly important for the Core to be able to transition from manual 96-well set up to a high-throughput 384-well format, which due to its small well size is very challenging to set up manually.

- **Vehicle replacements (Yr. 3 of 5) (Facilities and DCM) - $10,000 (Q. 6)**
  To keep the Facilities transportation fleet in good shape and replace older vehicles as needed, funds are requested to replace one per year in the next three years. These vehicles are used by the technicians to support maintenance and repair activities associated with research, administrative and NHP housing areas.

- **Development of PRIMe software through LabKey (Yr. 3 of 4) (IS) - $25,000 (Q. 8)**
  It is critical to have a contract in the software's initial years with LabKey Software for the purposes of: 1) continue enhancing the product for ONPRC in the "core" areas that will affect all users of the LabKey software, most notably the Electronic Health Records System for NHP's (PRIMe) and where it requires LabKey's assistance in making "core" area modifications; and 2) enhance the product wherever necessary as a supplement to internal staff as part of collaborating with other NHPRCs in a leveraged, synergistic effect. Software development rates are estimated in the $175-$185 per hour range.

- **VMWare Software and Server Hardware (IS) - $21,000 (Q. 42)**
  The existing ONPRC VMware cluster consists of (3) servers each running a copy of VMware vSphere in a cluster configuration. An expansion of this clustered environment is anticipated after 3.5 years of use on the existing cluster to accommodate more servers or servers that just require more CPU and Memory resources than what the existing cluster can provide. An alternative use of these funds would be to provision such resources via a Cloud services provider like VMware yet the purpose of this expansion

would remain the same: to allocate needed resources to ONPRCoperational applications and services such as PRIMe as it is further developed.

- **Overhead Surgery Lights-Ritter 355 (DCM) - $5,300 (Q. 43)**
  This is a mobile surgical light that would be used in the colony hospital. Surgical lights in the clinic are aging and planned replacement will help insure appropriate care of NHPs.

- **Two over Two NHP racks with** Specific Animal Location **tall, 12 @ $11,650 (DCM) - $139,800 (Q. 31)**
  These NHP housing racks are needed to add to existing inventory and to make rack change out more efficient. These allow for pair housing. These racks will hold up to a 15 kg animal/cage.

- **Mobile Shelter Housing racks (DCM) - $8,250 (Q. 45)**
  These are large single cages on wheels and are used to house and treat animals near their natal group in Specific Animal Location This methodology allows the animal to maintain social status while being medically treated.

- **Golf cart with P/U bed (DCM) - $4,000 (Q.16)**
  Electric golf carts are needed to replace existing well used equipment. Golf carts are used to move staff and light equipment in an environmentally friendly way reducing the need for standard vehicles. Lifespan of a golf cart is approximately four to six years.

- **Transfer box replacement each year, 12 @ $900 (DCM) - $10,800 (Q. 17)**
  Transfer boxes are needed to safely transfer awake or sedated animals from one area to another. The RFO needs to replace older broken transfer boxes.

- **Biosound MyLab 30 Gold Cardiovascular portable ultrasound (DCM) – $29,500 (Q. 48)**
  We use the ultrasound across the unit for a variety of clinical situations: to assess severity of musculoskeletal trauma and associated blood flow, echocardiogram studies, gestation and fetal viability, to guide hepatic biopsies and cystocentesis, and to measure SI thickness (which may be a reliable and non-invasive way to diagnosis enteric amyloidosis).

- **Endoscope refurbishment/replacement (Yr. 3 of 5) (DCM) - $10,000 (Q. 18)**
  With the emphasis on minimally invasive surgery, the endoscopy equipment gets heavy usage and requires continual repair or replacement. Although careful cleaning and maintenance is practiced, the heavy usage, especially of bronchoscopes, requires a consistent source of funding to keep scopes in proper working order.

ALTERATIONS AND RENOVATIONS

- **Install a new electrical service to the** Specific Animal Location **Facilities) - $115,000 (Q. 38)**
  On two occasions during hot weather the main breaker for the electrical feed to the Specific Animal has tripped because the system was overtaxed. This breaker and wiring feeds the air conditioning supply to numerous NHP rooms, as well as several NHP catch areas, and its failure causes uncomfortable living conditions for these animals. The building cooling system is local to the building and draws too much power. Our electrical consultants have strongly recommended installation of a new service.

- **Replace the Colony Generator (Facilities) - $140,000 (Q. 38)**
  Funds are requested to replace the emergency generator that serves the Specific Animal Location and Specific Animal Location units which are housing areas for numerous NHPs. The generator continues to leak oil even after multiple repairs. This equipment is old and contractors have recommended replacement.

- **Lighting efficiency upgrades (Yr. 3 of 5) (Facilities) - $10,000 (Q. 7)**
  Funds are requested to install a variety of energy saving devices like occupancy sensors and light timers, as well as fluorescent lamps and ballasts, and enable Facilities & Property to be proactive in maintaining energy efficient lighting throughout campus.

YEAR 58
EQUIPMENT

- **Upgrade confocal (Imaging) - $50,000 (Q. 51)**
  The Leica SP5 AOBS confocal was purchased in 2008 and has been very heavily used since its installation. Its computer is no longer top of the line, it has crashed and been reformatted a couple of times. We expect it will be completely obsolete by 2015 and it will not support the expected (and inevitable) software upgrades. Since our purchase, Leica has introduced HyD detectors with significantly increased sensitivity that would allow us to image live cells and tissue for longer times in better physiological conditions and also to obtain better contrast from samples with low signal. A software module that only became available recently would allow us to image 96-well plates in confocal mode that will enable us to perform small high-throughput studies without the need for dedicated equipment. Computer (factory installed with all required cards) $10,000, new detectors, $20,000, multi-well plates module $20,000.)

- **New refrigerated floor Centrifuge, Sorvall RC3BP+ (Endocrine) - $50,200 (Q. 52)**
  To replace the 25 year-old Sorvall RC3C which is long past warranty and has deficiencies (e.g. door closure) limiting its safe use. A new model will be used to prepare samples for analyses in the ETSL Core, and offers a 15-year limited warranty.

- **Emergency Diesel Storage and Delivery System (Facilities) - $100,000 (Q. 88)**
  The emergency diesel generators on campus are used to supply electrical power to critical buildings on campus, including all NHP holding and housing areas. Additionally the primary heating system for the campus is comprised of two natural gas fired boilers, one of which has the ability to also run diesel. These boilers also provide heat to several of the largest NHP housing areas on campus as well as office and research space. The emergency generator tanks are sized to ensure approximately 24 hours of service. During an emergency that lasted beyond the capacity of the generators, or a temporary shutdown of the gas supply to the heating boilers, a mobile tanker truck would be used to re-fuel the generators as necessary, and to act as an emergency source of fuel for the boiler. Funds are requested to purchase a 5000 gallon tanker truck and manifold delivery system that would be used for either of these emergency scenarios thereby allowing us to maintain electricity and/or heat to NHP and human areas until outside resources can be restored.

- **Vehicle replacements (Yr. 4 of 5) (Facilities and DCM) - $10,000 (Q. 6)**
  To keep the Facilities transportation fleet in good shape and replace older vehicles as needed, funds are requested to replace one per year in the next three years. These vehicles are used by the technicians to support maintenance and repair activities associated with research, administrative and NHP housing areas.

- **Development of PRIMe software through LabKey (Yr. 4 of 4) - $25,000 (Q. 8)**
  It is critical to have a contract in the software's initial years with LabKey Software for the purposes of: 1) continue enhancing the product for ONPRC in the "core" areas that will affect all users of the LabKey software, most notably the Electronic Health Records System for NHP's (PRIMe) and where it requires LabKey's assistance in making "core" area modifications; and 2) enhance the product wherever necessary as a supplement to internal staff as part of collaborating with other NHPRCs in a leveraged, synergistic effect. Software development rates are estimated in the $175-$185 per hour range.

- **Polycom + TV + Cart (IS) - $12,300 (Q. 60)**
  Most of the existing ONPRC Polycom videoconferencing units are now at least 3 years old and will be

well past normal expected lifetimes of such technology in year 4. While Polycom may not exist as a company and technology may change to the point of not needing a physical, self-contained unit, ONPRC is still expecting use of same or similar technology to accomplish the goal of virtual-remote collaboration and communication.

- **One over One NHP racks with** Specific Animal Location **16 @ $8,950 (DCM) - $143,200 (Q. 61)**
  These primate housing racks are needed for the ASB1 containment areas. These cages will hold up to a 15kg animal and allow social pairing in the containment area.

- **Transfer box replacement each year, 12 @ $900 (DCM) - $10,800 (Q. 17)**
  Transfer boxes are needed to safely transfer awake or sedated animals from one area to another. The RFO needs to replace older broken transfer boxes.

- **Golf cart with P/U bed (DCM) - $4,000 (Q. 16)**
  Electric golf carts are needed to replace existing well used equipment. Golf carts are used to move staff and light equipment in an environmentally friendly way reducing the need for standard vehicles. Lifespan of a golf cart is approximately four to six years.

- **Mobile indoor satellite racks, 3 @ $2,500 (DCM) - $7,500 (Q. 15)**
  Indoor satellite cages are used to house and treat animals near their natal group. The RFO needs to regularly phase out older satellite racks that are outdated and showing wear.

- **Endoscope refurbishment/replacement (Yr. 4 of 5) (DCM) - $10,000 (Q. 18)**
  With the emphasis on minimally invasive surgery, the endoscopy equipment gets heavy usage and requires continual repair or replacement. Although careful cleaning and maintenance is practiced, the heavy usage, especially of bronchoscopes, requires a consistent source of funding to keep scopes in proper working order.

ALTERATIONS AND RENOVATIONS

- **Re-roofing and re-flashing of Locker/Lunch Building (Facilities) - $47,000 (Q. 53)**
  Funds are requested for installation of a new roof and flashing on this building which was constructed in 1985 and still has the original roof.

- **Replace Gas Pack on Locker/Lunch Building (Facilities) - $15,000 (Q. 54)**
  Funds are requested to replace this deteriorating gas pack unit which dates back to 1985 when the building was constructed.

- **Upgrade ductwork for ASB I (Yr. 1 of 2) (Facilities) - $90,000 (Q. 4)**
  This building was constructed in 1992 and ductwork in the interstitial area is in need of repair and replacement due to damage over time. Funds are requested to replace this ductwork and assure proper airflow to NHP holding rooms.

- **Lighting efficiency upgrades (Yr. 4 of 5) - $10,000 (Q. 7)**
  Funds are requested to install a variety of energy saving devices like occupancy sensors and light timers, as well as fluorescent lamps and ballasts, to enable Facilities & Property to be proactive in maintaining energy efficient lighting throughout campus.

- **Campus utility metering (Yr. 1 of 2) (Facilities) - $15,000 (Q. 58)**
  Funds are requested for electrical, gas and water meters, as well as BTU meters for the campus central heating/cooling systems, to accurately track energy use in buildings and verify and identify efficiency measures. These buildings will include research, administrative, and NHP holding areas, allowing us to assure we are providing the required temperature control and air changes required by

code.

YEAR 59
EQUIPMENT

- **Hamilton automatic sample handler Model 600-Series (Endocrine) - $6,000 (Q. 20)**
  Most of the NHP and non-NHP samples handled by the ETSL Core are accomplished with a Hamilton automatic sample handler for precision and accuracy. Currently, we have two in use; one is new and the other one has been used for 4 years. The average "bench life" of a unit in our hands is estimated at 3 years. Before the new unit, we were using an old unit for about 5 years that required a replacement of the driving motor for $2,000, and then the motor broke down again in less than 2 years,. In hindsight, we should probably have replaced the broken unit with a new one instead of sending it to the company for repair; a new unit costs $6,000. We propose to replace our older unit during year 56 of the Core grant period, and the second unit (at 6 years of age) in year 59.

- **-80 Freezer (Genetics) - $12,800 (Q. 67)**
  The Genetics Resource needs a freezer for reliable, stable storage of NHP samples for DNA analyses.

- **Computer for image processing (Imaging) - $13,750 (Q. 68)**
  While most routine image processing and analyses will be performed on the user's laboratory computers, the IM Core needs a dedicated computer with an advanced graphics card, high RAM and processing power for particularly large files of NHP data not amenable to standard data processing. This computer will be equipped with fluorescence deconvolution software to complement the already available Volocity 3D rendering and analysis. While FIJI and ImageJ are used for most image processing and analysis needs, on existing Core or users own computers, we maintain a license for Volocity as a true 3D rendering and analysis software and for NewCast Visiopharm for stereology. Currently these are installed on an older computer that frequently runs out of memory. A fluorescence deconvolution module is necessary in addition to the Volocity software to further refine confocal images and definitely to remove the out-of-focus light for the images acquired in widefield, either on the MicroBrightField system or the Olympus slidescanner available in Pathology. The particularly large image files and complex algorithms that this computer will handle require it to be top of the line in terms of processing power and RAM volume. Computer $10,000, deconvolution software package $10,000.

- **Vehicle replacements (Yr. 5 of 5) (Facilities and DCM) - $10,000 (Q. 6)**
  To keep the Facilities transportation fleet in good shape and replace older vehicles as needed, funds are requested to replace one per year in the next three years. These vehicles are used by the technicians to support maintenance and repair activities associated with research, administrative and NHP housing areas.

- **VMWare software and Server Hardware + SAN replacement (IS) - $61,500 (Q. 27, 42)**
  Good lifecycle management practices require equipment refreshes. These components replace the existing ONPRC VMware cluster (3 servers) and SAN after six years of use and really must be purchased together due to needing the hardware to be compatible.

- **Powervault MD 1200 storage arrays plus hard drives or equivalent for Bioinformatics (IS) - $11,200 (Q. 10)**
  We request funds to purchase a PowerVault MD1200 direct attached storage disk array, with 12 X 2TB 7200RPM SAS disk drives to store raw and intermediate files for NGS data received for bioinformatics analysis. One MD1200 is requested in Year 1 to expand present capacity, and another in Year 5 to further expand or replace data storage resources.

- **Pentra 60 CPLUS Hematology Analyzer (DCM) - $49,000 (Q. 79)**

Current Pentra hematology analyzer was purchased in August 2011. AAHA recommended service life for this piece of equipment is 7 years.

- **Two over Two NHP racks with** Specific Animal Location **tall 12 @ $11,650 (DCM) - $139,800 (Q. 31)**
  These NHP housing racks are needed to add to existing inventory and to make rack change out more efficient. These allow for pair housing. These racks will hold up to a 15 kg animal/cage.

- **Mobile Shelter Housing racks (DCM) - $8,250 (Q. 45)**
  These are large single cages on wheels and are used to house and treat animals near their natal group in Shelter Group Housing. This methodology allows the animal to maintain social status while being medically treated.

- **Mobile indoor satellite racks, 3 @ $2,500 (DCM) - $7,500 (Q. 15)**
  Indoor satellite cages are used to house and treat animals near their natal group. The RFO needs to regularly phase out older satellite racks that are outdated and showing wear.

- **Transfer box replacement each year, 12 @ $900 (DCM) - $10,800 (Q. 17)**
  Transfer boxes are needed to safely transfer awake or sedated animals from one area to another. The RFO needs to replace older broken transfer boxes.

- **Endoscope replacement and refurbishment (Yr. 5 of 5) (DCM) - $10,000 (Q. 18)**
  With the emphasis on minimally invasive surgery, the endoscopy equipment gets heavy usage and requires continual repair or replacement. Although careful cleaning and maintenance is practiced, the heavy usage, especially of bronchoscopes, requires a consistent source of funding to keep scopes in proper working order.

- **Physiological monitors, 2 @ $10,000 (DCM) - $20,000 (Q. 85)**
  Current monitors are over 10 years old, require frequent repair, and lack capability to connect to computers for automated uploading of monitoring data.

ALTERATIONS AND RENOVATIONS

- **Replace chair lift or build a ramp for improved ADA access to Administration Building (Facilities) - $50,000 (Q. 69)**
  The current chair lift at this building was not meant for outside operation and has required an excessive amount of maintenance to keep running. Funds are therefore requested for installation of a new outdoor chairlift or installation of a ramp at the entrance of the building to provide better access and to meet current ADA code requirements.

- **Upgrade ductwork for ASB I (2nd yr. of 2) (Facilities) - $90,000 (Q. 4)**
  This building was constructed in 1992 and ductwork in the interstitial area is in need of repair and replacement due to damage over time. Funds are requested to replace this ductwork and assure proper airflow to NHP holding rooms.

- **Replace gas pack at** Facility Security **(Facilities) - $44,200 (Q. 70)**
  The four gas packs that serve this building are 100% outside air and designed for lab spaces. Since some of these areas are no longer used as lab space, this is a poor use of energy and makes control of the environment difficult and time consuming. Funds are requested to replace the units and modify ductwork to allow the systems to run more efficiently and more cost effectively.

- **Re-siding of the** Facility Security **(Facilities) - $30,200 (Q. 72)**

Funds are requested to install new siding on this building. The Research Annex was constructed in 1975 and the siding now has dry rot and is in a deteriorating condition.

- **Lighting efficiency upgrades (Yr. 5 of 5) (Facilities) - $10,000 (Q. 7)**
  Funds are requested to install a variety of energy saving devices like occupancy sensors and light timers, as well as fluorescent lamps and ballasts, to enable Facilities & Property to be proactive in maintaining energy efficient lighting throughout campus.

- **Campus utility metering (2nd yr. of 2) (Facilities)- $15,000 (Q. 58)**
  Funds are requested for electrical, gas and water meters, as well as BTU meters for the campus central heating/cooling systems, to accurately track energy use in buildings and verify and identify efficiency measures. These buildings will include research, administrative, and NHP holding areas, allowing us to assure we are providing the required temperature control and air changes required by code.

Improvements & Modernization Income Table

Last Funded Year (53)

Source	Funding (direct costs)
P51 base grant support	$600,000.00
Program income derived from P51 base grant	0
Other Sources	0
Total	$600,000.00

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$600,000.00
Program income derived from P51 base grant	0
Other Sources	0
Total	$600,000.00

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

Pages 1245-1331 (Vendor Quotes) Removed – Excluded by Requester

TITLE: **OUTREACH & COMMUNITY ENGAGEMENT**

CORE-SUPPORTED PERSONNEL:

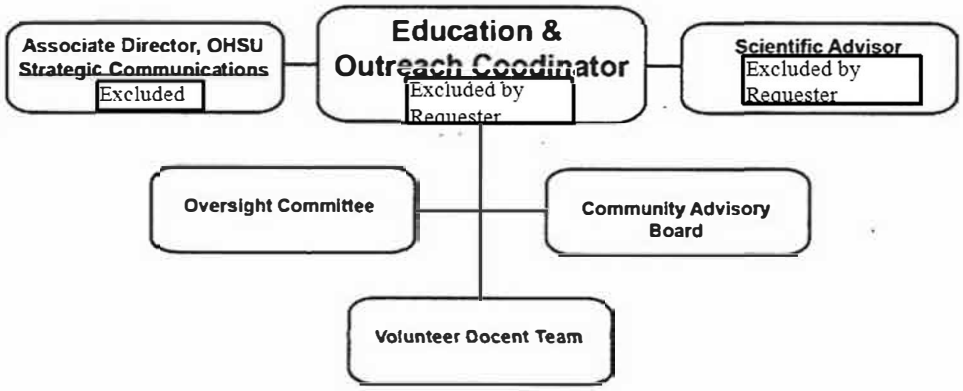
Core Scientist (See Biographical Sketch, listed alphabetically in the Overview of the ONPRC)

Excluded by Requester	Senior Scientist

Staff

Excluded by Requester	Education Outreach Coordinator
TBN	Administrative Assistant

OUTREACH & COMMUNITY ENGAGEMENT
Organizational Chart



OUTREACH & COMMUNITY ENGAGEMENT PERSONNEL AFFILIATION AND ROLE

Core Scientist:

Excluded by Requester	Senior Scientist, Scientific Advisor

OUTREACH & COMMUNITY ENGAGEMENT

DESCRIPTION:

The Outreach and Community Engagement program at ONPRC aims to increase public understanding of and support for biomedical research. This is accomplished through a philosophy of openness and transparency through three lines of endeavor: (1) We seek to improve community relations by providing opportunities for interested persons to visit the center through a variety of programs, all designed to enable frank discussion to take place around the often misunderstood topic of biomedical research; (2) We help to address the science literacy needs of the community by providing authentic science opportunities to students who are considering future careers in science and to others who are interested in updating their understanding of science in the 21st Century; and (3) We communicate directly to the public through social media and indirectly through the media to explain our research, provide transparency about our animal care and help the public understand the role of animals in health research.

OUTREACH & COMMUNITY ENGAGEMENT SPECIFIC AIMS

Support for biomedical research depends in great part on public awareness of the value of such research and an understanding of the process by which medical science discoveries are made. A number of studies indicate that science proficiency in the United States lags behind that in many other countries, creating a significant challenge for maintaining public support for research. Providing multiple opportunities for the general public to learn about biomedical research at the ONPRC and its value is, therefore, of critical importance to the long-term success and productivity of the research enabled by the core grant.

During the previous funding period, education outreach at the ONPRC involved a multi-faceted program that targeted a number of different populations using a variety of strategies. Thousands of students, teachers and members of the public participated in these programs. Our strategies included tours, classroom visits, an informal science program that is held weekly during the school year called *Science Ambassadors,* a docent program, courses for high school students, veterinary externships, and high school, undergraduate, and teacher apprenticeships and/or volunteer opportunities. Many students were exposed to hands-on learning opportunities thanks to the opening of a dedicated learning lab. The goal of each of these highly successful programs was to enhance science education and to provide unique experiences that strengthen public understanding of the value of biomedical research and the scientific process.

In the next funding period, we aim to continue and enhance these highly successful programs, and to expand their scope through additional outreach activities to the public and to state and federal legislators. Our specific aims are:

Specific Aim 1. To provide multiple outreach activities for the general public, teachers, and students. We will continue to use the multiple successful programs developed at ONPRC to provide unique experiences that educate students and adults from multiple backgrounds. We will enhance existing programs and introduce additional new programs that will expand our outreach aims.

Specific Aim 2. To communicate the activities and discoveries of ONPRC personnel to the general public. In conjunction with our outreach activities, we will work closely with the Department of Strategic Communications at OHSU to highlight the exciting discoveries of Center scientists and other Center activities to the media and to state and federal legislators.

Specific Aim 3. To engage with the general public in a series of programs to foster discussions around science and the value of science. As one of our major initiatives in the next five years, we will seek funding to host Science Discussions in the Portland area, advised by a Community Advisory Board.

Specific Aim 4. To continue to represent ONPRC through participation in OHSU's public outreach events as appropriate. The ONPRC Outreach Porgram is an active participant in multiple OHSU-sponsored events. This affords multiple opportunities to educate the public about the role of the Center as an important component of OHSU's mission.

OUTREACH & COMMUNITY ENGAGEMENT RESEARCH STRATEGY

SIGNIFICANCE

In international comparisons of mathematical and scientific proficiency, U.S. students on average lag behind their international counterparts (National Science Board, 2012). In addition, more than three-quarters of mathematics and science teachers said that they had received some professional development in their subject matter. However, few participated for as many hours as research suggests is desirable. Another challenge is the fact that public understanding of the value and process of biomedical science remains limited in the U.S. These challenges have led to a number of concerns for the ONPRC, including recent attempts by Oregon legislators ill-schooled in the methods of science to curtail protections for biomedical researchers at OHSU because they cannot discern the difference between a research protocol and a journal article. These legislators appear unaware of the critical importance of our relationship with the public to our mission. Educational outreach is, therefore, more important than ever before.

The ONPRC has been providing support for formal science education as a public service for at least 40 years. We provide a variety of opportunities for students, teachers and the general public to be exposed to the cutting-edge biomedical science that is occurring here at the Center. In addition, many of our programs provide the opportunity for our visitors to be exposed to the *culture* of science. The many hundreds of individuals who have experienced these programs come away better informed about the work performed at ONPRC, about the value of biomedical research, and about the scientific process. Each of these individuals becomes an ambassador for our mission in the greater community.

During the previous funding period, the ONPRC offered a number of opportunities for members of the public to learn about the research conducted at the Center and its value. These activities included public tours, lectures, and presentations both at the Center and at local science venues such as the Oregon Museum of Science and Industry. We continued to support the education of high school science teachers through the Partners in Science Program, offering teachers the opportunity to work on specific projects in laboratories over the course of two summers.

We also offered undergraduates, high school students, and younger students numerous opportunities to conduct research in ONPRC laboratories and in our new learning laboratory, funds for which were provided by a generous community benefactor. In the learning laboratory, ONPRC scientists and staff can provide hands-on opportunities to students of all ages in a safe and spacious environment.

Our unique, multi-faceted approach to public outreach and education is paired with a strong public relations team, led by Excluded by Requester from the OHSU Office of Strategic Communications. In addition to providing press releases, proactively pitching news stories, communicating through social media and providing other information to the media, we aim to highlight Center discoveries and events to state and federal legislators to insure that there is a broad understanding of the value of the ONPRC to the State of Oregon and the nation.

INNOVATION

We have instituted an Oversight Committee, composed of Center scientists, staff, and members of the community. This group meets every 6 months to review and critique the various outreach programs and activities that have been accomplished, as well as to provide direction for future events and activites.

Our outreach program has expanded to the extent that it cannot be effectively overseen and administered by one person. Moreover, it is impossible to develop additional outreach programs and events as we are now at maximum capacity. Still, there remain additional opportunities for us to engage the public. Because of this, we are proposing to expand Program leadership with the addition of Excluded by Requester Ph.D., a Senior Scientist in the Division of Neuroscience, as Scientific Advisor. Excluded by Requester has been an enthusiastic and committed participant in the Center's educational activities for many years, and has instituted his own laboratory experience-based programs that have been incorporated into the formal Center Outreach Orogram activities. The participation of Excluded by Requester will make it possible to further increase the participation of Center investigators in outreach activities and to reorganize the oversight and responsibility for the programs that are

currently in place, as well as designing and implementing new programs, including: Training scientists to better interface with the general public; identification and networking with political figures who can provide support and both the state and federal levels for ONPRC and other NPRCs; identification of funding opportunities and assistance with grant proposals to access those opportunities; building a menu of teacher professional development opportunities; and development of events and educational opportunities aimed at adults.

APPROACH

reviewers' comments

Progress Report.

In the previous funding period, the ONPRC outreach program has operated an extensive collection of activities, including tours, classroom visits, the Science Ambassadors, Science Saturdays, and Saturday Academy programs, as well as specific events such as Camp Monkey, which are described in detail below in the Specific Aims section. In addition, a large and active volunteer docent team has been established, and veterinary externships, apprenticeships, internships, and volunteer positions have been supported. Collectively, these efforts have resulted in bringing over 3,000 individuals to ONPRC on an annual basis for various educational activities. Of special note is the development of a relationship with a generous donor in the community who has, for the past 4 years, provided funds to support up to 20 high school and undergraduate students in summer apprenticeships with ONPRC scientists. In addition, the Private Source has funded the renovation of the space formerly occupied by graphic designer Excluded into a fully operational teaching lab that can accommodate up to 24 students. Other activities include generation of press releases and use of social media in coordination with the OHSU Office of Strategic Communications. These efforts have resulted in significant amounts of news coverage for the center. Recent news stories have included:

- International news coverage of a gene therapy method developed and tested at ONPRC
- The development of a promising AIDS vaccine candidate in non-human primates at the center
- The development of a new method for producing vaccines that's believed to be safer and result in more effective vaccines
- The discovery of a non-human primate model for MS that may greatly assist in the development of treatments for human patients
- Several advancements in the area of stem cell therapy including the transformation of monkey egg cells into stem cells
- The development of a newer, safer birth control method
- New information that helps debunk beliefs that birth control pills cause weight gain

In some cases, ONPRC breakthroughs have generated several hundred stories worldwide.

Specific Aims.

Specific Aim 1. To provide multiple outreach activities for the general public, teachers, and students. We will continue to offer a variety of programs that promote science education and public outreach. Our goal in the next funding period is to expand and enhance these programs, and to include active outreach to state and federal legislators highlighting the value of the work performed at the ONPRC. Each of these programs is outlined below.

Tours. The tour program is the cornerstone of our outreach endeavors, reaching over 3,000 persons each year with the messages that (1) biomedical research is critically important to continued improvements in our understanding of human (and animal) health and disease; (2) the research is highly regulated, and (3) the care of the animals that participate in this research is exemplary. Tours are offered to educational groups, civic groups, and the general public. The average group size is about 30 persons, but groups may vary in size from

12 persons to approximately 70. The trend toward larger group sizes over the past 5 years has been a result of tighter funding: Fewer field trips are funded, and teachers wish to bring as many students as possible. Our published upper limit is 60 students (with chaperones, etc., this number approaches 70 for very large groups, and has been over 100 for the Public Tour). A document entitled "Planning Your Visit to the Primate Center" is provided to all persons who schedule tours. The rules and regulations (including requirements for chaperones, expected student behavior, and the prohibition on photography) are described in this document. These are reinforced in the presentation, and throughout the course of the tour.

(1) *Elementary/Middle School Students.* Beginning in 4th grade (age 10), students are usually able to discern the difference between a biomedical research institution such as the ONPRC and the zoo. This difference is discussed with students in this age group who visit the Primate Center. Reaching students in this age group is particularly important, as this is the age group that is currently being targeted by animal rights groups such as PeTA. PeTA has produced a series of anti-research activity books which are made available to elementary educators, and often find their way into the hands of students (see PeTA publications "Your Mommy Kills Animals!" "Your Daddy Kills Animals!" and "A Rat's Life"). Young students attending tours of our facility may not always completely understand the scientific need for animals in research, or completely comprehend and incorporate the ethical issues involved into their own reasoning framework, but they leave with good feelings about the Primate Center. They know that we are nice people, that we are trying to help improve human and animal health, and that we care about our animals. Later, as they develop their own opinions, their experiences here will count for something. In advance of visiting the Center, students in this age group have a classroom presentation that focuses on biomedical research that is delivered to them at their school. When they come to the Primate Center, we focus on animal care and behavior. They do observations of the monkeys, and record these observations on an ethogram. This helps to focus their attention and assists with large group management.

(2) *High School/College Students.* High school and college-aged students have often developed very strong opinions about animal research, to the point where those who disagree with the concept typically will choose to opt out of the field trip. For this age group, we hope to provide some information to those who are as yet undecided about their support for biomedical research. At the conclusion of the tour, these students will often tell us that they appreciate the information we have provided and have been pleasantly surprised to see that the animals are well-treated (a sentiment we often hear from their teachers, and from those adults who attend the Public Tour, as well).

(3) *Public Tours.* Each spring, a Public Tour is scheduled (usually on the first Friday in May). Attendees are recruited for this tour at the Brain Awareness Lecture Series, held during the months of January and February each year. Additionally, persons who have called during the year indicating an interest in touring the Center are contacted at this time to remind them of this opportunity. All of these persons must provide their home addresses, e-mail addresses and telephone numbers. Each person is vetted by both Excluded by Requester We typically accommodate 90-100 persons on this tour each year. Center personnel who participate in this tour include the Director, Excluded by Requester the Head Veterinarian, Excluded by Requester (and other veterinary staff); and the Head of the Behavioral Services Unit, Excluded by Requester Excluded by Requester (and other BSU personnel). In addition, at least 4 Docents are on hand to help with crowd control and information dissemination. Any individual willing to recruit a group of 10 persons may schedule a tour of the Center. Any group of this sort must, as above, provide home addresses and contact information for each attendee. These names/addresses are vetted by both Excluded by Requester as above.

Classroom Visits/Speakers Bureau. A number of Center personnel enjoy speaking with students/civic groups off campus. These individuals are part of our Speakers Bureau, and speak on a variety of topics, including science, animal care, and ethics. Besides learning about a specific research program, students have the opportunity to interact with working scientists/vets/etc. and ask them questions about their work, how they became a scientist, etc. Classroom visits also provide an excellent opportunity to interact with the public and answer any questions/concerns students (or teachers) have about animal research.

Science Ambassadors. The Science Ambassadors program is a mentorship program that pairs high school-aged mentors with 5th grade students from the Beaverton School District. In providing an extracurricular, informal science learning opportunity for students, we are also building relationships with the students and their parents. Thirty-six students (and their 72 parents) are served each year. Twenty high School students are addressed by a different Center scientist each month. During other meetings, they work to produce hands-on lessons that relate in some way to biomedical research. Initial lessons involve animal care and enrichment activities. We move on to lessons and activities that support learning about cells and DNA, the immune system, nutrition, and brain health, relating lessons (as much as possible) to research that is conducted here at the Center. Scientific literacy is not the only outcome of importance here. It is at least equally important to build a relationship with these students (and their parents) that enables them to both question the claims of anti-research activists and have a resource to go to for the other side of the story. As proof of the effectiveness of this approach, several Docents are parents of Science Ambassadors.

Volunteer Docent Team. The Docents are a group of volunteers that assist with tours. As described above, they are engaged to help with crowd control and enhance interactive opportunities when larger groups visit the Center. The Docents attend monthly training sessions, which include an address by a Center scientist, information about ONPRC and OHSU policies and regulations concerning tours, and discussions about how to improve the tour experience for our visitors. Docents are well-informed about Center science, animal care, safety and liability concerns, and can also discuss ethical issues associated with biomedical science.

Saturday Academy. Saturday Academy is an organization that offers extracurricular science experiences to youth in the greater Portland area. Each year, we run two sessions of Saturday Academy classes. In the Winter Term, Excluded by runs a 6-session course based on concepts in fertility/oncofertility. In either the Fall or Spring Term, we run a 4-6 session course that is taught by various Center personnel, including PIs, veterinarians, and research staff. In both cases, students met in the learning lab, and perform hands-on activities that expose them to the techniques used in biomedical science.

Science Saturdays. Science Saturday events are built around the solution of a mock mystery, an approach that we find generates the authentic excitement of science. Participants (ranging in age from 5th grade students through adults) use the tools of science to solve a mystery, such as "The Case of the Missing Pizza," the "Case of the Confiscated Monkey, or "The Case of the Wobbly Monkey." Events are held approximately quarterly, and participants are selected on a first-come, first-served basis.

Camp Monkey. Camp Monkey is a day-long event held during the summer for middle school-aged students. It provides an opportunity for these students to participate in hands-on science activities relating to the theme of biomedical research. Activities change from year to year, but the general scheme of events (6 stations, through which students rotate), remains the same.

Veterinary Externships. We offer an extensive selection of externship opportunities to vet students from around the country. In order for this to happen, a contract must be negotiated between OHSU and the veterinary College/University that stipulates responsibility for liability during the course of the student's time with us. This is handled by the Contracts & Grants Offices of our respective Universities.

Apprenticeships/Internships/Volunteer Positions.

(1) *Apprenticeships in Science and Engineering (ASE).* Paid summer apprenticeships ($1000) are made available to high school students who are at least 16 years old through Saturday Academy's "Apprenticeships in Science and Engineering" (ASE) program. 6-8 students are supported for 8-weeks each summer.

(2) *Undergraduate Summer Fellowship.* This program provides stipends for 6-8 undergraduate students from around the US (and sometimes from other countries).

(3) *Murdock Trust "Partners in Science" Program.* High school science teachers are supported with a generous stipend for two consecutive summers in Center labs through a program run by the Murdock

Charitable Trust. Teachers work with a mentor for 8 weeks each summer.

(4) *Volunteers.* High school students, undergraduates, and unemployed professionals may seek volunteer opportunities in Center labs.

(5) *Miscellaneous Educational Opportunities.* Occasionally we have requests from high school/undergraduate students to undertake research projects here as part of an educational requirement. Occasionally a researcher will be willing to take on a student who is interested in conducting a short-term project; such students are enrolled as volunteers through OHSU. We have had several instances of undergraduate institutions contacting us to provide observation opportunities for their students as part of a research endeavor. We try to honor these requests whenever possible. This program is overseen by Excluded by Requester (Head, Behavioral Services Unit), who serves as the sponsoring scientist for students who fall into this category.

Specific Aim 2. To communicate the activities and discoveries of ONPRC personnel to the general public. OHSU Strategic Communications has utilized several avenues to communicate directly with the public and through the news media. These efforts include:

Press Outreach via News Releases and Story Pitches

OHSU Strategic communications issues several press releases each year to promote the research conducted at ONPRC. Strategic Communications also places news stories to highlight excellent animal care practices at the Oregon primate center.

Press release topics include:

- Research breakthroughs
- USDA inspection results
- Public events on campus
- Outreach activities including animal enrichment programs and the previously mentioned "Camp Monkey"

Social Media

OHSU Strategic Communications also manages social media for the primate center. These efforts include:

- Managing the @ONPRC Twitter Feed. The feed is used to share news stories, blog posts about the center and research breakthroughs in the area of primate science.
- Managing the Facebook page for ONPRC. The page is used to promote news stories and breakthroughs. It is also a place where discussions with the public, including those concerned with animal research take place.
- Production and distribution of videos that highlight the research conducted at ONPRC. These videos are produced in house and then shared with the press via YouTube and Vimeo. In some cases reporters use these videos as part of their stories.

Other Projects

OHSU Strategic Communications has also led several other communications efforts on behalf of ONPRC. Those efforts include:

- Collaboration with the outreach office to create and distribute a vide tour of the primate center to explain our research and promote transparency.
- Development of security measures, such as an instant mass cell phone messaging system in case of a protest or home harassment of scientists.
- Communications collaboration with several other institutions to increase public knowledge about the need for animal studies.

Specific Aim 3. To engage with the general public in a series of programs to foster discussions around science and the value of science. As one of our major initiatives in the next five years, we will seek funding to host Science Discussions in the Portland area, informed by members of a Community Advisory Board. The

Director of the Oregon Zoo and the Mayor of Hillsboro have both indicated interest in participating on this Board. Additional members will be recruited from the surrounding community as well as from the ONPRC campus. The role of the Board will be to build connections between ONPRC and the community and to help us more accurately gauge the perception of ONPRC in the community. Using this information, we can design our outreach efforts to respond to whatever need the community might have to better understand the role we at ONPRC play in improving health.

Specific Aim 4. To continue to represent ONPRC through participation in OHSU's public outreach events as appropriate. OHSU sponsors a number of outreach events each year, in which the ONPRC Outreach Program participates. These events include: OHSU/OMSI Brain Fair, On Track OHSU! (to increase diversity of the workforce through working with underrepresented populations), Portland Metro STEM Center (which serves the Portland Metropolitan community to provide underrepresented populations with opportunities to experience STEM-associated activities), Work Systems, Inc.'s "Ninth Grade Counts" program (Ninth Grade Counts connects at-risk youth with the supports that they need to stay on track to graduate), and other community non-profit agencies associated with education and health (Saturday Academy, SMART reading program, ARCS, etc.). These efforts contribute to the important linkages between ONPRC and the host institution by emphasizing the relationship between the Center and OHSU to the public.

REFERENCES

Excluded by Requester

RESOURCES

Follow the 398 application instructions in Part I, 4.7 Resources.

Outreach and Community Engagement

Laboratory:
The outreach and community engagement program maintains a laboratory space conveniently located adjacent to the ONPRC's Montagna Auditorium that is specifically designated for the use of outreach and educational programs on the ONPRC campus. This space, designated the Private Source Learning Laboratory, is an 800-sq. ft. space furnished with movable lab benches and stools that can accommodate up to 36 students. The lab is equipped with a laminar-flow hood, sink, refrigerator, and a wide variety of materials for numerous laboratory activities.

Computer:
A desktop PC computer and printer are available for use by persons who are conducting activities in the Learning Lab. WiFi is also available for additional computers brought into the learning lab.

Office:
The Education Outreach Coordinator maintains an 80-sq. ft. office that adjoins the Silver Family Learning Laboratory.

Other:
A number of additional spaces at ONPRC are available for outreach activities, including a large multi-purpose room that can comfortably accommodate 36 persons in both lecture and lab conformations (Malinow Meeting Hall), a small seminar room that can house up to 40 persons (VGTI 1st-floor seminar room), and three smaller conference rooms (the Administration Building Conference Room (ABC), the Research Building Conference Room (RBC), and the Voss Conference Room), each of which can comfortably seat 12-16 persons. Finally, for larger groups, the Montagna Auditorium has the capacity to seat 175 persons.

A significant resource for outreach at ONPRC is the faculty and staff who are willing to share their time and laboratory space for educational purposes. The culture of ONPRC includes a deep commitment to outreach. Over 20 ONPRC investigators consistently participate in one or more outreach activities each year. Importantly, the expansion and continued development of outreach programs has enjoyed the strong support of every administration since the Center opened in 1962. For the past 14 years, since ONPRC merged with the Oregon Health & Science University (OHSU), we have enjoyed collegial support from OHSU as well as support in identifying donors interested in supporting education and outreach activities in the community. It is this support that enabled us to renovate the Learning Lab and continues to support our summer apprentice programs.

Program Director/Principal Investigator (Last, First, Middle): Robertson, Joseph E./Haigwood, Nancy L.

OUTREACH & COMMUNITY ENGAGEMENT DETAILED BUDGET FOR INTIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Excluded by Requester	Education Outreach Special	% Effort			Institutional Base Salary	12,741	3,950	16,691
	Sr. Scientist					2,118	529	2,647
To Be Named	Admin Asst	0.45				1,253	501	1,754
	→ SUBTOTALS					16,112	4,980	21,092
CONSULTANT COSTS								
None Requested							0	0
EQUIPMENT *(Itemize)*								
None Requested							0	0
SUPPLIES *(Itemize by category)*								
Laboratory Supplies							68	
Operating Supplies							337	
								405
TRAVEL								
Domestic							337	337
INPATIENT CARE COSTS								0
OUTPATIENT CARE COSTS								0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*								
None Requested							0	0
OTHER EXPENSES *(Itemize by category)*								
Hosting Groups and Guests							371	
Membership in Profesnl Org							51	
								422
CONSORTIUM/CONTRACTUAL COSTS						DIRECT COSTS		0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*								$ 22,257
CONSORTIUM/CONTRACTUAL COSTS						FACILITIES AND ADMINISTRATIVE COSTS		0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD								$ 22,257

PHS 398 (Rev. 6/09) **Form Page 4**

OUTREACH & COMMUNITY ENGAGEMENT
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	21,092	21,725	22,376	23,048	23,739
CONSULTANT COSTS	0	0	0	0	0
EQUIPMENT	0	0	0	0	0
SUPPLIES	405	417	430	443	456
TRAVEL	337	348	358	369	380
INPATIENTS CARE COSTS	0	0	0	0	0
OUTPATIENTS CARE COSTS	0	0	0	0	0
ALTERATIONS AND RENOVATIONS	0	0	0	0	0
OTHER EXPENSES	422	435	448	461	475
DIRECT CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	22,257	22,924	23,612	24,321	25,050
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	22,257	22,924	23,612	24,321	25,050
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					118,164

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

PERSONNEL

Education Outreach Specialist – Excluded by Requester % Effort Income). Responsible for coordinating all outreach activities and for the direct implementation of all aspects of the educational outreach program, including oversight of ongoing programs as well as development of new programs; formatting curricular materials in order that the programs can be implemented in diverse settings (including other Primate Centers and classrooms). Also responsible for working closely with Excluded by to identify and secure funding to support ongoing and new outreach programs.

Senior Scientist – Excluded by Requester % Effort Responsible for promoting participation in the outreach program to fellow scientists on campus, at other NPRCs, and at other biomedical research facilities; identifying funding sources and assisting in securing additional funding for outreach programs; working with Education & Outreach Coordinator to develop and implement new outreach programs; reporting on all outreach-related developments to the Expanded Executive Committee.

Administrative Assistant – To be named (3 calendar months effort: 0.45 ORIP, 2.55 Program Income). Responsible for assisting the Education & Outreach Coordinator with curriculum development, new program development, and the record-keeping and organizational efforts associated with running a large, multi-faceted outreach program.

SUPPLIES

Laboratory Supplies: Funds are requested to purchase laboratory supplies necessary to support the hands-on activities offered in ONPRC's various education outreach program which includes agarose gel electrophoresis supplies (agarose, buffer, etc.), microscopy supplies (prepared slides, slides, cover slips, etc.), Mendelian Genetics activities support materials (PTC paper, etc.). Funding is also requested for craft materials and other supplies that support the hands-on activities offered in the outreach programs (for making models of molecular structures as well as a variety of other activities that serve to describe and explain a variety of key science concepts to a variety of age groups).

Operating supplies: Funds are requested for purchase of general office supply-type materials associated with the function of the outreach office, and other miscellaneous supplies including brochures/posters, exhibit/display items, tee shirts for participants in the *Science Ambassador* program, vests for participants in the Docent program, tyvek lab coats and misc. educational support materials for outreach activities (books, curriculum materials, etc.)

TRAVEL

Funds are requested to support travel and lodging costs associated with attendance at annual meetings such as OST, Partners in Science and one additional meeting, TBD (NSTA, NABT, AALAS, other).)

OTHER EXPENSES

Hosting Groups and Guests: Funds are requested to purchase snack items for the weekly meetings of the *Science Ambassadors* group, as well as food & beverage items served at the yearly parent information meetings (2 each fall), at the yearend celebration ice cream social held for the Science Ambassadors each Spring, beverages for the attendees of the Public Tour held each Spring, and to support general hospitality functions at a variety of outreach events that occur each year at the ONPRC.

Memberships in Professional Organizations: Funds are requested to support the annual fees assessed for Ms. Excluded by Requester membership in the Oregon Science Teachers Association and the National Science Teachers

Association, as well as the fee charged to participate as an exhibitor at the annual meeting of the Oregon Science Teachers Association.

Outreach and Community Engagement Income Table

Last Funded Year (53)

Source	Funding (direct costs)
P51 base grant support	$19,157.03
Program income derived from P51 base grant	123,120.71
Other Sources	0
Total	$142,277.74

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$22,256.74
Program income derived from P51 base grant	127,190.52
Other Sources	0
Total	$149,447.26

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

The Outreach and Community Engagement receives salary support and support for other expenditures from program income.

TITLE: NPRC CONSORTIUM-BASED ACTIVITIES

CORE-SUPPORTED PERSONNEL:

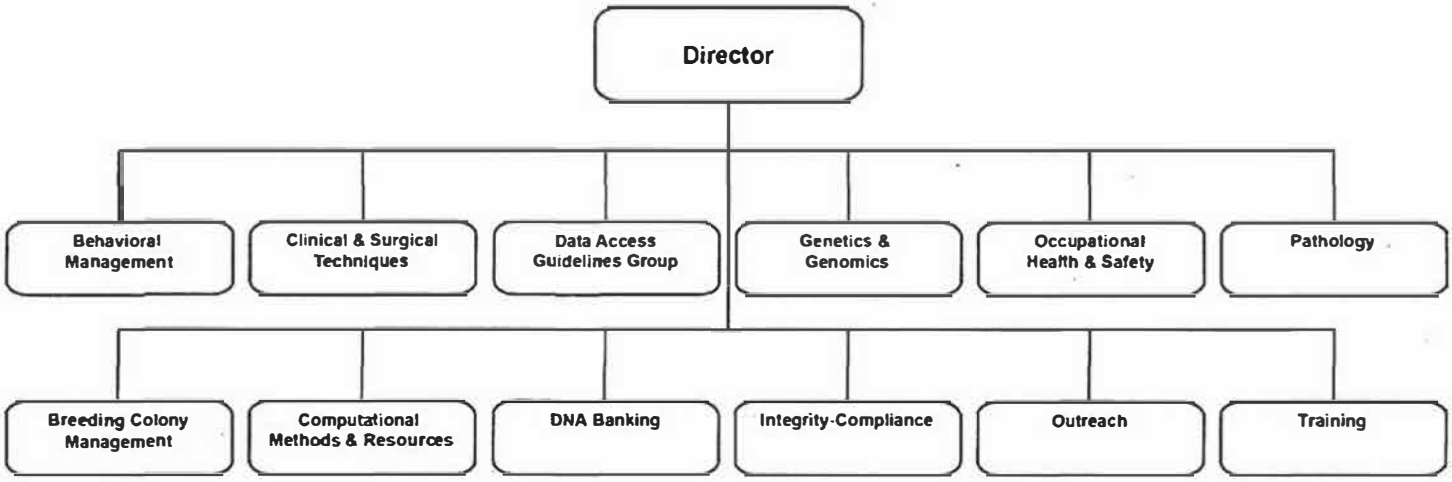
Core Scientists (See Biographical Sketches, listed alphabetically in the Overview of the ONPRC)

Excluded by Requester	Associate Scientist Assistant Professor

Research Support

Excluded by Requester	Research Analyst 2 Manager, Research Informatics

NPRC Consortium-Based Activities
Organizational Chart



NPRC CONSORTIUM-BASED ACTIVITIES

DESCRIPTION

The NPRC Consortium was established as the "Ninth Primate Center" to enhance cooperation between the eight NPRC programs and the NIH Office of Research Infrastructure Programs. The Consortium has twelve Working Groups that serve to facilitate sharing of best practices across the eight centers, and each center contributes time and effort to staffing and participating in these activities. The major goals are to share best practices, to enhance sharing of resources, and to establish channels of regular telephone, electronic, or in person communication amongst the experts in these areas of interest. The activities of the Working Groups have oversight from the NPRC Directors as well as the NIH ORIP staff, and budgets are approved annually to support the program in part. Each NPRC contributes time and effort to the Consortium. The ONPRC has a representative on each of the Working Groups and has made efforts to provide leadership in several of them. During the last funding period, the ONPRC has hosted a number of onsite meetings of various of these groups.

The twelve groups are:

1. Behavioral Management Consortium
2. Breeding Colony Management Consortium
3. Clinical and Surgical Techniques Working Group
4. Computational Methods & Resources Group
5. Data Access Guidelines Group
6. DNA Banking
7. Genetics & Genomics Working Group
8. Integrity-Compliance
9. Occupational Health & Safety Working Group
10. Outreach Working Group
11. Pathology Working Group
12. Training Consortium

NPRC-BASED CONSORTIUM ACTIVITIES: SPECIFIC AIMS

The ONPRC takes an active role in promoting and contributing to each of the NPRC-based Consortium Working Groups. The major goals of each of these groups are listed below.

1. **Behavioral Management (BMC).** This group has the goal to strengthen communication and research collaboration to help to identify behavioral management best practices and promote psychological well-being for captive nonhuman primates (NHP). To this end, the BMC promotes resource sharing, standardization of terminology and assessment tools, and scientific collaboration among participants.
2. **Breeding Colony Management (BCMC).** This group enhances collaborations between NHP colony mangers of all national primate centers with regard to breeding management, herd health, regulatory compliance, SPF surveillance, facility management/design and resource sharing.
3. **Clinical and Surgery Techniques (CAST).** This group seeks to accelerate information transmission among NPRCs, to serve as a resource to develop best clinical and surgical practices among and within the NPRCs, and to facilitate networking among NPRCs and relevant institutes beyond NPRCs.
4. **Computational Methods and Resources.** The role of this group is to identify new and more productive synergies between people and computing technologies, to provide methods and software application resources to support other Consortium working groups, and to facilitate and make rigorous the sharing of data, practices and expertise between NPRCs.
5. **Data Access Guidelines Group (DAGG).** This group will develop and maintain processes to ensure all website content and related access permissions are reviewed and approved by DAGG representatives. They will educate working group participants on best practices to prevent unauthorized access or unnecessary exposure of shared information.
6. **DNA Banking.** This group will establish a National NHP DNA Bank to facilitate the distribution of NHP genomic resources for research use, establish a centralized web portal to enable direct access to DNA Bank content and distribution information and promote use of the National NHP DNA Bank through publications and targeted presentations.
7. **Genetics and Genomics.** This group has to goal of designing and developing a custom SNP- array for parentage analysis of rhesus macaques at all NPRCs, and an array for rhesus macaque ancestry analysis at all NPRCs. They plan to develop web-based analysis pipelines to facilitate parentage and ancestry genotype interpretation and to develop colony genetic management guidelines for optimizing the genetic health of NHP colonies across the NPRCs.
8. **Integrity-Compliance.** The purpose of this working group is to cultivate open discussions and critical thinking about matters related to compliance with federal regulations and NIH guidelines at the National Primate Research Centers (NPRCs). The first focus is the development of an on-line resource to provide information about IACUC protocol review and NPRC-specific attention to OLAW, USDA, and AAALAC regulations, guidelines and recommendations.
9. **Occupational Health & Safety Working Group.** This group plans to achieve a better understanding of the most updated information for those working with NHPs between the NPRCs, National B-virus lab and the Centers for Disease Control and well as to increase sharing of injury and exposure data between NPRCs to look for trends in data and share successful injury reduction strategies.
10. **Outreach.** The goal of this group is to share best practices with respect to handling issues that are unique to research involving animals, to identify opportunities to educate the public (both at public events, via the internet, and through the press), and to develop appropriate responses to persons who are opposed to biomedical research that involves animals. They will share activities and information via the web and will develop marketing/ outreach/teaching materials that can be used by all NPRCs.
11. **Pathology.** This group seeks to foster cooperation between the NPRC's to effect improved understanding of NHP pathology and to share best practices for greater efficiency. They have a goal to increase availability of the pathology resource (data, images, etc.) between and outside centers to better serve as a national resource for NHP Pathology.
12. **Training.** This group contributes to, and takes a leadership role in promoting, the exchange of clinical or operational case presentations of NHPs amongst NPRCs and other contributing institutions to foster a collegial and communicative environment amongst these institutions, and ultimately to promote best practices.

NPRC CONSORTIUM-BASED ACTIVITIES: RESEARCH STRATEGY

NPRC CONSORTIUM WORKING GROUP	ONPRC PERSONNEL	TITLE
Behavioral Management Consortium	Excluded by Requester	Staff Scientist
Breeding Colony Management Consortium		Associate Director, Div. Comparative Medicine Associate Veterinarian Asst. Assoc. Director, Div. Comparative Medicine Manager, Research Informatics
Clinical and Surgical Techniques Working Group		Assoc. Veterinarian; Head, Surg. Services Unit Assistant Veterinarian
Computational Methods & Resources Group		Manager, Research Informatics
Data Access Guidelines Group		Manager, Information Technology
DNA Banking		Associate Scientist
Genetics & Genomics Working Group		Associate Scientist Assistant Professor, Molecular & Medical Genetics
Integrity-Compliance		Integrity Officer, West Campus
Occupational Health & Safety Working Group		
Outreach Working Group		Educational Outreach Specialist
Pathology Working Group		Senior Vet; Head, Pathology Services Unit Veterinary Pathologist
Training Consortium		Senior Vet; Head, Pathology Services Unit Asst. Assoc. Director, Div. Comparative Medicine

1. Behavioral Management

Excluded by Requester has been highly involved in the BMC working group since its inception. She participates in monthly meetings and contributed to all of the BMC major accomplishments. She took the lead role in the implementation of the BMC Self-Injurious Behavior Scoring System, a tool to help standardize terminology and assessment of this serious behavioral problem. She also participated in scientific collaborations with other BMC members. Along with other BMC members Excluded by Requester authored a paper in the dedicated volume of the journal *Applied Animal Behavior Science*. She also co-authored two additional papers In Press Submitted and two book chapters (one peer-reviewed) with other BMC members. In addition Excluded by co-authored 6 talks and three symposia (at national and international conferences), and co-moderated one pre-conference workshop ("Multidisciplinary preventative approach for managing large breeding groups of nonhuman primates") with BMC members. She collaborates with members of the Southwest NPRC, Washington NPRC, and the New England NPRC on an NIH-funded study examining self-injurious behavior. She also submitted a collaborative grant on aggression in social housed animals with the California NPRC,

Yerkes NPRC and Tulane NPRC. This grant will be resubmitted next year. Finally, the ONPRC and California NPRC behavioral management units have participated in exchange programs. Since 2009, the ONPRC has hosted four members of the CNPRC, and has sent two BSU technicians to the CNPRC for cross training.

2. Breeding Colony Management

Scientific Environment

The BCMC continues to be a unique, collegial, unassuming environment with a clear directive to meet desired goals as a full committee and within subgroups. The BCMC is an irreplaceable resource which has allowed the group to collectively study common NHP herd health and breeding issues as well as other management strategies across all centers. We therefore gain from each other's positive and negative management experiences. Commonly this is a "lessons learned" environment which has led to a resource savings by preventing mistakes already made.

Progress Report

The ONPRC has been an active leader in the BCMC since its conception. This year the ONPRC hosted the BCMC face to face meeting in March 2012 in which Kirk Andrews presented "New Technologies for SPF Surveillance". The ONPRC has contributed multiple samples to the virus testing panel; this is to verify that our different SPF testing platforms are similar. We have also lead and contributed to many sessions involving colony health benchmarks and genetic breeding management. To share resources and animal inventory, excess animals are now advertised between centers. Additionally, the ONPRC has presented the Animal Resource Simulation Project to the BCMC consortium, in which there has been significant interest in its use at other primate centers.

3. Clinical and Surgery Techniques (CAST)

Excluded by Requester (ONPRC) established and currently chairs the Clinical and Surgical Techniques (CAST) Working Group. The first meeting of this group was May 1, 2012. Since the first meeting, membership has grown to over 50 participants representing all eight National Primate Research Centers (NPRCs). Each monthly web conference begins with a presentation, typically a PowerPoint, about a given topic (15-20 minutes). Topics are limited to common procedures rather than unique case reports. Presentations include technical tips learned through experience that may or may not have been published or presented previously. Each presentation is followed by an open discussion about potential variations of the procedure described as well as experiences with the procedure at other centers (up to 40 minutes). Workflow management is necessarily an important part of discussions about procedures that are components of large-scale research protocols. While presenters rotate on a voluntary basis among the centers, ONPRC's participation has been substantial in order to successfully launch this group. Topics presented thus far include "Lymph Node Biopsies" Excluded by Request ONPRC), "Laparoscopic Follicle Aspiration" Excluded by Requester Yerkes and former ONPRC Resident), "Duodenoscopy and Biopsy" Excluded by Requester WiNPRC), "Workflow Automation Strategies" Excluded by Request ONPRC), "Intravenous Glucose Tolerance Testing" Excluded by Request NEPRC), and "Intestinal Resection and Anastomosis" Excluded by Requester TNPRC). These are practical discussions with the aim of improving members' procedural competency as well as their procedural repertoire. As Chair of the CAST working group Excluded by Requester recruits speakers, coordinates, and moderates each monthly meeting.

Importantly, the networking opportunities and computational expertise provided by the Consortium have resulted in the collaboration of veterinarians and investigators from ONPRC with WisNPRC. This collaboration has resulted in the development of software tools that are being utilized at both centers to help manage aging and diabetes resource animals. Since these populations are relatively small at each center, the software will enable the compilation of clinical experiences in a (virtual) larger population to better assess and evaluate treatment outcomes. This process serves to increase the pool of evidence on which to base clinical decisions. While this collaboration is a recent development, the synergistic effects of combined expertise will likely yield improvements in animal care at both centers. We hope to publish these advances as opportunities permit.

4. Computational Methods and Resources

The Computational Methods and Resources Group (CMRG) was established by [Excluded by Requester] at ONPRC in 2011 with the aim of providing the technical means to promote, facilitate and implement sharing of data and practices between the NPRCs. Our vision is the most economically and scientifically productive synergy between people and computing technologies, and our mission is to provide the computational methods and resources to pursue this goal. Participation of the other NPRCs is by means of the Consortium Working Groups including Breeding Colony Management, Clinical and Surgical Techniques, and Integrity/Compliance, as well as through spontaneous collaborations initiated by directly "marketing" tools to interested users in the NPRC community. ONPRC's role is to provide development expertise and application opportunities whereby prototype tools can be evaluated, refined and demonstrated for adaptation to related applications at other NPRCs. Accomplishments include deployment of a web-based system to integrate SPF-colony reporting across the Consortium, a prototype diabetes monitoring application that integrates institutional and laboratory record systems at two NPRCs, and deployment of an application to adaptively integrate multiple data sources to save approximately $80,000/year in NHP surgery. Underway are initiatives to automate SPF and colony health benchmarks reporting, and the development of a post-approval monitoring application suite for another NPRC

Resources & Environment:

CMRG applications make heavy use of Mathematica, a platform-independent technical computing environment that includes a potent programming language with built-in web and parallel-computing constructs. Though Mathematica itself is not open source, it ships with a free "player" that allows one to interact with its product; in the majority of applications this makes Mathematica a very economical solution. Substantial use is also made of open source web-programming languages and development environments.

5. Data Access Guidelines Group (DAGG)

As the DAGG representative for ONPRC beginning Jan. 1, 2012 [Excluded by] has attended all meetings to date, which have switched from a monthly to a quarterly schedule. Of the major accomplishments by the DAGG overall to date, the approval of reducing DAGG membership to one representative per center had no impact upon ONPRC's participation on the DAGG. However, there remains an unfinished plan item to identify an alternative DAGG representative for each center in order to ensure a higher percentage of attendance at the now reduced meeting schedule frequency. Efforts to identify the ONPRC alternate are under way.

6. DNA Banking

This group was led by [Excluded by Requester] The working group established the National NHP DNA Bank, a resource facilitating the distribution of genomic DNAs from 11 different NHP species housed in the NPRCs. The ONPRC 'branch' of the National NHP DNA Bank includes samples from Indian-origin rhesus macaques (50 unrelated and 10 family trios), Chinese-origin rhesus macaques (25 unrelated and 4 family trios) and Japanese macaques (16 unrelated and 6 family trios). [Excluded by] also consulted with [Excluded by Requester] and his team to develop the National NHP DNA Bank web portal, a searchable site detailing all bank holdings and providing contact information for direct NHP DNA Bank inquiries. To increase public awareness of the resource, [Excluded by] and her colleagues wrote and published a manuscript describing the National NHP DNA Bank [Excluded by Requester] She also worked with working group members to develop a National NHP DNA Bank poster presentation and informational brochure that was presented at five national and international meetings in 2012. Over 600 DNA samples have been distributed to academic institutions from the ONPRC branch of the National NHP DNA Bank since it was established in 2008.

7. Genetics and Genomics

The ONPRC was represented by [Excluded by Requester] (since 2008) and [Excluded by Requester] (since 2011). The first goals of the GGWG were to design and develop two 96 SNP arrays to inform genetic management of rhesus macaque colonies at the NPRCs. [Excluded by] worked in partnership with the CNPRC members of the group to develop, test and deliver two 96 rhesus macaque SNP arrays to the NPRC community. Since completion of this project, [Excluded by] has provided ancestry and parentage SNP genotyping services to four NPRCs, including the NEPRC, WNPRC, TNPRC and ONPRC. Since 2010, [Excluded by Requester] have worked with [Excluded by Requester] and his team to develop ancestry and parentage analysis pipelines via the NHPRC

web portal, including field testing the analysis pipelines and recommending improvements. In 2012, the GGWG turned its attention to establishing genetic metrics and guidelines for the assessment of colony genetic health in NPRC breeding colonies. Excl udedby is a leader in this effort, identifying and advising on best practices for genetic diversity assessment of captive breeding colonies. She is currently contributing to a GGWG manuscript that summarizes the recommendations.

8. Integrity-Compliance

This working group has not met at this point and we are currently in the planning stages for the first teleconference meeting. The agenda for the first meeting will concentrate on Post-Approval Monitoring (PAM) and the appropriate policies for implementing a PAM system that is available to all the NPRCs. This is a major initiative of the Oregon NPRC but has been delayed by concerns of implementing a non-regulated system. Consultation with other NPRCs will assist us in developing a system that will satisfy future regulations on PAM and provide other NPRCs with the basics of a system for their Centers.

Another important aspect of this working group is the development of electronic management systems to oversee compliance with approved IACUC protocols. An example of innovation that addresses workflow management are web-based systems developed by ONPRC for easy access by investigators for self-monitoring blood draw volumes, access to staff training records and current data on IACUC approved animal numbers and surgical procedures. There is great interest in the development of additional applications that can be added to the BIRN system and used by the member of the consortium to provide efficiency within their Centers and, most importantly, communication between the Centers.

With the assistance of Excluded by Reques ter we will also be setting up secure online information systems available to all NPRCs. Any funds necessary for prototype development of electronic applications would be covered by the Computational Methods and Resources Working Group and there is no cost associated with the operation of this Working Group.

9. Occupational Health & Safety Working Group

The West Campus Environmental Health and Radiation Safety (WCEHRS) Manager has participated in all scheduled webcast meetings of the OHS Working Group, and attended the June 2012 group meeting in Boston at the Preventing and Treating Biological Exposures Conference as a representative of the ONPRC. The WCEHRS Manager provided information regarding ONPRC specific strategies for preventing and managing injuries and exposures to nonhuman primates and their fluids, shared ideas, solutions and approaches to challenges; participated in face-to-face discussions and brainstorming, and gathered information on unpublished events that directly affect the ONPRC OHS program. The WCEHRS Manager has also shared ONPRC-specific processes and procedures to assist in standardization of such processes across all National Primate Research Centers.

Relevant resource and environment information.

There are no relevant resources or environmental information. A source of funding needs to be identified to allow for attendance at the 2013 annual meeting, with an estimated cost of $8,200.

10. Outreach

Over the past year, Excl udedby Reques ter ONPRC Education & Outreach Coordinator, has met monthly with the other members of the Education Outreach Working Group via conference call. Excl uded by Request represented the NPRCs (along with Outreach Working Group members from Wisconsin and California) at the USA Science & Engineering Festival in Washington, D.C. in April of 2012. Excluded by Requeste shared ONPRC outreach activities via the working group webpage, as well as by presentation at the Working Group meeting in San Antonio on October 26, 2012. At that meeting, Excl uded by Strategic Communications Officer, presented information regarding ONPRC anti-research activism response tactics. Also at that meeting, members of the Working Group agreed to take on certain roles with regard to outreach activities in the coming year. Excluded will work with other members of the group to develop a series of informative tri-fold flyers targeted to specific audiences (scientists, teachers, students, general public/politicians), and will again represent the NPRCs at the next USA Science &

Engineering Festival, as well as overseeing the opportunity for the NPRCs to conduct outreach at the 2013 Science Olympiad in Dayton, Ohio.

11. Pathology

Excluded by Requester serves as the chair of the Pathology Working Group. Excluded by Requester have been active in the PWG activities since its inception in 2006. The major accomplishments of the group have been the establishment of Primate Pathology Image Database (PPID), monthly virtual slide conferences and annual face to face meetings. The ONPRC received stimulus funding for development of the PPID which was developed in partnership with CNPRC BIRN and the Consortium development group. The PPID is a database of histologic and gross pathology images of the important spontaneous diseases of laboratory nonhuman primates which serves as a teaching and reference resource. Advanced and refined web-based curation and query application tools have been developed with input from pathologists from each of the primate centers. To date, 878 scanned digital slides and gross images representing 60 diseases entities and 8 NHP species material has been uploaded and curated by the PWG chair for inclusion in the PPID. Didactic material about disease processes has been added for many disease entities. Annotations have been added to many images to enhance their utility for teaching. Content from four NPRC's is now available through the federated query. The majority of the material is derived from ONPRC archives. The PPID with curated data has been available to all the NPRC pathologists since June 2012 (prior access was to development data.) Monthly web-based virtual slide conferences (VSC's) have been the back bone of the PWG since March of 2007. Each of the primate centers and several other NCRR funded primate programs present cases based on digital whole slide scans along with relevant case material for discussion with other primate center pathologists. ONPRC pathologists have presented 3 to 5 cases each year on a wide range of diagnoses including neoplastic, infectious and degenerative diseases in macaque species. Two Face to Face annual meetings of the PWG have occurred. Most recently, the ONPRC with support from the Consortium development group hosted the group in April 2012. Agenda items included brief overviews of the pathology units from each of the primate centers addressing staffing, report, image and data management, caseload, strengths and challenges; updates on NHP Disease database; tour of the primate center; half-day workshop on stereology: and discussion of protection of images from unauthorized use through copyright and MTA mechanisms.

12. Training

ONPRC faculty veterinarians and residents have consistently presented timely and important clinical and operational case presentations and broader topics at the VGR Seminar series. Presentations, attendance, and participation in discussion are expectations of the residency programs at ONPRC. In addition, faculty veterinarians are actively encouraged to present and often do; attendance and participation in consortium discussion is also expected. Excluded by Requester oversees the VGR component of consortium activities including scheduling and ensuring that residents and faculty have appropriate resources to gather, process, and present the material. In addition to providing exchange of information and promotion of best practices in general, VGR presentations also provide training and practice for residents and faculty alike in speaking to, and fielding questions from, a larger inter-institutional audience. Presentation topics have often progressed into poster presentations and papers submitted to peer-reviewed journals.

NPRC CONSORTIUM-BASED ACTIVITIES: PUBLICATIONS

Excluded by Requester

RESOURCES

Follow the 398 application instructions in Part I, 4.7 Resources.

Resources per se are only applicable to three of the Consortium-Based Activities, the Computational Methods and Resources, DNA Banking, and Genetics and Genomics Working Groups.

Computational Methods and Resources:
This Working Group makes heavy use of Mathematica, a platform-independent technical computing environment that includes a potent programming language with built-in web and parallel-computing constructs. Substantial use is also made of open-source web-programming languages and development environments.

DNA Banking:
The NHP National DNA Bank has a Thermo Scientific 18-sq ft., ultra-low-temperature freezer for storing NHP DNA Bank samples.

Genetics and Genomics:
This Working Group employs a LiftTech QuantStudio 12K Flex System, used for performing the Macaque SNP Ancestry Assay for multiple NPRCs and a Dell Optiplex 760 work station used for Macaque SNP Ancestry Assay data analysis and SNP Parentage Assay data analysis.

Program Director/Principal Investigator (Last, First, Middle): Robertson, Joseph E./Haigwood, Nancy L.

NPRC CONSORTIUM - BASED ACTIVITIES DETAILED BUDGET FOR INITIAL BUDGET PERIOD - DIRECT COSTS ONLY	FROM 5/1/14	THROUGH 4/30/15	GRANT NUMBER P51 OD011092-55

List PERSONNEL *(Applicant organization only)*

Use Cal, Acad, or Summer to Enter Months Devoted to Project

Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Excluded by Requester	Assoc Scientist	% Effort			Institutional Base Salary	7,117	1,779	8,896
	Asst Scientist					3,067	767	3,833
	Mgr, Res Informatics					46,458	11,615	58,073
	Res Analyst 2					1,502	526	2,028
	SUBTOTALS					58,144	14,686	72,831

CONSULTANT COSTS		
Consulting	20,000	20,000
EQUIPMENT *(Itemize)*		
None Requested	0	0
SUPPLIES *(Itemize by category)*		
Laboratory Supplies	25,805	
		25,805
TRAVEL		
Domestic	25,440	25,440
INPATIENT CARE COSTS		0
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		
None Requested	0	0
OTHER EXPENSES *(Itemize by category)*		
Server/Hosting/Licensing	5,000	
		5,000

CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 149,075
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 149,075

NPRC CONSORTIUM - BASED ACTIVITIES
BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITONAL YEAR OF SUPPORT REQUESTED	3rd ADDITONAL YEAR OF SUPPORT REQUESTED	4th ADDITONAL YEAR OF SUPPORT REQUESTED	5th ADDITONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	72,831	75,015	77,266	79,584	81,971
CONSULTANT COSTS	20,000	20,600	21,218	21,855	22,510
EQUIPMENT	0	0	0	0	0
SUPPLIES	25,805	26,579	27,377	28,198	29,044
TRAVEL	25,440	26,203	26,989	27,799	28,633
INPATIENTS CARE COSTS	0	0	0	0	0
OUTPATIENTS CARE COSTS	0	0	0	0	0
ALTERATIONS AND RENOVATIONS	0	0	0	0	0
OTHER EXPENSES	5,000	5,150	5,304	5,464	5,628
DIRECT CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	149,075	153,548	158,154	162,899	167,786
F&A CONSORTIUM/CONTRACTUAL COSTS	0	0	0	0	0
TOTAL DIRECT COSTS	149,075	153,548	158,154	162,899	167,786
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD					791,462

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

PERSONNEL

Associate Scientist – Excluded by Requester % Effort,Excluded by Requester will continue to contribute to the Genetics and Genomics Working Group goals, and to lead the National NHP DNA Bank efforts.

Assistant Scientist– Excluded by Requester % Effort,Excluded by Requester will continue to provide leadership towards the Genetics and Genomics Working Group goal of establishing NHP colony genetic health measures and metrics for use by all of the NPRC colony managers.

Manager, Research Informatics – Excluded by Requester % Effort,Excluded by Requester Excluded by Requester will continue his role as leader and principal software architect/developer for the Computational Methods & Resources Group.

Research Analyst 2 – Excluded by Requester % Effort,Excluded by Requester Responsible for providing statistical data for the Breeding Colony Management Consortium.

CONSULTANT COSTS

Funding is requested for software development consultant, Excluded by Requester. He works with the Computational Methods and Resources Group (CMRG) to provide web and database design and software development for systems supporting NPRC Consortium activities such as SPF colony reporting and colony health benchmarking.

SUPPLIES

Genotyping supplies and service fees. Funds are requested to support 768 rhesus macaque parentage and ancestry assays for animals housed at four NPRCs (ONPRC, WNPRC, NEPRC, and TNPRC).

TRAVEL

Funds are requested for participants in the respective consortiums to attend meetings together throughout the year.

- Behavioral Management Consortium
- Breeding Colony Management Consortium
- Computational Methods and Resources Group. Funds are requested to cover the travel costs for Mr. Excluded by Requester who will travel to each of the other seven NPRCs to discuss relevant local projects to facilitate research informatics implementation for each center. He will travel to certain centers 2-3 times, depending upon project needs.
- Genetics and Genomics Working Group. These funds are requested to cover travel costs for Drs. Vinson and Ferguson to attend one consortium meeting per year
- Occupational Health & Safety Working Group
- Outreach Working Group
- Pathology Working Group

OTHER EXPENSES

Server/Hosting/Licensing. These funds are requested for the Computational Methods and Resources Group (CMRG), which is leading the definition, development and deployment of advanced computational means to integrate animal record systems and related data resources within and between the NPRCs. In leading this effort, ONPRC is providing and maintaining the software applications and high-performance servers required

for this service, which includes costs associated with a Mathematica site license and fees accrued in the maintenance of three production servers.

NPRC Consortium - Based Activities Income Table

Last Funded Year (53)

Source	Funding (direct costs)
P51 base grant support	$141,799.44
Program income derived from P51 base grant	0
Other Sources	0
Total	$141,799.44

First proposed year of the P51 base grant renewal (55)

Source	Funding (direct costs)
P51 base grant support	$149,075.50
Program income derived from P51 base grant	0
Other Sources	0
Total	$149,075.50

The income table is an estimate that reflects the total funding required to operate each unit based on historical spending analyses, program operational requirements and changes, and anticipated price increases. The table is broken out by funds allocated to each unit from the base grant, program income, and other funding sources. Other funding sources are estimates of direct main campus contribution primarily through salary support and start up packages.

The table does not show the program income produced by each unit. Consistent with P51 administration guidelines, the program income is returned to the award and then allocated out through sound budgeting methodologies with final allocation being determined by the ONPRC Executive Leadership Team. Actual program income produced by units is reflected in the program income summary tables in appendix D.

RESOURCE SHARING PLAN

As for our plan to share materials and our management of intellectual property, we will adhere to the NIH Grant Policy on Sharing of Unique Research Resources including the Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources issued December 23, 1999. All 'model organisms' generated by this project will be distributed widely or deposited into a repository/stock center making them available to the broader research community, either before or immediately after publication, in accordance with University policies. If we assume responsibility for distributing the newly generated model organisms, we will fill requests in a timely fashion. In addition, we will provide relevant protocols and published genetic and phenotypic data upon request. Material transfers will be made with no more restrictive terms than in the Simple Letter Agreement (SLA) or the Uniform Biological Materials Transfer Agreement (UBMTA) and without reach through requirements. Should any intellectual property arise which requires a patent, we will ensure that the technology (materials and data) remains widely available to the research community in accordance with University policies and the NIH Principles and Guidelines document.

SELECT AGENT PROGRAM

1. **Select agent(s) at ONPRC**
   Monkeypox virus

2. **Registration status**
   Registration number: CDC# C20110620-1231, expires June 20, 2014

3. **Facilities**
   ONPRC operates three Select Agent (SA) laboratories:
   - NHP ABSL3 with 2 suites, each having animal holding areas, procedure rooms, and pass-through autoclaves.
   - Small-animal ABSL3 with one suite having animal holding areas/procedure rooms and pass-through autoclaves.
   - BSL3 with two suites, each with work areas, storage areas, and pass-through autoclaves.

4. **Describe the procedures that will be used to monitor possession**
   At ONPRC, only those individuals who have: 1) received a Criminal Justice Services Security Risk Assessment; 2) have been added to the ONPRC Select Agent Registration; and 3) received training are permitted to possess, use, or have access to any Select Agent. All Select Agents are stored within a Select Agent registered space under a stringent access and inventory control system that is monitored and audited by the RO (Biosafety Officer) and ARO (Assistant Biosafety Officer) as part of the Research Safety Program/Select Agent Program. All vendors/contractors that are not part of the SA program are escorted at all times by an SRA approved individual.

   All inter-entity transfers of Select Agents are transferred between an individual approved to possess them directly to a licensed commercial carrier or received from a licensed commercial carrier. All transfers occur only after CDC approval and will follow all regulations governing Select Agent transfers. Any intra-entity transfer at ONPRC will be conducted following approval and under the supervision of the RO (Biosafety Officer) and ARO (Assistant Biosafety Officer), and will be allowed only between individuals registered to possess the agent.

5. **Describe plans for appropriate biosafety, biocontainment, and security of the Select Agent(s).**
   ONPRC has developed and implemented a Biosafety Plan, a Security Plan, and an Incident Response Plan establishing policy and procedures that ensure the safe handling, containment, and security of areas containing Select Agents and toxins in accordance with 42 CFR 73. The Biosafety Plan addresses all practices and procedures involving the handling of Select Agents, entry and exit procedures including proper PPE, disinfection and decontamination procedures, and spill and adverse incident responses. The Biosafety Plan also describes the physical biocontainment requirements for the facilities where Select Agents are stored and handled. An Agent-specific Biosafety Plan describes the particular protocols and safety procedures for the specific Select Agent used by the investigators in a specific SA area. The Security Plan is based on a systematic approach in which threats are defined, vulnerabilities are examined, and risks associated with those vulnerabilities are mitigated with a security systems approach. The Security Plan applies to all employees working at, and all persons visiting, ONPRC and identifies the roles and responsibilities of all individuals involved in establishing security standards for the protection of Select Agents and other assets such as access control, keys, and locks.

6. **Describe the biocontainment resources available at all performance sites.**
   All registered Select Agent facilities at ONPRC are certified annually as BSL-3 or ABSL-3 facilities and conform with the NIH construction guidelines for BSL-3/ABSL-3 facilities, as well as the sections of the 5th Edition of the BMBL concerning BSL-3 and ABSL-3 facilities. These include single-pass, HEPA-filtered exhaust balanced to provide differential pressures and directional air flow, multiple secured locked doors with restricted access, validated autoclaving of all waste exiting the facilities, and a waste treatment facility for the NHP ABSL3.

Program Director/Principal Investigator (Last, First, Middle):

CHECKLIST

TYPE OF APPLICATION *(Check all that apply.)*

NEW application. *(This application is being submitted to the PHS for the first time.)*

RESUBMISSION of application number: _____
(This application replaces a prior unfunded version of a new, renewal, or revision application.)

RENEWAL of grant number: _____
(This application is to extend a funded grant beyond its current project period.)

REVISION to grant number: _____
(This application is for additional funds to supplement a currently funded grant.)

CHANGE of program director/principal investigator.

Name of former program director/principal investigator: _____

CHANGE of Grantee Institution. Name of former institution: _____

FOREIGN application Domestic Grant with foreign involvement List Country(ies) Involved:

INVENTIONS AND PATENTS *(Renewal appl. only)* No Yes

If "Yes," Previously reported Not previously reported

1. PROGRAM INCOME ***(See instructions.)***

All applications must indicate whether program income is anticipated during the period(s) for which grant support is request. If program income is anticipated, use the format below to reflect the amount and source(s).

Budget Period	Anticipated Amount	Source(s)

2. ASSURANCES/CERTIFICATIONS ***(See instructions.)***

In signing the application Face Page, the authorized organizational representative agrees to comply with the policies, assurances and/or certifications listed in the application instructions when applicable. Descriptions of individual assurances/certifications are provided in Part III and listed in Part I, 4.1 under Item 14. If unable to certify compliance, where applicable, provide an explanation and place it after this page.

3. FACILITIES AND ADMINSTRATIVE COSTS (F&A)/ INDIRECT COSTS. See specific instructions.

DHHS Agreement dated: _____ No Facilities And Administrative Costs Requested.

DHHS Agreement being negotiated with _____ Regional Office.

No DHHS Agreement, but rate established with _____ Date _____

CALCULATION* *(The entire grant application, including the Checklist, will be reproduced and provided to peer reviewers as confidential information.)*

a. Initial budget period:	Amount of base $	_____	x Rate applied	_____	% = F&A costs	$	_____
b. 02 year	Amount of base $	_____	x Rate applied	_____	% = F&A costs	$	_____
c. 03 year	Amount of base $	_____	x Rate applied	_____	% = F&A costs	$	_____
d. 04 year	Amount of base $	_____	x Rate applied	_____	% = F&A costs	$	_____
e. 05 year	Amount of base $	_____	x Rate applied	_____	% = F&A costs	$	_____
					TOTAL F&A Costs	$	

*Check appropriate box(es):

Salary and wages base Modified total direct cost base Other base *(Explain)*

Off-site, other special rate, or more than one rate involved *(Explain)*

Explanation *(Attach separate sheet, if necessary.):*

4. DISCLOSURE PERMISSION STATEMENT: If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)? Yes No