PRIMATE RESEARCH CENTER GRANT **Federal Award Date:** 06/09/2015
Department of Health and Human Services
National Institutes of Health
OFFICE OF THE DIRECTOR, NATIONAL INSTITUTES OF HEALTH

Grant Number: 5P51OD011106-54
FAIN: P51OD011106

Principal Investigator(s):
MARSHA RUTH MAILICK, PHD

Project Title: Wisconsin National Primate Research Center Support

BRENDA EGAN
INTERIM MANAGING OFFICER
RESEARCH & SPONSORED PROGRAMS
UNIVERSITY OF WISCONSIN
21 NORTH PARK ST, SUITE 6401
MADISON, WI 53715

Award e-mailed to: NIH@rsp.wisc.edu

Period Of Performance:
Budget Period: 05/01/2015 – 04/30/2016
Project Period: 06/10/1997 – 04/30/2017

Dear Business Official:

The National Institutes of Health hereby awards a grant in the amount of $9,402,376 (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to UNIVERSITY OF WISCONSIN-MADISON 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 P51OD011106. 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 – 5P51OD011106-54

Award Calculation (U.S. Dollars)

Salaries and Wages	$3,667,699
Fringe Benefits	$1,332,019
Personnel Costs (Subtotal)	$4,999,718
Consultant Services	$61,177
Equipment	$105,208
Supplies	$1,179,724
Other Costs	$633,817
Consortium/Contractual Cost	$51,045
Federal Direct Costs	$7,030,689
Federal F&A Costs	$2,371,687
Approved Budget	$9,402,376
Total Amount of Federal Funds Obligated (Federal Share)	$9,402,376
TOTAL FEDERAL AWARD AMOUNT	$9,402,376
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$9,402,376

SUMMARY TOTALS FOR ALL YEARS		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
54	$9,402,376	$9,402,376
55	$9,556,249	$9,556,249

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

Fiscal Information:

CFDA Name:	Research Infrastructure Programs
CFDA Number:	93.351
EIN:	1396006492A1
Document Number:	POD011106J
PMS Account Type:	G (Pooled)
Fiscal Year:	2015

IC	CAN	2015	2016
OD	8014499	$9,402,376	$9,556,249

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

NIH Administrative Data:
PCC: CMP01 / **OC**: 414E / **Released**: eRA Commons User Name 06/08/2015
Award Processed: 03/23/2015 01:36:12 PM

SECTION II – PAYMENT/HOTLINE INFORMATION – 5P51OD011106-54

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 – 5P51OD011106-54

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 75.
d. National Policy Requirements and all other requirements described in the NIH Grants

Policy Statement, including addenda in effect as of the beginning date of the budget period.

e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
f. 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.)

Research and Development (R&D): All awards issued by the National Institutes of Health (NIH) meet the definition of "Research and Development" at 45 CFR Part§ 75.2. As such, auditees should identify NIH awards as part of the R&D cluster on the Schedule of Expenditures of Federal Awards (SEFA). The auditor should test NIH awards for compliance as instructed in Part V, Clusters of Programs. NIH recognizes that some awards may have another classification for purposes of indirect costs. The auditor is not required to report the disconnect (i.e., the award is classified as R&D for Federal Audit Requirement purposes but non-research for indirect cost rate purposes), unless the auditee is charging indirect costs at a rate other than the rate(s) specified in the award document(s).

This institution is a signatory to the Federal Demonstration Partnership (FDP) Phase VI 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) P51OD011106. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

This award is not subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170.

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 – 5P51OD011106-54

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 FY2015

This non-competing award reflects the NIH Fiscal Policy for Grant Awards for FY2015 (see NIH Guide Notice NOT-OD-15-050) and the implementation of the ORIP FY2015 grants funding policy: http://dpcpsi.nih.gov/orip/rf/fyg_fp2015 .

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 individual(s) 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.

CONSTORTIUM/CONTRACTUAL COSTS:
This award includes funds awarded for subcontractual/consortium activity with the Baylor College of Medicine in the amount of $51,045 total costs. Consortia are to be established and administered as described in the NIH Grants Policy Statement (NIH GPS). The referenced section of the NIH GPS, Part II Chapter 15 is available at:
http://grants.nih.gov/grants/policy/nihgps/nihgps.pdf

SALARY CAP
None of the funds in this award shall be used to pay the salary of an individual at a rate in excess of the current salary cap. Current salary cap levels can be found at the following URL: http://grants.nih.gov/grants/policy/salcap_summary.htm.

PROGRAM INCOME:
Program income directly generated by the grant supported activity or earned as a result of the award must be reported on the Federal Financial Report.

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 Part II Chapter 8 the NIH Grants Policy Statement for the activities and/or expenditures that require NIH approval at http://grants.nih.gov/grants/policy/nihgps/nihgps.pdf

NON-COMPETING RENEWAL (NON-SNAP)
The NIH requires the use of the Research Performance Progress Report (RPPR) for all Type 5 progress reports. The RPPR and other documents applicable to this Non-SNAP grant are due the first of the month preceding the month in which the budget period ends (e.g., if the budget period ends 11/30, the due date is 10/1). Please see http://grants.nih.gov/grants/rppr/index.htm for additional information on the RPPR.

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: Christina Fleming
Email: fleminch@mail.nih.gov **Phone**: 301-435-0850 **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: 5P51OD011106-54

INSTITUTION: UNIVERSITY OF WISCONSIN-MADISON

Budget	Year 54	Year 55
Salaries and Wages	$3,667,699	$3,482,007
Fringe Benefits	$1,332,019	$1,649,259
Personnel Costs (Subtotal)	$4,999,718	$5,131,266
Consultant Services	$61,177	$53,919
Equipment	$105,208	$116,135
Supplies	$1,179,724	$1,210,360
Travel Costs		$62,165
Other Costs	$633,817	$557,639
Consortium/Contractual Cost	$51,045	
TOTAL FEDERAL DC	$7,030,689	$7,131,484
TOTAL FEDERAL F&A	$2,371,687	$2,424,765
TOTAL COST	$9,402,376	$9,556,249

Facilities and Administrative Costs	Year 54	Year 55
F&A Cost Rate 1	34.5%	34.5%
F&A Cost Base 1	$6,874,454	$7,028,303
F&A Costs 1	$2,371,687	$2,424,765

A. OVERALL COVER PAGE

Project Title: Wisconsin National Primate Research Center Support	
Grant Number: 5P51OD011106-54	**Project/Grant Period:** 06/10/1997 - 04/30/2017
Reporting Period: 05/01/2014 - 04/30/2015	**Requested Budget Period:** 05/01/2015 - 04/30/2016
Report Term Frequency: Annual	**Date Submitted:** 03/03/2015
Program Director/Principal Investigator Information: MARSHA RUTH MAILICK , PHD BA **Phone number:** (608) 263-5940 **Email:** mailick@waisman.wisc.edu	**Recipient Organization:** UNIVERSITY OF WISCONSIN-MADISON UNIVERSITY OF WISCONSIN MADISON 21 N PARK AVE, STE 6401 MADISON, WI 537151218 **DUNS:** 161202122 **EIN:** 1396006492A1 **RECIPIENT ID:** MSN173649
Change of Contact PD/PI: N/A	
Administrative Official: NICK N NOVAK VCRGE 321 Bascom Hall, 500 Lincoln Dr. Suite 6401 Madison, WI 53706 **Phone number:** 608-265-4868 **Email:** nick.novak@wisc.edu	**Signing Official:** NICK N NOVAK VCRGE 321 Bascom Hall, 500 Lincoln Dr. Suite 6401 Madison, WI 53706 **Phone number:** 608-265-4868 **Email:** nick.novak@wisc.edu
Human Subjects: No	**Vertebrate Animals:** Yes
hESC: No	**Inventions/Patents:** No

B. OVERALL ACCOMPLISHMENTS

B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

Wisconsin National Primate Research Center Year 53 Support
Principal Investigator: Martin Cadwallader, PhD
Director: Excluded by Requester PhD

The scientists and staff of the Wisconsin National Primate Research Center (WNPRC) are pleased to submit this P51 base grant non-competing renewal application for Year 53 support of nonhuman primate (NHP) research. In the past two years the WNPRC has undergone an exciting period of growth and scientific achievement, as well as preparation for a future of scientific discovery on many new fronts. Our progress is summarized in this report, beginning with a brief highlighting of some of the Center's research and administrative accomplishments and ongoing initiatives.

Please see attached report (Section B.2), which includes overall Center highlights, a Year 53 Budget Summary, 2012-2013 WNPRC Subproject information, and 2012-2013 Personnel Report.

B.1.a Have the major goals changed since the initial competing award or previous report?

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: Yr53 Overall_final_2-26-15opt.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?

Yes

Revision/ Supplements #	Revision/ Supplements Title	Specific Aims	Accomplishments
3P51OD011106-53S1		Specific Aim 1 - To provide excellent animal holding facilities and primary enclosures for the marmosets transferred from the New England Primate Research Center (NEPRC). Specific Aim 2 - To implement exceptional, USDA/PHS/OLAW/AAALAC compliant husbandry and veterinary medical practices for the marmosets transferred from the NEPRC. Specific Aim 3 - To implement appropriate genetic and reproductive management for the transferred marmosets. Specific Aim 4 - To implement a prudent financial plan to support the transferred marmosets as ORIP support for the animals is progressively reduced.	Supplement funds were utilized to perform necessary renovations and upgrades to the WNPRC Blue Mounds Quarantine and Housing (BMQH) facility to prepare for the transfer of 90-100 marmosets from the NEPRC. In preparation for the transfer of marmosets from the NEPRC, a team of WNPRC Animal Services personnel met repeatedly to review and update existing husbandry Standard Operating Procedures (SOPs) for housing marmosets at the BMQH facility. The NEPRC marmosets arrived safely to the WNPRC on 11/4/14. They have fully acclimated to their new surroundings and the husbandry practices of the WNPRC, and their utilization in funded research protocols has been initiated.
3P51OD011106-53S2		Aim 1. To use common marmoset fibroblasts and ESC to optimize targeting vectors for genomic editing of LRRK2 G2019S associated with human Parkinson's Disease. Aim 2. To define the feasibility and accuracy of LRRK2 genomic editing in IVF-derived common marmoset embryos.	Our major findings are: •Marmoset embryonic stem cells differentiate to neural lineages and support midbrain neuron development •Marmoset fibroblasts can be reprogrammed into cells with morphological and molecular characteristics of induced pluripotent cells •Standard protocols for reliable semen

			collection from male marmoset donors have been established •Ovarian stimulation of marmosets with human recombinant hormones will allow oocyte collection for in vitro fertilization and genomic editing

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

File uploaded: B.4_Training_opt.pdf

B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?

NOTHING TO REPORT

B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

Please see related Division Reports, which includes future goals for the next reporting period.

OVERALL

RESEARCH HIGHLIGHTS

The WNPRC made major progress in the research conducted by members of each of our four working groups. Monthly "Work-in-Progress" meetings held by each group has facilitated scientific progress, fostered many new collaborative efforts, and increased both the number and success rate of new grant applications. Similarly, each of the working groups has hosted seminar speakers who have served as both consultants on our projects and potential collaborators in new studies. In the **Energy Metabolism and Chronic Disease** (EMCD) working group, important new findings include the unequivocal demonstration that long-term caloric restriction reduces age-related and all-cause mortality in rhesus monkeys. Others in this group published new work that documents impairments in fat cell differentiation in subcutaneous tissue that may underlie the increase in visceral fat accumulation in polycystic ovary syndrome, and associated metabolic disease. Major advances have also been made by members of the **Neuroscience** working group, including the findings that alterations in the expression of key receptor genes, and epigenetic modifications of DNA regions controlling key developmental genes, occur in the amygdalar brain tissues of monkeys exhibiting anxious temperament (AT). These findings raise the possibility that new drug targets may be available to treat children with AT, who are at increased risk for developing psychiatric disease in adolescence and adulthood. Other members of this group (and EMCD) have discovered that the beneficial effects of estrogen on the expression of serotonin-related genes are reduced by a high-fat diet, strongly suggesting that a high fat diet may reverse any positive effects of hormone replacement therapy on mood in menopausal women. In the **Reproductive and Regenerative Medicine** (RRM) working group, investigators successfully developed induced pluripotent stem cell (iPSC) lines from Mauritian Cynomolgus monkeys, and iPSC-derived blood products are currently being tested as a therapeutic strategy for treatment of major blood disorders, including those induced by radiation therapies for cancer. Investigators in the **Global Infectious Disease** working group continue to make major progress in developing new vaccine regimens to restrain simian immunodeficiency virus replication, and in identifying and characterizing novel viruses in captive and wild non-human primate populations; the latter work includes a new study in which two novel simian arteriviruses were characterized in captive and wild baboons. In concert with the activities of the working groups has been the further development of the WNPRC **Bone Marrow Transplantation Core**, which has now successfully transplanted autologous CD34+ cells in cynomologus monkeys following complete myeloablation. A **Non-Human Primate Transgenesis** initiative has also been launched and progress has been made in deriving marmoset iPSCs to optimize genomic editing of selected target genes for Parkinson's disease, paving the way towards producing a transgenic marmoset model of this neurodegenerative disease. These advances and many others are summarized in this progress report, along with the new studies that have been based upon these recent developments.

In addition, WNPRC was able to successfully compete for two administrative supplements under the Year 53 Primate Center base grant. Detailed progress reports follow at the end of this section.

INCOME DERIVED BY SERVICE UNITS FROM OTHER GRANTS AND FUNDING SOURCES

Wisconsin National Primate Research Center
January 2014 - December 2014

DIVISION	INCOME
Animal Services Division	
Veterinary Services[a]	$ 362,393.44
Pathology Services[b]	$ 242,642.24
Colony Management[c]	$ 3,096,393.70
Scientific Protocol Implementation	$ 376,165.53
Division Total Income	**$ 4,105,849.84**
Research Services Division	
Assay Services	$ 396,807.35
Immunology Services	$ 188,229.61
Virology Services	$ 137,429.30
Genetics Services	$ 206,827.61
Division Total Income	**$ 929,293.87**
Operational Services Division	
Facilities Management & Shop Services	$ 117,723.96
Division Total Income	**$ 117,723.96**
Total Income	**$ 5,152,867.67**

[a] *Includes charges from Veterinary and Surgical Units*

[b] *Includes charges from Pathology and Clinical Pathology Units*

[c] *Includes charges related to animal per diems, blood draws and replacement costs*

Income generated by the chargeback system is managed in a single account allocated at the end of the fiscal year and distributed based on priority need. Remaining income is allocated for equipment and other core needs of the Center.

The Assistant Director of Administrative Services works with the Grants & Financial Team to analyze income and expenses on a monthly basis and generate reports to Senior Management and Unit Heads in order to evaluate charges for service, manage funds, and develop budgets.

ADMINISTRATIVE HIGHLIGHTS

During the current budget period, the WNPRC has continued to make major gains in efficiency, productivity, and optimization of resource utilization and management. Combining human resources, payroll and benefits, finance, purchasing, and grants administration into one Administrative Services unit continues to pay dividends in terms of increased productivity and quality of administrative support for our investigators. The physical relocation of these administrative personnel into one centralized WNPRC area has also enabled a seamless operation to evolve that expertly processes and administers our increasing grant portfolio. The reduction of the WNPRC library resource from a physical and electronic resource to an electronic resource only was completed during this past year, reflecting our decision to more specifically focus on the critical needs of the biomedical research community. In 2012, the WNPRC began to occupy a newly leased Specific Animal Location animal holding facility in Blue Mounds, WI owned by Harlan Laboratories. In the current year, the WNPRC has reached full utilization of the available rooms for quarantine and holding of monkeys from a variety of sources, including those that will accommodate major new projects in AIDS vaccine development, marmoset transgenesis, polycystic ovary syndrome, and a variety of studies utilizing the MHC-restricted Mauritian Cynomolgus macaques. Additional rooms at the facility are undergoing renovation to increase the holding capacity for additional space needs in the immediate future. The Labkey Electronic Health Records (EHR) system developed by WNPRC investigators came on-line two years ago, and work during the current year continues to enhance the system's capabilities, and thereby making continued gains in veterinary and research service efficiency, and opening new doors in the application of primate informatics in both clinical and research spheres.

SUMMARY AND FUTURE PLANS

We have continued to make excellent progress in the development our services and resources, and WNPRC investigators in all four of our Working Groups remain engaged in cutting-edge, high-impact scientific studies utilizing non-human primates. In the coming budget year, we are confident that our newest units - the NHP Transgenesis initiative, and our Bone Marrow Transplantation Core – will achieve continued success in producing new animal models of disease, and in establishing new therapeutic strategies in transplantation and regenerative medicine. The development of a curative, stem cell-based HIV treatment will also be launched during the coming budget year. With each of our Core-P.I.s funded to continue their individual and collaborative studies, we anticipate major progress in all of the high-impact studies described within this report. Equally important, the WNPRC will continue to host high-impact studies by major investigators located around the country, including studies to refine recently reported vaccine approaches for the prevention of HIV infection.

CRISPER/Cas9 Genomic Editing for a Nonhuman Primate Model of Parkinson's Disease

Grant Number: 3P51 OD011106-53S2

Reporting Period: July 8, 2014 – December 31, 2014.

Accomplishments

1. Major goals of the project

Nonhuman primates (NHP) are essential for preclinical examination of first-in-class and invasive therapies. Improvement of NHP models of human disease has been identified as a research priority for testing regenerative medicine approaches One of the most important recent breakthroughs in developmental and cell biology methods is the development and refinement of genomic editing with the CRISPR/Cas9 system in mammalian cells and embryos which holds promise for generating animals expressing disease-relevant levels of a mutated protein. Genomic editing has been recently shown to be feasible in cynomolgus macaques. Marmoset monkeys present several advantages for genomic editing approaches compared to macaques, including the ability to routinely carry multiple offspring (rapidly increasing cohort size), facile reproductive management, and a shorter lifespan, which facilitates the study of age-related diseases such as diabetes, arthritis and Parkinson's disease (PD). In regards to PD, identification of specific alleles of the leucine rich repeat kinase 2 (LRRK2) in familial and sporadic cases of PD supports the development of a NHP model expressing these variants, as proof-of-principle for the contribution of human alleles to disease pathophysiology. We propose to advance the development of NHP models of disease by genomic editing with two Specific Aims: **Aim 1.** To use common marmoset fibroblasts and ESC to optimize targeting vectors for genomic editing of LRRK2 G2019S associated with human Parkinson's Disease. **Aim 2.** To define the feasibility and accuracy of LRRK2 genomic editing in IVF-derived common marmoset embryos. Animal experiments will be performed at WNPRC, which is one of the few facilities in North America housing an experimental common marmoset colony, and the only Center where marmosets, primate embryology, and cutting edge neurological translational models are actively being used to test therapies for human disease. The proposed generation and analysis of genomic edited monkeys will provide a platform to assess the impact of LRRK2 mutations in PD, identify and assess biomarkers of prodromal PD and test therapeutic approaches.

2. Accomplishments

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results, including major findings, developments, or conclusions (both positive and negative); and 4) key outcomes or other achievements. Include a discussion of stated goals not met. As the project progresses, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

2.1 Major activities. First, we initiated studies to optimize hormonal stimulation of common marmosets to reestablish an SOP for ovarian induction of follicular growth, oocyte retrieval, and in vitro fertilization. Second, we have continued to monitor individual males to identify reliable donors of semen samples of excellent quality. While these studies were underway, we obtained initial aliquots of lentiviral vectors to overexpress LRRK2 for development of a Parkinson's Disease

model, and piloted transduction of marmoset embryo-derived pluripotent stem cells as embryonic surrogates, to insure that the vectors do not have any unexpected embryonic lethal effects. We also conducted initial studies with bovine oocytes to reestablish microinjection methodologies to prepare for lentiviral vector injection for transgene expression. With ESC we initiated neural differentiation protocols previously used in human and rhesus ESC, and we also initiated reprogramming of marmoset fibroblasts to iPSC. Finally, we have designed the CRISPR targeting vector and are poised to begin transfection experiments to determine efficiency in LRRK2 mutagenesis.

2.2 Specific Objectives. Reestablish and refine marmoset assisted reproductive technologies; initiate CRISPR/Cas9 targeting with marmoset cells; initiate targeting feasibility with marmoset embryos.

2.3 Significant results:

Hormone stimulation. We determined that the hormone preparation which provided adequate ovarian stimulation in our previous studies (Excluded by Requester et al, 2003) was ineffective in stimulating follicular growth and we had to explore different preparations, and subsequently higher doses of human recombinant FSH than previously used. We also carried out two stimulation cycles with pregnant mare serum gonadotropin (PMSG), a "classic" ovarian stimulation regimen, and while there was good follicle stimulation initially, poor fertilization rates were obtained, and we returned to the FSH regimen previously used.

Semen donors: at the outset of these studies, we had to spend more effort in obtaining reliable semen samples than originally expected. Several months of training and experience have shown that we can identify reliable semen donors among colony males, and we have now routinely been collecting semen in order to maintain a reliable animal pool.

Marmoset IVF. We have continued collection of oocytes for in vitro fertilization throughout the funding period. We have been reliably obtaining approximately 10-15 oocytes per stimulation cycle, and fertilization rates of 25-100%. Although development of fertilized embryos *in vitro* to blastocyst stage is not critical for our long-term experimental goals, this development can be a useful surrogate for *in vivo* developmental potential. We have had poor development to the blastocyst stage so far, in contrast to our previous rhesus monkey *in vitro* embryo culture. In a recent experiment, we obtained the development of embryos that were somewhat difficult to characterize, but when compared with bovine embryos being cultured in the Animal Science Department, gave the impression that they might have been blastocysts. For logistical reasons those embryos were not able to be further analyzed. Interestingly, these embryos were obtained from oocytes fertilized with a new male semen donor that hadn't previously been used. We will use him in additional rounds of IVF to determine if there is a male factor related to this apparent developmental difference from previous experiments. Parenthetically, this observation also illustrates that we have continued to monitor individual males including new candidates to identify reliable donors of semen samples of excellent quality.

Our ongoing activities will focus on now optimizing experimental microscope set-ups to transition to intracytoplasmic sperm injection (ISCI) which insures fertilization of each oocyte. We have been in consultation with (Excluded by Requester IVF lab director at the UW-Madison Generations Fertility Clinic for establishment of ICSI procedures, which have previously been used at the WNPRC.

Marmoset ESC differentiation: In collaboration with [Excluded by Requester] in the Dept. of Neurology and at the Waisman Center, we were able to recapitulate neuroectoderm differentiation and formation of motor neurons *in vitro.* This paradigm will be important in the study of marmoset cells expressing the LRRK2 G2019S mutation associated with human Parkinson's disease. In addition, we prepared marmoset skin fibroblasts and in collaboration with [Excluded by Requester] lab, have produced candidate marmoset iPSC. These cells express the pluripotency markers Oct4, nanog, Sox2, and klf4, similar to the marmoset ESC cultures. These cells will be an *in vitro* platform for the study of gene interactions which underly the neural phenotype of PD.

Although lentiviruses are still a viable candidate for transgene overexpression in embryos, we have also begun to consider the CRISPR/Cas9 system for **genomic editing** of nonhuman primate embryos, as a way to introduce the specific human mutation into the primate genome without the complexities of transgene overexpression. We have obtained tissue biopsies from common marmosets and have prepared fibroblasts appropriate for reprogramming as iPSC in order to test genomic editing in a pluripotent cell mode. We are currently designing targeting vectors to introduce the LRRK2 mutant into the marmoset LRRK2 gene.

Conclusions: We conclude from our studies that marmoset pluripotent stem cells will be a feasible platform for understanding gene interactions in Parkinson's disease. Marmoset assisted reproductive technologies will provide sufficient embryos to support genomic editing studies for specific genetic model development for PD as well as other neurodegenerative diseases for which nonhuman primates provide an optimal model for testing regenerative medicine therapeutic approaches.

Major Findings: Our major findings are:

- Marmoset embryonic stem cells differentiate to neural lineages and support midbrain neuron development
- Marmoset fibroblasts can be reprogrammed into cells with morphological and molecular characteristics of induced pluripotent cells
- Standard protocols for reliable semen collection from male marmoset donors have been established
- Ovarian stimulation of marmosets with human recombinant hormones will allow oocyte collection for in vitro fertilization and genomic editing

2.4 Key outcomes.

From our perspective, the collaboration was very instructive and rewarding. The [Excluded by Requester] labs have been able to formally collaborate in the marmoset ESC approaches, and the [Excluded by Requester] lab provided instruction in neural differentiation paradigms. [Excluded by Requester] lab provided facilities and expertise to initiate marmoset fibroblast reprogramming, and we established collaboration with [Excluded by Requester] of the NCI, an expert on the biochemistry and molecular biology of LRRK2, in marmoset ESC analysis.

With the initiation of studies in genomic editing of marmoset embryos [Excluded by Requester] has begun a new collaboration with [Excluded by Requester] and [Excluded by Requester] of the Dept. of Pathology and Laboratory Medicine to develop a new nonhuman primate model for AIDS research, utilizing CRISPR/Cas9

approach to introduce the delta32 mutation into the rhesus gene encoding CCR5, an HIV/SIV receptor. The experimental plan will be to use hematopoietic stem cell transplantation with rhesus macaques to determine the feasibility of HSC modification for protection from, or curing HIV infection. Pending Support

3. Future Plans

We have initiated LRRK2 targeting with marmoset fibroblasts and have identified cells expressing the GFP marker transgene indicating introduction of the targeting plasmid into the cells. We will analyze the currently transfected cells as well as optimize electroporation methods with the marmoset ESC. Effects of targeting of this embryonic surrogate cell on neural differentiation will be further evaluated with specific immunostaining.

We have set aside a number of control embryos to optimize the amplification of the LRRK2 DNA region where we will be targeting for introduction of the G2019S mutation from small numbers of marmoset embryos. Embryo injection with plasmid DNA will be done first to determine effectiveness of plasmid injection in Cas9 expression and editing before attempting to transfer embryos.

We have also rehabilitated our current microscopes in order to establish intracytoplasmic sperm injection (ICSI) to obviate limitations in success due to occasional suboptimal fertilization rates, and will proceed to establishing those methods which will also be directly applicable to CRISPR/Cas9 reagent microinjection.

4. Publications

None.

Supplement to Support Marmosets Transferred from the New England NPRC

Grant Number: 3P51 OD011106-53S1

Reporting Period: July 1, 2014 – December 31, 2014

Accomplishments

1. Major goals of the project

Currently, only three of the existing eight NPRCs possess the infrastructure and expertise to maintain common marmoset breeding colonies. The loss of one of these colonies due to the impending closure of the NEPRC would have devastating consequences on the availability and genetic diversity of common marmosets available to U.S. based investigators. Thus, transfer of the existing NEPRC common marmoset colony to the WNPRC and the SNPRC is imperative, as demand for these monkeys as animal models appears to be increasing significantly. The Specific Aims of the Animal Services Division in regards to the NEPRC marmosets to be transferred are as follows:

- **Specific Aim 1** - To provide excellent animal holding facilities and primary enclosures for the marmosets transferred from the NEPRC.

In April of 2012, the Wisconsin National Primate Research Center (WNPRC) leased a Specific Animal Location sq. ft. vivarium located in Blue Mounds, Wisconsin to perform nonhuman primate quarantine and holding. The ten-year old Blue Mounds Quarantine and Holding facility (BMQH) was constructed, renovated, and utilized by Harlan Laboratories to quarantine and perform biomedical contract research on macaques, marmosets, and beagles. Harlan decommissioned the facility when they moved all their nonhuman primate activities to Indianapolis, Indiana in 2010. The BMQH floor plan consists of Specific Animal Location animal quarantine rooms (NHP Quarantine Specific Animal Location with dedicated anterooms Specific Animal holding rooms large enough to house approximately 100 macaques each (NHP Holding Specific Animal Location additional large animal holding rooms previously utilized by Harlan to house beagles (NHP Holding Specific Animal Location 2 clinical procedure rooms; 2 laboratories, a cage wash suite, a freezer/refrigerator room sample storage, an animal food prep and storage area, 2 offices, and a large mechanical room.

NHP Holding Specific Animal Location each measure approximately Specific Animal Location wide and are equipped with Specific Animal Location Specific Animal Location Specific Animal Location In consultation with the WNPRC Facilities and Shop Supervisor Excluded by Requester has opted to renovate NHP Holding Specific Animal to house the NEPRC marmosets as the room has no external walls and thus is the easiest to maintain at a temperature range (75°F to 85°F) needed to ensure the wellbeing of callitrichids. Housing the animals Specific Animal Location BMQH in NHP will allow the colony to be quarantined in one large group and also allows it to remain separate from the existing WNPRC marmosets until it is determined that neither population is harboring infectious pathogens that may compromise the health of the other colony.

- **Specific Aim 2** - To implement exceptional, USDA/PHS/OLAW/AAALAC compliant husbandry and veterinary medical practices for the marmosets transferred from the NEPRC.

The WNPRC animal care program complies with all university, local, state, federal (USDA, PHS, OLAW, NIH) and independent (AAALAC) regulations, guidelines, and policies pertaining to animal research and is committed to achieving excellence in animal care and use. Through the Graduate School of the UW-Madison, the WNPRC is registered with the USDA as a research facility (Certificate # 35-R-001) and has an approved Animal Health Assurance on file with OLAW (A3368-01). The Graduate School (including the WNPRC) has maintained full AAALAC accreditation (Unit Number 000567) since 1982. The WNPRC will expand their exemplary husbandry and veterinary medical practices to cover the marmosets to be acquired from the NEPRC.

- **Specific Aim 3** - To implement appropriate genetic and reproductive management for the transferred marmosets.

The NEPRC provided extensive pedigree data (i.e., dams, sires, kinship coefficients, and inbreeding coefficients) to the WNPRC for all the marmosets to be transferred. All of the data regarding the individual NEPRC animals will be utilized to make informed breeding decisions that will maintain the genetic diversity of the existing NEPRC and WNPRC populations if they are maintained separately or mixed.

The WNPRC will provide all of the NEPRC pedigree as well as the pedigree data from its existing marmoset colony to Excluded by Requester of the Oregon National Primate Research Center's (ONPRC) Colony Genetics Core Unit for analysis. Excluded by Requester will perform an extensive review of the pedigree data utilizing a software package they recently developed to evaluate the genetic diversity of the WNPRC and NEPRC colony to be transferred and the effect that mixing the two colonies would have on the overall genetic diversity of the two populations. The analysis provided by the ONPRC will include the following:

- Curated pedigrees for the individual WNPRC and transferred ONPRC colonies
- A curated pedigree for a potential mixed WNPRC/ONPRC colony
- A variety of genetic value calculations including individual average mean kinship, Z-scores, and genome uniqueness for each member of the WNPRC, NEPRC, and mixed WNPRC/NEPRC colonies
- Overall genetic designation (i.e., high value vs. low value) for each member of the two individual populations of animals and the potential mixed population of animals indicating recommendations for breeding the animals for genetic diversity or simply for research purposes.

Pregnancy in the male/female pairs that are not assigned to the WNPRC marmoset breeding colony is controlled by the use of the synthetic prostaglandin analogue cloprostenol sodium (Estrumate®). Estrumate administration consistently causes functional and morphological regression of the *corpus luteum* (luteolysis) in marmosets that leads to abortion. Non-breeding colony females are manually palpated and also undergo abdominal ultrasound examination one to two times per month to verify pregnancy status. Females with unwanted pregnancies are treated with 0.75 µg of estrumate administered intramuscularly. In cases where a female marmoset is insensitive to the first dose of estrumate, 1.0 µg of the agent is administered for up to three successive days approximately 5-14 days after the first dose to render effective luteolytic action and subsequent abortion. WNPRC data strongly

demonstrates that estrumate treatment has no effect on future breeding success. The transferred NEPRC females' pregnancy status will be determined upon arrival and animals considered to be at less than 50 days of gestation will have their pregnancies terminated with estrumate. Animals with pregnancies greater than gestation day 50 will be allowed to deliver and raise their offspring. No NEPRC animals will be allowed to carry their pregnancies to term until decisions about combining the colonies are complete.

- **Specific Aim 4** - To implement a prudent financial plan to support the transferred marmosets as ORIP support for the animals is progressively reduced.

WNPRC investigators have several funded and pending grant proposals that call for the use of marmosets (See Table 4 below). A subset of the animals transferred from the NEPRC are aging or are vasectomized and will be utilized by WNPRC investigators within 6 months of their arrival. A subset of the maturing offspring from the mated NEPRC pairs will also be used for funded proposals or will be sold to outside investigators with NIH approved funding to subsidize support of the colony and to maintain the population at an appropriate number based on the capacity of the BMQ facility.

2. Accomplishments

Specific Aim 1 - To provide excellent animal holding facilities and primary enclosures for the marmosets transferred from the NEPRC.

Utilizing funding from the WNPRC and the ORIP administrative supplement, Excluded by Requester and personnel from his unit (with assistance from the University of Wisconsin Physical Plant) performed the following renovations and upgrades in NHP Holding Specific Animal Location to prepare for the transfer of the NEPRC marmosets:

- Resurfaced of the animal holding room cement floor with multiple layers of epoxy paint
- Installed a new double row reheat coil that allows the temperature of NHP Holding Specific Animal Location to be maintained between 75°F - 85°F.
- Installed a room pressurization monitor which provides real time pressure data to the building automation network
- Installed a stainless steel railing system around the waste trough to prevent marmoset cages from falling into the trough
- Installed "marmoset proof" drain covers in the waste trough
- Installed four separate, equally spaced walkways which span the trough to facilitate easy movement from one side of the trough to the other
- Installed steps to access the waste trough to facilitate cleaning of the trough by WNPRC animal care personnel
- Installed stainless steel diffusers on all the supply air vents and extended exhaust ducts to facilitate filter changes
- Augmented the existing automated watering system with Edstrom coiled water lines

In addition to the renovations performed in NHP Holding [Specific Animal Location] personnel of the WNPRC Facilities and Shop Services unit also constructed enclosures to house the 90-100 marmosets to be transferred to Wisconsin. Rather than acquiring cages from the NEPRC, the decision was made to house the transferred marmosets in cages identical to the ones already used at the WNPRC to promote identical husbandry practices for both colonies of marmosets. The following cages were constructed in preparation of the delivery of animals from the NEPRC.

- 13 double cages for breeding pairs + offspring
- 7 change-out double cages
- 12 single cages for pair-housed animals
- 6 change-out single cages

The NEPRC contracted [Specific Private Vendor] to transport marmosets to the WNPRC. The first shipment, which consisted of 90 animals, arrived safely in Wisconsin on November 4, 2014. One family group destined for the WNPRC was not shipped with the initial group as the matriarch of the group was near-term pregnant and subsequently gave birth to healthy twins on November 9, 2014. While awaiting transport, there was some social unrest in the final family to be transported and two females were removed from the group and paired in another enclosure. The remaining family, which consisted of a mated pair and five offspring, and the newly formed pair, arrived safely at the BMQH on December 3, 2014.

Specific Aim 2 - To implement exceptional, USDA/PHS/OLAW/AAALAC compliant husbandry and veterinary medical practices for the marmosets transferred from the NEPRC.

In preparation for the transfer of 90-100 marmosets from the NEPRC, a team of WNPRC personnel which included [Excluded by Requester] Staff Veterinarians, Colony Manager [Excluded by Requester] the Marmoset Breeding Coordinator, the BMQH Animal Care Supervisor, the Behavioral Management Head, the Facilities and Shop Supervisor, and the Compliance Coordinator met repeatedly to review how existing husbandry SOPs would have to be amended to apply to housing marmosets at the BMQH facility.

Due to differing nutrient levels between the NEPRC and WNPRC marmoset diets, the WNPRC has chosen to maintain the transferred marmosets on Teklad 8794N to ease the transition to their new environment.

The NEPRC provided water to their marmosets via standard water bottles attached to each enclosure. When the NEPRC animals were transferred to the WNPRC, water bottles were placed in each enclosure to ensure that the animals all had access to water and a small amount of honey was smeared on the lixits in each enclosure to help the animals discover the lixits. Within a week, the NEPRC marmosets discovered the lixits and no cases of dehydration were reported.

Initially, all of the transferred animals exhibited some inappetence, diarrhea, and subsequent weight loss as they acclimated to their new living conditions at the WNPRC, but a majority of the animals' weights have rebounded to pre-shipment levels and reports of diarrhea have reduced significantly.

Three days after the first group of animals arrived in Wisconsin, one adolescent female had to be euthanized after being severely traumatized by her young adult female cage mate (a half-sister). Eleven days after arrival of the first group, an aging female was treated for evidence of acute on chronic renal failure. Despite intensive fluid therapy, the animal's condition did not improve and euthanasia was elected. No further deaths have occurred among the transferred animals.

After their acclimation period, all reproductively intact female NEPRC marmosets paired with reproductively intact male marmosets have been manually palpated on a biweekly basis to determine if they are pregnant. Twenty-eight females determined to be less than 50 days pregnant have received estrumate to induce abortion.

Three animals that arrived pregnant have spontaneously aborted and two animals that arrived pregnant have given birth to a litter of two infants and three infants, respectively. All infants born just prior to transfer from the NEPRC and all infants born at the WNPRC are alive and appear healthy.

Specific Aim 3 - To implement appropriate genetic and reproductive management for the transferred marmosets.

The ONPRC analysis verified that the long-term consequences of maintaining two completely separate colonies without exchange of animals for breeding purposes would result in the inevitable loss of genetic variation over time. Thus, from the perspective of long-term genetic management, a clear case can be made for merging the NEPRC and WNPRC marmoset colonies and managing the population as one combined unit. This would increase the number of potential mates for each breeding individual and reduce average kinship among individuals. However, this possible action must be carefully considered. While the genetic variability within the combined colony and thus future genetic health would be increased by merging the two populations, this may be problematic if the two populations are genetically and taxonomically so different that merging the two would generate hybrid offspring from breeding adults that are too genetically divergent.

After their acclimation period, all reproductively intact female NEPRC marmosets paired with reproductively intact male marmosets have been manually palpated on a biweekly basis to determine if they are pregnant. Twenty-eight females determined to be less than 50 days pregnant have received estrumate to induce abortion.

Three animals that arrived pregnant have spontaneously aborted and two animals that arrived pregnant have given birth to a litter of two infants and three infants, respectively. All infants born just prior to transfer from the NEPRC and all infants born at the WNPRC are alive and appear healthy.

Specific Aim 4 - To implement a prudent financial plan to support the transferred marmosets as ORIP support for the animals is progressively reduced.

Now that the NEPRC marmosets have fully acclimated to their new surroundings and the husbandry practices of the WNPRC, their utilization in funded research protocols has been initiated. Two of the NEPRC animals (a vasectomized male and his female cage mate) have been transferred to the main WNPRC facility. The female has already been purchased by a WNPRC PI and been utilized on a neuroscience project. The vacsectomized male will be paired with another female and will be utilized in a transgenesis experiment using CRISPR technology.

3. Future Plans

Specific Aim 1 - To provide excellent animal holding facilities and primary enclosures for the marmosets transferred from the NEPRC

The NEPRC animals will continue to be housed in the new enclosures constructed for them at the BMQH facility and an additional room at the facility may be equipped with similar cages as the population increases in size.

Specific Aim 2 - To implement exceptional, USDA/PHS/OLAW/AAALAC compliant husbandry and veterinary medical practices for the marmosets transferred from the NEPRC

The WNPRC SOP committee will continue to amend SOPs relevant to work with the transferred marmosets at the BMQH as changes are required.

Serum samples will be collected from a subset of the animals transferred from the NEPRC and the WNPRC Assay Services Unit will assay these samples for circulating Vitamin D levels. Based on the results, the NEPRC diet may be supplemented with Vitamin D.

To ensure the health of the transferred marmosets, each animal will be evaluated twice daily by a veterinary technician for the evidence of disease or injury (e.g., inappetance, dehydration, diarrhea, depression, inactivity, trauma, etc.). Using paper forms or an iPad, the technician will generate a daily report of animals that need veterinary attention and the veterinary staff will evaluate each animal and treat them accordingly. A current problem and treatment list will be updated daily by the veterinary technicians and veterinarians to ensure that all clinical problems are treated appropriately. All clinical problems, treatments, and case outcomes will be entered into the WNPRC electronic health records database so that complete histories can be generated and ongoing clinical problems can be tracked. All demographic date (e.g., date of birth, gender, dam, sire, weight history, etc.) for each transferred animal will be entered into the WNPRC database upon arrival.

Specific Aim 3 - To implement appropriate genetic and reproductive management for the transferred marmosets

Excluded by Requester PhD (Associate Professor, Private Source & WNPRC Genetics Consultant) will collect and assess information necessary to make a decision about the possible colony merge. First, we will collect and evaluate all available records to determine (if possible) where and when the founders of these two marmoset colonies were captured in the wild. This will provide an indication of the likely genetic and taxonomic differences between them. If that investigation does not provide enough information to make a decision, we will pursue molecular genetic studies of the two populations. We would first assess mitochondrial DNA variation within and between the two colony populations and compare those results to published information about mtDNA variability across the geographic range of *Callithrix jacchus*. This will place the two populations in the overall context of genetic and geographic diversity across the species. If that approach is not satisfactory, we will pursue other molecular genetic tests to assess the potential consequences of merging the two breeding populations. Unless there is a strong reason to keep the colonies separate, the long-term genetic health of the animals will be best served by merging the two colonies into one breeding population.

Specific Aim 4 - To implement a prudent financial plan to support the transferred marmosets as ORIP support for the animals is progressively reduced

The WNPRC Attending Veterinarian has submitted a detailed budget request to ORIP in the revised P51 application that was submitted on January 26, 2015 to supplement the base grant to provide

support for the marmosets acquired from the NEPRC. This budget requests progressively decreasing support for per diems and salaries for animal caretakers and a veterinary technicians as the NEPRC non-breeding animals and offspring from the breeding NEPRC animals are purchased and utilized on experimental protocols by PIs funded to perform biomedical research using marmosets.

4. Publications

None.

OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT

The University of Wisconsin-Madison requires that all graduate students and postdoctoral researchers supported by NIH funding utilize Individual Development Plans to set academic and career goals and facilitate conversations with their mentors. Additionally, the university recommends that all graduate students and postdoctoral researchers utilize IDPs, regardless of funding source.

The university offers a collection of resources and tools to support mentees, mentors, and PIs in implementing IDPs. These include a UW-Madison IDP template, workshops for mentees (both face-to-face and online videos), peer learning groups for mentees, as well as guidelines for mentors. More information can be found here: http://grad.wisc.edu/pd/idp.

IDP activity for NIH-funded graduate students and postdoctoral researchers is tracked in the university's IDP reporting system, a tool that maintains mentee privacy yet allows mentors and PIs to monitor IDP-related activity.

C. OVERALL PRODUCTS

C.1 PUBLICATIONS

Are there publications or manuscripts accepted for publication in a journal or other publication (e.g., book, one-time publication, monograph) during the reporting period resulting directly from this award?

Yes

Publications Reported for this Reporting Period

Public Access Compliance	Citation
Complete	Excluded by Requester Excluded by Requester A rapid immunization strategy with a live-attenuated tetravalent dengue vaccine elicits protective neutralizing antibody responses in non-human primates. Front Immunol. 2014;5:263. PubMed PMID: 24926294; PubMed Central PMCID: PMC4046319.
Complete	Excluded by Requester Excluded by Requester High genetic diversity and adaptive potential of two simian hemorrhagic fever viruses in a wild primate population. PLoS One. 2014;9(3):e90714. PubMed PMID: 24651479; PubMed Central PMCID: PMC3961216.
Complete	Excluded by Requester Assessing anxiety in nonhuman primates. ILAR J. 2014;55(2):333-46. PubMed PMID: 25225310; PubMed Central PMCID: PMC4240439.
Complete	Excluded by Requester Cardiac sympathetic denervation in 6-OHDA-treated nonhuman primates. PLoS One. 2014;9(8):e104850. PubMed PMID: 25133405; PubMed Central PMCID: PMC4136781.
Complete	Excluded by Requester Abnormal infant islet morphology precedes insulin resistance in PCOS-like monkeys. PLoS One. 2014;9(9):e106527. PubMed PMID: 25207967; PubMed Central PMCID: PMC4160158.
Complete	Excluded by Requester Excluded by Requester Vaccination against endogenous retrotransposable element consensus sequences does not protect rhesus macaques from SIVsmE660 infection and replication. PLoS One. 2014;9(3):e92012. PubMed PMID: 24651676; PubMed Central PMCID: PMC3961289.
Complete	Excluded by Requester Excluded by Requester Discovery and characterization of distinct simian pegiviruses in three wild African Old World monkey species. PLoS One. 2014;9(2):e98569. PubMed PMID: 24918769; PubMed Central PMCID: PMC4053331.
Complete	Excluded by Requester Excluded by Requester Enhanced Vaccine-Induced CD8+ T Cell Responses to Malaria Antigen ME-TRAP by Fusion to MHC Class II Invariant Chain. PLoS One. 2014;9(6):e100538. PubMed PMID: 24945248; PubMed Central PMCID: PMC4063960.
Complete	Excluded by Requester Sex differences in effects of dopamine D1 receptors on social withdrawal. Neuropharmacology. 2014 Feb;77:208-16. PubMed PMID: 24120838; PubMed Central PMCID: PMC3865025.
Complete	Excluded by Requester Bach2 regulates homeostasis of Foxp3+ regulatory T cells and protects against fatal lung disease in mice. J Immunol. 2014 Feb 1;192(3):985-95. PubMed PMID: 24367030; PubMed

	Central PMCID: PMC3946995.
Complete	Excluded by Requester Steroidogenic factor 1 promotes aggressive growth of castration-resistant prostate cancer cells by stimulating steroid synthesis and cell proliferation. Endocrinology. 2014 Feb;155(2):358-69. PubMed PMID: 24265454; PubMed Central PMCID: PMC3891934.
Complete	Excluded by Requester Excluded by Requester ertiary mutations stabilize CD8+ T lymphocyte escape-associated compensatory mutations following transmission of simian immunodeficiency virus. J Virol. 2014 Mar;88(6):3598-604. PubMed PMID: 24371068; PubMed Central PMCID: PMC3957937.
Complete	Excluded by Requester Stress-induced elevation of oxytocin in maltreated children: evolution, neurodevelopment, and social behavior. Child Dev. 2014 Mar-Apr;85(2):501-12. PubMed PMID: 23865588; PubMed Central PMCID: PMC4127329.
Complete	Excluded by Requester Development of a sensitive LC/MS/MS method for vitamin D metabolites: 1,25 Dihydroxyvitamin D2&3 measurement using a novel derivatization agent. J Chromatogr B Analyt Technol Biomed Life Sci. 2014 Mar 15;953-954:62-7. PubMed PMID: 24576767; PubMed Central PMCID: PMC4050665.
Complete	Excluded by Requester Caloric restriction reduces age-related and all-cause mortality in rhesus monkeys. Nat Commun. 2014 Apr 1;5:3557. PubMed PMID: 24691430; PubMed Central PMCID: PMC3988801.
Complete	Excluded by Requester Hormones in infant rhesus monkeys' (Macaca mulatta) hair at birth provide a window into the fetal environment. Pediatr Res. 2014 Apr;75(4):476-81. PubMed PMID: 24418932; PubMed Central PMCID: PMC3961505.
Complete Excluded by Requester	Excluded by Requester Tetherin antagonism by Vpu protects HIV-infected cells from antibody-dependent cell-mediated cytotoxicity. Proc Natl Acad Sci U S A. 2014 Apr 29;111(17):6425-30. PubMed PMID: 24733916; PubMed Central PMCID: PMC4035966.
Complete	Excluded by Requester Characterization of transfusion-elicited acute antibody-mediated rejection in a rat model of kidney transplantation. Am J Transplant. 2014 May;14(5):1061-72. PubMed PMID: 24708533; PubMed Central PMCID: PMC4289595.
Complete	Excluded by Requester Excluded by Requester Effect of age and calorie restriction on corpus callosal integrity in rhesus macaques: a fiber tractography study. Neurosci Lett. 2014 May 21;569:38-42. PubMed PMID: 24686192; PubMed Central PMCID: PMC4105191.
Complete	Excluded by Requester Excluded by impaired preadipocyte differentiation into adipocytes in subcutaneous abdominal adipose of PCOS-like female rhesus monkeys. Endocrinology. 2014 Jul;155(7):2696-703. PubMed PMID: 24735327; PubMed Central PMCID: PMC4060192.
Complete	Excluded by Requester

	Nef gene fragments affords partial control of viral replication after mucosal challenge with SIVmac239. J Virol. 2014 Jul;88(13):7493-516. PubMed PMID: 24741098; PubMed Central PMCID: PMC4054456.
Complete	Excluded by Requester Excluded by Discovery and full genome characterization of a new SIV lineage infecting red-tailed guenons (Cercopithecus ascanius schmidti) in Kibale National Park, Uganda. Retrovirology. 2014 Jul 4;11:55. PubMed PMID: 24996566; PubMed Central PMCID: PMC4226943.
Complete	Excluded by Requester Excluded by Requester Direct induction of haematoendothelial programs in human pluripotent stem cells by transcriptional regulators. Nat Commun. 2014 Jul 14;5:4372. PubMed PMID: 25019369; PubMed Central PMCID: PMC4107340.
Complete	Excluded by Requester Measuring fecal testosterone in females and fecal estrogens in males: comparison of RIA and LC/MS/MS methods for wild baboons (Papio cynocephalus). Gen Comp Endocrinol. 2014 Aug 1;204:141-9. PubMed PMID: 24798581; PubMed Central PMCID: PMC4155009.
Complete	Excluded by Requester Excluded by Requester Syndecan-1 is required to maintain intradermal fat and prevent cold stress. PLoS Genet. 2014 Aug;10(8):e1004514. PubMed PMID: 25101993; PubMed Central PMCID: PMC4125098.
Complete	Excluded by Requester Excluded by Requester Rapid, repeated, low-dose challenges with SIVmac239 infect animals in a condensed challenge window. Retrovirology. 2014 Aug 14;11:66. PubMed PMID: 25125288; PubMed Central PMCID: PMC4149191.
Complete	Excluded by Requester Assessment of foraging devices as a model for decision-making in nonhuman primate environmental enrichment. J Am Assoc Lab Anim Sci. 2014 Sep;53(5):452-63. PubMed PMID: 25255067; PubMed Central PMCID: PMC4181686.
Complete	Excluded by Requester Both parents respond equally to infant cues in the cooperatively breeding common marmoset, Callithrix jacchus. Anim Behav. 2014 Oct 1;97:95-103. PubMed PMID: 25342858; PubMed Central PMCID: PMC4203656.
Complete	Excluded by Requester Excluded by Requester Genome Sequences of Simian Hemorrhagic Fever Virus Variant NIH LVR42-0/M6941 Isolates (Arteriviridae: Arterivirus). Genome Announc. 2014 Oct 9;2(5)PubMed PMID: 25301647; PubMed Central PMCID: PMC4192379.
PMC Journal - In process	Excluded by Requester Excluded by Requester Identification of adult stem cells in Schwalbe's line region of the primate eye. Invest Ophthalmol Vis Sci. 2014 Oct 16;55(11):7499-507. PubMed PMID: 25324280.
Complete	Excluded by Requester Excluded by Requester Modified vaccinia virus Ankara encoding influenza virus hemagglutinin induces heterosubtypic immunity in macaques. J Virol. 2014 Nov;88(22):13418-28. PubMed PMID: 25210172; PubMed Central PMCID:

	PMC4249095.
Complete	Excluded by Requester Social peptides: measuring urinary oxytocin and vasopressin in a home field study of older adults at risk for dehydration. J Gerontol B Psychol Sci Soc Sci. 2014 Nov;69 Suppl 2:S229-37. PubMed PMID: 25360024; PubMed Central PMCID: PMC4303104.
Complete	Excluded by Requester Excluded by Requester Whole genome sequencing of SIV-infected macaques identifies candidate loci that may contribute to host control of virus replication. Genome Biol. 2014 Nov 7;15(11):478. PubMed PMID: 25418588; PubMed Central PMCID: PMC4223156.
Complete	Excluded by Requester Excluded by Requester Compartmentalization of simian immunodeficiency virus replication within secondary lymphoid tissues of rhesus macaques is linked to disease stage and inversely related to localization of virus-specific CTL. J Immunol. 2014 Dec 1;193(11):5613-25. PubMed PMID: 25362178; PubMed Central PMCID: PMC4239212.
Complete	Excluded by Requester Excluded by Requester Linking pig-tailed macaque major histocompatibility complex class I haplotypes and cytotoxic T lymphocyte escape mutations in simian immunodeficiency virus infection. J Virol. 2014 Dec;88(24):14310-25. PubMed PMID: 25275134; PubMed Central PMCID: PMC4249162.
Complete	Excluded by Requester Excluded by Requester Tenascin C promotes hematoendothelial development and T lymphoid commitment from human pluripotent stem cells in chemically defined conditions. Stem Cell Reports. 2014 Dec 9;3(6):1073-84. PubMed PMID: 25448067; PubMed Central PMCID: PMC4263995.
Complete	Excluded by Requester High fat diet decreases beneficial effects of estrogen on serotonin-related gene expression in marmosets. Prog Neuropsychopharmacol Biol Psychiatry. 2015 Apr 3;58:71-80. PubMed PMID: 25542371; PubMed Central PMCID: PMC4339406.

C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

NOTHING TO REPORT

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Have inventions, patent applications and/or licenses resulted from the award during the reporting period?

No

C.5 OTHER PRODUCTS AND RESOURCE SHARING

C.5.a Other products

NOTHING TO REPORT

C.5.b Resource sharing

NOTHING TO REPORT

D. OVERALL PARTICIPANTS

D.1 WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

Commons ID	S/K	Name	SSN	DOB	Degree(s)	Role	Cal	Aca	Sum	Foreign Org	Component (s)	Country	SS
eRA Commons User Name	Y	MAILICK, MARSHA RUTH	SSN	DOB	BA,PHD	PD/PI	EFFORT						NA
	N	Excluded by Requester				Undergraduate Student					Other-7375 (Operational Services)		NA
	N					Undergraduate Student					Other-7373 (Animal Services Division)		NA
	N					Undergraduate Student					Other-7373 (Animal Services Division)		NA
	N					Undergraduate Student					Other-7373 (Animal Services Division)		NA
	N					Undergraduate Student					Other-7375 (Operational Services)		NA
	N					Undergraduate Student					Other-7373 (Animal Services Division)		NA
	N					Undergraduate Student					Other-7373 (Animal Services Division)		NA
	N					Undergraduate Student					Other-7373 (Animal Services Division)		NA
	N					Undergraduate Student					Other-7373 (Animal Services Division)		NA
	N					Undergraduate Student					Other-7373 (Animal Services Division)		NA
	N					Undergraduate Student					Other-7374 (Research Services Division)		NA
	N					Undergraduate Student					Other-7373 (Animal Services Division)		NA
	N					Undergradu					Other-7373		NA

eRA Commons User Name		Excluded by Requester				ate Student	EFFORT		(Animal Services Division)		
	N					Undergradu ate Student			Other-7373 (Animal Services Division)		NA
	N					Undergradu ate Student			Other-7373 (Animal Services Division)		NA
	N					Undergradu ate Student			Other-7375 (Operational Services)		NA
	N					Undergradu ate Student			Other-7375 (Operational Services)		NA
	N					Animal Research Technician			Other-7373 (Animal Services Division)		NA
	N					University Services Program Associate			Other-7373 (Animal Services Division)		NA
	N					Animal Research Technician			Other-7373 (Animal Services Division)		NA
	N					Animal Research Technician			Other-7373 (Animal Services Division)		NA
	N					Animal Research Technician			Other-7373 (Animal Services Division)		NA
	N					Senior Research Specialist			Other-7372 (Division of Research)		NA
	N					Animal Research Technician			Other-7373 (Animal Services Division)		NA
	N					Senior Media Specialist			Other-7375 (Operational Services)		NA
	N					Senior Research Specialist			Other-7373 (Animal Services Division)		NA
	N					HR Assistant			Other-7375 (Operational Services)		NA
	N					Unit Head,			Other-7375		NA

		Excluded by Requester				Compliance and Training	EFFORT		(Operational Services)		
	N					Senior Research Specialist			Other-7373 (Animal Services Division)		NA
	N					Associate Research Specialist			Other-7374 (Research Services Division)		NA
	N					Lab Technician Support Supervisor			Other-7373 (Animal Services Division)		NA
	N					Veterinary Technician I			Other-7373 (Animal Services Division)		NA
	N					Animal Research Technician OB			Other-7373 (Animal Services Division)		NA
	N					HR Assistant Advanced			Other-7375 (Operational Services)		NA
	N					Lab Technician Support Supervisor			Other-7373 (Animal Services Division)		NA
	N					IS Network Supervisor Technician I			Other-7375 (Operational Services)		NA
	N					Associate Director,Operational Srvcs; Unit Head, Admin Srvcs			Other-7375 (Operational Services)		NA
	N					Animal Research Technician OB			Other-7373 (Animal Services Division)		NA
	N					Veterinary Technician III			Other-7373 (Animal Services Division)		NA
	N					Animal Research Technician OB			Other-7373 (Animal Services Division)		NA
	N					Executive Assistant			Other-7372 (Division of Research)		NA

	N	Excluded by Requester				Grants Manager	EFFORT		Other-7375 (Operational Services)		NA
	N					Lab Technician Support Supervisor			Other-7373 (Animal Services Division)		NA
	N					Animal Research Technician			Other-7373 (Animal Services Division)		NA
	N					Animal Research Technician			Other-7373 (Animal Services Division)		NA
	N					Associate Research Animal Veterinaria n			Other-7373 (Animal Services Division)		NA
	N					Animal Research Technician Advanced			Other-7373 (Animal Services Division)		NA
	N					Senior Research Specialist			Other-7373 (Animal Services Division)		NA
	N					Animal Research Technician			Other-7373 (Animal Services Division)		NA
	N					Research Specialist			Other-7373 (Animal Services Division)		NA
	N					Associate Scientist			Other-7374 (Research Services Division)		NA
	N					Animal Research Technician Senior			Other-7373 (Animal Services Division)		NA
	N					Core-PI			Other-7374 (Research Services Division)		NA
	N					Associate Research Specialist			Other-7374 (Research Services Division)		NA
	N					Clinical Veterinaria n			Other-7373 (Animal Services Division)		NA

	N	Excluded by Requester				Animal Research Technician OB	EFFORT		Other-7373 (Animal Services Division)		NA
	N					Veterinary Technician III			Other-7373 (Animal Services Division)		NA
	N					Unit Head, Colony Management			Other-7373 (Animal Services Division)		NA
	N					Animal Research Technician Advanced			Other-7373 (Animal Services Division)		NA
	N					Senior Research Specialist			Other-7374 (Research Services Division)		NA
	N					Animal Research Technician			Other-7373 (Animal Services Division)		NA
	N					Associate Research Specialist			Other-7374 (Research Services Division)		NA
	N					Animal Research Technician OB			Other-7373 (Animal Services Division)		NA
	N					Animal Research Technician OB			Other-7373 (Animal Services Division)		NA
	N					Occupational Health and Safety Coordinator			Other-7373 (Animal Services Division)		NA
	N					Animal Research Technician			Other-7373 (Animal Services Division)		NA
	N					Veterinary Technician III			Other-7373 (Animal Services Division)		NA
	N					Mechanician			Other-7375 (Operational Services)		NA
	N					Animal Research Technician Advanced			Other-7373 (Animal Services Division)		NA
	N					Animal			Other-7373		NA

		Excluded by Requester				Research Technician	EFFORT		(Animal Services Division)		
	N					Admin Program Specialist			Other-7374 (Research Services Division)		NA
	N					Research Animal Veterinarian			Other-7373 (Animal Services Division)		NA
	N					Animal Research Technician			Other-7373 (Animal Services Division)		NA
	N					Training Coordinator			Other-7373 (Animal Services Division)		NA
	N					Animal Research Technician			Other-7373 (Animal Services Division)		NA
	N					Animal Research Technician OB			Other-7373 (Animal Services Division)		NA
	N					Research Specialist			Other-7373 (Animal Services Division)		NA
	N					Animal Research Technician			Other-7373 (Animal Services Division)		NA
	N					Grants Coordinator			Other-7375 (Operational Services)		NA
	N					Animal Research Technician			Other-7373 (Animal Services Division)		NA
	N					Animal Research Technician Senior			Other-7373 (Animal Services Division)		NA
	N					Animal Research Technician			Other-7373 (Animal Services Division)		NA
	N					Animal Research Technician			Other-7373 (Animal Services Division)		NA
	N					Assistant Director,			Other-7375 (Operational		NA

						Administrative Services					Services)		
	N	Excluded by Requester				University Services Program Associate	EFFORT				Other-7373 (Animal Services Division)		NA
	N					Associate Research Animal Veterinarian					Other-7373 (Animal Services Division)		NA
	N					Purchasing Associate					Other-7375 (Operational Services)		NA
	N					Lab Technician Support Supervisor					Other-7373 (Animal Services Division)		NA
	N					Associate Research Specialist					Other-7374 (Research Services Division)		NA
	N					Lab Technician Support Supervisor					Other-7373 (Animal Services Division)		NA
	N					Editor					Other-7372 (Division of Research)		NA
	N					Financial Specialist III					Other-7375 (Operational Services)		NA
	N					Unit Head, IT Services					Other-7375 (Operational Services)		NA
	N					Animal Research Technician Advanced					Other-7373 (Animal Services Division)		NA
	N					Lab Technician Support Supervisor					Other-7373 (Animal Services Division)		NA
	N					Assistant Scientist					Other-7372 (Division of Research)		NA
	N					Veterinary Technician II					Other-7373 (Animal Services Division)		NA
	N					Animal Research Technician					Other-7373 (Animal Services Division)		NA
	N					Associate					Other-7372		NA

		Excluded by Requester				Research Specialist	EFFORT		(Division of Research)		
	N					Veterinary Technician III			Other-7373 (Animal Services Division)		NA
	N					Pathologist			Other-7373 (Animal Services Division)		NA
	N					Senior Research Specialist			Other-7373 (Animal Services Division)		NA
	N					EHR Data Manager			Other-7375 (Operational Services)		NA
	N					Core-PI			Other-7374 (Research Services Division)		NA
	N					Animal Research Technician			Other-7373 (Animal Services Division)		NA
	N					Unit Head, Shop Services			Other-7375 (Operational Services)		NA
	N					Animal Research Technician			Other-7373 (Animal Services Division)		NA
	N					Associate Research Specialist			Other-7372 (Division of Research)		NA
	N					Animal Research Technician			Other-7373 (Animal Services Division)		NA
	N					Senior Research Specialist			Other-7373 (Animal Services Division)		NA
	N					Animal Research Technician Senior			Other-7373 (Animal Services Division)		NA
	N					Associate Research Specialist			Other-7374 (Research Services Division)		NA
	N					Research Specialist			Other-7373 (Animal Services Division)		NA

	N	Excluded by Requester				Associate Research Specialist	EFFORT		Other-7374 (Research Services Division)	NA
	N					Animal Research Technician OB			Other-7373 (Animal Services Division)	NA
	N					Research Specialist			Other-7372 (Division of Research)	NA
	N					Animal Research Technician			Other-7373 (Animal Services Division)	NA
	N					Veterinary Technician II			Other-7373 (Animal Services Division)	NA
	N					Research Specialist			Other-7373 (Animal Services Division)	NA
	N					Animal Research Technician			Other-7373 (Animal Services Division)	NA
	N					University Service Program Associate			Other-7373 (Animal Services Division)	NA
	N					Associate Research Specialist			Other-7373 (Animal Services Division)	NA
	N					Mechanician			Other-7375 (Operational Services)	NA
	N					Veterinary Technician III			Other-7373 (Animal Services Division)	NA
	N					Veterinary Technician II			Other-7373 (Animal Services Division)	NA
	N					Animal Research Technician Advanced			Other-7373 (Animal Services Division)	NA
	N					Research Specialist			Other-7374 (Research Services Division)	NA
	N					Unit Head, Pathology			Other-7373 (Animal	NA

						Services			Services Division)		
	N	Excluded by Requester				Animal Research Technician	EFFORT		Other-7373 (Animal Services Division)		NA
	N					Assistant Researcher			Other-7372 (Division of Research)		NA
	N					Animal Research Technician Advanced			Other-7373 (Animal Services Division)		NA
	N					Assistant Researcher			Other-7372 (Division of Research)		NA
	N					Senior Research Specialist			Other-7373 (Animal Services Division)		NA
	N					Unit Head, Stem Cell Resources			Other-7372 (Division of Research)		NA
	N					Animal Research Technician Senior			Other-7373 (Animal Services Division)		NA
	N					University Service Program Associate			Other-7373 (Animal Services Division)		NA
	N					Animal Research Technician Senior			Other-7373 (Animal Services Division)		NA
	N					Assistant Trainer			Other-7373 (Animal Services Division)		NA
	N					Animal Research Technician OB			Other-7373 (Animal Services Division)		NA
	N					Assistant Data Manager			Other-7375 (Operational Services)		NA
	N					Lab Technician Support Supervisor			Other-7373 (Animal Services Division)		NA
	N					Senior Research Specialist			Other-7374 (Research Services Division)		NA
	N					Senior			Other-7374		NA

		Excluded by Requester				Research Specialist	EFFORT		(Research Services Division)		
	N					Animal Research Technician OB			Other-7373 (Animal Services Division)		NA
	N					Senior Scientist			Other-7374 (Research Services Division)		NA
	N					Lab Manager			Other-7374 (Research Services Division)		NA
	N					Associate Research Specialist			Other-7373 (Animal Services Division)		NA
	N					Animal Research Technician			Other-7373 (Animal Services Division)		NA
	N					Animal Research Technician			Other-7373 (Animal Services Division)		NA
	N					Animal Research Technician			Other-7373 (Animal Services Division)		NA
eRA Commons User Name	N					Assistant Researcher			Other-7374 (Research Services Division)		NA
	N					Pathologist			Other-7373 (Animal Services Division)		NA
	N					Veterinary Student			Other-7373 (Animal Services Division)		NA
	Y		SSN	DOB	PHD	PD/PI					NA
	N					Core-PI			Other-7373 (Animal Services Division)		NA
	N					Associate Director,Research Srvcs; Unit Head,Genetics Srvcs			Other-7374 (Research Services Division)		NA

eRA Commons User Name	N	Excluded by Requester				Research Associate	EFFORT		Other-7372 (Division of Research)		NA
	N					Core-PI			Other-7373 (Animal Services Division)		NA
	N					Unit Head, Immunology Services			Other-7374 (Research Services Division)		NA
	N					Core-PI			Other-7374 (Research Services Division)		NA
	N					Core-PI			Other-7373 (Animal Services Division)		NA
	N					Veterinary Student			Other-7373 (Animal Services Division)		NA
	N					Unit Head, Bone Marrow Transplant Core			Other-7372 (Division of Research)		NA
	N					Veterinary Student			Other-7373 (Animal Services Division)		NA
	N		SSN	DOB	BA,PHD	Director					NA
	N					Co-Unit Head, SPI			Other-7373 (Animal Services Division)		NA
	N					Core-PI			Other-7372 (Division of Research)		NA
	N					Veterinary Student			Other-7373 (Animal Services Division)		NA
	N					Co-Unit Head, SPI			Other-7373 (Animal Services Division)		NA
	N					Unit Head, Behavior Management & Enrichment			Other-7373 (Animal Services Division)		NA
	N					Unit Head, Aging			Other-7372 (Division of		NA

eRA Commons User Name		Excluded by Requester	SSN	DOB		Resources	EFFORT		Research)		
	N				DVM	Associate Director,Animal Srvcs; Unit Head,Veterinary Srvcs			Other-7373 (Animal Services Division)		NA
	N					Unit Head, Virology Services			Other-7374 (Research Services Division)		NA
	N					Unit Head, Assay Services			Other-7374 (Research Services Division)		NA

Glossary of acronyms:
S/K - Senior/Key
DOB - Date of Birth
Cal - Person Months (Calendar)
Aca - Person Months (Academic)
Sum - Person Months (Summer)
Foreign Org - Foreign Organization Affiliation
SS - Supplement Support
RE - Reentry Supplement
DI - Diversity Supplement
OT - Other
NA - Not Applicable

D.2 PERSONNEL UPDATES

D.2.a Level of Effort

Will there be, in the next budget period, either (1) a reduction of 25% or more in the level of effort from what was approved by the agency for the PD/PI(s) or other senior/key personnel designated in the Notice of Award, or (2) a reduction in the level of effort below the minimum amount of effort required by the Notice of Award?

No

D.2.b New Senior/Key Personnel

Are there, or will there be, new senior/key personnel?

Yes

File uploaded: Yr53 New Personnel_opt.pdf

D.2.c Changes in Other Support

Has there been a change in the active other support of senior/key personnel since the last reporting period?

Yes

Excluded by Requester ded: ActiveOS_2-26-15_opt.pdf

D.2.d New Other Significant Contributors

Are there, or will there be, new other significant contributors?

No

D.2.e Multi-PI (MPI) Leadership Plan

Will there be a change in the MPI Leadership Plan for the next budget period?

NA

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

Excluded by Requester

Excluded by Requester

Excluded by Requester

Excluded by Requester

OTHER SUPPORT

Excluded by Requester

Excluded by Requester

Excluded by Requester

Excluded by Requester

D.2.c Excluded by Request ActiveOS_2-26-15_opt.pdf)

OTHER SUPPORT

Excluded by Requester

ACTIVE

P51 OD011106-53 (Mailick) 07/02/13 – 04/30/17 EFFORT calendar
NIH/OD Yr 53 Direct: $7,098,330
Director's Office
These funds support the Director's Office of the Wisconsin Primate Research Center.
Role: Director, WNPRC

P50 HD44405-12 (Excluded by Requester 07/01/13 – 06/30/17 EFFORT calendar
NIH/NICHD $231,473
Genes, Androgens and Intrauterine Environment in PCOS
Project IV: Effects of Androgens on Female Reproduction
This grant supports a Specialized Center of Research entitled "Genes, Androgens, and Intrauterine Environment in PCOS." The projects are designed to investigate the genetic and developmental basis of the pathogenesis of polycystic ovarian syndrome. Project III includes experiments that test the hypothesis that excess intrauterine androgen exposure leads to the programming of pancreatic and brain tissue to exhibit symptoms of PCOS in adulthood. The hypothesis specifically holds that the pathogenesis of PCOS arises from a disruption of the expression and functional activity of ATP-sensitive potassium channels in neurons and pancreatic beta cells.
Role: Center Co-Director and Principal Investigator of Project III

R01 HD068777-03 Excluded by Requester 03/30/12 – 02/28/15 EFFORT calendar
NIH/NICHD $118,518
Sex steroids, kisspeptin, and regulation of GnRH
The proposed experiments consist of the development and phenotypic analysis of mice bearing conditional deletions of steroid hormone receptors. These studies focus on the cell signaling and integrative mechanisms that mediate the positive and negative feedback actions of estrogen in the brain. Our experiments will also test the hypothesis that these mechanisms are altered by prenatal androgen exposure to produce the reproductive features of polycystic ovary syndrome, which include resistance to estrogen and resultant hypersecretion of reproductive hormones and hyperstimulation of the ovaries.
Role: P.I. on multiple P.I. grant

U54 HD028934-21 Excluded by Requester **04/01/14 – 03/31/19** EFFORT **calendar**
NIH/NICHD **$231,712**
Clinical and Basic Studies in Polycystic Ovarian Syndrome (RFA-HD-14-017)
Project II: Hypothalamic Steroid Receptors and the Pathogenesis of PCOS
Studies related to this project will make use of viral vector-mediated gene silencing and a validated nonhuman primate model of androgen induced reproductive PCOS phenotypes to address these major gaps in our understanding of the mechanisms that mediate the pathogenesis of PCOS.
Role: P.I., Project II

E. OVERALL IMPACT

E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES?

Not Applicable

E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE?

NOTHING TO REPORT

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

Not Applicable

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?

NOTHING TO REPORT

F. OVERALL CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

F.2 ACTUAL OR ANTICIPATED CHALLENGES OR DELAYS AND ACTIONS OR PLANS TO RESOLVE THEM

NOTHING TO REPORT

F.3 SIGNIFICANT CHANGES TO HUMAN SUBJECTS, VERTEBRATE ANIMALS, BIOHAZARDS, AND/OR SELECT AGENTS

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. OVERALL SPECIAL REPORTING REQUIREMENTS

G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT REPORTING REQUIREMENTS

File(s) uploaded:
Special Reporting Requirements_final_2-26-15opt.pdf

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

G.4.a Does the project involve human subjects?

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Does this project include one or more applicable clinical trials that must be registered in ClinicalTrials.gov under FDAAA?

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Are there personnel on this project who are newly involved in the design or conduct of human subjects research?

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?

No

G.7 VERTEBRATE ANIMALS

Does this project involve vertebrate animals?

Yes

G.8 PROJECT/PERFORMANCE SITES

Organization Name:	DUNS	Congressional District	Address
Primary: UNIVERSITY OF WISCONSIN MADISON	161202122	WI-002	UNIVERSITY OF WISCONSIN MADISON 21 N Park St. MADISON WI 537151218

G.9 FOREIGN COMPONENT

No foreign component

G.10 ESTIMATED UNOBLIGATED BALANCE

G.10.a Is it anticipated that an estimated unobligated balance (including prior year carryover) will be greater than 25% of the current year's total approved budget?

No

G.11 PROGRAM INCOME

Is program income anticipated during the next budget period?

Yes

Anticipated Amount	Source(s)
5153000	Income from fees for services & research projects performed

G.12 F&A COSTS

Not Applicable

SPECIAL REPORTING REQUIREMENTS

A. WNPRC ANIMAL CENSUS

1. Nonhuman primates supported partially, or in whole by the P51 base grant[1].

Census date: 2/2/2015

Genus, Species	Breeding Colony[2]				Animals not in breeding colony[3]				Total Colony Census
	M	F	U[4]	Total	M	F	U[4]	Total	
Macaca mulatta	210	356	0	566	301	289	0	590	1,156
Macaca fascicularis	0	0	0	0	65	57	0	122	122
Callithrix jacchus	13	12	0	25	136	143	3	182	307
Total	223	368	0	591	502	489	3	994	1,585

[1] In a footnote, indicate if this colony is also supported by a SPF U24 or U42 grant
[2] Total number of animals in breeding colony including adult breeding animals and designated juvenile replacements at time of report.
[3] Animals on protocol or otherwise not in the breeding colony at the time of report.
[4] Sex undetermined

2. Nonhuman primates not supported by the P51 base grant[1].

Census date: _____

Genus, Species	Breeding Colony[2]				Animals not in breeding colony[3]				Total Colony Census
	M	F	U[4]	Total	M	F	U[4]	Total	
Species A									
Species B									
Totals									

[1] In a footnote, indicate if this colony is supported by a SPF U24 or U42 grant
[2] Total number of animals in breeding colony including adult breeding animals and designated juvenile replacements at time of report.
[3] Animals on protocol or otherwise not in the breeding colony at the time of report.
[4] Sex undetermined

3. Non-primate colonies[1]

Census date: _____

Genus, Species	Total number of animals
Species A	
Species B	
Total	

[1] Include only those animals supported partially, or in whole by the P51 base grant.

B. Biological Specimens Distributed to Researchers (1/1/2014 – 12/31/2014)

WNPRC Unit	Number & Types of Samples Provided
Immunology Services	~5,000 Tissues
Nonhuman Primate Biological Materials Distribution Core (NHPBMD)	755 Tissues 641 Organs
SIV Elite Controller Resource	216
Stem Cell Resources	8 Cell Cultures
Virology Services	265 Virus Stock
TOTAL # of Specimens:	**6,885+**

C. Number of Projects Supported (1/1/2014 – 12/31/2014)

WNPRC Unit	Number of Projects Performed/Supported by Unit		
	Research	Pilot	Other
Assay Services	-	-	-
Compliance & Training	-	-	-
Genetic Services	3	-	-
Immunology Services	13	1	27 (FFS)
NHPBMD	37	2	3
Pathology Services	35	2	0
Clinical Pathology	42	2	3
Scientific Protocol Implementation	30	4	2
SIV Elite Controller Resource	-	-	-
Stem Cell Resource	1	-	3
Veterinary Services	30	4	2
Virology Services	2	-	16

D. Percentage of P51 Funding that was AIDS-Related

57%

E. CORE AND AFFILIATE INVESTIGATORS (1/1/2014 – 12/31/2014)

WNPRC Unit	Number of Investigators Supported by Unit	
	Core	Affiliate
Assay Services	7	21
Compliance & Training	13	10
Genetic Services	5	-
Immunology Services	5	22
NHPBMD	12	30
Pathology Services	16	8
Clinical Pathology	14	17
Scientific Protocol Implementation	8	12
SIV Elite Controller Resource	4	5
Stem Cell Resource	2	-
Veterinary Services	8	12
Virology Services	4	6

F. JOURNAL ARTICLES, BOOK CHAPTERS & OTHER PUBLICATIONS (1/1/2014 – 12/31/014)

Wisconsin National Primate Research Center and affiliate scientific journal publications. (Publications courtesy NPRC staff and PubMed, National Library of Medicine.)

DECEMBER 2014

Excluded by Requester High fat diet decreases beneficial effects of estrogen on serotonin-related gene expression in marmosets. Prog Neuropsychopharmacol Biol Psychiatry. 2014 Dec 24. pii: S0278-5846(14)00224-3. [Epub ahead of print] PMID25542371. PMC unavailable.

Excluded by Requester Positive, but not negative feedback actions of estradiol in female mice require estrogen receptor α (ERα) in kisspeptin neurons. Endocrinology. 2014 Dec 29:en20141851. [Epub ahead of print] PMID25545386. PMC unavailable.

Excluded by Requester GB virus C co-infections in West African Ebola patients. J Virol. 2014 Dec 3. [Epub ahead of print]. PMID25473056. PMC unavailable.

Excluded by Requester The trabecular meshwork in normal eyes and in exfoliation glaucoma. J Glaucoma. 2014 Oct-Nov;23(8 Suppl 1):S15-9. PMID25275898. PMC unavailable.

Excluded by Requester Neuropeptide y receptor gene expression in the primate amygdala predicts anxious temperament and brain metabolism. Biol Psychiatry. 2014 Dec 1;76(11):850-7 PMID24342924. PMC4022724.

Excluded by Requester Fear of the Unknown: Uncertain Anticipation Reveals Amygdala Alterations in Childhood Anxiety Disorders. Neuropsychopharmacology. 2014 Dec 15. PMID25502633. PMC unavailable.

NOVEMBER 2014

Excluded by Requester Differentially methylated plasticity genes in the amygdala of young primates are linked to anxious temperament, an at risk phenotype for anxiety and depressive disorders. J Neurosci. 2014 Nov 19;34(47):15548-56. PMID25411484. PMCID4236392.

Excluded by Requester Two Novel Simian Arteriviruses in Captive and Wild Baboons (Papio spp.). Journal of virology 2014 Nov 15. PMID25187550. PMC4249091.

Excluded by Requester

Excluded by Requester Whole genome sequencing of SIV-infected macaques identifies candidate loci that may contribute to host control of virus replication. Genome biology 2014 Nov 7. PMID25418588. PMC4223156.

Excluded by Requester

Impact of Repeated Vaccination on Vaccine Effectiveness Against Influenza A(H3N2) and B During 8 Seasons. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 2014 Nov 15. PMID25270645. PMC4207422.

Excluded by Requester Regional choroidal blood flow and multifocal electroretinography in experimental glaucoma in rhesus macaques. Invest Ophthalmol Vis Sci. 2014 Nov 4;55(12):7786-98. PMID25370515. PMCID4254281.

Excluded by Requester Influenza A virus polymerase is a site for adaptive changes during experimental evolution in bat cells. Journal of virology 2014 Nov. PMID25142579. PMC4248895.

Excluded by Requester Social peptides: measuring urinary oxytocin and vasopressin in a home field study of older adults at risk for dehydration. J Gerontol B Psychol Sci Soc Sci. 2014 Nov;69 Suppl 2:S229-37. PMID25360024. PMC unavailable.

OCTOBER 2014

Excluded by Requester

Excluded by Requester Identification of adult stem cells in Schwalbe's line region of the primate eye. Invest Ophthalmol Vis Sci. 2014 Oct 16. pii: IOVS-14-14872. [Epub ahead of print] PMID25324280. PMC unavailable.

Excluded by Requester

Excluded by Requester Simian Hemorrhagic Fever Virus Cell Entry is Dependent on CD163 and Uses a Clathrin-mediated Endocytosis-like Pathway. Journal of Virology 2014 Oct 29. PMID25355889. PMC unavailable.

Excluded by Requester Assessing anxiety in nonhuman primates. ILAR J. Oct 2014;55(2):333-46. PMID25225310. PMCID4240439.

Excluded by Requester

Compartmentalization of Simian Immunodeficiency Virus Replication within Secondary Lymphoid Tissues of Rhesus Macaques Is Linked to Disease Stage and Inversely Related to Localization of Virus-Specific CTL. J Immunol. 2014 Oct 31. pii: 1401161. [Epub ahead of print] PMID25362178. PMC unavailable.

Excluded by Requester

Excluded by Requester Linking pig-tailed macaque major histocompatibility complex class I haplotypes and cytotoxic lymphocyte escape mutations in SIV infection. J Virol. 2014 Oct 1. [Epub ahead of print] PMID25275134. PMC unavailable.

Excluded by Requester

Excluded by Requester Genome Sequences of Simian Hemorrhagic Fever Virus Variant NIH LVR42-0/M6941 Isolates (Arteriviridae: Arterivirus). Genome announcements 2014 Oct 9. PMID25301647. PMC4192379.

Excluded by Requester Both parents respond equally to infant cues in the cooperatively breeding common marmoset, Callithrix jacchus. Anim Behav. 2014 Oct 1;97:95-103. PMID25342858. PMC4203656.

Excluded by Requester

Excluded by Requester enascin C promotes hematoendothelial development and T lymphoid commitment from human pluripotent stem cells in chemically defined conditions. Stem Cell Reports. 2014 Dec 9;3(6):1073-84. Epub 2014 Oct 23. PMID25448067. PMCID4263995.

SEPTEMBER 2014

Excluded by Requester Assessment of foraging devices as a model for decision-making in nonhuman primate environmental enrichment. J Am Assoc Lab Anim Sci. Sept. 2014;53(5):452-63. PMID25255067. PMC4181686.

Excluded by Requester

Modified vaccinia virus ankara encoding influenza virus hemagglutinin induces heterosubtypic immunity in macaques. J Virol. 2014 Nov 15;88(22):13418-28. Epub 2014 Sep 10. PMID25210172. PMC unavailable.

Excluded by Requester Systemic administration of 6-OHDA to rhesus monkeys upregulates HLA-DR expression in brain microvasculature. J Inflamm Res. 2014 Sep 18;7:139-49. eCollection 2014. PMID25258551. PMC4173661.

Excluded by Requester

Excluded by Requester Prospects for lentiviral vector mediated prostaglandin F synthase gene delivery in monkey eyes in vivo. Curr Eye Res. 2014 Sep;39(9):859-70. PMID24559478. PMC unavailable.

Excluded by Requester Abnormal infant islet morphology precedes insulin resistance in PCOS-like monkeys. PLoS One. 2014 Sep 10;9(9):e106527. 7. eCollection 2014. PMID25207967. PMC4160158.

Excluded by Requester Bortezomib prevents acute doxorubicin ovarian insult and follicle demise, improving the fertility window and pup birth weight in mice. PLoS One. 2014 Sep 24;9(9):e108174. eCollection 2014. PMID25251158. PMC4176970.

Excluded by Requester Adolescent adrenocortical activity and adiposity: differences by sex and exposure to early maternal depression. Psychoneuroendocrinology. 2014 Sep;47:68-77. PMID25001956. PMC4106120.

Excluded by Requester Breath carbon stable isotope ratios identify changes in energy balance and substrate utilization in humans. Int J Obes (Lond). 2014 Sep;38(9):1248-50. PMID24441037. PMC unavailable.

Excluded by Requester A diffusion-tensor-based white matter atlas for rhesus macaques. PLoS One. 2014 Sep 9;9(9):e107398. eCollection 2014. PMID25203614. PMC4159318.

AUGUST 2014

Excluded by Requester

Excluded by Requester Extreme early-life anxiety is associated with an evolutionarily conserved reduction in the strength of intrinsic functional connectivity between the dorsolateral prefrontal cortex and the central nucleus of the amygdala. Mol Psychiatry. 2014 Aug;19(8):853. PMID25055941. PMC unavailable.

Excluded by Requester

Excluded by Requester Evolutionarily conserved prefrontal-amygdalar dysfunction in early-life anxiety. Mol Psychiatry. 2014 Aug;19(8):915-22. PMID24863147. PMC4111803.

Excluded by Requester A Translational Neuroscience Approach to Understanding the Development of Social Anxiety Disorder and Its Pathophysiology. Am J Psychiatry. 2014 Aug 26. [Epub ahead of print]. PMID25157566. PMC unavailable.

Excluded by Requester Stem cell therapy. Use of differentiated pluripotent stem cells as replacement therapy for treating disease. Science. 2014 Aug 22;345(6199):1247391. Review. PMID25146295. PMC unavailable.

Excluded by Requester

Excluded by Requester Rapid, repeated, low-dose challenges with SIVmac239 infect animals in a condensed challenge window. Retrovirology 2014 Aug 14. PMID25125288. PMC4149191.

Excluded by Requester

Excluded by Requester The effects of chronic alcohol self-administration on serotonin-1A receptor binding in nonhuman primates. Drug Alcohol Depend. 2014 Aug 29. pii: S0376-8716(14)01043-6. Aug. 29, 2014. [Epub ahead of print]. PMID25220896. PMC unavailable.

Excluded by Requester

Excluded by Requester Evolution of the central sulcus morphology in primates. Brain Behav Evol. 2014;84(1):19-30. Epub 2014 Aug 13. PMID25139259. PMCID4166656.

Excluded by Requester Cardiac sympathetic denervation in 6-OHDA-treated nonhuman primates. PLoS One. 2014 Aug 18;9(8):e104850. eCollection 2014. PMID25133405. PMC4136781.

Excluded by Requester Dopamine transporter gene susceptibility to methylation is associated with impulsivity in nonhuman primates. J Neurophysiol. 2014 Nov 1;112(9):2138-46. Epub 2014 Aug 13. PMID25122707. PMC unavailable.

Excluded by Requester

Excluded by Requester Initial in vivo PET imaging of 5-HT1A receptors with 3-[(18)F]mefway. Am J Nucl Med Mol Imaging. 2014 Aug 15;4(5):483-9. eCollection 2014. PMID25143866. PMC4138142.

JULY 2014

Excluded by Requester

Excluded by Requester Direct induction of haematoendothelial programs

in human pluripotentstem cells by transcriptional regulators. Nat Commun. 2014 Jul 14;5:4372. PMID25019369. PMC4107340.

Excluded by Requester

Excluded by Requester Discovery and full genome characterization of a new SIV lineage infecting red-tailed guenons (Cercopithecus ascanius schmidti) in Kibale National Park, Uganda. Retrovirology 2014 Jul 4. PMID24996566. PMC4226943.

Excluded by Requester Peripheral and cognitive signs: delineating the significance of impaired catecholamine metabolism in Parkinson's disease progression. J Neurochem. 2014 Jul 5. PMID25039428. PMC unavailable.

JUNE 2014

Excluded by Requester

Excluded by Requester Titer and product affect the distribution of gene expression after intraputaminal convection-enhanced delivery. Stereotact Funct Neurosurg. 2014;92(3):182-94. Epub 2014 Jun 12. PMID24943657. PMC4127999.

Excluded by Requester Morphological alterations within the peripheral fixation of the iris dilator muscle in eyes with pigmentary glaucoma. Invest Ophthalmol Vis Sci. 2014 June 55(7):4541-51. PMID24938519. PMC unavailable.

Excluded by Requester

Excluded by Requester Discovery and characterization of distinct simian pegiviruses in three wild African Old World monkey species. PloS one 2014. June 11;9(2):e98569. PMID24918769. PMC4053331.

Excluded by Requester (2014). Response normalization in the superficial layers of the superior colliculus as a possible mechanism for saccadic averaging. J Neurosci. 2014 June 4;34(23):7976-87. PMID24899719. PMC4044254.

Excluded by Requester Normalization of neuronal responses in cortical area MT across signal strengths and motion directions. J Neurophys. 2014 Sept. 15;112(6):1291-306. Epub 2014 Jun 3. PMID24899674. PMC4137245.

MAY 2014

Excluded by Requester Intrauterine environment and polycystic ovary syndrome. Semin Reprod Med. 2014 May;32(3):159-65. Review. PMID24715510. PMC unavailable.

Excluded by Requester Measuring fecal testosterone in females and fecal estrogens in males: Comparison of RIA and LC/MS/MS methods for wild baboons (Papio cynocephalus). Gen Comp Endocrinol. 2014 May 4. pii: S0016-6480(14)00151-8. [Epub ahead of print] PMID24798581. PMC unavailable.

Excluded by Requester Intralaminar and medial thalamic influence on cortical synchrony, information transmission and cognition. Front Syst Neurosci. 2014 May 9;8:83. Review. PMID24847225. PMC4023070.

Excluded by Requester Population variation in neuroendocrine activity is associated with behavioral inhibition and hemispheric brain structure in young rhesus monkeys. Psychoneuroendocrinology. 2014 Sep;47:56-67 Epub 2014 May 10. PMID24954302. PMC4205758.

Excluded by Requester

Excluded by Requester Interdisciplinary collaborative team for blastocyst implantation research: inception and perspectives. Am J Reprod Immunol. 2014 Jan;71(1):1-11. Epub 2013 Nov 29. No abstract available. Erratum in: Am J Reprod Immunol. 2014 May;71(5):485. Excluded by Requester [removed]. PMID24286196. PMC unavailable.

APRIL 2014

Excluded by Requester Tetherin antagonism by Vpu protects HIV-infected cells from antibody-dependent cell-mediated cytotoxicity. Proc Natl Acad Sci U S A. 2014 Apr 29;111(17):6425-30. Epub 2014 Apr 14. PMID24733916. PMC4035966.

Excluded by Requester Caloric restriction reduces age-related and all-cause mortality in rhesus monkeys. Nat Commun. 2014 Apr 1;5:3557. PMID24691430. PMC3988801.

Excluded by Requester Impaired preadipocyte differentiation into adipocytes in subcutaneous abdominal adipose of PCOS-like female rhesus monkeys. Endocrinology. 2014 Jul;155(7):2696-703. Epub 2014 Apr 15. PMID24735327. PMC4060192.

Excluded by Requester

Excluded by Requester Vaccination with Gag, Vif, and Nef gene fragments affords partial control of viral replication after mucosal challenge with SIVmac239. J Virol. 2014 Jul;88(13):7493-516. Epub 2014 Apr 16. PMID24741098. PMC4054456.

Excluded by Requester

Excluded by Requester Sequence variations in HIV-1 p24 Gag-derived epitopes can alter binding of KIR2DL2 to HLA-C*03:04 and modulate primary natural killer cell function. AIDS. 2014 Apr 30. [Epub ahead of print] PMID24785948. PMC unavailable.

Excluded by Requester

Excluded by Requester Metabolic Evidence of Diminished Lipid Oxidation in Women With Polycystic Ovary Syndrome. Curr Metabolomics. April 2014;2(4):269-278. PMID24765590. PMC3994884.

MARCH 2014

Excluded by Requester Application of canaloplasty in glaucoma gene therapy: where are we? J Ocul Pharmacol Ther. 2014 Mar-Apr;30(2-3):277-82. Epub 2014 Feb 10. PMID24512297. PMC3991989.

Excluded by Requester

Excluded by Requester High genetic diversity and adaptive potential of two simian hemorrhagic fever viruses in

a wild primate population. PLoS One. 2014 Mar 20;9(3):e90714. eCollection 2014. PMID24651479. PMC3961216.

Excluded by Requester

Excluded by Requester Tertiary mutations stabilize CD8+ T lymphocyte escape-associated compensatory mutations following transmission of simian immunodeficiency virus. Journal of virology 2014 Mar. PMID24371068. PMC3957937.

Excluded by Requester

Excluded by Requester Metabolic gene profile in early human fetal heart development. Mol Hum Reprod. 2014 Jul;20(7):690-700. doi: 10.1093/molehr/gau026. Epub 2014 Mar 27. PMID24674993. PMC unavailable.

Excluded by Requester Modeling and imaging cardiac sympathetic neurodegeneration in Parkinson's disease. Am J Nucl Med Mol Imaging. 2014 Mar 20;4(2):125-59. PMID24753981. PMC3992208.

Excluded by Requester Hydroxymethylation and DNA methylation profiles in the prefrontal cortex of the non-human primate rhesus macaque and the impact of maternal deprivation on hydroxymethylation. Neuroscience. 2014 May 30;268:139-48. Epub 2014 Mar 19. PMID24657458. PMC unavailable.

Excluded by Requester

Excluded by Requester Vaccination against endogenous retrotransposable element consensus sequences does not protect rhesus macaques from SIVsmE660 infection and replication. PLoS One. 2014 Mar 20;9(3):e92012. eCollection 2014. PMID24651676. PMC3961289.

Excluded by Requester

Excluded by Requester Effect of age and calorie restriction on corpus callosal integrity in rhesus macaques: A fiber tractography study. Neurosci Lett. 2014 May 21;569:38-42. Epub 2014 Mar 29. PMID24686192. PMC unavailable.

FEBRUARY 2014

Excluded by Requester

Excluded by Requester Array-based assay detects genome-wide 5-mC and 5-hmC in the brains of humans, non-human primates, and mice. BMC Genomics. 2014 Feb 13;15:131. PMID24524199. PMC3930898.

Excluded by Requester

Excluded by Requester Changes in the α4β2* nicotinic acetylcholine system during chronic controlled alcohol exposure in nonhuman primates. Drug Alcohol Depend. 2014 May 1;138:216-9. Epub 2014 Feb 15. PMID24602361. PMC3992705.

JANUARY 2014

Excluded by Requester

Excluded by Requester Fatal metacestode infection in Bornean orangutan caused by unknown Versteria species. Emerg Infect Dis. 2014 Jan;20(1):109-13. PMID24377497. PMC3884733.

Excluded by Requester Hormones in infant rhesus monkeys' (Macaca mulatta) hair at birth provide a window into the fetal environment. Pediatr Res. 2014 Apr;75(4):476-81. Epub 2014 Jan 13. PMID24418932. PMC3961505.

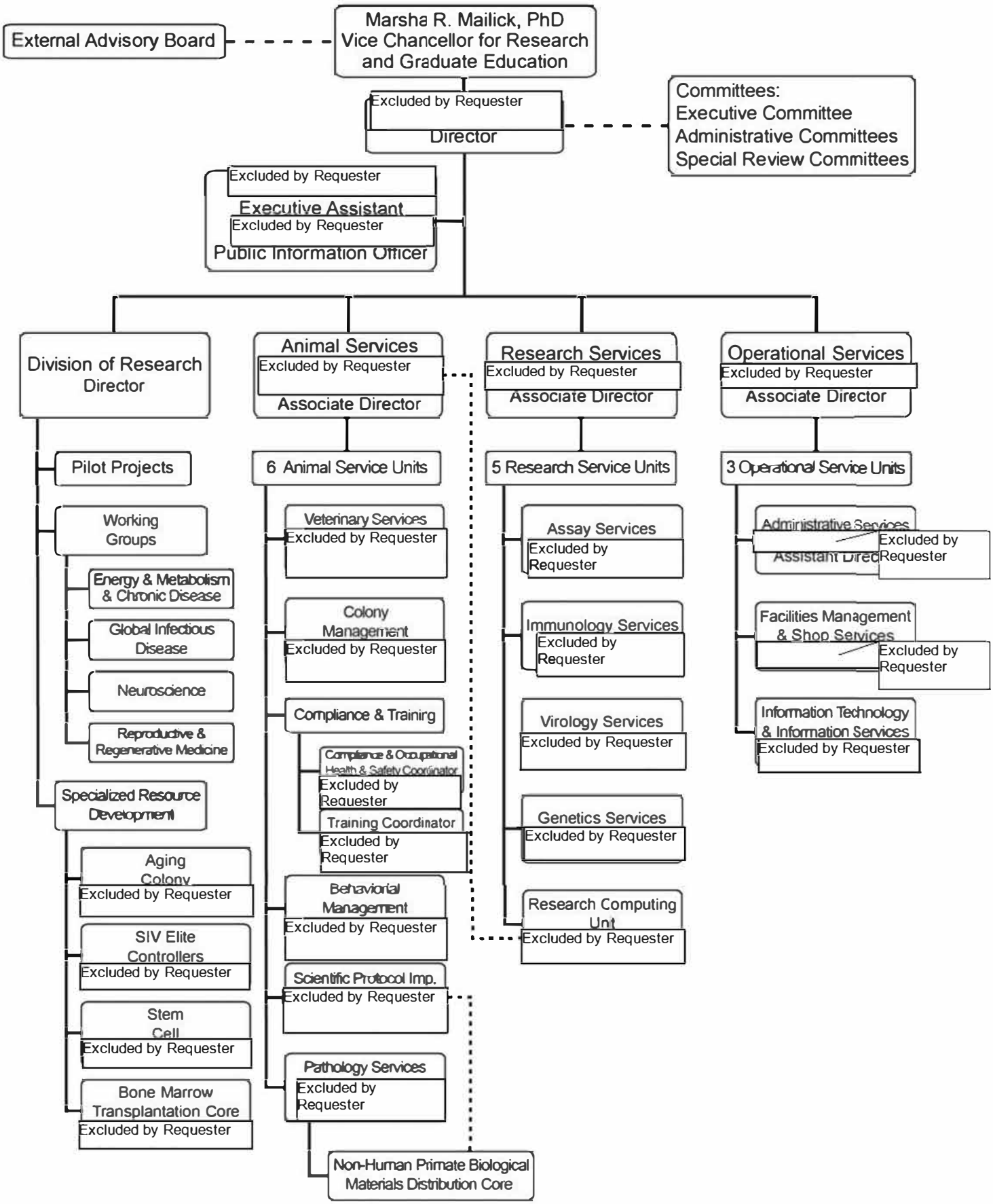
Excluded by Requester

KIR3DL01 recognition of Bw4 ligands in the rhesus macaque: maintenance of Bw4 specificity since the divergence of apes and Old World monkeys. J Immunol. 2014 Feb 15;192(4):1907-17. Epub 2014 Jan 22. PMID24453246.

G. INVESTIGATORS TRAINED (1/1/2014 – 12/31/014)

WNPRC Unit	Post-doctoral	Graduate	Undergraduate
Assay Services	1	1	2
Behavioral Management	-	-	7
Pathology Services	4	4	5
Scientific Protocol Implementation	-	-	5
Stem Cell Resources	1	-	1
Veterinary Services	5	30	4
Total Students by Category:	**11**	**35**	**24**

H. ORGANIZATIONAL CHART



I. Individual Project Descriptions

External Subprojects Supported by WNPRC, 1/1/2014 - 12/31/2014

RESEARCH

Institution & Department	External Principal Investigator(s)	WNPRC Core Scientist	Project Title	AIDS Research? (Y/N)
Private Source	Excluded by Requester		Dengue project	N
Private Source			Antibody Effector Function in Protection Against HIV-1	Y
Private Source Dept. of Immunology and Microbial Science			Antibody response to HIV-1 env BG505 variant-SOSIP trimer in immunized macaques (CHAVI-ID)	Y
Private Source Dept. of Immunology and Microbial Science			Mechanisms underlying persistent lentivirus replication in follicular T cells	Y
University of Colorado-Denver, Medicine			GAMMA-2 Herpesviruses as Vaccine Vectors for AIDS	Y
Private Source School of Medicine, Department of Microbiology			Immunoglobulins Delivered by AAV Vector for the Prevention of SIV Infection	Y
Private Source School of Medicine, Department of Microbiology			Delivery of Small Interfering RNA to Primates	N
University of Wisconsin, Medicine and Arrowhead Madison, Inc.			Sequence of Neuronal Generation in Marmoset Visual System	N
University of Washington, Department of Ophthalmology			Simianizing hepatitis C: Defining the species-tropism of a hepatotropic virus	N
Private Source Department of Immunology, Virology, and Microbiology			Womb to Womb: Transgenerational programming of reproductive development and function in the common marmoset monkey.	N
University of Illinois-Chicago			Evaluating rhesus macaque immune responses to SOSIP trimer and eOD-60mer prime/SOSIP trimer boost immunizations	Y
Private Source Private Source Dept. of Immunology and Microbial Science			The role of myeloid cells in viral replication, persistence, and neuroinvasion	Y
Private Source Medical School			Preclinical development of HIV-1 VIF antagonists	Y
Private Source Medical School, University of California San Diego-Pediatrics			Can vaccine-induced CD8 T cells prevent chronic phase AIDS virus replication?	Y
Private Source Pathology			The Functional Significance of CTL Escape	Y
Private Source Pathology				

Institution & Department	External Principal Investigator(s)	WNPRC Core Scientist	Project Title	AIDS Research? (Y/N)
Private Source Pathology	Excluded by Requester	Excluded by Requester	Yellow Fever, rDNA (EP+IL-12) and rAd35 as Vectors for AIDS Vaccine Development	Y
Pathology			Innovative persistent viral vector based vaccine against Dengue virus	N
Pathology			DENV infection for Neutralizing Ab isolation	N
Pathology			A Novel, Logical Approach to HIV Vaccine Development	Y
Private Source Medical School - Pathology			MHC-bound, SIV-derived, CTL and HTL Epitopes	Y
Private Source Pathology			SIV-specific Mamu-E-restricted CD8+ T cells	Y

PILOTS: None.

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	Proprietary Info	
Period of Support	12/23/2013 - 12/22/2016	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☒ No ☐ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** Private Source
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):** Excluded by Requester	**Affiliate Institution(s) & Department(s):** University of Wisconsin-Madison, Pathobiological Sciences
Principal Core Scientist Associated with Project		
Project Description *(One paragraph)*	Previous studies evaluating Proprietary Info Proprietary Info Proprietary Info Proprietary Info To improve the efficacy of Proprietary Info we will test new formulations and assess different strategies to provide critical pre-clinical data to support ongoing clinical trials with our collaborators. Proprietary Info	
Project Progress *(One paragraph)*		
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** Private Source	**Grant number(s):**

Subproject Description:

WNPRC Division-Unit	Research Services-Immunology Services	
Project Title	Antibody Effector Function in Protection Against HIV-1	
Period of Support	5/15/2003 – 1/31/2019	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☒ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** Private Source Dept of Immunology & Microbial Science
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	We wish to test that antibody effector function is critical to protection against HIV challenge. We can dissect the crucial functions important in vivo and we can use this knowledge to improve in vitro assays to predict the types of antibody responses that will provide optimal benefit against HIV exposure. We use the recombinant Simian Human Immunodeficiency Virus (SHIV) infected-Rhesus macaque model to understand the role of two different functions (ADCC and phagocytosis) of the protective antibodies against HIV infection in humans.	
Project Progress *(One paragraph)*	In 2014 we determined the efficacy of broadly neutralizing PGT121 antibody lacking Fc-domain-mediated effector functions against mucosal challenge with 300TCID50 SHIV162P3. We treated a group of five Rhesus macaques with 1 mg/kg wild type PGT121, a group of five animals with 1 mg/kg LALA mutant PGT121 lacking effector functions and a group of two animals with 1mg/kg DEN3 specific irrelevant antibody. We compared the viremia in the three groups of animals and found that the absence of Fc-domain mediated effector functions did not impair the protective effect of PGT121 antibody.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH, NIAID	**Grant number(s):** 5R37 AI055332

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	Antibody Effector Function in Protection Against HIV-1	
Period of Support	05/15/2003 - 01/31/2019	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☒ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** Private Source Department of Immunology and Microbial Science
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	In addition to neutralization, antibodies mediate a variety of Fc-dependent effector functions. Defining the role of these in vivo may be critical to determine antibody response or combination of responses to offer the most optimal protection against HIV exposure. We can dissect the crucial functions important in vivo and we can use this knowledge to improve in vitro assays to predict the types of antibody responses that will provide optimal benefit against HIV exposure. We use the recombinant Simian Human Immunodeficiency Virus (SHIV) infected-Rhesus macaque model to understand the role of two different functions (ADCC and phagocytosis) of the protective antibodies against HIV infection in humans.	
Project Progress *(One paragraph)*	In 2014 we determined the efficacy of broadly neutralizing PGT121 antibody lacking Fc-domain-mediated effector functions against mucosal challenge with 300TCID50 SHIV162P3. We treated a group of five Rhesus macaques with 1 mg/kg wild type PGT121, a group of five animals with 1 mg/kg LALA mutant PGT121 lacking effector functions and a group of two animals with 1mg/kg DEN3 specific irrelevant antibody. We compared the viremia in the three groups of animals and found that the absence of Fc-domain mediated effector functions did not impair the protective effect of PGT121 antibody.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH, NIAID	**Grant number(s):** R37 AI055332

Subproject Description:

WNPRC Division-Unit	Research Services-Immunology Services	
Project Title	Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery (CHAVI-ID)	
Period of Support	7/01/2014 - 6/30/2015	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☒ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** Private Source Department of Immunology and Microbial Science
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	In this study, we will evaluate antibody responses to HIV-1 env BG505 variant-SOSIP trimer in 4 previously immunized Rhesus macaques. We will assess: (i) overall immunogenicity, (ii) immunogenicity against specific epitopes targeted by broadly-neutralizing and non-neutralizing antibodies (iii) serum neutralizing potency and cross-reactivity.	
Project Progress *(One paragraph)*	Immunology Services at the Wisconsin National Primate Research Center (WNPRC) identified 4 Indian Rhesus macaques that are included in the experiment, and performed the first two vaccinations.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** NIH	**Grant number(s):** UM AI100663-03

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery (CHAVI-ID)	
Period of Support	07/01/2014 - 06/30/2015	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☒ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** Private Source Department of Immunology and Microbial Science
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	In this study, we will evaluate antibody responses to HIV-1 env BG505 variant-SOSIP trimer in 4 previously immunized Rhesus macaques. We will assess: (i) overall immunogenicity, (ii) immunogenicity against specific epitopes targeted by broadly-neutralizing and non-neutralizing antibodies (iii) serum neutralizing potency and cross-reactivity.	
Project Progress *(One paragraph)*	We have performed the first two vaccinations on 4 Indian Rhesus macaques that are included in the experiment.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH, NIAID	**Grant number(s):** UM AI100663-03

Subproject Description:

WNPRC Division-Unit	Research Services-Immunology Services	
Project Title	Mechanisms Underlying Persistent Lentivirus Replication	
Period of Support	12/01/2012 - 11/30/2017	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☒ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** University of Colorado/Dept. Medicine University of Minnesota/Veterinary & Biomedical Sciences
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	HIV-1 is highly concentrated in follicular CD4+ T cells, which are 30 to 40 times more likely to be productively infected than extrafollicular CD4+ T cells. T follicular helper cells (TFH) are a specialized subset of antigen-specific cells that migrate into B cell follicles. Whether the follicular cells that are preferentially infected by HIV-1 are TFH is unknown. The specific aims of this proposal are: to determine susceptibility of human and rhesus macaque lymphoid tissue follicular CD4+ T cells to productive HIV/SIV infection in vitro; to determine the frequency, distribution, and phenotype of T cells that propagate lentiviruses in lymphoid tissues during acute and chronic infection in vivo; and to determine whether follicular lentivirus-specific CTL are deficient in number and/or function compared to extrafollicular CTL in vitro and in vivo.	
Project Progress *(One paragraph)*	In 2014 we analyzed data from three chronically infected Mamu-A*01+ animals. At day 59 after SIVmac239 infection we depleted the CD8+ cells. 10 days later we euthanized the animals and performed in situ hybridization, in situ tetramer staining, and immunostaining techniques to locate virus-producing cells in follicular and extrafollicular compartments of lymph nodes, spleen and GALT .	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH, NIAID	**Grant number(s):** R01 AI096966-02

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	GAMMA-2 HERPESVIRUSES AS VACCINE VECTORS FOR AIDS	
Period of Support	12/01/2004 - 11/30/2017	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☒ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** Private Source School of Medicine/Department of Microbiology
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	Results of both monkey and human trials have highlighted the difficulties in achieving vaccine protection against SIV and HIV. Persistent, recombinant herpes viruses are being used in monkeys to try to match the degree of protection that can be achieved with live attenuated strains of SIV. Results to date have been promising but the absence of anti-Env antibody responses from the recombinant herpes viruses has been a glaring deficiency. The proposed experiments with replication-competent rhesus macaque rhadinovirus (RRV) vectors will overcome this deficiency and allow full testing of the promise of this approach.	
Project Progress *(One paragraph)*	This project was moved to University of Wisconsin WNPRC in 2014 after Harvard announced plans to close the New England National Primate Research Center. Setting up the funding and obtaining IACUC protocol approval at UW took several months. At the end of 2014 several potential animals have been identified for the project by intensive screening for RRV viral free animals. Experiments will begin in early 2015.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH, NIAID	**Grant number(s):** R37 AI063928

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	IMMUNOGLOBULINS DELIVERED BY AAV VECTOR FOR THE PREVENTION OF SIV INFECTION	
Period of Support	07/18/2012 - 06/30/2016	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☒ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** Private Source School of Medicine/Department of Microbiology
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	AAV vector has recently been used to deliver single chain Fv immunoadhesin (scFVI) versions of rhesus monkey antibodies with neutralizing activity against SIV. Two different approaches will be compared for AAV vector delivery of the authentic IgG version of these scFVIs. We will determine whether delivery of authentic IgG decreases the frequency with which anti-anti responses are observed. We will determine whether AAV vector can be used to deliver dimeric secretory IgA and whether secretory IgA provides a more effective barrier to SIV infection by the mucosal route. Finally, we will determine whether antibody-dependent cellular cytotoxicity is important for the protective effects of the IgG versions of 4L6 and 5L7. Results from these experiments in rhesus monkeys will inform and guide development of analogous vectors for the prevention of HIV-1 infection in humans.	
Project Progress *(One paragraph)*	In studies previously performed at NEPRC Under Review Under Review we used AAV1 vector to deliver a rhesus anti-SIV monoclonal antibody called 4L6 to six monkeys. All six had strong immune responses to the 4L6 mAB that drove the concentration of delivered 4L6 to low levels. We have had similar problems with the 8 monkeys in Wisconsin that have received an assortment of AAV-delivered mABs for therapeutic use in SHIV-infected monkeys. We have re-engineered the 4L6 vector in ways that we think will make the delivered 4L6 less immunogenic. Specifically, we will be using a promoter for expression that is specifically active only in muscle cells and we will be including microRNA target sequences that prevent expression in dendritic cells (the professional antigen-presenting cells). We plan on initiating these new vectors in 2015.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH, NIAID	**Grant number(s):** R01 AI098446

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	SEQUENCE OF NEURONAL GENERATION IN MARMOSET VISUAL SYSTEM	
Period of Support	07/01/2014 - 06/30/2015	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☒ No ☐ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** University of Washington/Department of Ophthalmology
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	We are interested in the sequence of development of neuronal cells and subtypes in the retina, and gain detailed information on how the cone neurons pack within the retina during foveal development. We will study the sequence of cell generation and movement of retinal neurons in the marmoset monkey using the thymidine analogue, BRDU to label embryos at different ages of gestation, then collect the eyes from infant twins, one approximately 1-3 days postnatal and the other at approximately 8 weeks of age.	
Project Progress *(One paragraph)*	We injected two marmoset dams, one at fetal gestation day 75 and another at fetal gestation day 80. Both dams are due in February 2015 (FD 75 is due with quadruplets and FD 80 is due with twins). We also plan to inject a dam in 2015 at fetal gestation day 72-73.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** University of Washington/Department of Ophthalmology funds	**Grant number(s):** PRJ89BX

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	SIMIANIZING HEPATITIS C: DEFINING THE SPECIES-TROPISM OF A HEPATOTROPIC VIRUS	
Period of Support	07/01/2010 - 06/30/2015	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☒ No ☐ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** Private Source Department of Immunology, Virology and Microbiology
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	Hepatitis C virus (HCV) is a leading cause of liver disease including cancer. The development of effective drugs or a vaccine against hepatitis C virus (HCV) has been severely hampered by the lack of a suitable animal model for HCV infection.This grant aims to create a NHP model for HCV infections and thus open new avenues to develop more effective treatments aimed at eradicating this deadly viral disease. We have adapted HCV for replication in rhesus macaque hepatocytes (liver cells) by passage in immunodeficient mice engrafted with rhesus macaque liver tissue. We now plan to inoculate immunosuppressed rhesus macaques with this virus to allow it to further adapt to this species in a subaward to the University of Wisconsin in 2014.	
Project Progress *(One paragraph)*	Three immunosuppressed rhesus macaques were infected with HCV to allow it to further adapt to this species. To achieve effective immune suppression, innate immunity will be impaired by RNA interference (RNAi) and adaptive immunity will be impaired by pharmacological depletion of lyphocytes by treatment with cyclophosphamide or a combination of anti-thymocyte globulin (ATG), mycophenolate mofetil (MMF) and tacrolimus (Tac). We monitoried immune status at baseline and during immunosupression and also measured protein expression after HCV challenge. Liver biopsies were collected at approximately 8 and 16 weeks after HCV inoculation to monitor virus replication in tissues. The animals were euthanized for necropsy and tissuecollection 26 to 52 weeks after HCV infection. Although we could not measure in infection in the blood samples, tissue analysis after necropsy did indicate that the animals were infected with HCV.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH, NIAID	**Grant number(s):** R01 AI090055

Subproject Description:

WNPRC Division-Unit	Research Services-Immunology Services	
Project Title	Proprietary Info	
Period of Support	11/01/2011 - 7/31/2014	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☒ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** Private Source Department of Immunology and Microbial Science
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	Proprietary Info	
Project Progress *(One paragraph)*	Proprietary Info	
Proprietary Info	Group 1 Group 2 Group 3	Proprietary Info
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** Private Source	**Grant number(s):**

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	Proprietary Info	
Period of Support	01/01/2014 - 07/31/2014	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☒ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** Private Source Department of Immunology and Microbial Science
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	Proprietary Info	
Project Progress *(One paragraph)*	Proprietary Info Group 1 Proprietary Info Proprietary Info Group 2 Group 3	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** Private Source	**Grant number(s):**

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	THE ROLE OF MYELOID CELLS IN VIRAL REPLICATION, PERSISTENCE AND NEUROINVASION	
Period of Support	08/01/2011 - 04/30/2016	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☒ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** Private Source School of Medicine/Department of Medicine
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	Research over the past several years has highlighted that mammalian cells are not passive to infection by primate lentiviruses such as HIV-1. Rather, some proteins within mammalian cells potently antagonize the replication of primate lentiviruses. As a consequence, primate lentiviruses have evolved counter defenses in order to circumvent these "cellular restrictions". We have evidence for the existence of a novel cellular restriction that is specifically expressed by myeloid lineage cells such as macrophages. In this project we propose to identify the nature of the cellular restriction, the mechanism by which it antagonizes primate lentivirus replication and the role it plays in the establishment of myeloid cell reservoirs in vivo. Information gathered from this study will reveal new drug targets with which to prevent the establishment of myeloid cell reservoirs by primate lentiviruses thereby decreasing the ability of these viruses to persist within the host.	
Project Progress *(One paragraph)*	This R01 was moved to University of Wisconsin WNPRC in August 2014 after Harvard announced plans to close the New England National Primate Research Center. Setting up the subaward and obtaining IACUC protocol approval at UW took several months. We plan to start experiments in 2015.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH, NIMH	**Grant number(s):** R01 MH093306

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	PRECLINICAL DEVELOPMENT OF HIV-1 VIF ANTAGONISTS - PROJECT 3	
Period of Support	08/01/2014 - 07/31/2018	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☒ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** Private Source School of Medicine/Department of Medicine
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):** Excluded by Requester	**Affiliate Institution(s) & Department(s):** University of California San Diego/Department of Pediatrics
Principal Core Scientist Associated with Project		
Project Description *(One paragraph)*	Despite the widespread use of anti-retroviral therapy in AIDS patients, the prevalence of HIV-Associated Neurocognitive Disorders (HAND), including Asymptomatic Neurocognitive Impairment (ANI), Mild Neurocognitive Disorder (MND), and HIV-Associated Dementia (HAD), remains significantly high. Even mild forms of neurocognitive impairment may impact quality of life and antiretroviral drug adherence in H1V+ individuals [redacted] 2004). The re[redacted] Excluded by Requester CNS complications may develop or persist in treated individuals is not kno[redacted] but failure to eliminate viral reservoirs and inadequate drug penetration to the CNS could play a role in allowing low level viral replication to persist. Project 3 will carry out proof-of-concept studies in nonhuman primates to test novel anti-Vif candidate drugs in support of efforts to accelerate basic and translational discoveries toward the advancement of new drug therapeutics for HAND. HIV-1 Vif is a highly attractive yet unrealized therapeutic target for the intervention of HIV-1 replication. HIV-1 Vif is essential for primate lentivirus replication in vitro. We have identified a lead Vif antagonist (RN18) that exhibits exquisite antiviral specificity against Vif-dependent viral replication. We plan to evaluate the in vivo efficacy ofthe most promising RN18 analogs in proof-of principal studies in a simian model of neuroAIDS. Vif antagonists with the most desirable antiviral activities, validated mechanism of action (Projects 1 and 2), and acceptable toxicity and pharmacokinetic profiles in rodents will be examined for in vivo antiviral activity in a monkey model of SIV. We anticipate in vivo analysis of 2-3 Vif antagonists/year in groups of 6 animals each.	

Project Progress *(One paragraph)*	Project 3 of this P01 was moved to University of Wisconsin WNPRC in August 2014 with Excluded by Requester as PI after Harvard announced plans to close the New England National Primate Research Center and [redacted] moved to [redacted]. The P01 group met with the Scientific Advisors at NIH in July 2014 to discuss plans for experiments. Setting up the subaward and obtaining IACUC protocol approval at UW took several months. The actual experiments are anticipated to begin in 2015.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH, NIMH	**Grant number(s):** P01 MH100942

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	PRECLINICAL DEVELOPMENT OF HIV-1 VIF ANTAGONISTS	
Period of Support	04/16/2007 - 3/31/2015	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☒ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** Private Source School of Medicine/Department of Medicine
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):** Excluded by Requester	**Affiliate Institution(s) & Department(s):** University of California San Diego/Department of Pediatrics
Principal Core Scientist Associated with Project		
Project Description *(One paragraph)*	The project proposes the identification and preclinical development of novel small molecule antagonists of the Vif protein of HIV-1. Apobec 3G is a cytidine deaminase which potently antagonizes HIV-1 infection. To counteract this cellular restriction, primate lentiviruses such as HIV-1 have evolved a Vif protein, the function of which is to target apobec for proteasomal destruction. Viruses containing mutations in Vif are severely compromised in vitro and in vivo. Therefore, Vif is a critical, yet unrealized, therapeutic target. Two lead compounds that block Vif-mediated apobec destruction have been identified. These compounds inhibit HIV- 1 replication only in the presence of apobec and as such, are bona fide Vif inhibitors. This provides proof-of-principle that novel inhibitors of the HIV-1 Vif protein can be identified. This program project application will combine individuals with expertise in drug discovery, HIV-1 virology and SIV immunopathogenesis for the preclinical development of novel antagonists of HIV-1 Vif. The program project comprises: Project 1, Vif antagonists: lead inhibitor identification and SAR analysis. Project 2, Vif antagonists: evaluation of antiviral activity and mechanism of action in vitro. Mechanisms of inhibitor resistance in vitro and in vivo. Project 3, Vif-antagonists: evaluation in chronic SIV infection model. Through this program project, we propose the preclinical development of a new class of compounds that antagonize HIV-1 and SIV Vif and which will be used to assess the consequences of Vif antagonism in lymphoid and CNS reservoirs of viral replication in vivo.	

Project Progress *(One paragraph)*	Project 2 of this U19 was moved to University of Wisconsin WNPRC in April 2014 after Harvard announced plans to close the New England National Primate Research Center. Setting up the subaward and obtaining IACUC protocol approval at UW took several months. We identified 4 rhesus macaques that have SIV viral infections with a viral burden that is moderate to low that are now assigned to the project. Plans to treat the monkeys with two promising anti-Vif compounds were underway and delayed due to getting a materials tranfer agreement set up between the University of California San Diego and the University of Wisconsin. The compounds will be tested on these 4 macaques in early 2015.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH, NIMH	**Grant number(s):** U19 MH081836

Subproject Description:

WNPRC Division-Unit	Research Services-Immunology Services	
Project Title	Can vaccine-induced CD8 T cells prevent chronic phase AIDS virus replication?	
Period of Support	1/01/2014 – 12/31/2018	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☒ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** Private Source Medical School/Department of Pathology
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	Vaccines developed between 2000 and 2010 and tested in the macaque-SIV (Simian Immunodeficiency Virus) model reduced virus replication, but did not achieve reduction of virus replication below detection level. New results using several new vaccine vectors suggest that suppressing SIV proliferation below detection level may be possible. The mentioned vaccinations used a large portion of the SIV virus proteins to elicit immune responses. The construction of a vaccine, containing multiple, large virus proteins is extremely expensive. Therefore in this project we wish to test whether suppression of SIV proliferation below detection level is possible with a novel vaccine regimen that contains only a small fraction of the AIDS virus.	
Project Progress *(One paragraph)*	We have finished the vaccination regimen of 16 Mamu-B*08 positive rhesus macaques. The regimen included a prime with DNA plasmids, and boosts with rAd5, rVSV and rRRV vectors containing SIV Nef, Vif, and Tat/Rev antigens. RRV is a gamma-2 herpesvirus that persistently infects rhesus monkeys and thereby promotes life-long antigen stimulation. RRV was discovered Excluded by Requester Excluded by Requester who agreed to provide the rRRV vectors needed for the completion of our experiment.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH, NIAID	**Grant number(s):** R01 AI108421

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	Can vaccine-induced CD8 T cells prevent chronic phase AIDS virus replication?	
Period of Support	01/01/2014 - 12/31/2018	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☒ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** Private Source Medical School/Department of Pathology
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	Vaccines developed between 2000 and 2010 and tested in the macaque-SIV (Simian Immunodeficiency Virus) model reduced virus replication, but did not achieve reduction of virus replication below detection level. New results using several new vaccine vectors suggest that suppressing SIV proliferation below detection level may be possible. The mentioned vaccinations used a large portion of the SIV virus proteins to elicit immune responses. The construction of a vaccine, containing multiple, large virus proteins is extremely expensive. Therefore in this project we wish to test whether suppression of SIV proliferation below detection level is possible with a novel vaccine regimen that contains only a small fraction of the AIDS virus.	
Project Progress *(One paragraph)*	We have finished the vaccination regimen of 16 Mamu-B*08 positive rhesus macaques. The regimen included a prime with DNA plasmids, and boosts with rAd5, rVSV and rRRV vectors containing SIV Nef, Vif, and Tat/Rev antigens. RRV is a gamma-2 herpesvirus that persistently infects rhesus monkeys and thereby promotes life-long antigen stimulation. RRV was discovered Excluded by Requester who agreed to provide the rRRV vectors needed for the completion of our experiment. Excluded by Requester	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH, NIAID	**Grant number(s):** R01 AI108421

Subproject Description:

WNPRC Division-Unit	Research Services-Immunology Services	
Project Title	The Functional Significance of CTL Escape	
Period of Support	4/01/2002 – 6/30/2018	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☒ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** Private Source Medical School/Department of Pathology
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	CD8+ T cells have been known to play a role in the containment of HIV and SIV infections for quite some time. Indian rhesus macaques vaccinated with minigenes that express three Mamu-B*08-restricted CD8+ T cell epitopes, located in two early expressed viral proteins Vif and Nef controlled initial replication of the highly pathogenic SIVmac239 virus. We published our findings in Excluded by Requester et al. Nature 2012. 491(7422): 129-133. The hypothesis tested in the current project is that Vif and Nef specific CD8+ T cells elicited by a novel, persistent Rhesus Rhadinovirus vector can protect Mamu-B*08 MHC-I allele positive animals against mucosal SIVmac239 challenge.	
Project Progress *(One paragraph)*	Two groups of eight Mamu-B*08 positive Indian Rhesus macaques were vaccinated against a portion (aa 45-210) of SIVmac239 Nef using an rAd5 prime/ VSV and RRV boost immunization regimen. One group of the animals was vaccinated with vectors containing SIVmac239 Nef and Vif genes, the other group was vaccinated with vectors containing no SIVmac239 genes. We will challenge all animals repeatedly with low dose SIVmac239 intrarectally.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH, NIAID	**Grant number(s):** R37 AI052056

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	The Functional Significance of CTL Escape	
Period of Support	04/01/2002 - 06/30/2018	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☒ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** Private Source Medical School/Department of Pathology
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	Ongoing investigations on vaccine-induced CDS* T cells against Nef epitope in control of replication of AIDS virus in the Mamu-B*08 model of HIV Elite Control. The hypothesis tested in the current project is that Vif and Nef specific CD8+ T cells elicited by a novel, persistent Rhesus Rhadinovirus vector can protect Mamu-B*08 MHC-I allele positive animals against mucosal SIVmac239 challenge.	
Project Progress *(One paragraph)*	Two groups of eight Mamu-B*08 positive Indian Rhesus macaques were vaccinated against a portion (aa 45-210) of SIVmac239 Nef using an rAd5 prime/ VSV and RRV boost immunization regimen. One group of the animals was vaccinated with vectors containing SIVmac239 Nef and Vif genes, the other group was vaccinated with vectors containing no SIVmac239 genes. We will challenge all animals repeatedly with low dose SIVmac239 intrarectally.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH, NIAID	**Grant number(s):** R37 AI052056

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	VECTORS FOR AIDS VACCINE IMMUNITY	
Period of Support	07/01/2014 - 06/30/2017	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☒ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** Private Source Medical School/Department of Pathology
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester - PI on Animal Core Project	
Project Description *(One paragraph)*	Finding a vaccine for HIV is probably one of the most important goals of biomedical research. SIV challenge of vaccinated Indian rhesus macaques is one of the best defined models available for pre-clinical development of HIV vaccines. The personnel of the Animal Core have extensive experience caring for SIV infected macaques and supporting investigators working with the SIV macaques model of HIV infection. Performance of the entire in-vivo NHP component of this grant proposal by the WNPRC Animal Core will allow the investigators to fully focus their attention on the in-vitro aspects of their projects. The six aims of this Core will be as follows: 1) To provide healthy, genetically characterized rhesus macaques for the projects outlined in this application. 2) To provide contemporary, well-equipped experimental facilities for the performance of the husbandry, clinical, experimental, and necropsy procedures outlined in this application. 3) To provide expert husbandry, veterinary, and technical assistance necessary to support and maintain the SIV infected animals utilized on this project. 4) To ensure compliance with all university and federal regulations regarding the use of NHP in biomedical research. 5) To provide the specialized environmental enrichment needed to maintain the psychological well being of the SIV infected macaques that will be utilized in the proposed projects. 6) To obtain quality biological samples from the experimental animals to fulfill the objectives of the individual projects.	

Project Progress *(One paragraph)*	Continuing experiments include vaccinations for groups 1-9 and adding new groups 11-13 in 2014. The rRRV vaccination material was delayed in production, but continued the rAd5 and rVSV vaccinations, with the rRRV vaccinations occuring later in the year. Vaccinations included both intrarectal and IV modalities. All groups vaccinated by the end of 2014 in the anticipation of beginning the repeated low dose SIV intrarectal challenges in 2015.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, NIH, NIAID	**Grant number(s):** P01 AI094420 (HIVRAD)

Subproject Description:

WNPRC Division-Unit	Research Services-Immunology Services	
Project Title	Yellow Fever, rDNA (EP+IL-12) and rAd35 as Vectors for AIDS Vaccine Development (HIVRAD)	
Period of Support	7/01/2012 - 6/30/2017	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☒ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** Private Source Medical School/Department of Pathology
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	The central hypothesis of this proposal that a recombinant yellow fever vaccine (rYF) or rDNA (delivered by electroporation along with IL-12; EP+IL-12) prime followed by a recombinant adenovirus boost can control viral replication after either a homologous or heterologous AIDS virus challenge. This hypothesis will be tested in macaques using rigorous challenges with highly pathogenic SIV isolates.	
Project Progress *(One paragraph)*	Immunology Services (IS) of the Wisconsin National Primate Research Center (WNPRC) has supported the preparations of vaccine inocula, and viral challenges, processed plasma samples for viral load quantification, and has shipped the samples to Excluded by Requester of NCI and Excluded by Requester of the Private Source School of Medicine.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH, NIAID	**Grant number(s):** P01 AI094420-03

Subproject Description:

WNPRC Division-Unit	Research Services-Immunology Services		
Project Title	Proprietary Info		
Period of Support	8/1/2014 - 7/31/2015		
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____		
AIDS Research *(No or Yes)*	☐ No ☒ Yes		
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** Private Source Medical School/Department of Pathology	
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**	
Principal Core Scientist Associated with Project	Excluded by Requester		
Project Description *(One paragraph)*	Proprietary Info		
Project Progress *(One paragraph)*	Proprietary Info		
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** Private Source	**Grant number(s):** N/A	

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	Proprietary Info	
Period of Support	08/01/14 - 07/31/15	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☒ No ☐ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** Private Source Medical School/Department of Pathology
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	Proprietary Info	
Project Progress *(One paragraph)*	Proprietary Info	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** Private Source	**Grant number(s):** N/A

Subproject Description:

WNPRC Division-Unit	Research Services-Immunology Services	
Project Title	Proprietary Info	
Period of Support	5/1/2014 - 7/31/2015	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☒ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** Private Source Medical School/Department of Pathology
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	Proprietary Info	
Project Progress *(One paragraph)*	Proprietary Info	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** Private Source	**Grant number(s):** N/A

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	Proprietary Info	
Period of Support	05/01/14 - 7/31/2015	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☒ No ☐ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** Private Source Medical School/Department of Pathology
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	Proprietary Info	
Project Progress *(One paragraph)*	Proprietary Info	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** Private Source	**Grant number(s):** N/A

Subproject Description:

WNPRC Division-Unit	Research Services-Immunology Services	
Project Title	A Novel, Logical Approach to HIV Vaccine Development	
Period of Support	3/15/2001 - 8/31/2014	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☒ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** Private Source Medical School/Department of Pathology
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	It is well known that antigen-specific CD8 T cells have a key role in controlling AIDS virus proliferation in vivo. However, envelope-specific antibodies have a critical role in protection against virus transmission. In the current project we investigate whether a DNA prime/recombinant Rhesus RhadinoVirus boost vaccine regimen against the viral proteins Vif, Nef and Env will increase the resistance against virus transmission with low-dose intrarectal SIVmac239 challenge and/or increase the number of elite controller animals in Mamu-B*17 positive macaques. rRRV vaccine viruses replicate indefinitely in the host. This type of antigen stimulation induces potent effector memory T-cell responses that can mediate immediate antiviral activity. Therefore, using rRRV to boost SIV-specific cellular immune responses in our current experiment will not only make it novel but it will also increase the likelihood of a positive outcome after challenge with the pathogenic SIVmac239 clone.	
Project Progress *(One paragraph)*	We have finished the vaccination regimen of 24 Mamu-B*17 positive rhesus macaques. The regimen included a boost of our cohort of animals with replication-competent rhesus macaque rhadinovirus (RRV) vectors encoding SIV Nef, Vif and Env antigens. RRV is a gamma-2 herpesvirus that persistently infects rhesus monkeys and thereby promotes life-long antigen stimulation. RRV was discovered by Excluded by Requester who agreed to provide the rRRV vectors needed for the completion of our experiment.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH, NIAID	**Grant number(s):** R56 AI049120

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	A Novel, Logical Approach to HIV Vaccine Development	
Period of Support	03/15/2001 - 08/31/2014	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☒ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** Private Source Medical School/Department of Pathology
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	It is well known that antigen-specific CD8 T cells have a key role in controlling AIDS virus proliferation in vivo. However, envelope-specific antibodies have a critical role in protection against virus transmission. In the current project we investigate whether a DNA prime/recombinant Rhesus RhadinoVirus boost vaccine regimen against the viral proteins Vif, Nef and Env will increase the resistance against virus transmission with low-dose intrarectal SIVmac239 challenge and/or increase the number of elite controller animals in Mamu-B*17 positive macaques. rRRV vaccine viruses replicate indefinitely in the host. This type of antigen stimulation induces potent effector memory T-cell responses that can mediate immediate antiviral activity. Therefore, using rRRV to boost SIV-specific cellular immune responses in our current experiment will not only make it novel but it will also increase the likelihood of a positive outcome after challenge with the pathogenic SIVmac239 clone.	
Project Progress *(One paragraph)*	We have finished the vaccination regimen of 24 Mamu-B*17 positive rhesus macaques. The regimen included a boost of our cohort of animals with replication-competent rhesus macaque rhadinovirus (RRV) vectors encoding SIV Nef, Vif and Env antigens. RRV is a gamma-2 herpesvirus that persistently infects rhesus monkeys and thereby promotes life-long antigen stimulation. RRV was discovered by Excluded by Requester who agreed to provide the rRRV vectors needed for the completion of our experiment.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH, NIAID	**Grant number(s):** R56 AI049120

Subproject Description:

WNPRC Division-Unit	Research Services-Immunology Services	
Project Title	MHC-bound, SIV-derived, CTL and HTL Epitopes	
Period of Support	7/01/2000 – 6/30/2015	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☒ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** Private Source Medical School/Department of Pathology
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	Definition of new CTL and HTL epitopes is critical to the construction of MHC class I, and II tetramer complexes, and to improve our ability to measure antigen-specific T cell responses. The aim of this project is to map SIV-specific epitopes. The project utilizes samples from Rhesus macaques that had already been infected in other AIDS-related experiments. WNPRC ships fresh or frozen samples to Excluded by Requester Excluded by Requester of the Private Source Medical School for further studies.	
Project Progress *(One paragraph)*	In the current period WNPRC sent more than 110 samples from different SIV-infected Indian rhesus macaques. The plasma viral burden of these animals was monitored and made available to Excluded by Requester regularly by the Elite Controller Resource Unit at WNPRC. Blood samples were used to detect the presence of antigen-specific responses, create CD4+ and CD8+ T cell lines, perform confirmatory tetramer, and ICS assays, and to develop new in vitro assays.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH	**Grant number(s):** R24 OD011088

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	MHC-bound, SIV-derived, CTL and HTL Epitopes	
Period of Support	07/01/2000 - 06/30/2014	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☒ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** Private Source Medical School/Department of Pathology
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	SIV challenge of vaccinated Indian rhesus macaques is the best-defined model available for pre-clinical development of HIV vaccines. Identification of MHC alleles and SIV-specific epitopes is critical in the definition of the immune response in this important biomedical system. The aim of this project is to map SIV-specific epitopes. The project utilizes samples from rhesus macaques that had already been infected in other AIDS-related experiments. WNPRC ships fresh or frozen samples to Excluded by Requester of the Private Source Medical School for further studies.	
Project Progress *(One paragraph)*	In the current period WNPRC sent more than 110 samples from different SIV-infected Indian rhesus macaques. The plasma viral burden of these animals was monitored and made available [redacted] regularly by the Elite Controller Resource Unit at WNPRC. Blood samples were used to detect the presence of antigen-specific responses, create CD4+ and CD8+ T cell lines, perform confirmatory tetramer, and ICS assays, and to develop new in vitro assays. Excluded by Requester	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH, NIAID	**Grant number(s):** R24 RR015371

Internal Subprojects Supported by WNPRC, 1/1/2014 - 12/31/14

RESEARCH

University of Wisconsin-Madison Department	Principal Investigator(s)	Project Title	AIDS Research? (Y/N)
Medical Physics	Excluded by Requester	Activation of PPAR-GAMMA in a monkey model of cardiac dysautonomia	N
Pathology & Laboratory Medicine		Lentiviral Resistance to Tetherin	Y
Pathology & Laboratory Medicine		KIR and MHC class I immunogenetics in SIV infection	Y
Wisconsin National Primate Research Center, SVM, Pathology, NIH integrated research facility		Develop new culture methods and new molecular diagnostics to facilitate virological research in nonhuman primates	N
Wisconsin National Primate Research Center, Johns Hopkins		Adapt co-culture method for virus outgrowth as a means for measuring the latent reservoir of SIV	Y
Pathobiological Sciences & Pathology		Defining the importance of CD8+ T cell breadth in SIV/HIV protective immunity	Y
Pathobiological Sciences		Correlates of broadly cross-protective immunity against influenza	N
Comparative Biosciences		Mechanisms of listeria-induced pregnancy loss	N
Comparative Biosciences		Primate placental MHC immunogenetics	N
Comparative Biosciences		Development of a transgenic monkey core at WNPRC	N
Comparative Biosciences, Department of Medical Physics		Development of marmoset assisted reproductive techniques	N
University of Wisconsin, Medicine and Arrowhead Madison, Inc.		Delivery of Small Interfering RNA to Primates	N
Department of Medical Physics, University of Utah-Obstetrics/Gynecology		Monitoring changes in cervical microstructure during pregnancy	N
Surgery/Transplant		Tomotherapy and hematopoetic cells for tolerance to kidney transplants	N
Wisconsin National Primate Research Center		Collection of exome sequences from 4 macaques and genome sequences from 4 macaques	Y
Wisconsin National Primate Research Center		Sequencing 15 SIV, influenza and dengue virus genomes per year	Y
Wisconsin National Primate Research Center		Generation of a multiplexed assay to genotype 12 immune and host restriction loci	Y

University of Wisconsin-Madison Department	Principal Investigator(s)	Project Title	AIDS Research? (Y/N)
Pathology & Laboratory Medicine	Excluded by Requester	Adoptive transfer of immunity elicited by attenuated HIV vaccines	Y
Pathology & Laboratory Medicine		Evaluating immunity elicited by CD8 T cell responses targeting invariant epitopes	Y
Neuroscience		Individualized cell therapy for Parkinson's disease	N

PILOTS

University of Wisconsin-Madison Department	Principal Investigator(s)	Project Title	AIDS Research? (Y/N)
Comparative Biosciences	Excluded by Requester	Transgenic marmosets for translational research	N
Pathology & Laboratory Medicine		MHC-Defined nonhuman primate model for bone marrow transplantation	Y
University of Minnesota, Microbiology; Wisconsin National Primate Research Center		Therapeutic vaccination during SIV infection	Y

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	ACTIVATION OF PPAR-GAMMA IN A MONKEY MODEL OF CARDIAC DYSAUTONOMIA	
Period of Support	04/15/2014 - 03/31/2016	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☒ No ☐ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** University of Wisconsin/Department of Medical Physics
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	Nonmotor symptoms of Parkinson's disease (PD), such as cardiac autonomic dysfunction (dysautonomia), greatly affect patients' quality of life. They are frequently unrecognized as PD symptoms, many times undiagnosed and overall poorly managed, as they do not respond to typical anti-parkinsonian therapies. We have developed a nonhuman primate (NHP) model of cardiac dysautonomia by intravenous delivery of the neurotoxin 6-OHDA and developed a battery of tests to characterize the model. We have also demonstrated that oral dosing of the peroxisome proliferator activator receptor gamma (PPAR gamma) agonist pioglitazone modulates inflammation and oxidative stress, inducing neuroprotection in a NHP model of PD with typical nigrostriatal degeneration. Based on these studies we hypothesize that pioglitazone can be neuroprotective in the NHP model of cardiac dysautonomia and that the therapeutic effects are mediated via a reduction in inflammation and oxidative stress. We will evaluate whether chronic oral dosing of the PPAR gamma agonist pioglitazone prevents 6-OHDA-induced peripheral catecholaminergic neurodegeneration and downregulates mechanisms of inflammation and oxidative stress in a NHP model of cardiac dysautonomia. We will use state-of-the-art PET imaging and radioligands to evaluate in vivo cardiac markers of catecholaminergic innervation ([C11]MHED), inflammation ([C11]PK11195) and oxidative stress ([61/64Cu]ATSM) before and after treatments. We will correlate the imaging data with clinical measures (ECG, blood pressure, activity), circulating metabolites (e.g.: catecholamines, cytokines and PGCα-1) and morphological data (e.g.: regional myocardial quantification of TH, HLA-DR, nitrotyrosine and alpha synuclein expression), to analyze how the different measures relate to catecholaminergic loss and preservation. These technologies will allow us to evaluate mechanisms of neurodegeneration and neuroprotection while validating biomarkers for clinical application.	

Project Progress *(One paragraph)*	First cohort of animals received baseline MRI and PET scans, treated with 6-OHDA, divided into treatment groups, and monitored by the various PET ligands, activity, EKG, and clinical rating through the remainder of 2014. A second cohort will begin in 2015.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH, Neuroscience	**Grant number(s):** R21NS084158

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	LENTIVIRAL RESISTANCE TO TETHERIN	
Period of Support	02/01/2012 - 01/31/2017	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☒ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** University of Wisconsin/Department of Pathology and Laboratory Medicine
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	Tetherin (BST-2 or CD317) is a component of innate immunity that inhibits virus release from infected cells. The goal of this proposal is to understan the mechanisms of HIV and SIV resistance to tetherin. A better understanding of the mechanisms used by AIDS viruses to overcome tetherin may lead to the development of novel antiretroviral drugs to enhance the ability of this factor to suppress HIV replication.	
Project Progress *(One paragraph)*	Excluded by Requester moved his laboratory and animals from Harvard and NENPRC to the University of Wisconsin and WNPRC in early 2014. We have taken over the animal portion of the experiments.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH, NIAID	**Grant number(s):** R01 AI098485

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	KIR AND MHC CLASS I IMMUNOGENETICS IN SIV INFECTION	
Period of Support	11/14/2011 - 10/31/2016	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☒ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** University of Wisconsin/Department of Pathology and Laboratory Medicine
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	We have identified an interaction between an inhibitory killer immunoglobulin-like receptor (KIR) on natural killer (NK) cells and a common MHC class I molecule in the rhesus macaque that is modulated by simian immunodeficiency virus (SIV) peptides. We will use KIR- and MHC class I-defined rhesus macaques to determine how this interaction affects the outcome of immunodeficiency virus infection, and to specifically address the role of viral peptides in modulating NK cell activation as a mechanism of immune evasion.	
Project Progress *(One paragraph)*	Excluded by Requester moved his laboratory and animals from Harvard and the NENPRC to the University of Wisconsin and WNPRC in early 2014. We have taken over the animal portion of the experiments.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH, NIAID	**Grant number(s):** R01 AI095098

Subproject Description:

WNPRC Division-Unit	Research Services-Virology Services	
Project Title	Develop new culture methods and new molecular diagnostics to facilitate virological research in nonhuman primates, to be deployed as future services.	
Period of Support	1/1/2014 - 12/31/2014	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☒ No ☐ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** Wisconsin National Primate Research Center
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):** Excluded by Requester	**Affiliate Institution(s) & Department(s):** Dept. of Pathobiological Sciences, University of Wisconsin School of Veterinary Medicine NIH Integrated Research Facility Wisconsin National Primate Research Center
Principal Core Scientist Associated with Project		
Project Description *(One paragraph)*	The objective of this project is to establish novel molecular diagnostic assays and culture conditions for new viral targets. Once established, these assays and culture procedures will be offered to clients on a fee-for-service basis. Our focus is primarily on emerging and re-emerging pathogens that infect nonhuman primates. We anticipate that this service will be attractive for the growing number of investigators studying pathogenesis and vaccine development for diverse viral pathogens, and also for managers of primate colonies.	
Project Progress *(One paragraph)*	In 2014 we performed the molecular diagnostic assay that we developed for the recently discovered SHFV-krc1 and SHFV-krc2 viruses for several investigators. We are currently developing a new molecular diagnostic assay to quantify the LVR virus from macaques infected in the laboratory. This assay will be used by Excluded by Requester to follow up on in vivo experiments he performed using this virus. Furthermore we are currently working on sequencing both the LVR virus and SHFV-krc1 from laboratory infected macaques from the same experiment. In addition with have consulted with a member of Excluded by Requester lab on development of a novel assay for detecting and quantifying GB virus C.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH	**Grant number(s):** P51 OD011106

Subproject Description:

WNPRC Division-Unit	Research Services-Virology Services	
Project Title	Adapt co-culture method for virus outgrowth as a means for measuring the latent reservoir of SIV, to be deployed as future service.	
Period of Support	1/1/2014 - 12/31/2014	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☒ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** Wisconsin National Primate Research Center
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):** Excluded by Requester	**Affiliate Institution(s) & Department(s):** Department of Medicine, Private Source Private Source School of Medicine
Principal Core Scientist Associated with Project		
Project Description *(One paragraph)*	There is a growing interest in the latent reservoir of HIV and SIV. In order to facilitate research in this area we plan to offer as fee-for-service an assay to detect this reservoir. We aim to adapt a viral co-culture method for detecting the presence of integrated provirus that retains the potential to reactivate. We anticipate that there will be growing interest in this assay from researchers interested in cure research and vaccine studies.	
Project Progress *(One paragraph)*	Currently the most sensitive assay for detecting latent virus that has the potential to reactivate is through a co-culture method where cells are stimulated, then cultured for 1-2 weeks and monitored for the outgrowth of HIV/SIV. We have been working in collaboration with the Excluded by Requester labs (who developed the current quantitative-outgrowth viral reservoir assays) to adapt this method in our lab. We have been successful in detecting and quantifying replication-competent virus from elite controller animals, whose plasma viral load is below the limit of detection. We are currently working on standardizing the method and determining the sensitivity of this assay. We plan to deploy the assay as fee-for service early in 2015.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH	**Grant number(s):** P51 OD011106

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	DEFINING THE IMPORTANCE OF CD8+ T CELL BREADTH IN SIV/HIV PROTECTIVE IMMUNITY	
Period of Support	09/15/2009 - 08/30/2015	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☒ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** University of Wisconsin/Department of Pathobiological Sciences
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):** Excluded by Requester	**Affiliate Institution(s) & Department(s):** University of Wisconsin/Department of Pathology and Laboratory Medicine
Principal Core Scientist Associated with Project		
Project Description *(One paragraph)*	Many T cell based vaccines against human immunodeficiency virus (HIV) are in clinical trials and yet a promising study was canceled in 2007 after showing no evidence of protection, underscoring how little is known about the nature of protective T cell responses against HIV. Mauritian cynomolgus macaques (MCM) infected with simian immunodeficiency virus (SIV) offer unprecedented opportunities for understanding protective T cell responses because of their very simple genetics, which allows investigators to identify groups of animals who will mount predictable T cell responses against SIV and use these animals to advance our understanding of T cell immunity to HIV and SIV. We hypothesize that the HIV vaccines tested so far have not been successful at least partially due to their failure to elicit a broad repertoire of T cell specificities. Our experiments rely on groups of MCM that are either homozygous or heterozygous for major histocompatibility complex (MHC) class I genes that present SIV-derived peptides to T cells. After infecting MHC homozygous and heterozygous MCM with pathogenic SIV, we wil; monitor SIV disease progression, the number of recognized T cell epitopes, and virus evolution. We anticipate that MHC homozygous animals will recognize fewer SIV CD8+ T cell peptides than MHC heterozygous MCM, and that this will result in higher viral burdens in the homozygous animals. Next, we will produce a strain of SIV where the T cell epitopes that are normally recognized during SIV infection are "knocked out" and ask whether this virus can be effectively controlled by the immune systems of MCM. Lastly, we will immunize MCM with a weakened vaccine strain of SIV that elicits potent immune responses. The MCM will be challenged with the "knockout" strain of SIV that does not contain specific T cell epitopes. Since the vaccine and challenge viruses will differ primarily within defined T cell epitopes, this experiment will determine how important broadly directed T cell responses are to the impressive control afforded by attenuated SIV.	

	Taken together, these experiments will fundamentally advance our understanding of the importance of T cell breadth in control of HIV and SIV, and help determine whether eliciting a broad CD8+ T cell "repertoire" should be a major goal for HIV vaccines.	
Project Progress *(One paragraph)*	Publication in 2014: [redacted] et al. Whole genome sequencing of SIV-infected macaques identifies candidate loci that may contribute to host control of virus replication. Genome Biol. 2014; 15(11): 478. PMCID: PMC4223156.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH, NIAID	**Grant number(s):** R01 AI084787

Excluded by Requester

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	Correlates of broadly cross-protective immunity against influenza	
Period of Support	07/01/2014 - 02/28/2015	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☒ No ☐ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** University of Wisconsin/Department of Pathobiological Sciences
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):** Excluded by Requester	**Affiliate Institution(s) & Department(s):** University of Wisconsin/Department of Pathobiological Sciences
Principal Core Scientist Associated with Project		
Project Description *(One paragraph)*	There is an acute need for novel influenza vaccines that are not susceptible to the annual mutations in circulating viruses that allow them to evade previous years' vaccines. In addition, recent advances suggest that a "universal" influenza vaccine, capable of protecting against even emerging strains such as H5N1 and H7N9, might be possible. However, promising results in small animals have generally translated poorly to humans. This project supports use of nonhuman primates and associated costs (per diems, procedure costs, veterinary technician time, etc) for a study that will use novel engineered influenza vaccines designed to induce broadly cross-reactive immunity. In this pilot study we will evaluate the protective efficacy of the vaccine and identify potential "correlates of protection," that is, the specific types of immune response necessary to provide protection against influenza virus challenge. We hypothesize that antibody-mediated cellular cytotoxicity (ADCC) is a previously unappreciated correlate of broadly protective immunity against influenza, and that our vaccine will induce potent ADCC responses. We will use the results of this study as preliminary data in an NIH R01 application to more carefully explore the role of ADCC in immunity to influenza.	
Project Progress *(One paragraph)*	Animals were vaccinated in late 2014. Influenza challenges scheduled to take place in January 2015. Planned submission for grant proposal using the preliminary data from this pilot to NIH-NIAID R01: ADCC as a novel mechanism for broad immunity to influenza in 2015.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** University of Wisconsin	**Grant number(s):** N/A

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	THE MATERNAL-FETAL INTERFACE IN LISTERIA-INDUCED PREGNANCY LOSS	
Period of Support	08/04/2014 - 07/31/2018	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☐ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** University of Wisconsin/Department of Comparative Biosciences
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):** Excluded by Requester	**Affiliate Institution(s) & Department(s):** University or Wisconsin/Department of Pathobiological Sciences
Principal Core Scientist Associated with Project		
Project Description *(One paragraph)*	Listeria monocytogenes is a bacterial organism which frequently contaminates the human food supply, particularly processed meats, soft cheeses and unpasteurized milk products. Infection in pregnant women causes miscarriage, stillbirth, preterm labor and neonatal infection. There is a gap in our understanding of mechanisms by which fetal loss occurs, and thus a lack of understanding of ways to address the risk which listeriosis poses for the community. This proposal will use the rhesus monkey provide a deeper understanding of the outcomes of maternal infection, defining responses among uterine immune cells, novel vascular inflammatory changes, and the risk that infection in early gestation poses for pregnancy loss. We will also provide definitive information on the impact of pregestational infection in sensitizing the maternal immune system to respond in a way which may be detrimental to pregnancy success, which is relevant for Listeria as a vaccine vector.	
Project Progress *(One paragraph)*	This grant was the outcome of the WNPRC project from 2013-2014. Two pregnancies were started in late 2014 with one dam infected with listeria in 2014 and another scheduled for early 2015.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH, NIAID	**Grant number(s):** R01 AI107157

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	PRIMATE PLACENTAL MHC IMMUNOGENETICS	
Period of Support	08/12/2013 - 7/31/2015	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☒ No ☐ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** University of Wisconsin/Department of Comparative Biosciences
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	A full understanding of the dialog between placental MHC class I molecules and specific receptors on decidual leukocytes in vivo, and their potential as therapeutic targets in cases of adverse pregnancy outcomes will require better development of appropriate animal models. We have extensively characterized the expression of Mamu-AG, a nonclassical MHC class I molecule with apparently restricted polymorphism expressed in rhesus monkey trophoblasts. We have formulated a new hypothesis that although the rhesus does not have an orthologous MHC-C locus, placental Mamu-AG will fulfill the placental role of human HLA-C. To test this hypothesis and move this important animal model forward, we propose three Specific Aims: (1) To define the polymorphism of placental MHC class I mRNAs expressed in rhesus monkey trophoblasts by high throughput pyrosequencing; (2) To define the expression of KIR and LILR mRNAs in rhesus monkey decidual and peripheral blood leukocytes using a novel pyrosequencing-based phenotyping approach; and (3) To express recombinant Fc-tagged rhesus decidual KIR/LILR receptors and use these as probes to identify candidate receptors for placental Mamu-AG. These studies propose to reframe our understanding of rhesus placental MHC expression, and move the field forward by defining the candidate receptors present on rhesus peripheral blood and decidual leukocytes. Defining the Mamu-AG receptor(s) on decidual leukocytes will strengthen interpretation of ongoing and future in vivo experiments with rhesus monkeys in the study of maternal immune recognition and response in implantation, early placental and decidual development, and fetal well-being and pregnancy outcome, as well as placental influences on the endometrial mucosal immunological environment.	

Project Progress *(One paragraph)*	SPI has coordinated rhesus macaque breeding to result in pregnancies for this project. Fetectomies are performed at selected timepoints for placental tissue analysis.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH, NIAID	**Grant number(s):** R21 AI100156

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	DEVELOPMENT OF MARMOSET ASSISTED REPRODUCTIVE TECHNIQUES	
Period of Support	07/08/2014 - 04/30/2015	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☒ No ☐ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** University of Wisconsin/Department of Biosciences
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):** Excluded by Requester	**Affiliate Institution(s) & Department(s):** University of Wisconsin/Department of Medical Physics
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	Development of clustered regularly interspaced short palindromic repeats (CRISPR) associated with CAS 9 as a better technology to alter genetic material in a primate embryo. We hope to use this new technology to insert the LRRK2 genetic mutation into marmoset embryos to create a phenotypic model of Parkinson's disease.	
Project Progress *(One paragraph)*	We have initiated LRRK2 targeting with marmoset fibroblasts and have identified cells expressing the GFP marker transgene indicating introduction of the targeting plasmid into the cells. We will analyze the currently transfected cells as well as optimize electroporation methods with the marmoset ESC and iPSC. We will continue to support the generation of IVF embryos to optimize the detection of the LRRK2 G2019S mutation introduced into individual embryos. Embryo injection with plasmid DNA will be done first to determine effectiveness of plasmid injection in Cas9 expression and editing before attempting to transfer embryos. Finally, we will establish intracytoplasmic sperm injection (ICSI) to obviate limitations in success due to occasional suboptimal fertilization rates, methods that will also be directly applicable to CRISPR/Cas9 reagent microinjection.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH, Office of Director	**Grant number(s):** P51 OD011106 Supplement

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	Transgenic marmosets for translational research	
Period of Support	07/01/2014 - 02/28/2015	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☒ No ☐ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** University of Wisconsin/Department of Comparative Biosciences University of Wisconsin/Department of Medical Physics
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):** Excluded by Requester	**Affiliate Institution(s) & Department(s):** University of Wisconsin/WNPRC
Principal Core Scientist Associated with Project		
Project Description *(One paragraph)*	The bridge funds were used to continue development of tecniques necessary for the goal of creating an LRRK2 transgenic marmoset as a new phenotype model for Parkinson's disease.	
Project Progress *(One paragraph)*	Progress was made in three aspects for developing the transgenic marmoset model: (1) for assisted reproductive technology (ART), we optimized marmoset follicular stimulation, development of in vitro, fertilized embryos to blastocyst stage, and identification of male semen paramenters necessary for good fertilization; (2) we have produced candidate marmoset induced pluripotent stem cells (iPSC) that express pluripotency markers and are able to differnetiate to neural progenitors; and (3) we have established a neurodevelopment assessment test to measure marmosets in the first month of life for comparison of the possible phenotype to normal development. In press: Development of a novel postnatal neurobehavioral scale for evaluation of common marmoset monkeys. Excluded by Requester J. American Primatology. Pilot data on ART and iPS used for submission of (1) Pending Support Pending Support Pending Support (2) Pending Support Pending Support Pending Support	
Funding Source(s) *(Include Sponsor name & complete grant number)*	University of Wisconsin-Madison, Office of the Vice Chancellor for Research and Graduate Education, Bridge funding	**Grant number(s):** PRJ79DL

Excluded by Requester

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	MONITORING CHANGES IN CERVICAL MICROSTRUCTURE DURING PREGNANCY	
Period of Support	01/15/2013 - 12-31-2017	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☒ No ☐ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** University of Wisconsin/Department of Medical Physics
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):** Excluded by Requester	**Affiliate Institution(s) & Department(s):** University of Utah/Department of Obstetrics/Gynecology
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	This is a project to develop and refine quantitative ultrasound technology for objective quantification of the microstructural changes (collagen organization and cervical softness) in the in vivo pregnant cervix in a nonhuman primate model. While microstructural change (evidenced by cervical softening and shortening) is an essential component of normal pregnancy, morbidity is likely when the cervix is too soft or short too early (preterm birth), or too firm too late (post-dates birth), and yet there are no tools to objectively quantify microstructural change. This alone makes quantification clinically useful; more critically objective description of cervical change in pregnancy is imperative to comprehensive study of abnormal birth timing, a significant public health problem.	
Project Progress *(One paragraph)*	Refinement of the ultrasound probe was the primary progress during the first part of 2014 for use in humans. Then adapting this probe to be used in monkeys required some innovative approaches, such as using the probe rectally to better access the monkey cervix. The animal portion of the work began mid-year with the first aim being to monitor cervical changes across the menstrual cycle of both nulliparous and multiparous female rhesus monkeys. This data collection is ongoing.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH, NICHHD	**Grant number(s):** R01 HD072077

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	TOMOTHERAPY AND HEMATOPOIETIC STEM CELLS FOR TOLERANCE TO KIDNEY TRANSPLANTS	
Period of Support	08/01/2012 - 07/31/2017	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☒ No ☐ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** University of Wisconsin School of Medicine and Public Health Department of Surgery
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):** Excluded by Requester	**Affiliate Institution(s) & Department(s):** University of Wisconsin SMPH Departments of Surgery and Medicine University of Wisconsin SVM Private Source
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	This project aims to test the hypothesis that tolerance to MHC mismatched living related kidney transplant can be effectively and safely achieved by establishing a stable immune mixed chimeric state in non-human primates using a novel non-myeloablative, helical tomotherapy-based total lymphoid irradiation (TLI) conditioning regimen followed by Mozobil + G-CSF mobilized donor hematopoietic cell infusions. Furthermore, we will test the hypotheses that the success of this protocol will depend upon "natural" maternal-fetal preconditioning of donor and recipient, and a cytokine bias of host Treg cells toward increased production of IL-10 and IL-4 in TLI/ATG recipients of HSCs. We propose to test these hypotheses by means of 2 specific aims: 1) Combined Hematopoietic Cell/Kidney Transplants: to determine the proportion of Rhesus macaques that can be withdrawn from all immunosuppressive drugs while maintaining normal graft function of MHC 1-haplotype mismatched living related donor kidney transplants. 2) Immune Monitoring, Immunopathology and Immunocompetence: a) to determine if serial monitoring of intracellular cytokine expression of recipients of combined kidney and HSC transplants supports a Th2 bias in animals with chimerism and no GVHD that allows successful withdrawal of immunosuppressive drugs after transplantation; b) to determine whether serial trans-vivo Delayed Type Hypersensitivity (tvDTH) and mixed lymphocyte reaction (MLR) analysis of tolerance on indirect and direct pathways of alloreactivity, respectively, beginning pre-transplant, can be used to predict recipients with chimerism and no GVHD allowing successful withdrawal of immunosuppressive drugs.	

Project Progress *(One paragraph)*	In 2014 we followed up on 4 previous kidney transplant animals and one HSC recipient from 2013, all allografts with some degree of directional T-cell regulation between donor and recipient. During 2014, we initiated 2 new donor recipient pairs of kidney transplants and 7 new donor recipient pairs of combined kidney and HSC transplants. One long-term immunosuppressed pilot animal (no transplant) developed diabeties. We have had various levels of kidney rejection, but some transplants are showing longer efficacy. We will continue to follow up on these animals in 2015. In addition, we acquired 3 new donor recipient pairs for transplant in early 2015.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH, NIAID and NIDDK	**Grant number(s):** U01 AI102456

Subproject Description:

WNPRC Division-Unit	Research Services-Genetic Services	
Project Title	Collection of exome sequences from 4 macaques and genome sequences from 4 macaques	
Period of Support	1/1/2014 - 12/31/2014	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☒ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** Wisconsin National Primate Research Center
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	We will collect exome sequences from 4 macaques and genome sequences from 4 macaques. This data will be used to optimize analysis pipelines for whole genome or exome sequencing that will eventually become standard genetic characterization of nonhuman primate models of disease.	
Project Progress *(One paragraph)*	The main goal of this aim was to become familiar with exome and genome sequencing data and analysis, which is likely to become important in the near future to develop new nonhuman primate models of disease as well as improve current model systems. In 2012 and 2013, we collected and analyzed genome sequences from 20 Mauritian cynomolgus macaques in collaboration with Excluded by Requester at Private Source Whole genome sequencing for an additional 21 Indian rhesus macaque SIV elite-controller samples from WNPRC is complete. Additionally, we completed studies with the Private Source to use a human HLA capture array and Illumina sequencing to collect macaque MHC genomic sequences. Following a successful pilot study with a homozygous Mauritian cynomolgus macaque, we obtained data from 30 additional samples (9 Mauritian cynomolgus and 21 Indian rhesus macaques). Preliminary analysis of this data generated 558 MHC class I alleles and 135 MHC class II alleles. During the past year, we established this comprehensive MHC target capture protocol at WNPRC with 8 additional Indian rhesus samples. Lastly, a pilot titration study has been performed to determine optimal multiplexing conditions and explore data analysis with an expanded	

Excluded by Requester

	MHC + Exome target capture probe set. An important component of this pilot study was to incorporate an additional ~12% of the rhesus macaque exome that was identified by our collaborators [Private Source] as poorly covered with existing capture reagents that are based on the human exome sequences. We are currently sequencing DNA from 12 prolific Indian rhesus macaque sires from the WNPRC breeding colony at the Baylor Genome Center that were captured with this expanded MHC + Exome probe set. In summary, we have far exceeded our goal to collect genome and exome sequences from 4 macaques and anticipate major advances in analysis of such data over the next year. Our experiences with whole genome and exome sequencing will position us to provide this service for WNPRC and other Primate Centers in the future.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH	**Grant number(s):** P51 OD011106

Subproject Description:

WNPRC Division-Unit	Research Services-Genetic Services	
Project Title	Sequencing 15 SIV, influenza and dengue virus genomes per year	
Period of Support	1/1/2014 - 12/31/2014	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☒ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** Wisconsin National Primate Research Center
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	To sequence 15 SIV, influenza and dengue virus genomes per year in order to expand our RNA viral sequencing capacity beyond SIV sequencing and improve techniques by incorporating leading edge technology.	
Project Progress *(One paragraph)*	One of the major goals of this aim was to test new sequencing technologies for viral genome sequencing, which was performed using Roche/454 pyrosequencing at the time of our renewal. In 2012 and 2013, we tested the Illumina MiSeq sequencing technology coupled with Nextera tagmentation with great success and have subsequently moved fee-for-service sequencing of all RNA virus genomes to the MiSeq platform. This new platform reduces cost, reduces error associated with the sequencing process, and increases multiplexing. A second goal of this aim was to develop primers to sequence two widely-used SHIV challenge strains SHIV89.6P and SHIVsf162P3. We have sequenced several viruses towards this aim including SHIVsf162, SHIV-1157, SHIVnef , SIVmac239, SIVsmE660 (NIH stock), SIVmac239Δnef, SIVdeltaB670, SIV17E, and SIVsmE041. Overall, 124 SIV or SHIV viral genomes were sequenced using primarily the new MiSeq pipeline. To date, no other sequencing technology has advanced sufficiently to warrant testing, though we still anticipate that pacific biosciences will represent a significant advance in sequence length once error rate profiles improve. In addition to SIV sequencing, we have also developed primers to sequence Dengue 2 viruses and Friend retrovirus. In 2012 we sequenced 10 Dengue 2 viruses using the Roche/454 pyrosequencing platform and in 2013 we sequenced 15 Friend retroviruses using the MiSeq approach.	

	Our clients were overwhelmingly interested in SIV stock sequencing and therefore we have not pursued additional Dengue virus or influenza sequencing to date. Lastly, another goal of this aim was to expand our capabilities to sequence other RNA viruses. The new Nextera/MiSeq platform allows us to sequence any virus provided to us as amplicons or as part of plasmids. Additionally, we have moved away from using sequence-specific primers to amplify viral RNA and now use an unbiased PCR approach to sequence SIV and SHIV virus stocks. This approach could be used to sequence other RNA viruses in the future. Overall, we met our goal to sequence 15 SIV, influenza or dengue viruses each year – we sequenced 125 SIV genomes in 2014 alone - and have significantly improved the viral sequencing pipeline with new technologies. We will continue to explore new approaches as they become available. We are also implementing unbiased deep sequencing of blood products from macaque colonies in order to facilitate rapid diagnosis and treatment of infectious disease outbreaks, with an aim towards improving colony health and reducing risk of zoonotic transmission of pathogens to animal caretakers.	
Funding Source(s)	**Sponsor(s):**	**Grant number(s):**
(Include Sponsor name & complete grant number)	DHHS, PHS, NIH	P51 OD011106

Subproject Description:

WNPRC Division-Unit	Research Services-Genetic Services	
Project Title	Generation of a multiplexed assay to genotype 12 immune and host restriction loci.	
Period of Support	1/1/2014 - 12/31/2014	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☒ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** Wisconsin National Primate Research Center
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	To create a multiplexed assay to simultaneously genotype 12 immune and host restriction loci including MHC class I, MHC class II, killer immunoglobulin receptors, and TRIM5a by next generation sequencing.	
Project Progress *(One paragraph)*	In 2013, an assay using the Fluidigm Access Array system was developed to simultaneously amplify the MHC class I A and B loci and MHC class II DRB, DQA, DQB, DPA, and DPB from 48 genomic DNA samples. This assay has been fully validated for Mauritian cynomolgus macaque samples and has completely replaced our traditional microsatellite assay in our fee-for-service pipeline. The cost of this assay is $98 for client-provided whole blood and $80 for client-provided gDNA/cDNA for Tier 1 clients, representing our lowest rates yet for sequence-based MHC genotyping. During 2014 we used this assay to genotype 1062 animals from 15 different fee-for-service clients. In addition, due to the increased multiplexing capacity of the Fluidigm assay, we have also developed primers for ABO blood typing to include with the comprehensive MHC class I and class II assay. We have also developed sequence specific PCR methods for Trim5a genotyping and are developing amplicons for Killer Immunoglobulin Receptor genotyping. During the coming year, we will work to incorporate these loci into Fluidigm/MiSeq assays that can be offered to fee-for-service clients. Since the MICA and MICB loci have not been prioritized by our clients, we may also shift assay development efforts to other polymorphic immune loci such as FcR where we have outstanding requests for assistance. Overall, we have now met our primary goal to develop a multiplexed assay for comprehensive MHC genotyping with the ability to detect 8 loci including ABO simultaneously. We will continue our development of Fluidigm assays for additional immune and host restriction loci such as TRIM5a, Killer Immunoglobulin Receptors and Fc Gamma Receptors over the coming year.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH	**Grant number(s):** P51 OD011106

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	ADOPTIVE TRANSFER OF IMMUNITY ELICITED BY ATTENUATED HIV VACCINES	
Period of Support	12/01/2007 - 03/31/2016	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☒ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** University of Wisconsin/Department of Pathology and Laboratory Medicine
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	The primary goal of this application is to learn whether cellular immune responses contribute to the success of attenuated vaccines by adoptively transferring these cells from immunized animals into naive recipients that are subsequently challenged with pathogenic simian immunodeficiency virus (SIV). The animals in this proposal can also be studied with new sequencing technology to better understand how and why HIV/SIV adapt to their hosts, possibly identifying new targets for prophylactic or therapeutic intervention. Specific aims will test the hypothesis that adoptively transferred cells from donors immunized with attenuated SIV establish conditions favorable for long-term immunologic containment of pathogenic SIV and, in the process, fundamentally advance our understanding of SIV sequence dynamics: 1) We will determine whether bulk lymphocytes transferred from SIVmac239?nef immunized donors significantly decrease setpoint SIVmac239 viremia. 2) We will characterize the evolutionary dynamics of SIVmac239 using genome-wide Roche/454 pyrosequencing.	

Project Progress *(One paragraph)*	We have made significant progress towards the completion of both aims. We have now monitored the recipient macques out to 26 weeks post-infection. (1) We found that the source of the donor cells did effect viral loads in the recipients. These results were counter to our first study, where now macaques that received cells from mock-vaccinated donors generally had lower viral loads than their counterparts. Again we found that cells persisted for a very limited amount of time (7-9 days). (2) We continued to advance sequencing virus from SIV+ macaques, including virus from those with less common MHC haplotypes. We sequenced virus from the adoptive transfer recipents to characterize the infecting virus and to assess whether the transferred donor cells impacted viral evolution. There was evidence of more rapid escape within CD8 T cell epitopes that may be due to either recombination between pre-escaped attenuated virus and challenge virus or from slective pressure by donor cells. We also found that MHC-matched macaques did not make matching T cell responses. In addition, we have identified the next set of adoptive transfer macaques and performed initial pre-infection sampling.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH, NIAID	**Grant number(s):** R01 AI077376

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	EVALUATING IMMUNITY ELICITED BY CD8 T CELL RESPONSES TARGETING INVARIANT EPITOPES	
Period of Support	12/05/2013 - 11/30/2018	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☒ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** University of Wisconsin/Department of Pathology and Laboratory Medicine
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	A successful HIV vaccine will need to elicit robust CD8 T cells to control replication of viruses that successfully reach the blood stream. Although there are some individuals with favorable host genetics that predisposes them to elite viral control, we do not know the characteristic profile of effective antiviral CD8 T cells within individuals who do no have these favorable host genetics. In this study, we will use a unique model of elite viral contro in monkeys with unfavorable host genetics to characterize the profile of CD8 T cells that contribute to this control, thus providing us with novel insight into the type of vaccine immunogens that will elicit the most effective antiviral CD8 T cells within any individual.	
Project Progress *(One paragraph)*	Infected five Mauritian cynomolgus macaques (MCM) with the mutant SIVmac239Δnef. These MCM were homologous with the alleles M3 which are not good at controlling SIV infection. The animals were followed after infection with the mutant SIV and some had better control of infection. Work continues in 2015 with more MCMs.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH, NIAID	**Grant number(s):** R01 AI108415

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	INDIVIDUALIZED CELL THERAPY FOR PARKINSON'S DISEASE	
Period of Support	06/01/2012 - 05/31/2017	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	◉ Research ○ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☒ No ☐ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** University of Wisconsin/Department of Neuroscience
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):** Excluded by Requester	**Affiliate Institution(s) & Department(s):** University of Wisconsin/Department of Medical Physics
Principal Core Scientist Associated with Project		
Project Description *(One paragraph)*	Parkinson's disease (PD) results from degeneration of midbrain dopamine (DA) neurons and can be effectively treated with L-dopa in the initial phase. However, DA supplementation does not halt the DA neuron degeneration process, nor does it correct the loss of DA neurons. Consequently, PD patients almost invariably lose responsiveness to L-dopa treatment over time. Transplantation of human fetal mesencephalic tissues to replace the lost DA neurons has shown efficacy in alleviating symptoms of some PD patients, however, depends on collection of tissues from multiple fetuses of particular ages for a single patient, which makes it impractical for general application and is ethically problematic. We explore the possibility of future personalized cell therapy for PD using a non-human primate model. We will derive safe and functional DA neurons from the skin tissue of individual Parkinsonian rhesus monkeys through generation of induced pluripotent stem cells (iPSCs) that are free of virus and transgenes and using our newly developed strategy for midbrain DA neuron differentiation. We will then label the cell genetically and transplant the midbrain DA neurons back to the monkey from which the cells are derived, and assess whether the DA neurons survive and contribute to therapy in a short term and whether the therapeutic outcome is sustained over a long term (2-3 years). Results from this study will determine the safety and efficacy of autologous stem cell therapy for PD in primates, thus setting up a foundation for future clinical trials using reprogrammed human cells.	

Project Progress *(One paragraph)*	First cohort of MPTP-treated monkeys received IPS cells in late 2013 and were continually monitored by clinical rating scores, fine motor testing, and activity prior to some being euthanized later in 2014. A second cohort of five MPTP-treated monkeys received IPS cells in April 2014 and have also been followed by clinical rating scores, fine motor testing, and activity and are being followed for a longer time post-cell transplant. Based on histological verification of the location of the IPS cells in the euthanized chohort, it has been decided that we need to improve our targeting of IPS cell infusion by using MRI-directed methodology along with convection-enhanced delivery infusion. Thus, the remaining animals in the 2nd cohort were postponed to receive IPS cells until early 2015.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** DHHS, PHS, NIH, Neuroscience	**Grant number(s):** R01 NS076352

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	Transgenic marmosets for translational research	
Period of Support	08/01/2013 - 07/31/2014	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	○ Research ◉ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☒ No ☐ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** University of Wisconsin/Department of Comparative Biosciences
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):** Excluded by Requester	**Affiliate Institution(s) & Department(s):** University of Wisconsin/WNPRC
Principal Core Scientist Associated with Project		
Project Description *(One paragraph)*	The overall goal for this aim is to sustain our in-house expertise and technical experience in ART with NHP models and support investigators planning research relying on these approaches. This will require mastering more innovative approaches as they develop including genomic editing and transgenic technologies. Traditional support for ART is well established at the WNPRC within the SPI Unit. SPI's role will continue to include coordinating experimental methodologies such as; gonadotropin stimulation, fertility regulation and monitoring, oocyte maturation, in vitro fertilization (IVF), and embryo micromanipulation (embryo splitting, blastomere biopsy, microinjection). SPI will also provide embryos as needed for derivation of embryonic stem cells (in collaboration with Stem Cell Resources. In addition, SPI will train potential semen donors, supervise ART-associated laboratory activities, maintain hormone and other supplies, develop protocols for quality control of animal responses, manage the husbandry of embryo recipients, and assign animals to appropriate projects as dictated by investigator-initiated requests. We have prepared cost rate analysis for costs per female stimulation cycle, gamete handling, IVF, embryo manipulation, and other laboratory-associated procedures to support ART.	
Project Progress *(One paragraph)*	With specific pilot funding from the UW-Madison CTSA, we have been reliably obtaining approximately 10-15 oocytes per stimulation cycle, and fertilization rates of 25-100%. Development of fertilized embryos in vitro to blastocyst stage, a useful surrogate for in vivo developmental potential, has been modest in contrast to our previous rhesus monkey in vitro embryo culture, we have preliminary evidence that there may be a male factor related to blastocyst development. This observation also illustrates that we have continued to monitor individual males including new candidates to identify reliable donors of semen samples of excellent quality.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** University of Wisconsin, Medical Foundation, ICTR	**Grant number(s):** PRJ75IF

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	MHC-DEFINED NONHUMAN PRIMATE MODEL FOR BONE MARROW TRANPLANTATION	
Period of Support	01/01/2014 - 12/30/2014	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	○ Research ◉ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☒ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** University of Wisconsin/Department of Pathology and Laboratory Medicine
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	Bone marrow transplantation [or hematopoietic stem cell (HSC) transplantation] is used in the clinic to treat blood cancer and genetic diseases. It also holds promise for treatment of infectious (AIDS) and autoimmune diseases. However, many patients do not benefit from bone marrow transplantation procedure due to lack of suitable donors and limitations of current technologies. These limitations could be overcome by improving the introduction of genes into HSCs (HSC gene transfer) and in growing cells in a culture dish (in vitro HSC expansion 4 technologies) and by establishing technologies for production of HSCs from skin cells converted to embryonic state, so called induced pluripotent stem cells (iPSCs). Preclinical testing of efficacy and safety of the novel technologies for HSC transplantation in nonhuman primate (NHP) models would be critical for their clinical translation. NHPs HSCs have a similar ability to incorporate into the bone marrow environment and give rise to blood cells (HSC engraftment properties) to humans which allows us to reliably assess the incorporation of HSCs into the bone marrow environment (hematopoietic engraftment) and long-term safety of stem cell therapies. In addition, NHPs make it possible to test HSC and iPSC-based therapies for AIDS.	
Project Progress *(One paragraph)*	One animal was funded for this project and received fludarabine chemotherapy and total body irradiation (TBI) in mid-2014. We learned much about clinical support after these treatments. In addition, bone marrow cells were collected prior to this treatment and the animal recieved an autograft of the modified HSCs the next day, with the animal progressing toward normal bone marrow towards the end of 2014 indicating good proof of concept for this pilot.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** University of Wisconsin, Medical Foundation, ICTR	**Grant number(s):** PRJ79KS

Subproject Description:

WNPRC Division-Unit	Animal Services - SPI	
Project Title	MHC-DEFINED NONHUMAN PRIMATE MODEL FOR BONE MARROW TRANPLANTATION	
Period of Support	01/01/2014 - 12/30/2014	
Type of Project *(Only select one. If "Other," please specify in space provided.)*	○ Research ◉ Pilot ○ Other, _____	
AIDS Research *(No or Yes)*	☐ No ☒ Yes	
Principal Investigator (PI) and Institutional Affiliation	**PI Name:** Excluded by Requester	**PI Institution & Department:** University of Wisconsin/Department of Pathology and Laboratory Medicine
Other Affiliate Scientists with Institutional Affiliation *(Doctoral level only)*	**Affiliate Scientist Name(s):**	**Affiliate Institution(s) & Department(s):**
Principal Core Scientist Associated with Project	Excluded by Requester	
Project Description *(One paragraph)*	Bone marrow transplantation [or hematopoietic stem cell (HSC) transplantation] is used in the clinic to treat blood cancer and genetic diseases. It also holds promise for treatment of infectious (AIDS) and autoimmune diseases. However, many patients do not benefit from bone marrow transplantation procedure due to lack of suitable donors and limitations of current technologies. These limitations could be overcome by improving the introduction of genes into HSCs (HSC gene transfer) and in growing cells in a culture dish (in vitro HSC expansion 4 technologies) and by establishing technologies for production of HSCs from skin cells converted to embryonic state, so called induced pluripotent stem cells (iPSCs). Preclinical testing of efficacy and safety of the novel technologies for HSC transplantation in nonhuman primate (NHP) models would be critical for their clinical translation. NHPs HSCs have a similar ability to incorporate into the bone marrow environment and give rise to blood cells (HSC engraftment properties) to humans which allows us to reliably assess the incorporation of HSCs into the bone marrow environment (hematopoietic engraftment) and long-term safety of stem cell therapies. In addition, NHPs make it possible to test HSC and iPSC-based therapies for AIDS.	
Project Progress *(One paragraph)*	One animal was funded for this project and received fludarabine chemotherapy and total body irradiation (TBI) in mid-2014. We learned much about clinical support after these treatments. In addition, bone marrow cells were collected prior to this treatment and the animal recieved an autograft of the modified HSCs the next day, with the animal progressing toward normal bone marrow towards the end of 2014 indicating good proof of concept for this pilot.	
Funding Source(s) *(Include Sponsor name & complete grant number)*	**Sponsor(s):** University of Wisconsin, Medical Foundation, ICTR	**Grant number(s):** PRJ79KS

Composite Application Budget Summary

Categories	Budget Period
Salary, Wages and Fringe Benefits	5,000,468
Equipment	105,208
Travel	0
Participant/Trainee Support Costs	0
Other Direct Costs (excluding Consortium)	1,874,960
Consortium Costs	51,050
Direct Costs	7,031,686
Indirect Costs	2,372,023
Total Direct and Indirect Costs	9,403,709

Component Budget Summary

Components	Categories	Budget Period
7373-001 (Other)	Salary, Wages and Fringe Benefits	2,649,906
	Equipment	0
	Travel	0
	Participant/Trainee Support Costs	0
	Other Direct Costs (excluding Consortium)	589,586
	Consortium Costs	0
	Direct Costs	3,239,492
	Indirect Costs	1,117,625
TOTALS	Total Direct and Indirect Costs	4,357,117
7374-002 (Other)	Salary, Wages and Fringe Benefits	849,553
	Equipment	0
	Travel	0
	Participant/Trainee Support Costs	0
	Other Direct Costs (excluding Consortium)	376,149
	Consortium Costs	51,050
	Direct Costs	1,276,752
	Indirect Costs	422,867
TOTALS	Total Direct and Indirect Costs	1,699,619
7375-003 (Other)	Salary, Wages and Fringe Benefits	883,913
	Equipment	0
	Travel	0

	Participant/Trainee Support Costs	0
	Other Direct Costs (excluding Consortium)	381,789
	Consortium Costs	0
	Direct Costs	1,265,702
	Indirect Costs	436,667
TOTALS	Total Direct and Indirect Costs	1,702,369
7372-004 (Other)	Salary, Wages and Fringe Benefits	617,096
	Equipment	105,208
	Travel	0
	Participant/Trainee Support Costs	0
	Other Direct Costs (excluding Consortium)	527,436
	Consortium Costs	0
	Direct Costs	1,249,740
	Indirect Costs	394,864
TOTALS	Total Direct and Indirect Costs	1,644,604
TOTALS		**9,403,709**

Categories Budget Summary

Categories	Components	Budget Period
R&R Budget - Senior/Key Person Funds Requested	7373-001 (Other)	559,704
	7374-002 (Other)	285,410
	7375-003 (Other)	210,325
	7372-004 (Other)	232,012
TOTALS		1,287,451
R&R Budget - Other Personnel Funds Requested	7373-001 (Other)	2,090,202
	7374-002 (Other)	564,143
	7375-003 (Other)	673,588
	7372-004 (Other)	385,084
TOTALS		3,713,017
R&R Budget - Section A & B. Total Salary, Wages and Fringe Benefits (A+B)	7373-001 (Other)	2,649,906
	7374-002 (Other)	849,553
	7375-003 (Other)	883,913
	7372-004 (Other)	617,096
TOTALS		5,000,468
R&R Budget - Section C. Total Equipment	7373-001 (Other)	0
	7374-002 (Other)	0
	7375-003 (Other)	0
	7372-004 (Other)	105,208
TOTALS		105,208

R&R Budget - Domestic Travel	7373-001 (Other)	0
	7374-002 (Other)	0
	7375-003 (Other)	0
	7372-004 (Other)	0
TOTALS		0
R&R Budget - Foreign Travel	7373-001 (Other)	0
	7374-002 (Other)	0
	7375-003 (Other)	0
	7372-004 (Other)	0
TOTALS		0
R&R Budget - Section D. Total Travel	7373-001 (Other)	0
	7374-002 (Other)	0
	7375-003 (Other)	0
	7372-004 (Other)	0
TOTALS		0
R&R Budget - Tuition/Fees/Health Insurance	7373-001 (Other)	0
	7374-002 (Other)	0
	7375-003 (Other)	0
	7372-004 (Other)	0
TOTALS		0
R&R Budget - Stipends	7373-001 (Other)	0
	7374-002 (Other)	0
	7375-003 (Other)	0
	7372-004 (Other)	0

TOTALS		0
R&R Budget - Trainee Travel	7373-001 (Other)	0
	7374-002 (Other)	0
	7375-003 (Other)	0
	7372-004 (Other)	0
TOTALS		0
R&R Budget - Subsistence	7373-001 (Other)	0
	7374-002 (Other)	0
	7375-003 (Other)	0
	7372-004 (Other)	0
TOTALS		0
R&R Budget - Other Participants/Trainee Support Costs	7373-001 (Other)	0
	7374-002 (Other)	0
	7375-003 (Other)	0
	7372-004 (Other)	0
TOTALS		0
R&R Budget - Section E. Total Participants/Trainee Support Costs	7373-001 (Other)	0
	7374-002 (Other)	0
	7375-003 (Other)	0
	7372-004 (Other)	0
TOTALS		0
R&R Budget - Materials and Supplies	7373-001 (Other)	555,774
	7374-002 (Other)	220,711
	7375-003 (Other)	231,823

	7372-004 (Other)	171,569
TOTALS		1,179,877
R&R Budget - Publication Costs	7373-001 (Other)	0
	7374-002 (Other)	0
	7375-003 (Other)	0
	7372-004 (Other)	0
TOTALS		0
R&R Budget - Consultant Services	7373-001 (Other)	0
	7374-002 (Other)	24,000
	7375-003 (Other)	0
	7372-004 (Other)	37,184
TOTALS		61,184
R&R Budget - ADP/Computer Services	7373-001 (Other)	0
	7374-002 (Other)	0
	7375-003 (Other)	0
	7372-004 (Other)	0
TOTALS		0
R&R Budget - Subawards/Consortium/Contractual Costs	7373-001 (Other)	0
	7374-002 (Other)	51,050
	7375-003 (Other)	0
	7372-004 (Other)	0
TOTALS		51,050
R&R Budget - Equipment or Facility Rental User Fees	7373-001 (Other)	0
	7374-002 (Other)	0

	7375-003 (Other)	0
	7372-004 (Other)	0
TOTALS		0
R&R Budget - Alterations and Renovations	7373-001 (Other)	0
	7374-002 (Other)	0
	7375-003 (Other)	0
	7372-004 (Other)	0
TOTALS		0
R&R Budget - Other Direct Cost 1	7373-001 (Other)	33,812
	7374-002 (Other)	131,438
	7375-003 (Other)	149,966
	7372-004 (Other)	292,376
TOTALS		607,592
R&R Budget - Other Direct Cost 2	7373-001 (Other)	0
	7374-002 (Other)	0
	7375-003 (Other)	0
	7372-004 (Other)	8,118
TOTALS		8,118
R&R Budget - Other Direct Cost 3	7373-001 (Other)	0
	7374-002 (Other)	0
	7375-003 (Other)	0
	7372-004 (Other)	18,189
TOTALS		18,189
R&R Budget - Section F. Total Other Direct Cost	7373-001 (Other)	589,586

	7374-002 (Other)	427,199
	7375-003 (Other)	381,789
	7372-004 (Other)	527,436
TOTALS		1,926,010
R&R Budget - Section G. Total Direct Cost (A thru F)	7373-001 (Other)	3,239,492
	7374-002 (Other)	1,276,752
	7375-003 (Other)	1,265,702
	7372-004 (Other)	1,249,740
TOTALS		7,031,686
R&R Budget - Section H. Indirect Costs	7373-001 (Other)	1,117,625
	7374-002 (Other)	422,867
	7375-003 (Other)	436,667
	7372-004 (Other)	394,864
TOTALS		2,372,023
R&R Budget - Section I. Total Direct and Indirect Costs (G +H)	7373-001 (Other)	4,357,117
	7374-002 (Other)	1,699,619
	7375-003 (Other)	1,702,369
	7372-004 (Other)	1,644,604
TOTALS		9,403,709

A. COMPONENT COVER PAGE

Project Title: Division of Research
Component Project Lead Information:
Excluded by Requester

B. COMPONENT ACCOMPLISHMENTS

B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

Division of Research Overview
Director: Excluded by Requester PhD

The Wisconsin National Primate Research Center (WNPRC) Division of Research is comprised of four Specialized Resource Units (Aging Specialized Resource, Bone Marrow Transplantation Unit, SIV Elite Controllers Resource and Stem Cell Resources); four Working Groups (Energy & Metabolism & Chronic Disease, Global Infectious Disease, Neuroscience and Reproductive & Regenerative Medicine); and, the WNPRC Pilot Research Program.

Throughout the current reporting period (1/1/2014 - 12/31/2014), the division has continued to develop and enhance research programs at the WNPRC via numerous work-in-progress Working Group meetings that continue to bring together NHP researchers from across a variety of institutions and disciplines.

Additionally, the Specialized Resource Units Heads continue to develop and enhance their respective Resources; while also continuing to support meritorious investigators in the fields of aging, bone marrow transplantation, SIV/HIV and stem cell research.

Finally, the WNPRC continues to have a robust Pilot Program, which supports novel and innovative research involving nonhuman primate (NHP) research. In association with the University of Wisconsin Institute for Clinical & Translational Research (ICTR), the WNPRC Pilot Program has supported a total of 3 pilot projects during the current report period, resulting in 6 applications (3 funded) and 2 new collaborations. Also,the WNPRC Pilot Program funded 7 new, 2-year Pilot projects during the current reporting period, with project periods of 1/1/2015 - 12/31/2016.

Please see attached detailed progress reports from each unit (Section B.2), which includes specific aims, accomplishments and goals.

B.1.a Have the major goals changed since the initial competing award or previous report?

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: Division of Research Yr53 RPPR_final_2-24-15v2opt.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

Not Applicable

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

NOTHING TO REPORT

B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?

NOTHING TO REPORT

B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

Please see attached detailed progress reports from each unit (Section B.2), which includes future goals for the next reporting period.

DIVISION OF RESEARCH

SPECIALIZED RESOURCE DEVELOPMENT REPORTS

AGING SPECIALIZED RESOURCE

Unit Head: Excluded by Requester, PhD
Core PI: Excluded by Requester, PhD

GOALS

The aged rhesus monkey is a well-established model for increasing our understanding of health and disease in aging and for gaining insight into the fundamental processes of primate aging. The WNPRC has one of the largest, well-documented colonies of aged rhesus monkeys in the world. This colony is extensively used by a large number of extramurally funded investigators. In order to meet the research needs and to optimize the use of this valuable resource, we propose the following:

Specific Aim 1 –To continue a systematic preventive medicine program for the older animals in our colony.

This includes close observation of the animals by experienced animal care technicians who are familiar with the individual animals, prompt veterinary intervention when problems arise, full semi-annual physical exams including complete blood counts and serum chemistries, monthly body weight assessments, careful documentation of each animal's health status, and strict recording of all clinical and experimental treatments.

Specific Aim 2 – To expand the size of the aged colony as appropriate animals become available.

These animals will have precisely known dates of birth, complete clinical and experimental histories, and record of minimally invasive manipulation.

Specific Aim 3 – To continue to make these animals available to investigators with meritorious proposals in a manner that makes efficient and effective use of the colony.

This will include quarterly banking of blood and urine samples to facilitate practical longitudinal study of the aged animals.

Specific Aim 4 – To conduct full necropsies on aged animals at the time of spontaneous or experimental demise.

In addition to the pathological analysis at the time of death, tissue samples will be banked for later use by local and extramural investigators.

The utility of the rhesus monkey model is clear, however, some limitations in this model (i.e. availability and ~40 year maximum life span) have led us to explore other opportunities. There is increasing interest in the development of the common marmoset model for studies of aging and age-related diseases/conditions. The marmoset offers several exciting advantages. While still a nonhuman primate, the small size and shorter lifespan of this species makes it highly amenable to aging research. In order to develop this model we propose the following:

Specific Aim 5 – To explore the potential of the common marmoset model of aging by examining age-related changes in common clinical parameters including body weight, health status, disease progression, life span, serum chemistries and complete blood counts.

Additionally, we will make these animals available to investigators with meritorious proposals and conduct full necropsies on aged animals including sample banking for later use by local and extramural investigators.

ACCOMPLISHMENTS

The Wisconsin National Primate Research Center has approximately 45 rhesus monkeys over 20 years of age. Support is provided in part by the National Institute of Aging to maintain a subset of these animals for studies relating to normal aging. During this reporting period, 12 rhesus monkeys (8 females and 4 males) have been supported by this specialized resource. At the time of assignment to this specialized resource these animals averaged 21.0 years of age (±0.4 years). There are currently 9 animals (8 females, 1 male, mean age = 26.6 ± 1.1 years) assigned to this specialized resource. The oldest animal in this group is now 31.4 years of age. The majority of these animals are in excellent health and are available for appropriate aging-related research. We continue to monitor the health and well-being of all animals in the colony and evaluate aging individuals from the general colony to evaluate their appropriateness for inclusion in the aging colony.

During this reporting period, approximately 10 investigators used these animals in studies related to brain structure and function, cognitive aging, calorie restriction, glucoregulatory function, lipid metabolism, cardiovascular function, senescent cell clearance, osteoarthritis, cellular metabolism, immunology, and reproduction. No request has been denied.

As has been standard practice, complete necropsies and tissue collections were performed for all animals 20 years of age and older that have died at the WNPRC during this reporting period. Tissues are recorded and banked and available to investigators studying various aspects of aging.

A goal of this resource has been to increase the number of rhesus monkeys available and to expand to offer access to a second species, the common marmoset, a small New World primate. Unfortunately, funding for this resource from the National Institute on Aging has been reduced. Given these financial constraints, we have been unable to expand the resource. Instead we have focused on maintaining the excellent care that the current aging animals receive.

FUTURE PLANS

We plan to continue to maintain the current population of aged rhesus macaques to the best of our ability given the limited resources available. We will continue to provide the complete medical care for these animals and perform full necropsies and tissue collections at the time of death. As much as we are able, we will continue to make these animals and their tissues available to meritorious investigators in the field of aging.

BONE MARROW TRANSPLANTATION (BMT) UNIT

Unit Heads: Excluded by Requester MD, PhD and Excluded by Requester VMD, PhD

Description:

The major goal of the bone marrow transplantation (BMT) unit is to establish an NHP model of hematopoietic stem cell (HSC) transplantation to advance HSC-based therapies for infectious (AIDS), neoplastic, and genetic diseases. Key functions of the BMT unit will include: 1) providing collection of bone marrow samples and isolation of different populations of stem cells and endothelial progenitors, 2) developing and optimizing transplantation regimens for bone marrow and induced pluripotent stem cell (iPSC)-derived NHP hematopoietic cells, 3) production of hematopoietic and endothelial progenitors and mature cells from NHP HSCs and iPSCs, 4) genetic modification of HSCs and other progenitor cells, 5) directing and consulting veterinarians regarding BM transplantation procedure, and pre- and post-transplant management of NHP, and 6) monitoring HSC engraftment.

A. Specific Aims:

HSC transplantation is currently a standard of care for the treatment of otherwise incurable blood cancers and genetic diseases. It is also holds promise for treating autoimmune and infectious diseases. HSC transplantation from an HIV-resistant patient bearing D32*CCR5* mutation into an HIV positive patient with leukemia cured both HIV and leukemia [1,2] indicating the power of HSC transplantation for HIV treatment. However, cell sources, low gene transfer efficiency, graft versus host diseases, graft failure, and potential contamination of HSCs with tumor cells remain major limitations of current HSC transplantation-based therapies. These limitations might be overcome by improving HSC gene transfer and *in vitro* HSC expansion technologies, and by employing induced pluripotent stem cells (iPSCs) as a source of therapeutic cells. In coming years, the BMT unit will establish an NHP model of bone marrow transplantation at WNPRC and develop technologies for the genetic manipulation of NHP HSCs. These services will provide an opportunity to 1) establish a platform for preclinical testing of the efficiency and safety of iPSC and HSC-based therapies for AIDS, 2) elucidate mechanisms underlying the HSC-based therapeutic effect in AIDS, 3) provide a foundation for development of NHP models for genetic and neoplastic blood diseases, 4) explore hematopoietic chimerism as an approach to establish an immune tolerance following islet and kidney transplantation, 5) evaluate induction of immunological tolerance for acceptance of cells/tissues derived from pluripotent stem cells, and 6) study the mechanisms of organ-specific leukocyte phenotypic specification and function to advance studies on reproductive health. In addition to HSCs, the BMT unit will supply mesenchymal stem cells (MSCs) and endothelial progenitor cells to investigators testing therapeutic efficiency of these cells in NHP models. The BMT unit will capitalize on the strong WNPRC expertise in stem cell biology, NHP AIDS models, and the availability of SPF MHC-defined NHP colonies. It will open opportunities for investigators at UW and the broad scientific community to utilize the unique WNPRC resources for developing stem cell-based therapies for AIDS, regenerative medicine, and transplant tolerance. It will also make it possible to develop NHP models for genetic and neoplastic blood diseases.

Specific Aim 1 - To provide NHP BM stem cell isolation and transplantation to investigators as a fee for service activity.

Specific Aim 2 - To develop an NHP model for evaluation of iPSC-based therapies for infectious and blood diseases.

Specific Aim 3 - To establish an efficient genetic modification of NHP HSCs and develop technologies to optimize engraftment of genetically-modified HSCs and achieve a therapeutic level of engrafted cells.

PROGRESS REPORT

Major activities

1. NHP BMT core has been established; 2. NHP BMT working group has been organized. 3. Collaboration Established/Submitted Grant Applications: i)Transplantation of Induced Pluripotent Stem Cell (iPSC) Derived Hematopoietic Cells to Achieve Stable Mixed Chimerism in a Rhesus Model [Excluded by Requester] Dept of Surgery [Excluded by Requester] WNPRC Opportunities Pool U01 Grant NIH); ii) Prevention of Delayed Graft Function in Kidney Transplantation by iPSC-derived MSCs [Excluded by Requester] Dept of Surgery [Excluded by Requester] WNPRC, R01 NIH); iii) [Excluded by Requester] (WNPRC) [Pending Support] [Pending Support]

Significant results

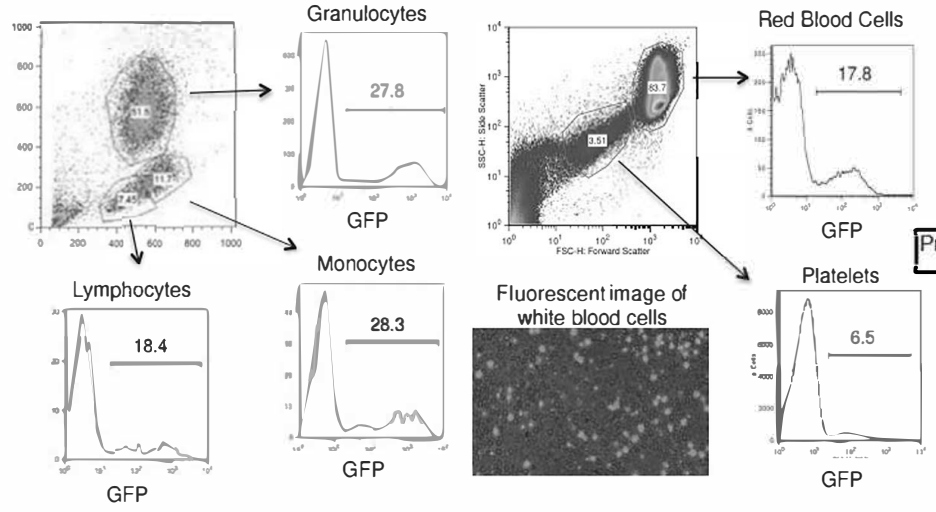


Figure 1. Multilineage engraftment of blood cells following transplantation of autologous CD34+ cells transduced with eGFP in MCM.

1. Developed protocol for efficient isolation of CD34+ hematopoietic stem cells (HSCs) from mauritian cynomolgus monkey (MCM).

2. In collaboration with [Private Source] (La Jolla, CA) developed method for highly efficient gene transfer into monkey HSCs (rapamycin-based protocol >90% gene transfer efficiency)

3. Successful bone marrow in MCMs using nonmyeloblative XF-RIC regimen.

4. Successful bone marrow in MCMs using myeloblative regimen (Figure 1).

5. System for efficient de novo production of blood from rhesus and cynomolgus monkey, including MCM, induced pluripotent stem cells was developed (Figure 2).

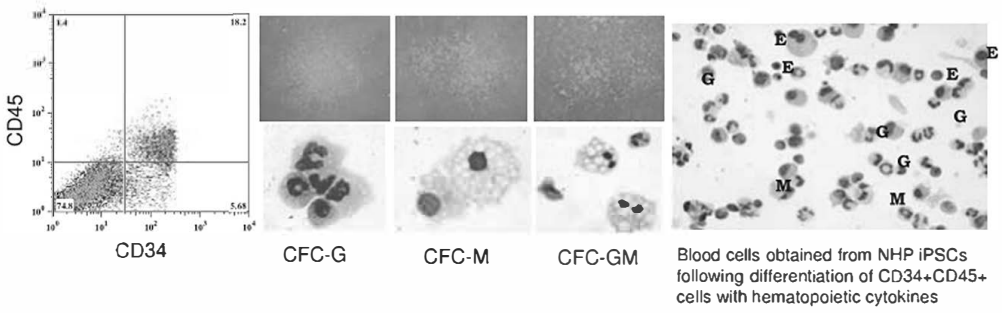


Figure 2. Hematopoietic differentiation of cynomolgus monkey iPSCs.

Key outcomes

MHC-defined nonhuman primate model for bone marrow transplantation has been established. Collaborative pilot project "MHC defined NHP model for BMT (ICTR pilot grant Excluded by Requester PIs) within BMT group renewed for funding in 2015. Collaborative pilot project "Prevention of delayed graft functio in kidney transplantation by iPSC derived MSC" (WNPRC pilot grant, Excluded by Requester PI, Excluded by Requester co-I) successfully completed.

PLANS FOR THE COMING YEAR

1. Continue monitoring of HSC engraftment to establish engraftment parameters.
2. Continue collaboration with Excluded by Requester (Private Source) on development of iPSC-based therapies for bone marrow failure. Perform transplantation of iPSC-derived hematopoietic progenitors. Pending Support Pending Support
3. Explore the potential of iPSC-derived hematopoietic cells in establishing mixed chimerism and tolerance to kidney allograft (collaborative project with Excluded by Requester
4. Establish collaboration with Excluded by Requester (WNPRC) to explore stem cell technologies for expression of HIV-neutralizing antibodies.
5. Continue studies of iPSC-derived MSCs for prevention of delayed graft function.

SIV ELITE CONTROLLERS

Unit Head: Excluded by Requester PhD

As in HIV-infected humans, a limited number of macaques spontaneously control SIV replication to a viral set point of less than 1,000 copies/ml after infection ("Elite Controllers"; ECs). Throughout the numerous AIDS-related studies conducted at the WNPRC, we have identified a number of EC Indian rhesus macaques. To increase the utility of these valuable animals, we have established a sample bank, database and provided prolonged housing for EC macaques at the WNPRC. Making these unique resources available to the community of investigators working on AIDS research is an extremely valuable service to the field at large.

At present we have more than 11,000 sample vials from more than 150 SIV-infected Indian rhesus macaques and from 13 SIVmac239-infected Mauritian cynomolgus macaques, that at one time controlled SIV replication. During 2014 we sustained 20 live animals. We have produced close to 500 sample vials from the 20 animals. The samples include plasma, serum, PBMC, and isolated lymph node cells.

A central mission of SIV Elite Controller Resource is to provide access to archived samples from SIV-infected EC macaques for retrospective analysis. In 2014 nine principal investigators requested samples from animals supported by this specialized resource. The resource unit shipped out more than 200 samples nationally. Findings of studies using Elite Controller Resource samples were published in two peer-reviewed papers.

STEM CELL RESOURCES

Unit Head Excluded by Requester VMD, PhD

GOALS

Specific Aim 1 – Improve the defined culture of primate iPS cells, and distribute unique culture reagents to other investigators.

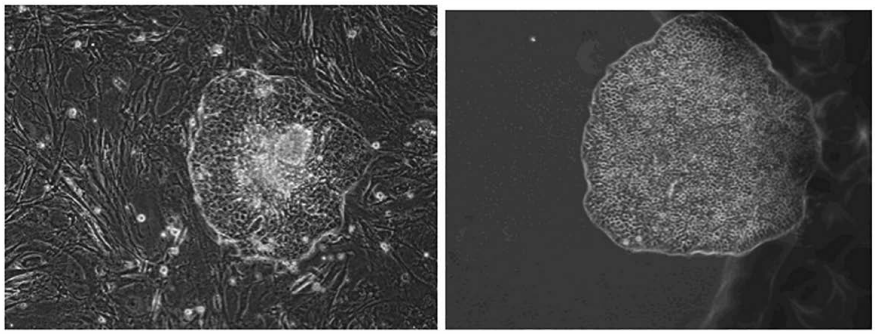
Specific Aim 2 – Improve iPS cell reprogramming efficiency of primate fibroblast and hematopoietic cells.

Specific Aim 3 – Derive, bank, and distribute iPS cells from Rhesus and Cynomologus macaques, including from naturally-occurring MHC homozygous Mauritian Cynomolgous monkeys.

Specific Aim 4 – Provide primate iPS cell gene targeting services for other investigators.

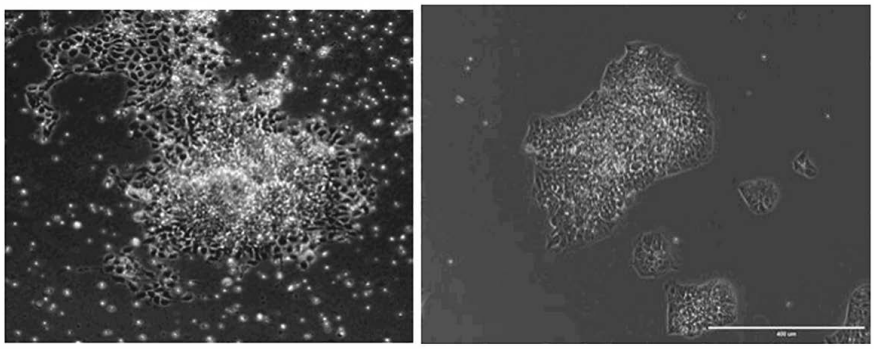
ACCOMPLISHMENTS

Specific Aim 1 – We are continuing to optimize a defined culture system for non-human primate (NHP) embryonic stem (ES) cells and induced pluripotent stem (iPS) cells. Our current media has been shared with other groups and found to be robust for several different NHP species. Please see Figures 1-3 for more detail. While our current media is more robust for several different NHP species, it is not optimal for all NHP species. We are currently optimizing our primate media for multiple NHP iPS cells for feeder free culture and performing RNA seq experiments on multiple iPS cell lines to better understand optimal culture conditions. Once the pluripotent media has been optimized we will begin to optimize differentiation medias for NHP iPS cell lines.



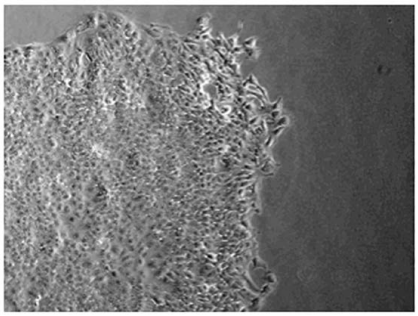
A. B.

Figure 1: Marmoset ES cells (cathrix jachhus) in feeder and serum depedent conditions (A) and serum free, defined conditions (B).

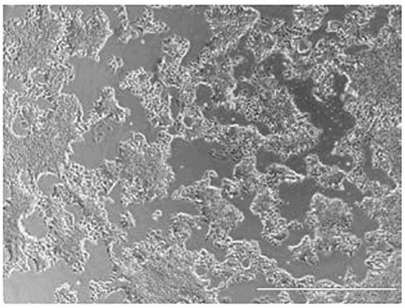


A. B.

Figure 2: Rhesus macaque iPS cells in previous media conditions (A) and serum free, defined conditions (B).



A.



B.

Figure 3: Cynomologus macaque iPS cells in feeder free conditions (A and B)

Specific Aim 2 – We have optimized the DNA purification protocol, replaced the c-myc gene with L-myc in reprogramming vector pCEP4-M2L, and cloned the miR302/367 cluster from mouse and human genomic DNA. We discovered that the replacement of c-myc gene with L-myc, combined with the usage of EBNA mRNA could significantly improve the reprogramming efficiency of primate fibroblast cells. In addition, we have generated a single vector that successfully reprograms human foreskin fibroblast cells into iPS cells. In addition to using a single vector, we are continuing work to optimize reprogramming efficiency by optimizing electroporation conditions and have developed a readout technology to receive more timely feedback. Recently, using a new electroporation system, we have been able to increase the reprograming efficiency of primate cells. We continue to work on improving reprogramming efficiency using small molecules and genetic factors found to be effective.

Specific Aim 3 – We have isolated fibroblast cells from skin punch samples [Excluded by Requester] laboratory) collected from 3 MHC heterozygous Mauritian cynomolgus monkeys. We have generated 2 iPS cell lines from the fibroblasts and delivered one cell line to [Excluded by Requester] Lab. We are currently working on generating the third iPS cell line for [Excluded by Requester] lab.

We have isolated fibroblast cells from skin punch samples from two Rhesus macaque monkeys for Dr. [Excluded by Requester] Lab. We are currently working on generating the iPS cells from these fibroblasts lines for delivery to [Excluded by Requester] group.

Lastly, we generated Common Marmoset iPS cells for [Excluded by Requester] lab. His lab has also been trained in reprogramming and primate stem cell culture.

Specific Aim 4 – We have identified the ROSA26 homologues in cynomologus (with the help of Dr. [Excluded by Requester] and rhesus monkey. Based on these information, we have cloned the homologous arms of the AAV-based targeting vector from cynomolgus and rhesus genomic DNA. We have also identified an AAV serotype that can transduce rhesus ES cells with high efficiency.

We are continuing to work on characterizing the iPS cell lines derived from MHC homozygous and heterozygous cynomolgus monkey fibroblasts, targeting the ROSA26 locus in rhesus ES cells and cynomolgus iPS cells, and continuing to optimize the defined culture condition for NHP pluripotent stem cells and the episomal reprogramming protocols for deriving iPS cells from primate fibroblasts and blood cells.

FUTURE PLANS

During the next reporting period, we intend to continue to reprogram various cell lines based on MHC typing with other investigators within the Wisconsin National Primate Center. There is significant demand with new primates located within the animal colony. We will continue to support new investigators beginning in their NHP pluripotent stem cell studies as well as provide targeted pluripotent cell lines if requested. To begin to move towards therapeutic projects, we will continue to reprogram

primates and will focus on specific MHC typing to investigate immune responses that would be applicable to the HLA immune response in human. Additionally, we will begin to optimize differentiation protocols in primate iPS cells for therapeutically relevant cell types. Recently, there has been an increased emphasis on creating HLA-typed stem cell banks. Based on ethnic background and region of origin, efforts are being made to create HLA-typed IPS cell banks that cover roughly 80% of a defined population. These banks will be used to perform donor matched stem cell based therapies. It will be important to understand the recipients response to transplants performed from donor matched IPS cell lines. We don't know what the immune response or rejection rates will be and we don't understand what the necessary immunosuppressive strategies that will be necessary. Preclinical testing of efficacy and safety of the novel technologies for IPS cell based transplantation therapies in nonhuman primate (NHP) models would be critical for their clinical translation.

Cynomolgus macaques were introduced to the island of Mauritius around 400-500 years ago by humans. The founder population is likely to be very small considering the restricted genetic variability within the population. Roughly 5% of cynomolgus macaques from Mauritius are MHC homozygous allowing us to ask questions about MHC matching and IPS cell transplantation therapies.

We are currently collaborating with Excluded by Requester lab to generate IPS cell lines from MHC homozygous and matched donors for the purpose to hematopoietic stem cell (HSC) transplantation. Excluded by Requester lab will be responsible for the differentiation of IPS cells generated blood cells capable of engraftment. By creating MHC matched IPS cell lines, we hope that we can alleviate complications of HSC transplantation including graft versus host diseases (GVHD) and graft rejection. Currently we are in the process of reprograming skin fibroblast cells from MHC matched monkeys and delivering iPS cells to Excluded by Requester laboratory for differentiation into blood cells. Excluded by Requester lab has received one iPS cell line from a MHC matched animal and we are characterizing a second iPS cell line from a different MHC matched animal for Excluded by Requester lab.

Additionally, we will perform arterial transplants between MHC matched and mismatched pairs to look at graft rejection and immune activation to establish a baseline for rejection in MHC matched animals. Based of information learned we will have a better understanding of the utility of MHC matched iPS cell therapies. These experiments involve collaborators with expertise in regenerative medicine, tissue transplantation, and immunology. We currently have an approved animal use protocol and have obtained MHC matched donor/recipient pairs for the studies. We have began arterial transplant pilot studies in collaboration with vascular surgeons in the department of surgery and Excluded by Requester lab at the department of surgery. We are also beginning to optimize differentiation protocols to make clinically relevant cell types for non-human primates.

WORKING GROUP REPORTS

ENERGY METABOLISM AND CHRONIC DISEASE (EMCD) WORKING GROUP OVERVIEW

Working Group Co-Chairs Excluded by Requester PhD and Excluded by Requester PhD

The previously titled "Aging and Metabolism" scientific program has been re-established as the "Energy Metabolism and Chronic Disease" (EMCD) Working Group. This new focus is a consequence of strengthening evidence linking many of the major diseases associated with aging to abnormalities in energy metabolism. These aging-related diseases are serious concerns for the world's rapidly expanding population of older adults and include type 2 diabetes mellitus (T2DM) (1), many cancers (2), Alzheimer's disease (3) and Parkinson's disease (PD). The new EMCD Working Group has been developed to facilitate progress in the study of the following areas: 1) caloric restriction (CR), 2) obesity, metabolic syndrome (MetS), and T2DM, 3) mitochondrial dysfunction, 4) polycystic ovary syndrome (PCOS), and 5) estrogen signaling. Originally co-chaired by Excluded by Requester as of September 2014, this group is co-chaired by Excluded by Requester

KEY ACCOMPLISHMENTS

Working group members have made significant progress in a variety of lines of research, including the following important observations:

- Long-term caloric restriction (CR) reduces age-related and all-cause mortality in rhesus monkeys Excluded by Requester laboratory)
- Rhesus macaques show an age-related decline in white matter integrity and an anterior-to-posterior gradient in white matter vulnerability to normal aging as do humans. Excluded by Requester laboratory)
- A shift in energy metabolism precedes the onset of sarcopenia in rhesus monkeys. Excluded by Requester laboratory)
- Markers of metabolic function can be successfully performed in common marmosets. Excluded by Requester Excluded by Requester
- Vitamin D metabolites can be measured with highly precision and sensitivity in common marmosets using LC/MS/MS methods. Excluded by Requester
- A high fat diet decreases the beneficial effects of estrogen on serotonin-related gene expression in marmosets Excluded by Requester laboratory)
- Abnormal infant islet morphology precedes insulin resistance in PCOS-like monkeys Excluded by Requester laboratory)
- There is impaired preadipocyte differentiation into adipocytes in subcutaneous abdominal adipose of PCOS-like female rhesus monkeys Excluded by Requester laboratory)
- There are metabolic consequences of early onset obesity in common marmosets. Excluded by Requester

WORKING GROUP MEETINGS

EMCD meetings are planned for the 2nd Friday of the month. Recent meetings of the EMCD group have included:

October 10, 2014

Organizational and planning meeting of leadership and select members of EMCD

November 14, 2014

Seminar: Excluded by Requester PhD, Assistant Professor, Department of Bacterioology, UW-Madison

"The Intestinal Microbiota and Its Role in Health and Disease"

December 12, 2014

Seminar: Excluded by Requester MPH, PhD, Departments of Surgery and Veterinary Population Medicine, University of Minnesota

"Improving Face, Construct, and Predictive Validity in Animal Models of Diabetes"

January 9, 2015

Seminar Excluded by Requester PhD, Department of Cell and Regenerative Biology, UW-Madison

"Metabolomic Approaches for Providing Insight into Chronic Disease"

Meetings will continue through May and begin again in September.

EMCD CORE AND ASSOCIATE PRINCIPAL INVESTIGATORS

Investigator	Department	Institution	Core	Affiliate
Excluded by Requester	OB/GYN	University of Wisconsin	X	
	WNPRC	University of Wisconsin	X	
	Medical Physics	University of Wisconsin	X	
	Cell and Regenerative Biology	University of Wisconsin	X	
	WNPRC	University of Wisconsin	X	
	Neuroscience	University of Wisconsin	X	
	WNPRC	University of Wisconsin	X	
	Pediatrics	University of Wisconsin	X	
	Medicine	University of Wisconsin	X	
	WNPRC	University of Wisconsin	X	
	Biostatistics	University of Alabama, Birmingham		X
	Medicine	University of Wisconsin		X
	Zoology	University of Wisconsin		X
	Medicine	University of Wisconsin		X
	Psychology	University of Wisconsin		X
	Biostatistics	University of Alabama, Birmingham		X

Excluded by Requester	Division of Endocrinology, Diabetes and Hypertension	UCLA Private Source		X
	Pharmacy	University of Wisconsin		X
	Comparative Biosciences	University of Wisconsin		X
	Obstetrics and Gynecology	University of California-Los Angeles		X
	Psychology	University of Wisconsin		
	Medicine	University of Wisconsin		X
	Surgery	University of Wisconsin		X
	Cell and Regenerative Biology	University of Wisconsin		X
	Medicine	University of Wisconsin		X
	Ophthalmology & Visual Sciences	University of Wisconsin		X
	Medicine	University of Wisconsin		X
	Kogod Center on Aging	Mayo Clinic		X
	Medicine	University of Wisconsin		X
	Biochemistry	University of Wisconsin		X
	Biochemistry/Nutritional Sciences	University of Wisconsin		X
	Surgery	University of Wisconsin		X
	Biochemistry	University of Wisconsin		X
	Radiology	University of Wisconsin		X
	Bacteriology	University of Wisconsin		X
	Nutritional Sciences	University of Wisconsin		X
	Ophthalmology & Visual Sciences	Washington University		X
	Neurology	Private Source		X
	Nutritional Sciences	University of Wisconsin		X
	Neurobiology & Anatomy	Private Source		X
	Paso del Norte Institute for Healthy Living	El Paso, Texas		X
	Nutritional Sciences	University of Wisconsin		X

[1,2] Collaboration with Neuroscience[1] and Regenerative and Reproductive Medicine[2] Working Groups. Such collaborative research may be described in more detail in those sections.

GLOBAL INFECTIOUS DISEASE (GID) WORKING GROUP OVERVIEW

Working Group Chair Excluded by Requester Ph.D.

The Global Infectious Disease (GID) Working Group brings together investigators using nonhuman primates to study infectious disease pathogenesis and immunity. Much of the working group's effort is concentrated on HIV/AIDS-related projects, but the portfolio continues to expand. GID investigators now have established research programs on influenza, tuberculosis, and dengue, among other pathogens that impact human health. GID members also study a range of emerging and re-emerging pathogens with the potential to cause disease in humans and/or captive primates, including simian hemorrhagic fever viruses and pegiviruses. The past year also saw the successful recruitment of Dr. Excluded by Requester from Private Source to join the UW-Madison faculty and become a WNPRC core investigator affiliated with GID. Working group members gather monthly at the AIDS Vaccine Research Laboratory for a seminar and brainstorming session. The Working Group also fosters junior-senior partnerships to increase the likelihood of early career investigator success.

KEY ACCOMPLISHMENTS

Working group members have enjoyed multiple successes in the last reporting period, including:

- Discovering a potential role for GB virus C coinfection in reducing mortality associated with Ebola virus disease in humans Excluded by Requester
- Discovering a potential role for antibody-mediated cellular cytotoxicity (ADCC) in broadly corss-reactive immunity to influenza Excluded by Requester
- Discovery that HIV uses its Vpu protein to downregulate tetherin on the host cell and evade ADCC immunity Excluded by Requester
- Using whole-genome sequencing of macaques to identify candidate loci that influence host control of SIV replication Excluded by Requester
- Discovery of multiple novel viruses, including SIVs, SHFV-related arteriviruses, and GB virus C-related pegiviruses, in wild nonhuman primates in Africa Excluded by Requester
- Development of a marmoset model for influenza infection and transmission Excluded by Requester
- Strengthened collaborations with industrial and international partners studying infectious disease
- Forging research collaborations with scientists in other WNPRC divisions to explore the use of cellular therapies for SIV and other infectious diseases

GID SEMINAR SERIES

The following list of speakers demonstrates the success of the GID seminar series. This series has attracted consistently outstanding seminar speakers, which in turn leads to outstanding attendance by core GID members and other researchers from around UW-Madison.

Date	Speaker Name	Institutional Affiliation
02/25/2014	Excluded by Requester	Dept. of Pediatrics, University of Wisconsin School of Medicine and Public Health
04/09/2014		Department of Pediatrics, Private Source School of Medicine
05/07/2014		David Geffen School of Medicine, University of California, Los Angeles
07/09/2014		Private Source School of Medicine
08/01/2014		Dept. of Microbiology and Immunology, Private Source School of Medicine
08/06/2014		University of Alabama-Birmingham
08/19/2014		Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention
08/29/2014		Private Source School
10/03/2014		Division of Infectious Diseases Private Source School of Medicine

GID CORE AND ASSOCIATE PRINCIPAL INVESTIGATORS

Investigator	Department	Institution	Core	Affiliate
Excluded by Requester	Pathology and Laboratory Medicine	University of Wisconsin	X	
	Pathology and Laboratory Medicine	University of Wisconsin	X	
	WNPRC	University of Wisconsin	X	
	Pathology and Laboratory Medicine	University of Wisconsin	X	
	Pathobiological Sciences	University of Wisconsin	X	
	Genetics	University of Wisconsin	X	
	Pathology and Laboratory Medicine	University of Wisconsin	X	
	Comparative Biosciences, Obstetrics and Gynecology	University of Wisconsin	X	
	Pathobiological Sciences	University of Wisconsin		X
	Pathobiological Sciences	University of Wisconsin		X
	Pathobiological Sciences	University of Wisconsin		X
	Pathobiological Sciences	University of Wisconsin		X
	Department of Medicine	University of Wisconsin		X
	Pathology	University of Miami		X
	Microbiology	University of Minnesota		X
	Immunology	Private Source		X
	Vaccine Discovery			X

Excluded by Requester	Microbiology and Immunology	University of Oklahoma		X
	Immunobiology	Private Source		X
	Medicine	Private Source		X
	Private Source			X
	Veterinary and Biomedical Sciences	University of Minnesota		X
	Medicine	University of Colorado		X

[1]Indicates investigators associated with the Reproduction and Regenerative Medicine working group and whose research may be described in more detail in that section.

NEUROSCIENCE WORKING GROUP OVERVIEW

Working Group Co-Chairs Excluded by Requester PhD and Excluded by Requester PhD

The current Neuroscience Working Group is the most recently formed at WNPRC and has been instituted by the Director to address a clear need for re-recognition of this dynamic and flourishing research WNPRC discipline, concomitant with the creation of the newly formed Department of Neuroscience at SMPH in which Excluded by Requester is a senior faculty member. Neuroscience at WNPRC comprises 38 investigators from multiple Colleges, including basic and clinical departments, dedicated to advancing our understanding of the nervous system across levels ranging from molecular mechanisms to NHP behavior. WNPRC Neuroscience includes major contemporary thematic areas such as learning and memory, development, stem cells, sensory and motor systems, cognition and affect, appetitive behaviors, plasticity, and neurobiology of disease. The Neuroscience Training program and the Center for Neuroscience provide two active centralized forums, in addition to the Department of Neuroscience, where interdisciplinary neuroscientists engaged in NHP research converge. Translational research is a major focus of neuroscience at WNPRC. Top-of-the-line neural imaging facilities on campus enable both high-resolution analysis of pathophysiological neural activity by magnetic resonance imaging (MRI)-determined positron emission tomography (PET) quantification of glucose metabolism, as well as MRI-directed delivery of transgene or stem cell therapy designed to combat progressively disabling neural diseases. Taking advantage of this wealth of campus support, neuroscientists have capitalized on NHP models provided by the WNPRC to compete for NIH, industry and foundation funding enabling cutting-edge research focused in three major areas:

- Cognition and Mental Illness
- Homeostasis/Neuroendocrine Function
- Neurodegenerative Diseases
- New and Improved Methods

KEY ACCOMPLISHMENTS

Cognition and Mental Illness:

Excluded by Requester and their colleagues Excluded by Requester Excluded by Requester have continuously reported on the role of the central nucleus of the amygdala in anxious temperament (AT) in juvenile and adolescent monkeys. AT in children and juvenile monkeys is a risk marker for developing psychiatric disorders including clinical depression in later life, and early life stress (ELS) due to activation of hypothalamo-pituitary adrenal axis predicts later psychological wellness. First, studies with positron emission tomography (PET) indicate almost identical changes in the central nucleus (Ce) of the amygdala of AT children and juvenile monkeys when compared to control Excluded by Requester al., 2014) Excluded by al. (2014) found lower mRNA levels of neuropeptide Y receptor 1 (NPY1R) and NPY5R but not NPY or NPY2R in the Ce in AT monkeys, in contrast to no changes in NPY1R and NPY5R mRNA levels in the motor cortex Excluded by Re et al. (2014) found that DNA of two genes, BCL11A and JAG1, in the Ce of AT monkeys is highly methylated, compared to control monkeys. Because BCL11A and JAG1 transcripts have been well-defined in neurodevelopmental processes, including neurite arborization and the regulation of neurogenesis, the findings represent a critical step toward understanding the effects of early environment on the underlying neuromolecular mechanisms which develop into anxiety and depressive disorders.

Excluded by Requester and his colleagues Excluded by Requester studied impulsivity (the predisposition to act without regard for negative consequences), a characteristic of several psychiatric disorders, in male rhesus monkeys. They found that impulsive monkeys had three single nucleotide polymorphisms (SNPs) in the 3'-UTR of the dopamine transporter (DAT) gene and DNA of one of the SNPs in the impulsive but not the calm subjects was methylated. Furthermore, there were altered neuronal circuits in the internal globus pallidus, an output nucleus of the basal ganglia and there was an association between increased methylation in the DAT gene and greater DAT availability in impulsive monkeys. These data suggest that mutations to the regulatory portion of the DAT gene lead to a susceptibility to epigenetic modification resulting in a discrete behavioral phenotype.

Homeostasis/Neuroendocrine Function:

Excluded by Requester with their collaborators Excluded by Requester Excluded by Requester n WNPRC and Excluded by in ONPRC) demonstrated beneficial effects of estradiol replacement therapy in brain function using a marmoset monkey model for menopause in women Excluded by Requester et al., 2015). They found that ~6 month treatment with estradiol in ovariectomized female marmoset monkeys increases gene expression of tryptophan hydroxylase 2 (TPH2, an enzyme crucial for the production of serotonin, the major neurotransmitter responsible for healthy mood), corticotropin-releasing factor receptor type 2 (CRF-R2, an anxiolytic receptor that is important for stimulating serotonin neurotransmission), and monoamine oxidase-B (MOA-B, an enzyme that preferentially degrades norepinephrine and dopamine, two additional neurotransmitters implicated in depression and mood disorders). Importantly, feeding marmosets a high fat diet prevented the beneficial effects of estradiol, suggesting that post-menopausal women eating a high fat diet, even when receiving estradiol replacement, could experience diminished TPH2 expression leading to depression and cognitive impairment, diminished CRF-R2 possibly leading to increased food consumption, and diminished MOA-B possibly leading to increased anxiety. These findings have significantly important implications for women's health and hormone replacement therapy. The group has received two (one P50 and one R01) NIH grants to investigate targeted knockdown of estrogen action in discrete areas of the hypothalamus of the adult female marmoset brain to pinpoint estradiol's mechanism of action on behavior and food consumption.

Excluded by Requester and her colleagues Excluded by Requester continue to study their hallmark finding indicating that estrogen rapidly induces excitatory action mimicking neuroestradiol, synthesized in the hypothalamus Excluded by Request et al., 2013). Recently, they found that estradiol induces direct excitatory effects on GnRH and kisspeptin neuroterminals in the stalk-median eminence, regardless of the dose and length of exposure. This finding has considerable importance and implications to the classical concept of the negative and positive feedback effects of estradiol, as it clearly demonstrates the requirement of estrogen action to the cell body of neurons with nuclear estrogen receptors In Press al., in press). The finding of neuroestradiol by Excluded by Requester led to funding of an NIH R21 grant.

Neurodegenerative Diseases:

Parkinson's disease (PD) is impaired motor function controlled by the brain, but also a multisystem disorder affecting several functions regulated by the peripheral nervous system. During 2014 Excluded by Requester Excluded by Requester and her colleagues created a monkey model of cardiac dysautonomia using iv injection of 6-hydroxydopamine (6-OHDA) in rhesus monkeys. Systematic analysis indicates that the 6-OHDA treatment results in cardiac sympathetic neurodegeneration and loss of catecholaminergic enzymes in the adrenal medulla. Therefore, the model established in the rhesus monkey can be used to evaluate disease-modifying strategies aiming to induce peripheral neuroprotection Excluded by Requester et al., 2014). This

finding led to an NIH R21 grant.

Excluded by Requester and their colleagues showed using a deterministic fiber tracking brain imaging method that there was an age-related decline in white matter integrity reported in humans and monkeys, and the anterior-to-posterior gradient in white matter vulnerability to normal aging in humans. The effect of calorie restriction on brain aging in this unique cohort of elderly primates remains to be examined Excluded by Requester et al., 2014).

Because of anatomical and functional similarities of the eye between the rhesus monkey and humans, but not other species, Excluded by Requester continue to investigate the etiology of presbyopia and glaucoma using rhesus monkeys Excluded by Requester et al., 2014). Their findings could lead to effective treatment tools for human patients suffering with glaucoma and severe forms of presbyopia.

New and Improved Methods:

Development of new approach or improving existing methods is critical for research in neuroscience. Excluded by Requester (2014) established a new method assessing hormonal environment during the fetal period by measuring hormone levels of hair obtained at birth.

Excluded by Requester and their colleague made an Atlas of young rhesus macaques brain based on diffusion tensor imaging (DTI) data Excluded by Requester et al., 2014), which will be greatly useful for non-human primate researchers.

Environmental enrichment plans for laboratory-housed nonhuman primates is also important for health of animals as well as for animal welfare, but it can be very expensive. Excluded by Requester Excluded by Requester compared 7 types of foraging devices and made recommendations for cost effective facility improvements with evidence-based practices and common standards to enhance laboratory animal welfare Excluded by Requester et al., 2014).

NEUROSCIENCE WORKING GROUP MEETINGS

During 2014, eight core and affiliate members of the Neuroscience Working Group gave talks.

January 17: Excluded by Requester (Associate Professor, Dept. Neuroscience) gave a talk entitled "In Search of the Mechanisms Underlying Impulsivity: Potential Contributions of the Dopamine Transporter".

February 21: Excluded by Requester (Professor, Dept. OBGYN and Senior Scientist, WNPRC) gave a talk entitled "Neuroimaging into Serotonergic Manipulation of Sexual and Affiliative Behavior in Female Marmosets".

March 21: Excluded by Requester (Professor, Dept. Neuroscience, and Director of WNPRC) gave a talk entitled "Of Mice and Monkeys: Do Estrogen Actions Translate?"

April 18: Excluded by Requester (Dept. Ophthalmology and Visual Sciences) gave a talk entitled "Presbyopia – Up Close".

May 23: Excluded by Requester (Professor, Dept. Psychiatry) gave a talk entitled "Developmental Factors Underlying the Risk toDevelop Anxiety and Depression"

October 17: Excluded by Requester (Professor, Dept. Ophthalmology and Visual Sciences) gave a talk entitled "Outer Retinal Injury in Glaucoma."

November 21 Excluded by Requester (W.B. Cannon Professor, Dept. Psychology, Director, Harlow Primate Lab) gave a talk entitled "Paradigm-Changing Discoveries about the Gut Microbiome".

December 19: Excluded by Requester (Professor Emeritus, Dept. Psychology) gave a talk entitled "The Evolution of Music".

All talks are new in respective research fields in neuroscience and unique in non-primate species. As such, findings by Excluded by Requester would lead to new treatment tools in Psychiatry (childhood depression) and Ophthalmology (presbyopia and glaucoma), respectively.

The table below outlines the content of each Neuroscience Working Group Meeting held in 2014.

Neuroscience Working Group Meetings and Seminar Series

Date	Speaker Name	Institutional Affiliation	Seminar Title
1/17/2014	Excluded by Requester Ph.D.	Associate Professor, Department of Neuroscience, University of Wisconsin	In Search of the Mechanisms Underlying Impulsivity: Potential Contributions of the Dopamine Transporter
2/21/2014	Excluded by Requester Ph.D.	Professor, Department of Obstetrics and Gynecology, and Senior Scientist, WNPRC, University of Wisconsin	Neuroimaging into Serotonergic Manipulation of Sexual and Affiliative Behavior in Female Marmosets"
3/21/2014	Excluded by Requester Ph.D.	Professor, Department of Neuroscience, University of Wisconsin, Director, WNPRC	""Of Mice and Monkeys: Do Estrogen Actions Translate?"
4/18/2014	Excluded by Requester M.D.	Professor, Department of Ophthalmology and Visual Sciences, University of Wisconsin	Presbyopia – Up Close".
5/23/2014	Excluded by Requester M.D.	Professor, Department of Psychiatry, University of Wisconsin	"Developmental Factors Underlying the Risk to Develop Anxiety and Depression"
10/17/2014	Excluded by Requester M.S., M.D.	Professor, Department of Ophthalmology and Visual Sciences, University of Wisconsin	"Outer Retinal Injury in Glaucoma."
11/21/2014	Excluded by Requester Ph.D.	W.B. Cannon Professor, Department of Psychology, Director, Harlow Primate Lab, University of Wisconsin	Paradigm-Changing Discoveries about the Gut Microbiome"
12/19/2014	Excluded by Requester Ph.D.	Professor Emeritus, Department of Psychology, University of Wisconsin	"The Evolution of Music".

NEUROSCIENCE CORE AND ASSOCIATE PRINCIPAL INVESTIGATORS

Investigator	Department	Institution	Core	Affiliate
Excluded by Requester	Neuroscience	University of Wisconsin	X	
	Pediatrics	University of Wisconsin	X	
	Medical Physics	University of Wisconsin	X	
	Obstetrics and Gynecology	University of Wisconsin	X	
	WNPRC	University of Wisconsin	X	
	WNPRC	University of Wisconsin	X	
	Pediatrics – SMPH	University of Wisconsin		X
	WNPRC	University of Wisconsin		X
	Psychiatry	University of Wisconsin		X
	Neuroscience	University of Wisconsin		X
	Psychology	University of Wisconsin		X
	Psychology	University of Wisconsin		X
	Neuroscience	University of Wisconsin		X
	Ophthalmology and Visual Sciences	University of Wisconsin		X
	Ophthalmology and Visual Sciences	University of Wisconsin		X
	Medicine	University of Wisconsin		X
	Medical Physics	University of Wisconsin		X
	Anatomy and Neurology	University of Wisconsin		X
	Psychology	University of Wisconsin		X
	Psychology	University of Wisconsin		X
	Psychology	University of Wisconsin		X
	Medical Physics	University of Wisconsin		X
	Psychology	University of Wisconsin		X
	Waisman Center	University of Wisconsin		X
	Obstetrics and Gynecology	University of Wisconsin		X
	Neuroscience	University of Wisconsin		
	Biology	UW-Whitewater		X
	Biology	UW-Milwaukee		X
	Molecular Physiology and Genetics	NIH-NIA		X
	Neuroscience	Oregon Health and Science University		X
	Neuropsychology	NIH-NIMH		X
	Physiology of Cognitive Processing	Private Source		X
	Division of Endocrinology, Diabetes and Hypertension	UCLA		X
	Neurology	Private Source		X
	Biology	University of California-Irvine		X
	Psychology	Private Source		X
	Psychiatry			X
	Mammal Research Institute			X
	Obstetrics and Gynecology	UCLA		X
	Pediatrics	University of California-Davis		X
	Medicine	Cedars-Sinai Medical Center, UCLA		X

Investigator superscript numbers indicate active collaboration with other WNPRC Working Groups: (1) Energy Metabolism and Chronic Disease, (2) Regenerative and Reproductive Medicine.

FUTURE PLANS

In 2015, we have plans to highlight postdoctoral research fellows, graduate students, and undergraduate students, who conduct experiments under the instruction of the PI. We will continue to facilitate collaborative projects among our members.

LITERATURE CITED

Excluded by Requester 2014 Differentially methylated plasticity genes in the amygdala of young primates are linked to anxious temperament, an at risk phenotype for anxiety and depressive disorders. J Neurosci 34:15548-15556.

Excluded by Requester 2014 Assessment of foraging devices as a model for decision-making in nonhuman primate environmental enrichment. J Am Assoc Lab Anim Sci 53:452-463.

Excluded by Requester 2015 High fat diet decreases beneficial effects of estrogen on serotonin-related gene expression in marmosets. Prog Neuropsychopharmacol Biol Psychiatry. 58:71-80.

Excluded by Requester

Excluded by Requester 2014 Evolutionarily conserved prefrontal-amygdalar dysfunction in early-life anxiety. Mol Psychiatry 19:915-922.

Excluded by Requester 2014 Morphological alterations within the peripheral fixation of the iris dilator muscle in eyes with pigmentary glaucoma. Invest Ophthalmol Vis Sci 55:4541-4551.

Excluded by Requester 2014 Cardiac sympathetic denervation in 6-OHDA-treated nonhuman primates. PLoS One 9:e104850.

Excluded by Requester 2014 Hormones in infant rhesus monkeys' (Macaca mulatta) hair at birth provide a window into the fetal environment. Pediatr Res 75:476-481.

Excluded by Requester 2013 Neuroestradiol in the hypothalamus contributes to the regulation of gonadotropin releasing hormone release. J Neurosci 33:19051-19059.

In Press

Excluded by Requester 2014 Dopamine transporter gene susceptibility to methylation is associated with impulsivity in nonhuman primates. J Neurophysiol 112:2138-2146.

Excluded by Requester 2014 Neuropeptide y receptor gene expression in the primate amygdala predicts anxious temperament and brain metabolism. Biol Psychiatry 76:850-857.

Excluded by Requester

Excluded by Requester 2014 Effect of age and calorie restriction on corpus callosal integrity in rhesus macaques: a fiber tractography study. Neurosci Lett 569:38-42.

Excluded by Requester 2014 A diffusion-tensor-based white matter atlas for rhesus macaques. PLoS One 9:e107398.

REGENERATIVE AND REPRODUCTIVE MEDICINE (RRM) WORKING GROUP OVERVIEW

Working Group Co-Chairs: Excluded by Requester PhD and Excluded by Requester MD, PhD

The Regenerative and Reproductive Medicine (RRM) working group includes investigators across a variety of disciplines. In the P51 renewal application, RRM set the broad goal of establishing highly collaborative efforts with other WNPRC working groups and units. Specifically, the WNPRC proposed to

1. Establish a novel Bone Marrow Transplantation core to advance the development and use of NHP models for hematopoietic, endothelial, islet, and neural cell transplantation.
2. Derive nonhuman primate transgene-free iPSC lines and optimize of conditions for their maintenance.
3. Define maternal and fetal outcomes in immunological and anemic stress, intrauterine metabolic stress, and infection, and
4. Refine and advance reproductive tract fertility and transgenesis opportunities.

Collectively, these efforts will expand the opportunities for translational studies in regenerative and reproductive medicine and provide exciting new breakthroughs in NHP models.

KEY ACCOMPLISHMENTS

1. **Establish a novel Bone Marrow Transplantation core to advance the development and use of NHP models for hematopoietic, endothelial, islet, and neural cell transplantation,**

Major activities

- NHP BMT core has been established.
- NHP BMT working group has been organized.
- Collaboration Established/Submitted Grant Applications:

  i)Transplantation of Induced Pluripotent Stem Cell (iPSC) Derived Hematopoietic Cells to Achieve Stable Mixed Chimerism in a Rhesus Model Excluded by Requester Dept. of Surgery Excluded by Requester WNPRC Opportunities Pool U01 Grant NIH)

  ii) Prevention of Delayed Graft Function in Kidney Transplantation by iPSC-derived MSCs Excluded by Requester Excluded by Requester Dept. of Surgery Excluded by Requester WNPRC, R01 NIH)

  iii Pending Support

  Pending Support

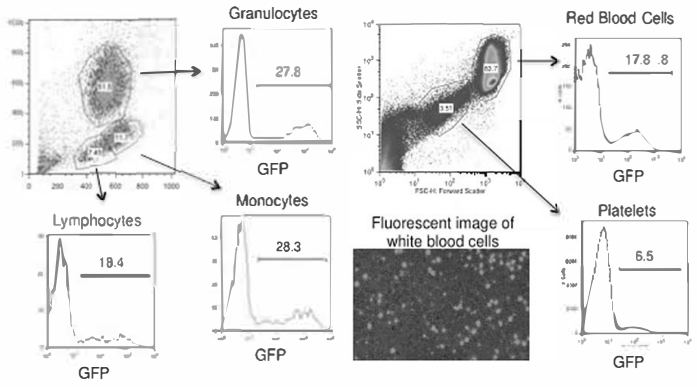


Figure 1. Multilineage engraftment of blood cells following transplantation of autologous CD34+ cells transduced with eGFP in MCM.

Significant results

- Developed protocol for efficient isolation of CD34+ hematopoietic stem cells (HSCs) from Mauritian cynomolgus monkey (MCM).
- In collaboration with Private Source (La Jolla, CA) developed method for highly efficient gene transfer into monkey HSCs (rapamycin-based protocol >90% gene transfer efficiency)
- Successful bone marrow in MCMs using nonmyeloblative XF-RIC regimen.
- Successful bone marrow in MCMs using myeloblative regimen (Figure 1).
- System for efficient de novo production of blood from rhesus and cynomolgus monkey, including MCM, induced pluripotent stem cells was developed (Figure 2).

Key outcomes

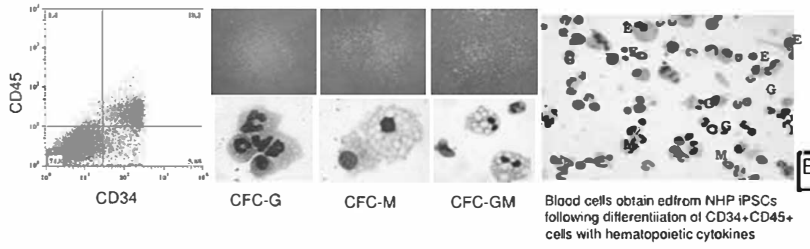


Figure 2. Hematopoietic differentiation of cynomolgus monkey iPSCs.

MHC-defined nonhuman primate model for bone marrow transplantation has been established. Collaborative pilot project "MHC defined NHP model for BMT (ICTR pilot grant, Excluded by Requester PIs) within BMT group renewed for funding in 2015. Collaborative pilot project "Prevention of delayed graft function in kidney transplantation by iPSC derived MSC" (WNPRC pilot grant, Excluded by Requester PI, Excluded by Request co-I) successfully completed.

2. Derive nonhuman primate transgene-free iPSC lines and optimize of conditions for their maintenance.

Major activities

- Derivation of transgene-free iPSC cell lines from Mauritian Cynomolgus Monkey (MCMs)
- Optimization of conditions for maintenance of MCM iPSCs.
- In collaboration with BMT core studies on transfusion of iPSC-derived blood products were initiated.
- The Excluded by Requester laboratories obtained skin samples for iPSC derivation from animals selected for MPTP-induced parkinsonism, with the goal of treating animals with autologous cells following disease induction.

Significant results

- Several iPSC cell line from MCMs were generated
- Chemically defined conditions for maintenance MCM iPSCs has been optimized
- 10 MPTP-treated rhesus monkeys have received intracerebral injections of autologous iPSC, or control CSF.

Key outcomes

- The generation of MCM iPSCs provided background for moving forward with developing MCM model for the preclinical testing stem cell derived cellular therapies.
- Following behavioral testing, brains of one control and one iPSC-engrafted animal were obtained at necropsy and preliminary analysis showed the presence of GFP+ cells in the iPSC-engrafted animal.

3. Define maternal and fetal outcomes in immunological and anemic stress, intrauterine metabolic stress, and infection

Major activities

- Demonstrated consistent abortifacient effect of Listeriosis in early pregnancy in cynomolgus macaques
- Established linkages with investigators working with other organisms that may contribute to adverse pregnancy outcomes
- Began discussion of how to approach the biology of the microbiome in reproductive tract biology

Significant results

- Reproducible fetal death in early gestation with intragastric infection with *Listeria* in pregnant cynomolgus monkeys established a new paradigm for assessing the ontogeny of infection on uteroplacental pathophysiology.
- *In vitro* experiments with tissue explants and cultured endometrial epithelial and endothelial cells demonstrated significant permissiveness of the endometrium for bacterial infection
- Epithelial and endothelial cells have substantial differences in supporting bacterial replication, possibly pointing towards the cellular route by which placental damage and fetal infection occur

Key outcomes

- An R01 proposal submitted by Excluded by Requester was funded to define the effects of infection on endometrial vs. peripheral blood immune responses, and the impact of pregestational infection on subsequent reinfection during pregnancy.
- Excluded by Requester University of Florida, have received a WNPRC Pilot Project to support pilot studies with *Porphyromonas gingivalis* to develop a model of periodontal disease and adverse pregnancy outcomes.

4. Refine and advance reproductive tract fertility and transgenesis opportunities.

Major activities

- The Excluded by R equester labs, supported by the WNPRC Stem Cell Resource, initiated the derivation of marmoset iPS cells to optimize genomic editing of selected target genes for Parkinson's Disease.
- Excluded by R equester has been developing a marmoset model of fertility protection against chemotherapeutic agents, in collaboration with Excluded by Requester
- Excluded by R equester further characterized the reproductive phenotype of adult female rhesus monkeys with high testosterone (T), a naturally occurring hyperandrogenism that may resemble the hyperandrogenism of women with polycystic ovary syndrome (PCOS).

Significant results

- A consistent marmoset ovarian stimulation paradigm was reestablished.
- Marmoset skin fibroblasts have been reprogrammed to cells expressing pluripotency markers and exhibiting morphological iPSC characteristics.
- Marmoset iPSC can be reliably differentiated to neuroectodermal progenitors, motor neurons, and neuroglia.
- Adult female rhesus monkeys with high T have elevated circulating levels of luteinizing hormone (LH) and antimullerian hormone (AMH), but normal circulating levels of follicle stimulating hormone (FSH). High LH in females with high T may indicate reduced negative feedback regulation of LH similar to the neuroendocrinopathy of LH hypersecretion in women with PCOS. High AMH, on the other hand, may indicate above normal numbers of growing ovarian follicles, a trait also found in women with PCOS.

Key outcomes

- Pending Support
- Pending Support
- Pending Support
- Additional characterization of this PCOS-like monkey model is being made possible by a newly acquired competitive P50 grant renewal, PI Excluded by Requester (University of Virginia), in April 2014.

Areas of Progress

- Continue monitoring of HSC engraftment to establish engraftment parameters.
- Continue collaboration with Excluded by R equester Private Source on development of iPSC-based therapies for bone marrow failure. Perform transplantation of iPSC-derived hematopoietic progenitors. Pending Support
  Pending Support
- Explore the potential of iPSC-derived hematopoietic cells in establishing mixed chimerism and tolerance to kidney allograft (collaborative project with Excluded by Requester
- Establish collaboration with Excluded by R equester (WNPRC) to explore stem cell technologies for expression of HIV-neutralizing antibodies.
- Continue studies of iPSC-derived MSCs for prevention of delayed graft function.
- Excluded by R equeste The lab will continue their collaboration with Excluded by R equester to evaluate the efficacy of transplantation of pluripotent stem cell-derived dopaminergic neurons in the NHP parkinsonian model.
- The Excluded by R equester labs will work to transfer CCR5 genomic editing to macaque embryos as funds become available to reestablish macaque embryology are pursued.
- Excluded by R equester The lab will initiate pilot studies with Excluded by R equester of the University of Florida to develop a NHP model of *Porphyromonas gingivalis*-mediated reproductive tract infection, relevant to the recognized association between periodontal disease and adverse pregnancy outcomes.
- Pending Support
- Excluded by R equester have been discussing opportunities for placental vascular imaging with primate models.

RRM CORE AND ASSOCIATE PRINICIPAL INVESTIGATORS

Investigator	Department	Institution	Core	Affiliate
Excluded by Requester	Cell and Regenerative Biology	University of Wisconsin		
	Pathology and Laboratory Medicine	University of Wisconsin	X	
	Comparative Biosciences, Obstetrics and Gynecology	University of Wisconsin	X	
	Medicine	University of Wisconsin	X	
	WNPRC	University of Wisconsin	X	
	Medical Physics	University of Wisconsin	X	
	Pediatrics	University of Wisconsin	X	
	Obstetrics and Gynecology	University of Wisconsin	X	
	Neuroscience	University of Wisconsin	X	
	Cell and Regenerative Biology	University of Wisconsin	X	
	Medicine	University of Wisconsin		X
	Surgery	University of Wisconsin		X
	Surgery	University of Wisconsin		X
	Surgery	University of Wisconsin		X
	Pediatrics	University of Wisconsin		X
	Surgery	University of Wisconsin		X
	Neuroscience	University of Wisconsin		X
	Surgery	University of Wisconsin		X
	Medical Physics	University of Wisconsin		X
	Psychology	University of Wisconsin		X
	Obstetrics and Gynecology	University of Wisconsin		X
	Neuroscience	Private Source		X
	Obstetrics and Gynecology			X
	Pathobiological Sciences	University of Wisconsin		X
	Pathobiological Sciences	University of Wisconsin		X
	Obstetrics and Gynecology	University of Wisconsin		X
	Obstetrics and Gynecology	University of Wisconsin		X

Investigator superscript numbers indicate active collaboration with other WNPRC Working Groups: (1) Energy Metabolism and Chronic Disease, (2) Regenerative and Reproductive Medicine.

RRM DETAILED MEETING HISTORY

Date(s) of meeting	Meeting location	Guest Speaker [name, credentials, institution] *(if applicable)*	Meeting topic(s)	Notable outcomes and/or impact
2/18/2014	WNPRC	Excluded by Requester	Discussion of the recent progress in BMT model and future needs.	1. The group emphasized the need for establishing technologies for efficient HSC collection and transduction 2. New collaborative projects were initiated, including how to apply BMT model to study AIDS and developing curative therapies Excluded by Requester iPSC-derived HSPCs for tolerance to kidney graft.
8/21/2014	WNPRC	Excluded by Requester	Primates and Prospects: Nonhuman Primate Transgenic Models for Human Therapeutic Advances	An overview was given of the new and traditional opportunities for transgenesis and genomic editing in nonhuman primate embryos.
12/18/2014	WNPRC	Excluded by Requester	Update of experiment plans for Listeria infection	Updated SOPs for *in vivo* Listeria infection studies.

ADDITIONS/DELETIONS:

New affiliate investigators have been added:

Excluded by Requester DVM, Ph.D., Dept. of Microbiology and Pathology, University of Florida.

Excluded by Requester M.D., Dept. of Obstetrics and Gynecology, UW-Madison

WNPRC PILOT PROGRAM

WNPRC PILOT PROJECTS FUNDED IN 2012-2013

	Project Title	Principal Investigator(s)	Dates of funding	Amount of funding	Co-funded?	Resources used*
1	Lymph nodes are reservoirs for increased viral diversity	Excluded by Requester	01/01/2013-12/31/2014	$49,820	WNPRC only	VS, GS, PS
2	Therapeutic Vaccination during SIV Infection	Excluded by Requester (Collaboration with Excluded by Requester	01/01/2013-12/31/2014	$50,000	WNPRC only	SPI, IS, VS, PS
3	MHC-defined Nonhuman Primate Model for Bone Marrow Transplantation	PI: Excluded by Co-PI: Excluded by Excluded by Requester	01/01/2014-12/31/2015	$81,550	Yes, ICTR/ WNPRC	SPI, VetS, PS

* Aging Colony (AC); Assay Services (AS); Behavioral Management (BM); Elite Controller (EC); Genetics Services (GS); Immunology Services (IS); Pathology Services (PS); Scientific Protocol Implementation (SPI); Stem Cell (SC); Veterinary Services (VetS); Virology Services (VS); Information Technology and Systems (IT); Compliance and Training (CT)

PILOT PROJECT PROGRESS OR FINAL REPORTS

Project Title: Lymph Nodes are a Reservoir for Increased Viral Diversity

Name, Title, Institutional Affiliation: Excluded by Requester Ph.D., Assistant Professor, Department of Pathology and Laboratory Medicine, University of Wisconsin, Madison

Years Funded: 01/01/2013-12/31/2014

Project Abstract: There is enormous potential for virus diversification in the lymph node, but most studies examine virus variability in the blood. There is likely extensive viral diversity in the lymph nodes that is entirely overlooked when sequence variability of only examined in the periphery, Virus diversity, however, is one of the major challenges to constructing a successful HIV vaccine. By understanding the extent of virus diversity in the lymphoid tissues, we can better design an HIV vaccine that bolsters host immunity at these critical sites to minimize virus diversification and reduce the likelihood that a highly fit virus will replicate systematically. Dissecting out the contribution of host immunity and viral fitness to the dynamics of replication in the lymphoid tissues and the periphery is impossible to do with SIV mixtures containing viruses of variable fitness. An SIV stock with both the properties of a mixture and a clone is needed to carefully study virus dynamics and vaccine efficacy in the lymphoid tissues and the periphery, but it does not exist. We have created SIVmac2.0, which is a challenge stock comprised of a library of unique virus genotypes based on the clonal SIVmac239 sequence. The population of genotypes in the tissues and the blood can be characterized by deep sequencing a 39 nucleotide in env. In this WNPRC pilot project, we will use SIVmac2.0 to test the hypothesis that there is greater SIV viral diversity in lymph nodes than in the blood.

For this project, we will infect two *Mamu-A1*001:01*+ Indian rhesus macaques intravenously with SIVmac2.0 and use deep sequencing to characterize virus diversity in the lymph nodes and blood. In the first aim, we will determine whether there are virus genotypes of SIVmac2.0 present in the lymph node that do not replicate systematically during acute infection. In the second aim, we will determine whether a single peripheral CD8 T cell escape mutation is derived from one of several independent mutation events in the lymph node. Consistent with our hypothesis, we expect that in the absence of fitness variability, the diversity of SIVmac2.0 virus genotypes will be greater in the lymph nodes than in the periphery. This observation would argue in favor of testing preclinical HIV vaccines that could specifically elicit T cell responses in lymph node tissues, potentially reduce virus diversity, and prevent the systematic replication of highly fit viruses.

Progress to Date: During this past year, we made a major shift in our approach to this project, but it greatly helped us make progress. We were unable to create the SIVmac2.0 virus as we originally proposed. After an extensive amount of sequencing, we learned that the plasmid stock that we were using to create the SIVmac2.0 virus was littered with point mutations that prevented functional virions from being created. So, we contacted Excluded by Requester at NCI/NIH (AIDS and Cancer Virus Program) to obtain a different virus stock for this study. Excluded by Requester prepared a virus stock based on SIVmac239 into which he inserted a 34 nucleotide barcode between the Vpx and Vpr genes. This way, the barcode did not affect any of the expressed SIV genes and replicate to high titer, while still being able to characterize the barcode. We decided to call Excluded by Requester virus SIVmac3.0

We obtained SIVmac3.0 and sequenced the virus stock to ensure that there was a diversity of barcodes detectable by our sequencing methods. We found between 5000 and 6000 barcodes present in the virus stock, which was on par with the numbers observed by Excluded by Requester We have since infected two animals with this virus stock: cy0428 and cy0575. Both animals were euthanized at 12 weeks after infection. We collected a large number of samples during infection. We collected blood twice weekly

during the first month and every 2 weeks thereafter. We collected lymph nodes at weeks 2, 4, and 8. We collected cells from bronchoalveolar lavage at week 8 from cy0428, and then we collected cells from the bronchoalveolar lavage during acute infection and at week 8 from cy0575. At necropsy, we worked closely with Pathology Services to collect tissues throughout the animal, including peripheral lymph nodes, gut lymph nodes, brain tissue, liver tissue, lung tissue, heart, spleen, bone marrow, GI tissues, and brain tissues. By sequencing the barcode in replicating virus and integrated virus, we expect to get a picture of the virus dynamics during the course of infection.

To date, we have deep sequenced virus populations replicating in cy0428 throughout infection and during the first four weeks of infection in cy0575. During the first four weeks of cy0428 infection, we found that the barcode sequences detectable in circulating plasma fluctuated. These sequences were diverse and they continued to change over time. After four weeks, a single barcode comprised a majority of the virus population in cy0428 and persisted throughout the remainder of infection. Remarkably, the barcode sequence present at high frequency in the plasma was present in less than 10% of the viruses circulating in the CSF at necropsy. To date, we only have sequence information up to week 4 in cy0575. We have observed similar fluctuations in the barcodes up to week 4, and then the virus population has begun to fixate on a single barcode. Further experiments will need to determine if this single barcode persists in the plasma until necropsy.

In addition to our analyses of circulating virus populations, we have generated amplicons spanning the barcode of integrated viruses present in cy0428 during infection and from the tissues at the time of necropsy. These will be tagged and sequenced on the Miseq in the coming weeks. Similar generation and tagging of amplicons from cy0575 will be performed in the coming months.

While we have not yet published any materials from this project, we have made great progress on our data collection in the past year. I anticipate that we will be able to describe the data collected in a manuscript later this year. In addition, [Excluded by Requester] is coming to visit UW as part of the Cellular and Molecular Pathology Program in March, and we hope to discuss this project and potential use of the SIVmac3.0 virus in the future.

Full bibliographic materials on each paper published, in press, or submitted: None.

Grant applications and funded grants resulting from this project: None.

Project Title: Therapeutic Vaccination During SIV Infection

Name, Title, Institutional Affiliation: PI: Excluded by Requester Ph.D., Assistant Professor, Department of Microbiology, University of Minnesota; Co-I: Excluded by Requester Ph.D., Assistant Scientist, Wisconsin National Primate Research Center, University of Wisconsin, Madison

Years Funded: 01/01/2013-12/31/2014

Project Abstract: A major goal in HIV biomedical research is to develop therapies to eradicate established HIV infection. Immunotherapy is one way of harnessing the immune system to target infected cells, however, this is hampered by T cell dysfunction or exhaustion. We have recently discovered a novel therapeutic vaccination strategy that reverses established T cell tolerance and exhaustion to self-antigen, as well as during a chronic viral infection in mice. This vaccination platform yields a significant drop in viral loads in chronically infected mice. We will test this same therapeutic vaccination strategy in SIV infected Rhesus macaques. Our hypothesis is that established T cell tolerance and exhaustion to HIV and SIV can be overcome in an antigen-specific way using our novel therapeutic vaccination strategy, leading to emergence of extremely large numbers of SIV-specific CD8 T cells mediating elimination of chronic infection. This will be accomplished by infecting Rhesus macaques with SIV, waiting about 80 days until viral set-point is reached. A portion of NHP will receive the therapeutic vaccination platform. This consists of sequential immunizations with different vectors, all producing the SIV gag protein. We have determined that the key factor in this therapy is the use of multiple, distinct boosting vectors. Simply, one boost is not enough. Therefore, the study will be structured as follows: the first immunization will consist of a recombinant vesicular stomatitis virus-SIVgag. 35 days later, the same NHP will be infected with vaccinia virus-SIVgag and a third vaccination will be given 35 days later, consisting of a different serotype of VSV-SIVgag. Before each new vaccination, viral load, T cell counts and T cell phenotype will be evaluated. This same analysis will occur at days 7, 14 and 35 after each vaccination step. Our aims are to: determine whether our heterologous therapeutic boosting strategy will decrease SIV viral load in chronically infected Rhesus macaques and investigate the SIV-specific CD4 and CD8 T cell response in therapeutically vaccinated Rhesus macaques. We expect that our heterologous therapeutic vaccination platform will mirror our murine studies and result in a significant decrease in SIV levels and increase in the number and functionality of SIV-specific T cells. If these experiments are successful, we can seek funding to expand our study to a larger number of animals, determine if this same strategy would work under conditions of low viral load (i.e. with HAART) and aim to translate this therapy for use in HIV infected individuals.

Progress to Date: Our project focuses on antigen-specific immunotherapy during established SIV infection in *Rhesus macaques* to boost immune responses to SIV. As shown in figure 1, we demonstrate that antigen-specific therapeutic vaccination greatly increased *functional* SIV-specific T cell responses. Indeed, there was a 40- to 115-fold increase in the numbers of these cells after our vaccination platform. Interestingly, the first vaccination (which we know is immunogenic in naïve NHP[data not shown]) did not alter the exhausted SIV-specific T cell population; it was the addition of subsequent heterologous boosts that resulted in large increases in the immune response. This mirrors our murine results, whereby reversal of tolerant T cell populations required multiple antigenic challenges; this had formed the rationale for these NHP experiments. Thus, we have tested our hypothesis as outlined in the pilot project proposal and found that we can rejuvenate immune responses in SIV infected NHP in an antigen-specific fashion. Another noteworthy result from our studies is the capacity of SIV chronically infected NHP with reduced T cells counts and/or monkey AIDS to tolerate i.v. infections with live, replicating viruses and have no adverse effects. We have at least 7 NHP, which have gone through this regimen, and no adverse events of vaccination were noted.

We found that SIV viremia did not change despite the large increase in SIV-specific T cells. We believe one reason for this is the high viral load in the SIV infected NHP. The number of SIV infected cells is

potentially so large that even with an elevated number of T cells they still may not keep pace with constant viral replication.

Therefore, we initiated a collaboration with Gilead Sciences to provide us with combined anti-retroviral therapy (cART) compounds for use in SIV+ NHP. Gilead Sciences has developed a new formulation, which mirrors the efficacy of human cART in NHP. In April 2014, we initiated the cART studies by giving SIV+ NHP cART. After 5 months on daily cART, SIV was stably controlled and therapeutic vaccination was started as outlined in Figure 1. After the 3rd boost, cART was removed and viremia will be monitored over a few months to determine whether the vaccinations were effective at altering SIV levels. At the writing of this progress report, we have just stopped cART treatment after vaccination and are currently assessing weekly viral loads. These experiments will inform us as to whether combining cART with therapeutic vaccination can control SIV infection. This is important for many reasons: 1) this scenario parallels what would happen in the clinic, with cART being the standard of care in humans; 2) placing patients on cART leads to a significant drop in HIV- specific T cells, thus for viral eradication purposes, these T cell numbers need to be boosted, as there will be few of them after cART; 3) the number of HIV infected cells will drop after cART, decreasing the numbers of target cells that would need to be eliminated. This would likely optimize the success of therapeutic vaccination, as the effector:target ratio would be bigger, with fewer target cells to survey and kill.

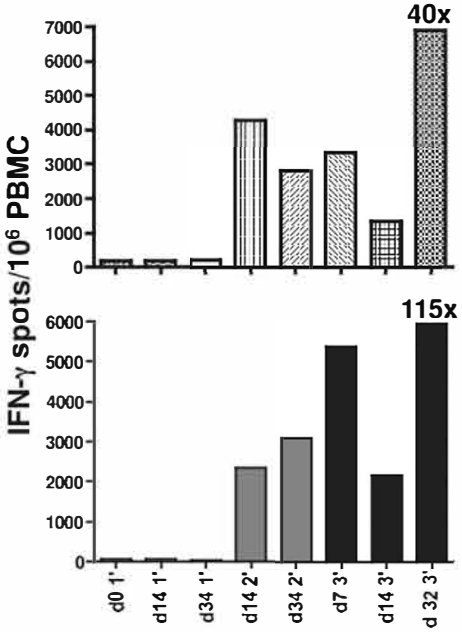


Figure 1. Antigen-specific therapeutic vaccination yields large increases in vaccine-targeted T cells. Female *Rhesus macaques*, infected with SIVmac251 i.vag. for at least 2 years, were subjected to our therapeutic vaccination strategy. NHP received 3 vaccinations, all given i.v. 42 days apart. 1' boost was VSV-New Jersey-SIVgag; 2' boost was vaccinia virus-SIVgag and 3' boost was VSV-Indiana-SIVgag. Blood was drawn at indicated timepoints pre- and post-vaccination. ELISpots were performed to enumerate T cell production of interferon-g in PBL after stimulation with the overlapping peptide pools encompassing the entire SIV gag sequence. Each graph is an individual animal. The number over the last bar reflects the fold change in SIVgag-specific T cells at the last timepoint compared to pre-vaccination levels (first column).

The data garnered through this pilot project has resulted in funding for this further development of this project: including an NIH R21/R33 grant, as listed below. The NHP studies for this current grant are sub-contracted and will be done at the WNPRC/

Full bibliographic materials on each paper published, in press, or submitted: None.

Grant applications and funded grants resulting from this project:

NIH

5R21AI116211-02

Therapeutic Vaccination Targeting SIV Viral Reservoirs

PI: Excluded by Requester

10/2014-9/2016

The major goal of this grant is to determine the efficacy of a three boost therapeutic vaccination approach on SIV+ NHP on cART.

University of Minnesota

Grant-In-Aid

Immunity to SIV Infection

PI: Excluded by Requester

7/2013-1/2015 $25,000 total

University of Minnesota

Development Center for AIDS Research (CFAR)

Therapeutic Vaccination for SIV/HIV

PI: Excluded by Requester

8/2013-8/2014 $30,000 total

Project Name: MHC-defined Nonhuman Primate Model for Bone Marrow Transplantation

Name, Title, Institution Affiliation: Excluded by Requester MD, Professor, Department of Pathology and Laboratory Medicine, University of Wisconsin-Madison;

Years Funded: 01/01/2014-12/31/2015

Progress to Date:

Milestones Achieved

1. Developed protocol for efficient isolation of CD34+ hematopoietic stem cells (HSCs) from mauritian cynomolgus monkey (MCM).

2. In collaboration with Private Source (La Jolla, CA) developed method for highly efficient gene transfer into monkey HSCs (rapamycin-based protocol >90% gene transfer efficiency)

3. Successful bone marrow in MCMs using nonmyeloblative regimen.

4. Successful bone marrow in MCMs using myeloblative regimen (Figure 1).

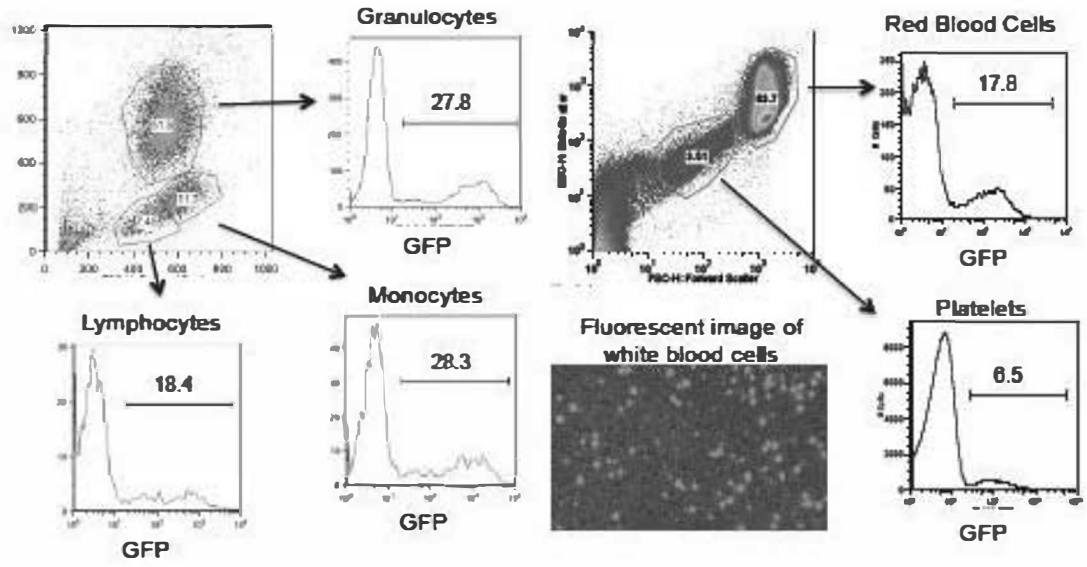


Figure 1. Multilineage engraftment of blood cells following transplantation of autologous CD34+ cells transduced with eGFP in MCM.

5. System for efficient *de novo* production of blood from rhesus and cynomolgus monkey, including MCM, induced pluripotent stem cells was developed (Figure 2).

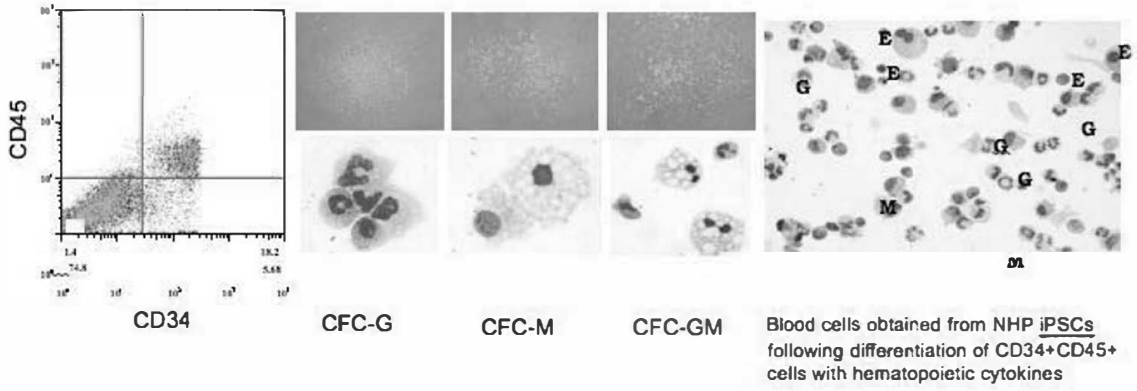


Figure 2. Hematopoietic differentiation of cynomolgus monkey iPSCs.

New Steps and New Collaborations

1. Excluded by Requester (Private Source). Develop NHP model for MHC homozygous iPSC- based therapies for acquired bone marrow failure. Bone marrow suppression is a common complication and major limiting factor for chemotherapy and main clinical manifestation of radiation-induced damage. MHC homozygous iPSCs could provide an off-the-shelf supply of MHC-compatible myeloid progenitors to mitigate bone marrow failure and reduce adverse effect associated with alloimmunization.

Pending Support ICTR funding will be used to generate preliminary data for this application.

2. Excluded by Requester (WNPRC): stem cell technologies for expression of HIV-neutralizing antibodies

3. Private Source optimization genetic modification of HSCs

Full bibliographic materials on each paper published, in press, or submitted: Pending

Grant applications and funded grants resulting from this project:

Collaboration Established/ Grant Applications Submitted

1.Transplantation of Induced Pluripotent Stem Cell (iPSC) Derived Hematopoietic Cells to Achieve Stable Mixed Chimerism in a Rhesus Model Excluded by Requester Dept of Surgery Excluded by Requester Excluded by Requester WNPRC Opportunities Pool U01 Grant NIH)

2. Prevention of Delayed Graft Function in Kidney Transplantation by iPSC-derived MSCs Excluded by Requester Excluded by Requester Dept of Surgery, Excluded by Requester WNPRC, R01 NIH)

3. Excluded by Requester (WNPRC) Pending Support Pending Support

NEW WNPRC PILOT PROJECTS FUNDED IN 2014

PERIOD OF SUPPORT: JANUARY 1, 2015 – DECEMBER 31, 2016

	Project Title	Principal Investigator(s)	Dates of funding	Amount of funding (Direct costs)
1	Evaluation of stem cell-derived photoreceptor transplantation	Co-PIs: Excluded by Requester (Collaborators: Excluded by Requester Excluded by Requester	01/01/2015-12/31/2016	$50,000
2	Detection of apoptosis in the developing primate brain	PI: Excluded by Requester (Collaborator: Excluded by Requester	01/01/2015-12/31/2016	$50,000
3	A Radiometabolism Study of Hair Hormones in Rhesus Macaques	PI: Excluded by Requester (Collaborator: Excluded by Requester	01/01/2015-12/31/2016	$42,376
4	Towards KSHV VLP-based vaccine development	PI: Excluded by Requester (Collaborator: Excluded by Requester	01/01/2015-12/31/2016	$50,000
5	Self-recognition in nonhuman primates	PI: Excluded by Requester (Collaborator Excluded by Requester	01/01/2015-12/31/2016	$50,000
6	*P. gingivalis*-macrophage interplay in obstetric disease	PI: Excluded by Requester (Collaborator Excluded by Requester	01/01/2015-12/31/2016	$50,000
7	Priming Protective CD8 T-Cell Memory in the Lung	PI: Excluded by Requester (Collaborator Excluded by Requester	01/01/2015-12/31/2016	$50,000

NEW PILOT PROJECT ABSTRACTS

Project Name: Evaluation of stem cell-derived photoreceptor transplantation

Name, Title, Institutional Affiliation: Excluded by Requester MD, PhD, Associate Professor, Department of Ophthalmology and Visual Sciences, University of Wisconsin-Madison Excluded by Requester Professor, Department of Ophthalmology and Visual Sciences, University of Wisconsin-Madison

Project Abstract: Many blinding retinal degenerative disorders are caused by the death of photoreceptors, the light sensing cells of the retina. Once these cells are lost, they are not replenished. However, recent studies in rodents have demonstrated restoration of vision following photoreceptor transplantation. Furthermore, stem cell-derived transplantation of another retinal cell type, retinal pigment epithelium (a supportive cell of the photoreceptors), is currently in Phase I/II clinical trials in humans. Combined, these studies suggest the efficacy of photoreceptor replacement therapy in rodents, and the safety of ocular stem cell therapy in humans. However, to move stem cell-derived photoreceptor replacement to human clinical trials, testing in the non-human primate (NHP) is essential. For this pilot study, we propose the use of adult-derived, human induced pluripotent stem cells (hiPSCs) to generate photoreceptors in a dish, using a patented, well-established protocol from Excluded by Requester Excluded by Requester laboratory. These hiPSC-derived photoreceptors will then be transplanted in the normal NHP retina by experienced vitreoretinal surgeon Excluded by Requester Following transplantation, the monkeys will be monitored for structural and functional changes by Excluded by Requester lab (fundus and OCT imaging) with additional functional testing (multifocal electroretinogram) by Excluded by Requester lab. This pilot grant will evaluate the following specific aim: To test the delivery, safety, survival, and integration of transplanted hiPSC-derived photoreceptors in the non-human primate retina. The proposed set of experiments will test the following hypothesis: Transplanted hiPSC-derived photoreceptors can be safely delivered into the non-human primate subretinal space, and will survive and integrate for at least three months, the latest time point of analysis. This study will allow us to evaluate the delivery of the cells, given that the surgery is identical to that performed in humans, while the rodent surgery is not. This study will also provide a more accurate assessment of safety and integration into the host retina, due to the conserved anatomy and physiology of human and non-human primate eyes. To achieve the goals of this grant, we have assembled a team of experts in their respective fields. As such, the proposed study has a high probability of success. Most importantly, it will provide pilot data for future funding applications using NHPs as this group pushes towards clinical trials.

Project Name: Detection of apoptosis in the developing primate brain

Name, Title, Institutional Affiliation: Excluded by Requester MD, PhD, Professor, Department of Pediatric Neurology, University of Wisconsin-Madison

Project Abstract: Pediatric drugs which are used as sedatives/anesthetics (SADs) and antiepileptics (AEDs) in neonatal and pediatric medicine can be harmful to the developing brain. They have been shown to cause widespread cell death, impair synaptic maturation and plasticity and inhibit neurogenesis in the brains of rodent and non-human primates (NHP). Studies in rodents and in NHPs have provided compelling evidence that early life exposure to these drugs also triggers behavioral toxicity, i.e. causes long-term behavioral and cognitive deficits that persist when the animals mature. Furthermore, retrospective clinical studies raise serious concerns that exposure of human infants to these classes of drugs may lead to neurocognitive and behavioral disorders. Millions of human fetuses and infants are exposed every year to SADs and/or AEDs at doses that have been shown to induce apoptotic injury in the developing animal brain. Currently, we are at an impasse in dealing with this potentially serious dilemma. The human epidemiological evidence, although generated by highly competent researchers, is considered inconclusive, so it remains debatable whether the developing human brain is susceptible to apoptotic injury induced by SADs and AEDs. Methods used in animal research to document the brain damaging properties of SADs and AEDs are invasive and cannot be used in human research. We need new research approaches that are reliable and can non-invasively address and answer the human susceptibility and related questions.

Here we propose to use diffusion weighted MRI and high frequency ultrasound, two modalities which non-invasively detect apoptosis in cancer, to study apoptotic cell death in the brains of infant NHPs exposed to isoflurane (ISO) anesthesia. The selected ISO protocol has been shown to consistently cause widespread apoptosis in the brains of 6 day old (P6) NHPs which is detectable by histological techniques within 10 hrs from the beginning of the exposure. The following specific aims will be pursued:

Aim 1: Using a P6 infant NHP model in which SAD exposure [isoflurane (ISO) x 5 hrs] is known to cause acute apoptotic brain injury, test the hypothesis that the brains of ISO-exposed infant NHPs will display changes that can be diagnosed non-invasively by diffusion weighted MRI.

Aim 2: In this same infant NHP model, test the hypothesis that the brains of ISO-exposed infant NHPs will display changes that can be diagnosed non-invasively by high frequency ultrasound.

If successful, this project would provide the first data to help develop non-invasive methodology that would allow us explore the phenomenon of drug-induced developmental neuro- and oligoapoptosis in humans and would also provide us with tools that allow to individually monitor treatment safety.

Project Title: A Radiometabolism Study of Hair Hormones in Rhesus Macaques

Name, Title, Institutional Affiliation: Excluded by Requester PhD, Assay Methodology Researcher, Wisconsin National Primate Research Center; Excluded by Requester PhD, Senior Scientist, Wisconsin National Primate Research Center

Project Abstract: Analysis of long-term endocrine activity can be challenging since traditional methods require repeated specimen collection, are sensitive to acute changes in hormone levels and sample collection can be invasive and difficult to obtain. Analysis of hormones in hair has become an increasingly widespread tool for assessment of long-term endocrine function as it circumvents many of these issues. While there are clear benefits of hair hormone analysis there have only been a handful of studies addressing the biological significance of hair hormones. In order to meaningfully interpret hair hormone results, validation studies for each steroid hormone measured in hair, in a species in which the data can be translated to humans, is required. Rhesus macaques are the ideal model for a validation study of hair hormones as they are closely related to humans and their hair growth and metabolism of steroid hormones are similar to those in the human. Assay Services at the Wisconsin National Primate Research Center (WNPRC) is at the forefront of hair hormone analysis.

Recently, we have developed the methodology for state-of-the-art hair hormone analysis to measure a panel of steroid hormones from one hair sample using liquid chromatography-tandem mass spectrometry (LC/MS/MS). In order to continue to lead this rapidly expanding field, we need to conduct the fundamental validation studies to understand the biological significance of the hair hormones in rhesus macaques. The WNPRC is uniquely positioned for this project, as the animals, the equipment and the expertise are available. Therefore, the overall aim of this pilot project is to conduct radiometabolism studies to provide basic data on hormone incorporation into hair in the rhesus macaque.

We will fulfill the following specific aims: (1) Determine the time course of ^{3}H-or ^{14}C-labeled hormone incorporation, and the proportion of radiolabeled hormone and metabolites in hair of rhesus macaques. We will inject a precise amount of either ^{3}H-cortisol, ^{14}C- testosterone, ^{14}C-progesterone or ^{3}H-estradiol to rhesus macaques and collect urine, feces and hair samples to determine when the radiolabeled hormone can been found in the hair, and the proportion of the radiolabeled that is incorporated into hair. This will inform us on how much hormone in circulation is actually integrated into the hair shaft, and precisely when this occurs. (2) Determine the characteristics of the major hormone (parent and/or metabolites) in the hair. We will use the hair that was collected from the monkeys in Specific Aim 1 to determine in which form each of the radiolabeled hormones is integrated in the hair shaft. For this we will use high-pressure liquid chromatography (HPLC) separation to visualize the radioactive peak(s), and compare them to authentic standards. This will provide us with the knowledge of which parent hormone or its metabolite to measure in hair that is relevant to the hormone in circulation. The results of this pilot study will be highly informative for interpretation of hair hormone data. We will provide information about the biological significance of important steroid hormones in hair, in a species that is closely related to humans.

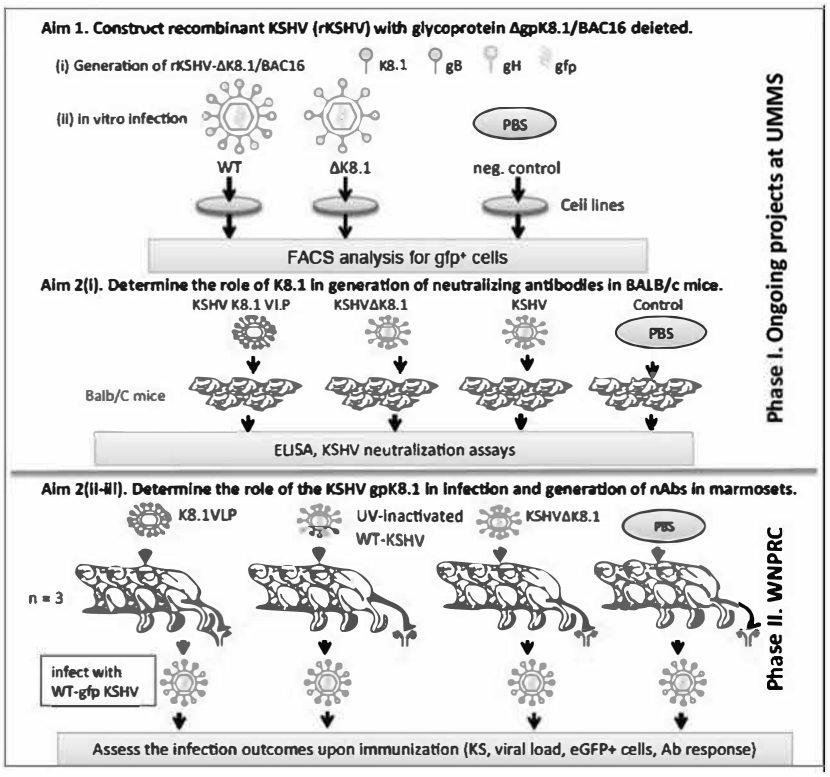
Project Title: Towards KSHV VLP-based vaccine development

Name, Title, Institutional Affiliation: Excluded by Requester PhD, Assistant Professor, Medicine, University of Massachusetts Medical School; Excluded by Requester PhD, Scientific Unit Head, Scientific Protocol Implementation, Wisconsin National Primate Research Center

Project Abstract: Efforts to develop Kaposi's sarcoma-associated herpesvirus (KSHV) vaccines are limited due to lack of animal models to test potential vaccine candidates. Recently, the successful transmission of KSHV into common marmosets (Callithrix jacchus) was reported. In this exciting new model, marmosets infected with recombinant KSHV (rKSHV) rapidly seroconverted and maintained a strong anti-KSHV antibody response, opening a new frontier for the study of KSHV infection in vivo and vaccine development.

The overall goal of this application is to define the role of KSHV glycoprotein (gp)K8.1 in mediating virus entry in vivo, a prerequisite step in designing vaccines that stimulate humoral immunity and evoke potent T-cell responses, thereby preventing infection. We hypothesize that immunization of marmosets, a recently developed non-human primate model susceptible to KSHV infection and disease with KSHV gpK8.1 incorporated into virus-like particles (VLPs), will be the ideal candidate for preventing KSHV infection. To begin to address our hypothesis, we propose two specific aims:

(1) Construct recombinant KSHV (rKSHV) with ΔgpK8.1/BAC16 deleted. To achieve this goal, Dr. Excluded by Requester at UMMS is currently at an advanced stage of deleting K8.1 from a bacterial artificial chromosome (BAC) system carrying the whole KSHV genome (BAC16wt-KSHV-JSC1). The infectivity of rKSHVΔK8.1 will be tested both in vitro and in the common marmoset. We anticipate to complete the project (Phase-I) as illustrated above before the end of 2014.\



(2) Determine the role of the KSHV gpK8.1 in generation of neutralizing antibody (nAbs) in BALB/c mice and in marmosets. First, we provide preliminary data on the construction and characterization of KSHVgpK8.1VLPs, the viral ligand most consistently implicated as the major target of nAbs response in vivo. To determine whether gpK8.1 VLPs are capable of eliciting nAbs response, a group of five 6-8 weeks old BALB/c mice were immunized with either gpK8.1 VLPs, purified UV-inactivated KSHV or phosphate buffered saline (PBS). All animals received boost immunizations at day 43, 173 and 183 and sacrificed at day 228. Serum samples were obtained from immunized mice every two weeks post immunization. Experiments are underway in Excluded by Requester lab to determine the presence of anti-K8.1 antibody titers and in vitro neutralization of KSHV by the sera from immunized mice. VLPs lack viral nucleic acids, and thus have no oncogenic potential.

After validating that antibodies against gpK8.1 VLPs can block infection, a group of three marmosets (3–4 years old) at WNPRC will be immunized with either 20μg of VLPs in 1 ml PBS, UV-inactivated KSHV particles, KSHVΔgpK8.1 or 1 ml PBS alone at week 0, 4 and 24. These animals will be challenged with wild-type KSHVexpressing green fluorescent protein to test the ability of K8.1-VLP to block viral infection and Kaposi's sarcoma (KS). The funds requested would be used primarily on proposed activities implemented at WNPRC (Phase-II) led by Excluded by Requester

Expected Outcomes: The knowledge gained from this project is critical to address the role of gpK8.1 in mediating KSHV entry and the ability of a gpK8.1 VLP-based vaccine candidate to generate nAbs capable of blunting KSHV infection in marmosets.

Project Title: Self-recognition in nonhuman primates

Name, Title, Institutional Affiliation Excluded by Requester PhD, Associate Professor, Department of Neuroscience, University of Wisconsin-Madison; Excluded by Requester PhD, Department of Medical Physics, University of Wisconsin-Madison

Project Abstract: Self-awareness refers to a state in which an organism directs attention inward toward the self, compared to the state in which it directs attention outward toward others or the environment. It is among the highest of cognitive functions and its disruption is a critical feature of serious psychiatric disorders, hence the importance of understanding its underlying neural mechanisms. Self recognition in front of a mirror is used as an indicator of self-awareness in animals (and very young humans) because they cannot articulate what they perceive and experience. Aside from humans, chimpanzees and orangutans have been shown to be self-aware using the mark test. Rhesus monkeys, on the other hand, the animal model closest to humans available for studies of nervous system function, have been conspicuously absent from the list of species thought to be self-aware because they fail the mark test. The macaque's failure in the mark test has been interpreted as evidence of a cognitive divide between hominoids and other primate species. As a consequence, very little is known about the neural mechanisms underlying self-awareness, given that mirror self-recognition has been demonstrated in species unavailable for physiological studies of the nervous system.

Excluded by Requester Recently, however, [redacted] et al. (2010) demonstrated that Rhesus monkeys do recognize themselves in the mirror despite failing the mark test, a finding that opens the door for the study of the physiological mechanisms underlying self-recognition. Importantly, the brain the macaque is endowed with a well-developed face recognition network, which has been studied exclusively from the sensory perspective. Using functional magnetic resonance imaging in awake, behaving monkey preparation, this project plans to build upon what is known about such network to test the hypothesis that self-recognition will be differentially encoded in the highest levels of face-recognition network.

The results of the proposed studies will provide a first glimpse of the physiological mechanisms underlying visual self-recognition and a starting point for future studies of self-awareness and self-recognition.

Project Title: *P. gingivalis*-macrophage interplay in obstetric disease

Name, Title, Institutional Affiliation Excluded by Requester PhD, Research Assistant Professor, Department of Infectious Disease and Pathology, University of Florida Excluded by Requester PhD, Professor, Department of Comparative Biosciences, University of Wisconsin-Madison

Project Abstract:

Rationale: Preterm birth (PTB), defined as a live birth between 20 and 37 weeks of gestation, is a major public health problem in the US. Intrauterine infection is one of the most consistently identified risk factors for preterm birth, and recent studies indicate that commensal oral bacteria such as Porphyromonas gingivalis (Pg), are causative agents of intrauterine infections and adverse outcomes (APO) such as low birth weight, fetal growth restriction, preeclampsia, and spontaneous preterm birth. Despite a strong association between Pg infection and APO, the circumstances or mechanisms by which this occurs remain elusive. Using a rodent model of infection Excluded by Requester laboratory has identified a causal link between the presence of Pg within the placental bed and macrophage mediated uterine arteritis with impaired trophoblast invasion. In a human study, we have also identified an association between severe prematurity and the presence of Pg within the villous mesenchyme with a significant decrease in fetal macrophages (Hofbauer cells).

Hypothesis: Pg within the intrauterine compartment promotes APO by perturbing maternal and/or fetal macrophage function. Specifically, Pg within the uterine perivascular stroma inappropriately activates macrophages producing chronic uterine atherosis and impaired spiral artery remodeling. In the fetal compartment, the presence of Pg within the villus mesenchyme perturbs paracrine mediated regulation of Hofbauer cells, which impairs villous growth and development.

Aims and Design: The objective of this application is to develop a macaque model of early Pg intrauterine infection in order to define Pg-induced changes in uterine macrophages, and Hofbauer cells. This will be achieved with the following aims: 1) will determine the intrauterine macrophage phenotype associated with Pg induced uterine atherosis, 2) will define the impact of Pg placental infection on Hofbauer cell density and activation state.

Unique advances: Completion of these studies will demonstrate a novel mechanism whereby an important periodontal bacterial pathogen induces APO. Aim 1 will define the immunological and histological manifestations of Pg-induced disruption of the physiologic remodeling of uterine spiral arteries, and its impact on placental blood flow and fetal development. Aim 2 will be the first study to elucidate the effect of local Pg infection on the microenvironment of the villous mesenchyme, and its effects on Hofbauer cell activation/viability. Changes in placental villous structure and fetal health will be correlated with the local presence of Pg and changes in Hofbauer physiology. This proposal is in keeping with the research objectives of the WNPRC working groups in Reproductive Medicine and Global Infectious Disease. With this pilot data, we will be in an excellent position for further R01-based studies that will 1) define the Pg virulence factors that perturb maternal macrophage function and contribute to uterine arterial pathology and subsequent APO, and 2) elucidate the role of Hofbauer cells in placental development and the maintenance of pregnancy. The complimentary collective expertise of Excluded by Requester will move the field forward with novel and innovative experimental approaches with the nonhuman primate model.

Project Title: Priming Protective CD8 T-Cell Memory in the Lung

Name, Title, Institutional Affiliation Excluded by Requester PhD, Professor, Department of Pathobiological Sciences, University of Wisconsin-Madison; Excluded by Requester PhD, Department of Pathobiological Sciences, University of Wisconsin-Madison

Project Abstract: Acute infections of the respiratory tract (RT) with viruses such as influenza A virus (IAV), respiratory syncytial virus, adenovirus, parainfluenza virus, and rhinovirus are the leading cause of morbidity and mortality in the US. In addition, emerging pathogens including avian influenza virus, Middle-East respiratory syndrome coronavirus and severe acute respiratory syndrome coronavirus cause severe lung disease and mortality. Except for IAV, there is neither a vaccine nor an effective therapy to treat acute viral infections of the RT. Moreover, vaccines for IAV are far from optimally effective and confer protection in only <60% of the vaccinees that are under 65 years of age. There is emerging consensus that defense against respiratory viruses will require both antibodies and CD8 T cells and induction of memory CD8 T cells in the lung airways might be crucial for maintaining broad protective immunity to IAV in the RT. *However, a daunting challenge is the development of safe adjuvants that can stimulate potent and durable CD8 T cell responses to non-replicating antigens in the RT mucosa.*

Carbomers (polymers of acrylic acid) have been used extensively to achieve controlled release of medications in tablets and as a bioadhesive in mucosal applications. We have strong preliminary data that similar to a live attenuated virus, intranasal (IN) or subcutaneous (SQ) immunization of mice with a carbomer-based adjuvant, Adjuplex® (ADJ) stimulated potent CD8 T cell memory to ovalbumin, a model soluble antigen. Intriguingly, memory CD8 T cells induced by immunization via the IN but not SQ route potently suppressed replication of IAV in the RT. While these findings are novel and promising, ADJ's efficacy in mice may not accurately predict its ability to induce protective CD8 T cell memory in the RT of humans. We therefore propose to investigate the T cell immunogenicity, protective efficacy and mechanism of protection of ADJ using an authentic pathogen-derived protein in macaques, a biologically relevant translational model of influenza immunity. The central hypothesis is that, "***a carbomeradjuvanted viral protein-based IN vaccine will induce potent CD8 T cell memory in lung and blood, and protect macaques against influenza***". The specific aims of this proposal are to: (1) test whether the programming of protective memory CD8 T cells in the lung airways of macaques requires mucosal delivery of a carbomer-based vaccine; (2) determine the extent to which an IN carbomer-based vaccine confers superior protection for macaques against IAV in the RT over a SQ vaccine. This project forges new collaboration between investigators with expertise in basic cellular immunology and in nonhuman primate models of influenza infection and immunity. The objective of this pilot project is to establish a novel subunit vaccine platform that elicits potent humoral and CD8 T cell immunity in the mucosa against respiratory viruses. If successful, we envision to leverage the data from this study in macaques to attract support for future projects aimed at translating basic immunology to preclinical applications and probe the molecular and cellular mechanisms of protective immunity in the respiratory mucosa.

2014 WNPRC Pilot Program Review Committee Members

Last, First Name	Title	Institution
Excluded by Requester	Associate Professor	Private Source
	Associate Professor	UCSF Benioff Children's Hospital.
	Associate Director	Georgia State University
	Associate Professor	U.W. Madison/Vet Med.
	Associate Professor	Private Source School of Medicine
	Professor	Oregon Health & Science University
	Associate Professor/Assoc. Dean	University of Illinois, Chicago
	Assistant Professor	Private Source PA
	Associate Professor	U.W. Madison
	Prof. and Associate Chair	MI State University
	Interim Division Chief, Senior Scientist	Oregon Health Sciences University
	Mark Stinski Chair	University of Iowa
	Associate Professor	University of Virginia
	Associate Professor	Private Source
	Professor	
	Professor and Director	
	Professor	California National Primate Research Ctr.
	Scientist	Private Source
	Director and Manager	Oregon National Primate Research Ctr.
	Associate Professor	Private Source School of Med.
	Division Director	Private Source Baltimore
	Professor	Private Source Medical Ctr.
	Assistant Professor	University of WI--Madison
	Professor and Chair	U.W. Madison, School of Vet Medicine
	Associate Professor	Private Source
	Professor	Private Source WV
	Senior Scientist/Professor	Oregon National Primate Research Ctr.
	Professor	U.W. Madison/Vet Med.
	Professor	Univ. of Colorado, Boulder
	Division Chief	Yerkes National Primate Research Ctr.
	Associate Professor	Univ. of Birmingham, AL
	Professor	U.W. Madison, Waisman Ctr.

C. COMPONENT PRODUCTS

C.1 PUBLICATIONS

Not Applicable

C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

Not Applicable

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Not Applicable

C.5 OTHER PRODUCTS AND RESOURCE SHARING

C.5.a Other products

NOTHING TO REPORT

C.5.b Resource sharing

NOTHING TO REPORT

D. COMPONENT PARTICIPANTS

Not Applicable

E. COMPONENT IMPACT

E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES?

Not Applicable

E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE?

Not Applicable

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

NOTHING TO REPORT

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?

Not Applicable

F. COMPONENT CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

F.2 ACTUAL OR ANTICIPATED CHALLENGES OR DELAYS AND ACTIONS OR PLANS TO RESOLVE THEM

NOTHING TO REPORT

F.3 SIGNIFICANT CHANGES TO HUMAN SUBJECTS, VERTEBRATE ANIMALS, BIOHAZARDS, AND/OR SELECT AGENTS

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. COMPONENT SPECIAL REPORTING REQUIREMENTS

G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT REPORTING REQUIREMENTS

Not Applicable

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

G.4.a Does the project involve human subjects?

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Not Applicable

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

RESEARCH & RELATED BUDGET - SECTION A & B FINAL

ORGANIZATIONAL DUNS*: 161202122

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: UNIVERSITY OF WISCONSIN-MADISON

Start Date*: 05-01-2015 **End Date*:** 04-30-2016

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1.		Marsha		Mailick	PhD	PD/PI	Institutional Base Salary	EFFORT			1,833.00	618.00	2,451.00
2.		Excluded by Requester			PhD	Center Director; Division Head, Division of Research					91,650.00	30,886.00	122,536.00
3.						Associate Director, Animal Srvcs Division					17,605.00	5,933.00	23,538.00
4.					PhD	Associate Director, Research Srvcs Division					18,330.00	6,177.00	24,507.00
5.						Associate Director, Operational Srvcs Division					12,960.00	4,368.00	17,328.00
6.					PhD	Unit Head, Aging Specialized Resource					8,951.00	3,016.00	11,967.00
7.					PhD	Core PI, Aging Specialized Resource					8,518.00	2,871.00	11,389.00
8.					PhD	Unit Head, SIV Elite Controller Resource					8,866.00	2,988.00	11,854.00
9.					PhD	Unit Head, Stem Cell Resources					0.00	0.00	0.00
10.					MD	Unit Head, Bone Marrow Transplant Core					4,818.00	1,624.00	6,442.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **232,012.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
8	Division Staff	12.0			288,021.00	97,063.00	385,084.00
8	**Total Number Other Personnel**					**Total Other Personnel**	**385,084.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**617,096.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E

ORGANIZATIONAL DUNS*: 161202122
Budget Type*: ● Project ● Subaward/Consortium
Enter name of Organization: UNIVERSITY OF WISCONSIN-MADISON

Start Date*: 05-01-2015 **End Date*:** 04-30-2016

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	Funds Requested ($)*
1. DNA sequencer	105,208.00
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**105,208.00**

Additional Equipment: File Name:

D. Travel	Funds Requested ($)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	0.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**0.00**

E. Participant/Trainee Support Costs		Funds Requested ($)*
1. Tuition/Fees/Health Insurance		0.00
2. Stipends		0.00
3. Travel		0.00
4. Subsistence		0.00
5. Other:		
0 Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 161202122

Budget Type*: ● Project ● Subaward/Consortium

Enter name of Organization: UNIVERSITY OF WISCONSIN-MADISON

Start Date*: 05-01-2015 **End Date*:** 04-30-2016

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	171,569.00
2. Publication Costs	0.00
3. Consultant Services	37,184.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. WNPRC Pilot Program Costs	292,376.00
9. NPRC Consortium Costs	8,118.00
10. Other	18,189.00
Total Other Direct Costs	**527,436.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**1,249,740.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. Modified Total Direct Cost Base	34.5	1,144,532.00	394,864.00
		Total Indirect Costs	**394,864.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): Department of Health & Human Services Contact: Arif Karim 214-767-3261

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**1,644,604.00**

J. Fee	Funds Requested ($)*
	0.00

K. Budget Justification* File Name: Yr 54_WNPRC_Div of Research_Budget Just_opt.pdf

(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
Director's Office

FROM 05/01/15 THROUGH 04/30/16

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	TOTAL
Mailick, Marsha	PD/PI	EFFORT			Institutional Base Salary	1,833	618	2,451
Excluded by Requester	Director					91,650	30,886	122,536
	Assoc Director					17,605	5,933	23,538
	Assoc Director					18,330	6,177	24,507
	Assoc Director					12,960	4,368	17,328
	Editor					33,853	11,408	45,261
	Exec Secretary					54,769	18,457	73,226
	SUBTOTALS →					231,000	77,847	308,847

CONSULTANT COSTS			
External Advisory Board Travel & Expenses		8,240	
External Advisory Board Honoraria @ $200/day		4,944	13,184
EQUIPMENT *(Itemize)*			0
SUPPLIES *(Itemize by category)*			
Office Supplies	0		0
TRAVEL		0	0
INPATIENT CARE COSTS			0
OUTPATIENT CARE COSTS			0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*			0
OTHER EXPENSES *(Itemize by category)*			
WNPRC Pilot Projects	292,376		
NPRC Consortium	8,118		300,494
CONSORTIUM/CONTRACTUAL COSTS		DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*			**$ 622,525**
CONSORTIUM/CONTRACTUAL COSTS		FACILITIES AND ADMINISTRATIVE COSTS	
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD			**$ 622,525**

PHS 398 (Rev. 08/12 Approved Through 8/31/2015) OMB No. 0925-0001
Form Page 4

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
Improvement & Modernization

FROM 05/01/15 THROUGH 04/30/16

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	TOTAL
SUBTOTALS →						0	0	0

CONSULTANT COSTS	0	0	0
EQUIPMENT *(Itemize)*			
Genetics Services - DNA sequencer	105,208		105,208
SUPPLIES *(Itemize by category)*			0
TRAVEL			0
INPATIENT CARE COSTS			0
OUTPATIENT CARE COSTS			0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*			0
OTHER EXPENSES *(Itemize by category)*			0
CONSORTIUM/CONTRACTUAL COSTS		DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*			**$ 105,208**
CONSORTIUM/CONTRACTUAL COSTS		FACILITIES AND ADMINISTRATIVE COSTS	
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD			**$ 105,208**

PHS 398 (Rev. 08/12 Approved Through 8/31/2015) OMB No. 0925-0001
Form Page 4

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
Aging Specialized Resource

FROM 05/01/15 THROUGH 04/30/16

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	TOTAL
Excluded by Requester	PD/PI	EFFORT			Institutional Base Salary	8,951	3,016	11,967
	Technician					4,769	1,607	6,376
	Co-I					8,518	2,871	11,389
SUBTOTALS →						22,238	7,494	29,732

CONSULTANT COSTS		0
EQUIPMENT *(Itemize)*		0
SUPPLIES *(Itemize by category)*		
Supplies for sample collection	4,205	4,205
TRAVEL		0
INPATIENT CARE COSTS		0
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		0
OTHER EXPENSES *(Itemize by category)*		0
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ 33,937
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ 33,937

PHS 398 (Rev. 08/12 Approved Through 8/31/2015) OMB No. 0925-0001
Form Page 4

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
SIV Elite Controller Resource

FROM 05/01/15 THROUGH 04/30/16

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	TOTAL
Excluded by Requester	Assoc. Scientist	EFFORT			Institutional Base Salary	8,866	2,988	11,854
	Research Specialist					9,933	3,347	13,280
SUBTOTALS →						18,799	6,335	25,134

CONSULTANT COSTS		
Excluded by Requester	24,000	24,000
EQUIPMENT *(Itemize)*		0
SUPPLIES *(Itemize by category)*		0
TRAVEL		0
INPATIENT CARE COSTS		0
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		0
OTHER EXPENSES *(Itemize by category)*		
Blood processing	5,085	
Subset analysis	864	
Viral load determination	3,240	
		9,189
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		$ **58,323**
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		$ **58,323**

PHS 398 (Rev. 08/12 Approved Through 8/31/2015) OMB No. 0925-0001
Form Page 4

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
Stem Cell Resources

FROM 05/01/15 THROUGH 04/30/16

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	TOTAL
Excluded by Requester	PD/PI	EFFORT				0	0	0
	Assistant Scientist				Institutional Base Salary	70,700	23,826	94,526
	Assoc Research Spec					31,500	10,616	42,116
SUBTOTALS →						102,200	34,442	136,642

CONSULTANT COSTS		0
EQUIPMENT *(Itemize)*		0
SUPPLIES *(Itemize by category)*		
Molecular reagents (transfection kits, DNA purification, primers)	17,986	
Cell culture reagents (media, matrix, plates, filters, pipets)	21,986	
Characterization reagents (antibodies, RNA-seq reagents, aptamers)	19,386	59,358
TRAVEL		0
INPATIENT CARE COSTS		0
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		0
OTHER EXPENSES *(Itemize by category)*		
Karyotypes for cells in media optimization and new iPS cell derivations (18 kt/year at $500/sample)	9,000	9,000
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		**$ 205,000**
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		**$ 205,000**

PHS 398 (Rev. 08/12 Approved Through 8/31/2015) OMB No. 0925-0001
Form Page 4

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
Bone Barrow Transplant Core

FROM 05/01/15 THROUGH 04/30/16

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	TOTAL
Excluded by Requester	PD/PI	EFFORT			Institutional Base Salary	4,818	1,624	6,442
	Asst Researcher					50,500	17,019	67,519
	Research Specialist					31,997	10,783	42,780
	SUBTOTALS →					87,315	29,426	116,741

CONSULTANT COSTS — 0

EQUIPMENT *(Itemize)* — 0

SUPPLIES *(Itemize by category)*

Tissue culture supplies	17,876	Monoclonal antibodies & flow cytometry	17,876	
Fetal calf serum replacement	18,876	Molecular biology supplies	20,875	
Cytokines, growth factors	14,876	Colony-assay media	17,627	108,006

TRAVEL — 0

INPATIENT CARE COSTS — 0

OUTPATIENT CARE COSTS — 0

ALTERATIONS AND RENOVATIONS *(Itemize by category)* — 0

OTHER EXPENSES *(Itemize by category)* — 0

CONSORTIUM/CONTRACTUAL COSTS — DIRECT COSTS — 0

SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)* — **$ 224,747**

CONSORTIUM/CONTRACTUAL COSTS — FACILITIES AND ADMINISTRATIVE COSTS

TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD — **$ 224,747**

PHS 398 (Rev. 08/12 Approved Through 8/31/2015) OMB No. 0925-0001
Form Page 4

A. COMPONENT COVER PAGE

Project Title: Animal Services Division

Component Project Lead Information:

Excluded by Requester

B. COMPONENT ACCOMPLISHMENTS

B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

Animal Services Overview
Division Head Excluded by Requester DVM, DACLAM

The Animal Services Division (ASD) consists of six units (Veterinary Services; Colony Management; Scientific Protocol Implementation; Pathology Services; Compliance and Training; and Behavioral Management) and one core (Nonhuman Primate Biological Materials Distribution) that are dedicated to maintaining the health of the nonhuman primate (NHP) colonies of the Wisconsin National Primate Research Center (WNPRC); supporting the scientific mission of the Center, ensuring regulatory compliance, and training personnel to work safely with NHP and their tissues. Throughout the current reporting cycle, the division personnel continued to redefine and expand the responsibilities and goals of each unit of the division to address the needs of WNPRC investigators, the constructive critiques of ORIP, and the changing regulatory guidelines governing NHP research. While each unit continued to maintain its own goals and responsibilities, the division is fully integrated into overall WNPRC activities and intra- and inter-divisional activities occurred on a daily basis.

Please see attached detailed progress reports from each unit (Section B.2), which includes specific aims, accomplishments and goals.

B.1.a Have the major goals changed since the initial competing award or previous report?

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: Animal Services Yr53 RPPR_final_2-23-15.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

Not Applicable

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

NOTHING TO REPORT

B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?

NOTHING TO REPORT

B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

Please see attached detailed progress reports from each unit (Section B.2), which includes future goals for the next reporting period.

ANIMAL SERVICES DIVISION

UNIT REPORTS

VETERINARY SERVICES

Unit Head: Excluded by Requester DVM, DACLAM

The Veterinary Services Unit of the WNPRC continued to utilize well-trained and experienced personnel, contemporary equipment, and sound medical policies to provide consistent and excellent clinical care to the NHP colonies housed at the WNPRC. During the current reporting period, the Veterinary Services Unit (in collaboration with the Scientific Protocol Implementation Unit) supported **18** core and affiliate investigators performing **37** individual research projects at the WNPRC by providing them with healthy experimental subjects and supplying clinical care for the NHP assigned to research projects. Through didactic and applied instruction, the Unit also provided training in basic and advanced NHP medicine techniques to **34** individuals, including laboratory animal medicine residents, veterinary students, veterinary technical students, visiting veterinarians and veterinary technicians, WNPRC and visiting investigators, and scientific support staff. The academic production of the Unit continued to increase as veterinary personnel authored and co-authored **3** manuscripts regarding hypothesis-driven research and clinical case reports and attended a variety of scientific conferences.

GOALS AND ACCOMPLISHMENTS

Specific Aim 1 - To provide consistent and excellent care to the NHP colonies housed at the WNPRC

To fulfill the primary aim of the Unit, providing consistent and excellent care to the NHP colonies, the Veterinary Services Unit maintained a staff of six full-time veterinarians and 9 full-time veterinary technicians from 1/1/2014-12/31/2014. The veterinary staff continued to implement an animal health program that safeguarded the psychological and physiological health of each animal in the colony during this funding period.

Procedures performed under Aim 1 during this funding period included the following:

- In order to identify clinical issues within the colony as quickly as possible, the veterinary staff evaluated **628,986** morning health observations made by the animal care staff.
- The veterinary staff performed **3,396** physical exams to evaluate the clinical condition of colony animals.
- The veterinary staff performed **66** dental procedures (e.g., cleanings, cleanings with extractions, or extractions alone) to maintain the overall oral health of the colony.
- The veterinary staff performed **3,424** tuberculin skin tests to ensure no animals had evidence of exposure to Mycobacterium tuberculosis.
- The veterinary staff ordered **2,406** complete blood counts, **1,131** serum chemistry panels, **4,480** fecal cultures, **2,973** parasitology exams, and **131** urinalyses to establish the clinical condition of colony animals.
- The veterinary staff performed radiographs on **195** animals and **2450** ultrasound exams to diagnose clinical conditions in colony or research assigned animals.

Specific Aim 2 – To provide support for the investigators performing research at the WNPRC

From 1/1/2014-12/31/2014, the WNPRC Veterinary Services Unit provided clinical and/or experimental support for 20 core or affiliate investigators and the 36 projects. This support consisted of all of the following:

- Assistance with experimental design and grant/IACUC protocol preparation
- Pre-project physical examination of potential experimental animals
- Clinical care of research assigned animals
- Research procedure execution or support (e.g., administration of experimental agents, tissue collection, anesthesia monitoring, surgical techniques)

During this period, veterinary staff performed **311** pre-project physical exams to ensure healthy and appropriate animals were assigned to projects listed in Table 1. Veterinary staff also provided support for **170** experimental surgical procedures, **102** experimental imaging procedures (e.g., CT, PET, and MRI scans), **101** total lymphoid irradiation procedures, and **16** apheresis procedures during the reporting period.

Specific Aim 3 - To provide training for personnel working with NHP at the WNPRC and at other institutions

Excluded by Requester continues to receive numerous requests from veterinary units at other institutions who wish to receive training in NHP medicine at WNPRC. Along with receiving access to our standard operating procedures and policies on NHP care, visiting veterinarians and veterinary technicians are given intensive training in their field of interest. Since 1/1/2014, Veterinary Services personnel have trained groups from Japan, Illinois, and Pennsylvania interested in learning about marmoset veterinary care, husbandry, and behavior.

The WNPRC also maintains a training program for veterinary students and clinicians interested in gaining experience in NHP medicine and husbandry. Undergraduates and first to fourth year veterinary students can opt to spend rotations lasting from one week to several months at WNPRC. Under the supervision of a veterinarian or a veterinary technician, students have the opportunity to administer clinical treatments, perform physical exams, collect blood via femoral or saphenous venipuncture, perform dental prophylaxis, suture minor lacerations, perform minor surgical procedures, provide anesthesia support for surgical procedures, and assist with major surgical procedures. From 1/1/2014-12/31/2014, Veterinary Services personnel provided training for 30 veterinary students, 4 undergraduates, and four post-docs. In 2014, one of our student veterinary assistants was accepted into a Small Animal Rotating Internship at Louisiana State University.

In April of 2014, former Veterinary Services clinician Excluded by Requester DVM, DACLAM and WNPRC veterinary pathologist Excluded by Requester DVM, DACLAM organized the 2nd annual WNPRC Lab Animal Medicine and Pathology Symposium for individuals preparing for the ACLAM and ACVP board examinations. The symposium attracted 52 attendees. The 3rd annual symposium is scheduled for April of 2015.

Specific Aim 4 - To increase the academic output of the Veterinary Services Unit

From 1/1/2014-12/31/2014, Veterinary Services personnel co-authored 3 publications in peer-reviewed journals in collaboration with WNPRC core and affiliate investigators

Several members of the Veterinary Services Unit actively participate in the following NPRC consortiums and their corresponding teleconferences:

- Clinical and Surgical Techniques
- Virtual Grand Rounds
- Breeding Colony Management Consortium

Several veterinarians from the unit attended the 42nd annual Association of Primate Veterinarians Workshop in San Antonio, Texas.

FUTURE GOALS

The WNPRC Veterinary Services Unit will continue to fulfill the four specific aims established by Dr. Excluded by Requestor when he joined the WNPRC staff in 2005. Following these aims has protected the clinical health of the WNPRC nonhuman primate colonies, provided excellent research support for the WNPRC core and affiliate investigators, provided training for numerous post-doctoral, graduate, and undergraduate students and personnel, and has generated a respectable amount of peer-reviewed publications during the reporting period.

COLONY MANAGEMENT UNIT

Unit Head: Excluded by Requester LATG

The Colony Management Unit continued to be responsible for all aspects of animal husbandry at the WNPRC. Additionally, the personnel of the Colony Management Unit executed a variety of tasks for the Veterinary Services, Behavioral Management, Scientific Protocol Implementation, and Compliance & Training Units of the Center. These tasks included documentation and communication of daily health reports on the NHP colonies, provision of environmental enrichment objects, administration of medical and experimental treatments, collection of blood and other biological samples for experimental and clinical purposes, transport of animals and biological samples, collection of behavioral and scientific data, and maintenance of colony records.

Specific Aim 1 - To provide a consistent and excellent husbandry program compliant with all the laws, regulations, and guidelines governing the care of captive NHP utilized in research

- From 1/1/2014 – 12/31/2014, Colony Management personnel performed daily cleaning and feeding and bi-weekly cage sanitation for the entire WNPRC population of nonhuman primates, which consisted of 1,194 rhesus macaques, 257 cynomolgus macaques, and 267 marmosets during the reporting period.
- In collaboration with the WNPRC Facilities and Shop Services Unit, Colony Management personnel expanded the animal holding capacity of the Blue Mounds Quarantine and Holding facility (BMQH) by converting a former dog room into a marmoset colony holding room. This holding room is now being utilized to hold 99 Common marmosets transferred from the New England Primate Research Center.
- In collaboration with the WNPRC Facilities and Shop Services Unit, the following renovations were made to the WNPRC animal holding areas:
  - The floors of the clean and dirty animal elevators in Specific Animal Location were resurfaced with diamond plate flooring.
  - All cage wash bays in Specific Animal Location are being renovated with FRP ceilings, stainless steel shelving and ductwork, and newly grouted tile.
  - One room of stationary caging was replaced with newly designed pens and mobile caging to improve socialization opportunities for the SPF rhesus macaque colony
  - Automated dispensing units have been installed in all wash bays and or chemical rooms in Specific Animal Location WIMR, and BMQ for the chemicals used to sanitize the animal racks. In addition, a proportioner has been installed that regulates the chemical to water ratio to ensure the correct proportion of solution is added to spray bottles and mop buckets.

Specific Aim 2 - To perform, document and communicate daily health observations from the NHP colonies

- From 1/1/2014 – 12/31/2014, personnel of the Colony Management Unit submitted 159,217 daily reports on individual animals that needed to be addressed by the WNPRC veterinary or Behavioral Management staff. These morning and afternoon health observations are pivotal to ensuring that clinically compromised animals receive rapid and appropriate care.

- During this same time period, Colony Management personnel performed 9,660 menses checks on female macaques in the SPF breeding colony. Data from these menses checks is used to populate monthly menstruation tables for each female in the SPF breeding colony that are used extensively by the rhesus breeding coordinator to determine the most appropriate time to breed an animal and to increase the possibility of conception.

Specific Aim 3 - To execute the delivery of environmental enrichment (food treats and manipulanda) to the NHP colonies

- In collaboration with the Behavioral Management Unit, Colony Management Unit personnel continue to ensure that each animal in the colony receives a foraging opportunity five days per week.
- In addition to the foraging opportunities listed above, Colony Management personnel also delivered 3,937 additional tactile foraging opportunities to animals exhibiting self-injurious behavior or recovering from injuries to assist in the improvement of their psychological wellbeing.

Specific Aim 4 - To support the clinical, behavioral, and research initiatives of the WNPRC by providing personnel to administer medical and experimental treatments, collect biological samples, transport animals and biological samples, and collect behavioral and scientific data

- From 1/1/2014 – 12/31/2014, Colony Management personnel provided support for all 92 experimental projects that were active during this reporting period.
- Colony Management personnel performed 5,293 blood collections (total volume = 55,556 ml) for experimental and clinical purposes during this reporting period.
- Colony Management personnel performed 204,803 clinical and experimental treatments that were prescribed during this reporting period.
- Colony Management personnel performed daily observations on newly formed social groups and reported any evidence of incompatibility to Behavioral Management personnel.

Specific Aim 5 - To meet the animal needs of investigators by managing the NHP breeding and stock colonies of the WNPRC

- From 1/1/2014 – 12/31/2014, the SPF macaque-breeding colony produced 132 offspring and the marmoset-breeding colony produced 60 offspring.
- During the same period, Colony Management personnel assisted in acquiring 128 macaques (111 rhesus, 17 cynomolgus) to fulfill PI needs that could not be fulfilled by animals from the existing WNPRC colonies. Colony Management also played a significant role in the preparation of the Blue Mounds Quarantine facility for the transfer of 99 marmosets from the New England Primate Research Center.
- In collaboration with the WNPRC Genetic Services Unit and the NPRC Genetics Consortium, the Colony Management Unit continues to obtain samples that have been utilized to identify the MHC type of the each new offspring of the rhesus macaque-breeding colony.
- In collaboration with the Veterinary Services Unit and in response to the needs of multiple investigators, the Colony Management Unit continues to collect samples that are used to identify SPF macaques that are also negative for Adeno-Associated virus (AAV) and/or Rhesus Rhadinovirus (RRV). These newly identified animals have been isolated from the existing SPF animals that are only negative for SRV, STLV, SIV, and Herpes B and are actively being used

by a newly recruited cohort of investigators from the New England Primate Research Center. Currently, the unit is successfully maintaining animals of the current viral status in the SPF colony.

- SRV, STLV, SIV, Herpes B negative status (SPF4)
- SRV, STLV, SIV, Herpes B, AAV negative status (SPF5a)
- SRV, STLV, SIV, Herpes B, RRV negative status (SPF5r)
- SRV, STLV, SIV, Herpes B, AAV, RRV negative status (SPF6)

Specific Aim 6 - To enter, retrieve, and verify the quality of data in the WNPRC Electronic Health Records (EHR) system

The two full-time and one part-time member of the Colony Records subunit executed the following duties during the reporting period:

- Data entry
- Quality assurance checks of data
- Data queries
- EHR development
- EHR training
- Research support and regulatory compliance

FUTURE GOALS

The Colony Management Unit will continue to be responsible for all aspects of animal husbandry at the WNPRC. Additionally, the personnel of the unit will continue to execute a variety of tasks for all six units of the Animal Services Division and the PIs of the WNPRC.

In collaboration with the WNPRC Facilities and Shop Services Unit, Colony Management personnel will prepare another empty room at the Blue Mounds Quarantine and Holding facility for expansion of the Center's rhesus macaque SPF breeding colony

SCIENTIFIC PROTOCOL IMPLEMENTATION UNIT

Unit Heads: Excluded by Requester PhD and Excluded by Requester DVM
Core PI: Excluded by Requester PhD

Scientific Protocol Implementation (SPI) continued to be an engine for collaborative research and a gateway for conducting studies utilizing WNPRC resources, as they continued support on 16 projects from the previous years and an additional 20 new projects over the 2014 reporting period. Six of these projects were investigators at the UW and WNPRC that were successful in obtaining new grants. SPI continued to attract new collaborations with high quality highly trained technical staff and the variety of procedures they perform. Three New England Primate Research Center (NEPRC) AIDS investigators transferred another 8 projects to the WNPRC in anticipation of the NEPRC closing. Additionally 6 projects were from outside investigators from other academic institutions. SPI, in collaboration with Veterinary Services, continued to provide innovative design and technical support for the best use of the animal resource and maintained exemplary compliance standards for projects. In collaboration with the Pathology Services Unit, SPI also provided numerous NHP tissues to satisfy the immediate and long-term research needs of registered investigators and educators through the Nonhuman Primate Biological Materials Distribution (NHPBMD) core.

Specific Aim 1 - To continue to support excellence in nonhuman primate (NHP) research through established animal research support protocols

The SPI Unit supported a total of 36 projects in various stages of completion during 2014. The Unit also participated in numerous sub award grant submissions from outside investigators and 4 of these have been funded and will initiate in early 2015. We continue to develop our portfolio by assisting more sub award grant submissions, identifying UW collaborators for investigators using the WNPRC for their first grant submissions, and attracting investigators from other institutions with existing funding looking for support using NHP. Two of these newly funded projects will begin in early 2015 as well. All new projects are reviewed by the WNPRC Executive Committee to insure that WNPRC resources, facilities, and personnel are available prior to start.

Specific Aim 2 - To provide continuing education opportunities for SPI staff (e.g., contemporary technique training, leadership development, academic development, etc.)

SPI continued to develop expertise in new techniques during the latest grant funding period. These techniques included large volume bone marrow collection, support for myeloblative total body irradiation, improvements to immunosuppressive therapy regimens, and establishment of a HAART treatment regime as more investigators focus on therapeutic AIDS therapies. Additionally, Excluded by Requester Excluded by Requester worked with Excluded by Requester of the WNPRC to establish a postnatal neurodevelopment assessment scale in marmosets. Excluded by Requester instituted journal article discussions at monthly staff meetings and also hosted presentations from local investigators that utilize SPI to ensure that unit personnel better understand the scientific concepts driving the projects they support. Excluded by Requester attended the annual meeting of the Association of Primate Veterinarians (APV) and frequently participates in the Clinical and Surgical Techniques Working Group teleconference supported by the NPRC consortium. Excluded by Requester attended the annual advisory committee meeting for a P01 headed by new collaborators from the Private Source on which she has recently assumed PI responsibility for a subproject. Funding for travel and continuing education was provided by the P51 or specific research grants.

Specific Aim 3 - To increase the academic output of the Scientific Protocol Implementation unit, measured by co-authorship of scientific studies

In 2014, SPI Unit members, including the two SPI Unit Heads and numerous SPI Research Technicians, have been working on publishing data from projects. Two published papers in 2014 include SPI personnel as co-authors. Another paper is in press and In Press Drs. Excluded by Requester are actively working on at least Pending Publication with their staff at this time.

Specific Aim 4 - To support the development of newer methodologies (e.g., transgenesis, gene therapy, embryonic stem cell differentiation) to increase the overall assisted reproduction technology (ART) expertise of the SPI unit

SPI has supported work to advance marmoset-assisted reproductive technologies and have modified this aim to better reflect the Unit's ongoing goals.

Hormone stimulation. To optimize marmoset follicular stimulation, we compared different recombinant human FSH preparations with pregnant mare serum gonadotropin (PMSG), a "classic" ovarian stimulation regimen, and while there was good follicle stimulation with PMSG, poor fertilization rates were obtained, and we returned to the FSH regimen previously used.

With specific pilot funding from the UW-Madison CTSA, we have been reliably obtaining approximately 10-15 oocytes per stimulation cycle, and fertilization rates of 25-100%. Development of fertilized embryos *in vitro* to blastocyst stage, a useful surrogate for *in vivo* developmental potential, has been modest in contrast to our previous rhesus monkey *in vitro* embryo culture, we have preliminary evidence that there may be a male factor related to blastocyst development. This observation also illustrates that we have continued to monitor individual males including new candidates to identify reliable donors of semen samples of excellent quality.

To maximize fertilization and development, we have been optimizing experimental microscope set-ups to transition to intracytoplasmic sperm injection (ISCI), which insures fertilization of each oocyte. We Excluded by Requester have been in consultation with IVF lab director at the UW-Madison Generations Fertility Clinic for establishment of ICSI procedures, which have not previously been used at the WNPRC.

Marmoset ESC and iPSC differentiation: In collaboration with Excluded by Requester in the UW Department of Neurology and at the Waisman Center, we were able to recapitulate neuroectoderm differentiation and formation of motor neurons *in vitro.* In addition, we prepared marmoset skin fibroblasts and in collaboration with Excluded by Requester laboratory, have produced candidate marmoset iPSC. These cells express the pluripotency markers Oct4, nanog, Sox2, and klf4, similar to the marmoset ESC cultures. In addition, our marmoset iPSC are able to differentiate to neural progenitors thus far indistinguishable from ESC-derived cells. We have prepared CRISPR targeting vectors for the human G2019S allele of LRRK2 associated with Parkinson's Disease, and are currently electroporating fibroblasts to define targeting efficiency. These cells will be an *in vitro* platform for the study of gene interactions which underlie the neural phenotype of PD.

Support of new proposals: With the initiation of studies in genomic editing of marmoset embryos, Dr. Excluded by Requester has begun a new collaboration with Excluded by Requester of the UW Department of Pathology and Laboratory Medicine to develop a new nonhuman primate model for AIDS research, utilizing CRISPR/Cas9 and IVF embryo production supported by SPI to introduce the delta32 mutation into the rhesus gene encoding CCR5, an HIV/SIV receptor. The experimental plan will be to use hematopoietic stem cell transplantation with rhesus macaques to determine the feasibility of HSC modification for protection from, or curing HIV infection. Pending Support

FUTURE GOALS

SPI will continue to utilize the four Specific Aims outlined above to provide exemplary service. The Unit will continue to seek ways to recruit new research projects by working with the WNPRC Director and the Executive Committee in order to fully utilize the WNPRC resources. There has been a significant increase in need for SPI staff to assist in after-hours and weekend project support for intensive projects involving kidney and bone marrow transplants. Subsequently, we continue to increase unit efficiencies and to find ways to maximize our productivity while alleviating undue strain on personnel. We also have two undergraduate students to assist in collating and distributing blood and tissue samples during the time unit personnel are busy with the animal procedures.

With regards to Specific Aim 4 we have initiated LRRK2 targeting with marmoset fibroblasts and have identified cells expressing the GFP marker transgene indicating introduction of the targeting plasmid into the cells. We will analyze the currently transfected cells as well as optimize electroporation methods with the marmoset ESC and iPSC. We will continue to support the generation of IVF embryos to optimize the detection of the LRRK2 G2019S mutation introduced into individual embryos. Embryo injection with plasmid DNA will be performed initially to determine effectiveness of plasmid injection in Cas9 expression and editing before attempting to transfer embryos. Finally, we will establish intracytoplasmic sperm injection (ICSI) to obviate limitations in success due to occasional suboptimal fertilization rates, methods that will also be directly applicable to CRISPR/Cas9 reagent microinjection.

PATHOLOGY SERVICES UNIT

Unit Head: Excluded by Requester DVM, DACVP
Core PI: Excluded by Requester MD, PhD

The Pathology Services Unit is essential to NHP colony health and research at the WNPRC. The Unit continued to collaborate with the clinical veterinary staff to provide rapid disease diagnosis and consistent monitoring of chronic diseases and metabolic conditions affecting animals assigned to long-term research studies. During the current reporting period, Unit personnel processed over 14,312 blood, feces, urine and other biological samples for clinical and research purposes including 2,258 CBCs, 129 urinalysis, and 302 in house fecal examinations. The Unit continued to play an integral role for the vast majority of research conducted at the WNPRC through advice concerning anatomy and disease pathogenesis; development of specialized collection protocols; clinical pathology testing; cytology evaluation; and surgical biopsy evaluation. The unit performed 228 gross post mortem examinations with 143 research and 84 diagnostic sample collections with histology with interpretation of lesions in reference to experimental questions and goals and colony health. The Unit remained responsible for the collection, banking, and distribution of NHP samples to numerous local, national, and internationally located investigators through the Nonhuman Primate Biological Materials Distribution core (NHPBMD). The unit continues to manage the NIA Aging Nonhuman Primate Tissue Bank contract (Excluded by Requester PI). The Unit also continued to train undergraduate, veterinary, and graduate students in clinical pathology, necropsy, anatomy, histology, disease pathogenesis, and other topics related to NHP and research.

Specific Aim 1 - To continue to support NHP colony health and experimental investigations by providing rapid diagnosis of disease, characterization of current and developing NHP models, and collaborative development of experimental paradigms.

The WNPRC Pathology Services unit focuses on providing excellent service while recognizing budget constraints. This role has been met through the performance of routine diagnostic and screening procedures as well as the development of innovative diagnostic methods and experimental techniques.

See tables for pathology and clinical pathology services provided to investigators and projects.

Supply purchases continue to be researched for competitive pricing on a regular basis. Contract laboratories are evaluated for service quality and price biannually, or as needed. Cost savings are implemented as they are identified to benefit both the WNPRC and investigators. Protocols, SOPs, training and QA/QC practices are continually evaluated and revised as needed. Unit members also regularly meet and coordinate efforts with members of other WNPRC units to refine and improve sample and data collection, medical records, and reports through the electronic health record system.

Excluded by Requester (veterinary services) are working with graduate students/post-docs Excluded by Requester to characterize and compare circulating viruses endemic in the WNPRC and newly arrived NEPRC marmoset populations. They are continuing to investigate the cause(s) of enteritis and intestinal neoplasia in the WNPRC marmoset colony and will be comparing typical pathologies (clinical and post-mortem) in both marmoset populations.

Excluded by Requester pilot project focusing on the immunohistochemical characterization of pancreatic intraepithelial neoplasia (PanINs) in rhesus macaques is progressing. Excluded by Requester joined the project as an Honorary Training Fellow in July 2014 and is now working in Excluded by Requester Lab as a graduate student.

Specific Aim 2 - To continue to curate and expand the NIA Tissue bank and manage the NHP Biological Materials Distribution (NHPBMD) Core in cooperation with SPI.

Pathology unit members continue to work with the NIA to receive samples donated to the NIA tissue bank and distribute samples as directed by the NIA. Four complete aged animal collections were donated by the WNPRC with 21 additional donations from other institutions and 84 samples were distributed as per NIA direction, during the reporting period. WNPRC and NIA staff work together on database improvements to increase the efficiency of data entry and analysis.

The Pathology Services Unit coordinates and cooperatively distributes biological specimens to researchers and educators through the Nonhuman primate biological materials distribution (NHPBMD) core and the number of specimens divided into tissue and organ categories is reported under that core service.

Specific Aim 3 - To serve as a resource for primate research, education, and conservation through participation in pathology consortium activities, scientific meetings, serving as advisors/consultants and training of students at the WNPRC.

Eight scholars and honorary fellows have been supported through the ACLAM externship award administered by [Excluded by Requester] the ACVP externship program, and the WNPRC extern program. Five undergraduate students have received training as part of the UW work-study program.

An ACLAM board examination preparation workshop was held at the WNPRC on April 3 & 4, 2014 with 47 attendees with both national and international representation. The conference will be held again May 7-9, 2015 with [Excluded by Requester] presenting as well as other invited experts.

[Excluded by Requester] continues serve as a participant and moderator for Latin Comparative Pathology Group (Branch of the CL Davis Foundation) and [Excluded by Requester] has presented as well [Excluded by Requester] is coordinator for the International Mock Exam Coalition; Peer reviewer for Journal of Medical Primatology and Journal of Visualized Experiments (JoVE). [Excluded by Requester] have lectured to the UW School of Veterinary Medicine Lab animal and Pathology clubs.

[Excluded by Requester] all participate in the national primate research center (NPRC) pathology consortium activiti es; present cases for the NPRC virtual slide conferences; and participate and present cases at numerous rounds at the UW medical school, UW veterinary school and the Wisconsin veterinary diagnostic laboratory.

[Excluded by Requester] participated in the Expanding Your Horizons learning labs with [Excluded by Requester] at the WNPRC on 11/8/14. She focused on the composition of blood and clinical pathology.

[Excluded by Requester] taught a 45 minute outreach class to 2nd grade children at a Waunakee school about blood on 11/24/14.

FUTURE GOALS

Pathology Unit members will continue to collaborate on current and developing projects to meet specific aims as listed above. The Unit will continue to improve and expand services for colony health and research. This will include ongoing work with WNPRC IT and other NPRCs to refine the LabKey based E.H.R. (electronic health record) to more efficiently meet colony and research needs. Unit members will continue to support training and outreach programs for education and conservation.

COMPLIANCE AND TRAINING UNIT

Unit Heads Excluded by Requester MS and Excluded by Requester DVM, DACLAM

The training component of the Unit continued to ensure that all personnel who enter the animal areas of the WNPRC and all personnel who handle animals or their tissue are fully educated and trained according to WNPRC standard operating procedures (SOP) and policies. During the current reporting period, the Compliance and Training Unit provided training to **263** new WNPRC, University, and visitors who required access to center animal areas. Training varied from Herpes B safety information and personal protective equipment requirements to complete hands-on training and oversight of training. During the reporting period, the SOP Review Committee reviewed and edited **41** SOPs and created **4** new SOPs. In addition, the committee reviewed and updated **79** forms, **67** signs, and **6** guideline documents. The compliance component of the Unit continued to ensure that all WNPRC personnel, procedures, policies, experiments, and facilities remain in compliance with the laws, regulations, and guidelines that govern the use of laboratory animals in research. The Compliance Coordinator performed **36** extensive IACUC protocol reviews for **13** core and **10** affiliate investigators during the current reporting period. During the reporting period, a new Occupational Health and Safety Coordinator was hired. She manages the Occupational Health and Safety program, including reviewing investigators' IACUC protocols, assisting with the submission of new and amended biosafety protocols, providing or assisting with safety training, organizing and coordinating clinics (e.g., tb testing, fit testing, influenza vaccination, etc.), generating and administering training for research associated hazards, managing the center's tb database, meeting and collaborating/consulting with other campus groups (e.g., EH&S, UHS), and growing and enhancing the Center's Occupational Health and Safety program. Overall, the Unit continued to work in collaboration with the various divisions and investigators of the WNPRC to standardize training and to promote a Center-wide atmosphere of regulatory compliance.

Specific Aim 1 - To educate and train all WNPRC staff, support personnel, and visitors who may come into contact with NHP or their tissues to ensure that they understand and follow WNPRC standard operating procedures

The process of ensuring that all WNPRC personnel (Animal Services Division as well as all other division and unit personnel), investigators, students, support staff, maintenance workers, and visitors are fully trained and aware of all Center standard operating procedures and polices remains the primary aim of the training component of the Unit. Table 1 shows the number of new individuals who have obtained access to WNPRC Animal areas for 2014 and completed the required training based on their access requirements.

Table 1. New Individuals Accessing WNPRC Animal Areas (2014)

Center Employees	35
Honorary Fellows	30
Students (Undergrads, Graduate students, Post-docs, Trainees)	102
Vendors	21
Visitors (Physical plant, Inspectors, Environmental Health and Safety University Health Service, Potential employees)	75
	263

There are two required species-specific training modules for all NHP users across the University of Wisconsin-Madison campus that have been created and are taught by personnel from the Compliance & Training, Behavioral Management, and Veterinary Services Units of the WNPRC. The first module, Primate Orientation, offers participants valuable information regarding primate behavior, psychological well-being programs, basic biology and ecology of the species of NHP we have on campus plus further Herpes B information, post-exposure procedures, and safety information. The first module is a prerequisite for the second module, Primate Health, which is guided by WNPRC Veterinary staff. Participants gain knowledge of NHP physical exam, body condition scoring, dental assessment, tuberculin skin testing, and proper blood collection and injection procedures. For staff who work only with NHP tissues, a separate training has been created that emphasizes Herpes B safety information and lab safety. Training over the last year has included the participation of **128** people for Primate Orientation, **81** people for Primate Health, and **29** people for NHP Tissue Handling training. All three modules remain as in-person training, which helps introduce new employees to the Compliance, Training, Behavior, and Veterinary staff and allow for interactive sessions where questions and concerns about working with NHPs can be answered.

The Training Unit focuses a large amount of their effort on training new Animal Research Technicians (ARTs). New ARTs receive four weeks of hands-on training in the animal area with a member of the training unit, with assistance from Animal Care Supervisors and Lead ARTs. During this period, the ART is trained in a step-by-step fashion to perform the basic duties outlined in their job description and are reminded repeatedly about safety precautions that must be adhered to at all times while working with NHP. Trainees are assessed weekly on their proficiency at performing the husbandry tasks and must consistently demonstrate that they are gaining proficiency at all the basic tasks before they are allowed to move to the next level of training. The length of training with the Compliance and Training Unit was extended to increase the proficiency of staff, expose them to husbandry in more areas prior to their transition, and expose them to cage sanitization procedures. During this past year, 19 new full-time ARTs and 8 part-time students ARTs were trained.

Training is a constant process at the WNPRC, especially for personnel who frequently contact animals and/or their tissues. Refresher courses, proficiency assessments, re-training, annual updates, and new instruction are provided to Center personnel throughout the year and throughout an individual's tenure at the WNPRC. Additional attention is paid to personnel who have committed errors while performing their duties or are not acquiring necessary job-related skills as quickly as expected to ensure that they receive the additional training or re-training that they require to successfully perform their job responsibilities. To reduce the frequency of loose animals, the Training Unit implemented a presentation that provided a detailed and comprehensive description of cage styles, lock requirements, and conscious animal transport using a transport box, which **138** personnel attended. In addition, hands-on proficiency assessments were performed for **74** staff that transport animals regularly. This training will be repeated on a quarterly basis. In this exercise, additional prevention strategies were also identified and implemented.

An online training module for the mandatory Annual Working Safely with Nonhuman Primates has been developed, which has improved the consistency of information, increased timely compliance and access to information, and decreased the need to schedule multiple in-person sessions. This annual refresher course will be tracked through the Graduate School, Research Animal Resources Center (RARC) and the Training Unit.

The Compliance and Training Unit also collaborates with other campus units to provide American Association for Laboratory Animal Science (AALAS) certification classes. AALAS certification is the highest recognition of professional achievement and competence for technicians in the laboratory animal science profession and continues their development as an animal care professional. The three

levels of certification are Assistant Laboratory Animal Technician (ALAT), Laboratory Animal Technician (LAT), and Laboratory Animal Technologist (LATG). Incumbent staff members are encouraged to attend and actively participate in the classes held at the RARC. A 14-week formalized didactic program guides employees through the ALAT level requirements and prepares them to sit for the examination. Of the Colony Management and technical staff (e.g., ARTs, Veterinary Technicians, SPI Technicians) at the Center, **18** have ALAT certification, **6** have LAT certification, and **3** have LATG certification.

Specific Aim 2 - To ensure a safe working environment for all WNPRC staff and students and to further develop the WNPRC Occupational Health and Safety Program to maintain compliance with new and existing standards

The Compliance and Training Unit members continue to develop and enhance the WNPRC Occupational Health and Safety Program (OHP) with the assistance of the staff of the UW Department of Environment, Health and Safety (UW Safety) and the University Health Services Occupational Medicine Department (UHS). As noted above, in April 2014, a new WNPRC Occupational Health and Safety Coordinator was hired. She assumed responsibility for providing new employee safety and OSHA compliance training, generating and providing safety training for research associated chemical and biological hazards, managing quarterly radiation dosimeter exchange, managing WNPRC respiratory safety program, coordinating in-house clinics (tb testing, fit testing, influenza vaccination, etc.), managing the center's tb database and incoming tb documentation, creating and managing new policies, assisting with building and program updates, coordinating safety training with external resources (i.e., CPR and first aid certification, fire extinguisher training, hearing protection), assisting with maintenance of post-exposure requirements and procedures, reviewing ACUC protocols for safety issues, etc.. In addition, she helped update and expand the WNPRC Continuity of Operations Plan (COOP Plan), provided training to all units, and coordinated an emergency exercise in conjunction with the UW-Madison Police Department.

Specific Aim 3 - To assist principal investigators with the development, preparation, submission, revision, and renewal of IACUC protocols and to assure continued compliance by conducting regular protocol audits

The Compliance Coordinator continues to provide an Animal Care and Use protocol development and review service for all investigators utilizing NHP at the WNPRC. During the reporting period the Compliance Coordinator performed **36** extensive protocol reviews. In August 2014, RARC launched ARROW-IACUC, the web-based system through which Principal Investigators in the Graduate School are required to submit animal care and use protocols. To prepare WNPRC PIs for the transition, the Compliance Coordinator prepared many custom tools and templates, and provided two training sessions relating to the new system. She also makes herself available to assist WNPRC PIs and their staff with their ARROW-IACUC protocol submissions.

The Compliance Coordinator is continuing to conduct protocol audits. Three audits are scheduled each month, but it is rare there is sufficient time to complete that many.

Specific Aim 4 - To ensure that WNPRC personnel and facilities remain compliant with all institutional, state, and federal regulations governing the use of NHP in laboratory animal research

To ensure that WNPRC personnel and facilities remain compliant, the Compliance Coordinator, Occupational Health and Safety Coordinator, and Colony Manager continue to regularly inspect all animal housing and support areas. During the inspections, the group verifies that all regulations and facility SOPs are being followed (e.g., appropriate sanitation, food storage, etc.) and checks required documentation (e.g., cage washing records, environmental enrichment records, health observation records, etc.) to ensure it is up to date and accurate. They also note all facility maintenance concerns.

After each inspection, a report describing details about the problems noted and possible solutions is generated and distributed, and resolutions scheduled.

The formalized incident-reporting program continues to ensure consistent reporting and follow-up on all errors involving NHP and the Incident Prevention Committee continues to meet monthly. The committee consists of the Compliance Coordinator, Attending Veterinarian, Training Coordinator, Colony Manager, Assistant Director for Administrative Services, HR Assistant Advanced, Occupational Health and Safety Coordinator, Co-Head of SPI, a clinical veterinarian, and a research staff member. The committee discusses the errors that occurred during the previous month, makes recommendations for preventing similar errors from occurring, and develops plans for instituting the recommendations. They also evaluate end-of-the-year statistics and trends to determine if additional preventive measures need to be taken.

Specific Aim 5 - To continue to review, revise, and expand the entire complement of WNPRC standard operating procedures (SOPs)

The Compliance Coordinator continues to oversee the creation, review and revision of all WNPRC SOPs and forms by the WNPRC SOP Review Committee. The SOP Review Committee continues to meet one to two times per month to modify and expand the compliment of SOPs to ensure they are current and contain sufficient detail to act as effective training tools. During the reporting period, the SOP Review Committee reviewed and edited **41** SOPs and created **4** new SOPs. In addition, the committee reviewed and updated **79** forms, **67** signs, and **6** guideline documents.

FUTURE GOALS

Training Unit goals: The Training Unit plans to continue to provide a high level of training to new ARTs so they are able to deliver the best husbandry for the colony and be more independent following their completion of the initial training program. The Unit also plans to continue to encourage AALAS certification, especially for the new ARTs hired once they are eligible. Additional learning modules are being developed, including an introduction to the Electronic Health Record (EHR) system and paper form submissions to Colony Records. The new module should provide a more consistent introduction to the resources available in EHR and improve consistency in documentation on paper forms. The Training Unit also continues to work on increased direct documentation of training into EHR, including creating templates for basic training requirements based on position (e.g., ARTs, research staff, veterinary staff, student employees), which will standardize training, documentation, and retrieval of information. The Training Unit is also working on creating an updated Lab Notebook to serve as a guide to new PIs and help provide a smooth transition to working at the WNPRC.

Compliance Unit goals: The Compliance Coordinator plans to devote more time to protocol audits and fulfill the goal of completing three per month. She also plans to develop many more ARROW-IACUC templates and tools to help WNPRC PIs with protocol submissions. In addition, she plans to start entering all protocol-approved procedures into EHR to help ensure compliance and make the scheduling of procedures easier.

The Occupational Health and Safety Coordinator plans to establish a WNPRC Safety Committee made up of the Occupational Health and Safety Coordinator, the Compliance Coordinator, the Head of the Training Unit, and other WNPRC staff. The committee will meet regularly to discuss and review safety issues and ways to mitigate identified issues. They will also assist with planning upcoming safety training (e.g., annual Continuity of Operations Planning (COOP) exercises). Additional goals include standardizing a process for identifying and informing staff about new and upcoming hazards, exploring and experimenting with new PPE technology and other new engineering controls, making wellness

activities available to staff, creating and implementing a travel policy, implementing the newly developed measles policy, continuing to improve our post-exposure procedures by including a mental health component, merging the Center's chemical hygiene plans, making improvements to and continuing to manage our tb database, and procedures for incoming visitors and employees, etc.

BEHAVIORAL MANAGEMENT UNIT

Unit Head: Excluded by Requester PhD
Core PI: Excluded by Requester PhD

The broad goal of the Behavioral Management Unit continues to be to promote animal welfare and facilitate scientific progress by providing state-of-the-art management of the NHP housed at WNPRC. The Unit's approach remains team-based, with an emphasis on integration of expertise and efforts across divisions of WNPRC research programs and support services. Our specific aims integrated discovery, implementation, and rigorous scientific evaluation of enrichment strategies using a dynamic process of try, evaluate, and modify. The evaluation of effectiveness and selection criteria for each strategy was determined by striking a balance between positive outcomes for the animals and the practicality with which a strategy can be initiated and maintained. At the level of the animal, our focus continued to be promoting species-typical behavior; decreasing the expression of abnormal or stereotypic behavior; and facilitating animals' resilience to stress and more rapid adaptation to research and husbandry procedures. Our approach adhered to a lifespan perspective, with consideration of the animals' unique species-typical needs as they mature from infancy to old age. The Unit's efforts have resulted in the Behavioral Management Unit becoming a more active and productive contributor to the universal enhancement of welfare practices in laboratory primate studies.

Specific Aim 1 - To ensure the psychological well-being of the WNPRC NHPs through continued focus on the importance of social interaction for animals across the lifespan and in accordance with research programs

Specific Aim 2 - To coordinate and maintain current components of the environmental enhancement plan (2a), while also investing significant, integrated and scientifically-driven effort to develop, implement, and evaluate novel components of the environmental enhancement plan (2b)

Specific Aim 3 - To maintain a surveillance program for animals that exhibit abnormal behaviors and require applied behavioral intervention for treatment

Specific Aim 4 - To train WNPRC staff to use behavioral methodologies to engender positive interactions and, in turn, facilitate animal welfare, husbandry, clinical treatment, and research

Specific Aim 5 - To develop a novel undergraduate training and education program that provides instruction in animal behavior and unique opportunities to work with NHP

The base grant reviewers were enthusiastic about the Behavioral Management Unit Aims, including a new emphasis on scientific approaches and evidence-based evaluation to inform continued changes and improvements in the WNPRC enrichment and behavioral management program (**SA2 A & B**). The reviewers were also enthusiastic about inclusion of undergraduates in the Unit's activities, with the dual complementary goals of providing research training opportunities while also fulfilling the Unit's aim of increased scientific productivity (**SA4 & SA5**). Thus, the Behavioral Management Unit retained and

moved forward with those aims, making significant progress. The basegrant review also highlighted a perceived weakness in our social housing of macaques within our colony. The importance of social pairing has been reiterated in subsequent External Advisory Board meetings. Thus, we prioritized social pairing as a primary immediate aim and continue to make significant progress in meeting this challenge (**SA1**). The presentation of this report will emphasize this point and cover progress for the specific aims proposed during this grant period. Service and academic progress will be highlighted within each section.

Nonhuman Primate Socialization (SA1).

Over the project period, the number of non-exempted single housed monkeys remained between 20%-30% of the WNPRC total macaque population monthly. While it may appear to be a large proportion, the number falls within current estimates of the other National Primate Research Centers in similar indoor housing environments (M=22%, Range 12-37 % 6/2013 & M= 18% 9/2014 across 8 National Primate Research Centers). Furthermore, in the case of our colony, calculation of the single housed proportion can be further divided by species (i.e. rhesus and cynomolgus macaques), sex (male:female), three SPF backgrounds, and four unique geographical locations creating subgroups of pair-able animals. Thus, the Behavioral Management Unit will continue to refine a corollary aim to our socialization initiative by tracking how dynamics of assignment to research projects affects the subgroups of animals to inform our pairing process.

Pairing and group formation has remained the primary aim of our Unit, with a high success rate. A total of 241 animals previously single-housed and not exempted from social housing were successfully paired (or grouped), or reunited into pairs following single-housing for experimental or clinical reasons, during the project period (Feb 14'-Dec14'). The Unit continues to troubleshoot and develop strategies that will allow us to better track the success and maintenance of these pairings. Socialization of single-housed animals will remain an on-going primary aim, as both research and clinical needs for animals in the colony will continue to result in a demand for socialization of animals following single-housing. Our unit is small compared to units in other primate centers and past cost-saving reductions in behavioral management staffing will remain a significant challenge to meeting our past projections for social pairing (e.g. 3 staff, 42 novel pairs per quarter stable to 1 mo); however, we will be allowed to hire another staff member during the upcoming project period.

A series of challenges to socialization were met during this project period. For example, research related consideration of novel viral status resulted in an increase in animals under evaluation and isolation of subgroups. These considerations began early in this project period (1/2014) and while successive testing and sorting continue the bulk of the animals viral status related subgroups were established by June 2014'. For a time, the sifting and winnowing of the sub groupings of animals within the colony provided challenges because of the availability of animals for "like-type" pairings. Taken together, these factors contribute to availability of compatible partners and pairing opportunities. We have taken measures to better track the effect of these factors on single housing within the colony and are rounding out a comprehensive analysis of these factors (Feb 14'-Feb 15') to provide some population values to address global questions of how colony usage profile may impact the socialization process. This is an ongoing effort for our unit; however, we expect to report on our progress in the upcoming project period.

Finally, the Behavioral Management Unit's socialization aims have benefitted from continued improvements in facilities and infrastructure, including an increase in the number of pen housing environments and we expect further upcoming structural enhancements and housing improvement. Funding was secured for the renovation of additional colony housing space to environments that

include social housing options (PI: Excluded by Requester The development of these new housing environments has been established following prototype assessment and constitutes a significant collaborative effort between Colony Management, Behavioral Management Unit, and Facilities and Shop Services. Our first of these novel environments was established and consisted of creating a small harem pen several and several cage group pairings (11/2014). A second harem pen was created in December 2014. Currently, we are poised to implement several more of these novel social environments for our NHPs and the manufacturer will deliver them during the next project period. Initiatives will continue to develop for the provision of further structural enhancements (e.g., tunnels, chutes and penthouses) in other colony areas.

However, one factor in the socialization process that is not often discussed remains: How many monkeys might we expect to be singly-housed without research exemption in a multi-use biomedical facility of our size and with our research profile? This dilemma was of further interest because the process of research is a dynamic, where individual animals are selected for study by investigators based on specific characteristics (e.g., gender, age, genetics, viral status, etc.). Thus, animals may remain on projects for varying periods of time where the investigator has IACUC justification for single housing. Assignment of group-mates based on research requirements may result in loss of stability and mates may not return.

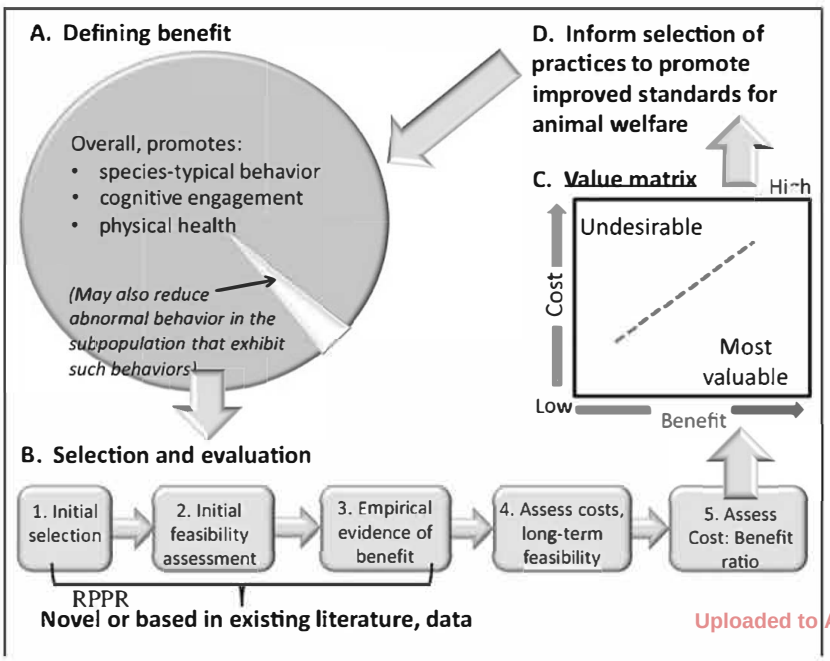
Evidence-based Evaluation (SA2).

Currently, the Behavioral Management Unit has a number of ongoing projects to refine the delivery of environmental enhancement opportunities and to continue to improve the welfare of our NHPs. The projects focus on two broad themes: 1) Evidence-based behavioral evaluation of enrichment strategies; and, 2) Identifying proximal and distal events that may modulate expression of alopecia. Both thematic research areas also serve our student research opportunity aim by providing students a meaningful and successful entry into research with NHPs (SA5).

Project 1 - Evidence-based behavioral evaluation of enrichment strategies (SA 2 A & B):

Briefly, the purpose of this Specific Aim is two-fold: First; provide data informing the selection of enrichment strategies that effectively promote welfare; and second, more generally inform the broader community by providing a standard method of comparison to empirically evaluate enrichment choices. There are few guidelines informing effective choices of enrichment (e.g. foraging enrichment see p. 67, The Guide, 2011); thus, our work fills a key gap in the field. The general aim of enrichment and enhancement plans is to increase species-typical behavior, cognitive engagement, physical health and psychological well-being. Our platform for selection of enrichment strategies is based on a scheme of "Try-Evaluate-Modify". This process is represented schematically in Figure 1 and the resulting manuscript was published in this project period Excluded by Requester

Excluded by Requester 2014).



One project under this thematic area addresses a question with implications not only for animal welfare and clinical health, but also scientific studies with the animals. The project is producing an empirical analysis of the caloric load associated

with 10 standard foraging devices used in our colony. The primary goal of this project is to perform a colony-wide analysis of the variance in food loading of foraging devices and the caloric content associated with foraging device delivery as it relates to daily caloric intake. A second goal of this study is to provide an inclusive analysis of device, maintenance, and labor cost associated with use of a given device. The final goal will be to employ direct usage analysis to determine the level of engagement with the device. The purpose and value of this project is to better inform future selection of devices and foods used in the Unit's Environmental Enhancement Plan (EEP), with prioritization of those that are most effective. The outcome data will also provide empirical support for decision-making that may lead to cost-savings. Additional follow up data will be added to this effort and a manuscript is in preparation.

Two student projects under the thematic umbrella of evidence-based evaluation of enrichment began in the Fall 2013 semester and continued through the current project period. Excluded by Requester a UW-Madison senior and Evolutionary Biology major, has completed a parametric evaluation of foraging devices in order to provide data on device construction that maximizes monkeys' manipulative engagement. Excluded by Requester presented this project entitled " Approaches for optimizing foraging devices: Effect of cup volume on retrieval time in rhesus macaques (*Macaca mulatta*)" as part of the undergraduate research symposium (May 2014). Data analysis and manuscript preparation is ongoing. Ms. Excluded by Requester a junior Biology and Life Science Communication major, recently completed data collection for a project evaluating the effectiveness of video stimuli as environmental enrichment to determine the effectiveness of this modality to engender species-typical engagement. The project co-authored with fellow student Excluded by Requester entitled "An evaluation of the efficacy of television as a form of environmental enrichment in rhesus macaques (*Macaca mulatta*)" has been accepted for presentation at the upcoming annual meeting of the Midwestern Psychological Association in May 2015. Data analyses and manuscript preparation is currently underway.

Project 2 - Identifying proximal and distal events that may modulate expression of alopecia: A refinement of strategies to quantify alopecia to better inform clinical treatment and case resolution:

This is a long-term study to evaluate population levels of the extent of alopecia within our colony. A *population* analysis will provide data on the expected levels, and inform sub-typing of alopecia in macaques. This is part of a cross-Center initiative discussed in the Primate Center's Behavioral Management Consortium to quantify not only extent of alopecia in our populations, but also subgroups of animals, that may express clinically-relevant alopecia and to determine whether the expression is related to environmental factors and/or normative developmental processes. The Behavioral Management Unit collects image data for subsequent analysis of coat condition and hair for exploratory analysis of hormone content in collaboration with the WNPRC Assay Services Unit. Examples of hormones of interest include cortisol as a surrogate marker for stress and sex hormones as markers for physiological maturity. The study design includes both within-subject analyses over time in those animals sampled repeatedly, as well as between-subject analysis across age group cohorts. This analysis strategy will provide novel descriptive information from of our entire macaque colony.

Our colony-wide samplings occurred concurrently with bi-annual TB surveillance and health evaluations. Consistent with the Unit's goal of integrative, team-based approaches, Unit leadership has recruited clinical veterinary staff to collaborate on this project to compare and refine the current clinical categorization and tracking of alopecia within the colony. In our first pass analysis, three samplings were completed in this grant period, January 2013 (n=534), July 2013 (n= 547) and January 2014 (n= 650). Sampling constituted a significant labor cost for the unit given its small size. Although we did provide sampling as a training and learning opportunity for students (SA4 & SA5), student participation did not significantly defray the labor required to continue sampling and concern remained that continued sampling would unduly interfere with other service aims. Thus, following the 2014 sampling,

which completed sampling over a full calendar year, we greatly decreased the level of sampling until we are able to garner additional support. We have continued to sample small groups in subsequent sampling period to assess the effect of relocation within colony on the duration of cortisol responses to relocation. Data analysis will continue into the next project period. The expectation is that these data will refine the Unit's strategies to identify, inform, and develop behavioral management interventions that will reduce alopecia within our colony.

Significant progress has occurred on this project during this grant period and this has contributed to our academic portfolio. We have submitted a Pilot Research Project proposal entitled "Measurement of hair steroid markers for alopecia in rhesus monkeys" in an effort to expand our hormone analysis panel (i.e., cortisol, cortisone, progesterone, DHEA, testosterone, DHT estradiol, estrone, and thyroid hormone). A second component of this application was to provide undergraduate training opportunities in image analysis and hair sample [Excluded by Requester] 7/14). Although favorably reviewed the proposal did not attain a fundable score. This work also provided preliminary data for a NSF Graduate Research Fellowship submission by ascending senior [ ] entitled "Towards Identifying [Excluded by Requester] Causal Mechanisms of Alopecia in Rhesus Macaques: Quantitative Analysis of Hormone Profiles and Alopecia in a Large Population" [Excluded by Requester] 11/14).

Behavioral Surveillance, and Training Service Aims (SA 3 and 4)

One of the primary directives of the Behavioral Management Unit is to monitor the behavioral health of the colonies under our care. In the past we have done this by performing a colony-wide bi-annual behavioral assessment. The Unit moved away from the biannual assessment because of the low incidence of abnormal behavior of imminent concern within the colony (i.e., approximately 10 animals with infrequent but recurrent SIB), a mechanism for daily observation and reporting was already in place (below) and the other demands on our minimal unit staff (2 BMU staff for 1200 macaques). While we have moved away from bi-annual assessment we acknowledge the importance of serving the adjustment needs of our animals in standard daily housing conditions. Briefly, several layers of daily observation inform behavioral surveillance: daily care staff observations, daily veterinary technician rounds and the daily area veterinary reporting structure and rounds. Thus, we employ a team-based approach where Colony Management and Veterinary Services staff reported any behavioral issues of concern to behavioral management for daily assessment.

The current approach is sufficient for daily tracking of the occurrence of abnormal behavior but will not measure whether or not abnormal behaviors escalate within an individual over time. During the current progress period we have developed several new methods to monitor behavior outside daily observation alone. We have developed several Ipad based behavior checklists for monitoring request for behavioral assessments, recording a baseline behavioral assessment when new animals enter the colony (6/2014) and a colony-wide behavioral assessment to add coverage across the entire colony (12/2014). The tools are in the initial implementation phase but have been designed with compatibility in mind to develop comparable data with the other National Primate Research Centers. There has been an expressed interest in the development of these "paperless" tools for broader applications and a manuscript describing them is in preparation [In Preparation] in prep).

The Unit has continued to explore avenues that will allow it to capture data that will inform the trajectories of development of behaviors of potential concern. For example we have worked with our ITSS group to add categorical codes to help us better track behaviors of interest and social housing status. We expect the added functionality of the WNPRC EHR system will aid by allowing the potential to include archival-based components to our long term surveillance of all of the animals under our care and chart the occurrence of behavioral issues.

During this grant period, we have engaged in a number of training opportunities for investigators and staff toward the goal of enabling research and increasing welfare of the animals. For example, we have trained staff in oral drug dosing for a recent project. This included training the animals to transfer, and habituating them to the dosing procedures involved. We also provided behavioral expertise to two upcoming projects that will require staff training in behavioral methodologies. The first will require developing a standard behavioral observation schedule and training of staff to perform these behavioral observations in infant macaques (PI: Excluded by Requester University of Wisconsin, "Hypothermia to prevent neurotoxic side effects of pediatric drugs"). The second will require our involvement in the determination of the viability of standard food items in the cross species measurement of mastication dynamics (PI: Excluded by Requester Private Source "Influence of dietary properties on chewing patterns in primates").

Finally, our role as a University training resource has evolved to include participation in the University's behavioral welfare interest group. This group discusses welfare related issues across the different species represented on campus in an effort to benefit from the wide range of expertise available across campus programs. Through interaction with this group we were able to securing funding from the University's Research Animal Resource Center to support four undergraduates over the summer in a training internship. Students assisted in coat image analysis and hair processing for the alopecia project, developed methodology to study auditory aspects of enrichment with an evidence based approach and began comparative analyses of enrichment strategies across different NHP facilities. Together, this unique opportunity provided for the students to develop expertise in imaging modalities, procedure development, and communication skills.

FUTURE GOALS

The primary service aims of the Behavioral Management Unit will continue with our concentration of Unit staff focused on socialization of single-housed animals (**SA1**). Along with establishing stable pairings and groupings, the Unit will continue to refine environments by bringing additional pen housing opportunities and structural enhancements on-line. Decreased staff size has necessitated a further shifting of focus to socialization of single-housed monkeys and to daily tasks such as behavioral observation and surveillance of reported behavioral issues. However, we will be adding to our staff in the next project period and expect a commensurate increase of the pursuit of our specific aims as the new candidate assimilates and acquires the requisite skills.

The Unit will continue to refine and implement efficiencies in tracking the success and progress of its pairing initiative and following behavioral treatments for cases of abnormal behavior. Ongoing cross-unit collaboration with ITSS will offset the effect of the small size of our unit on productivity and increase the functionality of the WNPRC's electronic health record system by creating categorical organization of behavior in favor of current text-based behavioral entries. This investment will increase the Unit's efficiency in tracking the welfare needs and treatment progress for our NHPs. Another advantage expected will be improvements in the Unit's ability to further define colony-wide behavioral outcomes and drive hypothesis-based archival studies. Lastly, the Behavioral Management Unit plans to accelerate other efficiencies in its service aims by creating computer-based interactive training modules to reallocate Unit staff from face-to-face training of University-wide personnel and also increase efficiencies in the training of off-site investigators and staff that use the WNPRC as a national research resource. The anticipated decreased workload in this area will allow the Unit to concentrate staff effort to the welfare requirements of the NHPs under its care. Continued development of these efficiencies is necessary to maintain the Unit's ability to both perform its service role and move academic progress forward under the current budget contraction and cost-saving measures directed by the WNPRC Senior Management team.

In the next period, the Behavioral Management Unit will continue to move forward with its projects aimed to refine strategies to ensure the psychological welfare of the NHPs (**SA 2 a & b**). A number of projects are long-term and will continue. First, data collection for the project identifying proximal and distal events that may modulate expression of alopecia is completed and has moved to the data analysis and writing phase. Second, the Unit's effort to determine nutritive content and caloric load of foraging devices continues to inform our refinement of delivery of foraging opportunities in terms of content and portion size. The refinement is important for animal health and to balance scientific interest in nutrition.

The Behavioral Management Unit's evidence-based approach will continue to refine how the Unit delivers enrichment and enhancement opportunities by empirically evaluating aspects of the EEP. For example, the Unit will provide new data on the presentation and effectiveness of sensory enrichment (i.e. visual, auditory and olfactory modalities) to address outstanding questions for which there is scant empirical data. Do NHPs attend to video/auditory enrichment and does this interaction engender increases in positive behavior such as sociality? For example, the background review of methods to experimentally evaluate audio content was completed and is awaiting another undergraduate candidate's interest. Do object qualities or affordances modulate species-typical interactive behaviors? In turn, the Unit will use this information to direct refinements of the enrichment and enhancement opportunities it delivers to maximize species-typical interactions without compromising research aims.

The student opportunity aim (**SA 5**) will continue to provide education opportunities with the evidence-based approach to test hypotheses concerning specific elements of the EEP. The Behavioral Management Unit will be a national research resource to training the pipeline of the next generation of scientists with skills and competence working with NHPs. The student scientists will be trained to integrate welfare needs and considerations within their research designs. The WNPRC is uniquely positioned to meet this goal because it is the single National Primate Research Center located within a major college campus and along with the Harlow Center for Biological Psychology, has a rich history in training undergraduates in NHP welfare science.

NONHUMAN PRIMATE BIOLOGICAL MATERIALS DISTRIBUTION (NHPBMD) CORE

Pathology and SPI Units

Specific Aim 1 - To continue to maximize the investigative use of each animal scheduled for post-mortem examination

This aim represents the traditional tissue distribution services, which are still highly valued by many investigators. The Pathology Services Unit evaluates all animals scheduled for necropsy in reference to the investigators and educators enrolled in the NHPBMD Core. WNPRC Core Scientists are aware of the program and often suggest collaborator registration with the NHPBMD core to maximize use of experimental animals. The Pathology Services Unit has banked samples of a variety of tissues (e.g., fresh frozen liver, spleen, kidney, plasma, serum, buffy coat, OCT frozen tissues, paraffin embedded tissues, etc.) from most clinical and some experimental necropsy cases with Systematized Nomenclature of Medicine (SNOMED)-coded morphologic diagnoses available for research purposes. These coded diagnoses are integral to the efficient identification and utilization of appropriate samples for retrospective studies as well as studies involving development of unique investigative methods such as immuno-histo chemistry. Aged animal tissues are routinely donated to the NIA tissue bank rather than being placed in the NHPBMD repository.

Specific Aim 2 - To increase the investigative usage of colony animals through minimally invasive manipulations

The Scientific Protocol Implementation Unit is responsible for requests that require sample collection from live subjects. Samples that may be collected from live animals not scheduled for necropsy may include: whole blood plasma, serum, urine, semen, CSF, broncho-alveolar lavage fluid, biopsies of skin, muscle, and superficial lymph nodes, and swabs for bacterial and viral evaluation.

Specific Aim 3 - To coordinate complex collection needs through ante-mortem manipulations prior to sample collections for both *in vivo* and post-mortem sampling

This aim has been and will continue to be an important mechanism for the provision of affordable NHP samples to extramural investigators who need specialized tissues or organs such as embryos or fetal tissues collected at specific time points.

Specific Aim 4 - To leverage and develop collaborative relationships with investigators, who may originally make simple research requests for pilot data, into projects utilizing full WNPRC research support in NHP models

The NHPBMD Core has the expertise and experience to mentor new investigators as well as collaborate with established individuals transferring their research to NHP models. The core serves as an initial point of contact for numerous investigators (especially those at other academic institutions lacking NHP resources) and makes use of the SPI service paradigm to support and advance NHP research from “inception to publication.” The strongest benefit in the change to a core service has been the leveraging effect for developing collaborative relationships with investigators, which have resulted in grant applications with members of both the SPI and Pathology Services Units serving as co-investigators and co-authors.

FUTURE GOALS

The NHPBMD Core plans to continue with its current goals as described above, which most importantly allow for short-term assignment of animals for minimally invasive collection of biological samples, short-term experimental manipulations followed by specific post-mortem collection of tissues, traditional post-mortem sample collection, as well as access to numerous banked samples.

Additionally, the NHPBMD Core plans to maintain consistent enrollment of core, affiliate, and extramural investigators for NHPBMD core services to easily facilitate access to samples acutely identified for pilot projects and tangential investigations. NHPBMD continues to rely upon referrals of previously satisfied customers for additional enrollment, thus reducing redundant experiments at multiple institutions and reducing the numbers of animals used in research.

The NHPBMD core will continue to focus on organizing cooperative collections and processing efforts while ensuring accurate MTA agreements, and reducing questions about cost sharing in this strained funding atmosphere. These functions will be refined with emphasis placed on excellent science with administrative support provided by the WNPRC Operational Services Division.

Finally, the NHPBMD core will continue to specialize in providing resources to meet the needs of investigators transitioning research paradigms from other species such as rodents or canids to nonhuman primate models.

C. COMPONENT PRODUCTS

C.1 PUBLICATIONS

Not Applicable

C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

Not Applicable

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Not Applicable

C.5 OTHER PRODUCTS AND RESOURCE SHARING

C.5.a Other products

NOTHING TO REPORT

C.5.b Resource sharing

NOTHING TO REPORT

D. COMPONENT PARTICIPANTS

Not Applicable

E. COMPONENT IMPACT

E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES?

Not Applicable

E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE?

Not Applicable

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

NOTHING TO REPORT

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?

Not Applicable

F. COMPONENT CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

F.2 ACTUAL OR ANTICIPATED CHALLENGES OR DELAYS AND ACTIONS OR PLANS TO RESOLVE THEM

NOTHING TO REPORT

F.3 SIGNIFICANT CHANGES TO HUMAN SUBJECTS, VERTEBRATE ANIMALS, BIOHAZARDS, AND/OR SELECT AGENTS

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. COMPONENT SPECIAL REPORTING REQUIREMENTS

G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT REPORTING REQUIREMENTS

Not Applicable

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

G.4.a Does the project involve human subjects?

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Not Applicable

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

RESEARCH & RELATED BUDGET - SECTION A & B FINAL

ORGANIZATIONAL DUNS*: 161202122

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: UNIVERSITY OF WISCONSIN-MADISON

Start Date*: 05-01-2015 **End Date*:** 04-30-2016

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1.		Excluded by Requester			PhD	Unit Head, Behavioral Management	Institutional Base Salary	EFFORT			53,555.00	18,048.00	71,603.00
2.						Unit Head, Colony Management					39,709.00	13,382.00	53,091.00
3.						Unit Head, Compliance and Training					40,591.00	13,679.00	54,270.00
4.						Unit Head, Pathology Services					51,242.00	17,269.00	68,511.00
5.					MD	Core PI, Pathology Services					12,335.00	4,157.00	16,492.00
6.					PhD	Unit Head, Scientific Protocol Implementation Unit					42,444.00	14,304.00	56,748.00
7.						Co-Unit Head, Scientific Protocol Implementation Unit					23,107.00	7,787.00	30,894.00
8.					PhD	Core PI, Scientific Protocol Implementation Unit					18,330.00	6,177.00	24,507.00
9.						Division Head, Animal Services Unit Head, Veterinary Services					123,234.00	41,530.00	164,764.00
10.					PhD	Core PI, Behavioral Management					14,079.00	4,745.00	18,824.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior/Key Persons:	File Name:	Total Senior/Key Person	559,704.00

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
99	Division Staff	12.0			1,508,193.00	582,009.00	2,090,202.00
99	**Total Number Other Personnel**					**Total Other Personnel**	**2,090,202.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**2,649,906.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E

ORGANIZATIONAL DUNS*: 161202122
Budget Type*: ● Project ● Subaward/Consortium
Enter name of Organization: UNIVERSITY OF WISCONSIN-MADISON

Start Date*: 05-01-2015 **End Date*:** 04-30-2016

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	Funds Requested ($)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	0.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**0.00**

E. Participant/Trainee Support Costs		Funds Requested ($)*
1. Tuition/Fees/Health Insurance		0.00
2. Stipends		0.00
3. Travel		0.00
4. Subsistence		0.00
5. Other:		
0 Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 161202122

Budget Type*: ● Project ● Subaward/Consortium

Enter name of Organization: UNIVERSITY OF WISCONSIN-MADISON

Start Date*: 05-01-2015 **End Date*:** 04-30-2016

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	555,774.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Other	33,812.00
Total Other Direct Costs	**589,586.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**3,239,492.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. Modified Total Direct Cost Base	34.5	3,239,492.00	1,117,625.00
		Total Indirect Costs	**1,117,625.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): Department of Health & Human Services Contact: Arif Karim 214-767-3261

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**4,357,117.00**

J. Fee	Funds Requested ($)*
	0.00

K. Budget Justification* File Name: Yr 54_WNPRC_Animal Srvcs_Budget Just_opt.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
Behavioral Management Unit

FROM 05/01/15 THROUGH 04/30/16

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	TOTAL
Excluded by Requester	BMRU Head	EFFORT			Institutional Base Salary	53,555	18,048	71,603
	BMRU Co-I					14,079	4,745	18,824
	Enrichment Coordinator					25,966	8,751	34,717
	Enrichment Technician					20,243	6,822	27,065
TBN	TBN Enrich Tech	6.00				15,650	5,274	20,924
TBN	Student	6.00				5,050	202	5,252
TBN	Student	6.00				5,050	202	5,252
TBN	Student	6.00				5,050	202	5,252
TBN	Student	6.00				5,050	202	5,252
	SUBTOTALS →					149,693	44,448	194,141

CONSULTANT COSTS		0
EQUIPMENT *(Itemize)*		0
SUPPLIES *(Itemize by category)*		
Food for enrichment	78,854	
Enrichment devices	23,000	
		101,854
TRAVEL		0
INPATIENT CARE COSTS		0
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		0
OTHER EXPENSES *(Itemize by category)*		0
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		**$ 295,995**
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		**$ 295,995**

PHS 398 (Rev. 08/12 Approved Through 8/31/2015) OMB No. 0925-0001
Form Page 4

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
Colony Management

FROM 05/01/15 THROUGH 04/30/16

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	TOTAL
Excluded by Requester	Colony Manager	EFFORT			Institutional Base Salary	39,709	13,382	53,091
	Lab Tech Supp Supv					19,452	9,045	28,497
	Lab Tech Supp Supv					26,675	12,404	39,079
	Lab Tech Supp Supv					19,941	9,273	29,214
	Lab Tech Supp Supv					23,866	11,098	34,964
	Lab Tech Supp Supv					21,141	9,831	30,972
	ART Advanced					16,523	7,683	24,206
	ART Advanced					17,489	8,132	25,621
	ART Advanced					17,575	8,172	25,747
	ART Advanced					16,978	7,895	24,873
	ART Senior					16,026	7,452	23,478
	ART Senior					15,357	7,141	22,498
	ART Senior					16,816	7,819	24,635
	ART Senior					16,135	7,503	23,638
	ART Objective					14,031	6,524	20,555
	ART Objective					14,031	6,524	20,555
	ART Objective					14,031	6,524	20,555
	ART Objective					14,139	6,575	20,714
	ART Objective					14,031	6,524	20,555
	ART Objective					14,223	6,614	20,837
	ART Objective					14,139	6,575	20,714

Excluded by Requester	ART Objective	EFFORT			Institutional Base Salary	13,680	6,361	20,041
	ART Entry					12,647	5,881	18,528
	ART Entry					12,911	6,004	18,915
	ART Entry					12,647	5,881	18,528
	ART Entry					12,647	5,881	18,528
	ART Entry					12,647	5,881	18,528
	ART Entry					13,295	6,182	19,477
	ART Entry					12,647	5,881	18,528
	ART Entry					12,647	5,881	18,528
	ART Entry					12,647	5,881	18,528
	ART Entry					12,647	5,881	18,528
	ART Entry					12,647	5,881	18,528
	ART Entry					10,179	4,733	14,912
	ART Entry					12,647	5,881	18,528
	ART Entry					12,647	5,881	18,528
	ART Entry					12,647	5,881	18,528
	ART Entry					12,647	5,881	18,528
	ART Entry					12,647	5,881	18,528
	ART Entry					12,647	5,881	18,528
	ART Entry					12,647	5,881	18,528
	ART Entry					12,647	5,881	18,528
TBN	ART Student	9.00				7,047	282	7,329
TBN	ART Student	9.00				7,047	282	7,329

TBN	ART Student	9.00			Institutional Base Salary	7,047	282	7,329
TBN	ART Student	9.00				7,047	282	7,329
Excluded by Requester	Rhesus Breed Coord	EFFORT				22,365	10,400	32,765
	Marmoset Breed Coord					9,302	4,325	13,627
TBN (Colony Records)	Unv Ser Prog Assoc	6.00				16,407	7,629	24,036
Excluded by Requester	Unv Ser Prog Assoc	EFFORT				10,575	4,917	15,492
	Unv Ser Prog Assoc					16,595	7,717	24,312
TBN	Student Adm Col Rec	9.00				7,047	282	7,329
	SUBTOTALS →					770,498	338,226	1,108,724

CONSULTANT COSTS					
	0			0	0
EQUIPMENT *(Itemize)*					
	0			0	
	0			0	0
SUPPLIES *(Itemize by category)*					
Personal Protective Equipment	179,208		Cleaning Supplies	39,208	
Husbandry Supplies	9,208		Uniforms	33,209	
NHP Food	149,208			0	410,041
TRAVEL					
	0			0	0
INPATIENT CARE COSTS				0	0
OUTPATIENT CARE COSTS				0	0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*					
				0	0
OTHER EXPENSES *(Itemize by category)*					
	0			0	
	0			0	
	0			0	
	0			0	0
CONSORTIUM/CONTRACTUAL COSTS				DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*					**$ 1,518,765**
CONSORTIUM/CONTRACTUAL COSTS				FACILITIES AND ADMINISTRATIVE COSTS	
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD					**$ 1,518,765**

PHS 398 (Rev. 08/12 Approved Through 8/31/2015) OMB No. 0925-0001

Form Page 4

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
Compliance & Training

FROM 05/01/15 THROUGH 04/30/16

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	TOTAL
Excluded by Requester	Compliance Coordinator	EFFORT			Institutional Base Salary	40,591	13,679	54,270
	Asst Res Anim Vet					10,711	3,610	14,321
	Training Coordinator					28,350	9,554	37,904
	Occ Health & Safety Coordinator					24,000	8,088	32,088
	Asst Trainer					21,773	7,338	29,111
	SUBTOTALS →					125,425	42,269	167,694

CONSULTANT COSTS			0
EQUIPMENT *(Itemize)*			0
SUPPLIES *(Itemize by category)*			
e-learning software	3,791	0	
		0	
		0	3,791
TRAVEL			0
INPATIENT CARE COSTS			0
OUTPATIENT CARE COSTS			0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*			0
OTHER EXPENSES *(Itemize by category)*			
Keller Online Subscription	616		
Occupational health services	9,379		
			9,995
CONSORTIUM/CONTRACTUAL COSTS		DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*			**$ 181,480**
CONSORTIUM/CONTRACTUAL COSTS		FACILITIES AND ADMINISTRATIVE COSTS	
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD			**$ 181,480**

PHS 398 (Rev. 08/12 Approved Through 8/31/2015) OMB No. 0925-0001
Form Page 4

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
Pathology Services

FROM 05/01/15 THROUGH 04/30/16

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	TOTAL
Excluded by Requester	PD/PI	EFFORT			Institutional Base Salary	51,242	17,269	68,511
	Pathologist					76,167	25,668	101,835
	Co-Investigator					12,335	4,157	16,492
	Research Specialist					25,708	8,664	34,372
TBN	Assoc Research Spec	6.00				15,650	5,274	20,924
Excluded by Requester	Research Specialist	EFFORT				18,713	6,306	25,019
TBN	Student	6.00				5,050	202	5,252
TBN	Student	6.00				5,050	202	5,252
	SUBTOTALS →					209,915	67,742	277,657

CONSULTANT COSTS		0
EQUIPMENT *(Itemize)*		0
SUPPLIES *(Itemize by category)*		
Pathology and Clinical Pathology Supplies	4,667	4,667
TRAVEL		0
INPATIENT CARE COSTS		0
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		0
OTHER EXPENSES *(Itemize by category)*		
Histology Services (SVM RARC)	14,280	14,280
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		**$ 296,604**
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		**$ 296,604**

PHS 398 (Rev. 08/12 Approved Through 8/31/2015) OMB No. 0925-0001
Form Page 4

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
Scientific Protocol Implementation Unit

FROM 05/01/15 THROUGH 04/30/16

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	TOTAL
Excluded by Requester	PD/PI	EFFORT			Institutional Base Salary	42,444	14,304	56,748
	Co-PI					23,107	7,787	30,894
	Co-Investigator					18,330	6,177	24,507
	Sr. Research Specialist					795	268	1,063
	Sr. Research Specialist					15,723	5,299	21,022
	Sr. Research Specialist					16,945	5,710	22,655
	Sr. Research Specialist					13,575	4,575	18,150
	Research Specialist					15,322	5,164	20,486
	Research Specialist					15,882	5,352	21,234
	Research Specialist					15,121	5,096	20,217
	Assoc Res Specialist					11,312	3,812	15,124
	Assoc Res Specialist					11,025	3,715	14,740
TBN	Student	10.00				8,417	337	8,754
TBN	Student	10.00				8,417	337	8,754
TBN	Student	10.00				8,417	337	8,754
TBN	Student	10.00				8,417	337	8,754
	SUBTOTALS →					233,249	68,607	301,856

CONSULTANT COSTS — 0

EQUIPMENT *(Itemize)* — 0

SUPPLIES *(Itemize by category)*

Misc. lab supplies	4,837	Office Supplies	2,500
Stockroom supplies	4,095		
Modify test apparatus supplies	1,748		

13,180

TRAVEL		0
INPATIENT CARE COSTS		0
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		0
OTHER EXPENSES *(Itemize by category)*		
Professional development	9,537	9,537
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		**$ 324,573**
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		**$ 324,573**

PHS 398 (Rev. 08/12 Approved Through 8/31/2015) OMB No. 0925-0001

Form Page 4

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
Veterinary Services

FROM 05/01/15 THROUGH 04/30/16

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	TOTAL
Excluded by Requester	Attending Vet	EFFORT			Institutional Base Salary	123,234	41,530	164,764
	Res Anim Vet					38,512	12,979	51,491
	Asst Res Anim Vet					35,704	12,032	47,736
	Interim Clinical Vet					31,667	10,672	42,339
	Assoc Res Anim Vet					36,900	12,435	49,335
	Asst Res Anim Vet					38,915	13,114	52,029
	Vet Tech 3					14,004	6,512	20,516
	Vet Tech 3					13,116	6,099	19,215
	Vet Tech 3					11,253	5,233	16,486
	Vet Tech 3					4,501	2,093	6,594
	Vet Tech 3					11,916	5,541	17,457
	Vet Tech 2					7,194	3,345	10,539
	Vet Tech 2					10,702	4,976	15,678
	Vet Tech 2					10,702	4,976	15,678
	Vet Tech 1					9,610	4,469	14,079
	Anim Service Program Asst					33,375	15,519	48,894
TBN	Vet Stud Hourly	4.00			10,100	3,367	135	3,502
TBN	Vet Stud Hourly	4.00			10,100	3,367	135	3,502
	SUBTOTALS →					438,039	161,795	599,834

CONSULTANT COSTS		0
EQUIPMENT *(Itemize)*		0
SUPPLIES *(Itemize by category)*		
Medical, Surgical, Dental Supplies 22,241		22,241
TRAVEL		0
INPATIENT CARE COSTS		0
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		0
OTHER EXPENSES *(Itemize by category)*		0
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		**$ 622,075**
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		**$ 622,075**

PHS 398 (Rev. 08/12 Approved Through 8/31/2015) OMB No. 0925-0001

Form Page 4

A. COMPONENT COVER PAGE

Project Title: Research Services Division

Component Project Lead Information:

Excluded by Requester

B. COMPONENT ACCOMPLISHMENTS

B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

Research Services Overview
Division Head: Excluded by Requester

The Research Services Division is comprised of four Units: Assay Services, Genetics Services, Immunology Services, and Virology Services. Each of these Units has two distinct roles. First, they perform resource-related research. This research is narrowly focused on the development of new and improved tools supporting laboratory studies of nonhuman primates. These tools are disseminated to the scientific community through publications and presentations at scientific meetings. Additionally, each Unit offers these services on a fee-for-service basis to investigators working with NHP. Research Service Units focus on those assays that:

1)Capitalize on unique strengths of research programs at the WNPRC not available elsewhere and;
2)Are of broad interest to NIH-funded nonhuman primate investigators throughout the country

As a consequence, Research Services is a national resource. A comparatively small amount of Research Services effort supports WNPRC core and affiliate investigators. The following narratives illustrate how each Research Services Unit attracted broad interest from outside investigators and advanced nonhuman primate research during the reporting period of January 1, 2014 to December 31, 2014.

Please see attached detailed progress reports from each unit (Section B.2), which includes specific aims, accomplishments and goals.

B.1.a Have the major goals changed since the initial competing award or previous report?

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: Research Services Yr 53 Progress Report_final2-24-15_opt.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

Not Applicable

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

NOTHING TO REPORT

B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?

NOTHING TO REPORT

B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

Please see attached detailed progress reports from each unit (Section B.2), which includes future goals for the next reporting period.

RESEARCH SERVICES DIVISION

UNIT REPORTS

ASSAY SERVICES

Unit Head: Excluded by Requester PhD
Core PI: Excluded by Requester PhD

SUMMARY

Assay Services supports more than 100 investigators and has developed many widely used hormone and biomarker assays.

GOALS AND ACCOMPLISHMENTS

Specific Aim 1 – Maintain an up-to-date, efficient, cost-effective Assay Service to provide hormonal and biomarker analysis for NIH-funded investigators affiliated with Primate Centers, CTSAs and other NIH supported research on primates.

Assay Services has continued to increase our services to NIH funded investigators. Between January 1, 2014 to December 31, 2014, we have analyzed nearly 65,000 samples for over 100 investigators. Many investigators have used our services over multiple months in the same year. Major users of Assay Services have been equally from the WNPRC, ICTR and other universities throughout the United States and Canada with less use from the other NPRCs and the CTSAs. The income generated has allowed us to cost – recover over 50% of our expenses and salaries.

Specific Aim 2 – Develop new assays for hormones, biomarkers, and other substances as requested by investigators after approval by Assay Services. Requests from WNPRC investigators, affiliates, and the NIH primate community are prioritized and developed as needed.

Between January 1, 2014 to December 31, 2014, Assay Services has developed many new hormonal, biomarker and other substances for investigators requesting development of new assay. We have created a multisteroid analyses method for the LC/MS/MS that allows for very sensitive measurements. This has allowed us to monitor low-level steroids in cell culture media, excretions from cancer cells, sensitive levels of estrogens in ovarectomized monkeys. We have developed methods for 25 hydroxyvitamin $D_{2\&3}$, 1,25 hdrozyvitamin $D_{2\&3}$, serum insulin, adiponectin, leptin, ghrelin and urinary glucocorticoids in marmosets. We have developed multisteroid analyses methods for hair in humans and macaque monkeys. Further developments have been salivary cortisol measurement for marmosets, urinary cortisol and estradiol marmoset assay, reproductive steroid measurement for baboons, BDNF in humans, salivary alpha amylase for humans, striatal biogenic amines, BSAP for human serum, levonorgestrel and ethinylestradiol for macaques, IL-beta for human serum, methdroxyprogesterone acetate for macaques and other methods.

Specific Aim 3 – Develop highly specific methods for the measurement of vitamin D metabolites $25(OH)D_{2\&3}$, $1,25(OH)_2D_{2\&3}$ in both human and non-human primates using our newly acquired QTRAP 5500 LC/MS/MS (AB Sciex).

Assay Services had adapted a method for 25(OH) $D_{2\&3}$ for the use of human serum. The method requires only 50 µl of serum for humans and macaques and less than 10 µl for marmoset monkeys. This has become a routine method and is currently in use by an ICTR investigator from the UW-medical school.

We have developed the state of the art method for measuring 1,25$(OH)_2D_{2\&3}$ working in conjunction the AB Sciex company who made the most sensitive derivitizer for ionizing 1,25$(OH)_2D_{2\&3}$ in serum of humans and monkeys. The following publications have resulted from this new development:

Excluded by Requester (2014). Development of a sensitive LC/MS/MS method for vitamin D metabolite, 1,25 dihydroxyvitamin D273 measurement using a novel derivatization agent. *Journal of Chromatography B*, 953-954:62-67.

In Press

Specific Aim 4 – Develop specific methods to support studies using lipidomics as the identification and quantification of lipids and factors that interact with lipids.

No work has been performed for this goal.

Specific Aim 5 – Develop separation methods that allow measurement of multiple biomarkers and hormones in a small blood volume.

We have developed assays for serum insulin, adiponectin, leptin, ghrelin and urinary glucocorticoids in marmosets. These methods have been validated and published in the following:

Excluded by Requester (2013). Development of metabolic function biomarkers in the common marmoset, *Callithrix jacchus*. *American Journal of Primatology* May;75(5):500-8. doi: 10.1002/ajp.22126, PMID:23447060

Additionally, we have tested these methods out in examining a high fat diet in the common marmoset and have the following publication:

Excluded by Requester (2013). Using snacks high in fat and protein to improve glucoregulatory function in adolescent male marmosets (*Callithrix jacchus*). *Journal of American Association of Laboratory Animal Science* 52:1-7.

FUTURE GOALS

We will continue to accomplish Specific Aims 1&2 as these are our daily activities. We have several long-term studies that we will be working on. We receive a yearly contract from the CDC and measure reproductive steroids for their studies in macaques as well as developing analyses for synthetic reproductive steroids for their projects. We receive thousands of samples from the MIDUS NIH Program grant at the Institute of Aging UW-Madison. We continue to measure salivary cortisol, urinary catecholamines, urinary cortisol/cortisone and salivary alpha amylase for this project.

We plan to begin a development project of examining vitamin D levels in hair. This project will utilize hair samples from several primate centers and also an NIH facility.

We are currently working on a multi vitamin D metabolite method development. This method will be unique in offering the most complete pathways of vitamin D metabolism with clinical applications for physicians determining the amount of vitamin D that a subject consumes versus how much the subject actually absorbs and utilizes. Additionally we are working on a free 25 hydroxyvitamin D method. We

are planning an analysis of feral baboon samples currently here at the WNPRC to compare with captive baboon samples in our new vitamin D methodology.

We will be continuing our studies on steroids in hair. We will be performing a radiolabelled study on rhesus macaques to determine the metabolites found in hair for cortisol, estradiol, testosterone and progesterone. There has never been a study in a nonhuman primate to determine the appropriate steroid metabolite to measure in hair. This will be funded by a WNPRC Pilot Grant.

As suggested by the review of Assay Services for the base grant application and by our external advisory board, we are not pursuing Specific Aim 4 to develop methods for lipidomics at this time. As this requires extensive expertise, we will delay this aim until there is more demand for the development and consultants can be found.

GENETIC SERVICES

Unit Head: Excluded by Requester PhD

SUMMARY

Genetics Services is the leading provider of MHC genotyping and virus sequencing for the NHP research community. We also lead and coordinate the genomic analyses of WNPRC animals, a component of our activities that we expect to grow in the coming years.

GOALS AND ACCOMPLISHMENTS

Specific Aim 1 – We will provide fee-for-service Genetics Services for the NHP community. We will perform major histocompatibility complex (MHC) class I genotyping of 425 animals per year. We will also perform fee-for-service sequencing of 10 SIV genomes per year.

Over the past year we have continued to improve the efficiency of our fee-for-service methods in order to keep up with the demand we have experienced for both our MHC typing and SIV genome sequencing services. At the time the genetic services renewal was written, MHC class I genotyping was performed using Roche/454 pyrosequencing of a 568bp diagnostic cDNA amplicon. To aid in cost reduction and expand MHC genotyping, we have transitioned all of our assays to the Illumina MiSeq platform. The MiSeq produces 12-15 million 300bp paired end reads per run, thereby increasing the multiplexing capabilities of the assay to >192 samples/run. The increased sequence read numbers also allowed extension of our basic genotyping assay to include MHC class II DRB exon 2 typing. In addition, to increase efficiency and flexibility of our typing service, we have transitioned from using cDNA to genomic DNA as the starting material for these combined MHC class I/class II DRB assay. We have also implemented automated nucleic-acid extractions with ProMega Maxwell instruments to improve consistency and DNA yields. The Illumina MiSeq assay combining MHC class I and class II DRB has a reduced cost of $146/animal (from $200) when starting with fresh blood or cryopreserved cells, and $88/animal when starting with user-provided purified genomic DNA samples for Tier 1 clients. This assay is currently available for Indian and Chinese rhesus macaques as well as non-Mauritian cynomolgus and pig-tailed macaques. Less-defined cynomolgus and pig-tailed macaque populations may still benefit from deep sequencing of cDNA templates in order to differentiate expressed transcripts from pseudogenes. Mauritian cynomologus macaques are routinely put through our new pipeline as outlined under Aim 2. The development of this genotyping assay has allowed us to triple the number of animals we typed for fee-for-service clients since our renewal from our original goal of 425 animals per year to 1343 animals in 2014. In 2014 we provided service for 26 different clients. These clients benefitted from new reports that were redesigned in consultation with clients (who were polled in a survey during early 2014).

To reduce cost and increase throughput of SIV genome sequencing, this assay was also moved to the Illumina MiSeq platform as the major development in 2013. This allows 25 genomes to be simultaneously sequenced rather than 5 genomes with a minimal 5000x coverage at each nucleotide position. This has significantly reduced the costs from $1500 per genome to $363 from plasma, $328 from vRNA and $213 from DNA amplicons. We have surpassed our goal of 10 SIV genomes per year and have sequenced 125 SIV genomes in 2014. Overall, we have met and exceeded the goals set under Specific Aim 1 and have in place methodology that allows us to continue our service at its current capacity or greater while reducing costs.

Specific Aim 2 – We will create a multiplexed assay to simultaneously genotype 12 immune and host restriction loci including MHC class I, MHC class II, killer immunoglobulin receptors, and TRIM5a by Roche/454 pyrosequencing.

In 2013, an assay using the Fluidigm Access Array was developed to simultaneously amplify the MHC class I A and B loci and MHC class II DRB, DQA/QB, and DPA/PB from 48 samples. The amplicons produced through the Fluidigm system are sequenced using the Illumina MiSeq. This assay has been fully validated for Mauritian cynomolgus macaque samples and has completely replaced our traditional microsatellite assay in our fee-for-service pipeline. The cost of this assay is $98 for client-provided whole blood and $80 for client-provided gDNA/cDNA for Tier 1 clients, representing our lowest rates yet for sequence-based MHC genotyping. In 2014 we genotyped 1062 Mauritian cynomolgus macaque samples with this multiplex assay. We have also extended this assay to 417 Indian rhesus samples in pilot studies for clients with special interests in class II genotypes (tuberculosis immune responses, transplantation, etc).

We envision the current Fluidigm assay remaining relevant for approximately two years before being displaced by low-cost exome sequencing combined with target-specific resequencing (see Aim 4), which has the advantage of interrogating all coding variants in the genome with specific, high-resoution genotyping of the MHC. We will focus our multiplex assay development on this new platform while using the existing Fluidigm assays for Mauritian macaque genotyping.

Specific Aim 3 – We will sequence 15 SIV, influenza and dengue virus genomes per year.

One of the major goals of this aim was to test new sequencing technologies for viral genome sequencing, which was performed using Roche/454 pyrosequencing at the time of our renewal. We have now converted to using exclusively Illumina MiSeq sequencing technology coupled with Nextera. This new platform reduces cost, reduces error associated with the sequencing process, and increases multiplexing. A second goal of this aim was to develop primers to sequence two widely-used SHIV challenge strains SHIV89.6P and SHIVsf162P3. We have sequenced several viruses towards this aim including SHIVsf162, SHIV-1157, SHIVnef , SIVmac239, SIVsmE660 (NIH stock), SIVmac239Δnef, SIVdeltaB670, SIV17E, and SIVsmE041. The success of this approach is evidenced by the 125 SIV genomes sequenced in the past year.

In 2014, we also introduced highly multiplexed “TruSeq” sequencing for simultaneously sequencing large numbers of subgenomic SIV regions, such as the regions of the viral envelope important for SIV-specific antibody recognition. This new technology is already available to fee-for-service clients.

Lastly, another goal of this aim was to expand our capabilities to sequence other RNA viruses. The new Nextera/MiSeq platform allows us to sequence any virus provided to us as amplicons or as part of plasmids. Additionally, we have moved away from using sequence-specific primers to amplify viral RNA and now use an unbiased PCR approach to sequence SIV and SHIV virus stocks.

Finally, we have added a new component to this Aim that will likely become a new Aim in the next base grant. The unbiased sequencing described above is also useful for diagnosing unknown viral infections in nonhuman primates. We are establishing a sequencing-based diagnostic service that can be used to rapidly identify the source of disease outbreaks that threaten primate colonies and animal caretakers.

Specific Aim 4 – We will collect exome sequences from 4 macaques and genome sequences from 4 macaques.

Genetics Services is now fully conversant with whole genome and whole exome sequencing. The [redacted] lab published an analysis of 6 SIV controllers and 6 SIV progressors who were all whole genome sequenced. This expertise is being transitioned into Genetics Services and we expect to make

whole exome sequencing (performed in collaboration with WNPRC affiliate Excluded by Requester at the Baylor Human Genome Sequencing Center) available to interested clients in the next two years.

Additionally, we are working with Excluded by Requester to develop a new platform for macaque genotyping. Recognizing that MHC genotyping is the most commonly requested genetic test in macaques, we developed a customized target-capture array that specifically enriches sequence coverage of the MHC class I and class II genes, allowing for extremely high resolution genotyping of these loci. This array can be combined in a single assay with a standard exome sequencing array, allowing for simultaneous interrogation of coding variants throughout the entire genome. A pilot experiment suggests that this combined MHC/exome genotyping can be performed economically. We expect this will be a popular service, though one that is more expensive (currently) than MHC-only genotyping. We intend to deploy this genotyping over the next 2 years, working with early-access clients in 2015 to optimize the assay.

FUTURE GOALS

Specific Aim 1 – We will provide fee-for-service Genetics Services for the NHP community. We will perform major histocompatibility complex (MHC) class I genotyping of 425 animals per year. We will also perform fee-for-service sequencing of 10 SIV genomes per year.

In the next year we anticipate exceeding our goals of MHC class I genotyping 425 animals and 10 SIV genomes for fee-for-service. We will continue to assess new sequencing technologies or techniques that will improve efficiency of our assays and pursue interesting prospects.

Specific Aim 2 – We will create a multiplexed assay to simultaneously genotype 12 immune and host restriction loci including MHC class I, MHC class II, killer immunoglobulin receptors, and TRIM5a by Roche/454 pyrosequencing.

In the next year we anticipate continuing to utilize Fluidigm PCR for Mauritian cynomolgus macaque MHC genotyping and expanding this assay to Indian rhesus on a fee-for-service basis. We will concentrate our efforts on multiplexed assays on the combined MHC/exome sequencing described in Aim 4.

Specific Aim 3 – We will sequence 15 SIV, influenza and dengue virus genomes per year.

Due to the problems linking mutations identified at long genetic distances apart on a viral genome using short 250bp Illumina sequences, we will continue to try new sequencing platforms and chemistries for viral genome sequencing in the next year. We anticipate that the combination of Pacific Biosciences full-length genome sequencing with error correction from Illumina MiSeq sequencing of the same sample, is the next technology we will test for this aim. This approach would allow us to link any mutation to another mutation on the same genome across the sequence of the pathogen. We also anticipate expanding our repertoire of viruses beyond SIV and SHIV as needs arise from our clients. We will also initiate unbiased viral diagnostics for monitoring disease outbreaks in primate colonies as described above.

Specific Aim 4 – We will collect exome sequences from 4 macaques and genome sequences from 4 macaques.

We have met our goal to obtain whole genome sequences from at least 4 macaques. Indeed, we have already generated whole genome sequences from 41 cynomolgus and rhesus macaques and exome sequenced 8 additional Mauritian animals. Currently we are obtaining MHC plus expanded exome data from 12 prolific Indian rhesus sires in the WNPRC breeding colony. We will learn optimal ways to analyze these large sets of data and report this data to end users. Our experiences with whole genome

or exome sequencing will position us to provide this service for WNPRC and other Primate Centers in the future.

IMMUNOLOGY SERVICES

Unit Head: Excluded by Requester PhD
Core PI: Excluded by Requester PhD

SUMMARY

Immunology Services performs fee-for-service immunology assays, develops new flow cytometric staining panels for single-cell immunologic analyses and performs vaccination experiments using nonhuman primates. In 2014 Immunology Services supported 27 investigators in 41 projects funded primarily by NIH. The income generated via the Primate Center's chargeback and subcontract mechanisms recovered more than 60% of our expenses and salaries.

Two recent accomplishments of Immunology Services are the introduction of live-cell flow cytometry sorting in a BSL-3 laboratory and the introduction of antibody-dependent cell cytotoxicity (ADCC) assay as a fee-for service activity in collaboration with Excluded by Requester

GOALS AND ACCOMPLISHMENTS

Specific Aim 1 – Maintain up-to-date, efficient flow cytometric assays in our FACS facility as a fee-for-service activity.

We expanded our flow cytometry services by introducing BL-3 level cell-sorting. Furthermore we upgraded our BD-LSR II flowcytometer by installing three additional fluorescence detectors. This upgrade enabled us to collect data on 16 parameters simultaneously.

We performed more than 1,000 FACS assays in 2014, including various T cell subset phenotypings, functional analysis, NK cell phenotyping, stem cell quantification, and monocyte phenotyping. This number represents approximately 20% increase compared to the previous year.

We continue training new users and encourage professional development of existing users of our facility on the area of flow cytometry.

Specific Aim 2 – Maintain cost-effective antigen-specific elispot assays as a fee-for-service activity.

The volume of this activity decreased substantially in 2014. Since the focus of our users shifted from T cell epitope mapping to measuring multifunctional phenotypes this is an anticipated development.

Specific Aim 3 – Produce fluorochrome-conjugated antibodies and develop new multicolor FACS staining designs to analyze cell populations of interest as requested by principal investigators.

We have developed eight multicolor staining panels for different investigators in 2014. Among them we have established a 10-color flow cytometric assay to characterize SIVmac239 antigen-specific T cells, and a 14-color panel to phenotype activated NK cells in SIVmac239-infected Rhesus macaques. We also developed a novel staining panel to quantify and sort transiently emerging plasmablast cells from Rhesus macaques vaccinated against Dengue serotype 2 or SIVmac239.

We sent out more than 3,000 test-worth fluorochrome conjugated SIVmac239 gag-specific antibody to three different laboratories.

Specific Aim 4 – Support vaccination and pathogenesis studies using various NHP *in vivo* model systems.

The number of vaccination projects supported by our laboratory further increased this year. We supported one to three vaccination projects/year before 2013, eight in 2013 and 12 in 2014. Among the twelve, we tested candidate vaccines against HIV/SIV for Excluded by Requester Private Source in four studies, for Excluded by Requester Private Source in three studies, for Excluded by Requester Private Source in one study and for Excluded by Requester Private Source in one study.

While most of our clients focus on infectious diseases, we are collaborating with several investigators from non-infectious disease research areas as well. We are performing extensive sample staining, flow data acquisition and analysis for a kidney transplantation project for Excluded by Requester of the University of Wisconsin. In a new and very exciting project with Excluded by Requester (University of Wisconsin) we test if anxiety influences the steroid sensitivity of T cell functions. We continue to train investigators from the area of stem cell research, surgery and regenerative medicine to use our flow cytometry facility.

VIROLOGY SERVICES

Unit Head: Excluded by Requester PhD

SUMMARY

The major goal of Virology Services is to provide expert support for virological research conducted at, or in collaboration with, the WNPRC. This has two primary components: (1) fee-for-service viral diagnostics and virus stock production and (2) development of new viral diagnostics and reagents for NHP virus studies.

GOALS AND ACCOMPLISHMENTS

Virology Services has continued to be productive over the past year. Fee-for-service revenue was generated by 17 different funded projects led by 10 different investigators, both within and outside of the University of Wisconsin-Madison. As anticipated in the last P51 base grant submission, fee-for-service activities have been concentrated on SIV. Virology Services performed about 1,000 SIV viral load determinations in 2014, while also producing a new large-scale SIVmac239 stock for use in vaccine challenge studies. Moreover, both core and affiliate investigators continue to use virus stocks produced by Virology Services in their experiments. In addition, Virology Services has begun offering a new service that includes consultation on assay design and instruction on use of the LC480 instrument so that users can perform their unique diagnostic assays.

In the next year, Virology Services plans to continue providing highly sensitive, validated molecular diagnostics, including new assays to detect the SIV latent reservoir. Demand for Virology Services may increase due to demand from investigators formerly working at the New England Primate Research Center. There has also been much interest in Virology Services from extramural investigators submitting new grants. Additionally, Virology Services will continue to collaborate with Genetics Services to develop rapid, economical molecular diagnostics for viruses identified by unbiased deep sequencing.

In the current budget period, we have set the following specific aims to accomplish this goal:

Specific Aim 1 – Provide validated molecular diagnostic assays for viruses as a fee-for-service.

Our main focus continues to be providing sensitive assays for quantifying simian immunodeficiency virus (SIV) RNA and DNA, however we are continuing to expand the "menu" of available services to provide assays specific for other viruses, such as influenza, dengue and simian hemorrhagic fever viruses.

Virology Services performed around 1,000 molecular diagnostic assays in 2014. This represents a decrease in overall demand from the past year. Feedback from clients suggests that loss of funding and natural turnover of projects are the main causes for the decrease. Excluded by Requester and his team anticipate an increase in demand for 2015, as new projects begin and existing ones move into a new viral challenge phase. We have provided budgets for new grants for multiple investigators, both WNPRC core and affiliates, interested in our services. There has been renewed interest in our standard molecular diagnostic assay as well as in newly developed assays to measure cell-associated viral RNA and DNA. There has also been interest in the quantitative-outgrowth reservoir assay that we plan to offer early in 2015, described in more detail below.

The HIV and SIV fields have seen an increased interest in detecting and quantifying the latent viral reservoir. There is a growing need for reliable assays to measure this difficult-to-detect source of virus, especially as the field shifts towards cure research. In order to meet this demand we have begun a new collaboration with Excluded by R equester at Private Source to adapt the quantitative HIV viral outgrowth assay they pioneered for use in detecting latent, replication-competent SIV. We plan to deploy this assay as fee-for-service early in 2015. Multiple investigators have already inquired about this assay, indicating that it will likely be a popular service. In addition, we continue to develop other novel reservoir assays to meet the anticipated need for robust measurements of the latent reservoir in SIV-infected monkeys.

SIV-specific assays accounted for about 99% of the total number performed in 2014. Assays to detect SIV therefore remained by far the major focus of activities by investigators supported by Virology Services, but the team anticipates that interest from clients in other viruses will continue to increase (see below).

Virology Services continued its regular sample exchange with Excluded by R equester and Excluded by R equester at NCI/NIH; results showed 95% or greater concordance across the dynamic range of the assay (more than 7 orders of magnitude), indicating that our methods are highly accurate. Personal Info Personal Info earlier this year, we are working to establish a new sample exchange with other NPRC core laboratories so that we may continue the important quality assurance and external validation of our assay results without placing additional strain on Excluded by Requester core.

Specific Aim 2 – Provide characterized SIV virus stocks as a fee-for-service.

In-vivo pathogenicity and vaccine challenge experiments in nonhuman primates depend on a consistent source of high-quality extensively characterized virus stocks. Another main focus of this Unit is therefore to produce and characterize high-titer large-scale virus stocks suitable for *in-vivo* experiments.

During the 2014 project period Virology Services produced one new large-scale SIVmac239 stock for use in challenge experiments. This stock was produced under contract with the NIH/Quality Biologicals Inc. This virus stock has been extensively characterized and is currently being titered in vivo for use in future challenge experiments. In addition we produced one small-scale stock of SIVmac239 harboring specific mutations for Excluded by R equester lab. The specific nature of the virus means it will have limited use for other studies, thus it was produced on a lesser scale.

Specific Aim 3 – Develop new culture methods and new molecular diagnostics to facilitate virological research in nonhuman primates, to be deployed as future services.

The scope of infectious disease research conducted at WNPRC has been expanding beyond HIV/AIDS to other pathogens that threaten global health, including influenza, dengue and other emerging or re-emerging viruses. To support these activities effectively, Virology Services will leverage our "AIDS-centric" experience to broaden our service portfolio in concert with this widening scope of virological research.

In recognition of the diversification of virological research conducted by WNPRC core and affiliate investigators, Virology Services set a new goal of developing two molecular diagnostic assays for new viral targets per year. We are currently working to develop a novel diagnostic assay to measure SHFV-LVR, the prototype simian arterivirus, for an affiliate investigator, Excluded by R equester has an ongoing study of SHFV-LVR and related viruses in infected rhesus macaques. This novel assay will be used to measure virus from these animals over the course of their infection. In addition we are working with Dr. Excluded by Requester to sequence virus in samples taken from both the LVR and SHFV infected monkeys.

In 2014, the team began offering as a new service, consultation on assay design and development for QPCR and QRT-PCR assays, and instruction on use of the LightCycler instruments. Members of the Excluded by Requester labs have used this service to develop assays for multiple strains of newly discovered human and simian pegiviruses (SPgV). These assays have been successfully used to measure virus from both human and simian samples. These viruses are members of the Flavivirus family and are related to the human pegivirus (HPgV, also known as GB virus C). SPgVs were found to infect wild red colobus, red-tailed guenons and baboons in East Africa at high prevalence. We anticipate interest in these viruses from AIDS investigators: coinfection with HPgV is known to slow progression to AIDS in HIV-positive individuals, but the mechanism is not understood. Discovery of SPgVs may make animal models of this interaction possible. We are therefore working with WNPRC investigators to isolate SPgVs.

Specific Aim 4 – Produce, characterize and titrate *in vivo* a large-scale influenza virus stock suitable for NHP challenge studies.

The past two years have seen the emergence of multiple novel avian influenza viruses in the human population. At the same time, there have been several new and promising developments toward a "universal" influenza vaccine that could protect against such emerging and potentially pandemic pathogens. As these vaccines develop past the initial evaluation stage, interest in NHP models of influenza for translational pathogenesis research and preclinical vaccine evaluation has increased. Yet there has been little progress in development of NHP influenza models in the past 10 years. University of Wisconsin–Madison and WNPRC are uniquely suited to produce an improved NHP model for influenza. As part of this effort, Virology Services will produce a large-scale stock of macaque-adapted, *in-vivo* titered influenza virus suitable for use in future challenge studies using biologically relevant routes of challenge.

This project is planned for the final fiscal year of the current award.

FUTURE GOALS

Specific Aim 1 – Provide validated molecular diagnostic assays for viruses as a fee-for-service.

We will continue to provide highly sensitive, validated molecular diagnostics. We anticipate that AIDS research will continue to account for the majority of our service in the coming reporting period. Existing clients Excluded by Requester all plan challenge experiments during this period, which will require SIV, SHIV, or influenza viral load monitoring in infected monkeys. We similarly anticipate projects from new clients, as investigators formerly working at the New England PRC perform studies at WNPRC and as new grants are funded.

We will begin offering our new SIV reservoir assay early in 2015. There has already been interest in this service and we anticipate demand for this service will increase over the coming year.

Specific Aim 2 – Provide characterized SIV virus stocks as a fee-for-service.

We will continue to provide SIV and SHIV stocks for investigators as a fee-for-service. Viruses for use in challenge experiments in the coming year will either come from our existing stocks or be produced under new service agreements. The P51 award will support the production of an additional SIV stock during the current funding cycle; we currently anticipate that this stock will not be needed in FY2015.

Specific Aim 3 – Develop new culture methods and new molecular diagnostics to facilitate virological research in nonhuman primates, to be deployed as future services.

With WNPRC's increasing focus on global health and emerging viruses, we anticipate increased interest from investigators in developing novel virus detection and isolation methods in the coming year. Currently we aim to isolate SHFVs, including krc2 and krtg, for a multicentric collaboration involving Drs. Excluded by Requester and investigators at NIH. We will continue supporting efforts to isolate and characterize simian pegiviruses. Moreover, we anticipate expanding interest in this service, as emerging data suggest that captive NHP populations may be subject to previously unappreciated chronic viral infections with unknown impact on colony health. We are therefore working with WNPRC Genetics Services to develop and deploy integrated approaches to detect and characterize novel viral pathogens infecting captive NHP.

Specific Aim 4 – Produce, characterize and titrate *in vivo* a large-scale influenza virus stock suitable for NHP challenge studies.

This project is planned for the final fiscal year of the current award.

RESEARCH COMPUTING

Unit Head: Excluded by Requester PhD (pending)

SUMMARY

Research Computing is a new Research Service Unit effective January 1, 2015. This Unit will be responsible for ongoing development of the WNPRC Electronic Health Records (EHR) system and integrating clinical EHR data with research datasets.

FUTURE GOALS

The 2015 goals for Research Computing include staffing the Unit, continuing to maintain and improve the EHR system. Research Computing will also work closely with WNPRC PIs and Service Units to incorporate additional datasets in the EHR. By the end of 2015, we expect that at least a subset of the data collected by each of the Research Services Units will be integrated into the EHR system.

These activities in 2015 are a prelude to the inclusion of Research Computing as a Unit in the 2016 WNPRC P51 renewal.

C. COMPONENT PRODUCTS

C.1 PUBLICATIONS

Not Applicable

C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

Not Applicable

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Not Applicable

C.5 OTHER PRODUCTS AND RESOURCE SHARING

C.5.a Other products

NOTHING TO REPORT

C.5.b Resource sharing

NOTHING TO REPORT

D. COMPONENT PARTICIPANTS

Not Applicable

E. COMPONENT IMPACT

E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES?

Not Applicable

E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE?

Not Applicable

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

NOTHING TO REPORT

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?

Not Applicable

F. COMPONENT CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

F.2 ACTUAL OR ANTICIPATED CHALLENGES OR DELAYS AND ACTIONS OR PLANS TO RESOLVE THEM

NOTHING TO REPORT

F.3 SIGNIFICANT CHANGES TO HUMAN SUBJECTS, VERTEBRATE ANIMALS, BIOHAZARDS, AND/OR SELECT AGENTS

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. COMPONENT SPECIAL REPORTING REQUIREMENTS

G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT REPORTING REQUIREMENTS

Not Applicable

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

G.4.a Does the project involve human subjects?

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Not Applicable

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

RESEARCH & RELATED BUDGET - SECTION A & B FINAL

ORGANIZATIONAL DUNS*: 161202122

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: UNIVERSITY OF WISCONSIN-MADISON

Start Date*: 05-01-2015 **End Date*:** 04-30-2016

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1.		Excluded by Requester			PhD	Unit Head, Assay Services	Institutional Base Salary	EFFORT			49,114.00	16,551.00	65,665.00
2.					PhD	Core PI, Assay Services					14,686.00	4,949.00	19,635.00
3.					PhD	Division Head, Research Services; Unit Head, Genetics Services					20,469.00	6,898.00	27,367.00
4.					PhD	Unit Head, Immunology Services					44,332.00	14,940.00	59,272.00
5.					PhD	Core PI, Immunology Services					14,544.00	4,901.00	19,445.00
6.						Unit Head, Research Computing					59,506.00	20,054.00	79,560.00
7.					PhD	Unit Head, Virology Services					10,820.00	3,646.00	14,466.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **285,410.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
17	Division Staff	12.0			423,630.00	140,513.00	564,143.00
17	**Total Number Other Personnel**					**Total Other Personnel**	**564,143.00**

RPPR - Other-7374	Total Salary, Wages and Fringe Benefits (A+B)	FUNDS 849,553.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E

ORGANIZATIONAL DUNS*: 161202122

Budget Type*: ● Project ● Subaward/Consortium

Enter name of Organization: UNIVERSITY OF WISCONSIN-MADISON

Start Date*: 05-01-2015 **End Date*:** 04-30-2016

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	Funds Requested ($)*
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	Funds Requested ($)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	0.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**0.00**

E. Participant/Trainee Support Costs		Funds Requested ($)*
1. Tuition/Fees/Health Insurance		0.00
2. Stipends		0.00
3. Travel		0.00
4. Subsistence		0.00
5. Other:		
0 Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 161202122

Budget Type*: ● Project ● Subaward/Consortium

Enter name of Organization: UNIVERSITY OF WISCONSIN-MADISON

Start Date*: 05-01-2015 **End Date*:** 04-30-2016

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	220,711.00
2. Publication Costs	0.00
3. Consultant Services	24,000.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	51,050.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Other	131,438.00
Total Other Direct Costs	**427,199.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**1,276,752.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. Modified Total Direct Cost Base	34.5	1,225,702.00	422,867.00
		Total Indirect Costs	**422,867.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): Department of Health & Human Services Contact: Arif Karim 214-767-3261

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**1,699,619.00**

J. Fee	Funds Requested ($)*
	0.00

K. Budget Justification* File Name: Yr 54_WNPRC_Research Srvcs_Budget Just_opt.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
Assay Services

FROM 05/01/15 THROUGH 04/30/16

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	TOTAL
Excluded by Requester	PD/PI	EFFORT			Institutional Base Salary	49,114	16,551	65,665
	Co-PI					14,686	4,949	19,635
	Asst Researcher					26,778	9,024	35,802
	Assoc Research Sped					7,750	2,612	10,362
	Lab Manager					34,675	11,685	46,360
	Research Specialist					23,462	7,907	31,369
TBN	Student	9.00				7,575	303	7,878
	SUBTOTALS →					164,040	53,031	217,071

CONSULTANT COSTS		0
EQUIPMENT *(Itemize)*		0
SUPPLIES *(Itemize by category)*		
Research and lab supplies	7,059	
		7,059
TRAVEL		0
INPATIENT CARE COSTS		0
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		0
OTHER EXPENSES *(Itemize by category)*		0
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		**$ 224,130**
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		**$ 224,130**

PHS 398 (Rev. 08/12 Approved Through 8/31/2015) OMB No. 0925-0001
Form Page 4

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
Genetics Services

FROM 05/01/15 THROUGH 04/30/16

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	TOTAL
Excluded by Requester	PD/PI	EFFORT			Institutional Base Salary	20,469	6,898	27,367
	Senior Scientist					19,455	6,556	26,011
	Asst Professor					5,101	1,719	6,820
	Assoc Scientist					28,053	9,454	37,507
	Assoc Research Specialist					15,150	5,106	20,256
	Assoc Research Specialist					15,650	5,274	20,924
	Sr Admin Program Specialist					25,184	8,487	33,671
	SUBTOTALS →					129,062	43,494	172,556

CONSULTANT COSTS		0
EQUIPMENT *(Itemize)*		0
SUPPLIES *(Itemize by category)*		
Research and lab supplies	23,663	
Computer equipment	2,000	
Publication and reprints	1,000	26,663
TRAVEL		
	0	0
INPATIENT CARE COSTS		0
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		0
OTHER EXPENSES *(Itemize by category)*		
Computing services and software	2,594	
Genotyping costs	48,727	
		51,321
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	32,620
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		**$ 283,160**
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	18,430
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		**$ 301,590**

PHS 398 (Rev. 08/12 Approved Through 8/31/2015) OMB No. 0925-0001
Form Page 4

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
Immunology Services

FROM 05/01/15 THROUGH 04/30/16

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	TOTAL
Excluded by Requester	PD/PI	EFFORT			Institutional Base Salary	44,332	14,940	59,272
	Co-PI					14,544	4,901	19,445
	Sr Res Specialist					31,701	10,683	42,384
	Research Specialist					26,488	8,926	35,414
	Assoc Res Specialist					22,557	7,602	30,159
	SUBTOTALS →					139,622	47,052	186,674

CONSULTANT COSTS

Excluded by Requester				24,000

EQUIPMENT *(Itemize)*

0

SUPPLIES *(Itemize by category)*

General laboratory supplies	30,000	Flow cytometric assay reagents	26,748	
IFN-y elispot assay reagents	8,948	Fluorospot assay reagents	27,446	
Tetramers, Peptides, Hybridomas	8,548			101,690

TRAVEL

0

INPATIENT CARE COSTS	0
OUTPATIENT CARE COSTS	0

ALTERATIONS AND RENOVATIONS *(Itemize by category)*

0

OTHER EXPENSES *(Itemize by category)*

Publication charges	9,000	
Data analysis software	5,000	
		14,000

CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		**$ 326,364**
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		**$ 326,364**

PHS 398 (Rev. 08/12 Approved Through 8/31/2015) OMB No. 0925-0001
Form Page 4

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
Research Computing

FROM 05/01/15 THROUGH 04/30/16

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	TOTAL
Excluded by Requester	PD/PI	EFFORT			Institutional Base Salary	59,506	20,054	79,560
TBN	Assoc Inform Proc Conslt	11.00				55,000	18,535	73,535
SUBTOTALS →						114,506	38,589	153,095

CONSULTANT COSTS		
EQUIPMENT *(Itemize)*		0
SUPPLIES *(Itemize by category)*		
Computer equipment	4,000	
		4,000
TRAVEL		0
INPATIENT CARE COSTS		0
OUTPATIENT CARE COSTS		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		0
OTHER EXPENSES *(Itemize by category)*		
Annual EHR Software Support Contract	65,000	
Backup and Archive Media	1,117	
		66,117
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		**$ 223,212**
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		**$ 223,212**

PHS 398 (Rev. 08/12 Approved Through 8/31/2015) OMB No. 0925-0001
Form Page 4

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
Virology Services

FROM 05/01/15 THROUGH 04/30/16

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	TOTAL
Excluded by Requester	PD/PI	EFFORT			Institutional Base Salary	10,820	3,646	14,466
	Sr Research Specialist					47,741	16,089	63,830
	Assoc Res Specialist					31,310	10,551	41,861
	SUBTOTALS →					89,871	30,286	120,157

CONSULTANT COSTS — 0

EQUIPMENT *(Itemize)* — 0

SUPPLIES *(Itemize by category)*

QRT-PCR supplies	50,150	Diagnostic virus isolation supplies	10,500
SIV virus stock production supplies	3,649		
New molecular diagnostics development supplies	17,000		

81,299

TRAVEL — 0

INPATIENT CARE COSTS — 0

OUTPATIENT CARE COSTS — 0

ALTERATIONS AND RENOVATIONS *(Itemize by category)* — 0

OTHER EXPENSES *(Itemize by category)* — 0

CONSORTIUM/CONTRACTUAL COSTS — DIRECT COSTS — 0

SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)* — $ **201,456**

CONSORTIUM/CONTRACTUAL COSTS — FACILITIES AND ADMINISTRATIVE COSTS

TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD — $ **201,456**

PHS 398 (Rev. 08/12 Approved Through 8/31/2015) OMB No. 0925-0001
Form Page 4

RESEARCH & RELATED BUDGET - SECTION A & B FINAL

ORGANIZATIONAL DUNS*: 051113330

Budget Type*: ○ Project ● Subaward/Consortium

Enter name of Organization: BAYLOR COLLEGE OF MEDICINE

Start Date*: 05-01-2015 **End Date*:** 04-30-2016

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1.		Excluded by Requester			PhD	Project Lead	Institutional Base Salary	EFFORT			27,495.00	5,125.00	32,620.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **32,620.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	**Total Number Other Personnel**					**Total Other Personnel**	**0.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**32,620.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E

ORGANIZATIONAL DUNS*: 051113330
Budget Type*: ❍ Project ● Subaward/Consortium
Enter name of Organization: BAYLOR COLLEGE OF MEDICINE

Start Date*: 05-01-2015 **End Date*:** 04-30-2016

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	Funds Requested ($)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	0.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**0.00**

E. Participant/Trainee Support Costs		Funds Requested ($)*
1. Tuition/Fees/Health Insurance		0.00
2. Stipends		0.00
3. Travel		0.00
4. Subsistence		0.00
5. Other:		
0 Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 051113330
Budget Type*: ❍ Project ● Subaward/Consortium
Enter name of Organization: BAYLOR COLLEGE OF MEDICINE

Start Date*: 05-01-2015 **End Date*:** 04-30-2016

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	0.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
Total Other Direct Costs	**0.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**32,620.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. Modified Total Direct Cost Base	56.5	32,620.00	18,430.00
		Total Indirect Costs	**18,430.00**

Cognizant Federal Agency
(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**51,050.00**

J. Fee	Funds Requested ($)*
	0.00

K. Budget Justification* File Name:
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

A. COMPONENT COVER PAGE

Project Title: Operational Services

Component Project Lead Information:

Excluded by Requester

B. COMPONENT ACCOMPLISHMENTS

B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

Operational Services Overview
Division Head: Excluded by Requester

Objective: To deliver proactive leadership and outstanding service to ensure WNPRC's mission attainment. To provide all necessary customer services and assistance to support the Center's infrastructure and the independently funded research projects of WNPRC principal investigators.

The Operational Services Division supports the research and animal care mission of the Wisconsin National Primate Research Center (WNPRC), University of Wisconsin-Madison. This mission support is provided by creating a positive work environment that embraces all team members and their contributions and by striving for "excellence in all we do," developing transparency, and instilling a proactive attitude. The Division consists of three units providing administrative support for the Center: Administrative Services (AS); Facilities Management & Shop Services (Shop); and Information Technology and Systems Services (ITSS). These units work closely with WNPRC researchers and staff, as well as Campus and external researchers/customers to provide grant support (pre- and post-award), personnel and financial management, acquisition of services, supplies, and equipment, infrastructure support, and information services furthering the research mission of the Center and the University. All personnel in Operational Services appreciate and promote a customer service approach in carrying out the day-to-day administrative functions. In addition, Operational Services staff work to assure compliance with all administrative and regulatory requirements of the university, State of Wisconsin, federal agencies, and other sponsors.

Operational Services Division interacts primarily with the Office of the Vice Chancellor for Research and Graduate Education through the Vice Chancellor for Research and Graduate Education and the Assistant Vice Chancellors, whose oversight includes accounting, human resources, information technology, research administration, and industrial partnerships, and with the Office of Research and Sponsored Programs. AS also coordinates closely with the UW-Madison Business Services, including Accounting Services and Purchasing Services. There are strong interpersonal relationships and lines of communication between these offices and Operational Services, which creates an efficient and responsive partnership that greatly enhances mission success of the WNPRC.

Please see attached detailed progress reports from each unit (Section B.2), which includes specific aims, accomplishments and goals.

B.1.a Have the major goals changed since the initial competing award or previous report?

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: Ops Services Yr 53 Progress Report_final2-26-15_opt.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

Not Applicable

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

NOTHING TO REPORT

B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?

NOTHING TO REPORT

B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

Please see attached detailed progress reports from each unit (Section B.2), which includes future goals for the next reporting period.

OPERATIONAL SERVICES DIVISION

UNIT REPORTS

ADMINISTRATIVE SERVICES UNIT

Unit Head: Excluded by Requester

Specific Aim 1 - Expand and continue to provide staff education/in-services and work with staff on career and personal professional development.

Specific Aim 2 - Improve new employee orientation and training processes.

Specific Aim 3 - Continue to support the overall administrative needs of the WNPRC.

Specific Aim 4 - Rapidly adapt to Campus organizational and administrative structure changes, such as HR Design.

Specific Aim 5 - Improve fiscal oversight of grant projects through use of PI Financials.

Specific Aim 6 - Achieve seamless pre-award to post-award transitions and post-award management.

The Administrative Services unit (formerly referenced as Personnel, Business and Grants Services) continues to provide critical operational and administrative support to the Animal Services Division, to the Research Services Division, to Primate Center investigators, and to the other Operational Services units. Due to continuing budgetary constraints, the unit's staffing was further reduced in 2014. The University Services Program Assistant (USPA)-Project who assisted with purchasing and electronic reimbursements resigned to take another position on campus and was not replaced. In addition, the Financial Specialist 3 position that assisted with invoicing and accounts receivable was eliminated. Remaining Administrative Services staff include the following:

- Excluded by Requester Assistant Director of Administrative Services
- Excluded by Requester Human Resources Assistant
- Excluded by Requester Human Resources Assistant Advanced
- Excluded by Requester Administrative Program Specialist (working title: Grants Manager)
- Excluded by Requester Associate Administrative Program Specialist (working title: Grants Coordinator)
- Excluded by Requester Purchasing Associate

Despite the reduced staffing and increased workload, the remaining staff made the following vital contributions to the operations of the Primate Center in 2014:

- Processed 72 funding actions, including 16 new award submissions, 3 award re-submissions, 19 continuations, 66 supplemental funding actions, 6 no-cost extension requests, 3 contracts, 7 just-in-time requests, 88 Fee-for-Service Agreements, 5 purchasing agreements, 1 animal care

training agreement, and 15 Material Transfer Agreements. Additionally, processed 6 donation or gift-in-kind agreements.

- Managed 103 accounts, including 83 Federal grants and contracts, 6 Foundation grants, 9 gift awards, and 5 departmental accounts. Processed 11 award closeouts.
- Processed total billings of $5.48M. Average number of internal invoices processed per month was 57, and average number of monthly external invoices was 16.
- Developed more robust system for tracking accounts receivable for external clients.
- In early 2014, spearheaded the electronic RPPR submission for Primate Centers.
- Managed over 2,600 order requests (not including blanket and standing orders). This included 1,832 purchasing card transactions and over 650 purchases through the UW-Madison's Shop@UW system.
- Reconciled all departmental purchasing card activity to ensure account activity compiles with Federal, State, and University policies.
- Processed 122 blanket and standing purchase orders, totaling a minimum of $1.97M.
- Through researching and comparing vendor prices, purchasing staff reduced costs to the Center by approximately $63K over the last year. An additional $11K was saved through the coordinated efforts of the purchasing staff and Excluded by Requester who manages Excluded by Requester laboratory and the Bone Marrow Transplantation Core. These efforts continue to be an ongoing priority.
- Handled 129 electronic reimbursements for employees traveling on Primate Center business, attending conferences or other professional development opportunities, incurring business expenses with personal funds, or requesting work-related tuition reimbursement. Also processed seven tuition remissions for graduate students working in Primate Center research laboratories.
- Managed the hiring process for 46 open staff positions, which included five employees transitioned from temporary to permanent positions, three internal promotions, and four job changes across Primate Center units. Also managed the hiring of 31 new student hourly employees. Handled 14 position vacancy listings (PVLs) for open academic staff positions and 45 certification listings (CERTs) for open classified positions.
- Processed 34 staff departures and 21 student hourly departures. The staff departures included one retirement and two layoffs due to program redirection related to continuing budgetary constraints.
- Managed 183 pay and job classification change transactions, including 129 mandatory base pay increase of 1% for all employees effective July 1, 2014, four rate/title changes for academic staff, seven mandatory promotions for academic staff, one reclassification for classified personnel, 21 mandatory Critical Compensation Fund (CCF) increases for academic staff, 17 mandatory Discretionary Merit Compensation (DMC) increases for classified personnel, four non-mandatory DMCs for classified personnel, and one Discretionary Equity or Retention Adjustment (DERA).
- Oversaw the onboarding of 39 students engaged in research at the Primate Center for course credit. Processed two Affiliation Agreements with other educational institutions sending their

students, primarily veterinary externs, to WNPRC for training, and processed two people who volunteered their services.

- Requested 115 criminal background checks for prospective employees, student hourlies, affiliates, and long-term visitors.
- Managed the processing of three Visa applications for international employees-in-training.
- Additionally, processed 162 visitors and vendors who required access to the WNPRC facilities. These included initiating 29 Honorary Fellowships for visiting scholars, researchers, and trainees, as well as coordinating with the Training and Compliance Unit to ensure visitors and vendors were compliant with the WNPRC tuberculin screening policy.

Other highlights:

The Human Resources team continues to work with members of the Animal Services Division on the Incident Prevention Committee to review and discuss errors involving NHPs that have occurred, to review recommendations and suggestions for preventing similar errors from occurring, and to monitor progress on the implementation of any resulting recommendations and/or modifications to procedures. Additionally, the HR team works closely with [Excluded by Requester] Colony Manager, and her supervisory team to screen, interview, and hire animal care staff.

[Excluded by Requester] worked with University Legal Counsel and with counsel in the Office of Industrial Partnerships to develop affiliation and training agreements for execution with educational institutions and other entities requesting to send their students or employees to the WNPRC for hands-on training with nonhuman primates. The purpose of these agreements is to help ensure that all parties are aware of their responsibilities and to help clarify issues surrounding liability.

FUTURE GOALS

Specific Aim 1 - Expand and continue to provide staff education/in-services and work with staff on career and personal professional development.

[Excluded by Requester] and the HR team has been rolling out a new process for professional development review of all staff, and has been working with supervisors on this implementation. Two key outcomes of these reviews will be to identify areas where additional training and skill building may be required, and to encourage supervisors to work with employees on career development opportunities.

Specific Aim 2 - Improve new employee orientation and training processes.

The HR team has implemented a basic onboarding process. To make it more robust, the "peer partner" program will be strengthened and broadened beyond Colony Management to other units. In addition, materials are being developed to delineate responsibilities to ensure a smoother onboarding process for new employees and students.

Specific Aim 3 - Continue to support the overall administrative needs of the WNPRC.

Specific Aim 4 - Rapidly adapt to Campus organizational and administrative structure changes, such as HR Design.

[Excluded by Requester] and the HR team will continue to keep WNPRC personnel informed about changes to the University's personnel system, as HR Design becomes effective July 1, 2015.

Specific Aim 5 - Improve fiscal oversight of grant projects through use of PI Financials.

The Grants and Finance team will continue to meet with PIs and Unit Heads to review their budgets. Additionally, a review of service rates will be undertaken again this spring before prices for FY16 are announced.

Specific Aim 6 - Achieve seamless pre-award to post-award transitions and post-award management.

While the Grants and Finance team has achieved a much more seamless transition from pre-award to post-award, the team will continue working on ensuring that accounts are monitored routinely.

INFORMATION TECHNOLOGY & SYSTEM SERVICES UNIT (ITSS)

Unit Head: Excluded by Requester

Objective: To provide data management, computer and networking services to support research, service units, and daily operations of the Wisconsin National Primate Research Center. The unit consists of the unit head, two programmers, a senior technical specialist, and a technician.

The Center's infrastructure consists of: 9 UNIX / Linux based servers for centralized computing, file, database, and network services. We also host several application servers for our Genetics services and Immunology services units and web servers for Primate Portal and the Primate Aging Database.

Centralized data storage is provided via a highly scalable multi-terabyte Storage Area Network (SAN) currently consisting of 5 file servers and storage administration servers.

Distributed computing resources take the form of 150 desktop computers, 50 laptops, and 50 tablet computers used for EHR data entry behind the animal barrier. Networking facilities are based on a Facility Security

Facility Security is owned by the campus network authority, the Division of Information Technology (DoIT), and managed collaboratively by DoIT and the Information Technology and Systems Services Unit.

Progress

In 2014, the ITSS unit continued to support and improve the non-human primate electronic health record (EHR) system which is based on the open source LabKey platform. The ITSS unit programmer and Unit head attended weekly EHR planning and support conferences with LabKey staff. ITSS staff also participated in numerous EHR development meetings with other Center units.

ITSS continued to develop and improve the Center's web based business systems for charge entry, invoicing, reporting, and purchase order requests.

We continue to see increased usage of the centralized storage system. The SAN is used by Center units and labs, network storage of "mobile" user accounts, and for 1st tier backup of desktop systems.

The IT network technician has taken over responsibility for the daily backups of desktop systems using our central backup server. This freed up time for the Unit head to plan and implement a new networking infrastructure with the University of Wisconsin DoIT. The new infrastructure includes a new enterprise level firewall and virtual firewall services for each primate center physical location. ITSS is also working to implement several other University of Wisconsin projects such as the Security Baseline and Server Room Consolidation. The new networking infrastructure is the first step in implementing these projects. To prepare for the Server Room Consolidation project, ITSS continues to reduce the number of servers in use at the Center by consolidating services onto single servers using virtualization. Three servers were retired by consolidating their services onto a single server. ITSS continues to follow the replacement cycle for servers and desktop systems. Servers have a lifetime of 4-6 years on average. Desktop systems are replaced by cascading 3-4 year old systems to less critical locations before they are obsolete.

ITSS continues to provide the day-to-day operation of the electronic resources of the former Jacobsen Library. We maintain the electronic integrity of the resources but not the content, i.e. we make sure that

the systems are running, if there is an error or a broken link we fix the error so that the resources continue to be accurate and available to researchers and the public. Facility Security

Facility Security that service has been suspended since October 2014.

FACILITIES MANAGEMENT & MACHINE SHOP SERVICES UNIT

Unit Head: Excluded by Requester

Objective: To monitor and maintain all major building and infrastructure systems along with implementing and coordinating system upgrades and remodel projects. The group is responsible for providing a compliant, secure and safe environment for all human and non-human occupants. Provide innovative and comprehensive ideas and designs used for the fabrication of specialized equipment used in the research, housing and enrichment of non-human primates. Specific Aims and key highlights are outlined below:

Specific Aim 1 - To monitor and maintain all aspects of WNRPC facility operations and coordinate system upgrades.

AHU (air handling unit) 3 of the Specific Animal Location received a new 100hp supply fan motor equipped with grounding rings to prevent electrical bearing damage as a result of the new frequency drives also installed. During the shutdown exhaust fan 4 was re-aligned and the gaskets were replaced.

Specific Animal Location one of the original sewage lift pump / grinder assemblies were replaced along with all new floats, piping and valves. The second assembly has arrived and will be installed soon. WNPRC will be doing a cost share with UW Physical Plant on this project.

Through funding received by the UW Police Department our existing Facility Security Facility Security

These are examples of a few of the upgrades that occurred last year Excluded by Requester s responsible for the coordination and scheduling of these upgrades working closely with Facility, Planning and Management (FP&M) along with outside contractors and vendors as required.

Specific Aim 2 - To participate in the planning and execution of all facility renovation and construction initiatives at the WNPRC.

Specific Animal Locat Building anima Specific Animal Location was completely refurbished with new epoxy floor and wall grout, fiberglass reinforced panels (FRP) installed to cover the ceiling, new stainless steel ductwork and new lights. Pipe insulation was replaced as needed and new stainless steel shelves were built and installed.

Specific Aim 3 - To support research and Colony Management staff with the design and fabrication of equipment.

In January of 2014 a ten month long project logging in over 1100 man-hours began. The WNPRC Instrument Maker Shop in preparation for a new group of Marmosets constructed 38 new cages. The project consisted of 18 single and 20 double cages fully equipped with nesting boxes and enrichment furniture. The original prototype cage was designed and built here in 1992. Although several features have been changed over the years the basic concept remains the same. The working drawings have been shared with numerous research groups and prove to be an effective cage design. The cages along with numerous other required components including holding room renovations were completed by the deadline date.

Along with Colony Management and Veterinary Services staff Excluded by Requester worked closely with cage manufacturer BRITZ and COMPANY on the design and installation of a prototype pen and one over

one rolling rack system. WNPRC provided several successful design features unique to this cage. Upon a finalized design Specific Animal Location was fitted with 4 (FLEXAGON) pens and 10 (MODSQUAD) rolling racks. Currently plans are to equip 2 additional rooms with the Britz cages.

Working closely with Excluded by Requester designed and built several MRI compatible stereotaxic frame attachments. Built new ear and pallet bars using plastic to replace the brass parts. Designed an adjustable MRI head coil holder that attaches to the frame. Other similar projects include a delrin pallet bar for Excluded by Requester and a polycarbonate PET scanner cradle for Excluded by Requester

Specific Aim 4 - To prioritize and coordinate repairs of equipment, minimizing the interruption of science.

Given the numerous buildings Excluded by Requester and his staff manage, multiple daily repairs are not uncommon. Systems and equipment are monitored 24/7 through the BAN (building automation network). Problems are assessed and prioritized, repairs are facilitated in an effective manor.

Equipment and system failures range from a -80 freezer loosing temperature to an animal holding room running warm.

Specific Aim 5 - To continue extensive animal holding room refurbishing projects.

Currently as mentioned in Specific Aim 3, two rooms will be renovated to accommodate the new BRITZ cages next year. Specific Animal Location and BMQ (Blue Mounds Quarantine) Specific Animal Location will be renovated once a cage layout is finalized.

Specific Aim 6 - To focus on staying compliant and surpassing all regulatory guidelines along with improving husbandry and housing operations.

ICS (Integrated Communication Services) of Madison was contracted as a second layer or backup for all + - 10 degree temperature alarms in our animal holding rooms assuring the alarm was acknowledged by Excluded by Request or designated staff.

In preparation for our 2014 AAALAC site visit the UW Sheet metal Shop was requested to generate an air balance report. BMQ Specific Animal Location was found to be in need of an additional exhaust duct to assure the room maintains negative pressure. Several other rooms at multiple locations required air balance adjustments to be in range of design specifications.

Facility fume hoods (20 total) were retrofitted with a flow monitor equipped with a low flow audible alarm. This work was performed and funded by UWFP&M.

It was noted that the vinyl floor covering in animal freight elevator Specific Animal Location was failing and unable to be sanitized. New 3/16" stainless steel diamond plate was installed, the joints were welded and the plate was sealed and bolted into place.

WNPRC Instrument Maker Shop worked closely with Colony Management and Compliance staff to generated pre-inspection lists for ACUC and AAALAC inspections. Numerous items were prioritized and repairs were made. Both inspections went well with positive feedback.

List of training sessions attended in 2014: Forklift refresher training. UW Animal User Orientation Class. Annual Herpes B Safety Training Class. First Aid, CPR, AED UW Health. Fire Extinguisher Training

Specific Aim 7 - To provide support and service in the design of new quarantine facilities.

In conjunction to the start of the Marmoset cage project mentioned in Specific Aim 3, BMQ Specific Animal Location needed to be renovated. The room was set up with dog pens that needed to be removed. Two replacement re-heat coils were engineered and installed to guarantee 80 degrees. An additional

monitor and control point was added to the Siemens BAN system assuring correct room pressurization. A stainless steel railing, crosswalk and access system was designed and installed over the 68' x 6' trench running down the center of the room. A watering loop with drop down coil hoses was installed. A mobile collapsible partition was modified to segregate some of the animals. Custom 6" drain covers were designed and built allowing waste to be washed down the drain along with keeping the possibility of a loose monkey out of the drain.

FUTURE GOALS

Complete Annex Specific Animal Location and BMQ Specific Animal Location renovation and BRITZ cage installation.

Complete MRI compatible restraint training chair design and fabrication for Excluded by Requester

Complete the renovation of Specific Animal Location from a lab to procedure room.

PRIMATE CENTER CAPITAL EQUIPMENT PURCHASES

The following capital equipment purchases were completed in 2014:

1) Fisher Scientific -86 Chest Freezer, $12,179 (Immunology Services)

Excluded by Requester 2) Nikon Color Camera System, $6,385.94 [redacted] laboratory)

3) Baker Sterilgard Laminar Flow Hood, $8,532.72 [redacted] laboratory) Excluded by Requester

Excluded by Requester 4) Revco Ultra Low Upright Freezer, $15,089 [redacted] laboratory)

5) Roche Diagnostic Corporation PCR System, $18,800 (Center faculty)

All units within Operational Services work with investigators and with staff from the Animal Services Division and the Research Services Division on the purchase and installation of new equipment for WNPRC units and laboratories.

C. COMPONENT PRODUCTS

C.1 PUBLICATIONS

Not Applicable

C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

Not Applicable

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Not Applicable

C.5 OTHER PRODUCTS AND RESOURCE SHARING

C.5.a Other products

NOTHING TO REPORT

C.5.b Resource sharing

NOTHING TO REPORT

D. COMPONENT PARTICIPANTS

Not Applicable

E. COMPONENT IMPACT

E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES?

Not Applicable

E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE?

Not Applicable

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

NOTHING TO REPORT

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?

Not Applicable

F. COMPONENT CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

F.2 ACTUAL OR ANTICIPATED CHALLENGES OR DELAYS AND ACTIONS OR PLANS TO RESOLVE THEM

NOTHING TO REPORT

F.3 SIGNIFICANT CHANGES TO HUMAN SUBJECTS, VERTEBRATE ANIMALS, BIOHAZARDS, AND/OR SELECT AGENTS

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. COMPONENT SPECIAL REPORTING REQUIREMENTS

G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT REPORTING REQUIREMENTS

Not Applicable

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

G.4.a Does the project involve human subjects?

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Not Applicable

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

RESEARCH & RELATED BUDGET - SECTION A & B FINAL

ORGANIZATIONAL DUNS*: 161202122

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: UNIVERSITY OF WISCONSIN-MADISON

Start Date*: 05-01-2015 **End Date*:** 04-30-2016

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1.		Excluded by Requester				Division Head, Operational Services; Unit Head, Administrative Services	Institutional Base Salary	EFFORT			12,960.00	4,368.00	17,328.00
2.						Unit Head, Information Technology and Systems Services (ITSS)					77,987.00	26,282.00	104,269.00
3.						Unit Head, Shop Services					60,565.00	28,163.00	88,728.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **210,325.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
14	Division Staff	12.0			486,897.00	186,691.00	673,588.00
14	**Total Number Other Personnel**					**Total Other Personnel**	**673,588.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**883,913.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E

ORGANIZATIONAL DUNS*: 161202122

Budget Type*: ● Project ● Subaward/Consortium

Enter name of Organization: UNIVERSITY OF WISCONSIN-MADISON

Start Date*: 05-01-2015 **End Date*:** 04-30-2016

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	Funds Requested ($)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	0.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**0.00**

E. Participant/Trainee Support Costs		Funds Requested ($)*
1. Tuition/Fees/Health Insurance		0.00
2. Stipends		0.00
3. Travel		0.00
4. Subsistence		0.00
5. Other:		
0 Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 161202122

Budget Type*: ● Project ● Subaward/Consortium

Enter name of Organization: UNIVERSITY OF WISCONSIN-MADISON

Start Date*: 05-01-2015 **End Date*:** 04-30-2016

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	231,823.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Other	149,966.00
Total Other Direct Costs	**381,789.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**1,265,702.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. Modified Total Direct Cost Base	34.5	1,265,702.00	436,667.00
		Total Indirect Costs	**436,667.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): Department of Health & Human Services Contact: Arif Karim 214-767-3261

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**1,702,369.00**

J. Fee	Funds Requested ($)*
	0.00

K. Budget Justification* File Name: Yr 54_WNPRC_Ops Srvcs_Budget Just_opt.pdf

(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
Administrative Services

FROM 05/01/15 THROUGH 04/30/16

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	TOTAL
Excluded by Requester	Associate Director	EFFORT			Institutional Base Salary	12,960	4,368	17,328
	Assistant Director					31,261	10,535	41,796
	Advanced Assistant					45,959	21,371	67,330
	HR Assistant					36,423	16,937	53,360
	Purchasing Assoc					27,974	13,008	40,982
	Grants Mgr					52,637	17,739	70,376
	Grants Coord					40,400	13,615	54,015
TBN	Grants Coord	9.60				40,000	13,480	53,480
TBN	Student	9.00				7,575	303	7,878
TBN	Student	9.00				7,575	303	7,878
	SUBTOTALS →					302,764	111,659	414,423

CONSULTANT COSTS				0
EQUIPMENT *(Itemize)*				0
SUPPLIES *(Itemize by category)*				
Office Supplies	3,622	Laboratory Gases	11,906	15,528
TRAVEL				0
INPATIENT CARE COSTS				0
OUTPATIENT CARE COSTS				0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*				0
OTHER EXPENSES *(Itemize by category)*				
Capital Equipment Service & Maintenance	28,326	Copy Machine Leases	2,183	
Vehicle Leases	27,338	Postage & Delivery	1,000	
Telephones	10,544			69,391
CONSORTIUM/CONTRACTUAL COSTS		DIRECT COSTS		0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*				$ 499,342
CONSORTIUM/CONTRACTUAL COSTS		FACILITIES AND ADMINISTRATIVE COSTS		
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD				$ 499,342

PHS 398 (Rev. 08/12 Approved Through 8/31/2015) OMB No. 0925-0001

Form Page 4

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
Information Technology and Systems Services

FROM 05/01/15 THROUGH 04/30/16

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	TOTAL
Excluded by Requester	Unit Head	EFFORT			Institutional Base Salary	77,987	26,282	104,269
	Asst Data Mgr					48,853	16,463	65,316
	Senior IP Consult.					46,836	15,784	62,620
	Network Tech.					32,410	15,071	47,481
	SUBTOTALS →					206,086	73,600	279,686

CONSULTANT COSTS				0
EQUIPMENT *(Itemize)*				0
SUPPLIES *(Itemize by category)*				
Microcomputer Software	9,229	Comm cables, connectors, interfa	4,729	
Printer Supplies	8,229			
Backup and Archive Media	5,079			27,266
TRAVEL				0
INPATIENT CARE COSTS				0
OUTPATIENT CARE COSTS				0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*				0
OTHER EXPENSES *(Itemize by category)*				
Professional Development	3,575			3,575
CONSORTIUM/CONTRACTUAL COSTS			DIRECT COSTS	0
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*				**$ 310,527**
CONSORTIUM/CONTRACTUAL COSTS			FACILITIES AND ADMINISTRATIVE COSTS	
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD				**$ 310,527**

PHS 398 (Rev. 08/12 Approved Through 8/31/2015) OMB No. 0925-0001
Page **Form Page 4**

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
Facilities Management and Instrument Maker Shop Services

FROM 05/01/15 THROUGH 04/30/16

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	TOTAL
Excluded by Requester	Shop Coord-Fac Mgr	EFFORT			Institutional Base Salary	60,565	28,163	88,728
	Mechanician					40,163	18,676	58,839
TBN	Mechanician-Entry	10.80				28,831	13,406	42,237
	SUBTOTALS →					129,559	60,245	189,804

CONSULTANT COSTS 0

EQUIPMENT *(Itemize)* 0

SUPPLIES *(Itemize by category)*

Water Conditioning	14,417	Lab Hood Certification	5,835
Pest Control	18,096	UW Physical Plant	116,473
Medical Waste Disposal	2,122	Shop Supplies	26,139
Warehouse Storage Lease	5,947		

189,029

TRAVEL 0

INPATIENT CARE COSTS 0

OUTPATIENT CARE COSTS 0

ALTERATIONS AND RENOVATIONS *(Itemize by category)* 0

OTHER EXPENSES *(Itemize by category)*

Security Guard	Salary	50,000
	Fringe	27,000

77,000

CONSORTIUM/CONTRACTUAL COSTS DIRECT COSTS 0

SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)* $ **455,833**

CONSORTIUM/CONTRACTUAL COSTS FACILITIES AND ADMINISTRATIVE COSTS

TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD $ **455,833**

PHS 398 (Rev. 08/12 Approved Through 8/31/2015) OMB No. 0925-0001
Form Page 4