PRIMATE RESEARCH CENTER GRANT **Federal Award Date:** 09/11/2015

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

Grant Number: 3P51OD011133-17S1 REVISED
FAIN: P51OD011133

Principal Investigator(s):
ROBERT W GRACY, PHD

Project Title: The Southwest National Primate Research Center

Ms Biediger, Ana M
Assistant Director
7620 NW Loop 410
San Antonio, TX 782275301

Award e-mailed to: nih-nga@txbiomed.org

Period Of Performance:
Budget Period: 09/07/2015 – 04/30/2016
Project Period: 06/06/1999 – 04/30/2016

Dear Business Official:

The National Institutes of Health hereby revises this award (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to TEXAS BIOMEDICAL RESEARCH INSTITUTE 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 P51OD011133. 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 – 3P51OD011133-17S1 REVISED

Award Calculation (U.S. Dollars)

Salaries and Wages	$15,275
Fringe Benefits	$4,323
Personnel Costs (Subtotal)	$19,598
Other Costs	$158,820
Federal Direct Costs	$178,418
Federal F&A Costs	$140,237
Approved Budget	$318,655
Total Amount of Federal Funds Obligated (Federal Share)	$318,655
TOTAL FEDERAL AWARD AMOUNT	$318,655
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$0

SUMMARY TOTAL FEDERAL AWARD AMOUNT YEAR (17)	
GRANT NUMBER	**TOTAL FEDERAL AWARD AMOUNT**
3P51OD011133-17S1	$318,655
5P51OD011133-17	$7,367,413
3P51OD011133-17S2	$440,610
TOTAL	**$8,126,678**

SUMMARY TOTALS FOR ALL YEARS		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
17	$318,655	$8,126,678

Fiscal Information:

CFDA Name:	Research Infrastructure Programs
CFDA Number:	93.351
EIN:	1741109630A1
Document Number:	POD011133D
PMS Account Type:	P (Subaccount)
Fiscal Year:	2015

IC	CAN	2015
OD	8014499	$318,655

NIH Administrative Data:
PCC: CMP01 / **OC**: 414C / **Released**: eRA Commons User Name 09/10/2015
Award Processed: 06/15/2015 11:31:44 PM

SECTION II – PAYMENT/HOTLINE INFORMATION – 3P51OD011133-17S1 REVISED

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

SECTION III – TERMS AND CONDITIONS – 3P51OD011133-17S1 REVISED

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

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 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).

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 System for Award Management (SAM). 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) P51OD011133. 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/.

This award represents the final year of the competitive segment for this grant. See the NIH Grants Policy Statement Section 8.6 Closeout for complete closeout requirements at: http://grants.nih.gov/grants/policy/policy.htm#gps.

A final expenditure Federal Financial Report (FFR) (SF 425) must be submitted through the eRA Commons (Commons) within 120 days of the expiration date; see the NIH Grants Policy Statement Section 8.6.1 Financial Reports, http://grants.nih.gov/grants/policy/policy.htm#gps, for additional information on this submission requirement. The final FFR must indicate the exact balance of unobligated funds and may not reflect any unliquidated obligations. There must be no discrepancies between the final FFR expenditure data and the Payment Management System's (PMS) quarterly cash transaction data. A final quarterly federal cash transaction report is not required for awards in PMS B subaccounts (i.e., awards to foreign entities and to Federal agencies). NIH will close the awards using the last recorded cash drawdown level in PMS for awards that do not require a final FFR on expenditures or quarterly federal cash transaction reporting. It is important to note that for financial closeout, if a grantee fails to submit a required final expenditure FFR, NIH will close the grant using the last recorded cash drawdown level. If the grantee submits a final expenditure FFR but does not reconcile any discrepancies between expenditures reported on the final expenditure FFR and the last cash report to PMS, NIH will close the award at the lower amount. This could be considered a debt or result in disallowed costs.

A Final Invention Statement and Certification form (HHS 568), (not applicable to training, construction, conference or cancer education grants) must be submitted within 120 days of the expiration date. The HHS 568 form may be downloaded at: http://grants.nih.gov/grants/forms.htm. This paragraph does not apply to Training grants, Fellowships, and certain other programs—i.e., activity codes C06, R13, R25, S10.

Unless an application for competitive renewal is submitted, a final progress report must also be submitted within 120 days of the expiration date. Instructions for preparing a Final Progress Report are at: http://grants.nih.gov/grants/funding/finalprogressreport.pdf. Any other specific requirements set forth in the terms and conditions of the award must also be addressed in the final progress report. Institute/Centers may accept the progress report contained in competitive renewal (type 2) in lieu of a separate final progress report. Contact the awarding IC for IC-specific policy regarding acceptance of a progress report contained in a competitive renewal application in lieu of a separate final progress report.

NIH strongly encourages electronic submission of the final progress report and the final invention statement through the Closeout feature in the Commons, but will accept an email or hard copy submission as indicated below.

Email: The final progress report and final invention statement may be e-mailed as PDF attachments to: NIHCloseoutCenter@mail.nih.gov.

Hard copy: Paper submissions of the final progress report and the final invention statement may be faxed to the NIH Division of Central Grants Processing, Grants Closeout Center, at 301-480-2304, or mailed to:

National Institutes of Health
Office of Extramural Research
Division of Central Grants Processing
Grants Closeout Center
6705 Rockledge Drive
Suite 5016, MSC 7986
Bethesda, MD 20892-7986 (for regular or U.S. Postal Service Express mail)
Bethesda, MD 20817 (for other courier/express deliveries only)

NOTE: If this is the final year of a competitive segment due to the transfer of the grant to another institution, then a Final Progress Report is not required. However, a final expenditure FFR is required and should be submitted electronically as noted above. If not already submitted, the Final Invention Statement is required and should be sent directly to the assigned Grants Management Specialist.

Treatment of Program Income:
Additional Costs

SECTION IV – OD Special Terms and Conditions – 3P51OD011133-17S1 REVISED

REVISION #1 : This award is revised to address the following issue:

Revised End Date to 4/30/2016 to coincide with the Parent Grant End Date.

All previous terms and conditions remain in effect.

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SUPPLEMENT
This supplemental award provides $318,655 ($178,237 direct costs and $140,237 associated facilities and administrative costs) for Marmosets 180 Animals transferred from New England Primate Research Center to Southwest National Primate Research Center. These funds may not be expended for any other purpose without the written prior approval of the ORIP.

BUDGET PERIOD/AWARD AMOUNT
This grant has been issued with an 8-month budget period with 8 months of monetary support.

PRE-AWARD AUTHORITY
This award includes 90 day preaward cost authorization to incur costs for approved grant activities.

SUBJECT FOA
This award is subject to the conditions set forth in PAR11-136, "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

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.

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) must be submitted to the assigned Grants Management Specialist and Programmatic Official. Please refer to the NIH Grants Policy Statement for the activities and/or expenditures that require NIH approval at http://grants.nih.gov/grants/policy/nihgps_2013/nihgps_ch8.htm#prior_approval_requirements.

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: Jean Richelsen
Email: richelsj@mail.nih.gov **Phone**: 301-594-9446 **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: 3P51OD011133-17S1 REVISED

INSTITUTION: TEXAS BIOMEDICAL RESEARCH INSTITUTE

Budget	Year 17
Salaries and Wages	$15,275
Fringe Benefits	$4,323
Personnel Costs (Subtotal)	$19,598

Other Costs	$158,820
TOTAL FEDERAL DC	$178,418
TOTAL FEDERAL F&A	$140,237
TOTAL COST	$318,655

Facilities and Administrative Costs	Year 17
F&A Cost Rate 1	78.6%
F&A Cost Base 1	$178,418
F&A Costs 1	$140,237

PRIMATE RESEARCH CENTER GRANT **Federal Award Date:** 09/07/2015

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

Grant Number: 3P51OD011133-17S1
FAIN: P51OD011133

Principal Investigator(s):
ROBERT W GRACY, PHD

Project Title: The Southwest National Primate Research Center

Ms Biediger, Ana M
Assistant Director
7620 NW Loop 410
San Antonio, TX 782275301

Award e-mailed to: nih-nga@txbiomed.org

Period Of Performance:
Budget Period: 09/07/2015 – 04/29/2016
Project Period: 06/06/1999 – 04/29/2016

Dear Business Official:

The National Institutes of Health hereby awards a grant in the amount of $318,655 (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to TEXAS BIOMEDICAL RESEARCH INSTITUTE 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 P51OD011133. 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.

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Sincerely yours,

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

Additional information follows

SECTION I – AWARD DATA – 3P51OD011133-17S1

Award Calculation (U.S. Dollars)

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GRANT NUMBER	**TOTAL FEDERAL AWARD AMOUNT**
3P51OD011133-17S1	$318,655
5P51OD011133-17	$7,367,413
3P51OD011133-17S2	$440,610
TOTAL	**$8,126,678**

SUMMARY TOTALS FOR ALL YEARS		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
17	$318,655	$8,126,678

Fiscal Information:

CFDA Name:	Research Infrastructure Programs
CFDA Number:	93.351
EIN:	1741109630A1
Document Number:	POD011133D
PMS Account Type:	P (Subaccount)
Fiscal Year:	2015

IC	CAN	2015
OD	8014499	$318,655

NIH Administrative Data:
PCC: CMP01 / **OC**: 414C / **Released**: eRA Commons User Name 09/01/2015
Award Processed: 06/15/2015 11:31:44 PM

SECTION II – PAYMENT/HOTLINE INFORMATION – 3P51OD011133-17S1

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SECTION III – TERMS AND CONDITIONS – 3P51OD011133-17S1

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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.

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National Institutes of Health
Office of Extramural Research
Division of Central Grants Processing
Grants Closeout Center
6705 Rockledge Drive
Suite 5016, MSC 7986
Bethesda, MD 20892-7986 (for regular or U.S. Postal Service Express mail)
Bethesda, MD 20817 (for other courier/express deliveries only)

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Treatment of Program Income:
Additional Costs

SECTION IV – OD Special Terms and Conditions – 3P51OD011133-17S1

SUPPLEMENT
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BUDGET PERIOD/AWARD AMOUNT
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PRE-AWARD AUTHORITY
This award includes 90 day preaward cost authorization to incur costs for approved grant activities.

SUBJECT FOA

This award is subject to the conditions set forth in PAR11-136, "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

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

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COMMUNICATIONS/PRESS RELEASE
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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: Jean Richelsen
Email: richelsj@mail.nih.gov **Phone**: 301-594-9446 **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: 3P51OD011133-17S1

INSTITUTION: TEXAS BIOMEDICAL RESEARCH INSTITUTE

Budget	Year 17
Salaries and Wages	$15,275
Fringe Benefits	$4,323
Personnel Costs (Subtotal)	$19,598
Other Costs	$158,820
TOTAL FEDERAL DC	$178,418
TOTAL FEDERAL F&A	$140,237
TOTAL COST	$318,655

Facilities and Administrative Costs	Year 17

F&A Cost Rate 1	78.6%
F&A Cost Base 1	$178,418
F&A Costs 1	$140,237

PI: **GRACY, ROBERT W**	Title: The Southwest National Primate Research Center	
Received: 01/26/2015	FOA: PAR14-226	Council: 10/2015
Competition ID: FORMS-C	FOA Title: LIMITED COMPETITION: NATIONAL PRIMATE RESEARCH CENTERS (P51)	
3 P51 OD011133-17S1	Dual: RI	Accession Number: 3779824
IPF: 7660801	Organization: TEXAS BIOMEDICAL RESEARCH INSTITUTE	
Former Number:	Department: Administration	
IRG/SRG: ZRG1 BBBP-T (46)P	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 17: 178,418 Year 18: 0 Year 19: 0 Year 20: 0 Year 21: 0	Animals: Y Humans: N Clinical Trial: N Current HS Code: 10 HESC: N	New Investigator: N Early Stage Investigator: N
Senior/Key Personnel:	*Organization:*	*Role Category:*
Robert Gracy	Texas Biomedical Research Institute	PD/PI

OMB Number: 4040-0001
Expiration Date: 06/30/2016

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	State Application Identifier

1. TYPE OF SUBMISSION*

○ Pre-application ○ Application ● Changed/Corrected Application

4.a. Federal Identifier
OD011133

b. Agency Routing Number

2. DATE SUBMITTED	Application Identifier	c. Previous Grants.gov Tracking Number
2015-01-26	15-012 Gracy	GRANT11814813

5. APPLICANT INFORMATION **Organizational DUNS*:** 007936834

Legal Name*: Texas Biomedical Research Institute
Department:
Division:
Street1*: 7620 NW Loop 410
Street2:
City*: San Antonio
County: Bexar
State*: TX: Texas
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 78227-5301

Person to be contacted on matters involving this application
Prefix: Ms First Name*: Ana Middle Name: M Last Name*: Biediger Suffix:
Position/Title: Assistant Director
Street1*: 7620 NW Loop 410
Street2:
City*: San Antonio
County: Bexar
State*: TX: Texas
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 78227-5301
Phone Number*: 210-258-9507 Fax Number: 210-670-3335 Email: abiediger@txbiomed.org

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** 741109630

7. TYPE OF APPLICANT* M: Nonprofit with 501C3 IRS Status (Other than Institution of Higher Education)

Other (Specify):
Small Business Organization Type ○ Women Owned ○ Socially and Economically Disadvantaged

8. TYPE OF APPLICATION*

○ New ○ Resubmission
○ Renewal ○ Continuation ● Revision

If Revision, mark appropriate box(es).
● A. Increase Award ○ B. Decrease Award ○ C. Increase Duration
○ D. Decrease Duration ○ E. Other *(specify)* :

Is this application being submitted to other agencies?* ○Yes ●No What other Agencies?

9. NAME OF FEDERAL AGENCY*
National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER
TITLE:

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
The Southwest National Primate Research Center

12. PROPOSED PROJECT
Start Date* 09/01/2015
Ending Date* 04/29/2016

13. CONGRESSIONAL DISTRICTS OF APPLICANT
TX-020

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: Dr First Name*: Robert Middle Name: Last Name*: Gracy Suffix:
Position/Title: President
Organization Name*: Texas Biomedical Research Institute
Department: Administration
Division:
Street1*: 7620 NW Loop 410
Street2:
City*: San Antonio
County: Bexar
State*: TX: Texas
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 78227-5301
Phone Number*: 210-258-9508 Fax Number: Email*: rgracy@txbiomed.org

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	$318,655.00
b. Total Non-Federal Funds*	$0.00
c. Total Federal & Non-Federal Funds*	$318,655.00
d. Estimated Program Income*	$53,466.00

16.IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

a. YES ○ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:
DATE:

b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR
○ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

● I agree*

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: Dr. First Name*: William Middle Name: H Last Name*: Caskey Suffix:
Position/Title*: Director, OSP
Organization Name*: Texas Biomedical Research Institute
Department: Administration
Division:
Street1*: 7620 NW Loop 410
Street2:
City*: San Antonio
County: Bexar
State*: TX: Texas
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 78227-5301
Phone Number*: 210-258-9544 Fax Number: 210-670-3335 Email*: whcaskey@txbiomed.org

Signature of Authorized Representative*
William H Caskey

Date Signed*
01/26/2015

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:Overall___Cover_Letter___REV1006418442.pdf

424 R&R and PHS-398 Specific Table Of Contents

Component Summary

Components	Component Project Title	Organization Name	Contact PD/PI Name or Project Lead Name
Overall	The Southwest National Primate Research Center	Texas Biomedical Research Institute	Gracy, Robert
Animal-Resources-001 (001)	The Southwest National Primate Research Center	Texas Biomedical Research Institute	Excluded by Requester

Project/Performance
Site Location(s) Summary

Applicant Organization	City	State/Province	Country
Texas Biomedical Research Institute	San Antonio	TX	UNITED STATES

Organization Name	City	State/Province	Country	Component
Texas Biomedical Research Institute	San Antonio	TX	UNITED STATES	Animal-Resources-001 (001)
Texas Biomedical Research Institute	San Antonio	TX	UNITED STATES	Overall

Human Subjects
Clinical Trial
Human Embryonic Stem Cells
Vertebrate Animals
Summary

Components	Human Subjects	Clinical Trial	HESC Involved	Vertebrate Animals
Overall	N		N	Y
Animal-Resources-001 (001)	N		N	Y

Composite Application Budget Summary

Categories	Budget Period 1	Budget Period 2	Budget Period 3	Budget Period 4	Budget Period 5	TOTALS
Salary, Wages and Fringe Benefits	19,598	0	0	0	0	19,598
Equipment	0	0	0	0	0	0
Travel	0	0	0	0	0	0
Participant/Trainee Support Costs	0	0	0	0	0	0
Other Direct Costs (excluding Consortium)	158,820	0	0	0	0	158,820
Consortium Costs	0	0	0	0	0	0
Direct Costs	178,418	0	0	0	0	178,418
Indirect Costs	140,237	0	0	0	0	140,237
Total Direct and Indirect Costs	318,655	0	0	0	0	**318,655**

Total Direct Costs less Consortium F&A

NIH policy (NOT-OD-05-004) allows applicants to exclude consortium/contractual F&A costs when determining if an application falls at or beneath any applicable direct cost limit. When a direct cost limit is specified in an FOA, the following table can be used to determine if your application falls within that limit.

Category	Budget Period 1	Budget Period 2	Budget Period 3	Budget Period 4	Budget Period 5	TOTALS
Total Direct Costs less Consortium F&A	178,418	0	0	0	0	**178,418**

Component Budget Summary

Components	Categories	Budget Period 1	Budget Period 2	Budget Period 3	Budget Period 4	Budget Period 5	TOTALS
Animal-Resources-001 (001)	Salary, Wages and Fringe Benefits	19,598	0	0	0	0	19,598
	Equipment	0	0	0	0	0	0
	Travel	0	0	0	0	0	0
	Participant/Trainee Support Costs	0	0	0	0	0	0
	Other Direct Costs (excluding Consortium)	158,820	0	0	0	0	158,820
	Consortium Costs	0	0	0	0	0	0
	Direct Costs	178,418	0	0	0	0	178,418
	Indirect Costs	140,237	0	0	0	0	140,237
TOTALS	Total Direct and Indirect Costs	318,655	0	0	0	0	**318,655**
TOTALS		**318,655**	**0**	**0**	**0**	**0**	**318,655**

Categories Budget Summary

Categories	Components	Budget Period 1	Budget Period 2	Budget Period 3	Budget Period 4	Budget Period 5	TOTALS
R&R Budget - Senior/Key Person Funds Requested	Animal-Resources-001 (001)	19,598	0	0	0	0	19,598
TOTALS		19,598	0	0	0	0	**19,598**
R&R Budget - Other Personnel Funds Requested	Animal-Resources-001 (001)	0	0	0	0	0	0
TOTALS		0	0	0	0	0	**0**
R&R Budget - Section A & B. Total Salary, Wages and Fringe Benefits (A+B)	Animal-Resources-001 (001)	19,598	0	0	0	0	19,598
TOTALS		19,598	0	0	0	0	**19,598**
R&R Budget - Section C. Total Equipment	Animal-Resources-001 (001)	0	0	0	0	0	0
TOTALS		0	0	0	0	0	**0**
R&R Budget - Domestic Travel	Animal-Resources-001 (001)	0	0	0	0	0	0
TOTALS		0	0	0	0	0	**0**
R&R Budget - Foreign Travel	Animal-Resources-001 (001)	0	0	0	0	0	0
TOTALS		0	0	0	0	0	**0**
R&R Budget - Section D. Total Travel	Animal-Resources-001 (001)	0	0	0	0	0	0
TOTALS		0	0	0	0	0	**0**

R&R Budget - Tuition/Fees/Health Insurance	Animal-Resources-001 (001)	0	0	0	0	0	0
TOTALS		0	0	0	0	0	**0**
R&R Budget - Stipends	Animal-Resources-001 (001)	0	0	0	0	0	0
TOTALS		0	0	0	0	0	**0**
R&R Budget - Trainee Travel	Animal-Resources-001 (001)	0	0	0	0	0	0
TOTALS		0	0	0	0	0	**0**
R&R Budget - Subsistence	Animal-Resources-001 (001)	0	0	0	0	0	0
TOTALS		0	0	0	0	0	**0**
R&R Budget - Other Participants/Trainee Support Costs	Animal-Resources-001 (001)	0	0	0	0	0	0
TOTALS		0	0	0	0	0	**0**
R&R Budget - Section E. Total Participants/Trainee Support Costs	Animal-Resources-001 (001)	0	0	0	0	0	0
TOTALS		0	0	0	0	0	**0**
R&R Budget - Materials and Supplies	Animal-Resources-001 (001)	0	0	0	0	0	0
TOTALS		0	0	0	0	0	**0**
R&R Budget - Publication Costs	Animal-Resources-001 (001)	0	0	0	0	0	0
TOTALS		0	0	0	0	0	**0**
R&R Budget - Consultant Services	Animal-Resources-001 (001)	0	0	0	0	0	0
TOTALS		0	0	0	0	0	**0**

R&R Budget - ADP/Computer Services	Animal-Resources-001 (001)	0	0	0	0	0	0
TOTALS		0	0	0	0	0	**0**
R&R Budget - Subawards/Consortium/Contractual Costs	Animal-Resources-001 (001)	0	0	0	0	0	0
TOTALS		0	0	0	0	0	**0**
R&R Budget - Equipment or Facility Rental User Fees	Animal-Resources-001 (001)	0	0	0	0	0	0
TOTALS		0	0	0	0	0	**0**
R&R Budget - Alterations and Renovations	Animal-Resources-001 (001)	0	0	0	0	0	0
TOTALS		0	0	0	0	0	**0**
R&R Budget - Other Direct Cost 1	Animal-Resources-001 (001)	131,158	0	0	0	0	131,158
TOTALS		131,158	0	0	0	0	**131,158**
R&R Budget - Other Direct Cost 2	Animal-Resources-001 (001)	2,198	0	0	0	0	2,198
TOTALS		2,198	0	0	0	0	**2,198**
R&R Budget - Other Direct Cost 3	Animal-Resources-001 (001)	25,464	0	0	0	0	25,464
TOTALS		25,464	0	0	0	0	**25,464**
R&R Budget - Section F. Total Other Direct Cost	Animal-Resources-001 (001)	158,820	0	0	0	0	158,820
TOTALS		158,820	0	0	0	0	**158,820**
R&R Budget - Section G. Total Direct Cost (A thru F)	Animal-Resources-001 (001)	178,418	0	0	0	0	178,418
TOTALS		178,418	0	0	0	0	**178,418**

R&R Budget - Section H. Indirect Costs	Animal-Resources-001 (001)	140,237	0	0	0	0	140,237
TOTALS		140,237	0	0	0	0	**140,237**
R&R Budget - Section I. Total Direct and Indirect Costs (G +H)	Animal-Resources-001 (001)	318,655	0	0	0	0	318,655
TOTALS		318,655	0	0	0	0	**318,655**

Senior/Key Personnel
Summary

Name	Organization	Role on Project	Components
Gracy, Robert	Texas Biomedical Research Institute	PD/PI(Contact)	Overall
Excluded by Requester	Texas Biomedical Research Institute	Co-Investigator	Animal-Resources-001 (001)
	Texas Biomedical Research Institute	Other: Project Lead	Animal-Resources-001 (001)

Program Director/Principal Investigator (Last, First, Middle):

Excluded by Requester

Program Director/Principal Investigator (Last, First, Middle):

Excluded by Requester

Program Director/Principal Investigator (Last, First, Middle):

Excluded by Requester

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

Excluded by Requester

Excluded by Requester

Excluded by Requester

Excluded by Requester

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

Excluded by Requester

Excluded by Requester

Excluded by Requester

Excluded by Requester

OMB Number: 4040-0010
Expiration Date: 06/30/2016

Project/Performance Site Location(s)

Project/Performance Site Primary Location

● I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	Texas Biomedical Research Institute
Duns Number:	007936834
Street1*:	7620 NW Loop 410
Street2:	
City*:	San Antonio
County:	Bexar
State*:	TX: Texas
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	78227-5301
Project/Performance Site Congressional District*:	TX-020

File Name

Additional Location(s)

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* ○ **Yes** ● **No**

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ○ Yes ○ No

If YES, check appropriate exemption number: __ 1 __ 2 __ 3 __ 4 __ 5 __ 6

If NO, is the IRB review Pending? ○ **Yes** ○ **No**

IRB Approval Date:

Human Subject Assurance Number

2. Are Vertebrate Animals Used?* ● **Yes** ○ **No**

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ○ Yes ● No

IACUC Approval Date: 03-14-2014

Animal Welfare Assurance Number A3082

3. Is proprietary/privileged information included in the application?* ○ **Yes** ● **No**

4.a. Does this project have an actual or potential impact - positive or negative - on the environment?* ○ **Yes** ● **No**

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ○ Yes ○ No

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place?* ○ **Yes** ● **No**

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* ○ **Yes** ● **No**

6.a. If yes, identify countries:

6.b. Optional Explanation:

	Filename
7. Project Summary/Abstract*	Overall___Project_Summary___REV1006418443.pdf
8. Project Narrative*	Overall___Project_Narrative1006418433.pdf
9. Bibliography & References Cited	Bibliography_and_References1006418430.pdf
10.Facilities & Other Resources	
11.Equipment	

PROJECT SUMMARY

The objective of grant P51-OD011133 to Texas Biomedical Research Institute is to continue support of the infrastructure of the Southwest National Primate Research Center (SNPRC). This base grant enables the SNPRC to be responsive to national biomedical research needs and to accommodate investigators who want to access Center resources for collaborative research purposes.

The Southwest National Primate Research Center has an active and growing program to develop and supply the common marmoset (*Callithrix jacchus*) as a biomedical research resource. We propose to further enhance this SNPRC resource through the inclusion of a segment of the marmoset colony from the New England Primate Research Center. This addition will provide SNPRC with two genetically distinct colonies of marmosets that can be utilized for infectious disease, metabolic disease, aging and regenerative medicine research. This revised proposal requests support for this activity.

The overall aims of the marmoset colony in the last competitive renewal were to: (1) continue production of marmosets for use in biomedical research; (2) further consortium arrangements with Wisconsin NPRC, New England PRC and the NIH Intra-mural program. Two specific goals within this aim are to have a defined, accepted profile of a marmoset diet and a SNP panel that can be used as a tool to define best animal use and animal breeding; (3) continue comparison of the SPF, barrier-maintained marmoset colony with the conventionally housed colonies, in order to identify those aspects of research use (e.g., healthy longevity) which will specifically benefit from this SPF, barrier approach to colony management and animal production.

The following revised additional aims are proposed with the addition of the NEPRC marmosets to the SNPRC: (1) continue production of marmosets for use in biomedical research with the NEPRC marmosets contributing to that continued production. The NEPRC marmosets will be maintained as a separate population (hereafter referred to as Colony 2), with husbandry and diet maintained as closely as possible to the original NEPRC protocols. The increased size of the total colony will greatly enhance our ability to meet the needs of NIH-funded investigators, some of which used the marmoset model at NEPRC; (2) conduct planned comparisons of factors that represent important sources underlying phenotypic variation within and among marmoset populations. These comparisons will provide a means to identify best practices as regards to husbandry and best methods for assigning subjects to studies or breeding in relation to genetic variation. This aim will be conducted in collaboration with the Wisconsin NPRC; (3) establish a specific resource of geriatric marmosets to be used in studies of aging and chronic disease.

PROJECT NARRATIVE

The Southwest National Primate Research Center (SNPRC) facilitates innovative biomedical research that advances human health through provision of nonhuman primate-related resources to investigators from around the country. The SNPRC maintains colonies of baboons, macaques, marmosets, and chimpanzees for support of biomedical research projects. The Center also has internal research efforts focused on genomics, metabolic disease, infectious disease, and behavior. The marmoset resources of the SNPRC have supported basic and translational research in infectious diseases, regenerative medicine, obesity and aging.

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: Dr | First Name*: Robert | Middle Name | Last Name*: Gracy | Suffix:

Position/Title*:	President
Organization Name*:	Texas Biomedical Research Institute
Department:	Administration
Division:	
Street1*:	7620 NW Loop 410
Street2:	
City*:	San Antonio
County:	Bexar
State*:	TX: Texas
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	78227-5301

Phone Number*: 210-258-9508 | Fax Number: | E-Mail*: rgracy@txbiomed.org

Credential, e.g., agency login: eRA Commons User Name

Project Role*: PD/PI | Other Project Role Category:

Degree Type: | Degree Year:

	File Name
Attach Biographical Sketch*:	BIO_Gracy_RW_08_06_141006418446.pdf
Attach Current & Pending Support:	

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

1. Project Director / Principal Investigator (PD/PI)

Prefix: Dr
First Name*: Robert
Middle Name:
Last Name*: Gracy
Suffix:

2. Human Subjects

Clinical Trial? ○ No ○ Yes
Agency-Defined Phase III Clinical Trial?* ○ No ○ Yes

3. Permission Statement*

If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)?

○ Yes ● No

4. Program Income*

Is program income anticipated during the periods for which the grant support is requested? ● Yes ○ No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

Budget Period*	Anticipated Amount ($)*	Source(s)*
1	53,466.00	Animal Sales

PHS 398 Cover Page Supplement

5. Human Embryonic Stem Cells

Does the proposed project involve human embryonic stem cells?* ● No ○ Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Cell Line(s): Specific stem cell line cannot be referenced at this time. One from the registry will be used.

6. Inventions and Patents (For renewal applications only)

Inventions and Patents*: ○ Yes ○ No

If the answer is "Yes" then please answer the following:

Previously Reported*: ○ Yes ○ No

7. Change of Investigator / Change of Institution Questions

❑ Change of principal investigator / program director

Name of former principal investigator / program director:

Prefix:

First Name*:

Middle Name:

Last Name*:

Suffix:

❑ Change of Grantee Institution

Name of former institution*:

PHS 398 Research Plan

Please attach applicable sections of the research plan, below.

OMB Number: 0925-0001

1. Introduction to Application (for RESUBMISSION or REVISION only)	Overall___Introduction1006418428.pdf
2. Specific Aims	Overall___Specific_Aims1006418431.pdf
3. Research Strategy*	Overall___Research_Strategy1006418427.pdf
4. Progress Report Publication List	
Human Subjects Sections	
5. Protection of Human Subjects	
6. Inclusion of Women and Minorities	
7. Inclusion of Children	
Other Research Plan Sections	
8. Vertebrate Animals	Overall___Vertebrate_Animals1006418429.pdf
9. Select Agent Research	
10. Multiple PD/PI Leadership Plan	
11. Consortium/Contractual Arrangements	
12. Letters of Support	
13. Resource Sharing Plan(s)	
Appendix (if applicable)	
14. Appendix	

INTRODUCTION.

The purpose of this revision to the SNPRC P51 base grant is to provide a second year of support for the SNPRC Marmoset Colony 2. The SNPRC Marmoset Colony 2 was derived from a portion of the NEPRC marmoset population. Colony 1 is the historical marmoset colony housed at SNPRC since 2001, and its support is currently provided by the base grant and project income. The first year of support for Colony 2 was provided as a supplement to the base grant. This funding was to cover the cost of quarantine and maintenance from the time of arrival (late 2014 and early 2015) until the P51 noncompetitive renewal date of April 30, 2015. We will experience a lapse in funding for these animals from May 1, 2015 to September 30, 2015, the projected start date of this Revision of the P51. We have sufficient funds to cover the animals during this lapse in funding. The Revision plus project income will cover the maintenance of these animals until the projected competitive renewal date for the P51 base grant (5 P51 OD011133-17) on May 1, 2016.

SPECIFIC AIMS.

The objective of this proposal is to continue support of the infrastructure of the Southwest National Primate Research Center (SNPRC). The SNPRC is located on the campus of the Texas Biomedical Research Institute, its host institution. The SNPRC maintains approximately 2,500 nonhuman primates, primarily baboons, macaques, marmosets, and chimpanzees. The base grant is composed of Administration components; Service components which include the veterinary and behavioral units; the Animal Colony components for the baboons, macaques, marmosets, and chimpanzees; the Research Facilitation Groups; and the Core Laboratories. These units provide expertise, training and support to investigators conducting research at the Center.

The base grant enables the SNPRC to be responsive to national biomedical research needs and to accommodate investigators who want to access Center resources for collaborative research purposes. Two genetically distinct colonies of marmosets are utilized for infectious disease, metabolic disease, aging and regenerative medicine research. The research opportunities at SNPRC and its host institute Texas Biomed include high containment research in primates at ABSL-3 and ABSL-4. SNPRC and Texas Biomed have a long history of research emphasis on genetic factors influencing common chronic diseases, development of vaccines, and therapeutics for infectious disease. More recently programs in regenerative medicine using stem cell biology and aging have been developed.

The SPECIFIC AIMS of the SNPRC as a whole are unchanged from the last competitive renewal and are listed below.

1) To maintain healthy and well-characterized breeding and research colonies of several nonhuman primate species that are required for biomedical research, and to make them available to qualified investigators.
2) To maintain and enhance veterinary and research technical capacities for research with nonhuman primates and to make them available to investigators.
3) To maintain and to enhance the physical and administrative infrastructure of the NPRC so that it can best serve biomedical research.
4) To advance training of staff, students, and visitors in the care and use of nonhuman primates in biomedical research.
5) To contribute to advances in science and translational medicine via publication of results obtained from research with nonhuman primates and educational outreach to the public.

The overall aims of the marmoset colony in the last competitive renewal were:

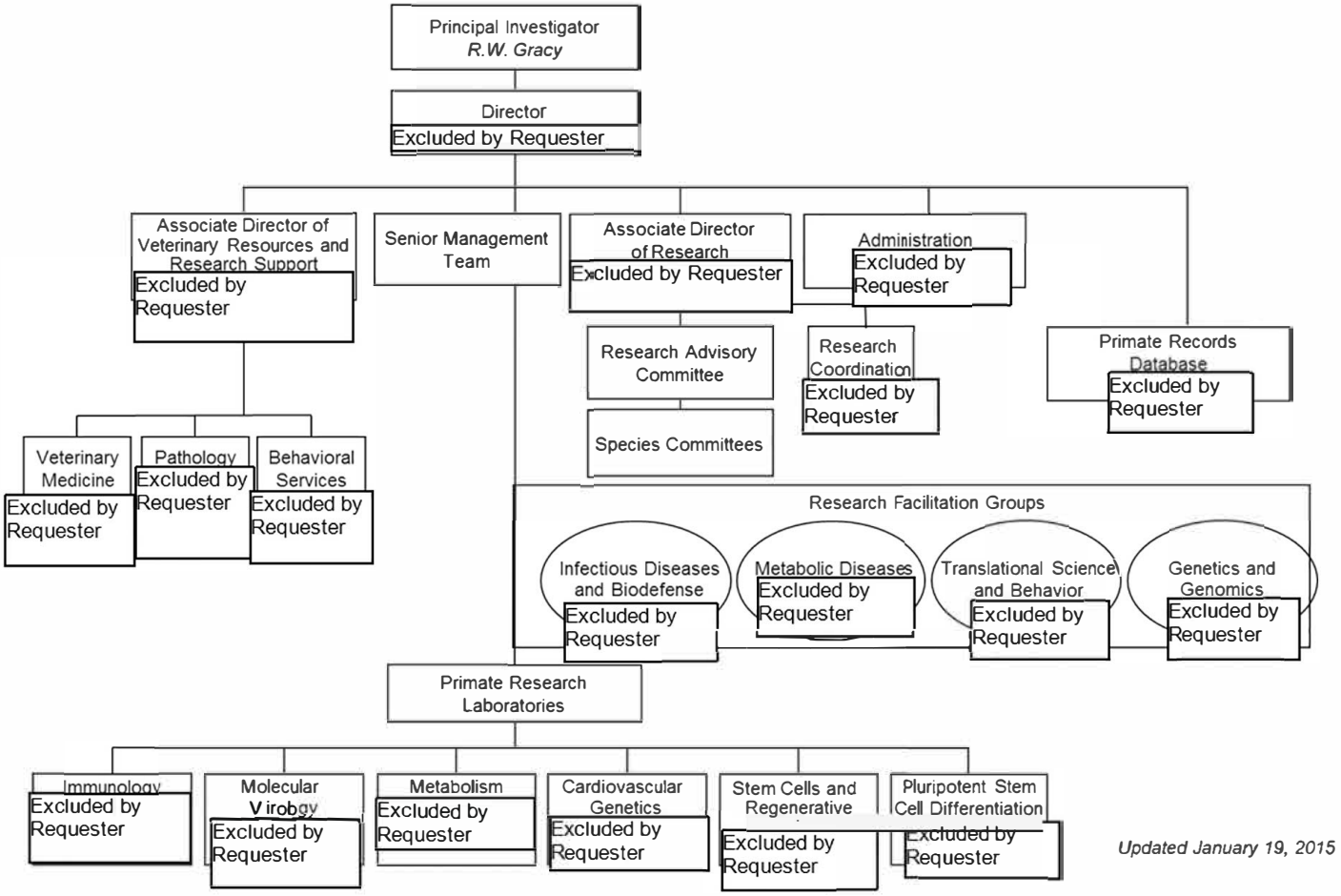
Aim 1: To continue production of marmosets for use in biomedical research.
Aim 2: To further consortium arrangements with Wisconsin NPRC, New England PRC and the NIH Intra-mural program. Two specific goals within this aim are to have a defined, accepted profile of a marmoset diet and a SNP panel that can be used as a tool to define best animal use and animal breeding.
Aim 3: To continue comparison of the SPF, barrier-maintained marmoset colony with the conventionally housed colonies, in order to identify those aspects of research use (e.g., healthy longevity) which will specifically benefit from this SPF, barrier approach to colony management and animal production.

The following **revised additional aims** are proposed with the addition of the NEPRC marmosets to the SNPRC:

Aim 1: To continue production of marmosets for use in biomedical research with the NEPRC marmosets contributing to that continued production. The NEPRC marmosets will be maintained as a separate population, with husbandry and diet maintained as closely as possible to the original NEPRC protocols. The increased size of the total colony will greatly enhance our ability to meet the needs of NIH-funded investigators, some of which currently use the marmoset model at NEPRC.
Aim 2: To conduct planned comparisons of factors that represent important sources underlying phenotypic variation within and among marmoset populations. These comparisons will provide a means to identify best practices as regards to husbandry and best methods for assigning subjects to studies or breeding in relation to genetic variation. This aim will be conducted in collaboration with the Wisconsin NPRC.
Aim 3: To establish a specific resource of geriatric marmosets to be used in studies of aging and chronic disease.

RESEARCH STRATEGY

SOUTHWEST NATIONAL PRIMATE RESEARCH CENTER



Background and mission of NPRC. On June 1, 1999, the Southwest National Primate Research Center (SNPRC) became the first new National Primate Research Center (NPRC) established since the early 1960s. The SNPRC brought a number of unique strengths to the NPRC program, stemming from a long, productive history of nonhuman primate research at its host institution, the Texas Biomedical Research Institute (Texas Biomed), previously known as the Southwest Foundation for Biomedical Research. The unique strengths that existed prior to becoming an NPRC included the world's largest captive baboon population that represents the oldest and best-characterized pedigreed for a nonhuman primate population, the largest chimpanzee census of any NRPC, and a veterinary technical staff experienced in the management and use of diverse species of nonhuman primates including chimpanzees, baboons, macaques and marmosets.

Over the first 16 years as a NPRC. the SNPRC has enhanced those strengths and has developed many new strengths. In 2001, the arrival of Excluded by Requester as the Associate Director also marked the commitment to maintain a large marmoset breeding colony (one of only two currently at NPRCs). Although marmosets had been housed at SNPRC at various times in the past, this would represent an effort to maintain a national resource that continues today. In 2014, SNPRC was selected as one of the recipients of the marmoset population from NEPRC such that SNPRC now provides access to two marmoset colonies that are maintained as physically and genetically separate populations. The maintenance of the NEPRC marmosets is the subject of this Revision application. The duration of support being requested is for less than one year. In addition, to the two SNPRC colonies, SNPRC collaborated with the Barshop Institute for Longevity and Aging at UTHSCSA to create a barrier colony of marmosets at that facility for use in long term aging studies. The collaboration was strengthened during a period time when Excluded by Requester had her primary appointment at the Barshop (2006-2014) and is further enhanced now that Excluded by Requester has resumed her role as the Associate Director of Research at SNPRC.

In the area of infectious disease research, SNPRC has maintained a focus in hepatitis and HIV since 1984 with the creation of the Department of Virology and Immunology by the host institute. In 2000, SNPRC acquired a unique SPF Indian-origin rhesus macaque population from the U.S. Air Force for SIV research, and in 2014, SNPRC was selected to be one of the recipients of the rhesus population from NEPRC. With the arrival of the NEPRC animals, the census of SPF Indian-origin rhesus macaques will be 740 and will continue to expand over the next few years. Hepatitis C virus research represented a major emphasis at SNPRC until recently. With the reduction in use of chimpanzees as a research animal model and the development of antiviral cocktails that cure HCV in 12 weeks (many of the preclinical studies were performed at SNPRC), this program will decrease while SNPRC will maintain a presence in HBV research.

The area of infectious diseases continued to expand at both TxBiomed and SNPRC with the development of high containment research in ABSL-3 and ABSL-4 facilities capable of research with nonhuman primate. In Excluded by Requester became the director of the Nonhuman Primate Core of the Western Regional Center of nce for Biodefense and Emerging Infectious Diseases Research (WRCE), in partnership with UTMB and other institutes. This core included the resources of the SNPRC and the Tulane NPRC. This provided the ability to initiate our program of NHP infectious disease research in the ABLS3 laboratories. Over time this affiliation with WRCE was discontinued, as our high containment research program expanded. The ABSL4 at TxBiomed is the only such facility available in affiliation with an NPRC. The research programs in the ABSL4 are under the Department of Virology and Immunology at TxBiomed, while the care of animals in this facility is provided by SNPRC.

SNPRC has always been one of the leaders in specialized genetic resources including a baboon gene linkage map (the first for any nonhuman primate species). We have greatly expanded our capabilities in the genetic analyses of multiple species of NHP. We are currently developing the methods for high throughput sequencing of the total genome of baboons, macaques and marmosets. Not only will this information be used to genetically manage our primate populations, but it will strengthen the research being conducted in these primate Excluded by Requester ions. This effort is led by the Leader of the Genomics Core Laboratory. In this approach, using high throughput sequencing methods to collect high-resolution genetic information on most of the animals in each of the colonies. This data will identify tens of thousands of variations and this information will be used to maximize genetic variation in the breeding structure of the colony. Our approach of genotyping by sequencing provides a cost effective means to identify variants in regions of the genome that harbor single copy genes. The new genetic data will dramatically increase the value of our NHP resources by providing the means to perform detailed investigations into gene by environment interactions in our NHP models of human disease.

We will continue to provide broad services in primate research to the national research community with an emphasis on specialized technologies, capabilities, and primate resources, many of which are unique to the SNPRC. We will continue to provide collaborative opportunities and services to outside investigators and to conduct technical procedures requested by them; and we will continue to contribute ideas and perspectives about how best to accomplish the goals of their projects, thereby increasing the productivity and efficiency of the research, and strengthening the value of the data derived from it.

Restructuring of the SNPRC and Texas Biomed Administrations. A number of significant changes have occurred in the leadership of both SNPRC and its host institute, Texas Biomedical Research Institute (Texas Biomed) during the past year. These changes have brought new strengths and expertise to the SNRPC Administration and have provided a clear delineation between the primate center and the host institute. The changes were initiated following the announcement by Excluded by Requester the Founding Director of SNPRC (1999), that Personal Info was both the Director of SNPRC and the Chief Scientific Officer of Texas Biomed. The perceived conflict of interest from this dual position and Excluded by Requester ension of effort by had been an area of concern in previous reviews of SNPRC. Dr. Personal Info provided an opportunity to restructure both the SNPRC and its relationship to the host institute for the first time, since the inception of SNPRC in 1999.

Excluded by Requester was selected as the Interim Director. After a period of enthusiastic support by the leadership and staff of both SNPRC and Texas Biomed, assumed the role as permanent Dir Excluded by Requester on July 30, 2014. Excluded by Requester (President of Texas Biomed) visited NIH in April to m

with Excluded by Requester and the ORIP leadership to discuss concerns for SNPRC future plans, and the pledge of Excluded by Requ by Texas Biomed to SNPRC and In September, Personal Info Personal Info as the Deputy Director of SNPRC and the Chair of the Department of Genetics at Texas Biomed to become the Director of the South Texas Diabetes and Obesity Institute at the newly formed University of Texas Rio Grande Valley. Several of her close colleagues from the Department of Genetics will join her over the next few months in this new Institute. SNPRC will maintain close relationships with this group of outstanding scientist, since many will continue to have collaborations with scientist at SNPRC. Texas Biomed has pledge support to the staff of the Department of Genetics for the recruitment of new faculty that will emphasize new strengths by the reorganized department. These new strengths in the Department of Genetics will provide a greater diversity of expertise for collaborations within the SNPRC.

Excluded by Requester moved rapidly to replace the vacancy created by the move of Excluded by Requester Excluded by Requester r ecruite Excluded by Requester to become the Associate Director of Research at SNPRC starting in Excluded by Requester y of 2015 Excluded by Requester will take on the previous responsibilities of Excluded by Requester but will do much more in the area of development of new research programs, building on our current strengths and Excluded by Requester pment of new strengths was previously the Associate Director of Research at SNPRC from 006. Since then, she has been the Director of the Marmoset Aging Center at the Barshop Institute for Longevity and Aging Studies at the University of Texas Health Science Center in San Antonio. During this period Excluded by Requester continued to be a Core Scientist at SNPRC and the Leader of the Marmoset Colony. In collaboration with SNPRC, Excluded by Requester created a barrier colony for marmosets at the Barshop Institute, to allow long term aging studies without the variable influences of infectious diseases. SNPRC and the Barshop will both benefit with assuming this new position Excluded by Requester Excluded by Requester ipated that will foster interactions between the two institutes on new programs in NHP a generative medicine.

One other significant change in leadership occurred with Personal Info as the President of Texas Biomed and the PI of the base grant. This change was anticipated. Dr. Robert Gracy moved from Chief Scientific Officer of Texas Biomed to the Interim President in a seamless transition. The Board of Trustees for Texas Biomed is currently searching for a new President that has both a strong scientific background and outstanding administrative skills. Texas Biomed is not currently seeking to replace the vacancy of Chief Scientific Officer. It is perceived that the right candidate for the position of President and distribution of some of the CSO responsibilities to other positions will make that position unnecessary. The Director of the SNPRC agrees with this assumption, but this decision will be made after a new President has been in office for a period of time.

NPRC and Host Relationship. The Texas Biomedical Research Institute serves as the host institution for the SNPRC. Texas Biomed began to establish its nonhuman primate facilities and resources in 1958 and has a long tradition of biomedical and behavioral research with nonhuman primates. As summarized in the application, Texas Biomed has provided generous financial support to the SNPRC since its inception, and continues to do so in a variety of ways. The Texas Biomed Interim President, Robert W. Gracy, Ph.D., is the Principal Investigator of the base grant. Dr. Gracy assumed the position of Interim President in 2014 following Personal Info TxBiomed has an active search ongoing for a new President that will have strong scientific and administration leadership skills Excluded by Requester reports directly to the President in the organization chart for SNPRC. Texas Biomed and SNPRC have a unique relationship due to the emergence from a single institute prior to 1999 and the continued sharing of a campus. Some aspects are clearly part of the host institute, the research departments; Department Virology and Immunology and the Department of Genetics are based in the host institute and the chairs of these departments report to the President of Texas Biomed. However, many of the scientists in these Departments are Core Scientist for SNPRC and provide other essential functions, e.g. Leaders of Core Laboratories. Many support functions are shared by Texas Biomed and SNPRC, with the host institute paying for the support service e.g. Human Resources, Information Technology, Public Relations, Office of Environmental Health and Safety (biosafety and select agent programs are based here), IACUC, library, technical publications, print shop, and maintenance department (SNPRC also has a dedicated maintenance shop). SNPRC has its own Administration Group led by an Assistant Director, Excluded by Requester which tracks and bills all animal costs, prepares grant budgets and monitors grant expenses. The SNPRC Administration Group works seamlessly with the Texas Biomed Finance and Accounting Offices and the Office of Sponsored Programs with regard to much of the grant and financial

functions of SNPRC. The use of shared resources dramatically increases the efficiency of SNPRC and reduces the total support required for SNPRC to function. The support by the host institute goes for beyond what is recognized here and includes assistance with facility renovation and capital equipment. The renovation of a building for the NEPRC macaques was financed with a supplement from NIH and a contribution from Texas Biomed of $267,000. Some of the equipment needed for both the marmosets and the macaques coming from NEPRC was supplied by NIH, but a substantial portion was funded by Texas Biomed.

Texas Biomed is closely allied with The University of Texas Health Science Center at San Antonio (UTHSC-SA), and many faculty based at each institution have cross appointments or adjunct appointments at the other. Some faculty based at Texas Biomed participate in teaching courses at UTHSC-SA, and some of the graduate students at that institution that do their research at Texas Biomed under the supervision of a Texas Biomed faculty member as their major professor. Some of those Texas Biomed faculty members are SNPRC Core Scientists and others are Affiliate Scientists. Both institutions are leading members of the Southwest Research Consortium, which includes a total of nine institutions in the San Antonio area committed to combining their resources to foster biomedical research.

Recruitment. The SNPRC's scientific programs have been greatly strengthened in recent years by several major recruitments into either Texas Biomed or SNPRC. Texas Biomed's Department of Virology and Immunology added a faculty member in 2012, Excluded by R equester who initiated his nonhuman primate research at ABSL4 with a pilot grant from SNPRC using marmosets. Excluded by R equester a proteomics specialist, joined the Department of Genetics in 2013 as a Scientist but in 2014 was selected to become the Chair of the department with the departure of Excluded by R equester joined Texas Biomed in the Excluded by Requester ment of Virology and Immunology. has a strong SIV/HIV research program that will rely on the SPF macaque colony at SNPRC. She has just initiated a large vaccine study funded by Private Source Private Source In 2014, SNPRC recruited two scientists in the area of stem cell research. Dr. Excluded by Requester works in the area of neural stem cells (Parkinson's Disease, stroke and brain trauma), and Dr. Excluded by Requester works on retinal stem cells (macular degeneration and eye trauma), as well as muscle stem cells (Muscular Dystrophy). Regenerative Medicine will be a clear focus in the renewal of the base grant with the creation of the Aging and Regenerative Medicine Scientific Unit lead by Excluded by R equester A critical mass of stem cell regenerative medicine researchers in San Antonio has developed as a result of recruiting efforts at the University of Texas Health Science Center, San Antonio, the University of Texas, San Antonio, Texas Biomed, and the SNPRC. To a large extent, this was recognized by choosing San Antonio to host the 2014 World Stem Cell Summit, the largest meeting dedicated to stem cell advancements. Excluded by R equester was recruited in 2015 to be the Associated Director of Research for SNPRC. Her strength in nonhuman primate research will impact nearly every research program on campus. This will be particularly evident in all Excluded by R equester ch using marmosets is the most experienced scientist in the country in this area, but she will llaborate in many of the efforts on aging, regenerative medicine and reproductive biology, which are emerging disciplines at SNPRC.

Expansion of Facilities. The new Earl Slick Research Center officially opened in April of 2014. This complex includes new laboratory and administration space for the Southwest National Primate Research Center. The Office of the SNPRC Director, Associate Director of Research, and Assistant Director for Administrative Services is housed in this building. SNPRC occupies the first floor of this building with both office and laboratory space. The space includes 7,128 net square feet of assignable laboratory space (eight BSL-2 laboratory modules), 1,772 net square feet of shared support space (blood processing, freezers, autoclave, etc.), and 6,079 net square feet of office space for research staff and Center administration.

Organization and Administration of SNPRC. The Organizational structure of SNPRC is presented in the Org Chart at the beginning of the Overall Research Plan. The Director reports to the PI of the base grant which is the President of Texas Biomed (Dr. Robert Gracy) for SNPRC. This relationship provides SNPRC with a direct and major voice on matters of importance to the host institute and SNPRC. SNPRC has two Associate Directors, Excluded by R equester is the Associate Director of Research and oversees Research Coordination, the Research Advisory Committee and the Species Committees. Research Coordination is responsible for interaction with the investigators to initiate and monitor experimental programs. Excluded by Requester is the Associate Director of Veterinarian Resources and Research Support and oversees the management of the animal colonies and implementation of experimental procedures. Excluded by Requester oversees the veterinarians, the

animal care staff and the veterinary technicians. The Assistant Director of Veterinary Resources is currently being recruited. Research Coordination and Veterinary Resources are highly interactive groups. The SNPRC [redacted] stration Group is led by the Assistant Director, [redacted] This group tracks and bills all animal [redacted] prepares grant budgets and monitors grant expenses. The SNPRC Administration Group works seamlessly with the Texas Biomed Finance and Accounting Offices and the Office of Sponsored Programs. All of the above Directors meet weekly in the Senior Management Team to discuss current issues that need to be addressed, to implement new directives, and to discuss long term planning for SNPRC. The Research Advisory Committee is comprised of the Core Scientist that are responsible for major components on the base grant or play instrumental roles at SNRPC. Each of the species is managed by a Species Advisory Committee that meets monthly and is comprised of a member of Research Coordination, at least one Veterinarian, and several Core Scientist. Many of the species have additional committees to perform functions beyond those normally handled by the Advisory Committees. All committees have representation within RAC to allow for appropriate dissemination of information and planning.

Excluded by Requester

OVERVIEW OF PRIMATE COLONIES

MARMOSET COLONIES

The common marmoset (*Callithrix jacchus*) is a small, South American primate poised to become a vital biomedical research resource. As a non-endangered anthropoid primate with small size, the highest fertility and the shortest life span, this species offers a remarkably cost-effective, high efficiency nonhuman primate model for biomedical research. In addition, many areas of research take advantage of unique features of its biology for application to human disease. The potential of the common marmoset to advance biomedical research in the United States is threatened, however, by its small and declining captive population. This proposed project will address these concerns through increased breeding and comparative studies aimed at development of more standardized management.

There has been an increasing expression of concern in the scientific community regarding the relatively low rate that therapeutic findings in rodents translate to effective therapies in humans (2,4-5,7,12-13) and models more closely related to humans are part of addressing these concerns. However, the large size, high zoonotic risk, slow reproduction and high cost associated with most nonhuman primates limit their usefulness as translational models. Combining close phylogenetic relationship to humans with the shortest lifespan and smallest sizes possible can help to make nonhuman primate translational research more affordable and feasible for a wider array of projects.

History and Breadth of Use

Common marmosets have been a biomedical research resource since the early 1960's, used predominately in studies of infectious disease, immunology and neuroscience. Historically, they have been a more commonly used research model in Europe and Japan than in the United States. However, cellular and molecular resources have recently been developed that greatly enhance the value of marmosets in research and have increased interest in the US. These include sequencing and annotation of the marmoset genome (22), development of marmoset-derived, induced pluripotent stem (iPS) cell lines (23), and the use of marmosets to develop the first transgenic nonhuman primate with germline transmission (11).

There is a continuing increase in publications using marmosets. A recent review [redacted] cites immunology/immunopathology, neuroscience, cognition, sleep behavior/circadian rhythm, obesity, infect disease and reproduction as areas in which the marmoset has demonstrated value as a preclinical and translational model. Of the 500 articles specifically citing common marmoset use in 2012-13 (Ovid Medline), approximately 50% were studies in neuroscience studies, 19% in reproduction and transgenics, 12% in infectious disease and immunology and 9% in obesity and metabolic function.

Excluded by Requester

One notable area of developing use is in infectious disease studies, particularly those involving high biocontainment agents. At SNPRC, the demand for marmosets for ABSL4 projects increased by over 60% between 2010 and 2011. Proposals currently in our queue would demand an additional 40 animals per year for this use, alone. Marmosets, and the closely related tamarin species, are the only nonhuman primates that can serve as a proxy model for Hepatitis C. GBV-B, a native tamarin virus, has high homology with human

Hepatitis C virus and has been used successfully in the past in vaccine testing. With the extremely limited resources available for research on Hepatitis C, this model use may be particularly relevant.

Unique Biological Features of Marmosets. In addition to their value as a model system that is phylogenetically closely related to humans, there are unique features of this group of primates that make marmosets particularly valuable for certain types of studies.

Small body size: Adult common marmosets weigh 300-400 grams.
Twinning: In the wild, marmosets typically produce dizygotic twins. In captivity, they often produce even larger, multi-zygotic litters of triplets or quadruplets. While obviously contributing to the fast pace at which populations can expand, these litters also offer unparalleled opportunities to conduct litter-matched studies in which two or more nonhuman primate siblings share the same prenatal environment.
Hematopoietic Chimerism: Marmosets born into the same litter are hematopoietic chimeras, sharing hematopoietic stem cells during development (14). This unusual developmental process results in littermates that share an immunologic profile and are immunologically tolerant to tissue transplants from each other. The use of immunologically matched littermates as paired control and test subjects greatly increases the power of infectious disease studies. In addition, the ability to perform T cell adoptive transfers between litter mates has been a valuable tool in the development of autoimmunity models in this species.
Lissenphalic Cortex: While marmosets have a rat-like body size, they have a primate-typical brain size of 2% of body weight, unlike a rat-typical 0.5%. However, marmosets combine the features of a nonhuman primate brain - such as large overall size, a large prefrontal cortex, reduced olfactory regions, and expansion of the cerebrum in relation to an enhanced visual system – with a smooth, or lissenphalic cortical surface. This lissephalic surface in a nonhuman primate brain is a significant advantage in neuroscience studies requiring manipulation of, or sampling from, given brain regions.
Fast Maturation and Short Life Span: Many of the most pressing U.S. human health concerns involve diseases that are chronic and for which aging is a strong risk factor. The fast maturation and relatively short life span of marmosets makes them a valuable resource to study chronic disease and aging. Marmosets are sexually mature at 16-17 months of age and display signs of age-related pathologies – such as beta-amyloid accumulation in the brain, impaired cochlear function and lean mass loss - by 8-13 years of age. This is a particularly attractive feature for transgenic models in which disease onset may depend on aging factors, such as neurodegenerative disorders like Parkinson's disease.
Unique opportunities for new nonhuman primate models through stem cell manipulations and transgenics:
A recent Editorial in Nature (Nov 6, 2013) entitled "Precision gene editing paves the way for transgenic monkeys" highlighted the use of genetically modified marmosets as a model for neurological disease. Using zinc finger nucleases individuals have created an animal model for autism and many more genetically modified marmoset lineages are expected in the near future. The marmoset due to size, rapid maturation and breeding is an idea animal for these purposes.
Marmosets present a unique opportunity for improving animal models for regenerative medicine: At a recent NIH workshop, the development of models that more accurately recapitulate diseases phenotypes were identified as a priority to ensure the success of stem cell based technologies. An example of possible application is the evaluation of personalized medicine using iPS-derived dopaminergic neurons for cell replacement in Parkinson's disease which is advancing towards clinical translation. In addition, a transgenic monkey model of Parkinson's disease would allow us to answer the question in nonhuman primates of whether the host's disease can spread to healthy grafted cells affecting their integration and function. An α-synuclein transgenic marmoset line has been developed as has the technology for production and derivation of neuritis from marmoset iPS cells. However, for these resources to significantly impact our understanding of PD and its treatment, these resources need to be readily available to a broad array of relevant investigators. That availability will be directly dependent upon an increased investment in production and maintenance of marmosets and associated resources in the United States.
Impediments to the Use and Development of this Model
The entire National Primate Research Centers (NPRC) marmoset population stands at approximately 650 animals. With smaller populations at other institutions (e.g., Johns Hopkins Medical School, University of California at San Diego) supporting the efforts of 1-2 investigators, we estimate that there is a US marmoset research population of less than 1,000 animals. Of those animals, less than 10% are available for expanded uses – i.e. the huge majority are already committed to on-going projects or to production. The NPRC system supports on-going projects that use, on average, 340 animals per year, with approximately half of those in

terminal studies and over 95% of those projects being federally funded. In the past four years, NPRC marmoset studies have included projects funded through NIA, NIAID, NICHD, NIEHS, NIDCD, NIDDK, and NINDS.

The SNPRC as an ideal environment for developing marmoset research resources

The SNPRC is one of only two NPRCs with the infrastructure and expertise already in place to not only maintain but further develop marmosets as a research resource. SNPRC is a part of the Texas Biomedical Research Institute (Texas Biomed). Texas Biomed is among the top ten independent, non-profit organizations dedicated to research on human diseases. Founded in 1941, Texas Biomed is comprised of two research departments, the Department of Genetics and the Department of Virology and Immunology and is the host institute for the SNPRC. The Department of Genetics focuses on characterizing the genetic components of susceptibility to common diseases in humans through the use of human and non-human primate populations. Cardiovascular disease, diabetes and obesity, fetal growth and development, osteoporosis, epilepsy, and mental illnesses are among the many well-established research focuses for this group. The department houses the world's largest computer cluster for human genetic and genomic research, the AT&T Genomics Computing Center, which currently contains 9,000 processors working in parallel to analyze the data to help scientists find disease-influencing genes. This capacity is critical to the high throughput sequencing of the marmoset genome. The Department of Virology and Immunology focuses on a broad array of human infectious diseases, including AIDS, hepatitis, and herpes virus. There is a research emphasis on high containment agents known as potential bioterror agents due to their high morbidity and mortality in humans, such as Ebola and Marburg viruses, SARS, avian flu and anthrax. The work on these agents is performed at Biosafety Level 4 (BSL4). Texas Biomed operates the only privately owned ABSL4 laboratory and is a leader in vaccine development for these agents.

The SNPRC provides an unparalleled combination of nonhuman primate resources and specialized scientific resources and capabilities for support of collaborative research activities. A unique asset that the host institution, Texas Biomed has pioneered over the last 30 years is its capabilities in genetic and demographic management, genotyping, gene mapping and genetic analysis techniques for nonhuman primates. We have unparalleled capabilities in genetic analysis and have developed a wide variety of analytical strategies and software packages for analyzing genetic data (1,6).

The SNPRC and its host institution, Texas Biomed, have a strong commitment to the development of resources needed for infectious disease research using nonhuman primates. Texas Biomed is the only institution in the country that has both a National Primate Research Center and a Biocontainment Level 4 laboratory which is available for experiments with monkeys, as well as NHP Biocontainment Level 3 housing. The combination of expertise in experimental manipulation of nonhuman primates and expertise in maximum biocontainment, positions the SNPRC to play a critical role in studies of select agents and emerging pathogens. Marmosets have played an important role as one of the NHP models for filovirus research including Ebola virus.

SNPRC provides access to three main nonhuman-primate species for biomedical research – a large, pedigreed baboon colony, a SPF rhesus macaque colony, and a marmoset colony. SNPRC presently houses two genetically and nutritionally distinct marmoset colonies, the original SNPRC colony and a colony derived from the NEPRC colony. In addition, in collaboration with the Barshop Institute for Longevity and Aging Studies at University of Texas Health Science Center at San Antonio, we have developed a barrier colony of marmosets for aging studies that are SPF for two viruses of marmoset origin and maintained on sterilized food and water to prevent infection with endoparasites and other pathogens.

Progress relevant to the Revision. We renovated a new building for housing the new marmoset population. They will be maintained physically and genetically separate for the foreseeable future. By January 28, we will have relocated >180 marmosets from NEPRC to SNPRC. The animals were shipped in intact social units as much as is possible given limitations of transport crate size. We set up the marmosets in caging configurations that, as closely as possible, mirrored their configuration at NEPRC, in terms of identity of neighboring groups. The primary aim of the coming grant period is to produce marmosets and provide them to NIH-supported investigators. Maintaining the SNPRC and NEPRC populations as separate entities, provides opportunities for the design and implementation of plans to determine the effects of dietary change upon health and microbiome in these two marmoset populations, ultimately defining the best diet for continued use. We will also define the

genetic diversity in the two populations. Based upon these findings, we will structure a long-term management plan to most effectively maintain the diversity present in the populations. This will include total genome high throughput sequencing as mentioned under Baboon Colony and will be conducted by the Genomics Core Laboratory.

BABOON COLONY

SNPRC provides baboons from the oldest and most highly characterized pedigree of nonhuman primates available for research. The goal of this colony is to provide pedigreed baboons for research projects investigating the etiology and pathogenesis of human diseases. The close physiological similarities between baboons and humans make baboons excellent models for a broad range of disease-related phenotypes. For more than three decades, we have developed and refined the baboon model for biomedical research through selective breeding, environmental and surgical manipulations, and identification of naturally occurring phenotypes. Current research projects are directed at metabolic diseases (including dyslipoproteinemia, hypertension, obesity, type II diabetes, neonatal programming), and physiology (endometriosis, aging, osteoarthritis, contraception, safety of drug exposure during pregnancy), efficacy of gene therapy methods, infectious diseases (pertussis vaccine, T. cruzi vaccine and Chagas disease), models for liver cancer, development of tissue engineered heart valves, and treatment for trauma related large volume blood loss, and regenerative medicine and stem cell biology programs. We have recently developed an STLV-1 negative baboon colony and will progressively increase this breeding colony, while reducing the STLV-1 positive colony (see Progress Report).

Specific Aims

1). To reduce the baboon colony steady-state population from 1,400 to approximately 900 animals.
2). To develop an STLV-1 SPF pedigree breeding colony that will replace the existing colony. This is a new aim since this last competitive review, but was a milestone requested by ORIP.
3). To adopt management strategies that make it possible to meet the needs of biomedical researchers.
4). To provide opportunities to develop the baboon as an animal model in new research areas.

RHESUS MACAQUE COLONIES

The need for specific pathogen free (SPF) rhesus monkeys (*Macaca mulatta*) of Indian-origin to address concerns in biomedical research, animal health, and occupational safety, was recognized by the National Institutes of Health when it established the SPF breeding program in 1989 (25, 26) and provided opportunities for U42 Cooperative Agreement grant mechanisms to sustain the SPF colonies starting in 2000. In addition, the need to identify unrelated research subjects or research subjects of known relatedness has necessitated genetic management programs to monitor pedigree relationships within nonhuman primate colonies (27-29).

Establishment of Two Genetically Distinct SPF Colonies. With the addition of the NEPRC macaques, SNPRC will maintain two genetically distinct and highly characterized SPF rhesus macaque colonies, designated Colony 1 and 2. Colony 1 was derived from the USAF and has been a closed colony for decades, long before the import of non-Indian rhesus to this country. Colony 2, derived from NEPRC, was one of the initial SPF colonies funded by the NIH program. Together, these colonies provide an innovative resource for supporting AIDS-related research especially with the addition of managed breeding based on genetic diversity with data derived from both MAMU typing (deep sequencing done at Wisconsin NPRC) and high throughput sequencing of the genome, conducted in the SNPRC Genomic Core Laboratory.

The specific aims are as follows: These are the updated aims from the recently reviewed U42 grant that supports these colonies.
1). To make approximately 75 SPF rhesus macaques available for research annually from Colony 1 (current census 474) and to produce offspring from Colony 2 (current census 260) for expansion of the colony and provision of 55 animals for research beginning in the fourth year of the grant, Year 17. We will maximize the long term efficiency of colony production by genetically and reproductively managing both colonies.
2). To verify and maintain the SPF status of the colonies by screening for herpes B virus, SIV, SRV, and STLV-1. The initial viral screening will be performed by serology for all four viruses using the Luminex technology with beads containing two antigens for each virus, and by PCR for SRV. Confirmatory screening by western blot and PCR will be outsourced to California NPRC and the National B Virus Resource Center.

3). To maximize the value of the animals for AIDS-related research purposes by characterizing them for MHC Class I alleles. All progeny will be typed for MHC Class I haplotypes using deep sequencing at the Wisconsin NPRC. The MHC Class I data will be used to maintain diversity in haplotypes, while ensuring appropriate frequencies of specific alleles for AIDS research. High throughput sequencing will provide the genetic markers to ensure Indian-origin and pedigree, but also will increase our capacity for genetic management of the colony and the ability to provide animals with greater genetic characterization to investigators.

CHIMPANZEE COLONY

SNPRC maintains a significant portion of the nation's chimpanzee research resource. It is one of only two National Primate Research Centers (NPRCs) that maintain chimpanzees, it is the only NPRC at which biomedical research is conducted on infectious diseases, and it maintains more chimpanzees than are available at the other NPRC. More important, SNPRC has maintained a track record in recent years in regard to number of publications and the impact factors of journals in which manuscripts are published.

Background of Chimpanzees at the SNPRC. Eighteen chimpanzees acquired by Texas Biomed (then Southwest Foundation) in 1967 constituted the initial colony. The colony grew by births and acquisitions until 1995 when NIH instituted the breeding moratorium. The current census is 107 animals that are NIH-owned and/or supported. Of these 20 are supported by a U42 grant (Excluded by Requester P.I.) and 87 are supported by the base grant.

The genetic, physiological, biochemical, and immunological similarities of chimpanzees to humans make them unique models to study infectious diseases that are caused by pathogens that infect only humans and chimpanzees (e.g., HBV, HCV, HIV), and to test the safety and efficacy of humanized monoclonal antibodies and novel immunomodulators. The primary objectives of the SNPRC chimpanzee colony is to provide the national biomedical research needs and to manage the research projects that are conducted with chimpanzees at the SNPRC. Despite significant uncertainties regarding the future of biomedical research with chimpanzees, NIH has recommended that a colony of 50 chimpanzees be available for research in the future. SNPRC is well positioned to meet the future needs of NIH for chimpanzees in research.

Specific Aims

1). To maintain a healthy, well defined population of chimpanzees and to make them available for research to the extent that is permitted by NIH.
2). To maintain chimpanzees, with well-defined research histories, for future projects that require naive animals or animals previously exposed to human pathogens.
3). To maintain a cohort of well characterized chimpanzees persistently infected with HBV or HCV for basic research on pathophysiology of hepatitis B and C, mechanisms of host-viral interactions, and immune response to HBC or HCV; as well as for testing the safety and efficacy of new candidate therapeutics and preventives.
4). To provide high quality care and enrichment for those chimpanzees that NIH does not permit to be used for research.
5). To manage all chimpanzees assigned to experimental protocols at the SNPRC.

CORE LABORATORIES AT SNPRC.

SNPRC currently funds two core laboratories.
Immunology Core Laboratory is directed by Excluded by Requester The Core provides assays based in flow cytometry for the characterization of blood cell subsets and the determination of cell mediated activity (T-cell proliferation, cytotoxic and natural killer cell activity) in nonhuman primate species. The Core also provides the methodologies for the simultaneous determination of multiple cytokines and chemokines in biological fluids derived from nonhuman primate species. This Core provides the Luminex serology based testing for the viral agents involved in the SPF rhesus macaque colonies.

Excluded by Requester **hics Core Laboratory** is directed by [redacted] This Core is providing high throughput sequencing genomes of baboons, rhesus macaques and marmosets in the SNPRC colonies. This effort helps direct the breeding management to maximize genetic diversity of the colony and provide information on the impact of genetic diversity on research programs using these colonies.

TRAINING AND OUTREACH.

A comprehensive training program is essential to the success of a laboratory animal facility. Over the last three years, the SNPRC has significantly enhanced its Training Program for technical staff with the goals of developing a comprehensive training program and generating systematic documentation of that training. The updated Training Program includes new methods and forms for documenting training, and defined procedures for selecting and training staff trainers. Skills training is standardized across the Center and there are clear guidelines for employee advancement. The Training Program provides customized student/intern training, general interest training sessions, and training sessions focused on achieving AALAS Certification. SNPRC financially supports those seeking AALAS certification and provides immediate salary incentives for those gaining certification. The Training Program is continually monitored to ensure that it remains relevant to all areas of the SNPRC. The program has been valuable for training employees and for collecting skill proficiency data.

Training Specific Aims

1). To produce highly capable, proficient, and well-rounded technicians and caretakers.
2). To standardize training methods in order to provide the consistency required to generate high quality scientific data .
3). To standardize employee advancement criteria across all areas of the SNPRC.

Summer Intern Program. The goal of the Student Intern Program is to provide summer research training opportunities to undergraduate, graduate, and veterinary students during an 8-week program of biomedical research with nonhuman primates. Because of the major expenses associated with maintaining the infrastructure of nonhuman primate research facilities, the NPRCs are among a few institutions in the world that are capable of providing extensive and varied opportunities for students to gain first-hand experience in biomedical research with nonhuman primates and in veterinary care of these important animals. The NRPCs are absolutely crucial for providing training opportunities in the care and use of nonhuman primates to the nation's students in science and veterinary medicine; the vast majority of universities conduct little if any direct research with nonhuman primates.

The Summer Intern Program provides training through a series of general seminars for all interns, in addition to the more specific training interns receive from their assigned mentors. Seminars cover the ethics of nonhuman primate research, regulatory issues affecting primate research and animal research in general, environmental enrichment, and behavioral programs for reducing animal stress among other topics. The interns also attend an overview of current research at Texas Biomed presented by investigators and technical staff during the "Science Teachers' Day at Texas Biomed" symposium.

OUTREACH

Excluded by Requester

der of the Outreach effort for SNPRC is [redacted]. A major component of the Outreach effort is ated through the Public Relations Office of Texas Biomed. The new director of this office participates with the other NPRCs with regard to the need for and the public image of nonhuman primate research.

The Public Relations Office handles all of the public media needs of SNPRC including local and national press inquiries. Public Relations coordinates a number of publications for Texas Biomed and SNPRC. These publications make biomedical research with nonhuman primates understandable to the general reader and explains how this research can positively impact the lives of people in San Antonio, Texas, the US and worldwide.

Roundup is the official newsletter of SNPRC and is published 3 times per year.
Progress is the newsletter of Texas Biomed.
Annual report.--The *Texas Biomed Annual Report* highlights for the general public the year's major scientific achievements and other institutional initiatives.
Scientific report.--This publication, produced biannually, describes the work of each scientist at Texas Biomed and the SNPRC. For each faculty member, the report includes a research summary, a list of recent publications, and a relevant science image. This publication is sent to officials of major medical schools, government agencies, scientific organizations, and science libraries. It serves as a way to inform the scientific peer community of the work of Texas Biomed and the SNPRC and is also a recruiting tool.

Other Community Outreach and Education Efforts

Tours.--Approximately 40 times during the year, the SNPRC welcome various community groups for tours of the facilities to inform participants about the extraordinary research resources at the SNPRC and Texas Biomed, and how they are being put to use for the benefit of human health. A tour of the primate facilities, including instruction about the value of nonhuman primates in research, is generally a highlight of these events.

Student tours.--Each spring, Texas Biomed and the SNPRC host a series of 10-15 campus tours for upper-level high school students who are members of honors programs and/or advanced science classes. These tours, which are meant to foster goodwill with area schools and encourage bright young students to consider careers in science.

Community requests.--In addition to these outreach opportunities coordinated in collaboration with Texas Biomed support groups, the organization responds to requests from community groups and schools to arrange for speakers at their events. Multiple requests are accepted each year for representatives from the SNPRC or Texas Biomed to address one local groups.

Outreach Specific Aims

1). To generate positive news coverage by preparing news releases, media strategies, and story pitches related to newsworthy research developments, major grant awards, or major scientific publications generated by the SNPRC.

2). To manage negative publicity by developing documents containing talking points. The documents to be eveloped include the following: potential questions and answers regarding controversial issues that might impact the SNPRC; providing media training to SNPRC administrators and investigators; and monitoring animal rights activity and related issues.

3). To promote the SNPRC through articles about SNPRC scientists and research programs in institutional publications including the *Roundup* newsletter, *Progress* newsletter, the *Texas Biomed Annual Report*, the *Texas Biomed Scientific Report*, and the Texas Biomed and SNRPC Web Sites.

4). To promote the SNPRC through a variety of community outreach and education efforts including tours, speaker events, and presentations to community groups.

PROGRESS AND ACCOMPLISHMENTS

Period Covered: 12-3-13 to 1-25-15

A series of significant changes are in progress at SNPRC. This progress report will directly address these changes, while highlighting the changes most relevant to this revision. Extensive publications are listed in the Progress Report Publications, but this Progress Report focuses on major efforts by the SNRPC during over the last year.

Establishment of SNPRC Marmoset Colony 2. The purpose of this revision to the SNPRC P51 base grant is to provide a second year of support for the SNPRC Marmoset Colony 2. Colony 1 is the historical SNPRC marmoset colony that was moved to SNPRC in 2001 with Excluded by Requester The SNPRC Marmoset Colony 2 was derived from a portion of the NEPRC marmoset population. These animals were transferred to SNRPC in two shipments in late 2014 and early 2015. Colony 2 is being maintained physically and genetically separate from the SNPRC Colony 1. In preparation for the arrival of these animals SNPRC renovated a building with a supplement to the P51 base grant. The first year of support for Colony 2 was provided from the same supplement. Several studies will capitalize on the arrival of marmosets with a different genetic background and that have been maintained on a different diet including studies on comparative microbiome.

Implementation of Recommendations for Marmosets by EPIDS. SNPRC formed an Expert Panel on Infectious Disease Surveillance (EPIDS) and had a meeting at the SNPRC between March 26 and March 28, 2014. The panel was provided the Summary Statement, relevant sections of the base grant, and historical data prior to the meeting. Core Scientist gave presentations to the Panel on all aspects of infectious diseases in our colonies. The Panel was comprised of distinguished individuals with extensive expertise in primates and infectious diseases and included Excluded by Requester

Excluded by Requester

Excluded by Requester The full report of this panel was submitted to DCM. Of relevance to this Revision was the

review of the suggestion from the Summary Statement reviewers' comments

reviewers' comments

reviewers' comments

We have developed PCR based assays for the screening. Of interest is the finding that a third colony derived SNPRC Colony 1 and being maintained as a barrier colony at the UTHSCSA Barshop Institute for Longevity and Aging appears to have a fecundity than Colony 1. This colony was founded by selecting animals negative for both viruses, but the relationship of virus to fecundity and health is unknown. The initial goal is to determine if Colony 1 and 2 differ in the prevalence of these viruses and whether the differences correlate with in health status correlate with these changes.

STLV-1 SPF Baboon Colony. With regard to the baboon colony, the EPIDS recommended establishment of an SPF colony for STLV-1. Although there are no conclusive data to support that STLV-1 infection is a health issue in the baboon, the elimination of this agent has merit. We have aggressively pursued establishment of an STLV-1 negative colony with host institute support until renewal of the base grant. We have screened the majority of the colony by serology (Luminex) and have segregated 375 STLV-1 negative animals ages 1-5 into social groups. The first breeding group has been established. The screening will be repeated on a regular basis to establish the SPF status. We have determined that most infections occur after the age of four and that infection spreads very slowly through a social group to reach a prevalence of approximately 80% in older adults.

Creation of Genomics Core Laboratory for Genetic Management of Primate Colonies. SNPRC created a Genomic Core Laboratory with Excluded by Requester as the Director and developed a cost effective plan for genetic management and characterization of all three breeding species at SNPRC; baboon, rhesus macaque and marmoset. The Core will use high throughput sequencing methods to collect high-resolution genetic information on each animal in each of the colonies. This data will be used to maximize genetic variation in the breeding structure of the colony. The approach of genotyping by sequencing provides a cost effective means to identify variants in regions of the genome that harbor single copy genes. The new genetic data will dramatically increase the value of our NHP resources by providing the means to perform detailed investigations into gene by environment interactions in our NHP models of human disease. More specifically, the genetic data integrated with pedigree data will facilitate the discovery of functional variants in genes and regulatory regions of genes that influence human health and disease by allowing investigators to select specific animals in a colony based on specific genetic variants, e.g obesity and gene variants in the marmoset.

Implementation of the LabKey EHR. SNPRC has a begun the implementation of LabKey Electronic Health Record (EHR) database and web-based interface. LabKey is currently used by both Oregon NPRC and Wisconsin NPRC as the animal database system and is being considered by other NPRCs. This will allow all NRPCs to interact with regard to animal demographics and data on a common format. It will also increase utility of the animal data by SNPRC and external investigators. We began importation of our demographic data into LabKey in November 2014 and expect to continue implementation of different functions through 2015. This is a highly interactive process between LabKey personnel and our Primate Records Database group.

Establishment of SNPRC Rhesus Macaque Colony 2. SNPRC received a portion of the NEPRC Indian-origin rhesus macaque colony, designated at SNPRC Rhesus Colony 2. This colony will be maintained physically and genetically separate from our existing colony. We renovated a new building for this colony and have plans to renovate a second building for expansion of the colony. The first shipment of animals occurred on Jan 22, 2015. Once all of the new animals are on campus, the census will be approximately 900 animals. Together, these colonies provide an innovative resource for supporting AIDS-related research especially with the addition of managed breeding based on genetic diversity.

VERTEBRATE ANIMALS

See the Marmoset Colony Component for details on Vertebrate Animals.

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OMB Number: 4040-0001
Expiration Date: 06/30/2016

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

5. APPLICANT INFORMATION **Organizational DUNS*:** 007936834

Legal Name*: Texas Biomedical Research Institute
Department:
Division:
Street1*: 7620 NW Loop 410
Street2:
City*: San Antonio
County: Bexar
State*: TX: Texas
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 78227-5301

Person to be contacted on matters involving this application

Prefix:	First Name*:	Middle Name:	Last Name*:	Suffix:
Ms	Ana	M	Biediger	

Position/Title: Assistant Director
Street1*: 7620 NW Loop 410
Street2:
City*: San Antonio
County: Bexar
State*: TX: Texas
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 78227-5301
Phone Number*: 210-258-9507 Fax Number: 210-670-3335 Email: abiediger@txbiomed.org

7. TYPE OF APPLICANT* M: Nonprofit with 501C3 IRS Status (Other than Institution of Higher Education)

Other (Specify):
Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
The Southwest National Primate Research Center

12. PROPOSED PROJECT

Start Date*	Ending Date*
09/01/2015	04/29/2016

OMB Number: 4040-0010
Expiration Date: 06/30/2016

Project/Performance Site Location(s)

Project/Performance Site Primary Location

● I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	Texas Biomedical Research Institute
Duns Number:	007936834
Street1*:	7620 NW Loop 410
Street2:	
City*:	San Antonio
County:	Bexar
State*:	TX: Texas
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	78227-5301
Project/Performance Site Congressional District*:	TX-020

File Name

Additional Location(s)

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* ○ **Yes** ● **No**

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ○ Yes ○ No

If YES, check appropriate exemption number: _ 1 _ 2 _ 3 _ 4 _ 5 _ 6

If NO, is the IRB review Pending? ○ **Yes** ○ **No**

IRB Approval Date:

Human Subject Assurance Number

2. Are Vertebrate Animals Used?* ● **Yes** ○ **No**

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ○ Yes ○ No

IACUC Approval Date:

Animal Welfare Assurance Number A3082

3. Is proprietary/privileged information included in the application?* ○ **Yes** ● **No**

4.a. Does this project have an actual or potential impact - positive or negative - on the environment?* ○ **Yes** ● **No**

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ○ Yes ○ No

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place?* ○ **Yes** ● **No**

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* ○ **Yes** ● **No**

6.a. If yes, identify countries:

6.b. Optional Explanation:

	Filename
7. Project Summary/Abstract*	Project_Summary__REV1006418445.pdf
8. Project Narrative*	
9. Bibliography & References Cited	Bibliography_and_References1006418426.pdf
10.Facilities & Other Resources	Facilities_and_Equipment1006418436.pdf
11.Equipment	

PROJECT SUMMARY

The objective of grant P51-OD011133 to Texas Biomedical Research Institute is to continue support of the infrastructure of the Southwest National Primate Research Center (SNPRC). This base grant enables the SNPRC to be responsive to national biomedical research needs and to accommodate investigators who want to access Center resources for collaborative research purposes.

The Southwest National Primate Research Center has an active and growing program to develop and supply the common marmoset (*Callithrix jacchus*) as a biomedical research resource. We propose to further enhance this SNPRC resource through the inclusion of a segment of the marmoset colony from the New England Primate Research Center. This addition will provide SNPRC with two genetically distinct colonies of marmosets that can be utilized for infectious disease, metabolic disease, aging and regenerative medicine research. This revised proposal requests support for this activity.

The overall aims of the marmoset colony in the last competitive renewal were to: (1) continue production of marmosets for use in biomedical research; (2) further consortium arrangements with Wisconsin NPRC, New England PRC and the NIH Intra-mural program. Two specific goals within this aim are to have a defined, accepted profile of a marmoset diet and a SNP panel that can be used as a tool to define best animal use and animal breeding; (3) continue comparison of the SPF, barrier-maintained marmoset colony with the conventionally housed colonies, in order to identify those aspects of research use (e.g., healthy longevity) which will specifically benefit from this SPF, barrier approach to colony management and animal production.

The following revised additional aims are proposed with the addition of the NEPRC marmosets to the SNPRC: (1) continue production of marmosets for use in biomedical research with the NEPRC marmosets contributing to that continued production. The NEPRC marmosets will be maintained as a separate population (hereafter referred to as Colony 2), with husbandry and diet maintained as closely as possible to the original NEPRC protocols. The increased size of the total colony will greatly enhance our ability to meet the needs of NIH-funded investigators, some of which used the marmoset model at NEPRC; (2) conduct planned comparisons of factors that represent important sources underlying phenotypic variation within and among marmoset populations. These comparisons will provide a means to identify best practices as regards to husbandry and best methods for assigning subjects to studies or breeding in relation to genetic variation. This aim will be conducted in collaboration with the Wisconsin NPRC; (3) establish a specific resource of geriatric marmosets to be used in studies of aging and chronic disease.

FACILITIES AND EQUIPMENT

Marmosets and tamarins at SNPRC are housed Specific Animal Location that house only these species. One additional building has housed marmosets during the current grant period, and it is available if needed for expansion of the colony. The building that houses Colony 2, the subject of this revision, is Specific Animal Location – there are no other animals in this building.

Specific Animal Location (see Figure) is a Specific Animal Location of the SNPRC campus, and was built in 1981 and renovated in 2014 in preparation for the arrival of marmoset Colony 2. It is an aluminum framed building and all of the support frame work is inside the building. Specific Animal Location building with Specific Animal Location of animal housing space, along with a procedure area, a kitchen and food preparation area, and an office/break area. The support rooms are in the center of the building and Specific Animal Location are located on either side. The ceiling has sky-lights and the exterior walls to the animal rooms have windows that have been painted over. Access to the Specific Animal Location Specific Animal Location was originally designed specifically to accommodate hanging cages. It had a structure of internal frames to support these hanging cages and a set of troughs on the floor below where the hanging cages were located. These structures severely limit the number of floor-rack cages that can be used in each animal room and constrains the arrangement of those racks. The renovations for the building include upgrading the electrical and mechanical areas, repairing a skylight, removing of hanging-cage support frames, providing and installing floor gratings for trench drains, and renovating the concrete area outside the building for vehicle access and cage staging.

The three support rooms are used for entry/office space, food preparation and utensil cleaning, and a PPE change and procedure room. A covered, protected clean storage area is near the PPE change and procedure room. This area is a concrete slab with chain-link fabric and a metal roof. It is not attached to the original structure.

The floors of Specific Animal Location are sealed concrete refinished with epoxy. All walls are aluminum and glass (60%). The doors in the building are painted metal. A DX system provides cooling and heating is supplied by forced-draft heaters. Temperature control is provided by local thermostat. There are no differential pressures used in this building. Supply is 100% outside air make-up. Local high/low temperature alarms are installed. HVAC and lighting loads are covered by this equipment. Interior lighting with animal rooms is provided by waterproof, fluorescent fixtures that provide the required luminosity. Fixtures are on timers set to coincide with the specific photoperiod required. Timers can be manually overridden.

Two pass-through cage washers are in close proximity to the marmoset housing areas and are used for marmoset cage sanitation.

Caging for individual, paired and group housing is available. All of these cages are specifically designed for housing marmosets and tamarins and most of them were designed by Excluded by Requester Excluded by Requester the colony manager. The majority of the caging is aluminum frame with PVC-coated hardware cloth; there are a small number of stainless steel cages. All cages are equipped with nest boxes and with removable wooden branches. We also have BL-4 marmoset cages that were designed by Excluded by Requester in collaboration with Excluded by Requester Excluded by Requester These cages are designed to house single animals and have a number of features built in to protect staff working with infected marmosets, including a front lexan panel to eliminate urine splash and a flexible squeeze-back mechanism.

Equipment that is specifically used by the marmoset program includes a GE Logiq$_{TM}$ ultrasound machine with a 7.5-10mHz probe and Doppler capability and an Echo$_{TM}$ quantitative magnetic resonance (QMR) imaging machine used to assess body composition.

Facility Security

Specific Animal Location

Renovations Scope of Work September 20, 2013

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Excluded by Requester

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 1

ORGANIZATIONAL DUNS*: 007936834

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: Texas Biomedical Research Institute

Start Date*: 09-01-2015 **End Date*:** 04-29-2016 **Budget Period: 1**

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				Project Lead	Institutional Base Salary	EFFORT			15,275.00	4,323.00	19,598.00
2.						Co-Investigator					0.00	0.00	0.00

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

Additional Senior Key Persons: File Name:

Total Senior/Key Person **19,598.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*

Total Number Other Personnel **Total Other Personnel**

Total Salary, Wages and Fringe Benefits (A+B) **19,598.00**

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

Funding Opportunity Number: PAR-14-226. Received Date: 2015-01-26T08:47:42.000-05:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 1

ORGANIZATIONAL DUNS*: 007936834

Budget Type*: ● Project ● Subaward/Consortium

Enter name of Organization: Texas Biomedical Research Institute

Start Date*: 09-01-2015 **End Date*:** 04-29-2016 **Budget Period: 1**

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

Total Equipment

Additional Equipment: File Name:

D. Travel **Funds Requested ($)***

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)
2. Foreign Travel Costs

Total Travel Cost

E. Participant/Trainee Support Costs **Funds Requested ($)***

1. Tuition/Fees/Health Insurance
2. Stipends
3. Travel
4. Subsistence
5. Other:

Number of Participants/Trainees **Total Participant Trainee Support Costs**

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

Funding Opportunity Number: PAR-14-226. Received Date: 2015-01-26T08:47:42.000-05:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 1

ORGANIZATIONAL DUNS*: 007936834
Budget Type*: ● Project ● Subaward/Consortium
Enter name of Organization: Texas Biomedical Research Institute

Start Date*: 09-01-2015 **End Date*:** 04-29-2016 **Budget Period: 1**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Per diem	131,158.00
9. Blood collection	2,198.00
10. Viral testing	25,464.00
Total Other Direct Costs	**158,820.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**178,418.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. Federal Primate Center Rate	78.6	178,418.00	140,237.00
		Total Indirect Costs	**140,237.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, Shon Turner (214)767-3261

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**318,655.00**

J. Fee	Funds Requested ($)*

K. Budget Justification* File Name: Animal_Resources___Justification1006418422.pdf
(Only attach one file.)

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

Tracking Number: GRANT11815068
Funding Opportunity Number: PAR-14-226. Received Date: 2015-01-26T08:47:42.000-05:00

BUDGET JUSTIFICATION

The marmosets for which support is budgeted in this application are the 180 animals transferred from the New England Primate Research Center (NEPRC) to the Southwest National Primate Research Center (SNPRC) during Year 16. The proposed budget period of the additional funding to the grant, P51 OD011133-17, is September 1, 2015 through April 30, 2016 (8 months, during Year 17).

Personnel

Excluded by R equester Leader of the Marmoset Colony component of the P51 grant, will serve as the Leader of this supplement (EFFORT months, or % Effort for 8 months). She will direct all aspects of the project, including oversight of the scientific aspects of the project (e.g., developing plans for further genetic characterization, planning and implementing diet studies) and resource management aspects (e.g., assessing demographic structure relative to resource needs and developing techniques and procedures for use in new models). She will be responsible for assembling and analyzing data, integrating NEPRC data into the SNPRC Excluded by R equester ase, and preparing reports for ORIP staff also will provide leadership for the project through e as Chair of the SNPRC Marmoset Advisory Committee and her continued participation in the NPRC/NIH marmoset management consortium that she established. Excluded by R equester Excluded by Requester (SNPRC marmoset colony manager) form the SNPRC marmoset colony management team. They consult with each other regularly on the daily management, breeding, health issues, and resource development of this colony.

Excluded by R equester Director of the SNPRC, will serve as the Co-Investigator. Excluded by Requester will work directly Excluded by R equester on the management of the colony. Using PCR-based assays, his laboratory will perform the ing of the NEPRC animals for infection with GBV-A and LCV known to be present in both the SNPRC Excluded by R equester EPRC colonies is a Co-Investigator on the Marmoset Colony component of the P51 grant rves on the Marmoset Advisory Committee, the Research Advisory Committee, and Senior Management Team, providing the link between these committees regarding matters relevant to the marmoset colony. He will provide oversight from the SNPRC Director's Office on the use and development of the colony, and he will work directly with NIH with regard to meeting the national needs for marmosets in biomedical Excluded by Requester ch. Salary support for is not budgeted as his effort is supported by the Director's Office and set components of the P51 grant.

Excluded by R equester is the veterinarian who has direct oversight responsibility for the marmoset colony. She will work with Excluded by R equester on the management of the NEPRC colony. She serves as a member of the SNPRC Marmoset Advisory Committee.

Three animal caretakers are required to oversee the daily care of the expected colony census of 200 marmosets during Year 17. They will commit all of their effort to these activities.

Personnel costs are not budgeted for Excluded by Requester or the animal caretakers in Year 17 because their effort will be paid by per diem.

Other Expenses

The NEPRC-origin population (hereafter referred to as Colony 2) will be maintained at approximately 200 animals. In the past year, the SNPRC has received requests in excess of 50 animals per year and has been unable to meet all those requests. The entire marmoset breeding population (Colonies 1 and 2) will, therefore, be increased to approximately 36 breeding pairs – a 70% increase over the number that will be in place when the NEPRC animals arrive. There will be 18 breeding pairs in Colony 2. The need to increase the breeding population means that animal sales and research income will continue to be low during Year 17, as animals are moved into breeding and retained as replacement breeders. The 9 new breeding pairs, along with the 9 breeding pairs already established, will increase Colony 2 to 18 NEPRC-origin breeding pairs.

Once all breeding pairs have become habituated and selection to replace poorly performing pairs (if necessary) is completed, approximately 70 young per year will be produced for sale or project assignment plus 10 animals for replacement breeders (36 breeders x 2.2 weaned young per year = 80) for both colonies, with breeding evenly divided between Colony 1 and Colony 2 (Colony 2 being the colony for which support is being requested). Therefore, Colony 2 is expected to produce approximately 40 weaned young in Year 17 (18 pairs x 2.2 weaned young per pair per year).

Per diem.--Per diem costs during the first year of the supplement are estimated to be $184,624. However, $131,158 is indicated on the budget page because the remainder of the per diem will be covered by program income. This figure is based on the estimated starting colony size of 200 marmosets. Moreover, we anticipate selling 14 marmosets at the end of the Year 17 at $3819 per animal.

Revenue from regular housing per diem pays the salaries of caretakers, supervisors, clinical veterinarians and veterinary technicians who conduct clinical procedures. It also covers routine health checks, non-research-related pathology services, medicines and drugs, special care required for sick or injured animals, and complete necropsies of marmosets that die or are euthanized for health reasons. It also covers routine environmental enrichment activities. Per diem charges begin at 3 months of age.

Procedures.-- During Year 17, blood serum will be taken from both adults and newborns (200 total animals) and is budgeted at $2,198 ($10.99 x 200 collections). This blood serum will be used to conduct viral screening on all adults and newborns during Year 17.

Viral screening.--Viral screening will be conducted on Colony 2 and their offspring. Two viruses commonly infect marmosets, GBV-A and mLCV. GBV-A is a positive-sense RNA virus in the family Flaviviridae, and mLCV is a herpesvirus related to human EBV and is also known as Callitrichine herpesvirus 3. The true prevalence of these infections in the various marmoset colonies is poorly understood. Neither virus is pathogenic in humans and the impact of these viruses on the health of marmosets is poorly defined. Recent data from the barrier colony maintained at the Barshop Institute suggests that the barrier colony may have increased fecundity in comparison to the SNPRC colony. The Barshop colony was initiated using animals from the SNPRC that were negative for these viruses, but other differences exist between these colonies. The status of the NEPRC colony is unknown.

The SNPRC recently convened a meeting of an Expert Panel on Infectious Disease Surveillance to review each of the primate colonies at SNPRC. The recommendations for marmosets suggested efforts for an increased understanding of the effects, if any, of GBV-A and mLCV on productivity of the SNPRC colony. To be consistent with these recommendations, we will screen Colony 2 for these viruses by PCR-based assays. The colony will be screened once in each of the first two years on the SNPRC campus. These data will be used for comparisons to the existing SNPRC colony.

PCR assays will be conducted by Excluded by Requester laboratory. Excluded by Requester established the assays used for GBV-A and mLCV. Each screen is budgeted at $127.32. For GBV-A, the screen requires purification of RNA from serum ($31.83 per sample), and for mLCV, the screen requires purification of DNA from PBMC ($31.83 per sample). The RT-PCR assay for GBV-A and the PCR assay for mLCV are budgeted at $31.83 each. Thus, the total cost per sample is $127.32 with an estimated 200 samples in Year 17.

Therefore, the viral testing in Year 17 is budgeted at $25,464 [($127.32 viral cost x 200 samples).

Cost Recovery

We anticipate 14 animal sales during Year 17 of this supplement ($3,819 x 14 sales = $53,466). The majority of available animals will be committed to breeding and colony growth; therefore, this figure is lower than anticipated future years' sales because the colony will only reach the steady state during Year 17.

After Year 17, we anticipate an increase in sales as the pairs put into production in Years 16 and 17 have offspring moving into the minimum useable age range (~ 17 months).

Below is a list of Year 17 costs that are financially supported by program income and the base grant supplement.

Year 17
NEPRC Marmosets - Support from Base Grant Supplement and Program Income

Category	Total Cost Dollars	Program Income Dollars	Program Income % of Total	Base Grant Supplement Dollars	Base Grant Supplement % of Total
Personnel	-	-	-	-	-
Equipment	-	-	-	-	-
Supplies	-	-	-	-	-
Alterations and Renovations	-	-	-	-	-
Other Expenses	231,884.00	53,466.00	23%	178,418.00	77%
Consortium/Contractual Costs (UTHSCSA - Excluded by Requester	-	-	-	-	-
Total	231,884.00	53,466.00	23%	178,418.00	77%

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals ($)	
Section A, Senior/Key Person		**19,598.00**
Section B, Other Personnel		
Total Number Other Personnel		
Total Salary, Wages and Fringe Benefits (A+B)		**19,598.00**
Section C, Equipment		
Section D, Travel		
1. Domestic		
2. Foreign		
Section E, Participant/Trainee Support Costs		
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other		
6. Number of Participants/Trainees		
Section F, Other Direct Costs		**158,820.00**
1. Materials and Supplies		
2. Publication Costs		
3. Consultant Services		
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8. Other 1	131,158.00	
9. Other 2	2,198.00	
10. Other 3	25,464.00	
Section G, Direct Costs (A thru F)		**178,418.00**
Section H, Indirect Costs		**140,237.00**
Section I, Total Direct and Indirect Costs (G + H)		**318,655.00**
Section J, Fee		

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

1. Project Director / Principal Investigator (PD/PI)

Prefix:
First Name*:
Middle Name:
Last Name*:
Suffix:

Excluded by Requester

2. Human Subjects

Clinical Trial? ○ No ○ Yes

Agency-Defined Phase III Clinical Trial?* ○ No ○ Yes

3. Permission Statement*

If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)?

○ Yes ● No

4. Program Income*

Is program income anticipated during the periods for which the grant support is requested? ● Yes ○ No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

Budget Period*	Anticipated Amount ($)*	Source(s)*
1	53,466.00	Sale of Animals

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5. Human Embryonic Stem Cells

Does the proposed project involve human embryonic stem cells?* ● No ○ Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Cell Line(s): Specific stem cell line cannot be referenced at this time. One from the registry will be used.

6. Inventions and Patents (For renewal applications only)

Inventions and Patents*: ○ Yes ○ No

If the answer is "Yes" then please answer the following:

Previously Reported*: ○ Yes ○ No

7. Change of Investigator / Change of Institution Questions

❑ Change of principal investigator / program director

Name of former principal investigator / program director:

Prefix:

First Name*:

Middle Name:

Last Name*:

Suffix:

❑ Change of Grantee Institution

Name of former institution*:

PHS 398 Research Plan

Please attach applicable sections of the research plan, below.

OMB Number: 0925-0001

1. Introduction to Application (for RESUBMISSION or REVISION only)	Animal_Resource___Introduction1006418423.pdf
2. Specific Aims	Animal_Resource___Specific_Aims1006418420.pdf
3. Research Strategy*	Research_Strategy___REV1006418439.pdf
4. Progress Report Publication List	Progress_Report_Publication_List1006418440.pdf
Human Subjects Sections	
5. Protection of Human Subjects	
6. Inclusion of Women and Minorities	
7. Inclusion of Children	
Other Research Plan Sections	
8. Vertebrate Animals	Vertebrate_Animals1006418425.pdf
9. Select Agent Research	
10. Multiple PD/PI Leadership Plan	
11. Consortium/Contractual Arrangements	
12. Letters of Support	
13. Resource Sharing Plan(s)	
Appendix (if applicable)	
14. Appendix	

INTRODUCTION

The purpose of this revision to the SNPRC P51 base grant is to provide a second year of support for the SNPRC Marmoset Colony 2. The SNPRC Marmoset Colony 2 was derived from a portion of the NEPRC marmoset population. Colony 1 is the historical marmoset colony housed at SNPRC since 2001, and its support is currently provided by the base grant and project income. The first year of support for Colony 2 was provided as a supplement to the base grant. This funding was to cover the cost of quarantine and maintenance from the time of arrival (late 2014 and early 2015) until the P51 noncompetitive renewal date of April 30, 2015. We will experience a lapse in funding for these animals from May 1, 2015 to September 30, 2015, the projected start date of this Revision of the P51. We have sufficient funds to cover the animals during this lapse in funding. The Revision plus project income will cover the maintenance of these animals until the projected competitive renewal date for the P51 grant of May 1, 2016.

SPECIFIC AIMS

The Southwest National Primate Research Center has an active and growing program to develop and supply the common marmoset (*Callithrix jacchus*) as a biomedical research resource. We propose to further enhance this SNPRC resource through the inclusion of a segment of the marmoset colony from the New England Primate Research Center. This revised proposal requests support for this activity.

The overall aims of the marmoset colony in the last competitive renewal were:

Aim 1: To continue production of marmosets for use in biomedical research.

Aim 2: To further consortium arrangements with Wisconsin NPRC, New England PRC and the NIH Intra-mural program. Two specific goals within this aim are to have a defined, accepted profile of a marmoset diet and a SNP panel that can be used as a tool to define best animal use and animal breeding.

Aim 3: To continue comparison of the SPF, barrier-maintained marmoset colony with the conventionally housed colonies, in order to identify those aspects of research use (e.g., healthy longevity) which will specifically benefit from this SPF, barrier approach to colony management and animal production.

The following revised additional aims are proposed with the addition of the NEPRC marmosets to the SNPRC:

Aim 1: To continue production of marmosets for use in biomedical research with the NEPRC marmosets contributing to that continued production. The NEPRC marmosets will be maintained as a separate population, with husbandry and diet maintained as closely as possible to the original NEPRC protocols. The increased size of the total colony will greatly enhance our ability to meet the needs of NIH-funded investigators, some of which currently use the marmoset model at NEPRC.

Aim 2: To conduct planned comparisons of factors that represent important sources underlying phenotypic variation within and among marmoset populations. These comparisons will provide a means to identify best practices as regards to husbandry and best methods for assigning subjects to studies or breeding in relation to genetic variation. This aim will be conducted in collaboration with the Wisconsin NPRC.

Aim 3: To establish a specific resource of geriatric marmosets to be used in studies of aging and chronic disease.

RESEARCH STRATEGY

Background and Significance

The common marmoset (*Callithrix jacchus*) is a small, South American primate poised to become a vital biomedical research resource. As a non-endangered anthropoid primate with small size, the highest fertility and the shortest life span, this species offers a remarkably cost-effective, high efficiency nonhuman primate model for biomedical research. In addition, many areas of research take advantage of unique features of its biology for application to human disease. The potential of the common marmoset to advance biomedical research in the United States is threatened, however, by its small and declining captive population. This proposed project will address these concerns through increased breeding and comparative studies aimed at development of more standardized management.

There has been an increasing expression of concern in the scientific community regarding the relatively low rate that therapeutic findings in rodents translate to effective therapies in humans (2,4-5,7,12-13) and models more closely related to humans are part of addressing these concerns. However, the large size, high zoonotic risk, slow reproduction and high cost associated with most nonhuman primates limit their usefulness as translational models. Combining close phylogenetic relationship to humans with the shortest lifespan and smallest sizes possible can help to make nonhuman primate translational research more affordable and feasible for a wider array of projects.

History and Breadth of Use

Common marmosets have been a biomedical research resource since the early 1960's, used predominately in studies of infectious disease, immunology and neuroscience. Historically, they have been a more commonly used research model in Europe and Japan than in the United States. However, cellular and molecular resources have recently been developed that greatly enhance the value of marmosets in research and have increased interest in the US. These include sequencing and annotation of the marmoset genome (22), development of marmoset-derived, induced pluripotent stem (iPS) cell lines (23), and the use of marmosets to develop the first transgenic nonhuman primate with germline transmission (11).

Figure 1 illustrates the continuing increase in publications using marmosets from 1994 to 2013. A recent review (17) cites immunology/immunopathology, neuroscience, cognition, sleep behavior/circadian rhythm, obesity, infectious disease and reproduction as areas in which the marmoset has demonstrated value as a preclinical and translational model. Of the articles specifically citing common marmoset use in 2012-13 (Ovid Medline), approximately 50% were studies in neuroscience studies, 19% in reproduction, including transgenic studies, 12% in infectious disease and immunology and 9% in obesity and metabolic function.

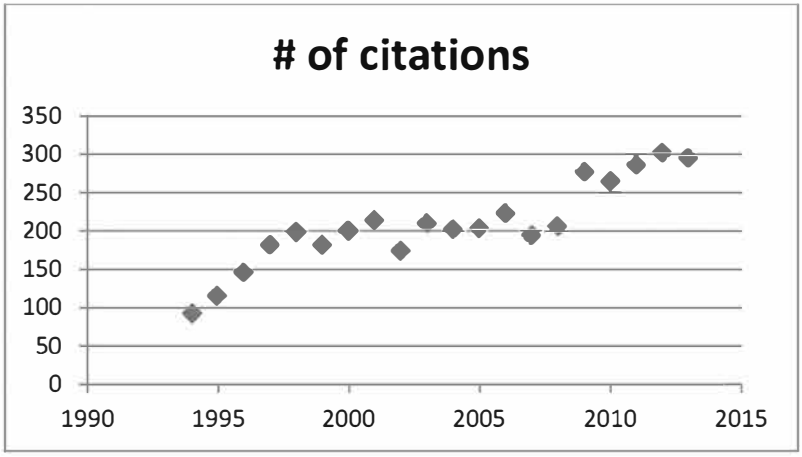


Figure 1. Marmoset citations by year - Indexes=BIOSIS Previews

One notable area of developing use is in infectious disease studies, particularly those involving high biocontainment agents. At the Southwest National Primate Research Center (SNPRC), the demand for marmosets for BL4 projects increased by over 60% between 2010 and 2011. Proposals currently in our queue would demand an additional 40 animals per year for this use, alone. Marmosets, and the closely related tamarin species, are the only nonhuman primates that can serve as a proxy model for Hepatitis C. GBV-B, a

native tamarin virus, has high homology with human Hepatitis C virus and has been used successfully in the past in vaccine testing. With the extremely limited resources available for research on Hepatitis C, this model use may be particularly urgent.

Unique Biological Features

In addition to their value as a model system that is phylogenetically closely related to humans, there are unique features of this group of primates that make marmosets particularly valuable for certain types of studies.

Small body size: Adult common marmosets weigh 300-400 grams – i.e. they are about the size of a laboratory rat. Their small size makes them easier to handle than large-bodied monkeys and allows for spacious, social housing in a relatively small space – including easy social housing in a barrier facility. Marmoset temperament makes them readily tractable. They require limited amounts of test compounds when used to study vaccines, therapeutics or other interventions – a decided advantage when test material is in limited quantities.

Twinning: In the wild, marmosets typically produce dizygotic twins. In captivity, they often produce even larger, multi-zygotic litters of triplets or quadruplets (18). While obviously contributing to the fast pace at which populations can grow, these litters also offer unparalleled opportunities to conduct litter-matched studies in which two or more nonhuman primate siblings share the same prenatal environment. This affords the opportunity to compare experimentally altered post-natal conditions within litter mates in a highly controlled fashion, something not possible in other nonhuman primate models. Cross-fostering of infants is readily accomplished in this species, providing increased opportunities for research in these multi-sibling litters.

Hematopoietic Chimerism: Marmosets born into the same litter are hematopoietic chimeras, sharing hematopoietic stem cells during development (14). This unusual developmental process results in littermates that share an immunologic profile and are immunologically tolerant to tissue transplants from each other. The use of immunologically matched littermates as paired control and test subjects greatly increases the power of infectious disease studies. In addition, the ability to perform T cell adoptive transfers between litter mates has been a valuable tool in the development of autoimmunity models in this species.

Lissencephalic Cortex: While marmosets have a rat-like body size, they have a primate-typical brain size of 2% of body weight, unlike a rat-typical 0.5%. However, marmosets combine the features of a nonhuman primate brain - such as large overall size, a large prefrontal cortex, reduced olfactory regions, and expansion of the cerebrum in relation to an enhanced visual system – with a smooth, or lissencephalic cortical surface. This lissencephalic surface in a nonhuman primate brain is a significant advantage in neuroscience studies requiring manipulation of, or sampling from, given brain regions (e.g. 3).

Fast Maturation and Short Life Span: Many of the most pressing U.S. human health concerns involve diseases that are chronic and for which aging is a strong risk factor. The fast maturation and relatively short life span of marmosets makes them a valuable resource to study chronic disease and aging. Marmosets are sexually mature at 16-17 months of age and display signs of age-related pathologies – such as beta-amyloid accumulation in the brain, impaired cochlear function and lean mass loss - by 8-13 years of age. Most importantly, the time period required to move from early to late life – i.e. to advance through the stages of development, aging or chronic disease, is within the range of a typical, funded project. (19). This is a particularly attractive feature for transgenic models in which disease onset may depend on aging factors, such as neurodegenerative disorders like Parkinson's disease.

Unique opportunities for new nonhuman primate models through stem cell manipulations and transgenics

A recent Editorial in Nature (Nov 6, 2013) entitled "Precision gene editing paves the way for transgenic monkeys" highlighted the use of genetically modified marmosets as a model for neurological disease. Using zinc finger nucleases, individuals have created an animal model for autism and many more genetically modified marmoset lineages are expected in the near future. The marmoset due to size, rapid maturation and breeding is an idea animal for these purposes.

Common marmosets produce 2-3 offspring every 5-6 months – the highest fertility of any anthropoid primate. This high fertility is a major advantage over any other laboratory nonhuman primate, enabling high-speed

population expansion, within 3-5 years in comparison to decades. It is a specific advantage for technologies, such as transgenics, for which rapid establishment of genetically defined lines is essential. As an example, 10 macaque breeding females will, in two years time, have produced a maximum of 30 offspring, all of which will be immature; i.e, the reproductive population will not have increased during that time. In contrast, in the same 2-year period, 10 marmoset breeding females will have produced a maximum of 80 offspring and the reproductive population will have tripled, as marmosets reach reproductive maturity by 1.5 years of age. While application of transgenic technologies to nonhuman primates will likely always remain an expensive enterprise when compared to rodents, the use of marmosets brings this technology within an acceptable financial range for applications to which the nonhuman primate is a particularly compelling model, such as Alzheimer's disease, Parkinson's disease, and other neurodegenerative diseases.

Marmosets present a unique opportunity for improving animal models for regenerative medicine. At a recent NIH workshop, the development of models that more accurately recapitulate diseases phenotypes were identified as a priority to ensure the success of stem cell based technologies (http://dpcpsi.nih.gov/orip/documents/summary_of_the_improving_animal_models.pdf). An example of possible application is the evaluation of personalized medicine using iPS-derived dopaminergic neurons for cell replacement in Parkinson's disease which is advancing towards clinical translation. In addition, a transgenic monkey model of Parkinson's disease would allow us to answer the question in nonhuman primates of whether the host's disease can spread to healthy grafted cells affecting their integration and function. An α-synuclein Excluded by Requester nic marmoset line has been developed personal communication) as has the technology for tion and derivation of neurites from marmoset iPS cells (23). However, for these resources to significantly impact our understanding of PD and its treatment, these resources need to be readily available to a broad array of relevant investigators. That availability will be directly dependent upon an increased investment in production and maintenance of marmosets and associated resources in the United States.

Impediments to the Use and Development of this Model

The entire National Primate Research Centers (NPRC) marmoset population stands at approximately 650 animals. With smaller populations at other institutions (e.g., Johns Hopkins Medical School, University of California at San Diego) supporting the efforts of 1-2 investigators, we estimate that there is a US marmoset research population of less than 1,000 animals. Of those animals, less than 10% are available for expanded uses – i.e. the huge majority are already committed to on-going projects or to production. The NPRC system supports on-going projects that use, on average, 340 animals per year, with approximately half of those in terminal studies and over 95% of those projects being federally funded. In the past four years, NPRC marmoset studies have included projects funded through NIA, NIAID, NICHD, NIEHS, NIDCD, NIDDK, and NINDS.

It should be noted that there is only one commercial source for marmosets in the US. Feedback from primary users of this commercial source suggests that it would be unable to accommodate any significant increase in demand.

In 2012-14, the SNPRC experienced increases in requests for information regarding marmosets from individuals with no experience with this species. Most often, these are individuals working with rodent models who are eager to translate the findings from their research into a species more closely related to humans. Many of these investigators must be told that resources are simply not available to consider an expansion of their work into marmosets. The biology and longer lifespan of other laboratory nonhuman primates commonly precludes their substitution.

The NRPC's with marmoset resources have been contacted by at least three prominent laboratories in the US that express their intention to develop a transgenic marmoset resource, with only one of these laboratories actually having its own marmoset resources. The present US marmoset population is inadequate to support such endeavors. The one institution that has successfully produced multiple transgenic marmoset lines Private Source devotes a population of 200-250 animals to the process of transgenic production and supports an additional population of > 1,000 animals for breeding, line maintenance, and other research demands Excluded by Requester personal communication). Based upon these numbers, the present US population is clearly insu Excluded by Requester the proposed demand stemming from transgenic production, alone.

If the US biomedical research community is going to be able to take advantage of the opportunities presented by this unique research resource, there must be a greater commitment to the development and maintenance of marmoset resources. Most importantly, seizing this opportunity will require

- a marmoset population adequate to meet growing research demands;
- concerted research and managerial efforts to establish more standardized husbandry practices;
- development of sufficient veterinary, animal care, and technical staff dedicated to the management and use of marmoset in biomedical research, such that the largest number of investigators can take advantage of the translational potential of this species.

The SNPRC as an ideal environment for developing marmoset research resources

The SNPRC is one of only two NPRCs with the infrastructure and expertise already in place to not only maintain but further develop marmosets as a research resource. SNPRC is a part of the Texas Biomedical Research Institute (Texas Biomed). Texas Biomed is one of the top independent, non-profit organizations dedicated to research on human diseases. Founded in 1941, Texas Biomed is comprised of two research departments, the Department of Genetics and the Department of Virology and Immunology and is the host institute for the SNPRC. The Department of Genetics focuses on characterizing the genetic components of susceptibility to common diseases in humans through the use of human and non-human primate populations. Cardiovascular disease, diabetes and obesity, fetal growth and development, osteoporosis, epilepsy, and mental illnesses are among the many well-established research focuses for this group. The department houses the world's largest computer cluster for human genetic and genomic research, the AT&T Genomics Computing Center, which currently contains 9,000 processors working in parallel to analyze the data to help scientists find disease-influencing genes. This capacity is critical to the high throughput sequencing of the marmoset genome. The Department of Virology and Immunology focuses on a broad array of human infectious diseases, including AIDS, hepatitis, and herpes virus. There is a research emphasis on high containment agents known as potential bioterror agents due to their high morbidity and mortality in humans, such as Ebola and Marburg viruses, SARS, avian flu and anthrax. The work on these agents is performed at Biosafety Level 4 (BSL4). Texas Biomed operates the only privately owned ABSL4 laboratory and is a leader in vaccine development for these agents.

The SNPRC provides an unparalleled combination of nonhuman primate resources and specialized scientific resources and capabilities for support of collaborative research activities. A unique asset that the host institution, Texas Biomed, has pioneered over the last 30 years is its capabilities in genetic and demographic management, genotyping, gene mapping and genetic analysis techniques for nonhuman primates. We have unparalleled capabilities in genetic analysis and have developed a wide variety of analytical strategies and software packages for analyzing genetic data (1,6).

The SNPRC and its host institution, Texas Biomed, have a strong commitment to the development of resources needed for infectious disease research using nonhuman primates. Texas Biomed is the only institution in the country that has both a National Primate Research Center and a Biocontainment Level 4 laboratory which is available for experiments with monkeys, as well as NHP Biocontainment Level 3 housing. The combination of expertise in experimental manipulation of nonhuman primates and expertise in maximum biocontainment, positions the SNPRC to play a critical role in studies of select agents and emerging pathogens. Marmosets have played an important role as one of the NHP models for filovirus research including Ebola virus.

SNPRC provides access to three main nonhuman-primate species for biomedical research – a large, pedigreed baboon colony, a SPF rhesus macaque colony, and a marmoset colony. SNPRC presently houses two genetically and nutritionally distinct marmoset colonies, the original SNPRC colony and a colony derived from the NEPRC colony. In addition, in collaboration with the Barshop Institute for Longevity and Aging Studies at University of Texas Health Science Center at San Antonio, we have developed a barrier colony of marmosets for aging studies that are SPF for two viruses of marmoset origin and maintained on sterilized food and water to prevent infection with endoparasites and other pathogens.

Progress and Major Accomplishments

Notable Accomplishments

Since the last competitive submission, the following are notable accomplishments stemming from the SNPRC marmoset program:

1. Implementation of Recommendations for Marmosets by EPIDS. SNPRC formed an Expert Panel on Infectious Disease Surveillance (EPIDS) and had a meeting at the SNPRC between March 26 and March 28, 2014 – see Overall Progress Report for more details on the panel. Of relevance to this Revision was the committee's review of the suggestion from the last SNPRC competitive review that SNPRC create a

reviewers' comments

reviewers' comments

We have developed PCR based assays for the screening. Of interest is the finding that a third colony derived from SNPRC Colony 1 and being maintained as a barrier colony at the UTHSCSA Barshop Institute for Longevity and Aging appears to have a higher fecundity than Colony 1. This colony was founded by selecting animals negative for both viruses, but the relationship of virus to increased fecundity and or health is unknown. The initial goal is to determine if Colony 1 and 2 differ in the prevalence of these viruses and whether the differences correlate with changes in health status. No samples from the NEPRC colony were available for testing at the time of this submission. We have screened the Barshop colony recently and confirmed that years after formation, the colony remains virus negative, suggesting that elimination of these viruses is possible if it was a justifiable expense that could be supported by investigators long term.
2. Genomics. The marmoset genome has been sequenced and annotated. The process of selection of the marmoset for genome sequencing was initiated with submission of a white paper that was co-authored by Excluded by Requester and SNPRC provided the material used for the sequencing. Excluded by Requester then served as the Excluded by Requester cies expert on the panel that assessed notable findings from the genome sequence, including po basis for the evolved miniaturization in this species, a refined understanding of the evolution of primate microRNAs, and a possible genetic basis for the derived feature of twinning, a finding that may be applied to better understanding of twinning in humans. Two publications, one in *Nature Genetics* and one in *PNAS*, report on these findings (8, 22)
3. iPS Cells and Regenerative Medicine. The laboratory of Excluded by Requester (UTHSCSA), using SNPRC resources, generated the first marmoset induced pluripotent stem cells (23) Excluded by Requester has since Excluded by Requester successfully reprogrammed these cells into diverse lineages. He is experimenting with their adminis into marmosets, with an ultimate goal of conducting such studies with an established neurodegenerative disease model. the MPTP-exposed marmoset. Toward this goal, collaborations have been established between Excluded by Requester is a new SNPRC Core Scientist, who was hired to establish a regenerative medicine program within the primate center. Excluded by Requester have already received pilot funding from UTHSCSA and from a private foundation to advance this collaboration.
4. Obesity. Obesity research at SNPRC resulted in seven publications with 4 in 2013 (10,15,20,24) describing both the development of pediatric obesity in this species, associated maturational differences in obese and non-obese individuals, and the presence of early-life insulin resistance.
5. Aging. The SNPRC has collaborated with the Barshop Institute for Longevity & Aging Studies (UTHSCSA) in the development of the marmoset as an aging model. With support from an NIH R24 grant, Excluded by Requester Excluded by Requester established a barrier-maintained colony of marmosets, verifying that this intensive management protocol decreased early adult mortality – a critical feature in development of any model to be used in longitudinal aging studies. We also recently reported our ability to rapidly and reliably dose socially housed marmosets with an oral form of rapamycin that is well tolerated and results in suppression of the mTOR pathway (21). Rapamycin is the first pharmaceutical intervention found to reliably increase lifespan in a rodent model (9), a finding that was touted as one of the top 10 scientific discoveries of 2009 by *Science*. Translation of this important finding to improving human health is dependent upon testing for both efficacy and side-effects in a model more closely related to humans. The marmoset is the only commonly used nonhuman primate model in which longitudinal studies that encompass an adequate expanse of the life-span can be conducted within a five year period. Those studies are planned to begin in 2015.
6. Intergenerational programming of reproductive function. Excluded by Requester (University of Illinois at Chicago) published results indicating that the litter size into which a female marmoset is born affects the likelihood of that female experiencing pregnancy loss as an adult (16). Based upon these findings, Dr. Excluded by Requester obtained an R01 grant from NICHD to further explore how the different intrauterine environment

of twin- versus triplet –born females may program reproductive development and adult female reproductive health.

The last two rounds of the SNPRC Pilot Grant program selected two marmoset grants at each round as the most meritorious of all applications. These included programs on high containment viruses, a model for multiple sclerosis, neural stem cell therapy using iPS derived stem cells, and a model for pulmonary fibrosis.

Marmoset Resource Use

Table1 provides information on research projects using the SNPRC marmosets from 2010 to present, with new projects since the 2013 competitive renewal submission indicated in bold italics.

Table 1

Principal Investigator & Institution	Project Title	Sponsor	Period Of Support	Animal Use	On-Site Research Use
Excluded by Requester SNPRC	GBV-B: A small primate model for hepatitis C infection	NIH/R01 AI049574	05/01/04-04/30/11	Animals	X
Excluded by Requester UTHSCSA Excluded by Requester COG	The common marmoset as a primate model of maternal obesity	NIH/R01 DK077639	09/01/06-09/01/11	Animals	X
Excluded by Requester SNPRC	Luminex technology for the quantification of cytokines in nonhuman primates	NIH/R24 RR023345	09/15/06-06/30/10	Tissues	X
Excluded by Requester UTHSCSA	A neuroimaging study of primate brain development and aging in the marmoset	NIH/R01 AG029412	09/15/07-06/30/12	Animals, Tissues	
Excluded by Requester Texas	The common marmoset as a model for Marburg hemorrhagic fever	NIH/U54 AI057156	10/01/07- present	Animals	X
Excluded by Requester Wisconsin	Neuroendocrine Control of Paternal Care in the Common Marmoset	NIH/R21-HD057684	01/5/09-12/31/10	Animals	
Excluded by Requester UTSA	Evoked otoacoustic emissions in the common marmoset (*Callithrix jacchus*): age and gender effects	NIH/R03 DC009050	01/31/09-01/31/11	Animals	X
Excluded by Requester UTHSCSA	Effects of aging on vaccine efficacy in nonhuman primate models	NIH/R01AG-030119-01A2	04/01/09- 03/31/12	Animals	X
Excluded by Requester UC San	Marmosets as a model of audition	University	10/13/09-11/02/10	Animals	
Excluded by Requester Excluded by UTSA & UTHSCSA	Age, hearing loss and the cocktail party problem	San Antonio Life Sciences Institute	02/01/10-01/30/11	Animals	
Excluded by Requester UTHSCSA	Development of a barrier colony of marmosets	NIH1R24 RR023344	03/01/10- 02/28/14	Animals	X
Excluded by Requester UTMB, y of Georgia	Non-invasive optical imaging of select agent bacteria in nonhuman primates	ARRA 09 092/1U01AI82103	03/09/10	Animals	
Excluded by Requester SNPRC	Nonhuman primate transcriptome reference sequence project	SNPRC	08/19/10	Tissues	
Excluded by Requester Excluded by UTHSCSA	Effects of rapamycin in a short-lived non-human primate	Barshop Institute, UTHSCSA	09/25/10-04/30/13	Animals	X
Excluded by Requester SNPRC	The innate immune response in the marmoset model of GBV-B infections: A surrogate model for HCV infection	1 R01 AI095680	07/01/11- 06/30/15	Animals	X
Excluded by Requester ACOG	Investigation of the Placental CRH System in a Common Marmoset	SNPRC Pilot Grant	05/01/12-04/30/13	Animals	X
Excluded by Requester UTHSCSA	Integrating Motor, Cognitive, and Affect Measures in a Parkinson's Disease Model	SNPRC Pilot Grant	05/01/12-04/30/13	Animals	X
Excluded by Requester UTHSCSA	Develop Assays to Characterize Marmoset Mammary Stem Cells During Aging	SNPRC Pilot Grant	11/01/12-10/31/14	Animals	X

Excluded by Requester Texas Biomed	Development Of An Animal Model For Crimean Congo Hemorrhagic Fever Virus (CCHFV)	SNPRC Pilot Grant	05/01/13-	Animals	X
Excluded by Requester UTHSCSA	Stem Cell Therapy In The Marmoset: Preliminary Trial Of Intranasal Delivery	SNPRC Pilot Grant	05/01/13-	Animals	X
Excluded by Requester ***Trinity Univ***	***Cognitive dysfunction in the marmoset EAE model***	***SNPRC Pilot Grant***	***9/4/13 – 8/30/14***	***Animals***	***X***
Excluded by ***Duke Univ***	***Gastrin-releasing peptide and pulmonary fibrosis***	***SNPRC Pilot Grant***	***9/24/13 – 8/30/14***	***Animals***	***X***
Excluded by Requester ***Univ Illinois Chicago***	***Transgenerational programming of reproductive development & health in the common marmoset***	***5R01HD076018***	***4/30/14 – 4/30/2018***	***Animals***	***X***
Excluded by Requester Excluded ***SNPRC & UTHSCSA***	***Parkinson's Disease: autologous cell therapy in the marmoset***	***TBRI,*** Private Source Private Source ***CTSA/IIMS Pilot Grant***	***8/12/14 -***	***Animals***	***X***
Excluded by Requester ***Univ Louisville***	***Development of new bivalent cross-protective arenaviral vaccines***	***5R01AI093450***	***4/1/11-3/31/16***	***Animals***	***X***
Excluded by Requester Excluded by Private Source ***Univ & U Washington***	***A metabolomics model of aging in the common marmoset***	***5R01AG038746***	***1/4/15-5/31/16***	***Animals***	***X***
Excluded by Requester ***UTHSCSA***	***A nonhuman primate model of nontuberculous mycobacterial (NTM) lung disease***	***UTHSCSA***	***1/16-14 -***	***Animals***	***X***
Excluded by Requester ***Texas Biomed***	***Antibody therapy in marmoset Ebola model***	***FDA contract***	***1/1/2015-***	***Animals***	***X***

Table 2 provides a list of investigators who have requested to purchase marmosets since 2014 whose requests remain active. From 2013-2014, we were unable to meet most requests for marmoset purchases as animals were not available. All save two of the investigators who contacted us in 2014 asked to remain in the queue for possible animals available in 2015, as they were unable to locate marmosets to meet their needs through other sources.

Table 2

Proprietary Info

Colony 2 Relocation

We successfully relocated 90 marmosets from NEPRC to SNPRC in November, 2014 and an additional 90 animals will arrive on January 28, 2015. The animals were shipped in intact social units as much as is possible given limitations of transport crate size. We set up the marmosets in caging configurations that, as closely as possible, mirrored their configuration at NEPRC, in terms of identity of neighboring groups. The November shipment completed quarantine with no mortality. Five breeder females were believed to be pregnant at the time of shipment. Four out of 5 appear to have retained their pregnancies and two deliveries of viable offspring occurred during the quarantine period.

The marmosets from NEPRC (hereafter referred to as colony 2) are maintained in a building that is physically separate from the buildings housing the original SNPRC marmoset colony (hereafter referred to colony 1) and that contain no other nonhuman primates. Specific Animal Location underwent renovation prior to the arrival of the first shipment. Renovations included the addition of drain trench grating to allow for cage rolling;

installation of a dishwasher and a water softener; repair of the roof skylights; the placement of a concrete slab at the exterior yard and the addition of Specific Animal Location containers for cage movement and storage.

Service Plan

Revisions in our planned service activities are described herein. The primary aim of the coming grant period continues to be to produce marmosets and provide them to NIH-supported investigators. Colony 1 was minimally able to meet the present SNPRC need and was not able to support any growth in projects or any sales to outside investigators. The addition of the colony 2 more than doubles the SNPRC marmoset population – from 146 to 327 animals. More specifically, it increases the SNPRC marmoset population available for use or breeding in 2015 by 60% - from 97 to 148 animals. After assessing the age/sex structure of each population, and the anticipated need for on-site projects in 2015 and 2016, we plan to provide some marmosets to at least 3-4 of the investigators who have unmet requests, with preference given to those investigators who will be using the animals in NIH-funded projects (see Table 2).

Production

Between the two marmoset colonies, the present breeding population is 21 breeding pairs – marmosets are routinely housed as mated male x female pairs plus up to 6-7 of their offspring, reflecting their social structure in the wild and ensuring that non-breeding individuals gain experience in cooperative infant care, increasing their value as future breeders (18). Our historic data on production of weaned offspring per pair per year indicates that an estimate of 2.2 young per pair per year is a conservative target. We propose to produce 70 weaned young per year, plus 10 replacement breeders, requiring a breeding population of 36 pairs for 2015. Therefore, we will be retaining 30 animals (15 males and 15 females) as new breeding stock, for a total of 18 breeding groups in each colony.

Genetic Management

While maintaining the SNPRC and NEPRC populations as separate entities, we will design and implement plans to define the genetic diversity in the two populations. Based upon these findings, we will structure a long-term management plan to most effectively maintain the diversity present in the populations.

The major goals of our breeding program are to maintain the genetic diversity present in each colony and, in the future be able to enrich for genetic variants of interest to investigators using these animals for biomedical research. Of immediate concern are the effects that loss of variability may have in reducing the chance that genes underlying biomedically relevant phenotypes can be detected and in reducing the generality of experimental outcome as animals become more genetically homogeneous. Even when study goals are not explicitly genetic, knowledge of pedigree relationships can greatly enhance the value of research animals - the assumption of independence among experimental subjects is a risky one if the animals are all derived from the same limited number of ancestors.

For the SNPRC marmoset colonies, breeding decisions are currently based on a multigenerational pedigree developed at the SNPRC for Colony 1 and developed at the NEPRC for Colony 2. Because of the manner in which marmosets are bred, clean demographic data generally provide clear pedigree information that can be used, directly to make breeding decisions that keep inbreeding coefficients and founder representation acceptable. Breeder selection is presently made to maintain inbreeding coefficients that are as low as possible - but not to exceed 0.0625 – and to maintain founder representation for as many founders as possible. That, on occasion, means that we will continue breeding individuals with less than optimal breeding performance if elimination of that breeding pair would reduce or eliminate representation of a given founder within the population.

Figure 2 illustrates findings on genetic diversity within the NPRC marmoset population, based upon a SNP variation study conducted by the Marmoset Genome Sequencing and Analysis Consortium in a small number of subjects from each of the NPRC colonies in existence in 2012 (22). The results indicate that there is significant variation both within and among these populations. The future management of this diversity will be aimed at not only maintaining the diversity but, as stated previously, identifying and enriching for genetic variants of interest to investigators. SNPRC and Texas Biomed historically have specialized in the molecular genetics of NHPs. We have adapted high throughput genotyping techniques initially developed for human DNA samples to nonhuman primates. These techniques have been used to construct gene maps for both rhesus monkeys and baboons. The SNPRC is now poised to move into what is clearly the future of this type of

genetic characterization, genotype by sequencing. The transition to genomic sequencing is predicted and supported – for example, as the future of genetic testing of SPF rhesus in the White Paper generated by the NPRC GGWG. Unpublished

Unpublished ." The technology developed by Excluded by Requester Excluded by Requester SNPRC has made this practical and affordable and is supported by a new Genomics Core within led The ultimate goal for the marmosets will be to identify >50,000 SNPs that will provide tion for genetic management, as well as determine the genetic differences in the two colonies that will benefit research scientists. In contrast to the limited detection of variation by traditional efforts such as microsatellite markers and SNP chips, the new efforts in genomic sequencing will capture tens of thousands of sequence variations between animals and between colonies.

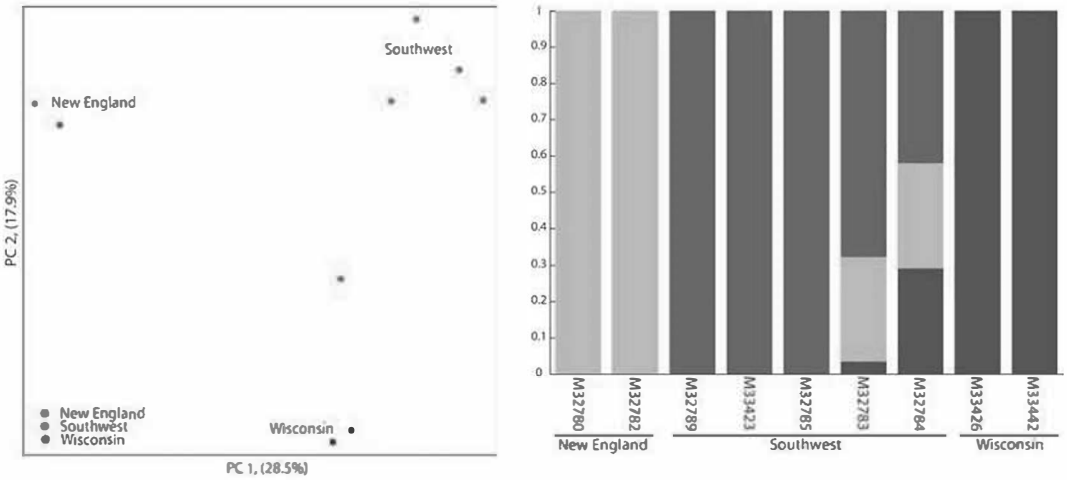


Figure 2. Summary of SNP Variation Analyses from Excluded by Requester (22) (a) Principal component analysis of SNPs separates 9 animals from the SNPRC, NEPRC and Wisconsin NPRC; (b) admixture among these 9 marmosets in the US.

The goals of maintaining genetic diversity and enriching for desired genetic variants are often conflicting goals and best addressed with the highest resolution genomic data possible to inform breeding decisions.
As genotype information becomes available for the marmoset colonies, we will establish a working group to direct the interpretation of these data; to determine the best mechanisms to advertise the availability of these data to the marmoset research community and receive their feedback regarding genotypes of interest; and to decide how breeding decisions may then take into account the need for these genotypes. This work group will include Excluded by Requester (primary marmoset veterinarian), and two scientists who represent marmoset users.

Nutritional Management

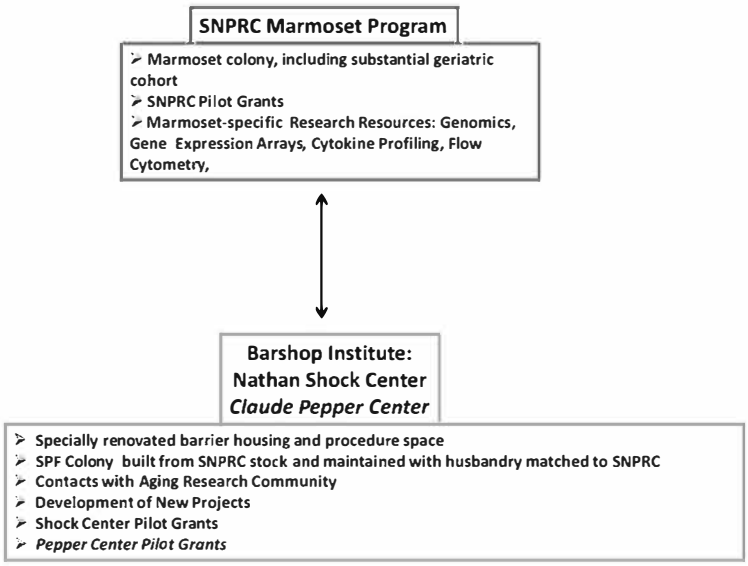
We also intend to design and implement plans to determine effects of dietary change upon health in these two marmoset populations, ultimately defining the best diet for continued use. The full potential of the marmoset as a research model has not been realized due to a lack of evidence-based, standardized procedures for their captive management, especially regarding diet and feeding husbandry. We, therefore, in collaboration with the Wisconsin NPRC (WNPRC) and the NEPRC prepared an application for an R24 grant to establish standards for a nutritionally healthy, captive common marmoset. After the announcement of the closure of the NEPRC, and the transfer of those marmosets to WNPRC and SNPRC, these studies were redesigned to take advantage of the natural experiment presented in having the NEPRC marmosets moved to these two new environments. The studies will identify critical features of a standardized basic diet for captive common marmosets; determine links between diet, gut microbiome, and disease; and establish standards for healthy weights, body condition, and biomarkers of metabolic function. The Specific Aims are: (1) conducting nutritional assessments regarding select macro- and micro-nutrient requirements for marmosets and their relations to biomarkers of gut function on different diets; (2) validating markers of healthy weight and metabolic function in captive common marmosets; (3) identifying links between nutrition and disease in captive common marmosets, concentrating on the most common chronic disease states – inflammatory bowel diseases and inflammatory kidney diseases – as well as more novel diseases that may be important biomedical models – hepatic steatosis, diabetes and atherosclerosis.

Geriatric Resource Development

We plan to establish a specific resource of geriatric marmosets to be used in studies of aging and chronic disease. With its small size and short life span, the marmoset presents unique opportunities for aging studies. The collaboration between the Barshop Institute for Longevity & Aging Studies (UTHSCSA) and the SNPRC – two, geographically close institutions with established expertise in marmoset research resource development and aging research - will allow us to parlay the strengths of each institution, to further aging research and ensure a stable base of support for the required resources. With the addition of colony 2, the SNPRC has one of the largest marmoset research populations in the U.S. and the only large (>70) population of aged (> 10 years) marmosets in the country, while the Barshop Institute has the only specially designed barrier facility for

Excluded by Requester

rm housing and research use of marmosets has appointments at both institutions. The mentary infrastructure, animal, laboratory and pilot funding resources of the SNPRC and the Barshop Institute are a unique and powerful combination that can advance aging research in nonhuman primates in a fashion not previously possible – see Fig 3.



Italics = resources under review for funding

Figure 3. San Antonio resources supporting aging research with the common marmoset.

Publications

This list provides publications from 2010 to present that resulted from the use of the SNPRC marmoset colony. Those publications since the last competitive renewal submission are indicated in bold italics.

2010

Excluded by Requester
Systems biology discoveries using non-human primate pluripotent stem and germ cells: Novel gene and genomic imprinting interactions as well as unique expression patterns. Stem Cell Res Ther. 2010; 1(3): 24. PMCID: PMC2941116.

Excluded by Requester Diffusion tensor and perfusion MRI of non-human primates. Methods. 2010 03; 50(3): 125-135. PMCID: PMC2828503.

Excluded by Requester Development of structural MR brain imaging protocols to study genetics and maturation. Methods. 2010 03; 50(3): 136-146. PMCID: PMC2828529.

Excluded by Requester
Excluded by Requester On the genetic architecture of cortical folding and brain volume in primates. Neuroimage 2010 53(3): 1103-1108. PMCID: PMC3137430.

Excluded by Requester
Excluded by Requester Evaluation of RepliVAX WN, a single-cycle flavivirus vaccine, in a non-human primate model of West Nile virus infection. Am J Trop Med Hyg. 2010 06; 82(6): 1160-1167. PMCID: PMC2877429.

Excluded by Requester Generation of induced pluripotent stem cells from newborn marmoset skin fibroblasts. Stem Cell Res 2010; 4: 180-188. PMCID: PMC2875323.

2011

Excluded by Requester
Attentuation of liver soluble protein carbonyls: indicator of a longevity determinant? Aging Cell. 2011; 10(4):720-723.

Excluded by Requester Vaccines against viral hemorrhagic fevers: Non-human primate models. Hum Vaccin. 2011 06/01; 7(6): 667-673.

Excluded by Requester A small nonhuman primate model for filovirus-induced disease. Virology. 2011 11/25; 420(2): 117-124. PMCID: PMC3195836.

Excluded by Requester Comparative studies of vertebrate lipoprotein lipase: A key enzyme of very low density lipoprotein metabolism. Comp Biochem Physiol Part D Genomics Proteomics. 2011 06; 6(2): 224-234. PMCID: PMC3102144.

Excluded by Requester Genomics and proteomics of vertebrate cholesterol ester lipase (LIPA) and cholesterol 25-hydroxylase (CH25H). 3 Biotech. 2011 09; 1(2): 99-109. PMCID: PMC3324826.

Excluded by Requester Vertebrate endothelial lipase: Comparative studies of an ancient gene and protein in vertebrate evolution. Genetica. 2011 03; 139(3): 291-304. PMCID: PMC3482104.

Excluded by Requester Stereotaxic Brain Atlas of the Marmoset. Plenum Press, 2011.

Excluded by Requester Hormones and reproductive cycles in primates. In: Excluded by Requester
Excluded by Requester Hormones and Reproduction of Vertebrates Vol 5 – Mammals. Pp. 291-328, Elsevier, 2011.

Excluded by Requester The marmoset as a model of aging and age-related diseases. ILAR J. 2011 02/08; 52(1): 54-65.

Excluded by Requester Differential endocrine responses to infant odors in common marmoset (Callithrix jacchus) fathers. Horm Behav. 2011; 59: 265-270. PMCID: PMC3040271.

2012

Excluded by Requester Nonhuman Primates in Biomedical Research. Elsevier, NY, 2012.

Excluded by Requester An animal model that reflects human disease: The common marmoset (Callithrix jacchus). Curr Opin Virol. 2012 06; 2(3): 357-362. PMCID: PMC3378983.

Excluded by Requester Comparative studies of glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1: Evidence for a eutherian mammalian origin for the GPIHBP1 gene from an LY6-like gene. 3 Biotech 2012 03; 2(1): 37-52. PMCID: PMC3339605.

Excluded by Requester Androgen receptor CAG repeat polymorphism in males of six non-human primate species. J Med Primatol. 2012 02; 41(1): 67-70. PMCID: PMC3479659.

Excluded by Requester The development of obesity begins at an early age in captive common marmosets (Callithrix jacchus) Am J Primatol. 2012 03; 74(3): 261-269.

Excluded by Requester

Excluded by Requester Meeting report: Spontaneous lesions and diseases in wild, captive-bred, and zoo-housed nonhuman primates and in nonhuman primate species used in drug safety studies. Vet Pathol. 2012 11; 49(6): 1057-1069.

Excluded by Requester Aging phenotypes of common marmosets (Callithrix jacchus). J Aging Res. 2012; 2012:567143. PMCID: PMC3312272.

In Press

Excluded by Requester Building marmoset babies: trade-offs and cutting bait. In: Clancy K, Hinde K, Rutherford J, eds. Building Babies: Primate Development in Proximate and Ultimate Perspective. Pp.169-186, Springer, NY, 2012.

Excluded by Requester Reproduction and breeding of nonhuman primates. In: C Abee, K Mansfield, S Tardif, T Morris, eds, Nonhuman Primates in Biomedical Research. Ch. 8. Pp. 197-249, Elsevier, NY, 2012.

Excluded by Requester Differential hypothalamic secretion of neurocrines in male common marmosets: Parental experience effects? J Neuroendocrinol. 2012 Mar;24(3):413-421. PMCID: PMC3288632.

Excluded by Requester Nonhuman primate induced pluripotent stem cells in regenerative medicine. Stem Cells Int. 2012; 2012: 767195. PMCID: PMC3345260.

2013

Excluded by Requester Accessibility of retinal cells to different AAV serotypes after intravitreal injection in Old versus New World

Primates. Abstract in preparation for the 2013 Association for Research in Vision and Ophthalmology conference. 2013.

Excluded by Requester Metabolic consequences of the early onset of obesity in common marmosets. Obesity (Silver Spring). 2013 Mar 20. doi: 10.1002/oby.20462. [Epub ahead of print].

Excluded by Requester Body mass growth in common marmosets: toward a model of pediatric obesity Am J Phys Anthropol. 2013 Jan;150(1):21-28. PMCID: PMC3607500.

Excluded by Requester ***2013. IACUC review of nonhuman primate research. ILAR J 54:234-245. PMCID:PMC3814393***

Excluded by Requester ***2013. Relation of food intake behaviors and obesity development in young common marmoset monkeys. Obesity 21(9):1891-1899. PMCID: PMC3722271***

Excluded by Requester

Excluded by Requester ***2013. Experimental cross-species infection of common marmosets by titi monkey adenovirus. PLoS ONE. 8(7):e68558. PMID: 23894316; PMCID: PMC3722195.***

Excluded by Requester ***2013. Development of metabolic function biomarkers in the common marmoset, Callithrix jacchus. Am J Primatol 75:500-508. doi:10.1002/ajp.22126. PMCID: PMC3771328***

2014

Excluded by Requester ***2014. Evolutionary genetics and implications of small size and twinning in callitrichine primates. Proc Natl Acad Sci U S A 111(4):1467-1472. PMCID: PMC3910650***

Excluded by Requester

Excluded by Requester ***Why primate models matter. Am J Primatol 2014 Sep; 76(9):801-827. PMID: 24723482; PMCID: PMC4145602 [Available on 2015/3/1].***

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VERTEBRATE ANIMALS

1. Description of Animal Use

Currently we are maintaining approximately 300 marmosets (*Callithrix jacchus*) of all ages and sexes. The research requirements encompassed by the SNPRC's scientific programs may require animals of both sexes and all ages, with varying numbers of animals for each project. We propose to maintain a breeding population of 36 breeding pairs. Based upon past experience, such a production population should result in approximately 80 offspring per year that can be used in research projects or as replacement breeders. We will monitor demand for use of marmosets closely throughout the funding period. There is potential to increase the breeding population if it appears that future demands will justify such an expansion. Because marmosets are considered mature at around 18 months of age and the gestation period is approximately 5 months, any expansion of the breeding population will result in expansion of the population useable for research in no less than 2 years time.

The proposed use of animals in this proposal is for all SNPRC-based observational and experimental studies, including clinical medical and surgical support for naturally-occurring and research-related clinical conditions, and standard preventive medicine for all non-human primates encompassed within its programs of animal care and use.

2. Justification of Animal Use

Through IACUC Committee review and approval mechanisms administered via the Texas Biomedical Research Institute, every SNPRC-based project must justify the numbers of animals to be used, including a statistically based power analysis wherever possible. In pilot studies, training protocols, or other types of work where power calculations are not applicable, a detailed written narrative describing how the requested animal numbers were determined is still required, including an appropriate rationale for group sizes and other attributes of experimental design and anticipated outcomes for the minimum animal numbers necessary to fulfill the study aims. Additionally, the internal process followed at the SNPRC requires investigators to consult with veterinary and research support staff regarding the proposed animal species, numbers involved, their availability, housing and care, and research-related procedures for all projects prior to study initiation. IACUC approval is required before any procedures are performed. The SNPRC takes its responsibility to conserve the animals under its care very seriously and every effort is made for the judicious selection and use in all programs and projects.

3. Veterinary Care

All nonhuman primates held and used within the SNPRC program of care at the Texas Biomedical Research Institute are maintained under conditions that meet or exceed USDA Animal Welfare Regulations, NIH standards as stated in the *Guide for the Care and Use of Laboratory Animals* (81h Edition, 2010), NAS-ILAR recommendations, and AAALAC accreditation standards for these species. Texas Biomed, including the SNPRC as a component of its overall program, is fully accredited by AAALAC International. The animals' home cages are in areas or rooms with other similarly housed animals of the same species. Cages, racks, and accessories are sanitized in mechanical cage washers at least once every 2 weeks, and waste pans are cleaned daily. The temperature inside animal quarters is maintained within a range of 62-82 degrees Fahrenheit. Animals are fed constant nutrition, complete life-cycle commercial monkey chows, supplemented daily with fruits and vegetables, and municipal drinking water is available at all times. All previous and current research activity has been conducted in accordance with the IACUC oversight process, as will be the case for the proposed grant period. The SNPRC employs a large number of full-time professional staff members to provide expertise in program administration, animal husbandry, clinical medicine, psychological well-being, facilities maintenance, animal records, and technical research support. Two of the veterinarians are board certified by the American College of Laboratory Animal Medicine and both pathologists are board certified by the American College of Veterinary Pathology. Veterinarians work closely with investigators through all stages of project planning and conduct, including participation in IACUC review and post-approval monitoring, and help oversee the delivery of research services in all SNPRC-based activities. Animal care personnel typically assist with research-related matters as part of their daily activities, and one-on-one plus broad-based training

sessions occur regularly. All members of the professional veterinary staff participate in continuing education plus veterinary science meetings and publications, to improve their clinical acumen.

4. Procedures to Minimize Pain and Discomfort

The standard procedure for handling all animals at the SNPRC is for them to be sedated before handling except for infants, marmosets, and tamarins. Any physical restraint that would be for brief periods of time for animals on IACUC approved protocols (such as chaired procedures) is accomplished by the use of various approved devices such as pole-and-collar systems. In such cases, persons involved are trained in their proper use. Procedures requiring restraint for more than brief periods of time are avoided unless absolutely essential. These procedures must be scientifically justified and approved by the IACUC, or required for clinical purposes in providing appropriate veterinary care for the minimum period necessary. For some projects, less restrictive systems which allow greater freedom of animal movement, such as jacket and tethering systems, may be used when required to meet research objectives as specified in the approved protocols. Conditioning processes involving food rewards with adequate adaptation time is allowed for all restraint-type systems, including close observation by staff members to ensure their proper use. SNPRC veterinarians have authority to terminate an animal's participation in protocols involving restraining devices. Issues of temperament, behavior, nonresponsive medical problems, among others, are considered sufficient justification to exclude animals from such studies.

Anesthesia and Anesthetic Agents Used

Sedation and anesthetic agents are used to render the animal unconscious and therefore insensate to handling, discomfort, or pain. Sedatives are used to immobilize the animals for performing minor procedures such as blood sampling or for pre-anesthesia. General anesthesia is used for procedures to produce unconsciousness by the controlled administration of a pharmacological agent for surgical procedures. The selection of the anesthetic agents used is at the discretion and direction of a veterinarian and as indicated in approved IACUC protocols. The following is a listing of drugs that are typically used and maintained in the SNPRC veterinary pharmacies. Other agents may be acquired and used if indicated at the professional discretion of a veterinarian.

Ketamine hydrochloride produces a dose-related response that ranges from mild sedation to profound unconsciousness. Ketamine is commonly administered to nonhuman primates that undergo manipulative procedures. It may be used as the single agent where mild to moderately painful procedures are anticipated, such as blood drawing, wound debridement, skin suturing and teeth scaling. Procedures that are likely to be more painful require the administration of another selective anesthetic or analgesic drug. (Dosage: 10-15 mg/kg body weight, depending on desired depth and duration.)

Tiletamine/Zolezpam (Telazol) is a proprietary dissociative/benzodiazepine. Telazol can be used as a sedative for short procedures or to produce a light plane of anesthesia. Telazol is commonly used on chimpanzees and other primates that have developed a tolerance to ketamine. Telazol must be reconstituted, held under refrigeration and then used within 2 weeks. (Dosage: 4-6 mg/kg body weight for sedation, 4-10 mg/kg body weight for light anesthesia.)

Isoflurane is a halogenated inhalant gas anesthetic. Isoflurane allows for close control of the depth of anesthesia for extended periods of time. In addition to providing for surgical anesthesia, it is used in research and diagnostic imaging procedures that require absence of animal movement. (Dosage: typically 1-3% with oxygen).

Atropine sulfate is not an anesthetic or analgesic but is administered to some animals receiving ketamine or Telazol or being prepared for general anesthesia to control salivary secretions, prevent vomiting and regurgitation, and strengthen cardiovascular function. This agent may be mixed in a syringe with ketamine. (Dosage: 0.04 mg/kg of body weight.)

Analgesia and Analgesic Agents Used

Analgesia is the reduction of pain without the loss of consciousness. A condition that would be considered painful to a human is presumed to be painful to animals, and appropriate analgesics are administered.

Similarly, analgesics are provided for all post-surgical animals. The selection of the analgesic agents used is at the discretion and direction of a veterinarian and as indicated in approved IACUC protocols (where applicable).

Following is a listing of analgesics that are typically used and maintained in the SNPRC veterinary pharmacies. Other agents may be acquired and used if indicated at the professional discretion of a veterinarian.

Aspirin and *acetaminophen* are used for relief of mild pain due to minor trauma, skin laceration, chronic inflammatory problems, menstruation, and extraction of deciduous teeth. (Dosage: *Aspirin:* 5-10 mg/kg body weight, T.I.D., *Acetaminophen:* 5-10 mg/kg, T.I.D or Q.I.D.)

Ketorolac and Meloxicam are non-narcotic, non-steroidal anti-inflammatory drugs (NSAIDs) in the same class as ibuprofen. Their analgesic and antipyretic properties make them effective drugs in controlling post-surgical, acute, or chronic pain and inflammation. For post-surgical analgesia, they are typically used with the initial dose given prior to recovery from surgical anesthesia. They are not recommended for use in animals with gastritis or thrombocytopenia. (Dosage: Ketorolac, 1 mg/kg; Meloxicam, 0.1mg/kg).

Butorphanol tartrate is a synthetic opioid analgesic used for relief of moderate to severe pain as may occur in cases of cage-mate trauma or wounds. Peak analgesia occurs 30-50 min after IM injection. (Dosage: 0.15 mg/kg body weight B.I.D. to T.I.D.)

Buprenorphine HCl and Buprenorphine SR are parenteral opioid analgesics used for the relief of moderate to severe pain. Buprenorphine HCL has a rapid onset (15-min) and persists for 6-8 hours. Peak activity is reached 60 min after IM injection. Buprenorphine SR has a rapid onset and persists for 3 – 5 days. These analgesics are typically used for relief of severe pain accompanying orthopedic repair, tooth extraction/endodontics, or extensive intra-abdominal surgery. (Buprenorphine HCl dosage: 0.015 mg/kg BID to TID; Buprenorphine SR dosage: 0.06mg/kg once.)

Hydromorphone and *fentanyl* are potent opioid analgesics used for the relief of moderate to severe pain. These agents are typically given pre- or peri-operatively to supplement analgesia and/or as an analgesic for post-operative pain. (Dosage: *Hydromorphone:* 0.1-0.2 mg/kg IM or IV; *fentanyl:* 5-10 mg/kg IV, by continuous infusion @ 10-25 mcg/kg/hr, or by transdermal patch such as Duragesic.)

Lidocaine and bupivicaine are local anesthetics used intra-operatively and post-operatively to provide preemptive local wound analgesia and to help reduce post-operative pain sensation. (Concentration: 1% to 2% local infiltrate.)

Tramadol is a synthetic opioid. It is used to treat moderate to severe pain. It is primarily used post-operatively or as an analgesic for trauma. It can be used for multimodal analgesia when coupled with an NSAID. (Dosage: 2-4 mg/kg B.I.D.)

5. Euthanasia

Humane euthanasia of nonhuman primates at the SNPRC is performed under the supervision of a staff veterinarian and in accordance with the professional principles and practices specified by the *American Veterinary Medical Association Guidelines for the Euthanasia of Animals: 2013 Edition.* Any animal to be euthanized is first rendered unconscious by administration of ketamine hydrochloride or Telazol, and then the animal is euthanized by one of the following methods:

- Rapid intravenous administration of sodium pentobarbital (100 mg/kg body weight IV).
- Intravenous administration of Fatal Plus® (or equivalent) while the animal is under deep anesthesia (1 ml solution per 10 lbs body weight).
- Exsanguination while the animal is under deep surgical planes of anesthesia, as provided by the injectable and inhalant anesthetic agents described above. This method is used only if the scientific requirements for a research protocol noted in corresponding IACUC approvals preclude the use of pentobarbital or euthanasia solution.

All of the following physiological criteria must be met for death to be declared:

- Absence of thoracic sounds by auscultation.
- Absence of respiratory effort.
- Dilation and immobility of pupils.

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