PRIMATE RESEARCH CENTER GRANT
Department of Health and Human Services
National Institutes of Health

Federal Award Date: 06/18/2019

OFFICE OF THE DIRECTOR, NATIONAL INSTITUTES OF HEALTH

Grant Number: 5P51OD011132-59
FAIN: P51OD011132

Principal Investigator(s):
JONATHAN S LEWIN, MD

Project Title: Support of Yerkes National Primate Research Center

Barry C. Pine
Director, Pre-award Grants Adm
1599 Clifton Road NE, 4th Floor
1599-001-1BA
Atlanta, GA 303224250

Award e-mailed to: osp@emory.edu

Period Of Performance:
Budget Period: 05/01/2019 – 04/30/2020
Project Period: 05/01/1997 – 04/30/2021

Dear Business Official:

The National Institutes of Health hereby awards a grant in the amount of $10,540,602 (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to EMORY UNIVERSITY in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

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

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the Office Of The Director, National Institutes Of Health of the National Institutes of Health under Award Number P51OD011132. 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,

Debbie Chen
Grants Management Officer
OFFICE OF THE DIRECTOR, NATIONAL INSTITUTES OF HEALTH

Additional information follows

SECTION I – AWARD DATA – 5P51OD011132-59

Award Calculation (U.S. Dollars)

Salaries and Wages	$3,903,118
Fringe Benefits	$960,168
Personnel Costs (Subtotal)	$4,863,286
Consultant Services	$8,000
Equipment	$584,305
Materials & Supplies	$1,000,086
Travel	$43,706
Other	$951,334
Federal Direct Costs	$7,450,717
Federal F&A Costs	$3,089,885
Approved Budget	$10,540,602
Total Amount of Federal Funds Obligated (Federal Share)	$10,540,602
TOTAL FEDERAL AWARD AMOUNT	$10,540,602
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$10,540,602

SUMMARY TOTALS FOR ALL YEARS		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
59	$10,540,602	$10,540,602
60	$10,540,602	$10,540,602

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

Fiscal Information:

CFDA Name:	Research Infrastructure Programs
CFDA Number:	93.351
EIN:	1580566256A1
Document Number:	POD011132J
PMS Account Type:	P (Subaccount)
Fiscal Year:	2019

IC	CAN	2019	2020
OD	8014499	$10,540,602	$10,540,602

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

eRA Commons User Name

NIH Administrative Data:
PCC: CMP01 / **OC**: 414E / **Released** 06/17/2019
Award Processed: 06/18/2019 12:17:12 AM

SECTION II – PAYMENT/HOTLINE INFORMATION – 5P51OD011132-59

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 – 5P51OD011132-59

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

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 75.
d. National Policy Requirements and all other requirements described in the NIH Grants

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

e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
f. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

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

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

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

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

This award is subject to the requirements of 2 CFR Part 25 for institutions to receive a Dun & Bradstreet Universal Numbering System (DUNS) number and maintain an active registration in the 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) P51OD011132. 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/.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts with cumulative total value greater than $10,000,000 must report and maintain information in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently the Federal Awardee Performance and Integrity Information System (FAPIIS)). Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75. This term does not apply to NIH fellowships.

Treatment of Program Income:
Additional Costs

Clinical Trial Indicator: No
This award does not support any NIH-defined Clinical Trials. See the NIH Grants Policy Statement Section 1.2 for NIH definition of Clinical Trial.

SUBJECT FOA
This award is subject to the conditions set forth in PAR-14-226, "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: https://grants.nih.gov/grants/guide/pa-files/PAR-14-226.html

ORIP FUNDING PLAN FOR FY2019
This non-competing award reflects the NIH Fiscal Policy for Grant Awards for FY2019 (see NIH Guide Notice NOT-19-031) and the implementation of the ORIP FY2019 grants funding policy: https://orip.nih.gov/funding/awards-funding-policy

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

Redacted by agreement

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.

FOREIGN COMPONENT
This award includes total costs in the amount of $64,800 for the following foreign sites:

SWEDEN - KAROLINSKA INSTITUTE

PRIOR APPROVAL REQUEST
Any prior approval request (e.g., changes to key personnel as noted on the award, changes in human and animal subjects requiring prior approval, carryover requests) must be submitted to the assigned Grants Management Specialist and Programmatic Official. Please refer to Part II Chapter 8 the NIH Grants Policy Statement for the activities and/or expenditures that require NIH approval at http://grants.nih.gov/grants/policy/nihgps/nihgps.pdf

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

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

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

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: Gavin Wilkom
Email: wilkomg@mail.nih.gov **Phone**: 301-435-0964 **Fax**: (301)480-3777

Program Official: Sheri Ann Hild
Email: hildsa@mail.nih.gov **Phone**: 301-435-8382 **Fax**: 301-402-4104

SPREADSHEET SUMMARY
GRANT NUMBER: 5P51OD011132-59

INSTITUTION: EMORY UNIVERSITY

Budget	Year 59	Year 60
Salaries and Wages	$3,903,118	$3,929,508
Fringe Benefits	$960,168	$966,666
Personnel Costs (Subtotal)	$4,863,286	$4,896,174
Consultant Services	$8,000	$7,791
Equipment	$584,305	$368,592
Materials & Supplies	$1,000,086	$992,146
Travel	$43,706	$30,189
Alterations and Renovations		$215,713
Other	$951,334	$940,112
TOTAL FEDERAL DC	$7,450,717	$7,450,717
TOTAL FEDERAL F&A	$3,089,885	$3,089,885
TOTAL COST	$10,540,602	$10,540,602

Facilities and Administrative Costs	Year 59	Year 60
F&A Cost Rate 1	45%	45%
F&A Cost Base 1	$6,866,412	$6,866,412
F&A Costs 1	$3,089,885	$3,089,885

A. OVERALL COVER PAGE

Project Title: Support of Yerkes National Primate Research Center	
Grant Number: 5P51OD011132-59	**Project/Grant Period:** 05/01/1997 - 04/30/2021
Reporting Period: 05/01/2018 - 04/30/2019	**Requested Budget Period:** 05/01/2019 - 04/30/2020
Report Term Frequency: Annual	**Date Submitted:** 03/01/2019
Program Director/Principal Investigator Information: JONATHAN S LEWIN , MD **Phone number:** 404-778-4432 **Email:** jon.lewin@emory.edu	**Recipient Organization:** EMORY UNIVERSITY EMORY UNIVERSITY 1599 CLIFTON RD, 4TH FLOOR ATLANTA, GA 303224250 **DUNS:** 066469933 **EIN:** 1580566256A1 **RECIPIENT ID:**
Change of Contact PD/PI: N/A	
Administrative Official: HOLLY SOMMERS Emory University Office of Sponsored Programs 1599 Clifton Road NE, 4th FL Atlanta, GA 30322 **Phone number:** 404.727.2503 **Email:** hsomme2@emory.edu	**Signing Official:** RYAN YOUNGBLOOD 1599 Clifton Rd. Atlanta, GA 30322 **Phone number:** 404-712-3027 **Email:** ryan.youngblood@emory.edu
Human Subjects: No	**Vertebrate Animals:** Yes
hESC: No	**Inventions/Patents:** Yes If yes, previously reported: Yes

B. OVERALL ACCOMPLISHMENTS

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

The Yerkes National Primate Research Center (YNPRC) of Emory University is one of seven National Primate Research Centers sponsored by the Office of Research Infrastructure Programs (ORIP) of the National Institutes of Health. The overarching goals of Yerkes are to conduct a research program focused on scientific problems relevant to human health and the NIH mission by providing resource infrastructure and expertise in appropriate scientific and veterinary specialties and to ensure the Center's ability to serve as a resource to Core Scientists, as well as to scientists regionally, nationally and internationally. With the support of the P51 Base Grant, the Yerkes Primate Center operates two principal facilities: a Main Station on the Emory University campus, which provides animal housing facilities, research laboratories and support services and a 117 acre Field Station located 30 miles north of Atlanta, which provides housing for nonhuman primate breeding colonies, research laboratories including a genetics laboratory, and facilities for studies of the social behavior and biology of semi-free ranging nonhuman primates.

During the current reporting period (5/1/2011 to present), the Yerkes Center has recorded remarkable progress, as evidenced by numerous (>790) publications, including multiple high-impact publications, construction of new animal facilities, including a state-of-the-art transplantation and ABSL3 facility, and expansion of its research funding base, even in the era of an extremely competitive NIH funding environment, with a 13% increase in research funding in FY 2014. Consequently, we have made significant contributions to behavioral, biomedical and translational research and research training at Emory University and via collaborations on a regional and national basis. In particular, the Yerkes Primate Center has maintained outstanding core research programs, extensive collaborative relationships with scientists based in other Emory University departments and provided resources and services to a broad multidisciplinary network of affiliate and collaborative investigators throughout the region and nation. These research programs, which involve the use of a variety of nonhuman primate species, are directed primarily toward four major research disciplines, representing the research divisions within the Yerkes Center: 1) Microbiology and Immunology; 2) Developmental and Cognitive Neuroscience, 3) Neuropharmacology and Neurologic Diseases and 4) Behavioral Neuroscience and Psychiatric Disorders. Also, through the Divisions of Animal Resources and Pathology, Yerkes provides support for outside investigators conducting research at the Yerkes Center, consistent with our ORIP mandated role as a regional and national resource.

Guided by ORIP NPRC program guidelines, NIH objectives and our own strategic planning process, we propose the following Specific Aims:

1. To carry out basic and translational research using nonhuman primates to expand knowledge, develop improved treatments, and advance cures that will benefit humanity;

2. To provide regional and national resources for data, consultative expertise, biologic materials, and specialized facilities useful in supporting nonhuman primate research;

3. To study basic nonhuman primate biology and improve nonhuman primate breeding, husbandry and genetic characterization to better serve the biomedical research community; and

4. To provide research and training opportunities involving nonhuman primates to graduate and undergraduate students, postdoctoral fellows, visiting scientists and faculty members.

The pursuit of these aims will enhance the Center's ability to serve as an enabling resource to Core and Affiliate Scientists for the conduct of nonhuman primate research, all for the ultimate goal of advancing human health.

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

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: B2 Accomplishments_Overall.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

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

Yes

Revision/ Supplements #	Revision/ Supplements Title	Specific Aims	Accomplishments
3P51OD011132-58S1	Support of Yerkes National Primate Research Center -- Year 58 Supplement	The goal of this project is to enhance disaster preparedness and continuity of operations in the event of a prolonged utility interruption. Specific	1. FS Emergency Power: the generator has been ordered; installation completion expected in April 2019.

		Aims of this supplement are: 1.Enhance emergency power at the Yerkes Field Station 2.Establish backup heating fuel capacity at the Yerkes Field Station 3.Install a reliable source of emergency potable water for drinking, husbandry and to operate the HVAC at the Yerkes Main Station	2. FS Propane Plant: We selected a vendor after the minimum gas pressure requirements and bidding process. We expect to obtain Gwinnett County permit in February, installation of vaporizing system equipment in March, and connection completion in April 2019. 3. MS Emergency Potable Water: feasibility report completed on the best locations and probability of success, selected an installation contractor based on a minimum of 3 bids, and obtained DeKalb County approval. We expect to obtain Ga EPD approval in February, installation completion in March, and connection completion in April 2019

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

File uploaded: B4 Training.pdf

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

The Yerkes National Primate Research Center shares its scientific advancements via researchers publishing in peer-reviewed scientific journals and presenting at local, national and international meetings. In addition, the Yerkes Public Affairs Department: 1) publishes an employee newsletter and distributes other information, such as news releases about scientific publications, via our center's internal listserv; 2) coordinates the NPRC presence at the annual Society for Neuroscience meeting, including overseeing an exhibit booth and managing the NPRC support of the Animals in Research panel; 3) organizes presentations to the public, such as lifelong-learning programs and educational outreach to elementary, junior, high school and college students; 4) arranges tours of the Yerkes Research Center's two campuses, including our twice annual Field Station Open House; 5) distributes informational materials to tour participants; 6) works with Woodruff Health Sciences Center (WHSC) and central university Communications and Public Affairs staff to ensure Yerkes information is included in Emory and WHSC publications, electronic newsletters, blogs and tweets; 7) maintains the Yerkes website, including the News page that contains releases about the center's scientific advancements and other accomplishments; 8) oversees NPRC.org and @nprcnews, and ensures Yerkes information is included on NPRCresearch.org; 9) works with Emory graduate students and Emory Vaccine Center employees to host a booth at the Atlanta Science Festival Expo; and 10) looks for other opportunities to distribute information, such as helping man the 2018 AALAS booth at the National Science Teacher Association meeting and the AALAS AREA program for veterinary tech students.

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

In the upcoming funding period, the Yerkes National Primate Research Center will continue to advance our overarching goals:

1. To carry out basic and translational research using nonhuman primates to expand knowledge, develop improved treatments, and advance cures that will benefit humanity;

2. To provide regional and national resources for data, consultative expertise, biologic materials, and specialized facilities useful in supporting nonhuman primate research;

3. To study basic nonhuman primate biology and improve nonhuman primate breeding, husbandry and genetic characterization to better serve the biomedical research community; and

4. To provide research and training opportunities involving nonhuman primates to graduate and undergraduate students, postdoctoral fellows, visiting scientists and faculty members.

Detailed plans for each of our Divisions and Units are provided in the reports for the individual components that follow.

B.2. Accomplishments—Overall

The proposed major activities of the Yerkes National Primate Research Center, which are unchanged, are to:

1. To carry out basic and translational research using nonhuman primates to expand knowledge, develop improved treatments, and advance cures that will benefit humanity;

2. To provide regional and national resources for data, consultative expertise, biologic materials, and specialized facilities useful in supporting nonhuman primate research;

3. To study basic nonhuman primate biology and improve nonhuman primate breeding, husbandry and genetic characterization to better serve the biomedical research community; and

4. To provide research and training opportunities involving nonhuman primates to graduate and undergraduate students, postdoctoral fellows, visiting scientists and faculty members.

The Yerkes National Primate Research Center has demonstrated significant progress in meeting each of our key objectives during the reporting period (5/1/18 to 4/30/19) and consequently, has made significant contributions to behavioral, biomedical and translational research at Emory University and via collaborations on a regional and national basis. In particular, the Yerkes Primate Center has maintained outstanding core research programs, extensive collaborative relationships with scientists based in other Emory University departments and provided resources and services to a broad collective network of affiliate and collaborative investigators throughout the region and nation. These research programs, which involve the use of a variety of nonhuman primate species, are directed primarily toward four major research disciplines, representing the research divisions within the Primate Center: 1) Behavioral Neuroscience and Psychiatric Disorders (BNPD), 2) Developmental and Cognitive Neuroscience (DCN), 3) Neuropharmacology and Neurologic Diseases (NND) and 4) Microbiology and Immunology (M&I). Also, through the Divisions of Animal Resources and Pathology, Yerkes provides support for outside investigators conducting research at the Yerkes Center, consistent with our ORIP-mandated role as a regional and national resource.

The project summaries that follow summarize the numerous contributions from our administrative units, animal resources and pathology units, pilot projects, service cores, and scientific programs.

We provide here a few vignettes to summarize representative achievements.

Research Funding

Research awards to Yerkes in FY18 exceeded $74 million. The overall trend of research funding at Yerkes since 2000 is one of progressive growth, amounting to a 170% increase in research funding during this time.

Publications

- Yerkes scientists published over 125 articles and 1 book in the past year, including a number of publications in high profile journals such as *Science Translational Medicine* and *JCI Insight*. Selected contributions include:
    - While much attention has been devoted to the effects of Zika virus infection on the developing fetus, very little was known about the effects of Zika on infants. Working with Yerkes scientists and veterinarians, Affiliate Scientist Redacted by agreement (Dept. of Pediatrics, SOM) demonstrated that infection of infant macaques with Zika virus resulted in persistent abnormalities in brain structure, function and behavior, thus highlighting the potential consequences of post-natal Zika infection of infants (Mavigner et al. *Science Translational Medicine* 2018).
    - Recent efforts to cure HIV and cancer have focused on check-point inhibitors to “remove the brakes on the immune system.” Redacted by agreement group at Yerkes demonstrated that the

administration of the checkpoint inhibitor anti-PD-1 given in conjunction with antiretroviral therapy to SIV-infected macaques resulted in improved immune responses and better control of viremia after interruption of antiviral therapy (Mylvaganam et al. *JCI Insight* 2018).

- Previous research by Yerkes faculty member Redacted by agreement published in *Nature Neuroscience* demonstrated that mice can inherit a learned sensitivity to smell. In a follow up study designed to study the ability of the effects of stress exposures to be passed from one generation to the next, the Redacted by lab showed that extinction training can reverse the effects of parental stress, suggesting that interventions directed at at-risk parents may be able to interrupt the cycle of transgenerational stress. (Aoued et al, *Biological Psychiatry* 2019)
- Efforts to understand the effects of stress on immune responses in humans are typically confounded by a number of factors that make it difficult to tease out the contributions of stress versus other factors. By studying a natural model of chronic stress related to social dominance in the Yerkes breeding colony at the Field Station, Yerkes researchers were able to demonstrate that although stress did not impair immune responses to tetanus immunization, it did impair the transfer of antibodies to their infants, a finding that suggests an additional mechanism by which stress may lead to an increased transmission of infectious diseases in at-risk children. (Stammen et al, *JAALAS* 2018)
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Selected Honors and Awards

- Redacted by agreement (Yerkes Division of Behavioral Neuroscience and Psychiatric Disorders) was named as a Fellow of the Association for the Advancement of Science (AAAS).
- Redacted by agreement Yerkes Associate Director for Animal Resources) was elected Vice President Elect of the Association of Primate Veterinarians.
- Redacted by agreement (Head, Yerkes Behavioral Management) assumed the position of President of the American Society of Primatologists.

Specific scientific accomplishments for each of the Yerkes Scientific Units are provided in the individual unit summaries.

B.4. Training and Professional Development Opportunities

Scientific

The Center is actively involved in training and continuing education activities. Students and Postdoctoral Fellows are an integral part of the scientific fabric of Yerkes and participate in all elements of the research mission. In the last year, 120 undergraduate and 108 graduate students received training and experience in Yerkes laboratories. During this same period, the Center employed 55 Postdoctoral Fellows. Yerkes currently is the focal point for a substantial portion of the Neuroscience Graduate Program at Emory. The Director of the NIH training grant that supports students in the Graduate Neuroscience Program and many members of the Neuroscience Program Executive committee, all reside at Yerkes. Additionally, almost 15% of graduate students in the Neuroscience and Immunology programs are carrying out their dissertation research in Yerkes laboratories, including several MD/PhD students. Essentially all of our Divisions have NRSA or NSF-supported students and we have worked with each Division in facilitating the process for trainees' applications to NIH/NSF or private foundations for financial support. The Yerkes Center is the administrative home for the NIH Training grant (T32GM08605-Training in Systems and Integrative Biology-Neuroscience) that supports trainees in the Emory Neuroscience Graduate Program and the NIH-funded Institute of Neuroscience (ION) training grant that supports high school students to participate in a summer research program in Neuroscience at the Yerkes Primate Center. The Yerkes Center is also the administrator of the NIH-funded Udall Center of Excellence for Parkinson's disease at Emory University and the home for three of the Core Scientists participating in this Center. In addition to research activities, the Parkinson's Disease Center is very active in education and community outreach for trainees and the public. It also provides pilot grants to young investigators interested in developing new areas of research for Parkinson's disease.

The Division of Animal Resources (DAR) at Yerkes and at Emory's School of Medicine (SOM) continue their joint effort in supporting the Emory Laboratory Animal Medicine Residency Training Program. Since 2009, one of Yerkes veterinary faculty members was the Training Program Assistant Director. In 2017, this veterinarian was promoted to Associate Director and a second Yerkes Veterinary Faculty member took the Assistant Director position. In addition, Yerkes veterinarians have taken responsibility as course directors for classes within the Residency Training program. Yerkes also supports two residency positionsper year. Our goal is to train and retain laboratory animal veterinarians who will grow with Yerkes, and help develop programs of research around their own specialties. All veterinary faculty continue to be actively involved in the Emory Laboratory Animal Medicine Program and remain closely partnered with the Division of Animal Resources at the School of Medicine. In 2007, an NCRR R25 training grant enabled Yerkes to include an additional third year of specialized NHP training for three residents. In 2009, an administrative supplement to the R25 provided support for a fourth resident to enter the program. The three-year YNPRC NHP Residency Program builds upon our successful Emory/YNPRC two-year program and provides extensive nonhuman primate clinical and resource management experience for the residents. We have successfully recruited four trainees, all of them having completed the program between June 2009 and June 2011. In addition, all have obtained their ACLAM Board Certification, the gold standard to measure success of a Laboratory Medicine Training program. One of those trainees is now a full time veterinarian at Yerkes and has recently been promoted as the Chief of Clinical Operations. In light of the success of this specialized Training Program, YNPRC decided to continue to support a third year Fellowship in Nonhuman Primate Medicine and Management. We have already recruited seven trainees for the Fellowship Program. Six of them completed the program between 2013 and 2018. Four of those trainees have successfully obtained their Board Certification. We were privileged to hire two of them as full time veterinarians at Yerkes, the most recent one in July 2018. The remaining two trainees are Board eligible, meaning they have a first author publication, and will take their Board exam in 2019. The fellow who is currently in training is also expected to sit for the Board exam in 2019.

YNPRC has continued to provide opportunities for veterinary internships and externships. These opportunities introduce veterinary students to the field of lab animal medicine and have sometimes led to students applying for lab animal residency positions as offered by the School of Medicine/YNPRC. One of our current residents has been through our externship program. In 2018, nine externs and one intern came to Yerkes for a period that varied between three to ten weeks. Students from veterinary technical schools also have participated in externships and have sometimes been motivated to apply for available technical positions at Yerkes where they could put to good use their newfound knowledge of nonhuman primates. We had one Veterinary

Technician intern in 2017 and have accepted two interns for 2019. They will complete their internship by April 2019. We hired several of those veterinary technician interns through the years, the last one was hired in 2014. The various students work closely with veterinary faculty, residents and technicians to gain a working knowledge and appreciation of the specialty of nonhuman primate medicine. The Center also hosted, for a second year in a row, a Drexel University Masters of Laboratory Animal Science intern. This intern participated in a twelve week rotation through all of the animal Resources units at both the Main Center and the Field Station. The intent of the internship is to provide the student with practical real life experience supervising and managing the multitude of tasks involved in operating a research animal facility.

The Yerkes Center is closely linked with several components of the Emory University Clinical Translational Science Award (CTSA); (now called the Georgia CTSA), which includes Morehouse School of Medicine, the Georgia Institute of Technology, and the University of Georgia. The key functional areas of the Georgia CTSA that the Yerkes Center is involved with include brain imaging and education.

Yerkes has collaborated with the Institute on Neuroscience (ION) at Georgia State University to continue to enable high school students and middle and high school teachers to participate in scientific research. Success with this program has led to the continuation of a five-year NIH grant to continue the ION program. Two high school students worked in Yerkes Neuroscience laboratories through this program last year.

In addition, the Center regularly hosts scientific seminars and sponsors frequent talks (Lunch and Learn, Frontiers in Neuroscience) by faculty for the staff to promote understanding of the scientific mission.

Employee Training

As noted in the Core Service Units section, prior to beginning employment, all personnel are given a packet that provides information on the Yerkes Center, general information on primate research, the nonhuman primate behavioral management program, laboratory animal zoonoses information, personnel policies, Center security information, standards and procedures for working safely at the Center, training information, and biosafety issues (e.g., B-virus information). Supervisors are responsible for training employees in procedures that specifically relate to their areas of responsibility. Individuals with practical experience are appointed to train new employees/students within their units. All new employees (investigators, animal care personnel, research technicians, etc.) and students/volunteers receive an approximately one hour orientation from the Yerkes Environmental Health and Safety Office that includes a slideshow related to organization of the Yerkes Center, procedures for handling incidents and potential exposures, and general guidelines for working safely in laboratory and animal research settings. In addition to the didactic orientation, all new employees complete online training on the Emory Learning Management System, including a “Yerkes Orientation” module and other modules as are relevant to the employee’s job responsibilities. All personnel who will have animal contact are required to complete Animal User Orientations that cover nonhuman primate and/or rodent biology and behavior, U.S. regulations and guidelines for laboratory animals, IACUC policies, identifying and reporting sick animals and reporting animal welfare concerns. Animal Research personnel are required to complete applicable AALAS Learning Library online training modules and be added to an existing IACUC protocol prior to working with animals. A hands-on instructional tour of the nonhuman primate and/or rodent research facility is required for research personnel to gain access to these areas. General information memoranda are circulated providing any new information or reminding personnel of existing standards when necessary.

Training classes are provided as part of Yerkes continuing education efforts. Animal care technician training needs and programs are assessed and enhanced by supervisors and managers on an ongoing basis and may be influenced by research designs as well as changes in husbandry and care. Animal care technicians receive initial general training upon hire and orientation. Over time, experienced care staff also receive additional specialized training focused on specific topics such as husbandry and care of nursery animals, automated feeder training, behavioral management certification training, forklift training, as well as cross training within other Animal Resources units such as the veterinary staff, research resources staff and colony management staff. In addition, each year during International Laboratory Animal Care Technician Week, research staff conduct presentations and provide updates on current study activities, data collection, and results. These training sessions, as well as information disseminated during staff meetings, presentations or review classes, are based on materials and resources that are part of the American Association for Laboratory Animal Science

certification program. Although all Animal Care Technicians are encouraged to work toward certification by AALAS, the AALAS certification examination is not mandatory. Regular staff meetings are conducted at which time there is generally a review of some aspects of husbandry and care that relate to certification. Manuals for the Assistant Laboratory Animal Technician, Laboratory Animal Technician and the Laboratory Animal Technologist are made available to Yerkes technicians without charge for use in the in-house training program or for self-study. Additionally, the Emory University IACUC Office subscribes to the AALAS Learning Library for online, individualized training. The Yerkes Center pays the fee for the certification examination at each level. A salary increase is provided to individuals who achieve certification. After successful completion of the AALAS ALAT review webinar series in which we participated, in collaboration with several other research facilities in the area, we started an AALAS LAT review webinar series. An AALAS LATG study class was also offered this past year. Currently, twenty seven percent (27%) of the Main Station animal care unit and thirty eight percent (38%) of the Field Station animal care unit are currently AALAS certified at some level. Opportunities for additional training are also available when Animal Care Technicians attend National AALAS, SEAALAS and AALAS District IV meetings in 2019. Supervisors and Managers have been attending webinars sponsored by NABR, OLAW, AALAS, USDA and AAALAC. One Manager and one Supervisor completed the second year of the ILAM program. Two individuals also completed their CMAR Certifications. Additionally, Continuing Education sessions are available for Veterinary Technicians through the Gwinnett Veterinary Medical Association monthly meetings as well as a series of lectures (scheduled 6-8 times a year) organized by the School of Medicine's DAR.

The Training Coordinator for the Yerkes Division of Animal Resources coordinates the training requirements for personnel who work with research animals. After completing the Animal User Orientations, training offered to animal users at Yerkes include 1) a didactic presentation on aseptic surgery technique (mandatory for anyone conducting surgery); 2) rodent biomethodology including restraint (required for anyone new to working with rodents), blood collection techniques and injection procedures; 3) humane rodent euthanasia methods; 4) weaning training (a review of the IACUC weaning policy for mice and rats; 5) restraint training (a 2-part series on preparing nonhuman primates for studies involving physical restraint, specifically chair restraint); 6) behavioral management of nonhuman primates; and 7) a facility refresher for all research staff working with animals. Instructional manuals for identifying sick rodents are developed and distributed to animal research and animal care personnel. The Training Coordinator is a member of the IACUC Subcommittee on Training and Continuing Education, which develops the policy on rate, frequency and types of training and continuing education requirements for animal users at Yerkes and the rest of Emory University. In 2017, the Training Coordinator established a Training and Education committee for the Division of Animal Resources Staff at both the Main Station and Field Station with the goal of creating a more centralized training program for staff and developing new training and continuing education opportunities to address specific goals within the Division. Incoming DAR employees now receive a more indepth walkthrough which provides more overview/information on each of the units within the Division. There is a more hands-on training for individuals involved in certain job duties such as boxing animals, manipulating the squeeze, etc. A 30 minute lecture provided by the Veterinary Department and a 30 minute lecture provided by Behavior Management will also be a part of this early on training. A dedicated training space was created last year to help provide an area for these additional trainings.

In addition to the initial orientation which includes information on zoonoses (including B-Virus), biosafety, personal protective equipment, and Center policies on safety, the Yerkes Environmental Health and Safety Office conducts and/or facilitates annual training programs for all personnel. These annual training programs include but are not limited to: (1) B-virus training for all staff who work with nonhuman primates or nonhuman primate blood or tissues; (2) annual updates on the use of personal protective equipment (PPE) to include a review of current requirements, demonstration on how to use PPE, and information on the storage, limitations of and decontamination and disposal of PPE; (3) information on hazards communications and the chemical hygiene plan, including how to work with hazardous chemicals, how to respond to a spill, labeling and storage requirements, disposal procedures and Safety Data Sheets (SDS); (4) biosafety reviews which include a review of biosafety level 1-4, blood borne pathogens standards, biological safety cabinets, emergency procedures, disposal practices, and a review of zoonoses; (5) radiation safety which includes discussion of the characteristics of radiation, safe use and storage, disposal, and employee monitoring; (6) ergonomics training for employees in animal care, research, or any other position that involves strenuous or repetitive physical activity; (7) fire safety training which includes fire prevention strategies, evacuation plans, emergency

procedures, and training for the use of fire extinguishers; (8) respirator program which includes annual fit testing, training, and medical surveillance; and (9) training for facilities management personnel that addresses general safety and industrial hygiene topics such as asbestos awareness, lockout/tagout, and confined spaces.

C. OVERALL PRODUCTS

C.1 PUBLICATIONS

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

Yes

Publications Reported for this Reporting Period

Public Access Compliance	Citation
Complete	Kuhar MJ. CART Peptides and Drugs of Abuse: A Review of Recent Progress. Journal of drug and alcohol research. 2016 June 28;5. PubMed PMID: 29238623; PubMed Central PMCID: PMC5726282.
Non-Compliant	Wood JS, Connor-Stroud F, Levesque D. Response to Protocol Review Scenario: Taking too many liberties can affect trust. Lab animal. 2016 October 20;45(11):424-425. PubMed PMID: 27763620.
Complete	Raper J, Bosinger S, Johnson Z, Tharp G, Moran SP, Chan AWS. Increased irritability, anxiety, and immune reactivity in transgenic Huntington's disease monkeys. Brain, behavior, and immunity. 2016 November;58:181-190. PubMed PMID: 27395434; PubMed Central PMCID: PMC5067193.
Complete	Galvan A, Devergnas A, Pittard D, Masilamoni G, Vuong J, Daniels JS, Morrison RD, Lindsley CW, Wichmann T. Lack of Antiparkinsonian Effects of Systemic Injections of the Specific T-Type Calcium Channel Blocker ML218 in MPTP-Treated Monkeys. ACS chemical neuroscience. 2016 November 16;7(11):1543-1551. PubMed PMID: 27596273; PubMed Central PMCID: PMC5510653.
Complete	Snyder-Mackler N, Sanz J, Kohn JN, Brinkworth JF, Morrow S, Shaver AO, Grenier JC, Pique-Regi R, Johnson ZP, Wilson ME, Barreiro LB, Tung J. Social status alters immune regulation and response to infection in macaques. Science (New York, N.Y.). 2016 November 25;354(6315):1041-1045. PubMed PMID: 27885030; PubMed Central PMCID: PMC5498102.
Complete	Alvarado MC, Malkova L, Bachevalier J. Development of relational memory processes in monkeys. Developmental cognitive neuroscience. 2016 December;22:27-35. PubMed PMID: 27833046; PubMed Central PMCID: PMC5135601.
Complete	Kohn JN, Snyder-Mackler N, Barreiro LB, Johnson ZP, Tung J, Wilson ME. Dominance rank causally affects personality and glucocorticoid regulation in female rhesus macaques. Psychoneuroendocrinology. 2016 December;74:179-188. PubMed PMID: 27639059; PubMed Central PMCID: PMC5494262.
Complete	Boisvert M, Zhang W, Elrod EJ, Bernard NF, Villeneuve JP, Bruneau J, Marcotrigiano J, Shoukry NH, Grakoui A. Novel E2 Glycoprotein Tetramer Detects Hepatitis C Virus-Specific Memory B Cells. Journal of immunology (Baltimore, Md. : 1950). 2016 December 15;197(12):4848-4858. PubMed PMID: 27849172; PubMed Central PMCID: PMC5136319.
Complete	Roberts ER, Carnathan DG, Li H, Shaw GM, Silvestri G, Betts MR. Collapse of Cytolytic Potential in SIV-Specific CD8+ T Cells Following Acute SIV Infection in Rhesus Macaques. PLoS pathogens. 2016 December 30;12(12):e1006135. PubMed PMID: 28036372; PubMed Central PMCID: PMC5231392.
Complete	Smith AL, Walum H, Connor-Stroud F, Freeman SM, Inoue K, Parr LA, Goodman MM, Young LJ. An evaluation of central penetration from a peripherally administered oxytocin receptor selective antagonist in nonhuman primates. Bioorganic & medicinal chemistry. 2017 January 1;25(1):305-315. PubMed PMID: 27838170; PubMed Central PMCID: PMC5207485.
Complete	Wheeler MG, Duncan E, Davis M. Low startle magnitude may be a behavioral marker of vulnerability to cocaine addiction. Synapse (New York, N.Y.). 2017 January;71(1):46-50. PubMed PMID: 27696533; PubMed Central PMCID: PMC5166556.
Non-Compliant	Brown EK, Templer VL, Hampton RR. An assessment of domain-general metacognitive responding in rhesus monkeys. Behavioural processes. 2017 February;135:132-144.

	PubMed PMID: 27939856.
Complete	Howell BR, McMurray MS, Guzman DB, Nair G, Shi Y, McCormack KM, Hu X, Styner MA, Sanchez MM. Maternal buffering beyond glucocorticoids: impact of early life stress on corticolimbic circuits that control infant responses to novelty. Social neuroscience. 2017 February;12(1):50-64. PubMed PMID: 27295326; PubMed Central PMCID: PMC5585074.
Complete	Raper J, Wilson M, Sanchez M, Payne C, Bachevalier J. Increased anxiety-like behaviors, but blunted cortisol stress response after neonatal hippocampal lesions in monkeys. Psychoneuroendocrinology. 2017 February;76:57-66. PubMed PMID: 27888771; PubMed Central PMCID: PMC5272817.
Complete	DePoy LM, Zimmermann KS, Marvar PJ, Gourley SL. Induction and Blockade of Adolescent Cocaine-Induced Habits. Biological psychiatry. 2017 April 1;81(7):595-605. PubMed PMID: 27871669; PubMed Central PMCID: PMC5359769.
Complete	Dehkharghani S, Fleischer CC, Qiu D, Yepes M, Tong F. Cerebral Temperature Dysregulation: MR Thermographic Monitoring in a Nonhuman Primate Study of Acute Ischemic Stroke. AJNR. American journal of neuroradiology. 2017 April;38(4):712-720. PubMed PMID: 28126752; PubMed Central PMCID: PMC5389900.
Complete	Masilamoni GJ, Groover O, Smith Y. Reduced noradrenergic innervation of ventral midbrain dopaminergic cell groups and the subthalamic nucleus in MPTP-treated parkinsonian monkeys. Neurobiology of disease. 2017 April;100:9-18. PubMed PMID: 28042095; PubMed Central PMCID: PMC5511687.
Complete	Kim SC, Wakwe W, Higginbotham LB, Mathews DV, Breeden CP, Stephenson AC, Jenkins J, Strobert E, Price K, Price L, Kuhn R, Wang H, Yamniuk A, Suchard S, Farris AB 3rd, Pearson TC, Larsen CP, Ford ML, Suri A, Nadler S, Adams AB. Fc-Silent Anti-CD154 Domain Antibody Effectively Prevents Nonhuman Primate Renal Allograft Rejection. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2017 May;17(5):1182-1192. PubMed PMID: 28097811; PubMed Central PMCID: PMC5409881.
Complete	Kuhar MJ, Job MO. CART Peptide Regulates Psychostimulant-Induced Activity and Exhibits a Rate Dependency. Journal of drug and alcohol research. 2017 May 26;6. PubMed PMID: 29225992; PubMed Central PMCID: PMC5718383.
Complete	Amadei EA, Johnson ZV, Jun Kwon Y, Shpiner AC, Saravanan V, Mays WD, Ryan SJ, Walum H, Rainnie DG, Young LJ, Liu RC. Dynamic corticostriatal activity biases social bonding in monogamous female prairie voles. Nature. 2017 June 8;546(7657):297-301. PubMed PMID: 28562592; PubMed Central PMCID: PMC5499998.
Complete	Raper J, Morrison RD, Daniels JS, Howell L, Bachevalier J, Wichmann T, Galvan A. Metabolism and Distribution of Clozapine-N-oxide: Implications for Nonhuman Primate Chemogenetics. ACS chemical neuroscience. 2017 July 19;8(7):1570-1576. PubMed PMID: 28324647; PubMed Central PMCID: PMC5522181.
Complete	Hong JJ, Silveira ELDV, Amancha PK, Byrareddy SN, Gumber S, Chang KT, Ansari AA, Villinger F. Early initiation of antiretroviral treatment postSIV infection does not resolve lymphoid tissue activation. AIDS (London, England). 2017 August 24;31(13):1819-1824. PubMed PMID: 28692537; PubMed Central PMCID: PMC5557084.
Complete	Pitts EG, Minerva AR, Chandler EB, Kohn JN, Logun MT, Sulima A, Rice KC, Howell LL. 3,4-Methylenedioxymethamphetamine Increases Affiliative Behaviors in Squirrel Monkeys in a Serotonin 2A Receptor-Dependent Manner. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2017 September;42(10):1962-1971. PubMed PMID: 28425496; PubMed Central PMCID: PMC5561347.
Complete	Ahlgrim NS, Raper J, Johnson E, Bachevalier J. Neonatal perirhinal cortex lesions impair monkeys' ability to modulate their emotional responses. Behavioral neuroscience. 2017 October;131(5):359-71. PubMed PMID: 28956946; PubMed Central PMCID: PMC5675115.
Complete	Magnani DM, Rogers TF, Beutler N, Ricciardi MJ, Bailey VK, Gonzalez-Nieto L, Briney B, Sok D, Le K, Strubel A, Gutman MJ, Pedreño-Lopez N, Grubaugh ND, Silveira CGT, Maxwell HS, Domingues A, Martins MA, Lee DE, Okwuazi EE, Jean S, Strobert EA,

	Chahroudi A, Silvestri G, Vanderford TH, Kallas EG, Desrosiers RC, Bonaldo MC, Whitehead SS, Burton DR, Watkins DI. Neutralizing human monoclonal antibodies prevent Zika virus infection in macaques. Science translational medicine. 2017 October 4;9(410). PubMed PMID: 28978754; PubMed Central PMCID: PMC6155977.
Complete	Diner I, Dooyema J, Gearing M, Walker LC, Seyfried NT. Generation of Clickable Pittsburgh Compound B for the Detection and Capture of β-Amyloid in Alzheimer's Disease Brain. Bioconjugate chemistry. 2017 October 18;28(10):2627-2637. PubMed PMID: 28862836; PubMed Central PMCID: PMC5845826.
Complete	Pereira-Pedro AS, Rilling JK, Chen X, Preuss TM, Bruner E. Midsagittal Brain Variation among Non-Human Primates: Insights into Evolutionary Expansion of the Human Precuneus. Brain, behavior and evolution. 2017 October 25;90(3):255-263. PubMed PMID: 29065406; PubMed Central PMCID: PMC5687995.
Complete	Gardinassi LG, Cordy RJ, Lacerda MVG, Salinas JL, Monteiro WM, Melo GC, Siqueira AM, Val FF, Tran V, Jones DP, Galinski MR, Li S. Metabolome-wide association study of peripheral parasitemia in Plasmodium vivax malaria. International journal of medical microbiology : IJMM. 2017 December;307(8):533-541. PubMed PMID: 28927849; PubMed Central PMCID: PMC5698147.
Complete	Weiss AR, Guo W, Richardson R, Bachevalier J. Intact perceptual ability, but impaired familiarity judgment, after neonatal perirhinal lesions in rhesus macaques. Developmental cognitive neuroscience. 2017 December;28:54-64. PubMed PMID: 29175539; PubMed Central PMCID: PMC5737963.
Complete	Bosch OJ, Young LJ. Oxytocin and Social Relationships: From Attachment to Bond Disruption. Current topics in behavioral neurosciences. 2018;35:97-117. PubMed PMID: 28812266; PubMed Central PMCID: PMC5815947.
Complete	Kamara DM, Gangishetti U, Gearing M, Willis-Parker M, Zhao L, Hu WT, Walker LC. Cerebral Amyloid Angiopathy: Similarity in African-Americans and Caucasians with Alzheimer's Disease. Journal of Alzheimer's disease : JAD. 2018;62(4):1815-1826. PubMed PMID: 29614657; PubMed Central PMCID: PMC6103628.
Complete	Li CX, Zhang X. Evaluation of prolonged administration of isoflurane on cerebral blood flow and default mode network in macaque monkeys anesthetized with different maintenance doses. Neuroscience letters. 2018 January 1;662:402-408. PubMed PMID: 29055725; PubMed Central PMCID: PMC5722273.
Complete	Osako Y, Nobuhara R, Arai YP, Tanaka K, Young LJ, Nishihara M, Mitsui S, Yuri K. Partner Loss in Monogamous Rodents: Modulation of Pain and Emotional Behavior in Male Prairie Voles. Psychosomatic medicine. 2018 January;80(1):62-68. PubMed PMID: 28872575; PubMed Central PMCID: PMC5741544.
Complete	Ulloa M, Portillo W, Díaz NF, Young LJ, Camacho FJ, Rodríguez VM, Paredes RG. Mating and social exposure induces an opioid-dependent conditioned place preference in male but not in female prairie voles (Microtus ochrogaster). Hormones and behavior. 2018 January;97:47-55. PubMed PMID: 29111331; PubMed Central PMCID: PMC5803795.
Complete	Walker LC. Prion-like mechanisms in Alzheimer disease. Handbook of clinical neurology. 2018;153:303-319. PubMed PMID: 29887142; PubMed Central PMCID: PMC6375694.
Complete	Zimmermann KS, Li CC, Rainnie DG, Ressler KJ, Gourley SL. Memory Retention Involves the Ventrolateral Orbitofrontal Cortex: Comparison with the Basolateral Amygdala. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2018 January;43(2):373-383. PubMed PMID: 28664926; PubMed Central PMCID: PMC5729558.
Complete	He Y, She H, Zhang T, Xu H, Cheng L, Yepes M, Zhao Y, Mao Z. p38 MAPK inhibits autophagy and promotes microglial inflammatory responses by phosphorylating ULK1. The Journal of cell biology. 2018 January 2;217(1):315-328. PubMed PMID: 29196462; PubMed Central PMCID: PMC5748971.
Complete	Palesch D, Bosinger SE, Tharp GK, Vanderford TH, Paiardini M, Chahroudi A, Johnson ZP, Kirchhoff F, Hahn BH, Norgren RB, Patel NB, Sodora DL, Dawoud RA, Stewart CB,

	Seepo SM, Harris RA, Liu Y, Raveendran M, Han Y, English A, Thomas GWC, Hahn MW, Pipes L, Mason CE, Muzny DM, Gibbs RA, Sauter D, Worley K, Rogers J, Silvestri G. Sooty mangabey genome sequence provides insight into AIDS resistance in a natural SIV host. Nature. 2018 January 3;553(7686):77-81. PubMed PMID: 29300007; PubMed Central PMCID: PMC5843367.
PMC Journal - In process	Herisson F, Zhou I, Mawet J, Du E, Barfejani AH, Qin T, Cipolla MJ, Sun PZ, Rost NS, Ayata C. Posterior reversible encephalopathy syndrome in stroke-prone spontaneously hypertensive rats on high-salt diet. Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism. 2018 January 19;:271678X17752795. PubMed PMID: 29350576.
Complete	Ortiz JJ, Portillo W, Paredes RG, Young LJ, Alcauter S. Resting state brain networks in the prairie vole. Scientific reports. 2018 January 19;8(1):1231. PubMed PMID: 29352154; PubMed Central PMCID: PMC5775431.
Complete	Singh A, Jenkins MA, Burke KJ Jr, Beck G, Jenkins A, Scimemi A, Traynelis SF, Papa SM. Glutamatergic Tuning of Hyperactive Striatal Projection Neurons Controls the Motor Response to Dopamine Replacement in Parkinsonian Primates. Cell reports. 2018 January 28;22(4):941-952. PubMed PMID: 29386136; PubMed Central PMCID: PMC5798888.
Complete	Diaz A, Yepes M. Urokinase-type plasminogen activator promotes synaptic repair in the ischemic brain. Neural regeneration research. 2018 February;13(2):232-233. PubMed PMID: 29557368; PubMed Central PMCID: PMC5879890.
Complete	Mitrano DA, Jackson K, Finley S, Seeley A. α1b-Adrenergic Receptor Localization and Relationship to the D1-Dopamine Receptor in the Rat Nucleus Accumbens. Neuroscience. 2018 February 10;371:126-137. PubMed PMID: 29229557; PubMed Central PMCID: PMC5809204.
Complete	Hernandes MS, Lassègue B, Hilenski LL, Adams J, Gao N, Kuan CY, Sun YY, Cheng L, Kikuchi DS, Yepes M, Griendling KK. Polymerase delta-interacting protein 2 deficiency protects against blood-brain barrier permeability in the ischemic brain. Journal of neuroinflammation. 2018 February 17;15(1):45. PubMed PMID: 29452577; PubMed Central PMCID: PMC5816395.
Complete	Fisher BS, Green RR, Brown RR, Wood MP, Hensley-McBain T, Fisher C, Chang J, Miller AD, Bosche WJ, Lifson JD, Mavigner M, Miller CJ, Gale M Jr, Silvestri G, Chahroudi A, Klatt NR, Sodora DL. Liver macrophage-associated inflammation correlates with SIV burden and is substantially reduced following cART. PLoS pathogens. 2018 February 21;14(2):e1006871. PubMed PMID: 29466439; PubMed Central PMCID: PMC5837102.
Complete	Carnathan DG, Mackel JJ, Sweat SL, Enemuo CA, Gebru EH, Dhadvai P, Gangadhara S, Hicks S, Vanderford TH, Amara RR, Esparza J, Lu W, Andrieu JM, Silvestri G. Intragastric administration of Lactobacillus plantarum and AT-2-inactivated SIV does not protect Indian rhesus macaques from intra-rectal SIV challenge nor reduce virus replication after transmission. Journal of virology. 2018 February 28. PubMed PMID: 29491157; PubMed Central PMCID: PMC5923080.
Complete	Masilamoni GJ, Smith Y. Chronic MPTP administration regimen in monkeys: a model of dopaminergic and non-dopaminergic cell loss in Parkinson's disease. Journal of neural transmission (Vienna, Austria : 1996). 2018 March;125(3):337-363. PubMed PMID: 28861737; PubMed Central PMCID: PMC5826821.
Complete	Smith Y, Galvan A. Non-human primate research of basal ganglia and movement disorders: advances and challenges. Journal of neural transmission (Vienna, Austria : 1996). 2018 March;125(3):275-278. PubMed PMID: 29423879; PubMed Central PMCID: PMC5826894.
Complete	Stavisky RC, Ramsey JK, Meeker T, Stovall M, Crane MM. Trauma rates and patterns in specific pathogen free (SPF) rhesus macaque (Macaca mulatta) groups. American journal of primatology. 2018 March;80(3):e22742. PubMed PMID: 29419883; PubMed Central PMCID: PMC5878745.
Complete	Villalba RM, Smith Y. Loss and remodeling of striatal dendritic spines in Parkinson's disease: from homeostasis to maladaptive plasticity?. Journal of neural transmission (Vienna, Austria : 1996). 2018 March;125(3):431-447. PubMed PMID: 28540422; PubMed Central PMCID: PMC5701884.

Complete	Vuong J, Devergnas A. The role of the basal ganglia in the control of seizure. Journal of neural transmission (Vienna, Austria : 1996). 2018 March;125(3):531-545. PubMed PMID: 28766041; PubMed Central PMCID: PMC5794644.
Complete	Wichmann T, Bergman H, DeLong MR. Basal ganglia, movement disorders and deep brain stimulation: advances made through non-human primate research. Journal of neural transmission (Vienna, Austria : 1996). 2018 March;125(3):419-430. PubMed PMID: 28601961; PubMed Central PMCID: PMC5723554.
Complete	Wu Y, Zhou IY, Lu D, Manderville E, Lo EH, Zheng H, Sun PZ. pH-sensitive amide proton transfer effect dominates the magnetization transfer asymmetry contrast during acute ischemia-quantification of multipool contribution to in vivo CEST MRI. Magnetic resonance in medicine. 2018 March;79(3):1602-1608. PubMed PMID: 28733991; PubMed Central PMCID: PMC5775916.
Complete	Wu Y, Zhou IY, Igarashi T, Longo DL, Aime S, Sun PZ. A generalized ratiometric chemical exchange saturation transfer (CEST) MRI approach for mapping renal pH using iopamidol. Magnetic resonance in medicine. 2018 March;79(3):1553-1558. PubMed PMID: 28686805; PubMed Central PMCID: PMC5756701.
Complete	Pitts EG, Li DC, Gourley SL. Bidirectional coordination of actions and habits by TrkB in mice. Scientific reports. 2018 March 14;8(1):4495. PubMed PMID: 29540698; PubMed Central PMCID: PMC5852142.
Complete	Yepes M. Urokinase-type Plasminogen Activator Promotes Synaptic Recovery in the Ischemic Brain. Journal of translational neurosciences. 2018 March 20;3(2). PubMed PMID: 29938252; PubMed Central PMCID: PMC6013270.
Complete	Masilamoni GJ, Smith Y. Metabotropic glutamate receptors: targets for neuroprotective therapies in Parkinson disease. Current opinion in pharmacology. 2018 March 30;38:72-80. PubMed PMID: 29605730; PubMed Central PMCID: PMC5949090.
Complete	Zhang X, Yan Y, Tong F, Li CX, Jones B, Wang S, Meng Y, Muly EC, Kempf D, Howell L. Progressive Assessment of Ischemic Injury to White Matter Using Diffusion Tensor Imaging: A Preliminary Study of a Macaque Model of Stroke. The open neuroimaging journal. 2018 March 30;12:30-41. PubMed PMID: 29785226; PubMed Central PMCID: PMC5897992.
Complete	Forger NG, Ruszkowski E, Jacobs A, Wallen K. Effects of sex and prenatal androgen manipulations on Onuf's nucleus of rhesus macaques. Hormones and behavior. 2018 April;100:39-46. PubMed PMID: 29510099; PubMed Central PMCID: PMC6084473.
Complete	Garas FN, Kormann E, Shah RS, Vinciati F, Smith Y, Magill PJ, Sharott A. Structural and molecular heterogeneity of calretinin-expressing interneurons in the rodent and primate striatum. The Journal of comparative neurology. 2018 April 1;526(5):877-898. PubMed PMID: 29218729; PubMed Central PMCID: PMC5814860.
Complete	Raper J, De Biasio JC, Murphy KL, Alvarado MC, Baxter MG. Persistent alteration in behavioural reactivity to a mild social stressor in rhesus monkeys repeatedly exposed to sevoflurane in infancy. British journal of anaesthesia. 2018 April;120(4):761-767. PubMed PMID: 29576116; PubMed Central PMCID: PMC6200105.
Complete	Bosch OJ, Pohl TT, Neumann ID, Young LJ. Abandoned prairie vole mothers show normal maternal care but altered emotionality: Potential influence of the brain corticotropin-releasing factor system. Behavioural brain research. 2018 April 2;341:114-121. PubMed PMID: 29288748; PubMed Central PMCID: PMC5800976.
Complete	Hunter CE, Pongos AL, Chi TY, Payne C, Stroud FC, Chan AWS. Longitudinal Anthropometric Assessment of Rhesus Macaque (<i>Macaca mulatta</i>) Model of Huntington Disease. Comparative medicine. 2018 April 2;68(2):163-167. PubMed PMID: 29663942; PubMed Central PMCID: PMC5897973.
Complete	Laforge M, Silvestre R, Rodrigues V, Garibal J, Campillo-Gimenez L, Mouhamad S, Monceaux V, Cumont MC, Rabezanahary H, Pruvost A, Cordeiro-da-Silva A, Hurtrel B, Silvestri G, Senik A, Estaquier J. The anti-caspase inhibitor Q-VD-OPH prevents AIDS disease progression in SIV-infected rhesus macaques. The Journal of clinical investigation. 2018 April 2;128(4):1627-1640. PubMed PMID: 29553486; PubMed Central PMCID: PMC5873886.

Complete	Mavigner M, Raper J, Kovacs-Balint Z, Gumber S, O'Neal JT, Bhaumik SK, Zhang X, Habib J, Mattingly C, McDonald CE, Avanzato V, Burke MW, Magnani DM, Bailey VK, Watkins DI, Vanderford TH, Fair D, Earl E, Feczko E, Styner M, Jean SM, Cohen JK, Silvestri G, Johnson RP, O'Connor DH, Wrammert J, Suthar MS, Sanchez MM, Alvarado MC, Chahroudi A. Postnatal Zika virus infection is associated with persistent abnormalities in brain structure, function, and behavior in infant macaques. Science translational medicine. 2018 April 4;10(435). PubMed PMID: 29618564; PubMed Central PMCID: PMC6186170.
Complete	Joas S, Parrish EH, Gnanadurai CW, Lump E, Stürzel CM, Parrish NF, Learn GH, Sauermann U, Neumann B, Rensing KM, Fuchs D, Billingsley JM, Bosinger SE, Silvestri G, Apetrei C, Huot N, Garcia-Tellez T, Müller-Trutwin M, Hotter D, Sauter D, Stahl-Hennig C, Hahn BH, Kirchhoff F. Species-specific host factors rather than virus-intrinsic virulence determine primate lentiviral pathogenicity. Nature communications. 2018 April 10;9(1):1371. PubMed PMID: 29636452; PubMed Central PMCID: PMC5893559.
Complete	Wetzel KS, Yi Y, Yadav A, Bauer AM, Bello EA, Romero DC, Bibollet-Ruche F, Hahn BH, Paiardini M, Silvestri G, Peeters M, Collman RG. Loss of CXCR6 coreceptor usage characterizes pathogenic lentiviruses. PLoS pathogens. 2018 April 16;14(4):e1007003. PubMed PMID: 29659623; PubMed Central PMCID: PMC5919676.
Complete	Abdel-Mohsen M, Kuri-Cervantes L, Grau-Exposito J, Spivak AM, Nell RA, Tomescu C, Vadrevu SK, Giron LB, Serra-Peinado C, Genescà M, Castellví J, Wu G, Del Rio Estrada PM, González-Navarro M, Lynn K, King CT, Vemula S, Cox K, Wan Y, Li Q, Mounzer K, Kostman J, Frank I, Paiardini M, Hazuda D, Reyes-Terán G, Richman D, Howell B, Tebas P, Martinez-Picado J, Planelles V, Buzon MJ, Betts MR, Montaner LJ. CD32 is expressed on cells with transcriptionally active HIV but does not enrich for HIV DNA in resting T cells. Science translational medicine. 2018 April 18;10(437). PubMed PMID: 29669853; PubMed Central PMCID: PMC6282755.
Complete	Huot N, Bosinger SE, Paiardini M, Reeves RK, Müller-Trutwin M. Lymph Node Cellular and Viral Dynamics in Natural Hosts and Impact for HIV Cure Strategies. Frontiers in immunology. 2018 April 19;9:780. PubMed PMID: 29725327; PubMed Central PMCID: PMC5916971.
Complete	Beck G, Maehara S, Chang PL, Papa SM. A Selective Phosphodiesterase 10A Inhibitor Reduces L-Dopa-Induced Dyskinesias in Parkinsonian Monkeys. Movement disorders : official journal of the Movement Disorder Society. 2018 May;33(5):805-814. PubMed PMID: 29508924; PubMed Central PMCID: PMC5992016.
Complete	Carnathan D, Lawson B, Yu J, Patel K, Billingsley JM, Tharp GK, Delmas OM, Dawoud R, Wilkinson P, Nicolette C, Cameron MJ, Sekaly RP, Bosinger SE, Silvestri G, Vanderford TH. Reduced Chronic Lymphocyte Activation following Interferon Alpha Blockade during the Acute Phase of Simian Immunodeficiency Virus Infection in Rhesus Macaques. Journal of virology. 2018 May 1;92(9). PubMed PMID: 29467313; PubMed Central PMCID: PMC5899190.
Complete	Ferrando-Martinez S, Moysi E, Pegu A, Andrews S, Nganou Makamdop K, Ambrozak D, McDermott AB, Palesch D, Paiardini M, Pavlakis GN, Brenchley JM, Douek D, Mascola JR, Petrovas C, Koup RA. Accumulation of follicular CD8+ T cells in pathogenic SIV infection. The Journal of clinical investigation. 2018 May 1;128(5):2089-2103. PubMed PMID: 29664020; PubMed Central PMCID: PMC5919804.
Complete	Godfrey JR, Diaz MP, Pincus M, Kovacs-Balint Z, Feczko E, Earl E, Miranda-Dominguez O, Fair D, Sanchez MM, Wilson ME, Michopoulos V. Diet matters: Glucocorticoid-related neuroadaptations associated with calorie intake in female rhesus monkeys. Psychoneuroendocrinology. 2018 May;91:169-178. PubMed PMID: 29567621; PubMed Central PMCID: PMC5899678.
Complete	Paspalas CD, Carlyle BC, Leslie S, Preuss TM, Crimins JL, Huttner AJ, van Dyck CH, Rosene DL, Nairn AC, Arnsten AFT. The aged rhesus macaque manifests Braak stage III/IV Alzheimer's-like pathology. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2018 May;14(5):680-691. PubMed PMID: 29241829; PubMed Central PMCID: PMC6178089.
Complete	Ryan S, Li C, Menigoz A, Hazra R, Dabrowska J, Ehrlich D, Gordon K, Rainnie DG. Repeated shock stress facilitates basolateral amygdala synaptic plasticity through decreased cAMP-specific phosphodiesterase type IV (PDE4) expression. Brain structure & function. 2018 May;223(4):1731-1745. PubMed PMID: 29204911; PubMed Central PMCID: PMC5886824.

Complete	Santangelo PJ, Cicala C, Byrareddy SN, Ortiz KT, Little D, Lindsay KE, Gumber S, Hong JJ, Jelicic K, Rogers KA, Zurla C, Villinger F, Ansari AA, Fauci AS, Arthos J. Early treatment of SIV+ macaques with an α₄β₇ mAb alters virus distribution and preserves CD4⁺ T cells in later stages of infection. Mucosal immunology. 2018 May;11(3):932-946. PubMed PMID: 29346349; PubMed Central PMCID: PMC5976508.
Complete	Walker LC. Sabotage by the brain's supporting cells helps fuel neurodegeneration. Nature. 2018 May;557(7706):499-500. PubMed PMID: 29777188; PubMed Central PMCID: PMC6329300.
Complete	Yin J, Sun H, Wang Z, Ni H, Shen W, Sun PZ. Diffusion Kurtosis Imaging of Acute Infarction: Comparison with Routine Diffusion and Follow-up MR Imaging. Radiology. 2018 May;287(2):651-657. PubMed PMID: 29558293; PubMed Central PMCID: PMC5929367.
Complete	Whyte AJ, Torregrossa MM, Barker JM, Gourley SL. Editorial: Long-Term Consequences of Adolescent Drug Use: Evidence From Pre-clinical and Clinical Models. Frontiers in behavioral neuroscience. 2018 May 3;12:83. PubMed PMID: 29773981; PubMed Central PMCID: PMC5943494.
Complete	Aguilar-Valenzuela R, Netland J, Seo YJ, Bevan MJ, Grakoui A, Suthar MS. Dynamics of Tissue-Specific CD8⁺ T Cell Responses during West Nile Virus Infection. Journal of virology. 2018 May 15;92(10). PubMed PMID: 29514902; PubMed Central PMCID: PMC5923067.
In Process at NIHMS	Hoang T, Date AA, Ortiz JO, Young TW, Bensouda S, Xiao P, Marzinke M, Rohan L, Fuchs EJ, Hendrix C, Gumber S, Villinger F, Cone RA, Hanes J, Ensign LM. Development of rectal enema as microbicide (DREAM): Preclinical progressive selection of a tenofovir prodrug enema. European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V. 2018 May 24. PubMed PMID: 29802984.
Complete	Donahue CJ, Glasser MF, Preuss TM, Rilling JK, Van Essen DC. Quantitative assessment of prefrontal cortex in humans relative to nonhuman primates. Proceedings of the National Academy of Sciences of the United States of America. 2018 May 29;115(22):E5183-E5192. PubMed PMID: 29739891; PubMed Central PMCID: PMC5984508.
Complete	Brady RJ, Hampton RR. Post-encoding control of working memory enhances processing of relevant information in rhesus monkeys (Macaca mulatta). Cognition. 2018 June;175:26-35. PubMed PMID: 29459237; PubMed Central PMCID: PMC5879026.
Complete	Buggert M, Nguyen S, Salgado-Montes de Oca G, Bengsch B, Darko S, Ransier A, Roberts ER, Del Alcazar D, Brody IB, Vella LA, Beura L, Wijeyesinghe S, Herati RS, Del Rio Estrada PM, Ablanedo-Terrazas Y, Kuri-Cervantes L, Sada Japp A, Manne S, Vartanian S, Huffman A, Sandberg JK, Gostick E, Nadolski G, Silvestri G, Canaday DH, Price DA, Petrovas C, Su LF, Vahedi G, Dori Y, Frank I, Itkin MG, Wherry EJ, Deeks SG, Naji A, Reyes-Terán G, Masopust D, Douek DC, Betts MR. Identification and characterization of HIV-specific resident memory CD8⁺ T cells in human lymphoid tissue. Science immunology. 2018 June 1;3(24). PubMed PMID: 29858286; PubMed Central PMCID: PMC6357781.
Complete	Dave RS, Sharma RK, Muir RR, Haddad E, Gumber S, Villinger F, Nehra AP, Khan ZK, Wigdahl B, Ansari AA, Byrareddy SN, Jain P. FDC:TFH Interactions within Cervical Lymph Nodes of SIV-Infected Rhesus Macaques. Journal of neuroimmune pharmacology : the official journal of the Society on NeuroImmune Pharmacology. 2018 June;13(2):204-218. PubMed PMID: 29288344; PubMed Central PMCID: PMC5757373.
Non-Compliant	McBrien JB, Kumar NA, Silvestri G. Mechanisms of CD8⁺ T cell-mediated suppression of HIV/SIV replication. European journal of immunology. 2018 June;48(6):898-914. PubMed PMID: 29427516.
Complete	Tedesco D, Thapa M, Chin CY, Ge Y, Gong M, Li J, Gumber S, Speck P, Elrod EJ, Burd EM, Kitchens WH, Magliocca JF, Adams AB, Weiss DS, Mohamadzadeh M, Grakoui A. Alterations in Intestinal Microbiota Lead to Production of Interleukin 17 by Intrahepatic γδ T-Cell Receptor-Positive Cells and Pathogenesis of Cholestatic Liver Disease. Gastroenterology. 2018 June;154(8):2178-2193. PubMed PMID: 29454797; PubMed

	Central PMCID: PMC5985208.
Complete	Zanoni M, Palesch D, Silvestri G. Longing for HIV protection. Nature microbiology. 2018 June;3(6):648-649. PubMed PMID: 29784974; PubMed Central PMCID: PMC6391887.
Complete	Velu V, Mylvaganam G, Ibegbu C, Amara RR. Tfh1 Cells in Germinal Centers During Chronic HIV/SIV Infection. Frontiers in immunology. 2018 June 6;9:1272. PubMed PMID: 29928280; PubMed Central PMCID: PMC5997779.
PMC Journal - In process	Diaz A, Merino P, Manrique LG, Cheng L, Yepes M. Urokinase-type plasminogen activator (uPA) protects the tripartite synapse in the ischemic brain via ezrin-mediated formation of peripheral astrocytic processes. Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism. 2018 June 12;:271678X18783653. PubMed PMID: 29890880.
Complete	Merino P, Diaz A, Manrique LG, Cheng L, Yepes M. Urokinase-type plasminogen activator (uPA) promotes ezrin-mediated reorganization of the synaptic cytoskeleton in the ischemic brain. The Journal of biological chemistry. 2018 June 15;293(24):9234-9247. PubMed PMID: 29720403; PubMed Central PMCID: PMC6005443.
In Process at NIHMS	Hampton R. Parallel overinterpretation of behavior of apes and corvids. Learning & behavior. 2018 June 20. PubMed PMID: 29926397.
Complete	Yalcin-Cakmakli G, Rose SJ, Villalba RM, Williams L, Jinnah HA, Hess EJ, Smith Y. Striatal Cholinergic Interneurons in a Knock-in Mouse Model of L-DOPA-Responsive Dystonia. Frontiers in systems neuroscience. 2018 June 27;12:28. PubMed PMID: 29997483; PubMed Central PMCID: PMC6030733.
Complete	Bhattacharya S, Ma Y, Dunn AR, Bradner JM, Scimemi A, Miller GW, Traynelis SF, Wichmann T. NMDA receptor blockade ameliorates abnormalities of spike firing of subthalamic nucleus neurons in a parkinsonian nonhuman primate. Journal of neuroscience research. 2018 July;96(7):1324-1335. PubMed PMID: 29577359; PubMed Central PMCID: PMC5980712.
Complete	Grakoui A, Walker CM. Of mice, rats, and men: Small animal model of hepatitis C virus infection. Hepatology (Baltimore, Md.). 2018 July;68(1):374-376. PubMed PMID: 29281849; PubMed Central PMCID: PMC6021213.
Complete	Hennessey T, Andari E, Rainnie DG. RDoC-based categorization of amygdala functions and its implications in autism. Neuroscience and biobehavioral reviews. 2018 July;90:115-129. PubMed PMID: 29660417; PubMed Central PMCID: PMC6250055.
Complete	Ploquin MJ, Casrouge A, Madec Y, Noël N, Jacquelin B, Huot N, Duffy D, Jochems SP, Micci L, Lécuroux C, Boufassa F, Booiman T, Garcia-Tellez T, Ghislain M, Grand RL, Lambotte O, Kootstra N, Meyer L, Goujard C, Paiardini M, Albert ML, Müller-Trutwin M. Systemic DPP4 activity is reduced during primary HIV-1 infection and is associated with intestinal RORC⁺ CD4⁺ cell levels: a surrogate marker candidate of HIV-induced intestinal damage. Journal of the International AIDS Society. 2018 July;21(7):e25144. PubMed PMID: 29987877; PubMed Central PMCID: PMC6038000.
Complete	Stammen RL, Cohen JK, Meeker TL, Crane MM, Amara RR, Hicks SL, Meyer JS, Ethun KF. Effect of Chronic Social Stress on Prenatal Transfer of Antitetanus Immunity in Captive Breeding Rhesus Macaques (<i>Macaca mulatta</i>). Journal of the American Association for Laboratory Animal Science : JAALAS. 2018 July 1;57(4):357-367. PubMed PMID: 29764539; PubMed Central PMCID: PMC6059219.
Complete	Palesch D, Bosinger SE, Mavigner M, Billingsley JM, Mattingly C, Carnathan DG, Paiardini M, Chahroudi A, Vanderford TH, Silvestri G. Short-Term Pegylated Interferon α2a Treatment Does Not Significantly Reduce the Viral Reservoir of Simian Immunodeficiency Virus-Infected, Antiretroviral Therapy-Treated Rhesus Macaques. Journal of virology. 2018 July 15;92(14). PubMed PMID: 29720521; PubMed Central PMCID: PMC6026735.
Complete	Scinto HB, Gupta S, Thorat S, Mukhtar MM, Griffiths A, Delgado J, Plake E, Vyas HK, Strickland A, Byrareddy SN, Montefiori DC, LaBranche C, Pal R, Treece J, Orndorff S, Ferrari MG, Weiss D, Chenine AL, McLinden R, Michael N, Kim JH, Robb ML, Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, Ruprecht RM. Novel Strategy To Adapt Simian-

	Human Immunodeficiency Virus E1 Carrying <i>env</i> from an RV144 Volunteer to Rhesus Macaques: Coreceptor Switch and Final Recovery of a Pathogenic Virus with Exclusive R5 Tropism. Journal of virology. 2018 July 15;92(14). PubMed PMID: 29743361; PubMed Central PMCID: PMC6026739.
Complete	Woodson E, Goldberg A, Michelo C, Basu D, Tao S, Schinazi R, Jiang Y, Kilembe W, Karita E, Allen S, Hunter E. HIV transmission in discordant couples in Africa in the context of antiretroviral therapy availability. AIDS (London, England). 2018 July 31;32(12):1613-1623. PubMed PMID: 29762171; PubMed Central PMCID: PMC6211178.
Complete	Gumber S, Amancha PK, Yen PJ, Villinger F, Gabuzda D, Byrareddy SN. In vivo characterization of macrophage-tropic simian immunodeficiency virus molecular clones in rhesus macaques. Journal of neurovirology. 2018 August;24(4):411-419. PubMed PMID: 29594984; PubMed Central PMCID: PMC6105460.
In Process at NIHMS	Zhang S, Jiang X, Zhang W, Zhang T, Chen H, Zhao Y, Lv J, Guo L, Howell BR, Sanchez MM, Hu X, Liu T. Joint representation of connectome-scale structural and functional profiles for identification of consistent cortical landmarks in macaque brain. Brain imaging and behavior. 2018 September 4. PubMed PMID: 30178424.
PMC Journal - In process	Shang L, Smith AJ, Duan L, Perkey KE, Wietgrefe S, Zupancic M, Southern PJ, Johnson RP, Carlis JV, Haase AT. Vaccine-Associated Maintenance of Epithelial Integrity Correlated With Protection Against Virus Entry. The Journal of infectious diseases. 2018 September 8;218(8):1272-1283. PubMed PMID: 29401315.
Complete	Mavigner M, Habib J, Deleage C, Rosen E, Mattingly C, Bricker K, Kashuba A, Amblard F, Schinazi RF, Jean S, Cohen J, McGary C, Paiardini M, Wood MP, Sodora DL, Silvestri G, Estes J, Chahroudi A. Simian Immunodeficiency Virus Persistence in Cellular and Anatomic Reservoirs in Antiretroviral Therapy-Suppressed Infant Rhesus Macaques. Journal of virology. 2018 September 15;92(18). PubMed PMID: 29997216; PubMed Central PMCID: PMC6146711.
Complete	Li G, Liu P, Andari E, Zhang A, Zhang K. The Role of Amygdala in Patients With Euthymic Bipolar Disorder During Resting State. Frontiers in psychiatry. 2018 September 19;9:445. PubMed PMID: 30283367; PubMed Central PMCID: PMC6156348.
Complete	Mylvaganam GH, Chea LS, Tharp GK, Hicks S, Velu V, Iyer SS, Deleage C, Estes JD, Bosinger SE, Freeman GJ, Ahmed R, Amara RR. Combination anti-PD-1 and antiretroviral therapy provides therapeutic benefit against SIV. JCI insight. 2018 September 20;3(18). PubMed PMID: 30232277; PubMed Central PMCID: PMC6237231.
Complete	Merino P, Yepes M. Urokinase-type Plasminogen Activator Induces Neurorepair in the Ischemic Brain. Journal of neurology and experimental neuroscience. 2018 September 26;4(2):24-29. PubMed PMID: 30417161; PubMed Central PMCID: PMC6225521.
Complete	Mudd JC, Busman-Sahay K, DiNapoli SR, Lai S, Sheik V, Lisco A, Deleage C, Richardson B, Palesch DJ, Paiardini M, Cameron M, Sereti I, Reeves RK, Estes JD, Brenchley JM. Hallmarks of primate lentiviral immunodeficiency infection recapitulate loss of innate lymphoid cells. Nature communications. 2018 September 27;9(1):3967. PubMed PMID: 30262807; PubMed Central PMCID: PMC6160474.
Complete	Curtis AD 2nd, Jensen K, Van Rompay KKA, Amara RR, Kozlowski PA, De Paris K. A simultaneous oral and intramuscular prime/sublingual boost with a DNA/Modified Vaccinia Ankara viral vector-based vaccine induces simian immunodeficiency virus-specific systemic and mucosal immune responses in juvenile rhesus macaques. Journal of medical primatology. 2018 October;47(5):288-297. PubMed PMID: 30204253; PubMed Central PMCID: PMC6158111.
Complete	Dobolyi A, Cservenák M, Young LJ. Thalamic integration of social stimuli regulating parental behavior and the oxytocin system. Frontiers in neuroendocrinology. 2018 October;51:102-115. PubMed PMID: 29842887; PubMed Central PMCID: PMC6175608.
PMC Journal - In process	Kovacs-Balint Z, Feczko E, Pincus M, Earl E, Miranda-Dominguez O, Howell B, Morin E, Maltbie E, Li L, Steele J, Styner M, Bachevalier J, Fair D, Sanchez M. Early Developmental Trajectories of Functional Connectivity Along the Visual Pathways in Rhesus Monkeys. Cerebral cortex (New York, N.Y. : 1991). 2018 October 1. PubMed

	PMID: 30272135.
Complete	Mathews DV, Dong Y, Higginbotham LB, Kim SC, Breeden CP, Stobert EA, Jenkins J, Tso JY, Larsen CP, Adams AB. CD122 signaling in CD8+ memory T cells drives costimulation-independent rejection. The Journal of clinical investigation. 2018 October 1;128(10):4557-4572. PubMed PMID: 30222140; PubMed Central PMCID: PMC6159972.
Complete	Parr LA, Mitchell T, Hecht E. Intranasal oxytocin in rhesus monkeys alters brain networks that detect social salience and reward. American journal of primatology. 2018 October;80(10):e22915. PubMed PMID: 30295946; PubMed Central PMCID: PMC6381825.
Complete	Putnam PT, Young LJ, Gothard KM. Bridging the gap between rodents and humans: The role of non-human primates in oxytocin research. American journal of primatology. 2018 October;80(10):e22756. PubMed PMID: 29923206; PubMed Central PMCID: PMC6202243.
Complete	Rogers CN, Ross AP, Sahu SP, Siegel ER, Dooyema JM, Cree MA, Stopa EG, Young LJ, Rilling JK, Albers HE, Preuss TM. Oxytocin- and arginine vasopressin-containing fibers in the cortex of humans, chimpanzees, and rhesus macaques. American journal of primatology. 2018 October;80(10):e22875. PubMed PMID: 29797339; PubMed Central PMCID: PMC6202198.
Complete	Cao Y, Cartwright EK, Silvestri G, Perelson AS. CD8+ lymphocyte control of SIV infection during antiretroviral therapy. PLoS pathogens. 2018 October 11;14(10):e1007350. PubMed PMID: 30308068; PubMed Central PMCID: PMC6199003.
In Process at NIHMS	Eckstein M, Bamert V, Stephens S, Wallen K, Young LJ, Ehlert U, Ditzen B. Oxytocin increases eye-gaze towards novel social and non-social stimuli. Social neuroscience. 2018 October 31;:1-14. PubMed PMID: 30378456.
Complete	Jeanneret V, Ospina JP, Diaz A, Manrique LG, Merino P, Gutierrez L, Torre E, Wu F, Cheng L, Yepes M. Tissue-type plasminogen activator protects the postsynaptic density in the ischemic brain. Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism. 2018 November;38(11):1896-1910. PubMed PMID: 29547062; PubMed Central PMCID: PMC6259311.
Complete	Johnson ZV, Young LJ. Evolutionary diversity as a catalyst for biological discovery. Integrative zoology. 2018 November;13(6):616-633. PubMed PMID: 29851228; PubMed Central PMCID: PMC6265060.
Complete	Li L, Bachevalier J, Hu X, Klin A, Preuss TM, Shultz S, Jones W. Topology of the Structural Social Brain Network in Typical Adults. Brain connectivity. 2018 November;8(9):537-548. PubMed PMID: 30280929; PubMed Central PMCID: PMC6249672.
Complete	Maple TL, Bloomsmith MA. Introduction: The science and practice of optimal animal welfare. Behavioural processes. 2018 November;156:1-2. PubMed PMID: 28927966; PubMed Central PMCID: PMC5857402.
Complete	Meng Y, Hu X, Zhang X, Bachevalier J. Diffusion tensor imaging reveals microstructural alterations in corpus callosum and associated transcallosal fiber tracts in adult macaques with neonatal hippocampal lesions. Hippocampus. 2018 November;28(11):838-845. PubMed PMID: 29978933; PubMed Central PMCID: PMC6282702.
Complete	Wakeford AGP, Morin EL, Bramlett SN, Howell LL, Sanchez MM. A review of nonhuman primate models of early life stress and adolescent drug abuse. Neurobiology of stress. 2018 November;9:188-198. PubMed PMID: 30450384; PubMed Central PMCID: PMC6236515.
Complete	Walum H, Young LJ. The neural mechanisms and circuitry of the pair bond. Nature reviews. Neuroscience. 2018 November;19(11):643-654. PubMed PMID: 30301953; PubMed Central PMCID: PMC6283620.
Complete	Fonseca LL, Joyner CJ, Saney CL, Moreno A, Barnwell JW, Galinski MR, Voit EO. Analysis of erythrocyte dynamics in Rhesus macaque monkeys during infection with

	Plasmodium cynomolgi. Malaria journal. 2018 November 6;17(1):410. PubMed PMID: 30400896; PubMed Central PMCID: PMC6219197.
In Process at NIHMS	Horie K, Inoue K, Suzuki S, Adachi S, Yada S, Hirayama T, Hidema S, Young LJ, Nishimori K. Oxytocin receptor knockout prairie voles generated by CRISPR/Cas9 editing show reduced preference for social novelty and exaggerated repetitive behaviors. Hormones and behavior. 2018 November 8. PubMed PMID: 30713102.
Complete	Parra M, Yang J, Weitner M, Derrick S, Yang A, Schmidt T, Singh B, Moreno A, Akkoyunlu M. TACI Contributes to <i>Plasmodium yoelii</i> Host Resistance by Controlling T Follicular Helper Cell Response and Germinal Center Formation. Frontiers in immunology. 2018 November 9;9:2612. PubMed PMID: 30473702; PubMed Central PMCID: PMC6237915.
Complete	Zheng C, Chen G, Tan Y, Zeng W, Peng Q, Wang J, Cheng C, Yang X, Nie S, Xu Y, Zhang Z, Papa SM, Ye K, Cao X. TRH Analog, Taltirelin Improves Motor Function of Hemi-PD Rats Without Inducing Dyskinesia via Sustained Dopamine Stimulating Effect. Frontiers in cellular neuroscience. 2018 November 13;12:417. PubMed PMID: 30555300; PubMed Central PMCID: PMC6282053.
Complete	Zimmerman MG, Quicke KM, O'Neal JT, Arora N, Machiah D, Priyamvada L, Kauffman RC, Register E, Adekunle O, Swieboda D, Johnson EL, Cordes S, Haddad L, Chakraborty R, Coyne CB, Wrammert J, Suthar MS. Cross-Reactive Dengue Virus Antibodies Augment Zika Virus Infection of Human Placental Macrophages. Cell host & microbe. 2018 November 14;24(5):731-742.e6. PubMed PMID: 30439342.
Complete	Kumar NA, McBrien JB, Carnathan DG, Mavigner M, Mattingly C, White ER, Viviano F, Bosinger SE, Chahroudi A, Silvestri G, Paiardini M, Vanderford TH. Antibody-Mediated CD4 Depletion Induces Homeostatic CD4⁺ T Cell Proliferation without Detectable Virus Reactivation in Antiretroviral Therapy-Treated Simian Immunodeficiency Virus-Infected Macaques. Journal of virology. 2018 November 15;92(22). PubMed PMID: 30185596; PubMed Central PMCID: PMC6206490.
Complete	Barfield ET, Gourley SL. Prefrontal cortical trkB, glucocorticoids, and their interactions in stress and developmental contexts. Neuroscience and biobehavioral reviews. 2018 December;95:535-558. PubMed PMID: 30477984; PubMed Central PMCID: PMC6392187.
Complete	Date AA, Halpert G, Babu T, Ortiz J, Kanvinde P, Dimitrion P, Narayan J, Zierden H, Betageri K, Musmanno O, Wiegand H, Huang X, Gumber S, Hanes J, Ensign LM. Mucus-penetrating budesonide nanosuspension enema for local treatment of inflammatory bowel disease. Biomaterials. 2018 December;185:97-105. PubMed PMID: 30236840; PubMed Central PMCID: PMC6193453.
Complete	Glavis-Bloom C, Bachevalier J. Neonatal hippocampal lesions facilitate biconditional contextual discrimination learning in monkeys. Behavioral neuroscience. 2018 December;132(6):480-496. PubMed PMID: 30359064; PubMed Central PMCID: PMC6263937.
Complete	Martin AL, Franklin AN, Perlman JE, Bloomsmith MA. Systematic assessment of food item preference and reinforcer effectiveness: Enhancements in training laboratory-housed rhesus macaques. Behavioural processes. 2018 December;157:445-452. PubMed PMID: 30003936; PubMed Central PMCID: PMC6240383.
Complete	Freeman SM, Palumbo MC, Lawrence RH, Smith AL, Goodman MM, Bales KL. Effect of age and autism spectrum disorder on oxytocin receptor density in the human basal forebrain and midbrain. Translational psychiatry. 2018 December 4;8(1):257. PubMed PMID: 30514927; PubMed Central PMCID: PMC6279786.
Complete	Petrovas C, Velu V. Editorial: Lymph Node T Cell Dynamics and Novel Strategies for HIV Cure. Frontiers in immunology. 2018 December 12;9:2950. PubMed PMID: 30619310; PubMed Central PMCID: PMC6311961.
Complete	Zheng C, Chen G, Tan Y, Zeng W, Peng Q, Wang J, Cheng C, Yang X, Nie S, Xu Y, Zhang Z, Papa SM, Ye K, Cao X. TRH Analog, Taltirelin Protects Dopaminergic Neurons From Neurotoxicity of MPTP and Rotenone. Frontiers in cellular neuroscience. 2018 December 20;12:485. PubMed PMID: 30618632; PubMed Central PMCID: PMC6306470.
Complete	Devergnas A, Caiola M, Pittard D, Wichmann T. Cortical Phase-Amplitude Coupling in a

	Progressive Model of Parkinsonism in Nonhuman Primates. Cerebral cortex (New York, N.Y. : 1991). 2019 January 1;29(1):167-177. PubMed PMID: 29190329; PubMed Central PMCID: PMC6294400.
Complete	Gross C, Banerjee A, Tiwari D, Longo F, White AR, Allen AG, Schroeder-Carter LM, Krzeski JC, Elsayed NA, Puckett R, Klann E, Rivero RA, Gourley SL, Bassell GJ. Isoform-selective phosphoinositide 3-kinase inhibition ameliorates a broad range of fragile X syndrome-associated deficits in a mouse model. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2019 January;44(2):324-333. PubMed PMID: 30061744; PubMed Central PMCID: PMC6300538.
Complete	Hoang TN, Harper JL, Pino M, Wang H, Micci L, King CT, McGary CS, McBrien JB, Cervasi B, Silvestri G, Paiardini M. Bone Marrow-Derived CD4⁺ T Cells Are Depleted in Simian Immunodeficiency Virus-Infected Macaques and Contribute to the Size of the Replication-Competent Reservoir. Journal of virology. 2019 January 1;93(1). PubMed PMID: 30305357; PubMed Central PMCID: PMC6288341.
Complete	Ji Y, Paulsen J, Zhou IY, Lu D, Machado P, Qiu B, Song YQ, Sun PZ. In vivo microscopic diffusional kurtosis imaging with symmetrized double diffusion encoding EPI. Magnetic resonance in medicine. 2019 January;81(1):533-541. PubMed PMID: 30260504; PubMed Central PMCID: PMC6258297.
Complete	Odabas-Geldiay M, Shields H, Berro LF, Rice KC, Howell LL. Effects of acute treatments with the serotonin 2A antagonist M100907 alone or in combination with the serotonin 2C agonist WAY163909 on methamphetamine self-administration in rhesus monkeys. Drug and alcohol dependence. 2019 January 1;194:252-256. PubMed PMID: 30469095; PubMed Central PMCID: PMC6312465.
Complete	Zhou IY, Lu D, Ji Y, Wu L, Wang E, Cheung JS, Zhang XA, Sun PZ. Determination of multipool contributions to endogenous amide proton transfer effects in global ischemia with high spectral resolution in vivo chemical exchange saturation transfer MRI. Magnetic resonance in medicine. 2019 January;81(1):645-652. PubMed PMID: 30058148; PubMed Central PMCID: PMC6258351.
Complete	Donahue CJ, Glasser MF, Preuss TM, Rilling JK, Van Essen DC. Reply to Barton and Montgomery: A case for preferential prefrontal cortical expansion. Proceedings of the National Academy of Sciences of the United States of America. 2019 January 2;116(1):5-6. PubMed PMID: 30559214; PubMed Central PMCID: PMC6320522.
Complete	Kick BL, Gumber S, Wang H, Moore RH, Taylor DK. Evaluation of 4 Presurgical Skin Preparation Methods in Mice. Journal of the American Association for Laboratory Animal Science : JAALAS. 2019 January 4;58(1):71-77. PubMed PMID: 30609948; PubMed Central PMCID: PMC6351048.
PMC Journal - In process	O'Neal JT, Upadhyay AA, Wolabaugh A, Patel NB, Bosinger SE, Suthar MS. West Nile virus-inclusive single-cell RNA sequencing reveals heterogeneity in the type I interferon response within single cells. Journal of virology. 2019 January 9. PubMed PMID: 30626670.
Complete	Collins PL, Cella M, Porter SI, Li S, Gurewitz GL, Hong HS, Johnson RP, Oltz EM, Colonna M. Gene Regulatory Programs Conferring Phenotypic Identities to Human NK Cells. Cell. 2019 January 10;176(1-2):348-360.e12. PubMed PMID: 30595449; PubMed Central PMCID: PMC6329660.
Complete	Smith SA, Burton SL, Kilembe W, Lakhi S, Karita E, Price M, Allen S, Derdeyn CA. VH1-69 Utilizing Antibodies Are Capable of Mediating Non-neutralizing Fc-Mediated Effector Functions Against the Transmitted/Founder gp120. Frontiers in immunology. 2019 January 15;9:3163. PubMed PMID: 30697215; PubMed Central PMCID: PMC6341001.
PMC Journal - In process	Burton S, Spicer LM, Charles TP, Gangadhara S, Reddy PB, Styles TM, Velu V, Kasturi SP, Legere T, Hunter E, Pulendran B, Amara R, Hraber P, Derdeyn CA. Clade C HIV-1 envelope vaccination regimens differ in their ability to elicit antibodies with moderate neutralization breadth against genetically diverse tier 2 HIV-1 envelope variants. Journal of virology. 2019 January 16. PubMed PMID: 30651354.
Complete	Snyder-Mackler N, Sanz J, Kohn JN, Voyles T, Pique-Regi R, Wilson ME, Barreiro LB, Tung J. Social status alters chromatin accessibility and the gene regulatory response to

	glucocorticoid stimulation in rhesus macaques. Proceedings of the National Academy of Sciences of the United States of America. 2019 January 22;116(4):1219-1228. PubMed PMID: 30538209; PubMed Central PMCID: PMC6347725.
PMC Journal - In process	Rowson SA, Bekhbat M, Kelly SD, Binder EB, Hyer MM, Shaw G, Bent MA, Hodes G, Tharp G, Weinshenker D, Qin Z, Neigh GN. Chronic adolescent stress sex-specifically alters the hippocampal transcriptome in adulthood. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2019 January 23. PubMed PMID: 30710108.
Complete	Aoued HS, Sannigrahi S, Doshi N, Morrison FG, Linsenbaum H, Hunter SC, Walum H, Baman J, Yao B, Jin P, Ressler KJ, Dias BG. Reversing Behavioral, Neuroanatomical, and Germline Influences of Intergenerational Stress. Biological psychiatry. 2019 February 1;85(3):248-256. PubMed PMID: 30292395; PubMed Central PMCID: PMC6326876.
In Process at NIHMS	Basile BM, Hampton RR. Nonnavigational spatial memory performance is unaffected by hippocampal damage in monkeys. Hippocampus. 2019 February;29(2):93-101. PubMed PMID: 30069946.
PMC Journal - In process	Diaz A, Jeanneret V, Merino P, McCann P, Yepes M. Tissue-type plasminogen activator regulates p35-mediated Cdk5 activation in the postsynaptic terminal. Journal of cell science. 2019 February 1. PubMed PMID: 30709918.
In Process at NIHMS	Ji Y, Lu D, Wu L, Qiu B, Song YQ, Sun PZ. Preliminary evaluation of accelerated microscopic diffusional kurtosis imaging (μDKI) in a rodent model of epilepsy. Magnetic resonance imaging. 2019 February;56:90-95. PubMed PMID: 30352270.
Complete	Pohl TT, Young LJ, Bosch OJ. Lost connections: Oxytocin and the neural, physiological, and behavioral consequences of disrupted relationships. International journal of psychophysiology : official journal of the International Organization of Psychophysiology. 2019 February;136:54-63. PubMed PMID: 29330007; PubMed Central PMCID: PMC6037618.
Complete	Porter-Stransky KA, Centanni SW, Karne SL, Odil LM, Fekir S, Wong JC, Jerome C, Mitchell HA, Escayg A, Pedersen NP, Winder DG, Mitrano DA, Weinshenker D. Noradrenergic Transmission at Alpha1-Adrenergic Receptors in the Ventral Periaqueductal Gray Modulates Arousal. Biological psychiatry. 2019 February 1;85(3):237-247. PubMed PMID: 30269865; PubMed Central PMCID: PMC6326840.
In Process at NIHMS	Hoang T, Zierden H, Date A, Ortiz J, Gumber S, Anders N, He P, Segars J, Hanes J, Mahendroo M, Ensign LM. Development of a mucoinert progesterone nanosuspension for safer and more effective prevention of preterm birth. Journal of controlled release : official journal of the Controlled Release Society. 2019 February 10;295:74-86. PubMed PMID: 30597245.
Complete	Bunnik EM, Venkat A, Shao J, McGovern KE, Batugedara G, Worth D, Prudhomme J, Lapp SA, Andolina C, Ross LS, Lawres L, Brady D, Sinnis P, Nosten F, Fidock DA, Wilson EH, Tewari R, Galinski MR, Ben Mamoun C, Ay F, Le Roch KG. Comparative 3D genome organization in apicomplexan parasites. Proceedings of the National Academy of Sciences of the United States of America. 2019 February 19;116(8):3183-3192. PubMed PMID: 30723152; PubMed Central PMCID: PMC6386730.
PMC Journal - In process	Chea LS, Wyatt LS, Gangadhara S, Moss B, Amara RR. Novel Modified Vaccinia Virus Ankara Vector Expressing Anti-apoptotic Gene <i>B13R</i> Delays Apoptosis and Enhances Humoral Responses. Journal of virology. 2019 March 1;93(5). PubMed PMID: 30541829.
In Process at NIHMS	Hoang TN, Paiardini M. Role of cytokine agonists and immune checkpoint inhibitors toward HIV remission. Current opinion in HIV and AIDS. 2019 March;14(2):121-128. PubMed PMID: 30585798.
Complete	Amir A, Paré JF, Smith Y, Paré D. Midline thalamic inputs to the amygdala: Ultrastructure and synaptic targets. The Journal of comparative neurology. 2019 April 1;527(5):942-956. PubMed PMID: 30311651; PubMed Central PMCID: PMC6347509.
Complete	Shapiro LP, Kietzman HW, Guo J, Rainnie DG, Gourley SL. Rho-kinase inhibition has antidepressant-like efficacy and expedites dendritic spine pruning in adolescent mice. Neurobiology of disease. 2019 April;124:520-530. PubMed PMID: 30593834; PubMed Central PMCID: PMC6365018.

In Process at NIHMS	Response: Taking too many liberties can affect trust. Lab animal.

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

Nothing to report

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

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

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

If yes, has this information been previously provided to the PHS or to the official responsible for patent matters at the grantee organization? Yes

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Nothing to report

D. OVERALL PARTICIPANTS

D.1 WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

Commons ID	S/K	Name	Degree(s)	Role	Cal	Aca	Sum	Foreign Org	Component(s)	Country	SS
eRA Commons User Name	Y	LEWIN, JONATHAN S	MD	PD/PI	EFFORT				Admin Core-8504 (Office of the Director)		NA
	N	Redacted by agreement		Technician					Other-8514 (Animal Care)		NA
	N			Technician					Other-8514 (Animal Care)		NA
	N			Technician					Other-8514 (Animal Care)		NA
	N			Technician					Other-8516 (Behavioral Management)		NA
	N			Technician					Other-8514 (Animal Care)		NA
	N			Technician					Other-8519 (Env. Health and Safety)		NA
	N			Technician					Other-8513 (Veterinary Medicine)		NA
	N			Technician					Core-8525 (Genomics Core)		NA
	N			Technician					Other-8516 (Behavioral Management)		NA
	N			Technician					Other-8514 (Animal Care)		NA
	N			Technician					Other-8514 (Animal Care)		NA
	N			Technician					Other-8513 (Veterinary Medicine)		NA
	N			Technician					Other-8514 (Animal Care)		NA
	N			Technician					Other-8514 (Animal Care)		NA
	N			Technician					Other-8513 (Veterinary Medicine)		NA
	N			Technician					Other-8520 (Division of Pathology)		NA
	N			Technician					Other-8514 (Animal Care)		NA

		Redacted by agreement			EFFORT				
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8513 (Veterinary Medicine)		NA
	N			Technician			Other-8515 (Colony Management)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Core-8523 (Imaging Core)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Core-8523 (Imaging Core)		NA
	N			Technician			Other-8516 (Behavioral Management)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8518 (Research Services)		NA
	N			Technician			Other-8515 (Colony Management)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Core-8524 (Virology Core)		NA
	N			Technician			Other-8515 (Colony Management)		NA
	N			Technician			Project-8530 (Pilot Projects)		NA
	N			Technician			Other-8514 (Animal Care), Other-8518 (Research Services)		NA

		Redacted by agreement			EFFORT				
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8520 (Division of Pathology)		NA
	N			Technician			Other-8516 (Behavioral Management)		NA
	N			Technician			Other-8513 (Veterinary Medicine)		NA
	N			Technician			Other-8513 (Veterinary Medicine)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8518 (Research Services)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8513 (Veterinary Medicine)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8513 (Veterinary Medicine)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8515 (Colony Management)		NA
	N			Technician			Other-8515 (Colony		NA

		Redacted by agreement			EFFORT				Management)		
	N			Technician					Other-8514 (Animal Care)		NA
	N			Technician					Other-8514 (Animal Care)		NA
	N			Technician					Other-8515 (Colony Management)		NA
	N			Technician					Other-8513 (Veterinary Medicine)		NA
	N			Technician					Other-8520 (Division of Pathology)		NA
	N			Technician					Other-8513 (Veterinary Medicine)		NA
	N			Technician					Other-8514 (Animal Care)		NA
	N			Technician					Other-8518 (Research Services)		NA
	N			Technician					Other-8514 (Animal Care)		NA
	N			Technician					Other-8514 (Animal Care)		NA
	N			Technician					Other-8514 (Animal Care)		NA
	N			Technician					Other-8514 (Animal Care)		NA
	N			Technician					Other-8514 (Animal Care)		NA
	N			Technician					Other-8514 (Animal Care)		NA
	N			Technician					Other-8520 (Division of Pathology)		NA
	N			Technician					Other-8518 (Research Services)		NA
	N			Technician					Core-8524 (Virology Core)		NA
	N			Technician					Other-8514 (Animal Care)		NA
	N			Staff scientist (Doctoral level)					Core-8523 (Imaging Core)		NA
	N			Technician					Other-8514 (Animal Care)		NA
	N			Technician					Core-8525 (Genomics Core)		NA

		Redacted by agreement			EFFORT				
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8520 (Division of Pathology)		NA
	N			Staff scientis (Doctoral level)			Core-8523 (Imaging Core)		NA
	N			Technician			Other-8515 (Colony Management)		NA
	N			Technician			Other-8520 (Division of Pathology)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care), Other-8515 (Colony Management)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8516 (Behavioral Management)		NA
	N			Technician			Other-8514 (Animal Care)		NA

		Redacted by agreement			EFFORT				
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8515 (Colony Management)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Core-8521 (Biomarkers Core)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8520 (Division of Pathology)		NA
	N			Technician			Other-8520 (Division of Pathology)		NA
	N			Technician			Other-8520 (Division of Pathology)		NA
	N			Technician			Core-8523 (Imaging Core)		NA
	N			Technician			Other-8520 (Division of Pathology)		NA
	N			Technician			Other-8515 (Colony Management)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8513 (Veterinary Medicine)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8513 (Veterinary Medicine)		NA
	N			Technician			Other-8516 (Behavioral Management)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8518 (Research Services)		NA
	N			Technician			Other-8514 (Animal Care)		NA

	N	Redacted by agreement		Technician	EFFORT		Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8518 (Research Services)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8518 (Research Services)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8513 (Veterinary Medicine), Other-8518 (Research Services)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8516 (Behavioral Management)		NA
	N			Technician			Other-8514 (Animal Care)		NA
	N			Technician			Other-8520 (Division of		NA

		Redacted by agreement			EFFORT				Pathology)		
	N			Technician					Other-8514 (Animal Care)		NA
	N			Technician					Other-8514 (Animal Care)		NA
	N			Technician					Other-8514 (Animal Care)		NA
	N			Technician					Other-8514 (Animal Care)		NA
eRA Commons User Name	N		BS,MA,PH D	Graduate Student (research assistant)					Project-8530 (Pilot Projects)		NA
	N			Supervisor					Other-8520 (Division of Pathology)		NA
	N			Supervisor					Other-8513 (Veterinary Medicine)		NA
	N			Manager					Other-8514 (Animal Care)		NA
	N			Facilities/Shop Staff					Admin Core-8510 (Facilities Management)		NA
	N			Facilities/Shop Staff					Admin Core-8510 (Facilities Management)		NA
	Y			Sr. Veterinarian					Other-8513 (Veterinary Medicine)		NA
	N			Facilities/Shop Staff					Admin Core-8510 (Facilities Management)		NA
	Y			Asst Dir, Animal Resources					Other-8512 (Asc. Dir. for Animal Resources), Other-8513 (Veterinary Medicine)		NA
	N			Supervisor					Other-8520 (Division of Pathology)		NA
	N			Supervisor					Other-8520 (Division of Pathology)		NA
	N			Manager					Other-8518 (Research Services)		NA
	N			Supervisor					Other-8514 (Animal Care)		NA

		Redacted by agreement			EFFORT				
	N			Facilities/Shop Staff			Admin Core-8510 (Facilities Management)		NA
	N			Manager			Other-8514 (Animal Care)		NA
	N			EHS Professional			Other-8519 (Env. Health and Safety)		NA
	N			Facilities/Shop Staff			Admin Core-8510 (Facilities Management)		NA
	N			Facilities/Shop Staff			Admin Core-8510 (Facilities Management)		NA
	N			Research Proj Coordinator			Other-8518 (Research Services)		NA
	N			Facilities/Shop Staff			Admin Core-8510 (Facilities Management)		NA
	N			Supervisor			Admin Core-8510 (Facilities Management)		NA
	N			Records Support			Other-8517 (Animal Records)		NA
	N			Records Support			Other-8517 (Animal Records)		NA
	N			Facilities/Shop Staff			Admin Core-8510 (Facilities Management)		NA
	Y			Veterinarian			Other-8513 (Veterinary Medicine)		NA
	Y			Veterinarian			Other-8513 (Veterinary Medicine)		NA
	N			Supervisor			Other-8514 (Animal Care)		NA
	N			Facilities/Shop Staff			Admin Core-8510 (Facilities Management)		NA
	N			Supervisor			Other-8517 (Animal Records)		NA
	N			Facilities/Shop Staff			Admin Core-8510 (Facilities Management)		NA
	N			Supervisor			Other-8514 (Animal Care)		NA
	Y			Veterinarian			Core-8523		NA

		Redacted by agreement										
										(Imaging Core), Other-8513 (Veterinary Medicine)		
	Y			Veterinarian	EFFORT					Other-8513 (Veterinary Medicine)		NA
	N			Supervisor						Core-8521 (Biomarkers Core)		NA
	N			Facilities/Shop Staff						Admin Core-8510 (Facilities Management)		NA
	N			Facilities/Shop Staff						Admin Core-8510 (Facilities Management)		NA
	N			Facilities/Shop Staff						Admin Core-8510 (Facilities Management)		NA
	N			Manager						Other-8514 (Animal Care)		NA
	N			Admin Support						Core-8523 (Imaging Core), Other-8529 (NND)		NA
	N			Training Coordinator						Other-8512 (Asc. Dir. for Animal Resources)		NA
	N			Manager						Core-8522 (Comparative AIDS Core), Other-8515 (Colony Management)		NA
	N			Supervisor						Other-8514 (Animal Care)		NA
	N			Manager						Other-8514 (Animal Care)		NA
	N			Facilities/Shop Staff						Admin Core-8510 (Facilities Management)		NA
	Y			Veterinarian						Other-8513 (Veterinary Medicine)		NA
	N			Manager						Other-8519 (Env. Health and Safety)		NA
	N			Manager						Core-8525		NA

		Redacted by agreement			EFFORT				(Genomics Core)		
	N			Manager					Other-8516 (Behavioral Management)		NA
	Y			Pathologist					Other-8520 (Division of Pathology)		NA
	N			Records Support					Other-8517 (Animal Records)		NA
	N			Supervisor					Other-8515 (Colony Management)		NA
	N			Supervisor					Other-8514 (Animal Care)		NA
	N			Records Support					Other-8517 (Animal Records)		NA
	N			Manager					Other-8514 (Animal Care)		NA
	N			Facilities/Shop Staff					Admin Core-8510 (Facilities Management)		NA
	N			Supervisor					Other-8518 (Research Services)		NA
	Y			Veterinarian					Other-8513 (Veterinary Medicine)		NA
	N			Supervisor					Other-8514 (Animal Care)		NA
	Y			Veterinarian					Other-8513 (Veterinary Medicine)		NA
	N			Bioinformatics Specialist					Core-8525 (Genomics Core)		NA
	N			Asst Dir, EHSO					Other-8519 (Env. Health and Safety)		NA
	N			Supervisor					Other-8516 (Behavioral Management)		NA
	N			Records Support					Other-8517 (Animal Records)		NA
	N			Animal Surgery Specialist					Other-8513 (Veterinary Medicine)		NA
	Y			Chief Veterinarian					Core-8522 (Comparative		NA

									AIDS Core), Other-8513 (Veterinary Medicine)		
eRA Commons User Name	Y	Redacted by agreement	MS,PHD, BS	Core Asst Director	EFFORT				Core-8522 (Comparative AIDS Core), Core-8525 (Genomics Core), Other-8515 (Colony Management)		NA
	Y		PHD,PHD, MS,BS,M S,BS	Behavioral Mgt Head					Other-8516 (Behavioral Management)		NA
	Y		BA,VMD	Asc Dir, Animal Resources/In terim AD, Pathology					Core-8522 (Comparative AIDS Core), Other-8512 (Asc. Dir. for Animal Resources), Other-8513 (Veterinary Medicine), Other-8520 (Division of Pathology)		NA
	Y		MD	Division Director					Core-8522 (Comparative AIDS Core), Other-8528 (M&I)		NA
	Y		BS,DVM,P HD	Veterinarian					Other-8513 (Veterinary Medicine)		NA
	Y		BA,DVM, MPH,PHD	Pathologist					Other-8520 (Division of Pathology)		NA
	Y		MD,BS	Center Director					Admin Core-8504 (Office of the Director)		NA
	Y			Colony Director					Other-8515 (Colony Management)		NA
	Y		PHD,DVM ,MS	Pathologist					Other-8520 (Division of Pathology)		NA
	Y		MD	Asc Dir, Scientific Pgms					Admin Core-8505 (Asc. Dir. for Scientific Programs),		NA

									Other-8529 (NND)		
eRA Commons User Name	Y	Redacted by agreement	PHD,BS	Core Directo	EFFORT				Core-8521 (Biomarkers Core), Core-8524 (Virology Core)		NA
	Y			Core Asst Director					Core-8523 (Imaging Core)		NA

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

D.2 PERSONNEL UPDATES

D.2.a Level of Effort

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

Yes

Redacted by agreement has retired from Emory and is no longer part of the senior/key personnel for this award.

D.2.b New Senior/Key Personnel

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

Yes

File uploaded: D2b_New Key Personnel.pdf

D.2.c Changes in Other Support

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

Yes

File uploaded: D2C_Other Support 2019.pdf

D.2.d New Other Significant Contributors

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

No

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

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

NA

D.2.b New Senior/Key Personnel

The following individuals are new key personnel for this award:

Redacted by agreement joined Yerkes as a veterinary pathologist in July 2018. She will be key personnel in the Division of Pathology component.

Redacted by agreement joined Yerkes as an associate veterinarian in July 2019. She will be key personnel in the Veterinary Medicine component.

Please see the following pages for their biosketches as well as other support information.

Page 044 of 816 to Page 077 of 816

Withheld pursuant to exemption

Redacted by agreement

of the Freedom of Information and Privacy Act

E. OVERALL IMPACT

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

Not Applicable

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

Please see Section G. Special Reporting Requirements, Item #13 for infrastructure improvements undertaken during the current reporting period.

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

Not Applicable

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

NOTHING TO REPORT

F. OVERALL CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

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

NOTHING TO REPORT

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

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. OVERALL SPECIAL REPORTING REQUIREMENTS

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

File(s) uploaded:
RPPR P51OD011132-58.pdf

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

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

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

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

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

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

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

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

No

G.7 VERTEBRATE ANIMALS

Does this project involve vertebrate animals?

Yes

G.8 PROJECT/PERFORMANCE SITES

Organization Name:	DUNS	Congressional District	Address
Primary: Emory University, Yerkes National Primate Research Center	066469933	GA-005	954 Gatewood Road Atlanta GA 303224250
Emory University, Yerkes National Primate Research Center Field Station	066469933	GA-007	2409 Taylor Lane Lawrenceville GA 300432921
EMORY UNIVERSITY	066469933		EMORY UNIVERSITY

			1599 CLIFTON RD, 4TH FLOOR ATLANTA GA 303224250

G.9 FOREIGN COMPONENT

No foreign component

G.10 ESTIMATED UNOBLIGATED BALANCE

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

No

G.11 PROGRAM INCOME

Is program income anticipated during the next budget period?

Yes

Anticipated Amount	Source(s)
3021217	Primate Use Fees, Per Diem, Services

G.12 F&A COSTS

Not Applicable

Yerkes NPRC
Information Requested in P51 RPPR Instructions

1.A. Nonhuman primates (NHPs) housed at NPRC supported partially, or in whole, by the P51 grant[1].

Census Date: 1/2/2019

Genus/Species	Breeding Colony[2]				Animals Not in Breeding Colony[3]				Total Colony Census
	M	F	U[4]	Total	M	F	U[4]	Total	
Macaque mulatta (Indian)	468	1,160	188	1,816	283	162		445	2,261
Macaque fascicularus					1			1	1
Cerocebus Torquataus Atys	13	28		41	37	43		80	121
Saimiri boliviensis					3			3	3
Saimiri sciuresus					4			4	4
Total	**481**	**1,188**	**188**	**1,857**	**328**	**205**		**533**	**2,390**

[1]This entry does not include animals supported by a U24 or U42 SPF grant.

[2]Total number of animals in breeding colony including adult breeding animals and designated juvenile replacements at time of report.

[3]Animals on protocol or otherwise not in the breeding colony at the time of report.

[4]Sex undetermined.

1.B. Nonhuman primates housed at NPRC - supported by U24 or U42 or other sources[1].

Census Date: 1/2/2019

Genus/Species	Breeding Colony[2]				Animals Not in Breeding Colony[3]				Total Colony Census
	M	F	U[4]	Total	M	F	U[4]	Total	
Macaque mulatta (Indian)	13	125		138	352	378		730	868
Macaque fascicularus						1		1	1
Macaque nemestrina					4			4	4
Cerocebus Torquataus Atys	10	9	1	20	10	20		30	50
Saimiri boliviensis					4			4	4
Total	**23**	**134**	**1**	**158**	**370**	**399**		**769**	**927**

[1]This entry does not include animals supported by a U24 or U42 SPF grant.

[2]Total number of animals in breeding colony including adult breeding animals and designated juvenile replacements at time of report.

[3]Animals on protocol or otherwise not in the breeding colony at the time of report.

[4]Sex undetermined.

1.C. Total Nonhuman primates housed at NPRC, irrespective of source of support.

Genus/Species	Total Number of Animals
Cerocebus Torquataus Atys	171
Macaque fascicularus	2
Macaque mulatta (Indian)	3,129
Macaque nemestrina	4
Saimiri boliviensis	7
Saimiri sciuresus	4
Total	**3,317**

Comments: for Table 1a, animals not in the breeding colony for Macaque mulatta (Indian) include non-SPF animals (69 male, 91 female). Remainder of the animals are SPF.

for Table 1b, animals not in the breeding colony for Macaque mulatta (Indian) include non-SPF animals (49 male, 37 female). Remainder of the animals are SPF. Table 1b includes animals supported by U42 grant (U42 OD011023, Maintenance of the SPF Breeding Colonies at Yerkes National Primate Research Center Redacted by agreement Redacted by agreement

2. Tissue Distribution Program Information. It is not necessary to report samples broken down by species.

Dates covered by the report: 5/1/2018 – 1/31/2019

Sample Type	Number of Samples Distributed
Tissue	207
Other	533
Total	**740**

Comments: Other category includes animal measurements as well as whole and partial organs.

3. Types of project. Include all projects performed in whole, or in part, during the reporting period.

Project Type	Number of Projects
Research	108
Management	12
Pilot	5
Total	**125**

4. Percentage of AIDS-related P51 grant dollars.

AIDS - related P51 %: 61

Description: AIDS-related P51 % reflects the percentage of the total direct cost award amount of AIDS-related grant awards ($39,068,273) made to Yerkes over all grant awards ($63,630,246) exclusive of the P51 award and P51 supplement ($11,026,103), for the most recently completed fiscal year for Emory University (9/1/17 – 8/31/18).

5. Information regarding the number of investigators by type.

Type of Investigator	Number
Core	13
Affiliate	39
Other	165
Total	**217**

6. The number of peer reviewed publications directly attributed to P51 activity. Explain how this number was derived; e.g., publications that directly cite the P51 grant, or other types of citation or information.

Source	Number
Articles	125
Book Chapters	1
Reviews	
Total	**126**

7. The number of individuals trained during the reporting period by type.

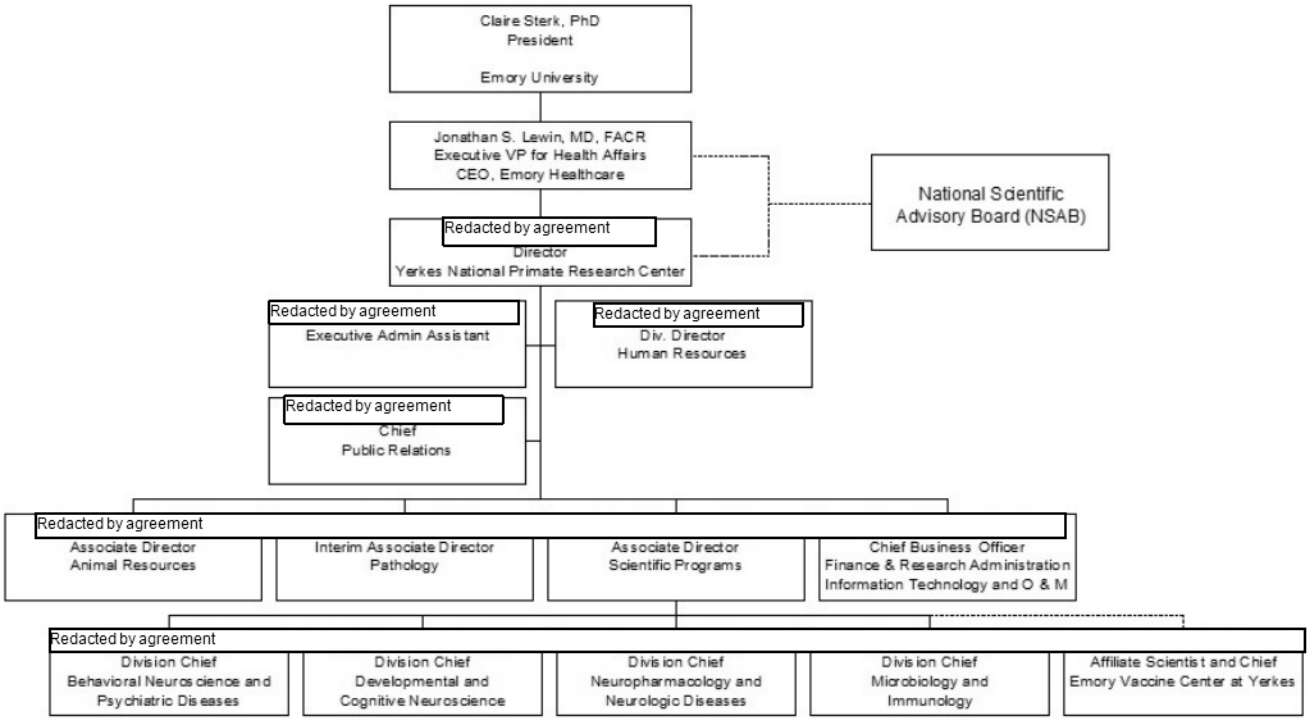
Type of Trainee	Number of Trainees
Post-doctoral	55
Graduate student	108
Undergraduate student	120
Veterinary trainee	13
Other trainee	2
Total	**298**

Description: Veterinary Trainee category includes two residents, one fellow, one intern and nine externs. Other trainee category includes two participants of the ION (Institute On Neuroscience) summer program.

8. Organizational chart that show the relationship of the NPRC to the Institution and the major organizational divisions within the NPRC.

See Next Page

Yerkes National Primate Research Center
Organizational Chart



9. Individual projects performed during the reporting period.

See Next Page

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: EMORY VACCINE CENTER

SPID#: 177

UNIT/DIVISION: Emory Vaccine Center

TYPE: Management

START DATE:

END DATE:

GENERAL CATEGORY:

SUB-CATEGORY:

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER:

SUPPORTING ORGANIZATION: NIAID/NIH, DoD

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Emory Vaccine Center
Prin. NPRC Core Sci.		
Other Core and Affil.		Emory Vaccine Center

PROJECT DESCRIPTION:

The mission of the Emory Vaccine Center (EVC) is to improve human health by conducting fundamental and clinical research that leads to the development of effective vaccines against diseases of global importance. The EVC is an epicenter of academic research and development of vaccines for both chronic and infectious diseases. With more than 250 faculty members and staff, it is the largest and most comprehensive academic vaccine research center in the world.
Our goal at the Emory Vaccine Center is to benefit people – to prevent and cure disease. That is why the Center's focus is on the continuum of vaccine research, from basic science to clinical trials to vaccine policy. We want to see what we do in the lab make a difference in – even save – people's lives. Working in our labs in Atlanta and New Delhi, with our partners across the United States and around the world, and with the assistance of thousands of supporters and volunteers in the community, we are improving human health.

PROGRESS REPORT:

The Emory Vaccine Center is making fundamental advances in immunology, virology and vaccine research to search for life saving cures against the world's most threatening diseases, plaguing millions of individuals around the globe. Comprehensive expertise in scientific, technological, and clinical research distinguishes the EVC as a world leader in the discovery, development and clinical analysis of safe, effective and affordable vaccines. Housed in one of the largest academic centers ever created to investigate new vaccine strategies, the EVC fosters a deeper understanding of the complexities of infectious diseases, cancer biology and vaccine development. Redacted by agreement an internationally renowned scientist in viral pathogenesis and immunity and one of the world's leading experts on T-cell memory, leads the Center. Redacted by agreement has been instrumental in shaping EVC's research agenda that encompasses a continuum of basic, clinical and translational science.
The EVC encourages interdisciplinary collaborative research with investigators throughout Emory University's Woodruff Health Sciences Center, the Centers for Disease Control and Prevention (CDC), the Georgia Research Alliance and nearby academic institutions including Georgia Institute of Technology. Collectively, scientists tackle

prevention and treatment of diseases, including HIV/AIDS, malaria, tuberculosis, influenza and respiratory illnesses that pose a global threat.
The Center's Affiliation with Emory's Yerkes National Primate Research Center also supports research at the forefront of immunology strategy and vaccine development. Long recognized as one of the leading centers for biomedical and biobehavioral research with non-human primates, Yerkes is home to a broad range of molecular and cellular research.
The Hope Clinic of the Emory Vaccine Center serves as the clinical arm, directing all current on-site clinical vaccine trials. As one of eight participating national sites in the NIAID's prestigious Vaccine Trials Evaluation Units (VTEUs), the Clinic plays a vital role in advancing the most promising pre-clinical vaccine research into human clinical trials. The Hope Clinic conducts trials in Atlanta and across the globe to better understand diseases in a multitude of populations.

PUBLICATIONS:

PMID	Title

Submitted by individual investigators, per their awards

FUNDING SOURCES:

Redacted by agreement funded by NIAID/NIH, DoD and foundation awards to all EVC investigators.

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: CENTER FOR AIDS RESEARCH AT EMORY UNIVERSITY (CFAR)

SPID#: 181

UNIT/DIVISION: EVC

TYPE: Management

START DATE: 5/1/2019

END DATE: 4/30/2020

GENERAL CATEGORY:

SUB-CATEGORY:

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER: P30AI050409

SUPPORTING ORGANIZATION: NIAID

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Hubert Department of Global Health, School of Public Health
Prin. NPRC Core Sci.		EVC
Other Core and Affil.		

PROJECT DESCRIPTION:

The CFAR provides research facilities, institutional infrastructure and leadership, support for the recruitment and development of faculty, communication of scientific findings, and the promotion of interactions between CFAR members and with outside institutions and the community through an Administrative Core, a Developmental Core, and five Science Cores: Biostatistics & Bioinformatics, Clinical Research, Immunology, Prevention Science, and Virology & Molecular Biomarkers.

PROGRESS REPORT:

CFAR Investigator Redacted by agreement was awarded an R01 (R01AI143414), "CD8 T Cell Suppression of HIV Latency Establishment and Maintenance in Virally Suppressed Individuals." Current antiretroviral therapy (ART) does not eradicate HIV as shown by the rapid rebound of viremia upon treatment interruption. Rescuing viral gene expression in latently infected cells by compounds termed Latency Reversing Agents (LRA) is a strategy to reduce the virus reservoir in ART-treated HIV-infected individuals (i.e., shock & kill). HIV latency is triggered by mechanisms that lead to the silencing of virus expression including epigenetic DNA modification through histone methylation and deacetylation, limited availability of critical transcription factors and inefficient elongation of the nascent viral transcripts. Recent studies in ART-treated SIV- infected macaques demonstrated that depletion of CD8+ lymphocytes is followed by reactivation of virus production, and increased susceptibility to the LRA effect of the IL-15 superagonist ALT803. These results strongly suggest that CD8+ lymphocyte play an important yet understudied role in silencing HIV expression. In this proposal, we hypothesize that CD8+ T cells suppress HIV gene expression by promoting the establishment and maintenance of HIV latency, and that reversal of this effect may result in a significant amplification of the LRA effect of various compounds, thus impacting the reservoir size and stability in vivo. We will use innovative approaches to identify the CD8+ T cell mediated mechanisms of HIV silencing.This study will define the mechanisms by which CD8+ lymphocytes promote HIV persistence in ART-treated HIV-infected individuals. The work proposed in this application will allow us to understand the how CD8+ lymphocytes impact the course of treated HIV disease and ultimately promote HIV latency in ART-treated HIV-

infected individuals. Our goal is to identify and evaluate therapeutic strategies to counteract these mechanisms, which will constitute the basis for the design of clinical studies aimed at eradication HIV.

CFAR Cores based at YNPRC continue to provide cutting-edge services to CFAR investigators. The Immunology Core provided services to 55 unique investigators, 30 unique projects. Twenty-eight individuals received Flow training. The Virology and Molecular Biomarkers Core supported 28 NIH sponsored research projects. The Core supported 20 unique investigators through the provision of over 2000 virologic and diagnostic assays. These projects have facilitated several key insights in to the basic biology and treatment of HIV patients as well as resulting in the publication of several high profile manuscripts

PUBLICATIONS:

PMID	Title
29467313	Reduced Chronic Lymphocyte Activation following Interferon Alpha Blockade during the Acute Phase of Simian Immunodeficiency Virus Infection in Rhesus Macaques.
29491157	Intragastric administration of Lactobacillus plantarum and AT-2-inactivated SIV does not protect Indian rhesus macaques from intra-rectal SIV challenge nor reduce virus replication after transmission.
29491157	Intragastric administration of Lactobacillus plantarum and AT-2-inactivated SIV does not protect Indian rhesus macaques from intra-rectal SIV challenge nor reduce virus replication after transmission.
28159893	Dynamics of SIV-specific CXCR5+ CD8 T cells during chronic SIV infection.
29300007	Sooty mangabey genome sequence provides insight into AIDS resistance in a natural SIV host.
29720521	Short-Term Pegylated Interferon α2a Treatment Does Not Significantly Reduce the Viral Reservoir of Simian Immunodeficiency Virus-Infected, Antiretroviral Therapy-Treated Rhesus Macaques.
29045906	CTLA-4⁺PD-1⁻ Memory CD4⁺ T Cells Critically Contribute to Viral Persistence in Antiretroviral Therapy-Suppressed, SIV-Infected Rhesus Macaques.
29685793	Correlates of Protection Against SIV_{mac251} Infection in Rhesus Macaques Immunized With Chimpanzee-Derived Adenovirus Vectors.
29669853	CD32 is expressed on cells with transcriptionally active HIV but does not enrich for HIV DNA in resting T cells.
29664020	Accumulation of follicular CD8+ T cells in pathogenic SIV infection.

FUNDING SOURCES:

Redacted by agreement funded by NIAID

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: OPERATION OF THE YERKES PRC

SPID#: 191

UNIT/DIVISION:

TYPE: Management

START DATE:

END DATE:

GENERAL CATEGORY:

SUB-CATEGORY:

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER: P51OD011132

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION: NIH/ORIP

INVESTIGATORS:

	Name	Dept
Principal Investigator	Lewin, Jon	Exec VP Health Sciences
Prin. NPRC Core Sci.	Redacted by agreement	Yerkes NPRC Director
Other Core and Affil.		

PROJECT DESCRIPTION:

This core provides overall direction of the following components for the Yerkes National Primate Research Center of Emory University to support the Center's scientific missions: Administration, Scientific Leadership, Management, Comprehensive Business Services, Information Technology, Human Resources, and Public Information. In addition, the Administrative Core oversees Facilities Management, Animal Resources, Veterinary Medicine, Animal Care, Animal Records, Environmental Enrichment, Research Services, Pathology, and several cores, including state-of-the-art genomics and imaging cores. General direction also is provided for four scientific divisions: Behavioral Neuroscience and Psychiatric Disorders, Developmental and Cognitive Neuroscience, Microbiology and Immunology, and Neuropharmacology and Neurologic Diseases. The Center's goals are to conduct a research program focused on scientific problems relevant to human health problems – such as HIV, neurodegenerative diseases, and the broad NIH mission, to provide the resource infrastructure and expertise in appropriate scientific and veterinary specialties to support such a program, and to enhance the Center's ability to serve as a resource to core investigators as well as to scientists regionally, nationally, and internationally.

PROGRESS REPORT:

FY18 represented another outstanding year for Yerkes, as reflected by $74.6M in sponsored research, over 110 peer-reviewed publications, the recruitment of several new faculty members, and the completion of several key renovation projects to improve and expand our nonhuman primate breeding and housing capabilities.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: THE NIH TETRAMER FACILITY

SPID#: 243

UNIT/DIVISION: Microbiology and Immunology

TYPE: Research

START DATE: 3/21/2013

END DATE: 3/20/2020

GENERAL CATEGORY: Immunology

SUB-CATEGORY: Immunology

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER: NIH Contract: 272201300006C

SUPPORTING ORGANIZATION: NIAID

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	EVC
Prin. NPRC Core Sci.		EVC
Other Core and Affil.		

PROJECT DESCRIPTION:

The NIH Tetramer Facility provides custom synthesis and distribution of soluble major histocompatibility complex (MHC)-peptide tetramer reagents that can be used to detect antigen-specific T cells. These reagents include custom class I tetramers for mouse, non-human primate, and human alleles; class II reagents for mouse, non-human primate and human alleles; mouse and human CD1d tetramers; and human CD1a-c tetramers. The NIH Tetramer Facility also is developing novel technologies to improve production and expand the range of available MHC and CD1 tetramers. The tetramer reagents can be applied to studies ranging from basic immunology and protection against microbial pathogens to control of immune-mediated diseases and tumor metastases.

PROGRESS REPORT:

We implemented new protocols for peptide exchange on class II MHC alleles using HLA-DM that substantially increase the efficiency of class II MHC production. We have developed MALDI-TOF protocols for monitoring peptide exchange into both class I and class II MHC. We continue to produce and supply thousands of MHC tetramers for investigators across the world.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: BIOLOGICAL MATERIAL PROCUREMENT PROGRAM

SPID#: 291

UNIT/DIVISION: Pathology

TYPE: Management

START DATE: 2/1/2018

END DATE: 1/31/2019

GENERAL CATEGORY:

SUB-CATEGORY:

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: P51OD011132

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	DAR
Prin. NPRC Core Sci.		
Other Core and Affil.		DAR
		DAR
		DAR
		DAR
		DAR
		DAR
		DAR
		DAR
		DAR
		Pathology
		Pathology
		DAR
		Pathology

PROJECT DESCRIPTION:

The provision of various biological specimens to Yerkes and non-Yerkes investigators is an important contribution to biomedical research at the host institution as well as other regional, national, and international institutions. Specimens provided to investigators result in a number of publications each year. These specimens have proven to be extremely valuable for educational purposes when used in undergraduate or graduate courses in anatomy, anthropology and will provide data to provide further support for future biomedical, and particularly HIV,

studies. Specimens provided to these investigators included a variety of tissues; for example, bone marrow, blood, eyes, brain, biopsies, liver, kidney, feces, and urine from two nonhuman primate species.

PROGRESS REPORT:

During the reporting period, the Yerkes Center processed 63 specimen requests that resulted in the collection and provision of 1,124 samples. The samples collected were provided to 26 investigators of which 16 were located at Yerkes, 3 at Emory and 7 investigators at other institutions within the U.S.

PUBLICATIONS:

PMID	Title
29743361	Novel Strategy To Adapt Simian-Human Immunodeficiency Virus E1 Carrying <i>env</i> from an RV144 Volunteer to Rhesus Macaques: Coreceptor Switch and Final Recovery of a Pathogenic Virus with Exclusive R5 Tropism.
30232277	Combination anti-PD-1 and antiretroviral therapy provides therapeutic benefit against SIV.
30185596	Antibody-Mediated CD4 Depletion Induces Homeostatic CD4⁺ T Cell Proliferation without Detectable Virus Reactivation in Antiretroviral Therapy-Treated Simian Immunodeficiency Virus-Infected Macaques.
29703519	Proteomics and immunohistochemistry identify the expression of α-cardiac myosin heavy chain in the jaw-closing muscles of sooty mangabeys (order Primates).
30305357	Bone Marrow-Derived CD4⁺ T Cells Are Depleted in Simian Immunodeficiency Virus-Infected Macaques and Contribute to the Size of the Replication-Competent Reservoir.
30262807	Hallmarks of primate lentiviral immunodeficiency infection recapitulate loss of innate lymphoid cells.
30185596	Antibody-Mediated CD4 Depletion Induces Homeostatic CD4⁺ T Cell Proliferation without Detectable Virus Reactivation in Antiretroviral Therapy-Treated Simian Immunodeficiency Virus-Infected Macaques.
29987877	Systemic DPP4 activity is reduced during primary HIV-1 infection and is associated with intestinal RORC⁺ CD4⁺ cell levels: a surrogate marker candidate of HIV-induced intestinal damage.
29669853	CD32 is expressed on cells with transcriptionally active HIV but does not enrich for HIV DNA in resting T cells.
29664020	Accumulation of follicular CD8+ T cells in pathogenic SIV infection.
29764539	Effect of Chronic Social Stress on Prenatal Transfer of Antitetanus Immunity in Captive Breeding Rhesus Macaques (<i>Macaca mulatta</i>).
29997483	Striatal Cholinergic Interneurons in a Knock-in Mouse Model of L-DOPA-Responsive Dystonia.
29605730	Metabotropic glutamate receptors: targets for neuroprotective therapies in Parkinson disease.
29423879	Non-human primate research of basal ganglia and movement disorders: advances and challenges.
28861737	Chronic MPTP administration regimen in monkeys: a model of dopaminergic and non-dopaminergic cell loss in Parkinson's disease.
28540422	Loss and remodeling of striatal dendritic spines in Parkinson's disease: from homeostasis to maladaptive plasticity?
29218729	Structural and molecular heterogeneity of calretinin-expressing interneurons in the rodent and primate striatum.
29797339	Oxytocin- and arginine vasopressin-containing fibers in the cortex of humans, chimpanzees, and rhesus macaques.
29241829	The aged rhesus macaque manifests Braak stage III/IV Alzheimer's-like pathology.

PMID	Title
30651354	Clade C HIV-1 envelope vaccination regimens differ in their ability to elicit antibodies with moderate neutralization breadth against genetically diverse tier 2 HIV-1 envelope variants.
30232277	Combination anti-PD-1 and antiretroviral therapy provides therapeutic benefit against SIV.
30185596	Antibody-Mediated CD4 Depletion Induces Homeostatic CD4⁺ T Cell Proliferation without Detectable Virus Reactivation in Antiretroviral Therapy-Treated Simian Immunodeficiency Virus-Infected Macaques.
29720521	Short-Term Pegylated Interferon α2a Treatment Does Not Significantly Reduce the Viral Reservoir of Simian Immunodeficiency Virus-Infected, Antiretroviral Therapy-Treated Rhesus Macaques.

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: MAINTENANCE OF YNPRC ANIMAL COLONY

SPID#: 292

UNIT/DIVISION: Animal Resources

TYPE: Management

START DATE:

END DATE:

GENERAL CATEGORY:

SUB-CATEGORY:

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: P51OD011132

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Animal Resources
Prin. NPRC Core Sci.		
Other Core and Affil.		Animal Resources
		Animal Resources
		Animal Resources
		Animal Resources
		Animal Resources

PROJECT DESCRIPTION:

The Yerkes National Primate Research Center maintains a large colony of nonhuman primates for use in biomedical and behavioral research. The Yerkes nonhuman primate colony is maintained by the Division of Animal Resources, which is responsible for all aspects of the animal care and use program, including veterinary medicine, breeding colony management, animal care and husbandry, behavioral management and environmental enrichment, animal records, and provision of research support. Colony animals may also be used for the collection of certain biological specimens for use in in-vitro studies. Maintenance of the Yerkes colony requires certain animal care and use procedures that are essential to the continued availability of these nonhuman primate resources.

PROGRESS REPORT:

The Division of Animal Resources continues to manage the colony husbandry, maintaining breeding colonies (including SPF macaques and mangabey colonies for AIDS research); movement and handling of the animals as required for management purposes; routine health surveillance, which may include physical examination, tuberculin testing, radiographs, blood collections, treatment of diseases and injuries. The DAR continues to expand the breeding colony in order to generate animals in support of increasing research demands. Additionally, the pedigree history and the genetics and genomics of individual animals is maintained by the Division of Animal Resources in collaboration with Genomics.

PUBLICATIONS:

PMID	Title
29764539	Effect of Chronic Social Stress on Prenatal Transfer of Antitetanus Immunity in Captive Breeding Rhesus Macaques (<i>Macaca mulatta</i>).

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: MAINTENANCE OF THE SPF BREEDING COLONIES AT THE YERKES NPRC

SPID#: 309

UNIT/DIVISION: Animal Resources

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: Animal

SUB-CATEGORY: Immunology

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER: P51 OD011132

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Animal Resources
Prin. NPRC Core Sci.		
Other Core and Affil.		M&I
		Animal Resources
		M&I
		M&I
		Animal Resources

PROJECT DESCRIPTION:

A central objective of this project is to breed Indian origin rhesus monkeys that are specific pathogen free (SPF) for Herpes B, STLV, SIV and SRV. In addition, animals are fully pedigreed and genetically characterized for MHC alleles.

This project provides trained personnel and resources that are necessary to maintain and expand the SPF breeding groups and to manage them in order to optimize health and reproductive performance in support of national health related priorities. This objective is achieved at the center by utilizing an existing colony of SPF macaques. This colony is expanded via breeding of dedicated animals with known pedigrees. The colonies are virally maintained by routine blood collection for testing at specified intervals. These animals are made available as subjects to NIH supported investigators for AIDS related research and contribute to national health priorities. The YNPRC works closely with the National Primate Research Centers Breeding and Colony Management Consortium to maintain current standards of husbandry, standardization of screening tests and such other matters as the committee may deem necessary. To maximize the potential that national priorities for SPF production will be met, the YNPRC works in conjunction with other facilities, and investigators identified by ORIP to maintain supported SPF colonies

PROGRESS REPORT:

The Yerkes NPRC continues to expand the SPF Indian rhesus monkey breeding colony which consists of 2056 Indian rhesus macaques managed for maximum production to support HIV/AIDS research. As the colony continues to expand to meet the increasing number of animal requests for AIDS-related studies, U42 program income will ensure sustainability of our AIDS-designated colony. All rhesus monkey breeding groups at the Yerkes Field Station have been SPF since April 2014, allowing us to optimize growth of this colony. For the 2018 birth season, the colony produced 532 offspring. Of these, 502 (94.4%) survived to at least four months of age.
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For the 2016 birth cohort, genetic paternity has been defined for 91.4% and MHC class I genotyping completed for 97.3% of animals . Parentage genotyping is currently in progress for the 2017 and 2018 birth cohorts. For 2017 births, parentage has been assigned for 12.5% of animals and MHC genotypes has been determined for 75.1% of the 2017 birth cohort. As part of our ongoing effort to improve the estimation of breeding and genetic value, we continue to genotype historically-prolific sires and dams with our internal goal to apply as much objective information to breeder selection and animal assignment as possible. At the end of 2018, we sent approximately 200 DNA samples from prolific breeders to Wisconsin National Primate Research Center for sequencing-based genotyping of MHC class I and class II. We are optimistic that these MHC genotyping data will provide us with a better understanding of the composition of the haplotypes and the distribution of alleles throughout the YNPRC breeding program.

During the course of this funding period, the Viral Testing Core has tested over 1600 animals by Luminex, the multiplexed first step in our testing algorithm. Over 2600 confirmatory Western blots were performed for B-virus, SIV, STLV, and SRV combined. Indeterminate Western blots for SIV and STLV were confirmed negative via 376 PCRs. No animal was confirmed positive for any SPF pathogen, although several animals were tested monthly due to persistent indeterminate follow-up B-virus testing. Additionally, the Core has begun validating a confirmatory SRV quantitative real-time PCR assay by testing samples side-by-side with the CNPRC's Pathogen Detection Lab. A preliminary test of its ability to detect positive samples with low background was performed using a battery of blinded proficiency testing samples sent from the CNPRC that contained SRV positive, indeterminate, and negative samples. Our implementation of the SRV qPCR successfully detected the positive samples with no false positives or false negatives. We plan to review all data regarding the qPCR's performance after a full year of testing. Upon successful discernment of all positive and negative samples, we plan to shift to in-house SRV testing using this new assay.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

U42 OD011023
P51 OD011132

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: YERKES BIOMARKERS CORE

SPID#: 360

UNIT/DIVISION: Biomarkers Core

TYPE: Management

START DATE:

END DATE:

GENERAL CATEGORY:

SUB-CATEGORY:

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER: P51 OD0111032

SUPPORTING ORGANIZATION: NIH / ORIP

SPECIFIC INFORMATION: NIH / ORIP

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	M&I
Prin. NPRC Core Sci.		
Other Core and Affil.		M&I

PROJECT DESCRIPTION:

The primary mission of the Yerkes Biomarkers Core is to develop, validate and perform steroid, protein and other biologically relevant assays in support of translational and clinical research performed at the Yerkes National Primate Research Center and by outside investigators. The Core currently provides an array of validated assays for reproductive function, stress physiology, growth, metabolism, circadian physiology, pituitary function, neuropeptides and neurotransmitters through the use of several immunoassay platforms and liquid chromatography mass spectrometry (LCMS) in multiple species. The Core recovers cost through recharges of clients for personnel, reagents, service contracts, and miscellaneous supplies by performing assays for Yerkes, Emory, and national investigators and clinicians. The facility is housed at the Yerkes Main Station and contains a Shimadzu UPLC system in tandem with an AB Sciex 6500 triple quadrupole mass spectrometer, a DRG Hybrid-XL, and a Molecular Devices SpectraMax i3x. We perform all necessary sample processing and data analysis, and work with investigators to provide the highest quality data. In addition to performing assays, the Core also consults with the scientific community to provide up-to-date methodology for the development, implementation, and validation of new assays with expanded sample types, lower sample size requirements, quicker assay turnaround, improved sensitivity and higher accuracy to meet their research needs. Furthermore, we strive to lower the cost and turnaround time of existing assays by validating immunoassays on our multiple LCMS platforms whenever possible.

PROGRESS REPORT:

Over the past year of funding, the Core has provided 2442 immunoassay and 369 LC/MS tests using our standardized assays in support of research with our collaborators at Yerkes, Emory University and throughout the United States. Additionally, we have developed and validated a new LC/MS assay to measure cortisol in rhesus macaque breast milk. Measurement of milk cortisol allows researchers to evaluate stress levels in breast feeding mothers of various social ranks and combining these results with cortisol levels in nursing infants to understand how early life stressors in both mother and fetus impact growth and cognitive development. Finally,

we continue to work on the development and validation of a highly sensitive LC/MS assay for oxytocin. This critical and difficult-to-quantify biomarker is a high priority for several researchers at Yerkes and Emory. In the past few months, the Core has had a significant breakthrough, and is able to accurately quantify oxytocin at 1 pg/mL to 500 pg/mL concentrations by LC/MS, which encompasses the biologically relevant range of oxytocin expected from most samples. Over the next funding period we will be working to increase the intensity of MS output detection in order to begin validation of this assay for several critical complex substrates, including cerebrospinal fluid, serum, saliva, and urine. We have been working to reach out to researchers to emphasize the importance of flash-freezing and consistent storage any sample that will be used in a future oxytocin assay.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: REGULATION OF MOTOR FUNCTION IN PARKINSON'S DISEASE

SPID#: 369

UNIT/DIVISION: Neuropharmacology and Neurologic Diseases

TYPE: Research

START DATE: 8/1/2018

END DATE: 7/31/2019

GENERAL CATEGORY: Neural

SUB-CATEGORY: Therapy

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R01NS045962

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Neuropharmacology and Neurologic Diseases
Prin. NPRC Core Sci.		
Other Core and Affil.		Neuropharmacology and Neurologic Diseases

PROJECT DESCRIPTION:

This project that has already completed two cycles is focused on the striatal mechanisms involved in the development of motor abnormalities in the evolution of Parkinson's disease. Specifically, studies in this project are concerned with the role of striatal glutamatergic transmission in the pathophysiology of abnormal motor responses to dopamine. The specific aims of this project were focused on characterizing the responses of striatal projection neurons to dopamine inputs in the context of chronic dopamine denervation and stimulation with dopaminergic drugs. The goal of the new studies (third cycle) is to identify changes in identified striatal neuronal populations that could be specifically targeted to develop new treatments focusing in the glutamatergic system to effectively restore motor function in Parkinson's disease.

PROGRESS REPORT:

Studies are just beginning (R56) with optogenetic identification of striatal units to characterize changes in the glutamatergic signaling that cause abnormal hyperactivity. Pilot tests in rodents were done to identify striatal neurons in slice recordings using normal rats. Also a new primate has been identified and assigned to the study for recordings in the normal condition to generate control data. These experiments will advance the studies involved in specific aims 1 (optogenetic characterization of firing abnormalities in differentiated striatal projection neurons) and 2 (analysis of the role of glutamate receptor subunit in synaptic currents on striatal projection neurons). An application for the complete funding of the third cycle has already been resubmitted to the NIH.

PUBLICATIONS:

PMID	Title
2862083	Regulatory properties of phenylalanine, tyrosine and tryptophan hydroxylases.

PMID	Title
28337120	Antidyskinetic Effects of MEK Inhibitor Are Associated with Multiple Neurochemical Alterations in the Striatum of Hemiparkinsonian Rats.
29386136	Glutamatergic Tuning of Hyperactive Striatal Projection Neurons Controls the Motor Response to Dopamine Replacement in Parkinsonian Primates.
29508924	A Selective Phosphodiesterase 10A Inhibitor Reduces L-Dopa-Induced Dyskinesias in Parkinsonian Monkeys.

FUNDING SOURCES:
NIH, NINDS

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: PRIMATE GENETIC ANALYSIS AND PEDIGREE MANAGEMENT

SPID#: 390

UNIT/DIVISION: Division of Animal Resources

TYPE: Management

START DATE:

END DATE:

GENERAL CATEGORY:

SUB-CATEGORY:

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER: P51OD011132

SUPPORTING ORGANIZATION: NIH/ORIP

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	M&I
Prin. NPRC Core Sci.		
Other Core and Affil.		Division of Animal Resources
		Division of Animal Resources

PROJECT DESCRIPTION:

Genetic characterization of the rhesus (SPF and non-SPF) colonies is an ongoing effort. At survey or clinical encounter, peripheral blood is collected, processed to DNA, and genotyped for parentage determination and MHC class I. Yerkes has adopted a panel of 96 probes that correspond to unlinked and bi-allelic single-nucleotide polymorphic loci (as identified by the NPRC Genetics and Genomics Working Group). Using 30 well-documented trios, this probeset was validated for specificity and genetic utility in determining parentage (QC'd across 3 independent testing sites as part of the GGWG collaboration). Internally, we identify potential sires as breeding age males co-housed with the observed dam during the period of conception, which is estimated based on birthdate. Among these potential sires, the genetic sire is defined as the individual exhibiting the highest proportion of genetic compatibility (with the offspring) across the 96 probes. These data, along with the MHC genotyping data, are invaluable to our efforts to intelligently identify and assign genetically-suitable animals to investigator-driven projects. All genetic data is internally-accessible through a web-based portal that is maintained in collaboration with the Yerkes Information Technology Department.

PROGRESS REPORT:

For animals born in 2016, genetic parentage has been defined for 91.4% and Mamu-A*01, Mamu-B*08, and Mamu-B*17 genotypes have been defined for 97.3%. At the time of this writing, MHC status has been determined for 75.1% of animals born in 2017. Parentage genotyping is currently in progress for the 2017 and 2018 birth cohorts; we have identified genetic parents for 12.5% of 2017 births. We continue to collect parentage and MHC genotyping data on prolific breeders as part of our ongoing effort to improve genetic and breeding value estimation. To ensure that investigators and animal resources are provided with timely genetic data, we developed methodology to automatically identify inconsistencies between genetic and non-genetic datasets (e.g. co-housing). We define a potential sire as a breeding aged male co-housed with an observed dam during the

estimated period of conception. Of potential sires, we define the genetic sire as the individual sharing the highest proportion of alleles (across 96 bi-allelic sites in the rhesus macaque genome) with the offspring. If the dam's or a potential sire's housing history is corrected, our new system recalculates parentage and alerts colony management to any changes that may impact assignment, breeding, or social health. This web-based resource is open to investigators and animal resources. We have developed several new tools that serve as a resource to colony managers and researchers alike. Oedipus, our new incestual breeding avoidance tool, aids colony management in constructing breeding groups by identifying genetically problematic pairings. Our new matriline tool accesses 10 generations of family line data and allows investigators and clinicians to quickly check whether experimental or clinical observations are shared among family members.

We are working with the Genetics Services group of the Wisconsin National Primate Research Center to better understand the MHC composition of our colony. In late 2018, we sent approximately 200 genomic DNA samples from prolific breeders to WNPRC for comprehensive MHC class I and class II genotyping by sequencing. Additionally, we are working, both internally through investigator-driven "test cases" and as part of the NPRC Genetics and Genomics Working Group, to establish colony breeding and management strategies that promote identification and development of novel genetic models.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE:	DETERMINANTS OF NEUTRALIZATION BREADTH IN EARLY HIV-1 INFECTION
SPID#:	405
UNIT/DIVISION:	Emory Vaccine Center
TYPE:	Research
START DATE:	4/1/2004
END DATE:	3/31/2019
GENERAL CATEGORY:	AIDS
SUB-CATEGORY:	Immunology
NIH GRANT:	☒ Yes ☐ No
GRANT NUMBER:	R01AI058706
SUPPORTING ORGANIZATION:	NIH
SPECIFIC INFORMATION:	

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Emory Vaccine Center
Prin. NPRC Core Sci.		
Other Core and Affil.		Emory Vaccine Center

PROJECT DESCRIPTION:

Antibodies that neutralize genetically diverse HIV-1 strains, known as broadly neutralizing antibodies (bnAbs) are rare and the mechanisms that expand the otherwise narrow neutralization capacity observed during early HIV-1 infection are currently undefined. The goals of this project are therefore to understand how viral and immune events that occur during early infection could be incorporated into HIV vaccination strategies that will elicit antibodies with neutralization breadth.

PROGRESS REPORT:

We have shown that anti-HIV envelope B cells with VH1-69 heavy chain genes are over-represented in early HIV-1 infection, and have identified novel features of these VH1-69 antibodies that are associated with Fc-mediated effector antiviral functions.

PUBLICATIONS:

PMID	Title

PMID not yet assigned

Unpublished

FUNDING SOURCES:

Redacted by agreement funded by NIAID.

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: VIROLOGIC CORRELATES OF HETEROSEXUAL TRANSMISSION

SPID#: 406

UNIT/DIVISION: Emory Vaccine Center

TYPE: Research

START DATE: 3/15/2002

END DATE: 1/31/2023

GENERAL CATEGORY: Infectious Disease

SUB-CATEGORY: Viral

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R01AI051231

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Emory Vaccine Center
Prin. NPRC Core Sci.		MGH, MIT, and Harvard
Other Core and Affil.		Emory Vaccine Center
		Emory Vaccine Center
		Project San Francisco, Kigali, Rwanda
		ZEHRP, Zambia

PROJECT DESCRIPTION:

Heterosexual HIV-1 transmission is an inefficient process that occurs on average roughly once for every 100 unprotected sexual encounters. We seek to understand why In approximately 85% of heterosexual epidemiologically linked couples within a Zambian cohort where clade C virus prevails and within a Rwandan cohort where clade A virus predominates, that a single virus from the large swarm of viral variants present in the chronically infected donor establishes a new infection in the recipient, a phenomenon known as the 'transmission bottleneck'. We hypothesized that transmitted/founder (TF) viruses possess one or more special characteristics allowing them to establish new infections compared to related non transmitted (NT) variants within the chronically infected partner. Understanding characteristics separating TF fron NT viruses would be of tremendous value in understanding viral transmission and in developing an effective vaccine. Moreover, understanding TF characteristics might also help elucidate the relationship between infection and the trajectory of the subsequent pathology. For example, highly replicating TFs might spread more rapidly in vivo, more rapidly deplete target CD4 cells, and hence lead to a more rapid onset of AIDS in the absence of antiviral drugs.

PROGRESS REPORT:

Antiretroviral therapy (ART) has had great appeal in lowering HIV-1 levels in infected individuals and in reducing subsequent viral transmissions. Unfortunately the limited access to or the compliance with taking ART, especially in resource poor nations, combined with variable degrees of compliance means that this strategy is not a panacea for combatting HIV. Using samples acquired from government couples' voluntary counseling and testing (CVCT) clinics in Africa, we examined factors related to transmission when chronically infected partners

were ostensibly receiving ART (Woodson et al., 2018). In nine Zambian couples, all transmitting partners had detectable viral loads, and 8/9 of these chronically infected individuals were not on therapeutic ART regimens. In the remaining couple, despite being on a therapeutic regimen, drug resistance mutations (DRMs) were present and also transmitted to the partner. In seven Rwandan couples, six transmitting partners had detectable viral loads near the time of transmission, and therapeutic levels of ART drugs were detected in plasma for four of these seven transmitters along with detected DRMs. In the remaining three couples, either no ART was detected in plasma or the drugs were at sub therapeutic levels. These findings show a combination of suboptimal ART administration combined with DRMs can contribute to the spread of this disease. Hence a reliance solely on ART, especially in resource limited settings, may not be sufficient to control the HIV epidemic in a post-ART era.

Prior results from this and from other labs have shown that high viremia and high in vitro viral replication rates are associated with an accelerated pathology. In an effort to early identify HIV infected patients who may be at risk for a heightened pathological response, we evaluated a number of clinical, demographic, and laboratory indicators that might be predictive of an extended high viremia (EHV) in infected sub-Saharan African individuals (Powers et al., 2018). The estimated date of infection (EDI) was based on a positive plasma viral load or a p24 positive antigen test prior to seroconversion. Logistic regression was employed to develop risk score algorithms for EHV based on sex, age, number of acute retroviral syndrome symptoms, and CD4 and viral load at diagnosis. Models incorporating the full set of 5 predictors exhibited excellent performance both with the full population and with the smaller subsets of subtypes A, C, and D. Hence, simple risk score algorithms may be useful identifying individuals likely to develop a potentially a more severe pathological trajectory.

Plasmacytoid dendritic cells (pDC) are the primary alpha interferon (IFN-a)-producing cells in response to viral infections and they are rapidly recruited to the female genital tract upon HIV-1 exposure. Since IFNs may act to counter viral infections, we asked whether IFN-a and TNF-a production from isolated pDCs obtained from healthy donors might differ when these cells were exposed to transmitted/founder (TF) viruses versus non-transmitted (NT) viruses (Schwartz et al., 2018). Although there was a trend toward enhanced IFN-a and TNF-a production in response to TF viruses, no significant differences were found in cytokine production. Hence, TF viruses do not appear to preferentially subvert pDC activation compared to non transmitted HIV variants.

Human Fc-gamma receptors (FcγRs) are able to bind IgG antibodies, and hence are potentially able to bridge the cellular and humoral immune responses. Prior reports have shown disparate findings regarding the role of these receptors in HIV infection. We therefore examined HIV acquisition in a large cohort consisting of 836 Zambian and Rwandan subjects where HIV subtypes C and A prevail in order to see if there was any evidence linking FcγRIIA and FcγRIIIA amino acid variants sporting high and low affinities for IgG with infection rates (Connolly et al., 2018). Briefly using cox proportional hazards models and linear regression models, we failed to see any significant effect linking these FcγRs with HIV transmission.

Finally, designing studies to evaluate HIV transmission and pathogenesis in humans is obviously not possible given the health consequences. For this reason studies are instead being performed using humanized mouse models or in nonhuman primates. We are currently working with Redacted by agreement at MGH/Harvard to test TF and NT viruses in a mouse model. Since every animal model has its pros and cons, there are also efforts to generate replication-competent simian-human immunodeficiency viruses (SHIV) and simian tropic HIV (stHIV) viruses that might allow testing of TF and NT derived viruses in a NHP model. Dutta et al., 2018 has described a cloning strategy to create such viruses without relying on restriction endonuclease-based cloning.

PUBLICATIONS:

PMID	Title
29762171	HIV transmission in discordant couples in Africa in the context of antiretroviral therapy availability.
29614069	Prediction of extended high viremia among newly HIV-1-infected persons in sub-Saharan Africa.
29997203	Characterization of the Plasmacytoid Dendritic Cell Response to Transmitted/Founder and Nontransmitted Variants of HIV-1.
30278383	Fc-gamma receptor IIA and IIIA variants in two African cohorts: Lack of consistent impact on heterosexual HIV acquisition, viral control, and disease progression.
29758076	High throughput generation and characterization of replication-competent clade C transmitter-founder simian human immunodeficiency viruses.
30358840	HIV testing and counselling couples together for affordable HIV prevention in Africa.

FUNDING SOURCES:

Support from the Emory Center for AIDS Research (P30 AI050409)
Yerkes National Primate Research Center base grant through the Office of Research Infrastructure Programs/OD P51OD11132
Redacted by agreement funded by NIAID (2R01AI051231)

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: MECHANISMS OF HEPATITIS C VIRUS PERSISTENCE

SPID#: 510

UNIT/DIVISION: Microbiology Immunology

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: Immunology

SUB-CATEGORY: Immunology

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R01AI070101

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Microbiology Immunology
Prin. NPRC Core Sci.		Microbiology Immunology
Other Core and Affil.		

PROJECT DESCRIPTION:

Persistent hepatotropic viral infections are a common etiologic agent of chronic liver disease. Unresolved infection can be attributed to non-functional intrahepatic immune responses

PROGRESS REPORT:

We have made significant progress in our work during the previous 9 months of funding in 2018. This has resulted in two published peer-reviewed manuscripts and two review articles during the past cycle.

PUBLICATIONS:

PMID	Title
29454797	Alterations in Intestinal Microbiota Lead to Production of Interleukin 17 by Intrahepatic γδ T-Cell Receptor-Positive Cells and Pathogenesis of Cholestatic Liver Disease.
29514902	Dynamics of Tissue-Specific CD8⁺ T Cell Responses during West Nile Virus Infection.
29281849	Of mice, rats, and men: Small animal model of hepatitis C virus infection.
28926189	Environmental peer pressure: CD4⁺ T cell help in tolerance and transplantation.

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: TRAINING IN SYSTEMS AND INTEGRATIVE BIOLOGY NEUROSCIENCE

SPID#: 513

UNIT/DIVISION: Neuropharmacology and Neurologic Diseases

TYPE: Research

START DATE: 7/1/2016

END DATE: 6/30/2021

GENERAL CATEGORY: Training

SUB-CATEGORY: Doctoral and PostDoctoral

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER: T32GM96050

SUPPORTING ORGANIZATION: NIH/NINDS

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Neuropharmacology and Neurologic Diseases
Prin. NPRC Core Sci.		Neuropharmacology and Neurologic Diseases
Other Core and Affil.		

PROJECT DESCRIPTION:

This NIH training grant represents the main source of funding for students enrolled in the Emory Neuroscience program.

PROGRESS REPORT:

During the past year, this training grant supported parts of the stipends, tuition fees, activity fees and other training expenses for 7 second year students in the neuroscience graduate program. Two of these trainees are from under-represented minority groups. As for previous years, these trainees were chosen based on their academic performance during their first year in the program and their general participation in program activities. In addition to financial support, the trainees use some of these funds to invite a guest speaker for the weekly seminar series sponsored by the program. The trainees are in charge of inviting their guest, organize their visit and host them when they come to Emory. This has proven to be an excellent opportunity for students to interact with well-known researchers in their field of interest. Many trainees also used funds to cover some expenses to attend a national scientific meeting, which provided them a unique exposure to the field of neuroscience research and helped launch their thesis project. It also provided them the opportunity to interact with other scientists in their field, broaden their research foundation, and improve their presentation skills.

PUBLICATIONS:

PMID	Title

None

FUNDING SOURCES:

Redacted by agreement Funded by NINDS

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: CTL AND HIV POLYMORPHISMS IN HETEROSEXUAL TRANSMISSION

SPID#: 516

UNIT/DIVISION: Emory Vaccine Center

TYPE: Research

START DATE: 7/1/2015

END DATE: 6/30/2020

GENERAL CATEGORY: Infectious Disease

SUB-CATEGORY: Viral

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R01AI064060

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Emory Vaccine Center
Prin. NPRC Core Sci.		
Other Core and Affil.		Emory Vaccine Center
		Emory Vaccine Center
		Univ of Alabama at Birmingham
		Univ of Alabama at Birmingham

PROJECT DESCRIPTION:

In most heterosexual HIV-1 transmissions, a single transmitted/founder (TF) virus establishes infection. This project examines how the immune system in a newly infected individual exerts pressure on an incoming TF virus and its progeny, which then accounts for the development of mutations that allow virions to escape from immune surveillance and to propagate efficiently within the new host. We previously showed a dramatic and early impact of the TF's viral replicative capacity (vRC) on HIV-1 immunopathogenesis that is independent of viral load (VL). In addition, we showed that the degree of preadaptation of the TF virus to the newly infected host's cellular immune system impacted both viral control and CD4 decline, with more highly adapted viruses demonstrating enhanced pathogenesis. Taken together, these findings support an unprecedented role for the genotype of the TF virus in influencing multiple facets of HIV-1-related immunopathology, and that a greater focus on this parameter could provide novel insights with respect to developing clinical interventions. The main objectives of this grant are to: (1) Define and study the diverse proteomes in 80 TF viruses from the Rwandan cohort and in 120 TF viruses from the Zambian cohort; (2) To characterize early CD4 and CD8 responses that account for early viral control; and (3) To explore fine mapping of the human leukocyte antigen (HLA) and related sequence elements which might account for effective immune control by the host.

PROGRESS REPORT:

HIV transmission and pathogenesis are complex processes that are dependent on a number of viral characteristics as well as a variety of cellular and humoral immune factors. A large focus of this project has been to seek a better understanding of how CD8 cytotoxic T cells work to control HIV infection and how the virus then

adapts through mutations to escape this immune pressure. CD8 T cells are able to target infected cells in part through recognition of viral peptides presented at the cell surface by human leukocyte antigen (HLA) molecules. It has been known for quite some time that HIV down regulates the expression of HLA-A and HLA-B, thus helping the virus to escape immune detection. It was also thought that HLA-C remained on the cell surface to allow binding to inhibitory killer immunoglobulin-like receptors, thereby preventing natural killer (NK) cell-mediated viral suppression. However, more recent evidence suggests that HIV might also down regulate HLA-C expression.

This and other laboratories have shown that heterosexual HIV transmission is associated with a bottleneck such that typically only one or a few viral quasispecies from the multitude of circulating viruses in a chronically infected individual act to establish a de novo infection in the partner. We have long suspected that transmitted/founder (TF) viruses might exhibit one or more properties distinct from non-transmitted (NT) viruses that account for their transmissibility.

In light of our interest in understanding HLA mediated pressure on HIV, we decided to use flow cytometry to evaluate the heterogeneity of HLA-A, HLA-B, and HLA-C class I downregulation using 40 well characterized TF and NT full-length primary viruses derived from six Zambian transmission pairs (Ende et al., 2018). Primary viruses mediated a range of HLA class I downregulation capacities (1.3- to 6.1-fold) which could differ significantly between transmission pairs. Downregulation of HLA-C surface expression on infected cells correlated with susceptibility to in vitro NK cell suppression of virus release. Despite this, transmitted/founder variants did not share a downregulation signature, and instead were more similar to the quasispecies of matched donor partners. These data indicate that a range of viral abilities to downregulate HLA-A, HLA-B, and HLA-C exist within and between individuals that can have functional consequences on immune recognition.

When considering HLA class I restriction, we typically think about the cell surface presentation of viral peptides derived from multiple open reading frames in the virus. However, it is also conceivable that antisense-derived HIV-1 cryptic epitopes (CEs) in alternate reading frames might also contribute toward this cell mediated immune response. This possibility was examined in a paper by Peng et al., 2018. A total of 66 CEs were predicted from analysis of viral genomes. Of these, 10 were recognized in 8/32 and 4/11 patients with chronic and acute infections, respectively. Interestingly, the immunogenic CE were all derived from a single antisense reading frame within pol, but none of these epitopes led to consistent escape mutations when performing a longitudinal analysis of samples. This suggests that while CEs may be immunogenic, they also may not be major drivers of viral escape, at least not in the early stages of infection, perhaps owing to the subdominant nature of these CE-specific responses, the low antigen sensitivity, or the magnitude of CE responses during acute infections.

Immune control of HIV-1 infection depends heavily on cytotoxic T-lymphocyte responses restricted by diverse HLA class I molecules. Recent work has uncovered specific amino acid residues (AARs) that seem to dictate the extent of immune control in African Americans, which prompted us to test these emerging hypotheses in seroconverters (SCs) from southern and eastern Africa (Wiener et al., 2018). Based on data from 196 Zambians and 76 Rwandans with fully resolved HLA alleles and pre-therapy HIV-1 viral loads (VL) in the first 3- to 36-month of infection (> 2300 person-visits), four AARs of primary interest (positions 63, 97, 116 and 245 in the mature HLA-B protein) were found to explain 8.1% and 15.8% of variance in set-point VL for these cohorts (P=.024 and 7.5×10−6, respectively). Two AARs not reported previously (167S in HLA-B and 116F in HLA-C) also showed relatively consistent associations with VL (adjusted P=.009–.069), while many population-specific associations were also noted (false discovery rate<0.05). Extensive and often strong linkage disequilibrium among neighboring AAR variants called for more extensive analyses of AAR haplotypes in diverse cohorts before the structural basis of antigen presentation can be fully comprehended.

PUBLICATIONS:

PMID	Title
29321314	HLA Class I Downregulation by HIV-1 Variants from Subtype C Transmission Pairs.
30021907	Antisense-Derived HIV-1 Cryptic Epitopes Are Not Major Drivers of Viral Evolution during the Acute Phase of Infection.
29289742	Immunogenetic factors in early immune control of human immunodeficiency virus type 1 (HIV-1) infection: Evaluation of HLA class I amino acid variants in two African populations.

FUNDING SOURCES:

Support from the Emory Center for AIDS Research (P30 AI050409)

Yerkes National Primate Research Center base grant through the Office of Research Infrastructure Programs/OD P51OD11132
Redacted by agreement unded by NIAID (5R01AI064060)

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: YERKES IMAGING CORE

SPID#: 519

UNIT/DIVISION: Admin

TYPE: Management

START DATE:

END DATE:

GENERAL CATEGORY: Imaging

SUB-CATEGORY: Neural

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER:

SUPPORTING ORGANIZATION: Yerkes NPRC

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	NND, Radiology
Prin. NPRC Core Sci.		DCN
		NND
		DCN
		NND
		DCN
		NND
		DNND
Other Core and Affil.		DCN
		Radiology
		DCN
		Radiology
		Morehouse SOM
		Psychiatry and Behav.
		EVC
		NND
		NND
		DCN
		NND
		EMORY COLLEGE/ANTHROPOLOGY

Name	Dept
Redacted by agreement	EMORY SOM/PHYSIOLOGY
	UNIV OF VERMONT, VT
	NND
	EMORY SOM/NEUROLOGY
	EMORY SOM/ PSYCHIATRY
	EMORY SOM/ ANESTHESIOLOGY

PROJECT DESCRIPTION:

The Yerkes Imaging Center is part of the Yerkes National Primate Research Center at Emory University and focuses on the development of in vivo magnetic resonance imaging (MRI) and positron emission tomography (PET) to study anatomy, physiology, and function non-invasively to address questions in neuroscience, neuropharmacology, and neurodegenerative diseases. Research at the Imaging Center includes high-resolution structural, perfusion and functional imaging of nonhuman primates, diffusion-tensor imaging (DTI), awake monkey fMRI, quantitative perfusion imaging, quantitation of monoamine transporters and receptors, brain metabolic mapping, diffusion, perfusion and functional imaging of stroke, and image data analysis and visualization.

PROGRESS REPORT:

The Imaging Center continues to support internal and external investigators with MRI and PET imaging as part of their individual research programs. In addition, we continued to commit significant resources to the development of a nonhuman primate model of ischemic stroke. Redacted by agreement a newly appointed endowed chair of stroke imaging joined the Imaging Center in 2017. Redacted by agreement a new director of the imaging center, has been recruited from MGH and started at Yerkes in January 2018. We have expanded our use of diffusion tensor imaging DTI to characterize brain development in longitudinal studies conducted at the Yerkes Field Station. We have also made significant progress in establishing technical approaches in novel MRI such as diffusion kurtosis imaging (DKI) and chemical exchange saturation transfer (CEST) MRI.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

P51OD011132

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: STUDIES OF NATURAL SIV-INFECTION OF SOOTY MANGABEYS

SPID#: 556

UNIT/DIVISION: Microbiology Immunology

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: AIDS

SUB-CATEGORY: AIDS

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER: R37 AI066998

SUPPORTING ORGANIZATION: NIAID

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Microbiology Immunology
Prin. NPRC Core Sci.		
Other Core and Affil.		Microbiology Immunology

PROJECT DESCRIPTION:

Understanding the reasons why SIV-infected sooty mangabeys (SMs) remain healthy despite high viremia is a key unanswered question in contemporary AIDS research, with important ramifications in terms of HIV pathogenesis, therapy, and vaccines. In recent studies, we have sorted stem-cell memory CD4+ T cells (CD4+ TSCM), central memory CD4+ T cells (CD4+ TCM) and effector-memory CD4+ T cells (CD4+ TEM) from SIV-infected SMs and rhesus macaques (RMs), and that, while CD4+ TEM were similarly infected in both species, CD4+ TSCM and CD4+ TCM of SMs show significantly (>1 log) fewer SIV-DNA copies in vivo than CD4+ TCM of RMs. Based on this result, we hypothesize that protection of CD4+ TSCM and CD4+ TCM from virus infection is a key mechanisms by which SIV-infected SMs avoid CD4+ T cell depletion, chronic immune activation, and progression to AIDS. To test this hypothesis we will expand upon this previous work and propose a series of studies that will clarify the main features of in vivo and in vitro SIV infection in CD4+ TCM of both SMs and RMs, and elucidate the mechanisms by which CD4+ TCM of SMs are protected from SIV infection. In addition, our progress to date has helped us identify a number of directly related new lines of investigation to pursue under the overall umbrella of the hypotheses and research articulated in our "Studies of natural SIV infection of sooty mangabeys" grant proposal. We believe that these studies will advance significantly our understanding of how naturally SIV-infected SMs are resistant to AIDS despite high viremia. We envision that answering this question will provide clues to AIDS pathogenesis in humans that will have ultimately an impact on the prevention and treatment of HIV infection.

PROGRESS REPORT:

To shed more lights on these mechanisms of AIDS resistance, we have recently sequenced the SM genome and identified novel host immunogenetic factors that may be involved in the ability of these animals to avoid progression to AIDS when infected with SIV. An article that includes all the relevant results of this study has been published in the journal Nature on January 4th, 2018. We identified a list of 34 candidate immune-related genes that are sequence divergent between SMs and RMs and/or humans. The most significant variations in SM amino

acid sequence compared to RM were observed in two immune-related gene products, intercellular adhesion molecule-2 (ICAM-2) and Toll-like receptor 4 (TLR4). In the past year, we further characterized the role of TLR4 differences in a set of in vitro studies in which (i) we first showed that CD80 is an easy-to-measure and strongly induced biomarker for LPS stimulation; (ii) we demonstrated that TLR4 can be detected on monocytes and B cells in rhesus macaques; (iii) we identified a TLR4 antibody clone that readily detects TLR4 surface levels on monocytes and B cells from rhesus macaques;(iv) we found no difference for surface molecules CD80, CD83, and CD86; (v) we found that TLR4 surface expression on monocytes correlates with cytokine secretion; and (vi) we showed that a TLR4 inhibitor (TAK-242, a cell-permeable cyclohexenecarboxylate that disrupts TLR4, but not TLR1-3 or TLR5-10, interaction with adaptor molecules TIRAP and TRAM via direct binding to TLR4 intracellular Cys747 residue) is effective in blocking TLR4 signaling in cells from rhesus macaques. This body of work will allow further in vivo exploration of TAK-242 in rhesus macaques. In addition, we have conducted a comparative study in which we have extensively examined the pattern of virus integration in the host genome (i.e., integration landscape) in both SIV-infected SMs (in which the infection is non-pathogenic) and SIV-infected rhesus macaques (in which the infection is pathogenic). Of note, in this latter species the analysis has been conducted both during the natural history of the infection and under ART. The comparative analysis of the pattern of virus integration in the SM and rhesus macaque genomes is based on the hypothesis that differences in the integration landscape may impact on both lifespan and activation level of latently infected cells, which are key determinants of the stability of the reservoir and the prevailing level of immune activation. Over the past year, we have adapted an experimental approach to generate deep sequencing libraries of SIV integration sites in rhesus macaques and SMs, and can both identify unique integration sites and also quantify the number of cells containing each integrant. In addition to the three chronically SIVmac239 infected rhesus macaques reported last time, we have performed this assay on PBMCs from nine naturally SIV-infected, chronic stage sooty mangabeys. We have identified SIV integration sites in all animals (1-85 integrants per animal), and have identified clonally expanded viral integrants in 4 of these SMs. The frequency of clonally expanded integrants ranged from 9% to 33% of the total number of integrants identified. In addition to enrolling new SMs in the study for integration site characterization, we are currently creating new sequencing libraries in order to increase the chances of capturing viral integrants from these original nine SMs. We are also identifying new chronically SIV-infected rhesus macaques from the control arms of several studies in order to increase their numbers for comparison of differences in integration pattern (i.e. proximity to genes, euchromatin vs heterochromatin, proximity to retrotransposable elements and endogenous retroviruses.) Overall the analysis of the generated sequences is almost complete, and while we experienced some delay due to some unanticipated technical difficulties in the past six months, it is our expectation that the relevant set of data will be finalized for publication in the next few months.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

R01 AI066998

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: MODULATION OF INNATE IMMUNE DEFENSES BY MYCOBACTERIUM TUBERCULOSIS

SPID#: 663

UNIT/DIVISION: Emory Vaccine Center

TYPE: Research

START DATE: 2/1/2015

END DATE: 1/31/2018

GENERAL CATEGORY: Infectious Disease

SUB-CATEGORY: TB

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R21AI117162

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Emory Vaccine Center
Prin. NPRC Core Sci.		
Other Core and Affil.		Emory Vaccine Center

PROJECT DESCRIPTION:

The original aims focused on delineating the role of a predicted hydrolase (Hip1/Rv2224c) in Mtb pathogenesis and the host immune response to M. tuberculosis.

PROGRESS REPORT:

This award was completed and data generated during the award period is reflected in the following publications.

PUBLICATIONS:

PMID	Title
29133346	Mycobacterium tuberculosis GroEL2 Modulates Dendritic Cell Responses.
29345365	Deletion of BCG Hip1 protease enhances dendritic cell and CD4 T cell responses.

FUNDING SOURCES:

NIAID 5 R01AIo83366

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: ADMINISTRATIVE CORE (UDALL CENTER, CORE A)

SPID#: 677

UNIT/DIVISION: Neuropharmacology and Neurologic Diseases

TYPE: Research

START DATE: 9/30/2016

END DATE: 7/31/2021

GENERAL CATEGORY: Neural

SUB-CATEGORY: Neural

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: P50NS098685

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Neuropharmacology and Neurologic Diseases
Prin. NPRC Core Sci.		Neuropharmacology and Neurologic Diseases
		Neuropharmacology and Neurologic Diseases
Other Core and Affil.		Emory SOM / Neurology

PROJECT DESCRIPTION:

The Udall Center's Administrative core supports Parkinson's disease-related research activities of the investigators at the Udall Center and facilitates communication between Center personnel, other Emory researchers, the Center's advisory boards, the general public, other Centers within the Udall Center network, and the NIH. The core organizes regular meetings of project leaders, quarterly meetings of the basal ganglia research community at Emory, meetings with internal and external scientific advisors, and meetings of the Center's outreach board. The core organized also the participation of center personnel at the annual Udall Center network meeting, and administers the Center's pilot grant program. Another essential function of the core is to work with the administrative staff at the Yerkes center to track the financial health of the center, and to compile progress and budgetary reports for the NIH. The Center provides educational opportunities for students, postdoctoral fellows, and clinical residents and fellows, such as lectures, journal clubs and hands-on training.

PROGRESS REPORT:

The Administrative Core of the Udall Center organized meetings between its investigators and the national Udall Center network, as well as a meeting of the external advisory committee (in June 2018). We also organized 5 scientific seminars on Parkinson's disease (with three from external speakers) last year. We also continued our new series of (internal) Udall Center progress meetings, where we focus on progress made in the individual projects, as well as our weekly Basal Ganglia Journal Club meetings. Several outreach events took place. Dr. Redacted by agreement participated in 'Lunch and Learn' support group meetings organized by APDA and the Parkinson Foundation, and most of the investigators (along with other members of the Emory University Parkinson's disease research community) participated in the Udall Center's Community Conversations event. The Community Conversations event followed a revised format from previous years, for the first time including poster presentations, as well as presentations where investigators and clinicians were paired for specific topics. We

also had several meetings with the Udall Center's community outreach board, planning this year's Community Conversations. The event planned for 2019 will again heavily focus on communicating research results, and will again feature a speaker from one of the other Udall Centers. The Administrative Core also logistically supported interactions with other Udall Centers, specifically including a visit of our Center personnel to the Center at the University of Minnesota. This has led to additional research endeavors (a recent joint R01 grant application).

PUBLICATIONS:

PMID	Title

None

FUNDING SOURCES:

The Administrative Core is a component of the NIH-funded Udall Center of Excellence at Emory University. All activities of the core are funded through NINDS.

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: UDALL CENTER PROJECT 2

SPID#: 679

UNIT/DIVISION: Neuropharmacology and Neurologic Diseases

TYPE: Research

START DATE: 9/30/2016

END DATE: 7/31/2021

GENERAL CATEGORY: Neural

SUB-CATEGORY: Neural

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: P50NS098685

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Neuropharmacology and Neurologic Diseases
Prin. NPRC Core Sci.		Neuropharmacology and Neurologic Diseases
Other Core and Affil.		Neuropharmacology and Neurologic Diseases

PROJECT DESCRIPTION:

This project explores parkinsonism-associated changes in thalamic and cortical information processing. Specifically, we are comparing between the normal and parkinsonian state how cortical inputs shape thalamic output, and how basal ganglia inputs alter the cortico-thalamic information transfer. Other studies examine the impact of thalamic inputs on cortical processing, both on a single cell and a neuronal ensemble level. Specific emphasis will also be put on an exploration of the impact of deep brain stimulation of the basal ganglia output nuclei on thalamic and cortical information processing. The experiments use newly developed optogenetic techniques to study the function of the closely related corticothalamic or thalamocortical projections in isolation.

PROGRESS REPORT:

One component of this project is concerned with the responses of neurons in the primate basal ganglia-receiving motor thalamus (BGMT) to activation of its thalamic afferents. Optogenetically activated responses of thalamic neurons were then studied at baseline and in parkinsonian animals. A large number of recordings were obtained which are currently being analyzed, focusing on single cell and local field potential responses of thalamic neurons to the stimulation.

The experiments in Aim 2 examine the responses of cortical neurons to activation of thalamocortical afferents in primates in the normal and parkinsonian states, pursuing the hypothesis that parkinsonism may affect the activity of thalamocortical projection neurons themselves. In these animals we also completed studies in which we conduct cortical recordings with a multi-electrode array to analyze responses of single neurons across cortical layers to thalamic neuron stimulation.

For the analysis of these results, we are studying the responses of single cortical neurons to the optogenetic stimulation of thalamo-cortical terminals, as well as changes in cortical phase-amplitude coupling (PAC) during optogenetic stimulation of these terminals. PAC analysis examines the coupling between the phase of slow and

the amplitude of fast oscillations in recorded signals. PAC between the amplitude of gamma band oscillations to the phase of alpha- or beta-range oscillations has recently been shown to increase in ECoG signals recorded in parkinsonian patients and primates (compared to recordings in normal individuals or those with other diseases). The reasons for the cortical PAC changes are not clear, but it is likely that cortical PAC patterns are heavily dependent on thalamic efferents to the cerebral cortex. We compared PAC during light stimulation to PAC results based on pre- or post-stimulation ECoG recordings. The results of these analyses suggest that activation of thalamic inputs to the frontal cortex leads to temporary entrainment of gamma oscillatory activity to oscillations at lower frequencies. Such entrainment effects triggered by thalamic activation could, in part, explain the finding of globally altered PAC patterns in the parkinsonian state.

PUBLICATIONS:

PMID	Title
29577359	NMDA receptor blockade ameliorates abnormalities of spike firing of subthalamic nucleus neurons in a parkinsonian nonhuman primate.
28324647	Metabolism and Distribution of Clozapine-N-oxide: Implications for Nonhuman Primate Chemogenetics.
29332070	Pathophysiologic Basis of Movement Disorders.
29730674	Models of Parkinson's disease revisited.
28601961	Basal ganglia, movement disorders and deep brain stimulation: advances made through non-human primate research.

FUNDING SOURCES:

This project is a component of the NIH/NINDS-funded Udall Center of Excellence at Emory University.

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: UDALL PARKINSON'S DISEASE CENTER AT EMORY UNIVERSITY: CIRCUITRY TO THERAPY

SPID#: 680

UNIT/DIVISION: Neuropharmacology and Neurologic Diseases

TYPE: Research

START DATE: 9/30/2016

END DATE: 7/31/2021

GENERAL CATEGORY: Neural

SUB-CATEGORY: Brain Structure/Function

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: P50NS098685

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Neuropharmacology and Neurologic Diseases
Prin. NPRC Core Sci.		Neuropharmacology and Neurologic Diseases
Other Core and Affil.		

PROJECT DESCRIPTION:

The goal of this project (since Nov 01, 2016) is to examine the anatomy and plasticity of the synaptic connections between the motor cortex and the basal ganglia-receiving regions of the ventral motor thalamus (BGMT) in control and MPTP-treated parkinsonian monkeys. To achieve this goal, we use a broad range of tract-tracing methods combined with immunocytochemical approaches at the light and electron microscopic level

PROGRESS REPORT:

During the past funding period, significant progress has been made towards the completion of aim 1 of this project.

Specific Aim 1: To assess pathological changes in the synaptic connectivity of thalamocortical terminals with corticostriatal and pyramidal tract corticofugal neurons in M1 and SMA of MPTP-treated parkinsonian monkeys.

During the past funding period, we have completed our ultrastructural analysis of the synaptic organization of thalamocortical terminals in the primary motor cortex (M1) and supplementary motor area (SMA) of control and MPTP-treated parkinsonian monkeys. In brief, this work was achieved in three control and three MPTP-treated parkinsonian monkeys using vGluT2 as a specific marker of thalamocortical terminals. Electron microscopic data were collected from both layer V and layers II/III, known as the main targets of thalamocortical inputs to motor cortices in primates. Overall, the findings of these studies confirmed and extended those presented in our previous progress report such that important ultrastructural differences were found in the pattern of synaptic connectivity of thalamocortical terminals between M1 and SMA, particularly in regards to the relative proportion of axo-dendritic synapses formed by vGluT2 terminals, which is far larger in M1 than SMA. Our data also demonstrate opposite changes in the prevalence of axo-spinous vs axo-dendritic connections of vGluT2-containing terminals in layers II/III between M1 and SMA of parkinsonian monkeys, ie while there is an increase in the relative proportion of axo-dendritic synapses over axo-spinous synapses in the SMA of parkinsonian

monkeys, the opposite is found for M1. Although the functional significance of these opposite changes in synaptic connectivity remains unknown, the fact that axo-dendritic glutamatergic synapses in the motor cortex mainly involve GABAergic interneurons, our findings may provide the substrate for an imbalanced drive of GABAergic and glutamatergic synaptic networks by thalamic inputs in the SMA and M1 of parkinsonian monkeys.

During the course of our studies of the thalamocortical system, we noticed some possible ultrastructural changes in the morphology and connectivity of non-vGluT2-containing terminals forming asymmetric synapses in M1 and SMA of parkinsonian animals. Knowing that the other major source of glutamatergic terminals to the motor cortices were vGluT1-containing cortical terminals, we undertook a comparative analysis of the synaptic connectivity of cortical and thalamic terminals in M1 and SMA of control and parkinsonian monkeys. Thus, light microscopy analysis has shown an extensive vGluT1 immunostaining in M1 without major differences between layer II-III and Vb in both control and parkinsonian animals, a feature strikingly different from the vGluT2-containing thalamocortical terminals, which underwent a massive loss in layer V of parkinsonian monkeys. Another distinguishable feature between the two systems in parkinsonian monkeys was also found at the electron microscopic level. Although the ratios of axo-dendritic vs axo-spinous synapses formed by vGluT2-containging thalamic terminals were significantly altered in both superficial and deep cortical layers of M1 and SMA of parkinsonian monkeys, such was not the case for vGluT1-positive cortical terminals. In both motor cortices, the relative proportions of axo-dendritic and axo-spinous synapses formed by vGluT1 terminals were the same between control and parkinsonian animals. These results help us better understand neuroplastic changes in the microcircuitry of thalamo-cortical and cortico-cortical glutamatergic connections, and increase our knowledge of the cortical pathophysiology in the state of parkinsonism. Combined with electrophysiological data gathered from functional studies in Project 2 Redacted by agreement, these results will help assess the potential role of disrupted thalamocortical microcircuitry in the pathophysiology of parkinsonism. These preliminary findings have been presented at the Society for Neuroscience and at the 2018 Gordon Research Conference on Basal Ganglia.

Plan for next funding period: During the next funding period, we plan to achieve the following goals: (1) Submit a peer-review manuscript for publication of findings, (2) Use electron microscopy unbiased synaptic counts approach to determine possible changes in the total number of vGluT2-positive terminals in M1 and SMA of control and parkinsonian monkeys, (3) Use 3D electron microscopy reconstruction methods to further characterize morphology and synaptic connections of vGluT2-immunoreactive terminals in M1 and SMA of control and parkinsonian monkeys, (4) Optimize retrograde viral vector strategy to study the extent of spine loss and the connectivity of specific populations of corticofugal neurons in M1 and SMA of parkinsonian monkeys.

PUBLICATIONS:

PMID	Title
29423879	Non-human primate research of basal ganglia and movement disorders: advances and challenges.
28861737	Chronic MPTP administration regimen in monkeys: a model of dopaminergic and non-dopaminergic cell loss in Parkinson's disease.
28540422	Loss and remodeling of striatal dendritic spines in Parkinson's disease: from homeostasis to maladaptive plasticity?

FUNDING SOURCES:

Redacted by agreement is PI of this project. This is Project 3 of the Udall Center for Parkinson's Disease at Emory University. Redacted by agreement is PI of the Center. The project is funded by NINDS.

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: UDALL PARKINSON'S DISEASE RESEARCH CENTER AT EMORY UNIVERSITY: CORE B

SPID#: 681

UNIT/DIVISION: Neuropharmacology and Neurologic Diseases

TYPE: Research

START DATE: 9/30/2016

END DATE: 7/31/2021

GENERAL CATEGORY: Neural

SUB-CATEGORY: Brain Structure/Function

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: P50NS098685

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Neuropharmacology and Neurologic Diseases
Prin. NPRC Core Sci.		Neuropharmacology and Neurologic Diseases
Other Core and Affil.		

PROJECT DESCRIPTION:

Core B of the Udall Parkinson's Disease Research Center serves to primary functions: (1) to prepare and process the brain tissue from experimental animals generated by all of the Udall Center's projects, and (2) to generate and evaluate parkinsonian Rhesus macaques. The Core provides standardized histology services to center researchers, which will be indispensable to interpret the functional experiments, Similarly, all parkinsonian monkeys to be used are treated and evaluated using standardized procedures by core B personnel. This will help to integrate and compare data generated from these projects. By providing these services, the Core helps to free up time and resources from the research projects, and center research will benefit by the use of standardized, well-establish anatomical and behavioral assessment techniques

PROGRESS REPORT:

The core has analyzed mouse brain tissue for markers for dopaminergic denervation in the cases of animals treated with neurotoxins to deplete the dopaminergic system, as well as markers for the expression of opsins. Several tissue slides have been digitalized using the Aperioscope at Yerkes, and made available for review to the investigators of the Udall Center. The core has also processed (sectioning of tissue, histological stains) the brain tissue from one monkey which was part of experiments in Project 2 of the Udall Center. We have continued to build and upgrade our brain tissue bank and associated database. The core has generated three parkinsonian monkeys. Finally, we have developed a novel method of video analysis to evaluate the motor behavior of monkeys before, during and after MPTP administration. We have prepared and submitted for publication a manuscript describing this method.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Redacted by agreement (PI), funded by NINH/NINDS P50 NS098685

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: MANIPULATING GENE EXPRESSION IN THE DYSKINESIAS OF PARKINSON'S DISEASE

SPID#: 688

UNIT/DIVISION: Neuropharmacology and Neurologic Diseases

TYPE: Research

START DATE: 8/1/2017

END DATE: 7/31/2018

GENERAL CATEGORY: Neural

SUB-CATEGORY: Therapy

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R01NS073994

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Neuropharmacology and Neurologic Diseases
Prin. NPRC Core Sci.		
Other Core and Affil.		Neuropharmacology and Neurologic Diseases

PROJECT DESCRIPTION:

This project is focused on the role of the transcription factor deltaFosB in the striatal mechanisms associated with the development of levodopa-induced dyskinesias in Parkinson's disease. The planned studies test the effects of transgenic manipulation of deltaFosB protein expression in non-human primates. The novel approach taken in this project is aimed at addressing pathophysiologic aspects and help develop new therapies. The project includes three specific aims that use viral vectors to induce or suppress gene expression in the striatum of parkinsonian primates that have developed abnormal responses to L-dopa, particularly levodopa-induced dyskinesias.

PROGRESS REPORT:

In the past year, we completed rodent studies of Aim 3 (effects of deltaFosB down-regulation). These studies using gene silencing in rodents show that deltaFosB suppression has a high impact in the dyskinesias induced by chronic L-Dopa treatment (LID). We are processing all data for publications reporting the results obtained in studies of aims 1, 2 and 3. Our data demonstrated that deltaFosb plays a major role in the development of LID and validated targeting its expression or associated molecular pathways for preventing these disabling complications of dopamine replacement therapy in Parkinsons's disease. We are now developing a strategic plan for tests of gene therapy in the primate.

PUBLICATIONS:

PMID	Title
28620834	Dysregulation of striatal projection neurons in Parkinson's disease.

PMID	Title
28337120	Antidyskinetic Effects of MEK Inhibitor Are Associated with Multiple Neurochemical Alterations in the Striatum of Hemiparkinsonian Rats.
29386136	Glutamatergic Tuning of Hyperactive Striatal Projection Neurons Controls the Motor Response to Dopamine Replacement in Parkinsonian Primates.
27771532	Intrastriatal injection of ionomycin profoundly changes motor response to l-DOPA and its underlying molecular mechanisms.
29508924	A Selective Phosphodiesterase 10A Inhibitor Reduces L-Dopa-Induced Dyskinesias in Parkinsonian Monkeys.
30555300	TRH Analog, Taltirelin Improves Motor Function of Hemi-PD Rats Without Inducing Dyskinesia via Sustained Dopamine Stimulating Effect.

FUNDING SOURCES:
NIH, NINDS

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: FUNCTION AND EVOLUTION OF COGNITIVE MONITORING AND COGNITIVE CONTROL

SPID#: 12012

UNIT/DIVISION: Developmental and Cognitive Neuroscience

TYPE: Research

START DATE: 8/1/2016

END DATE: 7/31/2020

GENERAL CATEGORY: Behavior

SUB-CATEGORY: Behavior

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER:

SUPPORTING ORGANIZATION: Natl Science Found

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Developmental and Cognitive Neuroscience
Prin. NPRC Core Sci.		
Other Core and Affil.		Developmental and Cognitive Neuroscience

PROJECT DESCRIPTION:

The proposed work will determine the functional role of cognitive monitoring for cognitive control in primates and will identify cognitive systems are accessible to cognitive monitoring and those that are not, across lemurs, monkeys, and apes. This work will extend studies of the role of monitoring in cognitive control using converging approaches. First, the extent to which monkeys regulate the amount of information they acquire prior to taking tests will be determined. Second, these studies will determine the extent to which monkeys strategically exercise cognitive control only when necessary and adaptively allocate monitoring among competing tasks. Third, the work will leverage access to a unique, language trained orangutan to evaluate the extent to which language-like mental representations contribute to cognitive monitoring and control. Fourth, the work will assess what information monkeys monitor when making metacognitive judgements. Cognitive systems accessible to cognitive monitoring in monkeys will be distinguished from those that are not by testing for dissociations between accuracy and confidence in tasks in which multiple memory systems contribute to accuracy, and in psychophysical tests that dissociate motor and perceptual processes. Comparative studies of lemurs, monkeys, and apes will determine the extent to which there have been changes in cognitive control through primate evolution

PROGRESS REPORT:

We have continued to characterize the role of metacognitive monitoring and control in nonhuman primate cognition. This work has enriched the rhesus macaque animal model in the cognitive and neural domains.

PUBLICATIONS:

PMID	Title
30503618	Nonverbal Working Memory for Novel Images in Rhesus Monkeys.
30069946	Nonnavigational spatial memory performance is unaffected by hippocampal damage in monkeys.
30068995	Rhesus monkeys metacognitively monitor memories of the order of events.
29459237	Post-encoding control of working memory enhances processing of relevant information in rhesus monkeys (Macaca mulatta).
28772188	Spatial representation of magnitude in gorillas and orangutans.

FUNDING SOURCES:

Redacted by agreement Co-PI (with Redacted by agreement NICHD T-32 Training Grant, Co-PI with Redacted by agreement
Mechanisms of learning across development and species

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: CENTER FOR HIV/AIDS VACCINE IMMUNOLOGY AND IMMUNOGEN DISCOVERY

SPID#: 12029

UNIT/DIVISION: Microbiology and Immunology

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: AIDS

SUB-CATEGORY: AIDS

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER: UM1 AI100663

SUPPORTING ORGANIZATION: NIAID

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Scripps Research Institute
Prin. NPRC Core Sci.		Microbiology and Immunology
Other Core and Affil.		Emory Vaccine Center

PROJECT DESCRIPTION:

Infection of macaques with simian immunodeficiency virus (SIV) or simian-human immunodeficiency virus (SHIV) is a key animal model for HIV-1 infection. The Nonhuman Primate (NHP) Scientific Research Support Component (SRSC) aims to support this CHAVI-ID by providing all the expertise, infrastructure, reagents, personnel, and animals for the conduct of complex in vivo immunogenicity and challenge studies in NHPs. This SRSC leadership will work closely with the research discovery teams responsible for the studies included in Scientific Foci 1 & 2 and participate actively to the scientific mission of CHAVI-ID. The main role of SRCS is to provide leadership and technical expertise to ensure consistency and quality control in animal selection, execution of study protocols, experimental procedures, sample acquisition and distribution, immunologic and virologic studies, and data collection and analysis. The Specific Aims of the SRSC are:

1. To support this CHAVI-ID by selecting and providing rhesus macaques, providing exceptional animal care, conducting experimental studies with monoclonal antibodies and vaccines, collecting samples for immunologic and virologic testing, and performing necropsy studies. These studies will initially evaluate:
   A. Protective efficacy of HIV-1 Env-specific monoclonal antibodies against SHIV challenge;
   B. Immunogenicity and protective efficacy of novel HIV-1 Env immunogens;
2. To support this CHAVI-ID by providing blood and tissue samples from SIV-infected and uninfected NHPs to collaborating investigators to underpin basic research studies. These samples are especially central to the activities of Scientific Focus #2, as they will help elucidate the characteristics of HIV-specific CD4+ “follicular helper” T cell (Tfh) responses, with initial emphasis on the development of Tfh cells during a vaccine-induced immune response, and the role of these cells in providing help to B cells and promoting the critical process of affinity maturation of antibodies.

PROGRESS REPORT:

We have completed a large-scale immunization study of 42 rhesus macaques designed to address key questions related to antigenic diversity, immunomasking, and evolving immunogens. This study was conducted in collaboration with Redacted by agreement labs. The purpose of the study was to directly compare soluble immunogens, to those presented in nanoparticles. Further, a group of animals received an antibody meant to mask the immunodominant bottom of the trimer and promote uptake by the follicular dendritic cells. These groups were compared to animals receiving osmotic pumps with either control or evolving immunogens delivered monthly via osmotic pumps for six months. The animals received a variety of SOSIP immunogens and nanoparticle counterparts with the adjuvant Matrix M via bolus injection or osmotic pumps changed monthly. The animals had blood and LN fine needles aspirates taken at several timepoints over the course of the study. We were able to provide serum and plasma to the collaborators for antibody binding, neutralization, and electron microscopy polyclonal epitope mapping. These results allowed for decisions about the evolving immunogens to occur in real time. We boosted the pump animals with nanoparticles via a bolus injections with a TLR7/8 adjuvant. Finally, 12 weeks after the final immunizations we boosted again. Animals that received pumps were boosted 16 weeks after the pumps. The final boosts were completed with the novel ISCOMPLA adjuvant. All animals were tracked 8-12 weeks following the final immunization. Throughout the study we ran flow cytometry to track the immune response over time. Further, we performed several cell sorts for further genomic analysis of antigen specific B cells.

PUBLICATIONS:

PMID	Title
29474444	Epitopes for neutralizing antibodies induced by HIV-1 envelope glycoprotein BG505 SOSIP trimers in rabbits and macaques.

FUNDING SOURCES:

UM1 AI100663

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: STRESS AND THE GENOME: TESTING THE IMPACT OF SOCIAL EFFECTS ON GENE REGULATION

SPID#: 12034

UNIT/DIVISION: Developmental and Cognitive Neuroscience

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: Aging

SUB-CATEGORY: Immunology

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R01AG057235

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Duke Univ.
Prin. NPRC Core Sci.		
Other Core and Affil.		University of Montreal Division of Cognitive and Developmental Neuroscience

PROJECT DESCRIPTION:

The social environment has a profound impact on human health. Chronic social stress and reduced access to social support lead to dysregulation of the immune system, increase the risk for diseases ranging from cardiovascular disease to the common cold, and, through these effects, influence mortality risk itself. Understanding the basis for these effects and how best to address them are important priorities for improving human health. However, the mechanistic relationships linking social stress to disease risk are still poorly understood, particularly on the level of genome regulation. A major obstacle in studying this relationship is the sheer complexity of the human social environment. An individual's exposure to social stress at work may differ substantially from the same individual's exposure to social stress in the family or community. Additionally, the effects of social stress, especially that induced by socioeconomic status, may be complicated by associated differences in access to resources, occupation, and other health risk factors. Isolating the direct biological effects of social stress per se therefore presents a substantial challenge. However, the social environment is also of demonstrated importance in other highly social species, including many nonhuman primates. Using a well characterized, translation model, this project is assessing the impact of social status to investigate the genomic mechanisms underlying the biological effects of dominance rank-induced chronic social stress in female rhesus monkeys. Our study is focusing on captive macaque females organized into social groups in which individual social status is experimentally manipulated. This design allows us to establish causal relationships between social status and gene regulation and test the degree to which an individual's history of exposure to social stress continues to influence gene regulation if stress is resolved or newly imposed.

PROGRESS REPORT:

Studies began in early 2018 to investigate how genotypic differences, endogenous signals (gonadal steroids, leptin), and exogenous signals (isoflavones) modify rank dependent immune response that was characterized during the first project funded by NIGMS, and whether the response to vaccination is affected by subordination induced chronic stress. In 2018, subjects were identified and new social groups (10 groups of 5 female each) were formed. Baseline in vitro and in vivo outcomes were collected from all females in their first social status position as outlined in the grant. Analyses of these measures are underway.

PUBLICATIONS:

PMID	Title
30538209	Social status alters chromatin accessibility and the gene regulatory response to glucocorticoid stimulation in rhesus macaques.

FUNDING SOURCES:

Redacted by agreement Redacted by agreement MPI funded by NIGMS (R01 GM GM102562 through Aug 2017) and Redacted by agreement NIA (R01 AG057235 began Sep 2017))

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: OXYTOCIN AND SOCIAL BEHAVIOR

SPID#: 12036

UNIT/DIVISION: Behavioral Neuroscience and Psychiatric Disorders

TYPE: Research

START DATE: 9/19/2012

END DATE: 6/30/2018

GENERAL CATEGORY: Neural

SUB-CATEGORY: Psychiatric

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R01MH096983

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Behavioral Neuroscience and Psychiatric Disorders
Prin. NPRC Core Sci.		Behavioral Neuroscience and Psychiatric Disorders
Other Core and Affil.		

PROJECT DESCRIPTION:

The goal of this project is to explore the relationship between genetic polymophisms in the oxytocin receptor gene, oxytocin receptor gene expression in the brain, and social behaviors in prairie voles. In addition, we explore the effect of early-life social deprivation on later life social behaviors. Finally, we explore the effect of oxytocin on neural communication between brain regions involved in social information processing and reward.

PROGRESS REPORT:

Melanocortin Evoked Oxytocin Release. We have previously reported that the melanocortin agonist, melanotan II (MT II), facilitates pair bonding in male and female prairie voles (Modi et al. 2015). We also demonstrated that MT II activated PVN neurons as measured by Fos and others had reported that MTII evokes somato-dendritic OT release within the PVN. We showed that MTII alone does not evoke oxytocin release in the nucleus accumbens (NAc), but it does potentiate release in response to hypertonic saline in prairie voles. In the last funding period we examined the effect of MT II on neural activity in multiple areas of the prairie vole brain known to be involved in social bonding, the social salience network. We found that MT II injected into an isolated prairie vole does not induced FOS activation in the nucleus accumbens (NAc) or prefrontal cortex (PFC). However, when MT II is injected followed by a 30 min social interaction, there is a robust activation of the NAc and PFC compared to saline. This induction of reward area activation by MT II during a social encounter is eliminated by central infusion of an OT antagonist (Figure 1C). This demonstrates that MT II causes local release of OT within the PVN (but not other areas) which primes those neurons so that they robustly release OT under the appropriate condition (e.g. a social encounter) which then engages social reward centers.
Oxytocin modulates the social salience network. We previous had shown that oxytocin facilitates the coordinated activity of brain regions involved in social information processing and reward and that blocking oxytocin receptors eliminates coordinated brain activity in this network during mating (Johnson et al. 2016). This gave us the idea that oxytocin facilities the flow of social information across a social salience network to enhance social cognition. In the last funding period we followed up on those findings by determining the effect of

specifically blocking oxytocin receptors in the NAc on social salience network coordination. By infusing oxytocin antagonist into the NAc prior to mating, and examining mating-induced neural activity (measured by Fos) we demonstrated that NAc is indeed a central hub of the social salience network and oxytocin signaling in the NAc is necessary for coordinating the activity of the NAc with other nodes of the social salience network. This work was published in Hormones and Behavior (Johnson et al. 2016).

Development of a CRISPR Oxytocin Knockout Vole. In the last funding period we collaborated with Dr. Redacted by agreement in Japan to develop CRISPR technology to introduce targeted mutations in prairie vole. We successfully generated oxytocin receptor knockout prairie voles. We verified that the mutant voles do not show any oxytocin receptor binding in the brain. We also performed a preliminary behavioral screen and found that oxytocin receptor knockout prairie voles show an impairment in preference for social novelty and increased repetitive behavior in the marble burying test, phenotypes that are relevant to autism. Future studies will examine pair bonding, consoling and other behaviors.

Reviews and Conceptual Papers. In this funding period, we published or have had accepted several review manuscript synthesizing findings from the overall project. These include a review on comparative perspectives on oxytocin and vasopressin research in rodents and primate models published in Journal of Neuroendocrinology (Freeman and Young 2016) and another with Redacted by agreement on using non-human primates to bridge the gap between rodent studies and humans when it comes to oxytocin research (Putnam et al. 2018). Another review in Neuroscience and Biobehavioral Reviews by Redacted by agreement summarized how oxytocin and vasopressin function in neural networks to regulate social cognition and produce behavioral diversity (Johnson and Young 2017). Two reviews were published in collaboration with Redacted by agreement discussing the role of oxytocin in social attachment and social loss or neglect, synthesizing several study published in previous reporting periods (Bosch and Young 2018; Pohl et al. 2018). In collaboration with Redacted by agreement I published a review in Frontiers in Neuroendocrinology, that synthesized our two complementary perspectives, on the role of thalamic nuclei in regulating parental behavior and the oxytocin system (Dobolyi et al. 2018). Unpublished

Unpublished

PUBLICATIONS:

PMID	Title
30301953	The neural mechanisms and circuitry of the pair bond.
29923206	Bridging the gap between rodents and humans: The role of non-human primates in oxytocin research.
29842887	Thalamic integration of social stimuli regulating parental behavior and the oxytocin system.
28812266	Oxytocin and Social Relationships: From Attachment to Bond Disruption.
29330007	Lost connections: Oxytocin and the neural, physiological, and behavioral consequences of disrupted relationships.
29288748	Abandoned prairie vole mothers show normal maternal care but altered emotionality: Potential influence of the brain corticotropin-releasing factor system.

FUNDING SOURCES:

Redacted by agreement Funded by NIMH

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: ONTOGENIC FACTORS IN ADOLESCENT-EMERGENT DEPRESSION AND DECISION-MAKING

SPID#: 13004

UNIT/DIVISION: Behavioral Neuroscience and Psychiatric Disorders

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: Neural

SUB-CATEGORY: Behavior

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R01MH101477

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Behavioral Neuroscience and Psychiatric Disorders / Peds
Prin. NPRC Core Sci.		
Other Core and Affil.		Behavioral Neuroscience and Psychiatric Disorders / Peds

PROJECT DESCRIPTION:

Depression symptom onset in adolescence increases the rate of depression recurrence and treatment-resistance across the lifespan, and treatment options for adolescents are increasingly limited since the FDA issued a black box warning in 2007 for common antidepressant medications for individuals aged 25 and younger. A history of stressor exposure is the primary predictor of depression, begging the questions: Are adolescent populations uniquely impacted by exposure to stressors and adversity? And if so, why? The answers may relate to the impact of stressor exposure on the prefrontal cortex, which reaches full structural maturity only at the end of adolescence.

This proposal aims to: 1) delineate critical periods during which exposure to corticosterone or social isolation — both of which confer long-term depressive-like behavior — impact dendritic spine pruning and refinement during adolescence. These experiments will chart the developmental trajectory of deep-layer dendritic spine remodeling during adolescence under both normal and pathological circumstances.

We will then 2) test the antidepressant-like utility of pharmacological compounds that act on neurotrophin systems and Rho-kinase, both of which regulate structural maturation. Finally, 3) we will identify neuroanatomical and neurophysiological mechanisms of goal-directed decision-making. This is critical because goal-directed action is diminished in depression, resulting in cyclical patterns of malaise, unemployment, and social withdrawal.

PROGRESS REPORT:

This year, we have made considerable progress, in particular on: 1) Mapping the developmental trajectory of deep-layer neurons exposed to social isolation;
2) determining the role of integrin-mediated signaling events in regulating actions and habits and behaviors associated with depression;

3) preparing our final manuscripts for publication as the grant nears its end

PUBLICATIONS:

PMID	Title
28664926	Memory Retention Involves the Ventrolateral Orbitofrontal Cortex: Comparison with the Basolateral Amygdala.
29540698	Bidirectional coordination of actions and habits by TrkB in mice.
30477984	Prefrontal cortical trkB, glucocorticoids, and their interactions in stress and developmental contexts.
30593834	Rho-kinase inhibition has antidepressant-like efficacy and expedites dendritic spine pruning in adolescent mice.

FUNDING SOURCES:

Redacted by agreement funded by NIMH

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: SILVIO O. CONTE CENTER FOR OXYTOCIN AND SOCIAL COGNITION

SPID#: 13006

UNIT/DIVISION: CTSN

TYPE: Research

START DATE: 6/1/2013

END DATE: 1/31/2023

GENERAL CATEGORY: Neural

SUB-CATEGORY: Psychiatric

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: P50MH100023

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Behavioral Neuroscience and Psychiatric Disorders
Prin. NPRC Core Sci.		Behavioral Neuroscience and Psychiatric Disorders
		Developmental and Cognitive Neuroscience
Other Core and Affil.		Behavioral Neuroscience and Psychiatric Disorders

PROJECT DESCRIPTION:

The goal of this project is to maintain an interdisciplinary to explore the effects of oxytocin on functional connectivity and social cognition using prairie voles, rats, rhesus macaques, healthy human subjects and individuals with autism. The Conte Center uses a highly collaborative, coordinated and integrative approach across all models to discover general principles of oxytocin function and mechanisms of action.

PROGRESS REPORT:

This grant was renewed and the renewal started on April 4th 2018. We have successfully maintained a coordinated, interdisciplinary research program that has, and promises to continue to, advance our understanding of the neural mechanisms underlying social salience and reward and will have a significant impact on the international social neuroscience community. In the past year, we have had many discussions on how to enhance our innovation through incorporating state-of-the-art technology into our research programs in order to keep up with a rapidly changing field. We are pursuing many of those ideas and excited about what we can achieve together as a team. In the current funding period we faced a significant challenge when Redacted by agreement left Emory University. However, we have turned that challenge into an opportunity and recruited a phenomenal new and energetic member to our Center to lead Project 3, Redacted by agreement She has extensive experience with viral vector manipulations and DREADDs in transgenic mouse models. Her research as historically focused on how challenges during adolescence influences vulnerability to adult rewards system related to addiction and feeding. She focuses on the BLA-NAc-PFC circuitry, giving her the expertise to lead Project 3 of this Conte Center. She is very excited to be part of our team and she brings vitality and positive energy to our Conte Center meetings. She is eager to be actively engaged with our Conte Center and to incorporate social neuroscience into her research program, and all members of our Conte team are excited that she has joined us. Our Conte team continue to play leadership roles in the larger social neuroscience community by organizing or participating

in national meetings, workshops and symposia while publishing excellent reviews and original papers. We continue to cultivate collaborations from around the world that ultimately benefit the Center. In collaboration with Redacted by agreement in Japan, we have now created oxytocin receptor knockout and Cre prairie voles, using CRISPR, which will greatly expand the utility of this model organism. Redacted by agreement is collaborating to develop novel viral vector tools. Redacted by agreement published are review on the neurobiology and circuitry of pair bonding in Nature Reviews Neuroscience which summarizes many of the findings from the Center of the past few years and establishes the rationale for our future work. Redacted by agreement published a review entitled “Bridging the gap between rodents and humans: The role of non-human primates in oxytocin research” which highlights the need for integrating rodent and primate research, a core tenant of our Center. We have been developing CRISPR viral vector approaches to meet the goals of our Aims and are actively identifying novel approaches to enhance the precision and rigor of our research. Our Projects will no doubt evolve from what was originally proposed in 2017 as new opportunities arise and challenges are faced. But our overall scope has not changed.

PUBLICATIONS:

PMID	Title
29660417	RDoC-based categorization of amygdala functions and its implications in autism.
29842887	Thalamic integration of social stimuli regulating parental behavior and the oxytocin system.
29797339	Oxytocin- and arginine vasopressin-containing fibers in the cortex of humans, chimpanzees, and rhesus macaques.
30378456	Oxytocin increases eye-gaze towards novel social and non-social stimuli.
30283367	The Role of Amygdala in Patients With Euthymic Bipolar Disorder During Resting State.
29923206	Bridging the gap between rodents and humans: The role of non-human primates in oxytocin research.
29797339	Oxytocin- and arginine vasopressin-containing fibers in the cortex of humans, chimpanzees, and rhesus macaques.
29851228	Evolutionary diversity as a catalyst for biological discovery.
30301953	The neural mechanisms and circuitry of the pair bond.

FUNDING SOURCES:

Redacted by agreement NIMH (1P50MH100023)

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: TRANSCRIPTOME RESOURCES FOR COMPARATIVE PRIMATE MODELS OF LENTIVIRUS INFECTION

SPID#: 13018

UNIT/DIVISION: Microbiology Immunology

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: Immunology

SUB-CATEGORY: AIDS

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R24OD010445

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Microbiology Immunology
Prin. NPRC Core Sci.		Microbiology Immunology
Other Core and Affil.		Microbiology Immunology

PROJECT DESCRIPTION:

The goal of this project is to generate whole transcriptome reference databases for several immune cell types at baseline and during the acute and chronic phases of HIV and SIV infection, with emphasis on the comparative models of pathogenic (i.e., humans and rhesus macaques (RMs)) and non-pathogenic (i.e., sooty mangabeys (SMs) and African green monkeys (AGMs)) infections. Specific Aim 1 is to generate baseline reference transcriptomes for several key immune cell subsets in healthy individuals belonging to four primate species (humans, RMs, SMs, and AGMs). Specific Aim 2 is to generate reference transcriptomes for the key immune cell subsets in the context of acute SIV infection in the pathogenic RM and the non-pathogenic AGM models. Specific Aim 3 is to generate reference transcriptomes for the key immune cell subsets in the context of chronic HIV and SIV infection in humans, RMs, SMs, and AGMs. Resource applications include: (i) improvements to gene models for already sequenced species (humans and RMs) and assistance for genome assem¬bly/annotation for new species (i.e., SMs and AGMs); (ii) development of tools (e.g., species-specific gene probes or microarrays) for AIDS-related systems biology research; (iii) investigation of the interaction between lentiviruses and the immune system during acute and chronic infection. The project was funded in September 2013 and the work conducted so far includes: (i) the optimization of the flow cytometric assays necessary to appropriately sort the immune cell subsets whose transcriptome is analyzed, (ii) the definition of the best strategies to conduct the microarray and next-generation sequencing analysis with related bioinformatics, and (iii) the first set of staining, sorting, and analyses relative to Aims 1 and 2.

PROGRESS REPORT:

In the current reporting period we completed RNA-Seq of an additional 200 samples representing all Natural Killer cells samples from NHP species Unpublished

Unpublished

Unpublished

Lastly we have completed single-cell RNA-Seq on plasmacytoid DCs for our next manuscript on pDCs between natural host and rhesus macaques.

Unpublished

we examined how this is achieved by comparing a natural SIV host, African green monkey (AGM) to an AIDS susceptible species, rhesus macaque (RM). By RNA sequencing and a novel systems biology approach, we discovered rapid activation of regenerative wound healing mechanisms in AGM rectal mucosa. In AGMs, wound healing protein fibronectin showed a distinct concentration to cells, where the protein is polymerized. In addition, AGM monocytes exhibited a stronger embryonic development profile, including the wound healing regulator TGF-β, with lower expression of immune genes. In RMs, but not AGMs, interferon responses included anti-bacterial immune signatures. This study suggests that natural SIV hosts avoid AIDS by a regenerative wound healing process, which preserves mucosal integrity and prevents bacterial translocation, an important pathogenic mechanism in RMs. It also identifies mucosal macrophages as potential targets for intervention in HIV.

PUBLICATIONS:

PMID	Title
29300007	Sooty mangabey genome sequence provides insight into AIDS resistance in a natural SIV host.

FUNDING SOURCES:

1R24OD010445

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: THALAMIC INTERACTIONS WITH THE STRIATUM

SPID#: 13022

UNIT/DIVISION: Neuropharmacology and Neurologic Diseases

TYPE: Research

START DATE: 6/1/2013

END DATE: 5/31/2019

GENERAL CATEGORY: Neural

SUB-CATEGORY: Neural

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R01NS083386

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Neuropharmacology and Neurologic Diseases
Prin. NPRC Core Sci.		Neuropharmacology and Neurologic Diseases
		Neuropharmacology and Neurologic Diseases
Other Core and Affil.		Neuropharmacology and Neurologic Diseases

PROJECT DESCRIPTION:

The 'motor' thalamus is known to receive prominent basal ganglia input. Studies have demonstrated that thalamic projections do not only reach the cerebral cortex, but also project back to the basal ganglia. The most prominent of these projections arise from the intralaminar thalamic nuclei, with additional projections from other thalamic centers, including specifically the ventral anterior and ventrolateral nuclei. These projections differ anatomically, and may also be differentially affected by neurodegenerative diseases, such as Parkinson's disease. This project utilizes cutting-edge optogenetic techniques to examine the functional effect of the thalamostriatal projections in normal and parkinsonian monkeys (with electrophysiology), and to examine their anatomic patterns of termination in the striatum (using light- and electron microscopic methods). The optogenetic work utilizes AAV transfection. Transfection and the subsequent recording studies are done using MRI-based targeting approaches.

PROGRESS REPORT:

We continued experiments comparing the effects of optogenetically activating thalamostriatal terminals in normal and parkinsonian animals. Based on recordings from almost 1000 striatal neurons in the normal state and more than 200 neurons in the parkinsonian state, we found that the predominant response of striatal neurons to the stimulation of thalamic terminals in the striatum is a reduction in firing (seen in 25% of neurons), while increases in firing are (surprisingly) rare. This result is likely explained by stimulation-induced activation of inhibitory networks of neurons, either inside of the striatum, or acting long distance. Anatomical data that have emerged over the last years suggest that the thalamostriatal pathway degenerates (along with the loss of centromedian and parafascicular nucleus neurons in the thalamus). Our data in the parkinsonian state support this view – only 1% of neurons recorded in the same striatal area that was also examined in the normal state recordings responded to the stimulation. In anatomic studies, we continued the analysis of thalamostriatal terminals with

studies of vGluT2 expression in these terminals. In previous studies, vGluT2 expression had been used as a sensitive marker for these terminals (assumed to be expressed by all terminals). To test this hypothesis injections of an anterograde tracer (PHA-L) into the thalamus were combined with vGluT2 immunostaining in mice. These studies showed that almost 40% of terminals that contained the anterograde tracer did not contain vGluT2. Other anatomical studies focused on striatal cholinergic interneurons in the parkinsonian state which are primary recipients of thalamostriatal inputs. We found that the number of these interneurons in the portions of the striatum increased, consistent with evidence of an abnormal increase in cholinergic transmission in the parkinsonian state (including the longstanding use of anticholinergic medications to treat parkinsonian signs). The grant is currently in no cost extension, and we are in the final steps of analysis for publication of these results.

PUBLICATIONS:

PMID	Title
29332070	Pathophysiologic Basis of Movement Disorders.
29730674	Models of Parkinson's disease revisited.
28238201	Advances in optogenetic and chemogenetic methods to study brain circuits in non-human primates.
28540422	Loss and remodeling of striatal dendritic spines in Parkinson's disease: from homeostasis to maladaptive plasticity?
28861737	Chronic MPTP administration regimen in monkeys: a model of dopaminergic and non-dopaminergic cell loss in Parkinson's disease.

FUNDING SOURCES:

This study is funded through R01NS083386.

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: EVALUATION OF NOVEL ANTIPSYCHOTICS WITH FMRI IN PRIMATES

SPID#: 13025

UNIT/DIVISION: Neuropharmacology and Neurologic Diseases

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: Behavior

SUB-CATEGORY: N/A

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER: Private Source

SUPPORTING ORGANIZATION:

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Imaging Center
Prin. NPRC Core Sci.		Neuropharmacology and Neurologic Diseases
Other Core and Affil.		SOM Radiology

PROJECT DESCRIPTION:

The aim of this project is to evaluate the neural effects of novel pharmatherapeutics in a translational nonhuman primate model.
This novel compound enhances cognitive performance in rats, reducing impulsivity and improving novel object recognition while presenting a unique pharmacological profile with no known molecular targets. Neuroimaging with cFos and 2-DG in mice shows increased neural activity in areas related to attention, memory, and executive function including prefrontal cortex, amygdala, and hippocampus. Rodent micro-dialysis shows increased concentrations of dopamine (and other monoamine neurotransmitters) in the prefrontal cortex and hippocampus, but not the nucleus accumbens. Overall, this profile resembles atomoxetine but with unknown mechanism of action, suggesting potential therapeutic utility as a novel non-stimulating ADHD treatment with low potential for abuse. The current project will investigate the effects of this novel compound on brain activity in awake nonhuman primates.

PROGRESS REPORT:

Experiments were performed in one group of awake female rhesus monkeys (N=3) to examine the effects of the test article on brain activity using the blood oxygen level dependent (BOLD) method. BOLD pharmacological MRI response analysis was performed both at whole-brain level and within a priori regions of interest (ROIs) in attention, executive function, cognitive control, sensorimotor processing, and default mode networks. Results showed that the test article evoked a significant and sustained 1.5%-4% BOLD phMRI response that was dose-dependent in both magnitude and extent. At a dose of 1 mg/kg, the test compound evoked significant BOLD activation (vs. vehicle) in subcortical ROIs involved in attention and executive function: including caudate, putamen, thalamus and hippocampus. At a dose of 3 mg/kg, the test compound evoked significant BOLD activation (vs. vehicle) in the same subcortical areas involved in attention and executive function: caudate, putamen, thalamus and hippocampus; as well as cortical attention and executive function areas: dlPFC, SMG, SPL, SMA, cingulate gyrus, ACC, insula and MTG.

Clinical observations noted no adverse effects to SEP-0380359 at the high dose (3 mg/kg) and it was not evident that the animals had even received a drug. These data show a robust profile of effects for this novel agent as potentially favorable for a cognitive focus enhancing medication lacking the adverse side-effects of stimulants currently in clinical use to treat attention deficit disorder and other related disorders.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: GENOMICS CORE LABORATORY

SPID#: 13030

UNIT/DIVISION: Admin

TYPE: Management

START DATE:

END DATE:

GENERAL CATEGORY:

SUB-CATEGORY:

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER: P51OD011132

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION: NIH/ORIP

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	M&I
Prin. NPRC Core Sci.		EVC
		M&I
		M&I
Other Core and Affil.		Psychiatry and Behavioral Sciences, VA
		Pediatrics
		BNPD
		Cardiology
		Immunology and Molecular Pathogenesis
		Pathology
		Medicine
		Microbiology and Immunology
		Pathology
		Biochemistry
		Digestive Diseases
		Medicine
		Pediatrics
		Pediatrics
		Rheumatology
		Microbiology and Immunology

Name	Dept
Redacted by agreement	Microbiology and Immunology
	Microbiology and Immunology
	Radiation
	Genetics
	Pediatrics
	Surgery
	Microbiology and Immunology
	Microbiology and Immunology
	Biomedical Engineering Emory / GA TECH
	Microbiology and Immunology
	Biomedical Engineering
	Pathology
	Pediatrics
	Microbiology and Immunology
	Medicine
	Pediatrics
	BNPD
	Microbiology and Immunology
	Infectious Diseases and Microbiology
	Gastroenterology
	Microbiology and Immunology
	Microbiology and Immunology
	Microbiology and Immunology
	Department of Chemistry
	SOM: Transplant surgery
	Microbiology and Immunology
	Pediatrics
	Pediatrics

PROJECT DESCRIPTION:

Unique Species:
Rhesus Macaque - Macaca mulatta
Sooty Mangabey - Cercocebus atys
Pigtail Macaque - Macaca leonina
Chimpanzee - Pan troglodytes
African Green Monkey - Chlorocebus
Mouse - Mus musculus
Rat - Rattus rattus
Human - Homo sapiens
C. Diff - Clostridium difficile
Plasmodium Vivax - Plasmodium Vivax
Plasmodium Brazi - Plasmodium Brazi
Plasmodium Coatneyi - Plasmodium Coatneyi

White-throated sparrow - Zonotrichia albicollis
Rhizopus spp(fungi) - Rhizopus
Fly - Drosophila melanogaster
Enterobacter cloacae - Enterobacter cloacae

The primary mission of the Yerkes Genomics Core (GenCore) is to provide researchers in the Yerkes, Emory community, and NHP researchers nation-wide with access to cutting-edge high throughput genomic technologies and bioinformatics. The primary users of the GenCore are monkey-model researchers at the Yerkes Center and immunologists within the Emory Vaccine Center; however, the GenCore is also utilized by members of the greater Emory community. The main services offered by the GenCore include RNA-Seq and array-based transcriptomics, DNA-Seq, miRNA-sequencing, microbiome 16s rRNA sequencing and sample preparation.

PROGRESS REPORT:

The Yerkes NHP Genomics Core Laboratory is funded at a rate of 6% from the Yerkes P51 base grant. In the current reporting period, (3/1/2017 – 2/28/2018) we accomplished the following goals that were (i) defined in our P51 proposal and (ii) additional goals achieved relevant to NHP Genetics/Genomics.

1. Defined Goal: Decreased Turn Around Time. To meet the increase in demand for GenCore services, in the prior reporting period we obtained a new high throughput sequencing instrument: an Illumina HiSeq3000, which became operational in March 2016. In the past year we implemented several strategies to have a fast turnaround time and have continued to utilize these.

2. Defined Goal: Developed a low cost single-cell RNA-Seq assay and validated it NHPs. We developed an in-house single-cell RNA-Seq assay that sequences full-transcript RNA from single-cells in a cost effective manner. This assay can also extract the sequence data for the variable gene segments (VJ, VDJ) for individual B cells and T cells. We have also developed a computational algorithm to reconstruct these VJ/VDJ sequences correctly, and we have validated this assay to sequence the paired antigen receptor in rhesus macaque B cells. 2018 progress: (i) we have obtained a robotic liquid handler to accelerate production of sc-RNA-Seq libraries (TTP LabTech Mosquito). (ii) we have finished development of the algorithm to reconstruct rhesus macaque antibody genes and published these data (Upadhyay et al. Genome Medicine 2018).

3. Defined Goal: Established a repertoire assay for NHP B cell Receptors/Antibodies We validated a non-commercial assay to sequence the B cell repertoire of either heavy or light chain from RNA samples, and validated it for human and rhesus samples. Update for 2018: We have now expanded this assay to include amplification and sequencing of IgM and IgD heavy chains (previously we had established it only for IgG). Over the past reporting period we have implemented this into our current research on UM1AI124436.

4. Established a microbiome assay for NHPs We tested and validated a 16S amplicon sequencing assay for microbiome population sequencing in NHP samples. This has been performed on 3 NHP projects, and is now offered as a listed service. Update for 2018: In the most recent reporting period, we continued to conduct microbiome sequencing, and did primary optimization research to compare the most effect of published methods for 16s amplification: V3+V4 based amplification vs. V4-only amplification. We determined that V4-only is the most effective due to reduced noise and improved error correction.

5. Improved Bioinformatics Availability to Yerkes/Emory In addition to hiring another 50% FTE bioinformaticist to handle fee-for-service projects, we installed a user-dedicated workstation so that users can have access to our software licenses and analyze their own dataset under the in-person guidance of GenCore analysts. Update for 2018: To continually improve bioinformatics availability, we have achieved the following: (i) we administrate an Emory license for Ingenuity Pathway Analysis that's lets user conduct several of their own gene expression network analysis. (ii) we purchased and implemented a new computational server with 64-threads and 192 GBs of memory for increased analysis speed (iii) we implemented usage of Amazon Web Services as an Emory hub and allows user access through us when needed or through contracting our services. In the past reporting period we have now increased effort from 50% to 100% to have two full time FTE bioinformaticists.

Additional Goals Achieved (not defined in the P51 goals but relevant to the YNPRC Genomics Core.) in the past year.

6. In collaboration with the Scripps Immunology Institute completed a de novo PACBio assembly of a rhesus macaque and completed annotation and assembly of the rhesus IG loci. These studies are being used to inform UM1 and CHAVI-ID preclinical vaccine studies in which germline targeting immunogens are adminstered to macaques.

7. Applied for and was awarded a grant to obtain a 10X genomics sequencing device to allow users access to long-read sequencing technology and droplet-based single-cell RNA-Seq. We have actively been developing protocols for macaques.

PUBLICATIONS:

PMID	Title
30626670	West Nile virus-inclusive single-cell RNA sequencing reveals heterogeneity in the type I interferon response within single cells.
30232277	Combination anti-PD-1 and antiretroviral therapy provides therapeutic benefit against SIV.
30185596	Antibody-Mediated CD4 Depletion Induces Homeostatic CD4⁺ T Cell Proliferation without Detectable Virus Reactivation in Antiretroviral Therapy-Treated Simian Immunodeficiency Virus-Infected Macaques.
30142226	Type I IFN signaling blockade by a PASylated antagonist during chronic SIV infection suppresses specific inflammatory pathways but does not alter T cell activation or virus replication.
30076667	Progestin-based contraception regimens modulate expression of putative HIV risk factors in the vaginal epithelium of pig-tailed Macaques.
29973404	The human naive B cell repertoire contains distinct subclasses for a germline-targeting HIV-1 vaccine immunogen.
29720521	Short-Term Pegylated Interferon α2a Treatment Does Not Significantly Reduce the Viral Reservoir of Simian Immunodeficiency Virus-Infected, Antiretroviral Therapy-Treated Rhesus Macaques.
29685793	Correlates of Protection Against SIV_{mac251} Infection in Rhesus Macaques Immunized With Chimpanzee-Derived Adenovirus Vectors.
29636452	Species-specific host factors rather than virus-intrinsic virulence determine primate lentiviral pathogenicity.
29558968	BALDR: a computational pipeline for paired heavy and light chain immunoglobulin reconstruction in single-cell RNA-seq data.
29300007	Sooty mangabey genome sequence provides insight into AIDS resistance in a natural SIV host.
28798047	mTOR regulates metabolic adaptation of APCs in the lung and controls the outcome of allergic inflammation.

FUNDING SOURCES:

P51 OD011132 (Lewin) 05/01/2016 – 04/30/2021 CMNIH/OD/ORIP

Emory VTEU RTOP 14-0107 Redacted by agreement (PI) 7/1/15 Source: NIH/NIAID/DMID
Title: A Phase I Trial to Evaluate the Safety, Reactogenicity, and Immunogenicity of MVA-BN Yellow Fever Vaccine with and without ISA 720 Adjuvant in 18-45 Year Old Healthy Volunteers

Emory VTEU RTOP 14-0094 Redacted by agreement (PI) 7/1/15 Source: NIH/NIAID
Title: A Phase I Trial to Utilize Systems Biology Approaches to Examine the Safety, Immunogenicity, and 'Omics Response to MVA-multi filo and Ad26 Zaire vaccines in Healthy Volunteers

RTOP FY.2015.A3D12.0031 Redacted by agreement (PI) 9/10/15 Source: NIH/NIAID
Contract Title: VTEU Consultation and 'OMICS Testing of Clinical Samples

DARPA-15-21-THoR-FP022 Redacted by agreement (PI) 9/15/15 Source: DARPA
Contract Title: THOR's HAMMER; Host Acute Model of Malaria to study Experimental Resilience

U24 AI120134 Redacted by agreement (PI) 7/1/15 Source: NIH/NIAID
Title: Simultaneous antigen receptor repertoire profiling and single-cell transcriptomics in T and B lymphocytes from limited clinical samples

UM1AI124436 [Redacted by agreement] MPD) 06/01/2016 – 05/31/2021
NIH/NIAID
B and T Cell Biology of Protection from and Eradication of SIV/SHIV Infection

R01 HD089831 [Redacted by agreement] 07/01/2016 -06/30/2021
NIH/NICHD
Effects of hormonal contraceptives on genital immunity and HIV susceptibility

R01 AI128837 [Redacted by agreement] 07/01/2017 – 06/30/2022
NIH/NIAID
Using DNA/MVA/protein immunization of rhesus macaques to investigate how the background of the HIV-1 envelope and nature of the protein boost shape the genetic and functional antibody landscape

R01 AI136533-01 [Redacted by agreement]
NIH/NIAID 12/2017 – 11/20/2018
Dynamics of antigen specific B and TFH responses during acute and chronic HCV.

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: YERKES VIROLOGY CORE

SPID#: 13031

UNIT/DIVISION: Virology Core

TYPE: Management

START DATE:

END DATE:

GENERAL CATEGORY:

SUB-CATEGORY:

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER: P51 OD011132

SUPPORTING ORGANIZATION: NIH / ORIP

SPECIFIC INFORMATION: NIH/ORIP

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	M&I
Prin. NPRC Core Sci.		
Other Core and Affil.		M&I

PROJECT DESCRIPTION:

The primary purpose of the Yerkes Viral Testing Core is to provide accurate, rapid, and cost-effective serological and molecular viral diagnostic testing in support of the Specific Pathogen Free (SPF) colony at the Yerkes National Primate Research Center. The Core employs a pipeline of diagnostic screens and tests which provide definitive diagnoses for the presence of infection by the four viruses that constitute the standard panel of viruses that are screened for by the NIH Office of Research Infrastructure Programs (ORIP)-supported SPF macaque colonies: Simian Immunodeficiency Virus (SIV), Simian T Lymphotropic Virus (STLV), Simian type D retroviruses (SRV), and Macacine herpesvirus 1 (B-virus). Testing for these viruses in the Yerkes SPF colony has been ongoing for 15 years, and the SPF colony has been free of any of these 4 NHP viruses since 2013. In addition to supporting the Specific Pathogen Free colony with viral testing services, the Yerkes Virology Core performs both custom virological assays (virus titration and growth) and kit-based CBA assays (e.g. rhesus cytokine assays) for clients across Emory University. The Core also screens for pre-existing immunity to Adeno-Associated Viruses (AAV) and is conducting preliminary experiments to begin screening for Zika infection in the rhesus macaque colony at Yerkes. Through the combined expertise of the leadership and technicians within this lab, and a close collaboration with the CFAR Virology and Molecular Biomarkers Core pre-clinical laboratory, the Yerkes Virology Core is extremely well-positioned to be the primary hub of virological and molecular diagnostic services across Emory University

PROGRESS REPORT:

During the course of this funding period, the Virology Core has tested over 1600 animals by Luminex, the multiplexed first step in our testing algorithm. Over 2600 confirmatory Western blots were performed for B-virus, SIV, STLV, and SRV combined. Indeterminate Western blots for SIV and STLV were confirmed negative via 376 PCRs. No animal was confirmed positive for any SPF pathogen, although several animals were tested monthly due to persistent indeterminate follow-up B-virus testing. For SRV confirmatory molecular testing, the Core has begun validating an SRV quantitative real-time PCR by testing samples side-by-side with the CNPRC's Pathogen

Detection Lab. This is a multiplex real-time PCR that simultaneously quantifies SRV as well as a cellular gene with a constant copy number, oncostatin-M (OSM), as a positive control. A preliminary test of its ability to detect positive samples with low background was performed using a battery of blinded proficiency testing samples sent from the CNPRC that contained SRV positive, indeterminate, and negative samples. Our implementation of the SRV qPCR successfully detected the positive samples with no false positives or false negatives. After this initial success, we have performed a real-time PCR on 69 of the 94 samples that have been identified as SRV indeterminant in our confirmatory Western blots. All samples have been confirmed SRV-negative. We have discussed with Redacted by agreement at the CNPRC Pathogen Detection Lab about the provision of more SRV-positive samples for spot testing the sensitivity and specificity of our SRV qPCR implementation. We plan to review all data regarding the qPCR's performance after a full year of testing. Upon successful discernment of all positive and negative samples, we shift to in-house SRV testing using this new assay. We will rely on the CNPRC Pathogen Detection Lab only for confirmation of putative qPCR-positive samples that may happen. In addition, the Virology Core has screened 93 animals at Yerkes and outside facilities for pre-existing immunity to AAV serotypes 2, 5, and 9 using our in-house developed AAV neutralization assay. Finally, in order to address the potential for flavivirus infection (Zika and West Nile Virus, specifically) of the rhesus macaque SPF breeding colony we have begun identification of ~200 breeding age females for detection of anti-Zika and anti-West Nile Virus antibodies. identification of Zika virus is most important in breeding females due to the documented neurocognitive deficits of infected newborns and the increased propensity for still-births and miscarriages in Zika infected pregnant dams. Likewise, West Nile Virus (which is endemic in Georgia) could potentially contribute to clinical morbidity in the SPF colony at large.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Redacted by agreement - NIH, U42 OD011023

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: SEX DIFFERENCES IN THE SOCIAL BRAIN

SPID#: 13036

UNIT/DIVISION: Developmental and Cognitive Neuroscience

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: Behavior

SUB-CATEGORY: Women's Health

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R01MH110212

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Psychology
Prin. NPRC Core Sci.		
Other Core and Affil.		Developmental and Cognitive Neuroscience

PROJECT DESCRIPTION:

In most mammalian species, social interactions among individuals of the same species are governed by dominance relationships. These hierarchical relationships are established and maintained by agonistic behaviors, including aggression. Importantly, data indicate that the mechanisms in the brain underlying aggression and attaining dominance also make individuals resilient to social stress while the mechanisms underlying subordinate status increase susceptibility to social stress. Despite the relation between social status and stress, the mechanisms that underlie dominance have received only limited attention in males and almost no attention in females. This project will fill this critical gap in our knowledge using rhesus monkeys to test an integrated series of hypotheses using rhesus monkeys that the agonistic behaviors responsible for the formation and maintenance of dominance relationships are regulated in dramatically different in males and females. Specifically, we propose that inhibition of serotonin (5-HT) promotes dominant status and a stress resistant phenotype in males while activation of 5-HT promotes dominance and a stress resistant in females. Positron Emission Tomography (PET) imaging will assess sex differences in 5-HY receptor !A binding to be used as predictors of stress physiology and behavior. Together, these data will significantly expand our knowledge of sex differences in brain chemistry that define social phenotypes and will provide innovative gender specific strategies for promoting resistance to social stress. The data obtained in this project could have an almost immediate clinical impact by guiding drug treatments for stress reduction in men and women.

PROGRESS REPORT:

The overall goal of the project is to determine whether social dominance is differently regulated in males and females. Data collected thus far have used only adult females as analyses with males will begin in year 03 of the project. Using PET neuroimaging, serotonin (5-HT) 1A receptor (1AR) binding potential (BP) is used as a marker of 5HT signaling in corticolimbic regions of the brain. Studies conducted in 2018 evaluated the effects of fluoxetine treatment compared to placebo in for improving 5HT signaling and diminishing stress reactivity in females. Fluoxetine enhanced aggression in dominant females and decreased aggression in subordinate

females. Fluoxetine treatment decreased affiliation in dominant females and increased it in subordinates. Anxiety-like behaviors were reduced only in subordinate females by fluoxetine treatment. CSF 5HIAA concentrations were reduced by fluoxetine regardless of social status. Overall, these data show that increased 5HT activity following fluoxetine treatment in female monkeys alters socioemotional behavior in a status-dependent manner. These data were presented in poster form at the annual meeting of the American College of Neuropsychopharmacology in December 2018.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Redacted by agreement MPI funded by NIMH 1R01 MH110212

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: CYCLES OF SOCIAL CONTINGENCY: PIVOTAL TRANSITIONS THAT SHAPE BRAIN-BEHAVIOR DEVELOPMENT IN MONKEYS

SPID#: 13037

UNIT/DIVISION: Developmental and Cognitive Neuroscience

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: Behavior

SUB-CATEGORY: Neural

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: P50MH100029

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Developmental and Cognitive Neuroscience
Prin. NPRC Core Sci.		Developmental and Cognitive Neuroscience
		Developmental and Cognitive Neuroscience
Other Core and Affil.		Development and Cognitive Neuroscience
		Marcus Autism Center, Atlanta

PROJECT DESCRIPTION:

The criticality of non-human primate (NHP) models for understanding deviations from normative complex human development and, particularly social behavior, has been emphasized repeatedly and recently. In humans, recent discoveries point to the importance of early-emerging and highly-conserved, quantitative mediating phenotypes to advance understanding of the brain-behavior pathogenesis of Autism Spectrum Disorders (ASD). Our current Emory ACE showed that: (1) social disability in ASD is associated with foundational mechanisms of socialization; (2) densely-sampled measurements of social visual engagement point to initial intact, subcortically-guided, reflexive performance followed by a failed transition to cortically-guided, voluntary/reward-driven transition in early infancy; (3) social visual engagement is under stringent genetic control, highlighting its biological significance in socialization and strengthening its value as a mediating phenotype of social disability in ASD. Collectively, our NHP brain-behavior findings suggest that the period between 2-24 weeks (≈ 2-24 months in human infants) represents a critical period for the refinement of social skills, paralleled by neurodevelopmental changes indicating fine-tuning of neural connections in social visual engagement pathways. Here, we propose a new generation of NHP studies that capitalize on remarkable convergence of findings between our human and NHP ACE research and related work. The goals are to (1) characterize early cycles of social contingency using behavioral measures of translational value to those used in humans P-I), adding a strong focus on mother-infant reciprocal behaviors given the central role of social contingency in moving social-communication development forward; (2) identify early social predictors shaping later social development/competence and detect potential

outlier cases for follow up studies; (3) map the unfolding maturation of neural networks mediating changes in perception and attention to social stimuli, in mother-infant contingency cycles, and in the development of social competency, using longitudinal, non-invasive neuroimaging methods.

PROGRESS REPORT:

Study animals were given a behavioral testing and neuroimaging procedures at different time points from 1 weeks to 24 weeks of age. This included: (1) Eye-tracking measures while infants explored social videos, using an ISCAN eye-tracker; these measures were collected every week from Week 1 to Week 5 and every 2 weeks from Week 6 to Week 24 and are used to assess developmental transitions of attention to specific regions of the face, including eye, mouth and entire body; (2) Infant monkeys received the Schneider Neonatal Assessment for Primates to capture parallel transitions in orienting and neuromotor behaviors. This scale was adapted from the human Brazelton Neonatal Behavioral Assessment Scale to measure visual and auditory attention and orienting reflexes, neuromotor functioning/reflexes, muscle tone, coordination and temperament (e.g. irritability, self-soothing) and will be administered for 20 min at birth, 7, 14, 21 and 28 days of age. After 1 month of age, a macaque version adapted from the human Bailey Scales of Infant Development was given to measure problem-solving, motor functioning, sensorimotor processing, temperament and general behavioral characteristics from Weeks 5-24; (3) In these 4 animals, scans (structural T1 and T2, DTI and rsFMRI) were acquired at 2-week intervals from 2-12-weeks and at 6 months. Neural networks to be analyzed include (a) visual object and motion pathways, (b) ventral and dorsal attention networks for voluntary deployment of attention, (c) mother-infant social contingent and affiliative networks (amygdala, nucleus accumbens, ventromedial prefrontal cortex, anterior cingulate cortex and insula, and (d) neuromotor control networks, including a functionally important pathway at birth, the corticospinal tract. The behavioral and neuroimaging data are being prepared for detailed analyses during the current year.

PUBLICATIONS:

PMID	Title
30272135	Early Developmental Trajectories of Functional Connectivity Along the Visual Pathways in Rhesus Monkeys.

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: IMPACT OF SELECTION PRESSURE FOR SOCIAL BEHAVIOR ON CANID BRAIN

SPID#: 13038

UNIT/DIVISION: Neuropharmacology and Neurologic Diseases

TYPE: Research

START DATE: 6/1/2015

END DATE: 7/31/2019

GENERAL CATEGORY: Neural

SUB-CATEGORY: Imaging

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER: NSF IOS 145729

SUPPORTING ORGANIZATION: NSF

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Emory / Neurology
Prin. NPRC Core Sci.		Neuropharmacology and Neurologic Diseases
Other Core and Affil.		

PROJECT DESCRIPTION:

This project studies variation in brain structure related to selection for specific social behaviors in different dog breeds and in wild vs. tame strains of silver foxes.

PROGRESS REPORT:

We have completed comparative MRIs of multiple dog breeds and of wild vs. tame strains of silver foxes. Behavioral testing of the different dog breeds continues. We continue developing a reference beagle atlas (with MRIs and correlative sections stained—the the slides scanned—for Nissl, vasopressin, and oxytocin). We have finished staining sections from wildtype and tame-bred silver fox brains for Nissl and vasopressin. The first paper resulting from the comparative MRI studies of different dog breeds has been completed and is out for review.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: EFFECTS OF CHRONIC OXYTOCIN ON THE DEVELOPMENT OF BRAIN AND SOCIAL BEHAVIOR IN INFANT RHESUS MONKEYS

SPID#: 13042

UNIT/DIVISION: Neuropharmacology and Neurologic Diseases

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: Behavior

SUB-CATEGORY: Imaging

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R01MH104534

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Psychobiology
Prin. NPRC Core Sci.		Psychobiology
Other Core and Affil.		

PROJECT DESCRIPTION:

This R01 examines the effects of chronic oxytocin administration on the development of behavior and neural functioning in infant rhesus monkeys. Major activities during this period included continued dosing of our infant cohort with intranasal oxytocin or placebo. To facilitate the distribution of the aerosol, we incorporated 2 nebulizers and halved the dose of OT. Dosing will continue until the infants are 2 years of age. The oldest infants, born in March of 2015 are nearing this milestone

PROGRESS REPORT:

The grant is in its final year so the concentration of effort is on data analysis and publication.

PUBLICATIONS:

PMID	Title
30295946	Intranasal oxytocin in rhesus monkeys alters brain networks that detect social salience and reward.

Parr, L.A., Mitchell, T. & Hecht, E. (2018). Intranasal oxytocin in rhesus monkeys alters brain networks that detect social salience and reward. American Journal of Primatology.

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: EARLY LIFE STRESS AND ADOLESCENCE COCAINE ABUSE: NEUROBIOLOGICAL VULNERABILITIES

SPID#: 13043

UNIT/DIVISION: Developmental and Cognitive Neuroscience

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: Neural

SUB-CATEGORY: Addiction

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R01DA038588

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Developmental and Cognitive Neuroscience
Prin. NPRC Core Sci.		Developmental and Cognitive Neuroscience
Other Core and Affil.		Developmental and Cognitive Neuroscience
		Emory Dept of Radiology
		Emory School of Nursing

PROJECT DESCRIPTION:

Adolescence is a period of high vulnerability for the development of lifelong drug addiction (including to psychostimulants, such as cocaine) with tremendous health and society costs in the US. However, the unerlying neurobiological mechanisms are not understood. Here we examine this question in a highly translational nonhuman primate (NHP) model during adolescence testing the hypothesis that exposure to early life stress (ELS) is an important risk/vulnerability factor. The premise is that ELS increases emotional/stress reactivity in primates, particularly in females, making them particularly vulnerable to cocaine addiction and relapse through developmental alterations in emotion/stress and reward neurocircuits. The project builds on longitudinal studies of developmental alterations reported by our group in the animals with ELS experience, which have been characterized by our group since birth using a unique crossfostering design that rules out confounding effects of heritability on outcome measures. We have evidence that the adverse experience leads to increased emotional and stress reactivity, as well as alterations of prefrontal connectivity with emotion and reward regulatory regions, such as the amygdala and ventral striatum. We are now examining whether these neurobiological alterations (1) persist during adolescence and (2) underlie increased risk to cocaine addiction. The project focuses on ELS alterations in brain dopaminergic and serotonergic (5HT) systems, in addition to the impact on prefrontal connectivity with the striatum and amygdala. We hypothesize that the increased emotional reactivity and poor stress regulation characteristic of ELS individuals exacerbates cocaine sensitivity and intake, as well as risk for reinstatement (relapse), and that females will be more vulnerable than males. The study also uses pharmacological interventions that target 5HT receptors, through pharmacological activation of the 5HT2C

receptor to reduce cocaine intake, and blockade of the 5HT2A receptor during cocaine abstinence to reduce the risk of relapse. A critical aspect of this proposal is its focus on adolescence, as it is the developmental period when humans initiate drug consumption and has been rarely examined in NHP models.

PROGRESS REPORT:

We have completed data collection for all baseline neurobiological, behavioral and emotional/stress measures in all 25 animals. These include: (1) baseline measures of emotional and stress neuroendocrine reactivity to a novelty challenge, (2) baseline and fear-potentiated acoustic startle using an AX+/BX- paradigm, plus modulation of fear responses using safety signals, (3) neurobiological measures of dopaminergic (DA) and serotonergic (5HT) systems via colletion of cerebrospinal fluid and in vivo positron emission tomography (PET) to examine binding potential of 5HT1A, 5HT2A and D2 receptors, as well as (4) prefrontal connectivity with the striatum and amygdala using resting state functional connectivity MRI. Alhough we are still processing and analyzing some of these data, our findings so far suggest a long-term impact of ELS on emotional and stress regulation during adolescence, so that ELS animals are more emotionally reactive and anxious than controls (exaggerated baseline acoustic startle; interference of threatening social stimuli on cognitive processes), and had impaired ability to discriminate fear from safety signals; this is consistent with findings in children with ELS and to impairments reported in populations with PTSD and other anxiety disorders. We also detected important neurobiological alterations in the group with ELS, in particular, weaker functional connectivity of the prefrontal cortex with both amygdala and ventral striatum (Nucleus Accumbens) and lower levels of 5HT1A and 5HT2A receptor binding in prefrontal cortex, amygdala and ventral striatum using PET imaging. More importantly, the lower levels of 5HT receptors in these cortico-limbic regions important for emotional/stress regulation and reward were associated with increased anxiety in the ELS animals, consistent with reports in anxiety disorders.
Although data collection is still undergoing, we have made significant progress in the cocaine self-administration (COC SA) studies, where we are examining acquisition, escalation, extinction and reinstatement of COC SA. Our preliminary data suggests that females with ELS history show higher sensitivity to COC. More importantly, pharmacological interventions targeting the 5HT2C receptor (i.e. pretreatment with the selective receptor agonist WAY163909) dose-dependently reduced COC SA, particularly in ELS animals, suggesting this may be an effective treatment for ELS individuals with increased sensitivity to psychostimulant abuse.
We will continue collecting, analyzing and publishing data as planned in the grant.

PUBLICATIONS:

PMID	Title
30450384	A review of nonhuman primate models of early life stress and adolescent drug abuse.
30272135	Early Developmental Trajectories of Functional Connectivity Along the Visual Pathways in Rhesus Monkeys.

Peer-reviewed Publications:

Wakeford AGP, Morin E, Bramlett SN, Howell L, Sanchez MM (2018). A review of nonhuman primate models of early life stress and adolescent drug abuse. Neurobiology of Stress 9:188-198. PMID:30450384. PMCID:PMC6236515.

Kovacs-Balint Z, Feczko E, Pincus M, Howell B, Morin E, Earl E, Li L, Steele J, Styner M, Bachevalier J, Fair D, Sanchez M (2018). Early developmental trajectories of functional connectivity along the visual pathways in rhesus monkeys. Cerebral Cortex. PMID:30272135, DOI:10.1093/cercor/bhy222.

Unpublished

Unpublished

Unpublished

Unpublished

Published Abstracts (posters & talks):

Wakeford AGP, Sanchez MM, Howell LL (2018). Examining the effects of a selective serotonin 2C (5HT2C) receptor agonist WAY 163909 (WAY) on cocaine self-administration in adolescent male and female rhesus macaques exposed to early life stress. Oral Presentation at BBC, San Antonio, TX; March.

Wakeford AGP, Shields HL, Sanchez MM, Howell LL (2018). Examining the effects of a selective serotonin 2C (5HT2C) receptor agonist WAY 163909 (WAY) on cocaine self-administration in adolescent male and female rhesus macaques exposed to early life stress (2018). Poster Presentation at ASPET, San Diego, CA; April.

Morin E, Wakeford A, Howell BR, Siebert E, DG Guzman, Kazama A, Nye J, Sanchez MM (2018). Maternal Care controls the Development of Fear Learning in Adolescent Nonhuman Primates: relationship with prefrontal 5HT1A receptor binding. 48th Annual Meeting of the SfN. San Diego, CA. Nov 3-7.

Bramlett S, Wakeford A, Morin E, Guzman DG, Siebert E, Howell BR, Meyer JS, Kazama A, Sanchez MM (2018). Early hypothalamic-pituitary-adrenal axis activity predicts anxiety and sensitivity to the reinforcing effects of cocaine in adolescent macaques: early life stress as a risk factor. 48th Annual Meeting of the SfN. San Diego, CA. Nov 3-7.

Morin E, Pincus M, Wakeford A, Howell BR, DG Guzman, Siebert E, Kazama A, Nye J, Sanchez MM (2018). Maternal Care Controls the Development of Fear Learning in Adolescent Nonhuman Primates: relationship with prefrontal 5HT1A receptor binding & gut microbiome. ISDP 51st Annual meeting. San Diego, Oct 31-Nov 2.

Wakeford AGP, Sanchez MM, Nye JM, Howell LL (2018). Examining the relationship between dopamine 2 (D2) receptor availability, early life stress, and vulnerability to the reinforcing effects of cocaine in male and female rhesus macaques. Poster Presentation at CPDD, San Diego, CA; April.

FUNDING SOURCES:

FUNDING SOURCES (other than P51):

PI Redacted by agreement funded by NIH/NIDA (DA038588-01, R01)

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: AUTOMATED TRACKING OF MONKEY GROUPS:RECOGNITION OF SOCIAL STRUCTURE AND BEHAVIOR

SPID#: 13044

UNIT/DIVISION: Developmental and Cognitive Neuroscience

TYPE: Research

START DATE: 4/15/2016

END DATE: 4/15/2020

GENERAL CATEGORY: Behavior

SUB-CATEGORY: Model

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R24OD020174

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Developmental and Cognitive Neuroscience
Prin. NPRC Core Sci.		Developmental and Cognitive Neuroscience
Other Core and Affil.		

PROJECT DESCRIPTION:

Develop an RfID automated tracking system to track multiple monkeys in a complex social group at the Yerkes Field Station. Develop a customized monkey collar containing multiple active RfiD tags. Instrument an outdoor compound to detect and use RfiD signals to located and identify individuals 24hrs per day, 7 days per week. Develop a behavioral inference engine to extract social behavior from tracking data. Develop and RfiD guided video system that will allow collection of video snips of individually identified animals. Develop computer vision programs that can automatically identify individuals and patterns of social behavior.

PROGRESS REPORT:

Collars have been placed on 28 monkeys encompassing the matrilineal hierarchy of the social group. 13 monkeys have worn their collars for a year or more with no signs of discomfort. Battery life has been one year. Installed 4 4K high resolution video cameras that are controlled be the RfID system. This allows entering a monkey's ID into the RfID/ camera system and it will find and then visually track that monkey, while at the same time collecting 3D tracking data that is synched with the visual data. This will allow verifying behavioral inferences derived from the tracking data using the synced video data.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: APPLICATION OF IFENPRODIL FOLLOWING ADOLESCENT COCAINE EXPOSURE

SPID#: 13045

UNIT/DIVISION: Behavioral Neuroscience and Psychiatric Disorders

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: Neural

SUB-CATEGORY: Behavior

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R03DA042358

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Behavioral Neuroscience and Psychiatric Disorders / Peds
Prin. NPRC Core Sci.		
Other Core and Affil.		Behavioral Neuroscience and Psychiatric Disorders / Peds

PROJECT DESCRIPTION:

Adolescent cocaine abuse increases the risk and severity of lifelong addiction and decreases the likelihood that cocaine-abusing individuals will seek treatment. Developing and understanding therapeutic approaches that mitigate maladaptive decision-making and cocaine-seeking behaviors in organisms with a history of cocaine exposure during adolescence could reduce the high societal cost of cocaine addiction.

In Aim I, we will test the hypothesis that individual differences in cocaine self-administration in adolescence determine effects on orbitofrontal cortex (oPFC) dendritic spines, such that mice that escalate are more susceptible to spine deficiencies in adulthood. We will then assess whether ifenprodil, an NR2B-selective NMDA receptor antagonist that blocks the reinstatement of heroin-, nicotine-, and alcohol-seeking behaviors in rodent models will also have therapeutic-like effects after adolescent cocaine exposure, occluding cocaine-induced habits.

In humans, adolescent cocaine exposure increases the risk of substance use, dependence, and relapse in adulthood. In Aim II, we will examine whether individual differences in cocaine self-administration in adolescence are associated with individual differences in cocaine self-administration and the reinstatement of cocaine seeking in adulthood. We expect that mice with a history of escalating cocaine exposure will respond more for cocaine as adults and be more likely to reinstate responding after extinction conditioning. In these experiments, ifenprodil will be paired with extinction training in an attempt to mitigate the reinstatement of cocaine seeking. This approach models the use of ifenprodil as a therapeutic adjunct to behavioral therapy in humans and is strongly supported by our preliminary findings.

PROGRESS REPORT:

We find that ifenprodil treatment interferes with the development of cocaine-induced habits, and the effects of ifenprodil depend on intact interactions between the basolateral amygdala and orbitofrontal cortex. A manuscript

describing these findings is in preparation.

PUBLICATIONS:

PMID	Title

None current; manuscripts are in preparation

FUNDING SOURCES:

Redacted by agreement funded by NIDA

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: ROLIPRAM REVISITED: NEW ROLES FOR PDE4 AND AMPK IN THE ETIOLOGY OF AFFECTIVE DISORDERS

SPID#: 13047

UNIT/DIVISION: Behavioral Neuroscience and Psychiatric Disorders

TYPE: Research

START DATE: 3/1/2018

END DATE: 2/28/2021

GENERAL CATEGORY: Neural

SUB-CATEGORY: Psychiatric

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R01MH069852

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Behavioral Neuroscience and Psychiatric Disorders
Prin. NPRC Core Sci.		Behavioral Neuroscience and Psychiatric Disorders
Other Core and Affil.		

PROJECT DESCRIPTION:

The goal of this proposal is to investigate the effects of metabolic challenge on the physiology of principal neurons in the basolateral amygdala and subsequent affective behavior.

PROGRESS REPORT:

In the previous funding period, we investigated the effects of a metabolic challenge on the electrophysiological properties of BLA principal neurons during early adulthood. We could not report any diet induced changes, and we reported a high variability in the behavioral response. Since previous studies were conducted in Wistar rats and not Sprague Dawley, we further reasoned that the genetic background of the animals might explain the resilience to the metabolic challenge. In this funding period we conducted a comparative study of the effects of high fructose diet on the BLA principal electrophysiological properties in Sprague Dawley and Wistar.
Early life is a period of high vulnerability, and there is now evidence that infants can be exposed to fructose through maternal breastmilk. During this reporting period, we investigated if an indirect exposure to HFrD during the first 3 weeks of like impacts the metabolism and the affective behavior of adolescent rats.
The PDE4 inhibitor Rolipram has been shown to have fast acting antidepressant properties in human, however failed clinical trials due to emetic side effects. One potential effector of Rolipram's antidepressant action is the AMPK pathway. In this report period, we also further investigated the effects of AMPK activation on the electrophysiological profile and the affective behavior of the animals.
Significant results
We examined the relationship between dysregulated metabolism and BLA principal neurons hyperexcitability in Sprague Dawley rats. We recorded BLA in acute brain slices from 20 control rats and 19 treated rats. We analyzed the membrane resistance, the spike threshold, the stimulation evoked response. We found that the

exposure to HFrD did not alter any of those properties. We further analyzed the dendritic spine morphology of BLA neurons in both groups, control and HFrD, using the biocytin filling and software assisted spine reconstructions. HFrD apical and basal dendrites show the same branching and length that their control diet counterparts. Those results support the report from our previous funding period, where we show that adolescent Sprague Dawley rats exposed to HFrD did not exhibit the same increased in anxiety and depressive like behavior observed in Wistar. The genetic background of Sprague Dawley seems to increase resilience to HFrD metabolic stressor.
Another goal of this funding period was to better understand the mechanism of action of the fast-acting antidepressant Rolipram. We used suction electrode patch recording to investigate the action of Rolipram on BLA principal neurons. We found that Rolipram increases the excitability of the BLA in adult Sprague Dawley rats. We are currently recording cells exposed to Rolipram and AMPK modulators in order to determine if the Rolipram response is mediated through the AMPK pathways of other effectors. We also investigated how modulation of AMPK activity affects affective behavior. We used ICV infusion of AMPK activator (AICAR) and inhibitor (Compound C) in adult rats six hours prior to running open field and social interaction tasks. We found that Compound C significantly reduced the time the animals spent in the center of the open field, an indication that decreasing AMPK activity increases anxiety-like behavior in rats. The social interaction test results did not seem to be affected.
Finally, we investigated the metabolic state of the offspring from HFrD dams. We showed that the indirect exposure does not affect the weight of the animals, however their insulin and leptin levels were significantly higher, in males and females, during infancy and adolescence. The blood glucose of the HFrD animals was not significantly higher than the control animals. At the adolescent stage, the animals exhibit a pre-diabetic stage. Contrary to what is observed when adolescent rats are exposed to HFrD, the offspring of HFrD did not show any increase in anxiety as seen on the acoustic startle and open field paradigms.
Those results were presented in a poster format during the SfN meeting this year and we expect to submit that data for publication during the next funding period.

Key outcomes: Our findings highlighted the importance of the genetic background for behavior study. We also show that Rolipram increases BLA excitability, potentially unveiling one of the mechanisms underlying the rolipram paradox. Finally, our study of the behavioral effects of AMPK activity showed that AMPK might be a new therapeutic avenue for the treatment of affective disorder.

PUBLICATIONS:

PMID	Title
29204911	Repeated shock stress facilitates basolateral amygdala synaptic plasticity through decreased cAMP-specific phosphodiesterase type IV (PDE4) expression.
29660417	RDoC-based categorization of amygdala functions and its implications in autism.

FUNDING SOURCES:

Redacted by agreement funded by NIMH.

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: USING NON-HUMAN PRIMATE PLURIPOTENT STEM CELLS TO TREAT MALE-FACTOR INFERTILITY

SPID#: 13049

UNIT/DIVISION: Neuropharmacology and Neurologic Diseases

TYPE: Research

START DATE: 4/1/2015

END DATE: 3/31/2018

GENERAL CATEGORY: Reproductive

SUB-CATEGORY: Regenerative Medicine

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R21OD020182

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Neuropharmacology and Neurologic Diseases
Prin. NPRC Core Sci.		Neuropharmacology and Neurologic Diseases
Other Core and Affil.		UGA-NND

PROJECT DESCRIPTION:

Spermatogenesis is a critical process that ensures transmission of the paternal genome to offspring during fertilization. However there are a number of external factors that can affect spermatogenesis even resulting in sterility. Males, who would normally be fertile, are rendered sterile by exposure to environmental and industrial toxicants, medical interventions such as chemotherapies and immune suppressant treatments, and injury. While advances in fertility preservation during cancer therapies has improved fertile outcomes after treatment cessation, there still exists a number of male patients that have survived cancer but are permanently sterile. In cases where a sperm sample is not available or provided before the onset of sterility, these males are unable to ever father a child with their partner due to a lack of production of functional gametes. To date, there are no treatment options for these individuals and they are permanently sterile. Stem cell treatment options resulting in in vitro derived functional gametes represent one potential solution to enable these male patients to produce offspring with their partner. Thus an in vitro model for spermatogenic differentiation culminating in functional spermatids is essential for advancing stem cell treatments to treat infertility. This proposal seeks to build upon our recently published model that shows the ability of human pluripotent stem cells to differentiate into advanced germ cell lineages, including spermatogonia, spermatocytes, and spermatids. Using rhesus pluripotent stem cells, we propose to examine whether in vitro derived spermatids generated by our protocol are capable of fertilizing an oocyte and developing to the blastocyst stage in culture. In order to perform this research, we propose to stimulate female rhesus macaques and collect follicles for fertilization by ICSI.

PROGRESS REPORT:

Our team has established an in vitro spermatogenesis model in monkey using a 10-day differentiation protocol. We are able to generate viable spermatids in vitro from NHP ESCs. The resulting SSCs express promyelocytic

leukemia zinc finger protein (PLZF), a marker for SSCs, demonstrating that monkey PSCs can be differentiated into advanced spermatogenic lineages similar to our work done in humans. Furthermore, spermatids from our differentiation express the post-meiotic spermatid markers acrosin, protamine 1 (PRM1) and transition protein 1 (TNP1), provide evidence that extensive, sperm-specific chromatin remodeling events occur during this 10-day in vitro differentiation and establish the fidelity of our spermatogenesis model.

We successfully demonstrated that spermatids derived from NHP ESCs could fertilize a rhesus oocyte and develop to the blastocyst stage. We utilized a NHP ESC line with GFP reporter tagged with Histone 2B (H2B-GFP). We fertilized rhesus macaque mature oocytes with in vitro derived H2B-GFP spermatids followed by in vitro culture. The expression of GFP can be observed in one of the pronuclei in the zygote and the expression of GFP also found in the nucleui of four-cell stage embryo, blastomeres of a morula and blastocyst stage embryo. While further confirmation on the competence of the in vitro derived spermatids is to produce offspring as our next step which is strongly supported by our preliminary data that H2B-GFP spermatids contribute to early embryonic development evidenced by H2B-GFP expression. To improve spermatid fertilization and embryo development, we have adapted the protocols for SCNT and examined different oocyte activation protocols and strategies to enhance the erasure of the methylated marks in male pronuclei. Co-injection of in vitro derived spermatids, sperm extract and TET3 protein followed by trichostatin A (TSA; an HDAC inhibitor) treatment has resulted in high quality embryos comparable to normal embryos fertilized with rhesus sperm with a blastocyst rate at 17%. This study is consistent with TET3 gene expression study on differentiating sperm cells which has much lower levels compared to mature spermatozoa, which support our findings on the co-injection of TET3 protein to improve fertilization and embryo development. With this success, our work positions us to hypothesize and formulate a novel and unorthodox approach to create competent male germ cells in vitro using NHP PSCs and generate viable embryos.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: TRANSGENIC HUNTINGTON'S DISEASE MONKEY RESOURCE

SPID#: 13050

UNIT/DIVISION: Neuropharmacology and Neurologic Diseases

TYPE: Research

START DATE: 3/1/2015

END DATE: 12/31/2018

GENERAL CATEGORY: Genetic

SUB-CATEGORY: Huntington's Disease

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R24OD010930

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Neuropharmacology and Neurologic Diseases
Prin. NPRC Core Sci.		Developmental and Cognitive Neurosciences
Other Core and Affil.		

PROJECT DESCRIPTION:

The proposed study has evolved based on our success in the creation of a transgenic Huntington's disease (HD) monkey model sponsored by the ORIP. Transgenic HD monkeys recapitulate disease progression and develop clinical features similar to HD patients. In order to facilitate the preclinical application of the HD monkey model, a Transgenic Huntington's Disease Monkey Resource (THDMR) will be established to provide a high quality HD monkey model for investigators. In addition, a biomaterial repository will also be established and served as a resource for HD research. To further safeguard the unique genetics of the HD-NHPs and availability of the HD-NHPs, HD sperm cryopreservation methods will be developed and optimized. Sperm cryobank will be established for future distribution and reanimation of the HD monkeys.

PROGRESS REPORT:

We have installed the social group housing cage, automatic feeders, TrackLab surveillance systems and DEXA scanner for measurement of body composition and providing service. We have introduced two F1 monkeys to the social group housing , trained to use the automatic feeder as well as being able to monitor activity 24 hours per day and seven days per weeks remotely using the TrackLab surveillance. The DEXA scan has been used to perform longitudinal assessment of F1 monkeys and a cohort of surrogate females as well as F0 HD monkeys. Thus the setup is ready fro service.

By the end of the project, all HD animals have been euthanzied. Peripheral and brain tissues were also preserved and deposit to the THDMR biomaterial repository. The THDMR biomaterial repository has an extensive inventory with longitudinal biological samples collected and preserved since 2008. Our inventory include longitudinal plasma, serum and lymphocyte, lymphoblast cell lines, annual skin biopsy, cerebrospinal fluid, cryopreserved semen, embryonic and induced pluripotent cell lines. For euthanized animal, one brain hemisphere was designated for snap frozen based on brain region, the contralateral hemisphere was post-fixed, cryopreserved and serial sectioned for immunohistochemical studies. Peripheral tissues and blood samples were

collected and preserved at the time. Most animal also have primary culture established from multiple tissues. All these samples are available for interested investigator upon request.

PUBLICATIONS:

PMID	Title
29663942	Longitudinal Anthropometric Assessment of Rhesus Macaque (<i>Macaca mulatta</i>) Model of Huntington Disease.
25917881	Germline transmission in transgenic Huntington's disease monkeys.
25966278	Progressive cognitive deficit, motor impairment and striatal pathology in a transgenic Huntington disease monkey model from infancy to adulthood.
27657705	Cryotolerance of Sperm from Transgenic Rhesus Macaques (Macaca mulatta).
27395434	Increased irritability, anxiety, and immune reactivity in transgenic Huntington's disease monkeys.
28336929	Developmental Whole Brain White Matter Alterations in Transgenic Huntington's Disease Monkey.
24581271	A two years longitudinal study of a transgenic Huntington disease monkey.
18488016	Towards a transgenic model of Huntington's disease in a non-human primate.
21910887	Characterization of dental pulp stem/stromal cells of Huntington monkey tooth germs.
20179764	Human multipotent stromal cells (MSCs) increase neurogenesis and decrease atrophy of the striatum in a transgenic mouse model for Huntington's disease.
20132560	Monkey hybrid stem cells develop cellular features of Huntington's disease.
29127484	Progress in developing transgenic monkey model for Huntington's disease.
28027448	Induced Pluripotent HD Monkey Stem Cells Derived Neural Cells for Drug Discovery.
27631085	miR-196a Ameliorates Cytotoxicity and Cellular Phenotype in Transgenic Huntington's Disease Monkey Neural Cells.
25358787	Reversal of cellular phenotypes in neural cells derived from Huntington's disease monkey-induced pluripotent stem cells.
25431746	Cryopreservation of transgenic Huntington's disease rhesus macaque sperm-A Case Report.
23190281	Pathogenic cellular phenotypes are germline transmissible in a transgenic primate model of Huntington's disease.
23957861	Longitudinal transcriptomic dysregulation in the peripheral blood of transgenic Huntington's disease monkeys.
21225414	Transgenic Animal Models of Huntington's Disease.
19467335	Generation of transgenic monkeys with human inherited genetic disease.
24929669	microRNA-128a dysregulation in transgenic Huntington's disease monkeys.
22629284	The Path to microRNA Therapeutics in Psychiatric and Neurodegenerative Disorders.

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: ASYNCHRONOUS DISTRIBUTED MICROELECTRODE NEUROMODULATION FOR EPILEPSY

SPID#: 13051

UNIT/DIVISION: Neuropharmacology and Neurologic Diseases

TYPE: Research

START DATE: 6/1/2017

END DATE: 5/31/2022

GENERAL CATEGORY: Neural

SUB-CATEGORY: Therapy

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: UG3NS100559

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	SOM / Neuropharmacology and Neurologic Diseases
Prin. NPRC Core Sci.		
Other Core and Affil.		SOM / Neuropharmacology and Neurologic Diseases

PROJECT DESCRIPTION:

Epilepsy occurs in 1 percent of the world's population; of this population, 30 percent of epilepsy cases are medically intractable, leaving surgical interventions as the only option for treatment. Whereas open resection, the current surgical standard of treatment, can yield seizure freedom rates as high as 60-80 percent, these are often associated with cognitive dysfunction, particularly in patients with dominant hemisphere mesial temporal lobe epilepsy (MTLE). We have recently found in a rodent MTLE model, that delivering asynchronous pulses distributed across a multielectrode array, at low frequency, is more effective than macrostimulation. The objective of this project is to optimize asynchronous distributed multielectrode stimulation (ADMES) on a non-human primates (NHP) model.

In aim 1, we implement ADMES in our NHP model and quantify effects on seizure and adverse effects on memory. In parallel, we will characterize the response of physiological biomarkers such as synchrony to allow us to develop both open-loop and closed-loop control policies to optimize these biomarkers as a proxy for seizure control.

In aim 2, the most effective stimulation parameters will be implemented in 8 NHPs using the RC+S neurostimulator and benefit on seizure frequency and memory will be evaluated. If seizure reduction is ≥50% then we will advance to an early clinical study.

In aim 3, we will identify electrophysiological biomarkers and characterize the effects of stimulation parameters informed from our NHP study on those biomarkers during invasive monitoring of MTLE patients and then move to an early feasibility trial of ADMES in 6 patients.

In aim 4, the final stimulation parameters will be implemented in RC+S and behavioral seizure reduction and memory testing for safety will be quantified over 12 months. Positive results should lay the foundation for a larger clinical trial for MTLE, with possible application to the other epilepsies.

PROGRESS REPORT:
Two monkeys have been successfully implanted with two 32-channel electrode arrays in the hippocampus and injection canula targeting Ca1 for penicillin injection. We are currently recording baseline on one monkey and we already succefully induced 6 sessions of focal temporal lobe seizures in the other monkey. We tested twice the effect of asynchronous distributed stimulation (ADMES). Stimulation at 7Hz was applied via the two electrodes for 10 trials of 2-minute intermittent ADMES and 4 minutes of SHAM stimulation. LFPs were recorded simultaneously using the same electrode array. Power spectral features for each electrode were extracted from 5s windows of LFPs after each ADMES and SHAM stimulation. This data was then used to train a classifier to determine whether the post-ADMES state was discernably different from the sham state. Results: Cross-validation of the neural state classifier for each electrode-pair indicated that there were specific locations in the array where the ADMES induced observable changes in the hippocampal neural states. Next, we verified that this effect was not due to a difference in the seizure incidence between the two states by classifying between stimulation and sham for the ictal and inter-ictal segments independently. Isolating the effect of stimulation during ictal and interictal segments we achieved an accuracy of 0.66±0.08. Conclusions: These findings suggest that ADMES maximally modulates neural activities at certain locations in the hippocampus in our model. Analysis of this relationship will allow identifying controllable subcircuits in the hippocampus. Finally, characterizing the modulated biomarkers of neural state and comparison with seizure biomarkers can be used to optimize this novel stimulation paradigm.

PROGRESS REPORT:

We are currently analyzing baseline and post-ictal responses in monkeys. We tested twice the effect of asynchronous distributed stimulation (ADMES). Stimulation at 7Hz was applied via the two electrodes for 10 trials of 2-minute intermittent ADMES and 4 minutes of SHAM stimulation. LFPs were recorded simultaneously using the same electrode array. Power spectral features for each electrode were extracted from 5s windows of LFPs after each ADMES and SHAM stimulation. This data was then used to train a classifier to determine whether the post-ADMES state was discernibly different from the sham state. Results: Cross- validation of the neural state classifier for each electrode-pair indicated that there were specific locations in the array where the ADMES induced observable changes in the hippocampal neural states. Next, we verified that this effect was not due to a difference in the seizure incidence between the two states by classifying between stimulation and sham for the ictal and inter-ictal segments independently. Isolating the effect of stimulation during ictal and interictal segments we achieved an accuracy of 0.66±0.08. Conclusions: These findings suggest that ADMES maximally modulates neural activities at certain locations in the hippocampus in our model. Analysis of this relationship will allow identifying controllable subcircuits in the hippocampus. Finally, characterizing the modulated biomarkers of neural state and comparison with seizure biomarkers can be used to optimize this novel stimulation paradigm.

PUBLICATIONS:

PMID	Title
28766041	The role of the basal ganglia in the control of seizure.

FUNDING SOURCES:

startup from Private Source

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: DOPAMINE NEUROTRANSMISSION IN A MODEL OF DOPA-RESPONSIVE DYSTONIA

SPID#: 13052

UNIT/DIVISION: Neuropharmacology and Neurologic Diseases

TYPE: Research

START DATE: 2/1/2015

END DATE: 1/31/2020

GENERAL CATEGORY: Neural

SUB-CATEGORY: Brain Structure/Function

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R01NS088528

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Pharmacology
Prin. NPRC Core Sci.		Neuropharmacology and Neurologic Diseases
Other Core and Affil.		

PROJECT DESCRIPTION:

The goal of this project is to further characterize the synaptic plasticity of the glutamatergic corticostriatal system in a mouse model of dopamine-responsive dystonia (DRD). The mutant mice used in these studies were developed in the laboratory of Redacted by agreement (Dept Pharmacology, Emory Univ), the PI of this project. Based on recent findings gathered from these animals (Rose et al., 2015, Brain 138:2987), we hypothesized that striatal neurons undergo spine pruning and that the morphology and ultrastructural features of corticostriatal glutamatergic terminals are altered in DRD.

PROGRESS REPORT:

As co-investigator on this grant, we contribute to aim 4 of the project: To examine the dendritic morphology and ultrastructural changes in corticostriatal synapses onto D1R and D2R-expressing MSNs in response to early-life DA deprivation in DRD mice.

Experiments in this aim are still in progress. The hypothesis being tested in this aim is that reduced dopamine transmission in the striatum of DRD mice induces structural changes similar to those seen in PD models. To address this issue, we immunostained striatal tissue of 2 WT and 2 DRD mice with a vGluT1 antibody to specifically label corticostriatal terminals. Immunostained sections were shipped to RENOVO Neural Inc for serial block face scanning electron microscope (SBF/SEM). Series of 200-300 blockface images were captured with a Zeiss Sigma VP scanning EM, Gatan 3 View in-chamber ultramicrotome and shipped to us for 3D EM reconstruction using the RECONSTRUCT software.

Outcome: So far, a total of 80 corticostriatal axo-spinous complexes from WT animals and 60 from DRD mice have been reconstructed. In line with our recent data from MPTP-treated parkinsonian monkeys (Villalba and Smith, 2011, JCN 519:989), data obtained so far suggest a robust (1.2-2X) increase in the volume of the vGluT1-positive terminals and the post-synaptic spines. These findings suggest that striatal dopamine loss in DRD

animals results in structural reorganization of corticostriatal synapses consistent with an increased activity of this projection. These data lay a solid foundation for aim 3 studies which will examine the physiological properties of corticostriatal synapses in DRD mice.
During the next funding period, we plan to determine if similar plastic changes also characterize thalamostriatal synapses, the other main source of glutamatergic inputs to the striatum. The approach will be the same, except that a vGluT2 antibody will be used to specifically label thalamostriatal terminals in WT and DRD mice.

Additional related studies: In addition to studies described above, we also completed a series of experiments aimed at assessing the integrity of striatal cholinergic interneurons (ChIs) in DRD mice. Although not originally planned in our proposal, we felt important to take advantage of our animal model to address this important issue. The rationale for these studies relies on the fact that anti-cholinergic drugs have some therapeutic benefits in most forms of dystonia and that the prevalence of striatal cholinergic interneurons is reduced in various animal models of dystonia. To achieve this work, we used 3 months old and 15 months old DRD and WT mice. Three main issues were addressed: 1) Do DRD mice exhibit a loss of striatal ChIs, as recently reported in a model of DYT-1 dystonia? 2) Do ChIs undergo morphological changes that affect their soma size and/or the extent and complexity of their dendritic tree in DRD mice? 3) Is the prevalence of GABAergic striatal interneurons affected in DRD mice? To address these issues, we immunostained series of sections through the striatum of WT and DRD mice for choline acetyl transferase (ChAT) or parvalbumin (PV-marker of fast spiking striatal GABAergic interneurons) and used unbiased stereological method, Scholl analysis and Cavalieri principle to count and analyze the morphology of ChIs and PV-positive GABAergic interneurons in the two animal groups. To assess the potential effect of aging on the number of ChIs, both young (3 months old) and aged (15 months old) mice were studied. In brief, the prevalence of both ChIs and GABAergic PV-positive interneurons is not significantly changed in the striatum of DRD mice. Similarly, only subtle structural changes in the dendritic arborization of ChIs were found. Thus, in line with our recent report of lack of major morphological changes in the striatum of a knockin mouse model of DYT-1 dystonia (Song et al., 2014, Neurobiol. Diseases 54:362), our current data provide further evidence that the dysregulation of striatal cholinergic transmission in dystonia is not induced by major neuroplastic changes in the morphology and prevalence of striatal ChIs. These findings were recently published in a peer-reviewed manuscript.
Outcome. Some results have been published (Rose et al., Brain, 138:2987-3002, 2015). Experiments involving 3D reconstruction to assess corticostriatal and thalamostriatal synapses will be published in a peer reviewed journal and the findings of striatal TH-immunoreactive interneurons expression in DRD mice will be submitted for peer-reviewed publication during the next funding period.

PUBLICATIONS:

PMID	Title
29997483	Striatal Cholinergic Interneurons in a Knock-in Mouse Model of L-DOPA-Responsive Dystonia.

FUNDING SOURCES:

Redacted by agreement is a co-investigator on this grant. Redacted by agreement is PI. Funding is from NINDS

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE:	PATHOMECHANISMS OF DOPAMINE DYSREGULATION IN DYT1 DYSTONIA
SPID#:	13053
UNIT/DIVISION:	Neuropharmacology and Neurologic Diseases
TYPE:	Research
START DATE:	9/15/2015
END DATE:	9/15/2018
GENERAL CATEGORY:	Neural
SUB-CATEGORY:	Brain Structure/Function
NIH GRANT:	☐ Yes ☒ No
GRANT NUMBER:	
SUPPORTING ORGANIZATION:	Dept. of Defense
SPECIFIC INFORMATION:	

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Pharmacology
Prin. NPRC Core Sci.		Neuropharmacology and Neurologic Diseases
Other Core and Affil.		

PROJECT DESCRIPTION:

The goal of this project is to elucidate the cellular and neurochemical mechanisms that underlie the reduced release of dopamine in the striatum of DYT1 mice model of dystonia. The specific contribution of our laboratory to this project is to determine if dopamine terminals in the striatum of DYT1 mice undergo ultrastructural changes that might account for a low release of striatal dopamine. More specifically, we use high resolution three dimensional electron microscopy immunocytochemistry to analyze in fine details the morphometry of individual dopamine terminals and compare those between WT and DYT1 mutant mice.

PROGRESS REPORT:

During the previous funding period, we pursued our comparative ultrastructural analysis of the morphometric characteristics of individual dopaminergic axon and terminals in the striatum of WT and DYT1 mice. As described in our previous report, striatal tissue from 5 WT and 5 DYT1 mice is used in this study. In each of these mice, series of striatal sections are processed to localize tyrosine hydroxylase (TH) immunoreactivity at the electron microscopic level. In brief, areas of striatal tissue have been embedded in resin and prepared for 3D electron microscopy analysis using Serial Block Face scanning EM (SBF/SEM). Various morphometric measurements (volume of terminals, number and size of synaptic vesicles, area of synaptic contacts, postsynaptic targets) have been collected from fully reconstructed TH-positive terminals. So far, a total of 32 TH-positive terminals from 2 WT and 3 DYT1 mice have been reconstructed and analyzed. Preliminary data obtained so far suggest that the relative prevalence of synaptic specializations formed by single dopaminergic axons is reduced by ~20% in DYT1 mice compared with control animals. Thus, the decreased number of synapses formed by individual dopaminergic axons might account for the reduced striatal dopamine release in DYT1 dystonia. Our goal for the next funding period is to increase the sample of reconstructed axons and terminals to ~30 per group (ie 60 terminals total for both groups of animals). Overall, data from this project will help further understand the

anatomical substrate of nigrostriatal dopaminergic dysfunction in DYT1 dystonia.

PUBLICATIONS:

PMID	Title

None

FUNDING SOURCES:

Redacted by agreement is co-investigator on this project Redacted by agreement from Dept Pharmacology at Emory is PI. The project is funded by a grant from the US Department of Defense.

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: ION: A SUMMER RESEARCH IMMERSION FOR HIGH SCHOOL STUDENTS AND TEACHERS

SPID#: 13058

UNIT/DIVISION: Neuropharmacology and Neurologic Diseases

TYPE: Research

START DATE: 5/1/2018

END DATE: 12/31/2018

GENERAL CATEGORY: Training

SUB-CATEGORY: Neural

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R25MH095735

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Biology Georgia State University
Prin. NPRC Core Sci.		Neuropharmacology and Neurologic Diseases
Other Core and Affil.		

PROJECT DESCRIPTION:

This project aims at supporting rising senior high school students and high school or middle school teachers interested in neuroscience to join research laboratories at the Yerkes Primate Center, Emory University and Georgia State University for a period of 10 weeks during the summer. In addition to provide students with faculty mentoring and resources to achieve their project, this grant covers the trainees' stipends and allow them to attend series of workshops and mentored activities to prepare for college education and neuroscience research. At the end of the training period, each student and teacher must present the results of their summer project orally to their peers, ION program leaders and research colleagues from the laboratories they trained in.

PROGRESS REPORT:

During the past funding period, two students joined the Yerkes Primate Center as part of this program. Overall, this NIH-funded training program supported the 10-weeks research program these young students were involved in, which gave the unique opportunity to be exposed to the daily activities of a neuroscience research laboratory and helps them set a research foundation they can build on as they undertake their college education. In addition to their research, the two Yerkes students and other ION trainees met once a week with teachers to gain some broad knowledge in various aspects of neuroscience research, college education, graduate school and career development. At the end of the program, each student gave a 15 minutes oral presentation of their work to their ION peers and lab members where they completed their research training.

PUBLICATIONS:

PMID	Title

None

FUNDING SOURCES:

Redacted by agreement was the Yerkes PI of this grant. Redacted by agreement from Georgia State University was the Project PI. This project was funded by NIMH

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: DEFINING THE PROPERTIES OF PATHOGENIC AB STRAINS IN ALZHEIMER'S DISEASE

SPID#: 13059

UNIT/DIVISION: Neuropharmacology and Neurologic Diseases

TYPE: Research

START DATE: 5/1/2015

END DATE: 4/30/2020

GENERAL CATEGORY: Aging

SUB-CATEGORY: Pathology

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: P50AG025688

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Neuropharmacology and Neurologic Diseases / Neurology
Prin. NPRC Core Sci.		
Other Core and Affil.		Chemistry Emory GA TECH

PROJECT DESCRIPTION:

Project 3 of the Emory Alzheimer's Disease Research Center (ADRC; Redacted by agreement PI). The goal of the project is to evaluate the variability in the structure and function of aggregated Aβ as it relates to the pathogenesis of AD. The overarching objective is to clarify the role of proteopathic strains in neurodegenerative disease, i.e., how does variant 3-D structure influence the pathogenicity of abnormal proteins.

PROGRESS REPORT:

In a collaborative study with Redacted by agreement (Neurology) and others, we analyzed cerebral Abeta-amyloid angiopathy in large vessels and capillaries of African-Americans and Caucasians. Given the higher incidence of dementia and lobar hemorrhage among elderly African-Americans, we hypothesized that Abeta might be more prominent in cerebral blood vessels of African-Americans. Our findings indicate instead that amyloid angiopathy is similar in the two ethnoracial groups. These findings were recently published in the Journal of Alzheimer's Disease.

We also continued our collaborative studies with Redacted by agreement (Tuebingen) to assess the strain-like characteristics of Aβ deposits in high-pathology, nondemented (HPND) cases and in cases of AD using luminescent conjugated oligothiophenes (LCOs). The preliminary findings indicate that the parenchymal Abeta deposits in the HPND cases are much more likely to be diffuse in nature, thus emitting a distinct spectral pattern. In further preliminary analyses, we have begun to assess the basic pathology of AD and HPND cases (immunoreactive plaques and tangles). These findings indicate that tauopathy is much less in the HPND cases and confirm the work of others that an important determinant of symptomatic cognitive decline is the spread of tauopathy into neocortical regions. An important question for future work is whether the HPND Abeta assemblies

evolve into a more pathogenic form, or whether they are a relatively benign assembly type, an important question that relates to both diagnosis and treatment. Interestingly, our analyses of plaques in aged nonhuman primates (which express human-sequence Abeta) indicate that the LCO spectral patterns of the plaques are largely similar to those in the HPND human cases.

Having shown previously that aggregated Abeta forms structurally distinct strains in different types of idiopathic and familial AD, and that the strain-like properties of aggregated Abeta from these distinct cases of AD can be partially transmitted to APP-transgenic mice (Rasmussen et al., PNAS 2017), in Year 4 of the project we began to turn our attention to potential sources Abeta (and other proteins, such as alpha-synuclein) strain variability in humans, and to the broader implications of the strain phenomenon. In particular, given that type-2 diabetes is a known risk factor for AD, we have become interested in the potential link between Abeta-amyloidosis and islet amyloid polypeptide (IAPP/amylin). Emerging data indicate that diabetes, like AD, is phenotypically diverse. Our preliminary findings in nonhuman primates with T2D (in collaboration with Redacted by agreement indicate that Abeta is present in pancreatic islets, and that LCOs bind avidly to islet amyloid in T2D. We have not yet detected IAPP in brain amyloid deposits in AD (rather, it is in superficial and some perivascular astrocytes).

PUBLICATIONS:

PMID	Title
29614657	Cerebral Amyloid Angiopathy: Similarity in African-Americans and Caucasians with Alzheimer's Disease.
30220236	A standard model of Alzheimer's disease?
30258241	Propagation and spread of pathogenic protein assemblies in neurodegenerative diseases.
29887142	Prion-like mechanisms in Alzheimer disease.
29777188	Sabotage by the brain's supporting cells helps fuel neurodegeneration.

Kamara DM, Gangishetti U, Gearing M, Willis-Parker M, Zhao L, Hu WT, Walker LC. Cerebral Amyloid Angiopathy: Similarity in African-Americans and Caucasians with Alzheimer's disease. J Alzheimers Dis. 2018, 62:1815-1826. PMID: 29614657. PMC6103628.

Walker LC, Lynn DG and Chernoff YO. A Standard Model of Alzheimer's disease? Prion. 2018;12(5-6):261-265. doi: 10.1080/19336896.2018.1525256. PMID:30220236. PMC6277193.

Jucker M and Walker LC. Propagation and spread of pathogenic protein assemblies in neurodegenerative diseases. Nat Neurosci. 2018 Oct;21(10):1341-1349. doi: 10.1038/s41593-018-0238-6. PMID:30258241. NIHMS1004291.

Walker LC. Prion-like mechanisms in Alzheimer disease. Handb Clin Neurol. 2018;153:303-319. doi: 10.1016/B978-0-444-63945-5.00016-7. Review. PMID: 29887142. NIHMS1004590.

Walker LC. Sabotage by the brain's supporting cells helps fuel neurodegeneration. Nature. 2018 May;557(7706):499-500. doi: 10.1038/d41586-018-04988-3. PMID: 29777188. PMC6329300.

FUNDING SOURCES:

NIH P50AG025688

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: UDALL PARKINSON'S DISEASE CENTER AT EMORY UNIVERSITY

SPID#: 13060

UNIT/DIVISION: Neuropharmacology and Neurologic Diseases

TYPE: Research

START DATE: 9/30/2016

END DATE: 7/31/2021

GENERAL CATEGORY: Neural

SUB-CATEGORY: Neural

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: P50NS098685

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Neuropharmacology and Neurologic Diseases
Prin. NPRC Core Sci.		Neuropharmacology and Neurologic Diseases
		Neuropharmacology and Neurologic Diseases
Other Core and Affil.		Emory College (Biology)
		Neuropharmacology and Neurologic Diseases
		Emory SOM / Neurology

PROJECT DESCRIPTION:

This Center helps electrophysiologists and anatomists to collaboratively study the pathophysiology of parkinsonism, and to examine and optimize the effects of existing treatments for Parkinson's disease. It receives strong internal support that helps it to fund Parkinson's disease related pilot grants, invite seminar speakers, and organize effective education and outreach programs. The Center consists of three tightly linked projects and two cores. The research sheds light on the poorly understood parkinsonism-related activity changes in thalamus and cortex which, in turn, will help us to better understand the pathophysiology of parkinsonism, and to optimize existing neuromodulation strategies and to develop new ones. Project 1 (led by Redacted by agreement utilizes brain slice and in vivo recordings in rodents, as well as a neural computational approach to develop mechanistic models of thalamocortical dysfunction in parkinsonism. Project 2 Redacted by agreement explores thalamic and cortical abnormalities in parkinsonian monkeys, using selective activation and inactivation approaches which are designed to study corticothalamic, pallidothalamic and thalamocortical information transfer. Project 3 Redacted by agreement examines morphological changes in the thalamic and cortical microcircuitry in parkinsonian primates. All projects are supported by an administrative core (Core A, Redacted by agreement PI, Redacted by agreement Co-I, Redacted by agreement Co-I, Redacted by agreement Redacted by agreement administrator), and an anatomy and behavior core (Core B, Redacted by agreement which provides immunohistochemistry and electron microscopy services to all of the center projects, and standardized MPTP treatment and quantification of parkinsonism to the primate experiments in projects 2 and 3. The Center has a strong educational goal of helping young scientists to develop a career in Parkinson's disease research, and engages in significant outreach efforts.

PROGRESS REPORT:

All Center projects and the two Center cores have made excellent progress in the last year. The specific results are detailed in the descriptions of the individual components.

PUBLICATIONS:

PMID	Title

Publications resulting from work conducted in the Udall Center are communicated in reports from the individual projects.

FUNDING SOURCES:

The Udall Center of Excellence in Parkinson's Disease Research at Emory University is funded through NIH/NINDS.

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: HUMAN SPECIFIC BRAIN DNA METHYLATION AND NEUROPSYCHIATRIC DISEASES

SPID#: 13063

UNIT/DIVISION: Neuropharmacology and Neurologic Diseases

TYPE: Research

START DATE: 4/1/2015

END DATE: 1/31/2020

GENERAL CATEGORY: Neural

SUB-CATEGORY: Genetic

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER: R01MH103517

SUPPORTING ORGANIZATION: NIH/NIMH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	GA TECH
Prin. NPRC Core Sci.		Neuropharmacology and Neurologic Diseases
Other Core and Affil.		

PROJECT DESCRIPTION:

This project seeks to identify human-specific changes in DNA methylation sites in adult higher-order association cortex and determine effects of these changes on gene and protein expression in human controls, humans with schizophrenia, and nonhuman primates.

PROGRESS REPORT:

Using whole-genome methylation mapping, we examined human, chimpanzee, and macaque cortex and identified loci that are differentially regulated in humans compared to the other two species. Subsequently, we isolated nuclear DNA from neurons and oligodendrocytes to identify cell-type-specific differences in methylation and gene expression. Two manuscripts, one comparing schizophrenic and control humans, the other comparing humans, chimpanzees, and macaques, are in advanced stages of development. Currently, we are refining the bioinformatic analysis of the genomic results and are using immunohistochemistry to validate the cell-type-specific expression results in the control human and schizophrenic groups and in the cross-species comparisons.

PUBLICATIONS:

PMID	Title
27563052	Comparative Methylome Analyses Identify Epigenetic Regulatory Loci of Human Brain Evolution.

FUNDING SOURCES:

NIH R24 NS092988, A National Chimpanzee Brain Resource

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: TARGETING PD-1 PATHWAY FOR FUNCTIONAL CURE OF AIDS

SPID#: 13064

UNIT/DIVISION: Microbiology and Immunology

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: AIDS

SUB-CATEGORY: Therapy

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R37AI112787

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Microbiology and Immunology
Prin. NPRC Core Sci.		Microbiology and Immunology
Other Core and Affil.		Microbiology and Immunology

PROJECT DESCRIPTION:

The overall goal of this proposal is to evaluate the safety and therapeutic potential of in vivo blockade of the PD-1 (Programmed death-1) co-inhibitory pathway to achieve a functional cure (long-term control in the absence of antiretroviral therapy) for HIV/AIDS using the SIV/macaque model. Dysfunctional anti-HIV immunity and persistence of viral reservoirs represent the two major issues that must be addressed by therapeutic approaches targeting functional cure. Combination antiretroviral drug therapy (ART) helps only to some extent. We believe that these two issues can be addressed effectively by targeting the PD-1 co-inhibitory pathway during ART. First, our recent studies showed that PD-1 blockade during chronic SIV infection (in the absence of ART) is safe and restores function of SIV-specific cellular and humoral immunity, improves gut permeability barrier function and prolongs survival. These results demonstrated that in vivo blockade of PD-1 represents a novel treatment strategy to restore anti-HIV immunity. Second, recent studies have demonstrated that the majority of HIV-1 latently infected cells express PD-1 and blocking PD-1 signaling on these cells reactivates the latent virus in vitro, suggesting that in vivo blockade of PD-1 may result in reactivation of the latent virus that can subsequently be cleared by the functional anti-viral immunity. Here we propose to achieve a functional cure for HIV/AIDS by combining PD-1 blockade with ART and therapeutic vaccination. This proposal has three specific aims. In aim 1, we will optimize conditions for enhancing anti-viral immunity and reducing the establishment of latently infected cells following the initiation of ART. In aim 2, we will optimize conditions to purge the viral reservoirs during ART. In aim 3, we will use the best condition from aims 1 and 2, and combine with therapeutic vaccination to achieve a functional cure.

PROGRESS REPORT:

We tested the ability of SIV-infected Rhesus macaques to respond to PD-1 blockade both at the initiation of ART and during fully suppressive ART. PD-1 blockade therapy at the onset of ART resulted in rapid proliferation (Ki-67+) of functional (IFNg+ TNFa+) CD4 and CD8 T cells, and this was associated with more rapid viral suppression following initiation of ART (42 days in the PD-1 group versus 140 days in saline group; p = 0.01).

Furthermore, responses to this initial blockade correlated with improved viral control after the cessation of ART. RNA-seq analysis of PBMCs from monkeys treated with anti-PD-1 antibody during suppresive ART showed an up-regulation of genes associated with effector function and proliferation. These same cells also showed down-regulation of genes involved in interferon-associated responses and regulatory T cells. Given the success of PD-1 blockade alone, a new trial was initiated to examine the effect of combination PD-1 blockade and DNA/MVA vaccination (aim 3 above). Rhesus macaques were infected with SIVmac239, and given 5 infusions of 3mg/kg anti-PD-1 antibody over 14 days starting 10 days prior to initiation of ART. In agreement with our previous findings, monkeys treated with PD-1 blockade showed a burst of proliferating (Ki-67+) CD4 and CD8 T cells, as well as an increase in effector functions (perforin and granzyme B) within those cells. Infected monkeys are currently at 53-56 weeks post ART initiation. While under ART, these animals have received a combination of PD-1 blockade and two DNA vaccination priming at week 28 and 32, followed by two MVA boosts at week 36 and 50 post ART initiation. We have successfully completed the proposed vaccination. Compared to control group (ART only), vaccination groups (Vaccine group and Vaccine+PD-1 group) have shown significantly improved antigen specific cytokine response. The treated groups have also demonstrated considerably higher breadth and increased polyfunctional-cytokine response. We also observed increase in the frequency of antigen specific CD8+T cells with a proliferative burst and having improved cytolytic potential. These results indicate that the treated groups have higher potential to control viremia after ART interruption. Following, ART interruption, these subjects will be closely monitored for viral rebound and control thereafter. Concomitantly, we are analyzing germinal center homing of SIV-specific CXCR5+ CD8 T cells, viral reservoir size estimation, B and T cells' phenotypic characterization as well as global changes identified by RNA-seq of CD4+ and CD8+ T cells before and after therapy.

PUBLICATIONS:

PMID	Title
28159893	Dynamics of SIV-specific CXCR5+ CD8 T cells during chronic SIV infection.
30232277	Combination anti-PD-1 and antiretroviral therapy provides therapeutic benefit against SIV.

FUNDING SOURCES:

Redacted by agreement funded by NIAID

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: B AND T CELL BIOLOGY OF PROTECTION FROM AND ERADICATION OF SIV/SHIV INFECTION

SPID#: 13065

UNIT/DIVISION: Emory Vaccine Center

TYPE: Research

START DATE: 6/1/2016

END DATE: 5/31/2021

GENERAL CATEGORY: Infectious Disease

SUB-CATEGORY: Vaccine

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: UM1AI124436

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Emory Vaccine Center
Prin. NPRC Core Sci.		Microbiology Immunology
Other Core and Affil.		

PROJECT DESCRIPTION:

A major challenge in public health is to develop an effective way to combat the HIV-1 pandemic. One approach is to utilize antiretroviral therapy (ART) drugs to reduce circulating levels of virus. This has the dual advantage of preventing or delaying the onset of AIDS and reducing subsequent HIV transmission. Unfortunately, poor access to drugs in resource poor nations, poor compliance in taking medications on a regular schedule, and development of drug resistance all limit the overall effectiveness of this approach. An alternative might involve the development of an effective HIV vaccine, but this has been difficult in early clinical studies. This project extends efforts from a prior 5-year Emory-based U19 consortium that evaluated antigen and adjuvant combinations in a Rhesus macaque model as a means of preventing infection from a subsequent heterologous SIV vaginal challenge. This UM1 consortium differs from the prior U19 in that the two central foci are protection and eradication whereas the prior consortium focused exclusively on protection. Initial vaccinations will use a BG505 SOSIP to leverage available immunology reagents and repeated vaginal challenges will utilize a homologous SHIV. Efforts will focus on generating potent and persistant antibodies against the virus and robust CD8 T cell responses elicited against infected cells. We will test the utility of using Rapamycin (mTOR inhibitor) to limit CCR5 expression on CD4+ target cells as a means of inhibiting viral entry during challenge. A promising vaccine regimen will be tested in Rhesus neonates to generate strong early anti-HIV responses before immune responses are circumvented by recognition of similar epitopes present in gastrointestinal flora. We will also test 'shock and kill' strategies for virus eradication by providing ART treated infected monkeys with the best available latency reactivating drugs coupled with optimal vaccine strategies in an effort to eliminate viral reservoirs.

PROGRESS REPORT:

During the past reporting period, members of this consortium have continued work related to two ongoing vaccine studies conducted using Rhesus macaques. Both studies have employed the use of a trimeric BG505

SOSIP antigen as opposed to prior studies in which the envelope protein was in all likelihood more monomeric. Here the thought is that trimeric env might better mimic HIV exposure in the real world and it might also offer different epitopes to the immune system in order to produce more effective immune responses. Based upon results from multiple prior studies, we have also begun using the TLR 7/8 agonist, 3M-052, as an adjuvant because it has been shown to significantly bolster and prolong immune responses.

In the first of these trials locally referred to as UM1, the objective has been to compare protection against multiple SHIV challenges by repeatedly treating animals with env SOSIP trimer plus 3M-052 in nanoparticles. The second leg of this UM1 trial was similar, but animals were also exposed to gag protein expressed from three heterologous viral vectors in an effort to amplify the number and activities of survailling cytotoxic T cells located within the genital mucosa. We are currently monitoring longitudinal viral loads in these experimental and control groups and beginning to evaluate correlates of protection against viral challenges. These and other consortium efforts will be augmented through the inclusion of experimental data within a FileMaker based relational database.

The second ongoing study known as UM2 utilizes 3M-052 and DNA-expressed CD40L as adjuvants. CD40L is known to co-stimulate dendritic cells and B cells, and by doing so it might promote a more robust immune response. MVA-expressed SOSIP antigen is also provided either alone or in combination with Rapamycin treatment. Rapamycin down regulates CCR5 expression, and in so doing it might act to reduce the infection of CCR5 positive CD4 target cells during challenges.

Most vaccine trials to date that have been designed to induce robust humoral responses have failed to show significant efficacy in protecting subjects from infection. There are numerous reasons for this lack of success. Most virus specific antibodies will bind to envelope regions including the base or stem of the envelope, and these interactions fail to block the infection of target cells. Another possibility is that much of the total antibody response has already been directed toward epitopes presented from within the microbiome, thereby diverting humoral responses away from HIV. In order to test this latter hypothesis, we will be treating newborn and 6-8 month old macaques with BG-505 trimer and 3M-052 in order to see whether early immunization prior to the formation of a complex microbiota might prove advantageous in promoting more targeted clonal selection, expansion, and ultimately a more effective humoral response, perhaps one with even greater breadth.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Redacted by agreement (Co-Principal Investigators); Funded by NIAID (5UM1AI124436)
Support from the Emory Center for AIDS Research (P30 AI050409)
Yerkes National Primate Research Center base grant through the Office of Research Infrastructure Programs/OD P51OD11132

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: OPTIMIZING ADJUVANTS AND NEEDLE FREE DELIVERY METHODS FOR ORAL HIV VACCINATION

SPID#: 13066

UNIT/DIVISION: Microbiology Immunology

TYPE: Research

START DATE: 7/1/2016

END DATE: 4/30/2021

GENERAL CATEGORY: AIDS

SUB-CATEGORY: Vaccine

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R01DE026333

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Microbiology and Immunology
Prin. NPRC Core Sci.		Microbiology and Immunology
Other Core and Affil.		

PROJECT DESCRIPTION:

The majority of HIV infections world-wide occur via mucosal routes (genital, oral, rectal). The overall goal of this proposal is to develop a vaccination approach that induces strong HIV-specific humoral and cellular immunity in genital, intestinal, and oral mucosa. We hypothesize that vaccine strategies that elicit strong anti-HIV immunity at mucosal sites will prevent infection and rapidly clear infected cells at the early site of transmission. The oral cavity is rich in antigen presenting cells and drains to local lymphoid tissue containing T cells and B cells, providing an excellent opportunity for mucosal delivery of vaccines. However, this route of immunization has been under utilized to deliver vaccines in part due to the presence of proteases in saliva that can degrade vaccines, as well as a thick squamous epithelium covering the sublingual and buccal tissue. Here, we aim to target the oral mucosa for immunization using a needle free device (Syrijet) as an oral vaccine delivery system to induce strong immune responses both systemically and mucosally. By using a needle-free injector we can inject vaccinations directly into the oral mucosa, bypassing both the thick epithelium and protease degradation. To test our hypothesis, in Aim 1 we will first evaluate oral delivery to the sublingual and buccal tissue via a needle-free injector or topical application, which allows vaccines to be naturally absorbed, and compare these routes with a conventional systemic intradermal/subcutaneous route in rhesus macaques. We will also evaluate the use of the mucosal adjuvant dmLT for protein immunizations. Additionally, we will test the protective efficacy of this vaccination by challenging the animals with an intrarectal challenge with clade B SHIV. In Aim 2 we will further examine the use of different adjuvants in generating favorable responses, as well as repeating the challenge studies with larger number of animals

PROGRESS REPORT:

Progress has been made in evaluating HIV-1 vaccination to the oral mucosa via needle-free injection in rhesus

macaques. In this study, we show that needle-free injection to the sublingual and buccal tissue within the oral cavity is superior in generating systemic and mucosal vaccine-specific immune responses compared to topical application of vaccines to the tissues. Additionally, needle-free oral injection is comparable or superior to the conventional intradermal/subcutaneous (ID/SC) vaccination route in generated these immune responses. The mucosal adjuvant dmLT was used to adjuvant protein immunogens in this study, and we show that dmLT is a robust adjuvant that promotes both systemic and mucosal antibody responses. Immunized macaques were subsequently challenged weekly with a low dose heterologous SHIV-SF162p3 to determine vaccine efficacy. We show that both needle-free oral and ID/SC immunization, but not topical oral immunization, results in a significant delay in acquisition of SHIV-SF162p3 infection. Major correlates of protection include non-neutralizing antibody effector function, Env-specific CD4 T-cell responses, gp120 V2 loop specific antibody responses, and vaccine specific rectal IgG levels. Unpublished

Unpublished

PUBLICATIONS:

PMID	Title

Unpublished

FUNDING SOURCES:

Redacted by agreement NIDCR

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: CD40L ADJUVANTED CLADE C DNA AND MVA HIV VACCINES

SPID#: 13067

UNIT/DIVISION: Microbiology Immunology

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: AIDS

SUB-CATEGORY: Vaccine

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: U19AI109633

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Microbiology Immunology
Prin. NPRC Core Sci.		Microbiology Immunology
Other Core and Affil.		Pathology

PROJECT DESCRIPTION:

Development of an effective vaccine against HIV-1 has been an elusive goal for the past three decades. As a result it has been a major challenge to stem the tide of the epidemic caused by this virus globally. The results of the RV144 efficacy trial in Thailand have spurred a new level of excitement for the development of HIV vaccine and strongly support the development of vaccination approaches that enhance the titer and functional quality of anti-HIV Env antibody that may significantly enhance protection against HIV.
The overall goal of this program is to develop novel vaccination approaches that not only enhance the magnitude but also enhance the functional quality of anti-HIV cellular and humoral immunity. Specifically, we propose to combine two new vaccination approaches developed recently at Emory University that showed great promise in rhesus macaques. The first approach uses CD40L, a co-stimulatory molecule for dendritic cells (DC) and B cells, expressed on the surface of HIV VLPs as a genetic adjuvant for enhancing the magnitude and functional quality of HIV-specific cellular and humoral immunity leading to enhanced protection from acquisition of SIV infection. The second approach uses a new MVA that lacks 4 immune modulatory genes (MVAΔ4) as a vaccine vector that showed a significant increase in the magnitude of HIV-specific cellular and humoral immunity in rhesus macaques. In this program, we hope to combine these two new complementary approaches to develop a novel vaccination strategy against HIV. This program is a collaborative effort between scientists at the Emory University Redacted by agreement NIH Redacted by agreement and Louisiana State University (LSU; Redacted by agreement
Successful completion of the program will result in the clinical development of two new vaccine products and a novel HIV vaccine.

PROGRESS REPORT:

M23 trial - After successful generation of novel Clade C SHIV vaccine immunogens, we commenced vaccination of 40 rhesus macaques (RM). All groups received the same CD40L adjuvanted DNA expressing C.1086 HIV Env gp160 protein and SIV Gag (DNA/SHIV). From there the 40 RM were further vaccinated, in groups of 10, with 4 different vaccine regimens. Animals in Group 1 received intradermal boosting with MVA/SHIV at weeks 16, and

32, expressing membrane bound gp147 envelope protein on VLPs. Animals in Group 2 received MVA/SHIV at weeks 16, and 32, which secretes stabilized native flexible linker (NFL) version of gp140 protein. Group 3 received two MVA/SHIV boosters (same as group 2) on weeks 16 and 32 (intradermally), and corresponding purified native-like trimeric protein (NFL) (200□g/dose, sub-cutaneously adjuvanted with dmLT). Group 4 received MVA/SHIV boosters (same as group 1) on weeks 16 and 32 (intradermally) along with purified CycP-gp120 protein (200□g/dose, sub-cutaneously adjuvanted with dmLT). A fifth group, which was not vaccinated, was added to the trial to serve as unvaccinated controls. Five months after the MVA/SHIV vaccinations, groups 1, 2, and 5 proceeded to challenge with SHIV1157ipd3N4. At the completion of 10 challenges we observed a significant delay in acquisition of SHIV1157ipd3N4 infection in both vaccinated groups. The immune correlate analyses are on going.

Groups 3 and 4, since we did not see the boost in antibody responses that we were anticipating, went on to receive an additional protein immunization adjuvanted with 3M052/alum. Group 3 received 200ug/dose of C.1086 NFL and group 4 received 100ug/dose of NFL and 100ug/dose of CycP protein to be given in different sites. These two groups have completed their protein boost. These animals will be challenged ~5 months after the protein boost.

PUBLICATIONS:

PMID	Title
30651354	Clade C HIV-1 envelope vaccination regimens differ in their ability to elicit antibodies with moderate neutralization breadth against genetically diverse tier 2 HIV-1 envelope variants.

FUNDING SOURCES:

Redacted by agreement NIAID

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: EXPERIMENTAL DEPLETION OF PLASMACYTOID DENDRITIC CELLS IN SIV INFECTION

SPID#: 13068

UNIT/DIVISION: Microbiology Immunology

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: AIDS

SUB-CATEGORY: AIDS

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER: R21AI118542

SUPPORTING ORGANIZATION: NIAID

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Microbiology Immunology
Prin. NPRC Core Sci.		
Other Core and Affil.		Microbiology Immunology

PROJECT DESCRIPTION:

The basis of this proposal is a novel reagent – a monoclonal antibody that specifically depletes plasmacytoid dendritic cells (pDCs) in rhesus macaques. This proposal will test the hypothesis that the elimination of pDCs, in vivo, from SIV-infected rhesus will substantially reduce immune activation. This hypothesis will be addressed by the experiments in the following Specific Aims: (Aim1) To test the effect of experimental pDC depletion on global IFN responses in SIV infection; and (Aim 2) Determine the effect of pDC depletion on immune activation, CD4+ depletion and control of viral replication. At the conclusion of these exploratory studies, we will have definitively established the role of pDCs and IFN in driving immune activation, determined if the IFN response to SIV is primarily due to pDCs, developed a novel research tool for immunological studies in NHPs, and characterized the potential of this reagent for translation into clinical trials.

PROGRESS REPORT:

We tested if the humanized depletion would occur at the high end of the of recommended dosage (50 mg/kg). We infused a rhesus macaque that was chronically infected (46 weeks SIV-infected) with SIVmac239 at a single dosage of 50 mg/kg. This infusion did not exhibit any discernible depletion. We then tested if high-dose infusion (50 mg/kg) would be more efficient in an animal that was SIV-negative. We then performed an infusion experiment in which an SIV-negative rhesus macaque was administered 50 mg/kg of mAb 125 C antibody. This infusion was able to affect reproducible depletion of CD123+ pDCs over 40 days.

Our data to this point demonstrated that the Mab 125 C antibody was capable of depletion in vivo in rhesus macaques. However, the observation that only 2 of the 4 animals had observable depletion was a significant

concern.

In the original proposal, we had planned to use the MAb 125 C antibody to conduct a depletion experiment in five SIV-infected monkeys to test the impact on pDC depletion on SIV pathogenesis. However, given the considerable concerns with achieving reproducible depletion – rather than proceeding with the originally planned Aim 2 depletion experiments, we decided to focus our efforts on further optimization of the depleting antibody. We established a collaboration with Redacted by agreement who oversees the development of depleting monoclonal antibody, at NIH NHP Reagent Resource to optimize the depleting activity of the antibody – such as making the antibody "macaquized" by swapping in a rhesus macaque Fc region, and adding Fc mutation that enhance in vivo depletion. As a first step, we first compared the binding affinity of the MAb 125 C clone, including its original mice clone 12B and several other clones we had developed against BDCA2, to both human and rhesus macaque
BDCA2 (CD303) using Biacore assays. These analyses showed that all adaptions of the
original 12b clone, 12bch, 12b and the Mab 125 C used in our study here, had high binding affinity (kd = 1x10-8 – 1x10-9 M.) We also identified a clone, 1D3, that had exceptional affinity for rhesus BDCA2 (1x10-10).Based on the vastly superior binding of the 1D3 clone for rhesus macaque BDCA2, we decided to pursue this
clone for future development, and decided not to pursue modifying the Mab125 C antibody (ie. adding a macaque
Fc region).

Final Progress In Aim 1 of this R21 proposal – we tested the dosing and consistency of pDC depletion at low dose, and at high dose, in four macaques. These data demonstrated that our clone was able to achieve depletion
at either dose – but was not achieved in all animals, and was unlikely to be able to achieve depletion in chronically
SIV-infected macaques, despite our demonstration that the antibody was able to bind to monkey pDCs in vivo in all monkeys. Therefore, we made the decision to forgo our original Aim 2 experiments (testing if depletion would impact SIV pathogenesis) and instead focus on improving the in vivo depletion ability of the reagent. We established a collaboration with Redacted by agreement to accomplish these goals, and sent Redacted by agreement our antibodies for testing. These experiments identify an additional clone, 1D3, with vastly superior binding activity than the Mab 125.

At the completion of our allotted funding, we have now made the additional progress:
(1) Simianization of 1D3 clone Fc, and production of sufficient quantities for in vivo testing. We had provided Redacted by agreement with the sequences for the 1D3 clone, and his facility has recently finished producing 200 mg of 1D3 with rhesus macaque Fc containing depletion enhancing mutations.
(2) Recruitment and baseline testing of an additional rhesus macaque for 1D3 testing. We have completed baseline pDC testing in an SIV-negative macaque and are initiating infusion of 1D3 in late summer 2018.
Overall, while we did not conduct the experiments in Aim 2, due to our judgment that the reagent would not yield conclusive results, we changed the focus of the proposal to further development of a pDC depleting reagent for HIV pathogenesis and cure studies, and made advancement in this area.

PUBLICATIONS:

PMID	Title

no publications.

FUNDING SOURCES:

based on this progress we have now obtained a new round of funding: R01 AI136990

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: SIMULTANEOUS ANTIGEN RECEPTOR REPERTOIRE PROFILING AND SINGLE-CELL TRANSCRIPTOMICS IN T AND B LYMPHOCYTES FROM LIMITED CLINICAL SAMPLES

SPID#: 13069

UNIT/DIVISION: Microbiology Immunology

TYPE: Research

START DATE: 6/1/2018

END DATE: 5/31/2019

GENERAL CATEGORY: Immunology

SUB-CATEGORY: AIDS

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: U24AI120134

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Microbiology Immunology
Prin. NPRC Core Sci.		Microbiology Immunology
Other Core and Affil.		Dept. of Microbiology and Immunology

PROJECT DESCRIPTION:

In the vast majority of vaccine trials, the primary readouts are empirical do not collect information about the immunological determinants of a vaccine's success or failure. In recent years, several vaccine studies have combined high-throughput transcriptomic data with measures of antigenicity. These "systems vaccinology" studies have proven invaluable insight into the determinants of efficacy and antigenicity, and have demonstrated the enormous value in mechanistic studies of human vaccination. However, one area that is particularly understudied is the composition of antigen specific receptors that arise during successful and unsuccessful vaccinations. Collection of antigen-specific clonotype information in clinical vaccine studies would provide valuable data that could be used to accelerate vaccine development. The utility of current methodology for repertoire sequencing for immunological studies has been limited due to several factors (i) high-cost and low-throughput of cloning based assays (ii) most high-throughput assays only provide information on a single gene(typically the H-chain of immunoglobulin or β-chain for TCRs), or (iii) do not link ag-receptor sequences with immunophenotypic or transcriptomic data. In preliminary work, we have developed a protocol that simultaneously queries the transcriptome and paired antigen receptor sequences in B lymphocytes derived from human bone marrow after flu vaccination using next generation sequencing. The goal of this proposal is to complete development of this combined "-Seq" assay for both B and T cells, including establishment of its limitations and benchmark against contemporary repertoire sequencing techniques.

PROGRESS REPORT:

In the last reporting period we have published a primary manuscript resulting from this work (Upadhyay, Genome Medicine 2018). We have completed single-cell RNA-Seq on over 600 single B cell plasmablasts after seasonal influenza vaccination and performed repertoire sequencing on the Heavy and Light chains from matched bulk plasmablast samples These data are currently being analyzed and written up into a manuscript. We have also developed an immunophenotyping panel for our T cell studies, and prepared Gag tetramers to assess rectal T cells. We also used our BALDR pipeline to analyze naive precursor B cells binding to the eODGT8 immunogen in human donors in preparation for VRC01 phase I trials.

PUBLICATIONS:

PMID	Title
29558968	BALDR: a computational pipeline for paired heavy and light chain immunoglobulin reconstruction in single-cell RNA-seq data.
29973404	The human naive B cell repertoire contains distinct subclasses for a germline-targeting HIV-1 vaccine immunogen.

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: MAXIMIZING GERMINAL CENTERS AND SOMATIC HYPERMUTATION TO HIV ENV IMMUNOGENS

SPID#: 13071

UNIT/DIVISION: Microbiology Immunology

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: AIDS

SUB-CATEGORY: AIDS

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER: R01AI157851

SUPPORTING ORGANIZATION: NIAID

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	La Jolla Institute for Allergy and Immunology
Prin. NPRC Core Sci.		Microbiology Immunology
Other Core and Affil.		

PROJECT DESCRIPTION:

HIV-specific broadly neutralizing antibody (bnAbs) are challenging to develop and have traits indicative of extensive affinity maturation. We propose that the features of germinal center biology important for developing high affinity B-cells to a Tier 2 neutralizing antibody epitope on HIV Env trimer are very different than the features for conventional antigens, such as haptens or even HIV gp120 V3 loop (a non-Tier 2 neutralizing epitope) for which a very small number of mutations suffice for maturation of high affinity B-cells and antibodies. We will use innovative slow immunogen release vaccine technologies as candidate HIV vaccines and as tools to probe the biology of germinal centers relevant to affinity maturation against the difficult HIV trimer target in non-human primates. Our innovative slow immunogen release vaccine strategies provide two advantages: (1) protection of the immunogen for sustained release of intact trimer epitopes for B-cell recognition, and (2) sustained provision of antigen to germinal centers. This study will be extremely valuable to the HIV vaccine effort because it will test novel approaches to induce high quality HIV neutralizing antibodies and assess immunological relationships between germinal center size, duration, sequence space explored, and Tfh cells to understand which parameters are most important for affinity maturation to the bnAb epitopes of HIV Env. Aim 1. Determine how sustained Env immunogen availability impacts the quality of the germinal center and nAb responses, using slow release osmotic pumps. Aim 2. Determine whether intradermal silk microneedle patches delivering immunogen in a sustained manner maximize germinal center activity and affinity maturation to HIV Env trimers. Aim 3. Determine the Env trimer immunogen kinetics that maximize germinal center quality and duration. Aim 4. Assess the relatedness and predictive capacity of immunological parameters in the blood with the actual germinal center activity present in the lymph nodes after immunization.

PROGRESS REPORT:

Generating broadly neutralizing antibodies to HIV has long been a goal of the vaccine community. The overall objective of this grant is to further understand the biology of the germinal center and affinity maturation in the context of slow release antigen delivery that will mimic antigen kinetics of acute viral infection. In the third year of the study, we completed at study where we compared osmotic pump delivery of SOSIP with silk microdots injected subcutaneously in carboxy methylcellulose gel. The total antigen delivery time for each antigen was four weeks beginning at week 0 and week 12. At the end of each slow delivery immunization we gave subcutaneous bolus injections. We had six rhesus macaques per group with a total of twelve animals. Blood and lymph node fine needle aspirates were collected throughout the study. A lymph node biopsy was collected four weeks following the final slow delivery method was complete. We performed flow cytometry and antigen specific cell sorting through out the study to monitor the immune response and the B cell repertoire. Serum and plasma was collected to analyze the antibodies generated by the immunizations. The animals were necropsied at the end of the study. We have obtained 18 rhesus macaques for our next immunization study.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

R01 AI157851

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: T CELL COMPARTMENTALIZATION AND ANTIVIRAL RESPONSE

SPID#: 13072

UNIT/DIVISION: Microbiology Immunology

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: Immunology

SUB-CATEGORY: Viral

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R01AI126890

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Microbiology Immunology
Prin. NPRC Core Sci.		Microbiology Immunology
Other Core and Affil.		Georgia Institute of Technology

PROJECT DESCRIPTION:

We hypothesize that anatomic compartmentalization regulates TCR–pMHC interaction and fate of CD8+ T cells during the early contraction phase of viral infection.

PROGRESS REPORT:

We have made significant progress in our work on Aims 1 and 2 during the previous 9 months of funding in 2018. This has resulted in four published peer-reviewed manuscripts and two review articles during the past cycle.

PUBLICATIONS:

PMID	Title
30420628	A TCR mechanotransduction signaling loop induces negative selection in the thymus.
30498196	Cis interaction between sialylated FcγRIIA and the αI-domain of Mac-1 limits antibody-mediated neutrophil recruitment.
29454797	Alterations in Intestinal Microbiota Lead to Production of Interleukin 17 by Intrahepatic γδ T-Cell Receptor-Positive Cells and Pathogenesis of Cholestatic Liver Disease.
29514902	Dynamics of Tissue-Specific CD8⁺ T Cell Responses during West Nile Virus Infection.
29281849	Of mice, rats, and men: Small animal model of hepatitis C virus infection.

PMID	Title
28926189	Environmental peer pressure: CD4⁺ T cell help in tolerance and transplantation.

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: HIGHLY-PARALLEL PCR ANALYSIS OF LATENTLY-INFECTED RESERVOIRS

SPID#: 13073

UNIT/DIVISION: Microbiology and Immunology

TYPE: Research

START DATE: 5/1/2018

END DATE: 4/30/2019

GENERAL CATEGORY: AIDS

SUB-CATEGORY: Immunology

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER: Private Source

SUPPORTING ORGANIZATION:

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Microbiology and Immunology
Prin. NPRC Core Sci.		Microbiology and Immunology
Other Core and Affil.		Microbiology and Immunology
		Microbiology and Immunology
		Microbiology and Immunology

PROJECT DESCRIPTION:

Substantial evidence suggests HIV-1 can establish a latent infection of long-lived quiescent cells, which carry an integrated provirus that is largely transcriptionally silent, functionally invisible to immune surveillance and impervious to the activity of antiretroviral drugs. The long half-life of these cells and their capacity to be reactivated and produce infectious virions remains the primary obstacle to viral eradication. We propose a novel approach using a highly sensitive qPCR technique to analyze the lymphoid tissues most likely to harbor latent reservoirs, to identify the cellular compartments and subsets most enriched for latently-infected cells at higher resolution than previous analyses, and to use highly-parallel qPCR transcriptional analysis to identify novel cell surface biomarkers expressed on these subsets. The use of highly-parallel simultaneous genome/transcriptome qPCR represents a unique approach to address the fundamental challenges in characterizing latently-infected reservoirs and should provide essential information necessary for the development of strategies for viral eradication.

PROGRESS REPORT:

Experiments in the past year have focused on single cell transcriptional profiling with T follicular helper cells obtained from SIV-infected animals maintained on potent antiretroviral therapy. Single cell analysis of over 1000 cells has identified SIV transcripts in a small subpopulation of cells, thus demonstrating the feasibility of this approach to characterize the reservoir of SIV-infected cells in macaques on ART. To facilitate our efforts to increase throughput and provide an unbiased approach to transcriptional analysis, we are exploring the use of the 10X Chromium single cell RNA-Seq platform. Initial experiments have been conducted on a cell line (3D8)

that contains a defective integrated SIV provirus mixed with uninfected cells. Analysis of these data are underway, with plans to extend this approach to primary CD4+ T cells if the initial results are promising.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: VACCINE DESIGN TO CONCENTRATE PROTECTIVE ANTIBODIES AT THE MUCOSAL BORDER

SPID#: 13074

UNIT/DIVISION: Microbiology and Immunology

TYPE: Research

START DATE: 5/1/2018

END DATE: 4/30/2019

GENERAL CATEGORY: AIDS

SUB-CATEGORY: Vaccine

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R01AI102625

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Microbiology and Immunology
Prin. NPRC Core Sci.		Microbiology and Immunology
Other Core and Affil.		Univ. Of MN

PROJECT DESCRIPTION:

Recent collaborative experiments from the Redacted by agreement laboratories have suggested that the presence of antibodies against an oligomeric form of gp41 in the female reproductive tract may play a role in mediating protection against vaginal challenge induced by the live attenuated SIV vaccine, SIVdeltanef. The present experiments further extend these observations to determine the ability of antibodies directed against oligomeric gp41 to mediate protection against vaginal challenge. Initial studies will focus on a more detailed characterization of antibody responses induced by SIVdeltanef, as well as antibodies induced by immunization of macaques with oligomeric forms of gp41. Subsequent experiments will analyze the protective effects of passive immunization with rhesus antibodies that are specific for oligomeric gp41 and their ability to provide protection against vaginal challenge with SIV.

PROGRESS REPORT:

We have completed passive transfer experiments involving transfer of: 1. A gp41-specific rhesus antibody; 2. A gp41-specific antibody with modifications to enhance binding to a Fc receptor (FcRN) that is expressed in the female reproductive tract; or 3. A control rhesus antibody. Following vaginal challenge of animals undergoing passive transfer, no evidence of a protective effect was observed. Studies to determine serum, mucosal and tissue levels of infused antibodies and the anatomic distribution of antibody within the female reproductive tract of these animals are ongoing by the Redacted by lab. We have also published a paper from this collaboration with the Haase laboratory that documents the impact of vaginal challenge on epithelial integrity in the female reproductive tract, and the ability of vaccination with SIVdeltanef to suppress the stress response and maintain epithelial integrity.

PUBLICATIONS:

PMID	Title
29401315	Vaccine-Associated Maintenance of Epithelial Integrity Correlated With Protection Against Virus Entry.

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: ANTIVIRAL ROLE OF CD8+T CELLS IN ART-TREATED SIV-INFECTED MACAQUES

SPID#: 13078

UNIT/DIVISION: Microbiology Immunology

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: AIDS

SUB-CATEGORY: AIDS

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R01AI125064

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Microbiology Immunology
Prin. NPRC Core Sci.		Microbiology Immunology
Other Core and Affil.		Pediatrics

PROJECT DESCRIPTION:

The use of ART results in reduction of plasma viremia to below detectable levels in HIV-infected individuals but infection with HIV persists despite suppressive ART and treatment interruption results in viral rebound. In absence of ART, CD8+ T cells inhibit virus replication during SIV infection of rhesus macaques (RMs). However, the precise role of CD8+ lymphocytes in controlling virus replication during ART is unknown. Understanding the mechanisms controlling HIV/SIV reservoir dynamics under ART is critical to design effective strategies to reduce the size of these reservoirs and promote HIV/SIV remission.
In this proposal, we build upon our preliminary data indicating that CD8+ lymphocytes act in concert with ART to maintain virus suppression. We will answer three important questions regarding the mechanism(s) of CD8+ lymphocyte-mediated virus suppression. First, we will determine if the antiviral effect of CD8+ lymphocytes is present in SIV-infected ART-treated RMs with prolonged suppression of viremia (as an extension of our preliminary results demonstrating this effect in the setting of short-term virus suppression). In this study, we will perform CD8 depletion in SIV-infected RMs treated with ART for at least one year to moNonere closely mimic long-term ART-treated HIV-infected individuals with a stable virus reservoir. Second, we will determine if the observed antiviral effect of CD8+ lymphocytes under ART is mediated by CD8+ T cells vs. CD8+ NK cells. This critical experiment is made possible by a newly available monoclonal antibody (mAb) that targets cells expressing CD8□ (i.e., CD8□□+ T cells, but not CD8□+ NK cells) for depletion. Third, we will quantify the contribution of CD4+ T cell activation/proliferation to the increase in viremia that follows in vivo CD8 depletion. By using a neutralizing anti-IL-15 mAb together with CD8 depletion we can selectively block homeostatic CD4+ T cell activation and measure subsequent virologic outcomes

PROGRESS REPORT:

We investigated whether treatment of long-term ART-treated SIV-infected RM with the IL-15 super-agonist N803

in the setting of CD8 depletion amplifies the previously observed latency-reversing agent (LRA) effect by this compound. For this purpose, fourteen RM underwent a weekly 4 dose regimen of N-803 at the time of CD8+ T cell depletion, while fourteen animals underwent CD8 depletion alone. Also, seven RMs were treated with N803 alone without undergoing CD8 depletion. All RMs included in this study were inoculated with the pathogenic SIVmac239 and then, at week 8 post infection, started on a potent, three-drug ART regimen that was be maintained for 12 months. After at least 12 months of ART and at least 4 months of consecutive undetectable plasma viremia with our standard viral load assay (LOD = 60 copies/ml of plasma), the animals received the previously used anti-CD8α Ab, M-T807R1 (obtained from the Nonhuman Primate Reagent Resource), via subcutaneous injection of 50 mg/kg. and/or a weekly four dose regimen of 100ug/kg N-803. Treatment with N-803 and/or CD8 depletion was overall very well tolerated from the clinical point of view, with no macaques showing adverse effects that resulted in changes of the experimental design. Consistent with previous studies, treatment with MT-807R1 (+/- N-803) depleted 99.1% of CD3+CD8+ T cells in peripheral blood (standard deviation of 1.8%), 97.9% in the lymph node (standard deviation of 5.3%), and 99.5% in the rectal biopsies (standard deviation of 0.35%). In addition, treatment with MT-807R1 (+/- N-803) depleted a large proportion of CD8αα-expressing NK cells in peripheral blood, lymph node and rectal biopsies. As expected based on previous studies, N-803 administration alone resulted in an expansion of CD8+ T cells in the blood and lymph node, as well as increased proliferation of peripheral CD8+ T cells, CD4+ T cells, and NK cells. Of note, while CD8 depletion alone did not result in a rapid increase of CD4+ T cell proliferation, combination of CD8 depletion with N-803 resulted in a significant increase of CD4+ T cell proliferation. To better characterize the biological effects of N-803 we conducted a transcriptomic analysis by RNAseq in sorted CD4+ T cells collected before and three days after this intervention. Regardless of concurrent CD8 depletion, N-803 induced significant upregulation of gene sets associated with cell cycling and proliferation, antiviral responses, and cell signaling. Specifically, we observed a significant enrichment for genes in the IL-2/STAT-5 signaling gene set, which is also indicative of IL-15 signaling as the receptor for this cytokine shares two out of three subunits with IL-2 and uses STAT-5 as the key adaptor molecule. We next examined the latency reversing effect of the conducted interventions by longitudinally assessing plasma viremia. Administration of N-803 was not associated with increase of plasma viremia >60 copies/mL in any of the treated animals, indicating that this IL-15 super-agonist is not able to exert a major in vivo LRA effect in ART-treated SIV-infected macaques when used alone. As expected based on previous studies (Cartwright et al., Immunity 2016), rhesus macaques undergoing CD8+ lymphocyte depletion showed a moderate but significant increase in virus production, with plasma viremia >60 copies/ml detected in 11/14 animals (78.6%) and 18/56 samples (32.1%) collected one week after each N-803 administration. In all cases, the level of virus production returned below 60 copies/ml of plasma at the time of CD8+ lymphocyte reconstitution. Overall, the level of virus reactivation was consistent with a previous experiment, even though the magnitude of virus production post CD8 depletion was less dramatic, possibly related to the longer period of ART treatment. Interestingly, rhesus macaques treated with N-803 and CD8 depletion showed very robust and persistent levels of virus production, with viremia >60 copies detected in 14/14 animals and 41/56 samples (73.2%) and viremia >1,000 copies was observed in 6/14 animals (42.9%) and 13/56 samples (23.2%). After the last treatment of N-803, the level of viremia rapidly declined also in coincidence with the reconstitution of the CD8+ T cell pool, and all animals returned to viremia below 60 copies/ml of plasma by week 6 after N803 and CD8 depletion. We next investigated the correlates of the level of virus reactivation in ART-treated SIV-infected rhesus macaques that received N-803 and CD8 depletion, and observed that the area under the curve of virus production was directly correlated with average level of residual viremia at the three time points before CD8 depletion (alone or associated with N803). In addition, we found that in the macaques undergoing CD8 depletion and N803 treatment the level of virus production (AUC) was directly correlated to the level of CD8+T cells in lymph nodes and NK cells in peripheral blood.

PUBLICATIONS:

PMID	Title
29427516	Mechanisms of CD8⁺ T cell-mediated suppression of HIV/SIV replication.

FUNDING SOURCES:

NIH R01 AI125064

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: TARGETING SIV RESERVOIRS WITH TYPE I INTERFERONS

SPID#: 13079

UNIT/DIVISION: Microbiology Immunology

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: AIDS

SUB-CATEGORY: AIDS

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER: R21AI116200

SUPPORTING ORGANIZATION: NIAID

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Microbiology Immunology
Prin. NPRC Core Sci.		Microbiology Immunology
Other Core and Affil.		

PROJECT DESCRIPTION:

Despite many major advances in AIDS research, a treatment that can cure the infection is still not available. Indeed, antiretroviral therapy (ART) must be taken for life, thus posing significant challenges in terms of costs and clinical safety, and interruption of therapy results in a rapid rebound of viremia. To this end, new approaches are required to eradicate the reservoirs of latently infected cells that persist during ART. The overarching Aim of this proposal is to explore the therapeutic potential of type I interferon (IFN-I), that activates a very potent natural antiviral molecular system, in reducing the reservoirs of virus-infected cells that persist under ART. In the R21 phase of this grant application we propose to use the existing, well-established nonhuman primate model of SIVmac infection of rhesus macaques (RMs) to evaluate, in a pilot study, the potential impact of pegylated IFN-□2a (pIFN-□2a) on the overall size, anatomic location, and cellular distribution of the reservoirs of latently infected cells in ART-treated, SIV-infected RMs. We will use this very robust model to investigate directly in vivo and in multiple organs (i.e., blood, lymph nodes, spleen, mucosal tissues, etc) and cell types (i.e., memory CD4+ T-cell subsets and macrophages) whether and to what extent pIFN-□2a administration enhances the effect of ART on the virus reservoir. The results of the studies proposed in the R21 part of this application will pave the way for further experiments, to be conducted in the R33 phase of this proposal, in which we will test, in a larger cohort of SIV-infected RMs treated with long-term ART and exhibiting full suppression of virus replication, the effect of two consecutive cycles of pIFN-□2a treatment on (i) the size of the persisting reservoirs of latently infected cells, and (ii) the time of rebound of plasma viremia after ART interruption.

PROGRESS REPORT:

This project is now completed and the relevant work has been published:

Palesch D, Bosinger SE, Mavigner M, Billingsley JM, Mattingly C, Carnathan DG, Paiardini M, Chahroudi A, Vanderford TH, Silvestri G. Short-Term Pegylated Interferon α2a Treatment Does Not Significantly Reduce the Viral Reservoir of Simian Immunodeficiency Virus-Infected, Antiretroviral Therapy-Treated Rhesus Macaques. J

Virol. 2018 Jun 29;92(14). pii: e00279-18. doi: 10.1128/JVI.00279-18. Print 2018 Jul 15.

PUBLICATIONS:

PMID	Title
29720521	Short-Term Pegylated Interferon α2a Treatment Does Not Significantly Reduce the Viral Reservoir of Simian Immunodeficiency Virus-Infected, Antiretroviral Therapy-Treated Rhesus Macaques.

FUNDING SOURCES:
NIAID R21AI116200

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: COLLABORATORY OF AIDS RESEARCH FOR ERADICATION

SPID#: 13080

UNIT/DIVISION: Microbiology Immunology

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: AIDS

SUB-CATEGORY: AIDS

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER: U19AI096113

SUPPORTING ORGANIZATION: NIAID

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	University of North Carolina at Chapel Hill
Prin. NPRC Core Sci.		Microbiology Immunology
Other Core and Affil.		

PROJECT DESCRIPTION:

The Scientific Research Support 2 (SRS 2): Primate Virology aims to support CARE by consolidating and focusing the preclinical evaluation of novel concepts and products. The SRS 2 will provide all the expertise, infrastructure, reagents, and personnel for the conduct of complex in vivo studies in RMs that will involve (i) experimental infection with SIV or SHIV; (ii) long-term treatment with ART; (iii) administration of specific anti-reservoir agents (i.e., LRAs and others); (iv) longitudinal monitoring of virus replication, virus reactivation, and overall reservoir size through validated, state-of-the-art assays; and (v) functional evaluation of the reservoir via analytical treatment interruption (ATI). The SRS 2 is based at the Yerkes National Primate Research Center (YNPRC), one of the seven NIH-funded primate research centers. This facility possesses all the necessary animal resources, infrastructure, and veterinarian and animal care expertise to fully meet the CARE goals. The SRS 2 is directed by Redacted by agreement (YNPRC, Emory University), who has >15 years experience in leading research projects involving complex in vivo interventions in SIV/SHIV-infected nonhuman primates.
The SRS 2 will work in close collaboration with Redacted by agreement (University of North Carolina) for the overall coordination of the pre-clinical studies included in the CARE program, with Redacted by agreement and Redacted by agreement (University of Pennsylvania) on the validation of novel, pathogenic clade-C envelope (Env) SHIVs for studies of latency and reservoirs in ART-treated RMs, and with Redacted by agreement (Duke University) for the coordination of the complex studies that will involve the combined use of LRAs and next-generation immune-based anti-reservoir approaches.

PROGRESS REPORT:

Efficacy of LRAs in SIV-infected, ART-suppressed RMs: (i) 22 RM (leveraging collaboration with Emory CIAR-NHP project to support these animals): all SIVmac239-infected and started on ART (TDF+FTC+DTG) at week 8 after infection; (ii) Based on unfavorable PK and adverse event results in healthy RMs, the originally planned intervention for latency reversal (EZH2 inhibitor) was modified. A novel class of drug has been investigated by CARE / Qura in in vitro and murine studies and, based on results described elsewhere in this progress report, we

elected to test a SMAC mimetic in a group of 6 SIV-infected ART-suppressed RMs, with 4 additional RMs serving as placebo controls. These animals received either 3 or 10 doses of the drug or placebo and were sacrificed while still on ART. It should also be noted that PK/PD work done in healthy RMs preceeded this study and informed the dose used; (iii) A follow up study testing in 6 SIV-infected, ART-suppressed RMs vs. 6 placebo controls is scheduled to start in the late Spring / Summer 2018 with dosing informed by study #1 and including ART interruption to define rebound kinetics. Efficacy of Env DART in SHIV-infected, ART-suppressed RMs:14 RMs were infected with SHIV.CH505.375H.dCT (supplied by George Shaw) in early March 2018 with ART initiation planned for 16 weeks post infection. Following ~9 months of ART, RMs will be divided into 3 groups: 4 controls, 5 DART, 5 DART + LRA. The specific DART or DARTs to be used will be determined by in vitro work using cells obtained from the SHIV.CH505-infected RMs.
In addition, banked splenocytes from six SIV-infected ART-suppressed RM were sent to Redacted by agreement to perform pharmacodynamic biomarker assays to measure EZH2 inhibition of host target genes. In addition, in vitro studies of the combination of GSK047 and panobinostat for HIV/SIV reactivation were conducted. As stated above, unfavorable PK and adverse event results from healthy RMs led us to re-evaluate the candidate LRAs to be tested in SIV-infected, ART-suppressed RMs.
LRA efficacy experiment underway (Emory CIAR-NHP animals): 22 RM were challenged intravenously with 3,000 TCID50 of SIVmac239. All RM experienced a rapid, exponential increase in virus replication that peaked at day 14 post infection (106-107 SIV RNA copies/ml plasma). ART (Tenofovir + Emtricitabine + Dolutegravir) was initiated at week eight after infection. All RMs exhibited undetectable plasma viral load (below 60 SIV RNA copies/ml) in an expected amount of time and remained suppressed prior to additional interventions. Plasma and PBMC were collected and cryopreserved every week or every other week. At selected time points, larger volumes of blood as well as rectal and lymph node biopsies were collected and cells have been cryopreserved or tissues embedded in paraffin for further analyses. The SMACm has been administered to 6 SIV-infected, ART-suppressed RMs with promising preliminary results regarding virus reactivation (as measured by increased plasma viral loads while still receiving ART). Analysis of cell-associated SIV RNA and DNA from CD4+ T cells isolated from PBMCs and LNMCs is in process. Up to 10 doses of SMACm at 100µg/kg have been infused weekly i.v. and groups of 3 RM are sacrificed after 3 or 10 doses. The pharmacokinetics of the SMACm after dose 1 showed an expected drug exposure in the plasma of the SIV-infected, ART-suppressed RMs as compared to previously dosed healthy RMs. Interestingly, preliminary results showed an increase in plasma viral loads during the first 4 doses of SMACm in 3 of 6 ART-suppressed SIV-infected RMs. Finally, the first DART experiment is now underway: 14 RMs were infected with SHIV.CH505.375H.dCT i.v. dose of 10 ng p27. All RMs were infected with a single dose, with peak plasma viral loads ranging from 1.07-8.85 x 106 at day 14 after infection. ART initiation is planned for week 16 post infection.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

U19AI096113

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: SYNTHETIC DNA AND NOVEL ENV VACCINE FOR HIV

SPID#: 13081

UNIT/DIVISION: Microbiology Immunology

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: Immunology

SUB-CATEGORY: AIDS

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER: U19AI109646

SUPPORTING ORGANIZATION: NIAID

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Wellstar
Prin. NPRC Core Sci.		Microbiology Immunology
Other Core and Affil.		

PROJECT DESCRIPTION:

The broad goal of the Integrated Preclinical and Clinical AIDS Vaccine Development (IPCAVD) program “Synthetic DNA & Novel Env Vaccine for HIV” (U19 AI109646) is to produce a novel enhanced adaptive skin electroporation + gene adjuvanted DNA vaccine (E-DNA) as a prime to combine with a highly novel polyvalent A, B, C, A/E recombinant protein boost (PEB) as a vaccine to induce broad immunity to HIV. By using this combination of immunogens we hope to generate an improved spectrum of T and B anti-HIV immune responses compared to current HIV vaccine modalities. Currently, there is no HIV vaccine available that can drive a broad collection of functional antibody responses and potent Tfh as well as CD8 effector T cell responses. In the past few years we have reported exciting clinical results that a combination of adaptive EP + IL-12 cytokine gene adjuvant in normal healthy volunteers safely drives potent and long-lived CD4+ and CD8+ T cell responses. This program focuses on bringing forward a combined new EP delivered, enhanced DNA + gene adjuvant + adjuvanted polyvalent protein boost in a clinically manageable vaccine regime through development to present such a majorly improved clinical vaccine candidate to HVTN for examination in the clinic. The highly interrelated, translational focused Projects supported by this IPCAVD program include the DNA/adjuvant development with commensurate monitoring for cellular responses (Project 1), monitoring of humoral responses (Project 2), and product development including dermal EP development and GMP Envelope (Env) protein production (Project 3). Initial NHP experiments will be conducted as part of Projects 1 and 2, including two separate challenge experiments. These efforts will include screening of potential Env immunogens, prime-boost strategy using DNA prime with protein boost, novel adjuvant developments, and EP device advances, resulting in the final selection of a regimen for clinical evaluation

PROGRESS REPORT:

- The first large NHP trial that was conducted as part of the IPCAVD U19AI109646 program consisted of a four-arm, 40-rhesus macaque (i.e., 10 animals per arm) experiment that includes a 50-week immunization phase (three EP-DNA administrations followed by two Env protein boosts, all at a four-week interval) followed by a

challenge phase in which the vaccinated rhesus macaques were exposed weekly (for up to 15 weeks) to a low dose of SHIV-CH505 intra-vaginally for up to a total of 15 challenges. The immunization and challenge phases of this experiment have been successfully completed. The main results of the challenge phaes of the study is that none of three vaccination arms showed any significant protection from SHIV-CH505 acquisition as compared to control animals. In addition, we observed only a relatively small, non-significant trend towards better control of post-transmission virus replication in the groups of DNA envelope + Env proteins + IL-12 plasmid and DNA-Envelope + Env proteins + Mec-CCL28 plasmid (as compared to unvaccinated control rhesus macaques), but not in the animals vaccinated with non-adjuavnted DNA-envelope + Env proteins only. Further immunological analyses were conducted in collaboration with Redacted by agreement at Duke University to determine potential association between specific aspects of the cellular and humoral immune response against HIV Envelope induced by the used immunization regimens and the observed level of protection from either virus acquisition or virus replication after transmission. These analyses were conducted in pre-immunization, week10 (post 3xDNA) and week 18 (post 2x gp120) plasma samples from the three vaccinated groups.15-mer peptides overlapping by 12 were used, covering gp160 of consensus A, B, C, D, CRF01_AE, CRF02_AG, and group M; gp120 for virus strains B.MN, C.1086, C.ZM651, C.TV1, AE.A244, and AE.TH023; and a series of CH505 strains. Data processing and analysis included: (i) Array data are processed by pepStat (Gottardo et al. PLOS One 2013); (ii) Binding Signal for each peptide defined as: = log2(Intensity of post sample/intensity of baseline sample); (iii) Positivity criteria (applied for each peptide for each post-immunization sample) as signal (Log2-fold of intensity, post/pre) > FDR0.01 cutoff determined by pepStat with study data set, and signal for every peptide > peptide-specific cutoff, which is 95th percentile of all baseline binding to the peptide. The main observations of these immunological anlyse were the following: (i) DNA prime elicited binding to linear epitopes in C1, C1V1, V2, C2, V3, C4, V5, C5 in gp120, and every epitope, gp41 IDR, and Kennedy epitopes in gp41; (ii) No apparent difference among 3 groups in magnitude of IgG linear epitope response for either wk10 or wk18; (iii) Protein immunizations boosted the magnitude of gp120 responses that were primed by DNA. Only one new specificity (C1V1) was observed after protein boost; (iv) In contrast to gp120 responses, binding to gp41 epitopes was not boosted – consistent with the fact that boost proteins are gp120; (v) Cross-clade V2 hotspot response was elicited and boosted, mostly against AE.A244, A.con, B.con, C.con and C.1086. Future studies will include investigating whether the magnitude of binding to certain epitopes correlate with antibody functions (ADCC, infected cell staining), and whether the level of boosting for different clade of antigens is associated with sequence similarity between priming DNA and boosting proteins of the clade.

PUBLICATIONS:

PMID	Title

None

FUNDING SOURCES:

NIAID U19 AI109646

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: VACCINE INDUCED IMMUNITY IN THE YOUNG AND AGED

SPID#: 13082

UNIT/DIVISION: Emory Vaccine Center

TYPE: Research

START DATE: 5/1/2018

END DATE: 4/30/2019

GENERAL CATEGORY: Immunology

SUB-CATEGORY: Viral

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: U19AI057266

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Emory Vaccine Center
Prin. NPRC Core Sci.		Dept. Pathology, Stanford University
Other Core and Affil.		

PROJECT DESCRIPTION:

A major goal of Project 2 is to understand the molecular mechanisms of the integrated stress response. A fundamental feature of the integrated stress response is the formation of stress granules. Our previous work with the live attenuated yellow fever vaccine YF-17D demonstrates that this virus infects dendritic cells and stimulates the stress response kinase GCN2, which is necessary for antigen cross presentation and induction of antigen specific CD8+ T cell responses. In addition, YF-17D induces the formation of stress granules. During the past year we have focused our efforts in understanding the molecular mechanisms that regulate stress granule formation and in defining the molecular structures of stress granules. In particular, we have addressed the following questions:

- To determine whether other flaviviruses such as dengue or West Nile or the yellow fever Asibi strain are also capable of inducing stress granules.
- To determine if pattern recognition receptor (PRR) ligands could induce stress granule formation.
- To define the molecular mechanisms controlling the stress granule formation triggered by YF-17D and PRR ligand.

To determine the protein components of the stress granules and their biological functions to YF-17D virus infection, and their impact in mediating the innate response to YF-17D

PROGRESS REPORT:

During the reporting period we focussed on Zika virus which is causally linked to severe neonatal birth defects, and our recent observations demonstrate that Zika virus blocks cell cycle progression, which may contribute to fetus growth arrest or neonatal birth defects. The specific objectives for this reporting year were as follows: (i) To characterize the changes of cell cycle profile after Zika virus and other flaviviruses infection. (ii) To determine the molecular mechanisms controlling the cell cycle arrest by Zika virus. (iii) To explore the possibility to block Zika virus replication with small drug molecules that targeting the key regulators we defined.

We discovered is that Zika virus could stall DNA replication, trigger host DNA double strand breaks, activate

DNA damage response, arrest cell cycle at the beginning of early S phase. This phenomenon benefits the growth of Zika virus because blocking the activation of CHK2 and other DNA damage regulators (data not shown) significantly abolished Zika virus replication. Together, these data enhance our understanding of the molecular mechanisms of action of Zika virus in modulating cell cycle progression, and highlight the potential of antiviral strategies that use small drug inhibitors to block DNA damage responses.

PUBLICATIONS:

PMID	Title
28193898	Systems analysis of protective immune responses to RTS,S malaria vaccination in humans.
28502771	Metabolic Phenotypes of Response to Vaccination in Humans.
28798047	mTOR regulates metabolic adaptation of APCs in the lung and controls the outcome of allergic inflammation.

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: NK CELL-MEDIATED REGULATION OF T CELL IMMUNITY IN TV/HIV CO-INFECTION

SPID#: 13083

UNIT/DIVISION: Emory Vaccine Center

TYPE: Research

START DATE: 4/1/2014

END DATE: 3/31/2019

GENERAL CATEGORY: Infectious Disease

SUB-CATEGORY: TB

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER: R01AI111948

SUPPORTING ORGANIZATION: NIAID

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Emory Vaccine Center
Prin. NPRC Core Sci.		Emory Vaccine Center
Other Core and Affil.		

PROJECT DESCRIPTION:

One third of the world's population is infected with Mycobacterium tuberculosis (Mtb), and over 10 million are co-infected with human immunodeficiency virus (HIV). Latent Mtb infection (LTBI) represents immune containment, however HIV infection increases the risk of reactivation of LTBI from a 5-10% lifetime risk in HIV-uninfected individuals to a 10% annual risk in HIV-positive individuals. HIV-associated dysregulation of innate immunity and impairment of adaptive immunity by depletion of CD4 T helper cells likely contribute to loss of immune control of LTBI and progression to TB disease in HIV co-infected individuals. However, the parameters of immune control of LTBI that are perturbed in the setting of HIV co-infection have not been defined. The focus of this project is to examine how the innate immune response modulates Mtb-specific T cell immunity and determine how the regulatory pathways linking innate and adaptive immunity to Mtb are perturbed in the setting of HIV co-infection. We are (1) defining the phenotypic profiles, functional capacities, and NK cell receptor genotypes in persons with LTBI and HIV co-infection; (2) determining the relationship between NK cell profiles and the phenotype and function of Mtb-specific CD4 and CD8 T cell responses; and (3) defining the direct and indirect mechanisms whereby NK cells modulate Mtb-specific T cell immunity in LTBI, and how the mechanisms of cross-talk between NK cells and Mtb-specific T cells are dysregulated in the setting of HIV co-infection. Defining immune pathways involved in the generation, maintenance, and regulation of protective memory T cell responses to Mtb infection, and identifying the mechanisms whereby HIV infection impairs protective T cell immunity to Mtb, will be of vital importance to facilitate development of effective TB vaccines and targeted immunotherapeutic interventions and treatment of individuals co-infected with HIV and Mtb that are necessary to curb the TB epidemic worldwide.

PROGRESS REPORT:

During this reporting period, annual renewals for the study were obtained from the Emory University IRB, and the Kenya Medical Research Institute (KEMRI) Scientific and Ethics Unit. The Principal Investigator, Redacted by agreement, U.S.-

based project supervisor(s) and coordinator(s) completed regular monitoring visits at the project site in Kenya to provide additional guidance and oversight on research-related activities, which was further supported by bi-monthly conference calls between the U.S. and Kenya-based research teams. Follow-up samples from HIV-positive LTBI donors will be completed in March 2018. All study participant data and CRFs have been entered into the study database. All biological specimens collected for the study have been shipped from the KEMRI/CDC study site in Kisumu and received at the Emory Vaccine Center at Yerkes. Multiparameter flow cytometry antibody panels have been optimized for measurement of inhibitory receptor expression by Mtb-specific T cells, and for characterization of NK cell responses. Characterization of expression of inhibitory receptors on Mtb-specific CD4 and CD8 T cells in HIV-infected and HIV-uninfected individuals, with LTBI and active TB disease, has been completed. The data are currently being prepared for publication. NK cell phenotypic and functional profiles have been conducted using PBMC samples collected from HIV-infected and HIV-uninfected individuals, with and without Mtb infection. Data analysis is ongoing.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Redacted by agreement funded by NIAID

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: ROLE OF ANTIGEN-SPECIFIC T CELL RESPONSES IN THE CONTROL OF TB PROJECT 1: IDENTIFICATION OF HUMAN MTB-SPECIFIC T CELL SIGNATURES THAT ARE ASSOCIATED WITH RESOLVED AND PERSISTENT MTB INFECTION

SPID#: 13084

UNIT/DIVISION: Emory Vaccine Center

TYPE: Research

START DATE: 8/1/2014

END DATE: 7/31/2021

GENERAL CATEGORY: Infectious Disease

SUB-CATEGORY: TB

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER: U19AI111211

SUPPORTING ORGANIZATION: NIAID

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Emory Vaccine Center
Prin. NPRC Core Sci.		Emory Vaccine Center
Other Core and Affil.		Emory Vaccine Center

PROJECT DESCRIPTION:

Identifying immune correlates of control and protection to Mycobacterium tuberculosis (Mtb) infection is essential for designing vaccines for TB. The overall goals of our TBRU project are to identify antigen-specific T cell responses that are associated with distinct outcomes of Mtb infection: clearance, persistence, and progression to active disease. We currently lack the knowledge or tools to distinguish individuals who harbor persistent Mtb infection from those who may have resolved infection via immune-mediated clearance of bacteria. In Project 1 we are focusing on “Identification of human Mtb-specific T cell signatures that are associated with resolved and persistent Mtb infection.” We are testing the hypothesis that distinct Mtb-specific memory T cell profiles are associated with bacterial clearance or persistence. This is supported by our data showing that distinct antigen-specific memory T cell phenotypes and functions are associated with LTBI, active TB disease and clinically resolved TB. We are using chemotherapy-mediated clearance to model immune-mediated clearance of Mtb, as the treatment regimen for LTBI should result in significant reduction or elimination of bacteria. We are enrolling individuals with LTBI in a low-exposure setting (Atlanta, GA) and systematically comparing their antigen-specific T cell responses before and after treatment. We are delineating the spectrum of antigens recognized by Mtb-specific memory T cells, characterizing their memory phenotypes, functional capacities and transcriptional profiles. Using statistical analyses, we are deriving Mtb-specific T cell signatures that represent bacterial clearance and persistence, and determining the prevalence of these signatures in treatment-naive individuals with LTBI in Kenya. We are longitudinally assessing the dynamics of Mtb-specific memory T cell responses and their homeostatic turnover in LTBI. We are also comparing clearance/persistence signatures with those

associated with progression to TB. Overall, these studies will provide insights into protective immunity to TB and new tools to evaluate Mtb persistence or clearance in LTBI

PROGRESS REPORT:

During this reporting period, the study protocol received annual renewal of approval by the Emory University IRB. Standard operating procedures (SOPs), case report forms (CRFs) and databases have developed for the study and are currently in use. Monthly conference calls are in place to facilitate regular communication between all PI's of the projects and cores of this TBRU U19 project. Study procedures at the KEMRI/CDC study site in Kisumu, Kenya were discontinued. Shipments were completed of plasma, PBMC, and PAXgene DNA tubes from study participants enrolled at KEMRI/CDC and received at the Emory Vaccine Center at Yerkes. Longitudinal follow-up of participants with LTBI enrolled at the DeKalb County Board of Health Refugee Clinic were completed in March 2018. Enrollment of participants with LTBI in DeKalb county who decline treatment for LTBI was completed in December 2018. Participants in the Declined Treatment cohort will be followed up at 3-monthly intervals through December 2019. Blood samples are received from each participant at each time point, including EDTA blood for plasma isolation and storage; and sodium heparin blood for RSA, PBMC isolation, and plasma isolation and storage. Diluted whole blood response spectrum assays (RSA) have been conducted on all samples received to measure mycobacteria-specific T cell responses to a panel of 60 functionally diverse Mtb antigens. Data analysis is currently ongoing in collaboration with the TBRU Data Management Center. Experiments have been initiated to utilize cryopreserved PBMC samples from participants with LTBI in DeKalb County to measure Mtb-specific T cell responses by multiparameter flow cytometry. Additional experiments have been conducted to define individual Mtb epitopes eliciting T cell responses and identify immunodominant Mtb epitopes and determine how these responses change over time with treatment for LTBI. Data acquisition and analysis are ongoing.

PUBLICATIONS:

PMID	Title
29540577	A High Throughput Whole Blood Assay for Analysis of Multiple Antigen-Specific T Cell Responses in Human <i>Mycobacterium tuberculosis</i> Infection.

FUNDING SOURCES:

Redacted by agreement funded by NIAID
Redacted by agreement funded by NIAID

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE:	HOST ACUTE MODELS OF MALARIA TO STUDY EXPERIMENTAL RESILIENCE (THOR HAMMER)
SPID#:	13085
UNIT/DIVISION:	Emory Vaccine Center
TYPE:	Research
START DATE:	3/8/2016
END DATE:	7/31/2019
GENERAL CATEGORY:	Infectious Disease
SUB-CATEGORY:	Malaria
NIH GRANT:	☐ Yes ☒ No
GRANT NUMBER:	W911NF-16-C-0008
SUPPORTING ORGANIZATION:	DARPA
SPECIFIC INFORMATION:	Contract

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Emory Vaccine Center
Prin. NPRC Core Sci.		Pathology
Other Core and Affil.		Dept. Pediatrics, Emory
		Dept of Mathematics, UGA

PROJECT DESCRIPTION:

The THoR's HAMMER project (Technologies for Host Resilience: Host Acute Models of Malaria to study Experimental Resilience) is a multi disciplinary, multi-institutional, multi-investigator project along with national and international collaborators to investigate the mechanisms behind "resilience" following Plasmodium knowlesi infection of Macaca fascicularis monkeys compared to M. mulatta where severe infections ensue, and from analyses of clinical human samples from Malaysia. The project incorporates data generated across the team in malaria, immune profiling, functional genomics, proteomics, metabolomics, and pathology, with support from informatics, mathematical modeling, and computational analysis cores to evaluate key features associated with resilience. An overarching goal is to identify interventions that could enhance resilience against malaria.

PROGRESS REPORT:

We completed all agreed contract experiments, analyzed and integrated data sets, and arrived at a list of possible host-directed interventions and strategies. We are currently continuing analysis and integration of data, validation experiments, and writing a set of manuscripts and new proposals in support of continued investigation in several areas of interest.

PUBLICATIONS:

PMID	Title
30400896	Analysis of erythrocyte dynamics in Rhesus macaque monkeys during infection with Plasmodium cynomolgi.

FUNDING SOURCES:

The Defense Advanced Research Projects Agency and the U.S. Army Research Office, cooperative agreement W911NF16C0008 awarded to Redacted by agreement as the principal investigator.

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: DYNAMICS AND EVOLUTION OF RECALL IMMUNE RESPONSES TO INFLUENZA VIRUSES-YERKES PROJECT 2 (PI: ANTIA)

SPID#: 13087

UNIT/DIVISION: Emory Vaccine Center

TYPE: Research

START DATE: 4/1/2015

END DATE: 3/31/2020

GENERAL CATEGORY: Immunology

SUB-CATEGORY: Influenza

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: U19AI117891

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Biology
Prin. NPRC Core Sci.		Emory Vaccine Center
Other Core and Affil.		

PROJECT DESCRIPTION:

Affinity maturation – the progressive increase in antibody affinities – is a hallmark of humoral immunity. Somatic hypermutation generates a plethora of antibody mutants in antigen-specific B cells, including those with mutations in immunoglobulin frameworks. Survival of mutants is dependent on the functional preservation of the immunoglobulin framework as well as the increasingly fine specificity of the complementarity determining regions (CDRs) to antigen during selection.

PROGRESS REPORT:

Gene conversion (templated mutagenesis) is an evolutionarily-ancient mechanism of DNA repair. From use in fungi and yeast for maintenance of genetic stability, to the generation of somatic diversity in the adaptive immune system of vertebrates, gene conversion plays an integral role in shaping and maintaining genetic landscapes. For Agnathans (jawless vertebrates) – who possess the oldest adaptive immune system – gene conversion conducts the genetic assembly of antibody analogues, known as VLRs. Descendants of Gnathostomes (jawed vertebrates), which share a common ancestor with Agnathans ~500 million years ago, include the classes Aves (birds) and Mammalia (mammals). These two classes diverged ~310 million years ago from each other, yet they both retain widespread use of conversion during somatic diversification of antibodies. Despite the evolutionarily-conserved use of gene conversion, it has been reported that this mechanism does not contribute to antibody maturation in terminal members of Mammalia, Mus musculus and Homo sapiens.

Immunological dogma states that murine and human antibody diversification in response to antigen occurs through the process of somatic hypermutation (SHM). This process, like gene conversion, requires the master

mutator activation-induced cytidine deaminase (AID), a member of the APOBEC family which is conserved in all animals with an adaptive immune system. However, these processes fundamentally differ in that mutations generated through gene conversion are encoded in the germline, whereas those in canonical SHM are not.

In our studies, we have found that there is a significant amount of templated mutagenesis occurring at the murine and human IgH locus. By employing a rigorous statistical approach, we also demonstrate that this effect is exceedingly unlikely to occur by canonical mechanisms of somatic hypermutation. We demonstrate that templates largely come from 5' upstream donors with a lesser contribution from the trans allele. We also demonstrate that non-immunoglobulin sequences, despite their lack of apparent homology with the IgHV gene segments, acquire mutations statistically derived from the IgHV repertoire.

In sum, our work suggests that the prolific ability of the humoral immune system to respond to a wealth of antigens is in part driven by a constrained germline-encoded mechanism. This is in opposition to the current paradigm where random mutagenesis is the driving force of antibody maturation. Thus, this work reveals a surprising and important feature of general mutagenesis in the B cell and despite its roots in immunology, we believe the findings of this work may inform features of mutagenesis across disciplines.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: NOVEL DC TARGETED ADENOVIRUS VECTOR FOR MALARIA VACCINE DEVELOPMENT

SPID#: 13088

UNIT/DIVISION: Emory Vaccine Center

TYPE: Research

START DATE: 4/1/2016

END DATE: 3/31/2018

GENERAL CATEGORY: Immunology

SUB-CATEGORY: Vaccine

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R21AI117459

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Emory Vaccine Center
Prin. NPRC Core Sci.		
Other Core and Affil.		Emory Vaccine Center

PROJECT DESCRIPTION:

We have developed a vaccine strategy that combines the flexibility of adenovirus vectors with the use of chimeric recombinant proteins tailored to deliver highly immunogenic multi-stage vaccine candidates using heterologous prime-boost immunization regimens. DCs are a specialized subset of antigen-presenting cells (APCs) that express high levels of MHC class I and II proteins and are responsible for capturing, processing, and presenting antigens to naïve T cells, thereby activating the T cells. The central role of DCs in priming T cell responses provides a strong rationale for DC-targeted vaccination to enhance T cell responses. We are exploring in this project novel strategies for DC targeting to test if superior efficacy can be achieved

PROGRESS REPORT:

Generation of single domain antibodies (sdAb) ligands binding Clec9A and CD40. To develop high fidelity ligands allowing Ad vector targeting to DC we generated sdAb against Clec9A and CD40. We employed recombinant murine Clec9A (mClec9A) or mCD40 proteins to immunize alpacas in collaboration with Redacted by agreement Redacted by agreement PBMCs were used to isolate total RNA for cDNA synthesis, and a phage-display sdAb library was constructed. To detect phages displaying sdAbs, the library was first incubated with mClec9A or mCD40 proteins immobilized on ELISA plates allowing sdAb binding and the plates were washed extensively while bound phages were recovered directly by adding bacteria to the wells. The eluted phages were then amplified and used for a second panning cycle performed similarly to the first. Panning, phage recovery, and clone fingerprinting was then performed. Seven unique sdAb clones were selected against mClec9A while only three unique sdAb clones emerged against mCD40 antigen following phage panning.

These sdAbs were engineered for soluble expression, purified, and evaluated by ELISA for mClec9A or CD40 recognition. Positive sdAbs were also analyzed by flow cytometry for their DC-binding ability. The recognition of

murine DC by anti-Clec9A sdAbs was tested using mBMDC. Commercial anti-Clec9A (Miltenyi Biotech) was used as a control. The anti-Clec9A sdAbs had a more efficient binding to the cells than the commercial antibodies. Furthermore, the panel of generated sdAb against Clec9A showed a high degree of cross-reactivity with simian myeloid DC.

Gene transfer assessment of DC. Ad5 derivatives containing a chimeric fiber protein carrying anti-Clec9A sdAb or anti-CD40 sdAb ligands were successfully produced containing CMV promoter-driven eGFP reporter gene in place of the deleted E3 region. The recombinant vectors were constructed by homologous recombination in E. coli strain BJ5183 between Ad5 genomic DNA and the shuttle plasmid corresponding to fiber or E3 region. The recombinant Ad5 vectors were rescued and propagated using G28 cells, purified after infection of 293 cells by CsCl gradient centrifugation, and validated by Western blot for a fiber-fibritin-SdAb chimera. We determined the efficiency of Ad-mediated gene transfer to mouse DC by the fiber modified and unmodified vectors encoding only eGFP as a transgene using purified mBMDC for gene transfer experiments. At 48 hours, the infectivity of the Ad5-Anti-CD40-GFP vector was compared to the infectivity of the Ad5-Control-GFP vector by flow cytometry. When we assessed the percentage of GFP+ CD11b+ DCs, we found that the Ad5-Anti-CD40-GFP cells were much more efficient at infecting the DCs at the lower 500 vp dosage. These differences may allow for much lower doses of DC-targeted Ad vectors to be used in comparison with the traditional untargeted Ads.

Maturation of murine BMDCs by DC-targeted Ad vectors. We next assessed the ability of the vectors to promote maturation of the DCs. BMDCs were co-cultured for 48 hours with 500 or 5000 vp of either Ad5-Anti-CD40 or Ad5-Anti-CD1.8 and compared with the Ad5-Control vector. Flow cytometry assessment of the expression of the markers CD80, CD86, and MHC II in the infected (GFP+) CD11c+CD11b+ myeloid DC population was conducted. We observed significantly higher levels of the maturation marker CD80 in DCs that were cultured with the Ad5-Anti-CD40 vector as compared with the Ad5-Anti-DC1.8 vector at 5000 vp. Assessment of CD86 revealed higher levels of CD86 on myeloid DCs infected with the Ad5-Anti-CD40 vector as compared to the Ad5-control vector at the 500 vp dose. We also observed increased CD86 expression in the Ad5-Anti-CD40 group at the 5000 vp dose, and this difference was significantly higher than the expression induced by the Ad5-Anti-CD1.8 vector. Similarly, assessment of CD86 expression in the infected DCs following co-culture revealed that the Ad5-Anti-CD40 vector co-culture group had significantly higher levels of this molecule when compared to the Ad5 control vector at both the 500 and 5000 vp doses. Due to the role of the CD80 and CD86 molecules as essential co-stimulatory signals to T cells during antigen presentation, and the observed upregulation following infection of immature DCs with the DC-targeted Ad5-Anti-CD40 vector the results suggests that this vector may improve antigen presentation over the unmodified Ad5 vector. Consistent with this, higher levels of MHC class II molecules were induced with the Ad5-Anti-CD40 vector, a desirable feature to improve the ability of the infected DCs to present the vector transgene to T cells.

Despite the progress made during this award period, our group was not able to conduct immunogenicity studies using DC targeted vectors carrying anti-Clec9A sdAb or anti-CD40 sdAb ligands. Clec9A and CD40 targeted vectors expressing a multi-stage P. yoelii vaccine are currently being produced to test immunogenicity and efficacy using a stringent mouse model.

PUBLICATIONS:

PMID	Title
27128437	A Plasmodium Promiscuous T Cell Epitope Delivered within the Ad5 Hexon Protein Enhances the Protective Efficacy of a Protein Based Malaria Vaccine.
27708348	A chimeric protein-based malaria vaccine candidate induces robust T cell responses against Plasmodium vivax MSP1₁₉.
27574299	A Recombinant Chimeric Ad5/3 Vector Expressing a Multistage Plasmodium Antigen Induces Protective Immunity in Mice Using Heterologous Prime-Boost Immunization Regimens.
28483199	A prime-boost immunization regimen based on a simian adenovirus 36 vectored multi-stage malaria vaccine induces protective immunity in mice.
29657070	Inclusion of the murine IgGκ signal peptide increases the cellular immunogenicity of a simian adenoviral vectored Plasmodium vivax multistage vaccine.

FUNDING SOURCES:

Redacted by agreement funded by NIAID.

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: PERTURBATION OF ANTIGEN-SPECIFIC T CELL RESPONSES IN LATENT TB/SIV CO-INFECTION

SPID#: 13094

UNIT/DIVISION: Emory Vaccine Center

TYPE: Research

START DATE: 7/1/2015

END DATE: 12/31/2018

GENERAL CATEGORY: Infectious Disease

SUB-CATEGORY: Immunology

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R01AI111943

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Emory Vaccine Center
Prin. NPRC Core Sci.		
Other Core and Affil.		Emory Vaccine Center

PROJECT DESCRIPTION:

The goal of this project is to investigate how co-infection with HIV impairs the functional capacities of Mtb-specific CD4 and CD8 T cells to drive reactivation of LTBI and study how antiretroviral therapy (ART) restores these functions. Mechanistic studies require precisely determining the timing and sequence of Mtb and HIV infections, experimental verification of bacterial and viral loads and detailed study of immune responses at the site of infection by longitudinal sampling of broncheoalveolar lavage (BAL) and lung tissue, studies that are difficult to conduct in humans. The rhesus macaque NHP model of low-dose aerosol Mtb infection overcomes these limitations and recapitulates the spectrum of human lung pathological lesions, including LTBI and its reactivation to ATB by Simian Immunodeficiency Virus (SIV). In this highly collaborative dual-PI R01 application with Dr. Redacted by agreement at Tulane Primate Center, we are using state-of-the-art immunological approaches to delineate the mechanisms underlying how SIV perturbs Mtb-specific CD4 and CD8 T cell functions, as well as to provide critical new tools for pre-clinical studies in NHPs.

Aim 1. Define the nature of Mtb-specific CD4 and CD8 T cell responses associated with immune control of Mtb infection in the lungs, BAL and peripheral blood of Indian rhesus macaques with LTBI.

Aim 2. Test the hypothesis that co-infection with SIVmac239 progressively impairs Mtb-specific CD4 and CD8 T cell functions, leading to reactivation of LTBI.

Aim 3. Examine the effect of antiretroviral therapy on reconstitution of Mtb-specific CD4 and CD8 T cell responses in Mtb/SIV co-infected NHP.

PROGRESS REPORT:

We have completed experiments for the first Aim of the study and have analyzed the data. Some of our major findings are: 1. Mtb antigen specific IFN-γ and IL-17 producing T cells were higher in BAL as compared to PBMC

in animals with latent infection. 2. Mtb antigen specific activated CD4+ T cells persisted in BAL whereas they declined over time in PBMC during latent infection in rhesus macaques. 3. Mtb antigen specific cells were mostly of central memory and effector memory CD8+ T cells and were higher in BAL and PBMC compared to CD4+ T cells during latent infection. We are preparing a manuscript based on these results.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: IDENTIFYING HOST GENETIC DETERMINANTS THAT REGULATE DENDRITIC CELL ACTIVATION

SPID#: 13096

UNIT/DIVISION: Emory Vaccine Center

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: Immunology

SUB-CATEGORY: Genetic

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R21AI113485

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Emory Vaccine Center
Prin. NPRC Core Sci.		
Other Core and Affil.		Emory Vaccine Center

PROJECT DESCRIPTION:

Host genetic diversity can have a strong impact on susceptibility to viral infection and disease severity. For instance, studies with West Nile virus (WNV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), as well as other viral infections in humans, have identified causal genetic variants that influence viral replication, tissue tropism, disease severity, and infection outcome. However, narrow windows of symptoms, combined with confounding environmental factors, have made it difficult to dissect the genetic mechanisms underlying immunity, pathogenesis and infection outcome. Recent international efforts have developed a novel mouse genetic resource, called the Collaborative Cross (CC), designed to model the complexities of the human genome and support an integrative systems genetics approach to understand complex human diseases (e.g. host response to virus infection). The CC is the only mammalian resource with an infinitely reproducible population comprised of high and uniform genome wide variation. In fact, the CC is being used to study diverse medically-relevant traits, including obesity, psychiatric disorders, cancer, autoimmunity, as well as to identify risk factors of fungal, bacterial, and viral infection. At this time, little is known about how genetic diversity influences innate immune signaling in response to virus infection and vaccination. We seek to address this gap in our knowledge. We hypothesize that host genetic variation impacts innate immune sensing and antiviral responses within dendritic cells (DCs). The RIG-I like receptors (RLRs) are pattern recognition receptors that are essential for inducing type I interferon (IFN), antiviral gene expression and promoting B and T cell immunity in response to WNV and other RNA virus infections. We recently observed that WNV-infected primary mouse embryonic fibroblasts derived from the eight CC founder strains exhibited differences in kinetics and magnitude of IFN-ß induction. Through a preliminary screen to evaluate RIG-I signaling within DCs derived from a set of CC lines, we identified a hyper-responsive (AU8005 17.8 fold increased) and hypo-responsive CC line (OR3032- 9.8 fold decreased) that differentially triggered IFN-ß expression relative to C57BL/6J mice. In support of our findings, a recent analysis within human monocytes and DCs identified causal genetic variants that impact

toll-like receptor signaling and the antiviral response to influenza virus infection. To investigate our hypothesis, we will use an interdisciplinary approach involving genetics, immunology, virology, and systems biology to identify genetic variants that regulate RLR signaling and DC innate immune responses. Specifically, we will: 1) investigate the impact of genetic diversity on innate immune sensing; and 2) identify genetic variants that regulate RLR signaling in DCs. These studies will provide a greater insight into host genetics and innate immune signaling and establish a foundation for development of immune-modulatory drugs that can more efficiently activate the innate-adaptive immune interface across a wide range of genetic backgrounds.

PROGRESS REPORT:

Host genetic diversity can have a strong impact on susceptibility to viral infection and disease severity. For instance, studies with West Nile virus (WNV), hepatitis C virus (HCV), human immunodeficiency virus (HIV) as well as other viral infections in humans have identified causal genetic variants that influence viral replication, tissue tropism, disease severity, and infection outcome. However, narrow windows of symptoms, combined with confounding environmental factors, have made it difficult to dissect the genetic mechanisms underlying immunity, pathogenesis and infection outcome. At this time, little is known about how genetic diversity influences innate immune signaling in response to virus infection and vaccination. This proposal seeks to address this gap in our knowledge. We hypothesized that host genetic variation impacts innate immune sensing and antiviral responses within dendritic cells (DCs).
Aim 1: To investigate the impact of genetic diversity on innate immune sensing. In this Aim, we will utilize in vitro and in vivo approaches to identify CC lines which show extreme phenotypes in RLR signaling, perform pathway mapping and QTL mapping analysis to identify polymorphic genetic loci that influence RLR-mediated IFN-β induction in DCs.

We would like to report the results from our initial screen of 20 mouse CC lines. In this study, we received 2 batches of 10 mouse CC lines from Redacted by agreement UNC-CH (20 total lines). We generated bone marrow derived dendritic cells from each of the lines. In each study, we included 2 C57BL/6 and 2 MAVSko mouse lines (positive and negative controls). On day 8 following BM-DC generation, we magnetically purified CD11c+ cells and treated with either RIG-I agonist transfected into cells (100 ng/10^6 cells) or infected with WNV (MOI 1.0). The major findings from this study are described below:
A) RIG-I agonist treatment
To evaluate IFN-beta transcription, we harvested cells at 6 and 24 hours post-transfection. We included a time-matched mock samples for each line (each sample collected as a biological triplicate). RNA was extracted and qRT-PCR was performed for GAPDH and IFN-beta (Figure 1). At 6 hours post-transfection, we observed approximately a 64-fold difference in IFN-beta transcription between the extreme tails of the CC lines. By 24 hours post-transfection, this difference grew to over 1000 fold.
We also evaluated DC activation at 24 hours post-RIG-I agonist transfection. DC activation is measured by the cell surface upregulation of key co-stimulatory molecules. In our study, we focused on the upregulation of CD86 and CD40. Similar to the findings with IFN-beta transcription, we observed major differences in CD86 and CD40 expression following RIG-I agonist transfection. Several lines appeared to upregulate CD86 and CD40 similar to that of C57BL/6 mice, whereas other lines showed minimal expression, comparable to that of MAVSko cells. In addition, we found a few lines which showed discordance between CD86 and CD40 expression, suggesting that expression of these molecules are influenced by separate factors downstream of RIG-I signaling activation. These findings firmly demonstrate that RIG-I signaling in DCs is influenced by host genetics. We are now performing a similar analysis to the 50-60 mouse lines that have now screened.
B) WNV infection
To evaluate IFN-beta transcription, we harvested cells at 24 hours post-infection. We included a time-matched mock samples for each line (each sample collected as a biological triplicate). RNA was extracted and qRT-PCR was performed for GAPDH, IFN-beta and WNV RNA. In terms of IFN-beta transcription, at 24 hours, we observed an approximate 500 fold difference between the extreme CC lines. A few of the lines showed concordance between IFN-beta transcription and viral RNA levels. Interestingly, a few of the lines did not show a similar trend, suggesting that host genetics can impact the ability of a cell to transcribe RNA based on the levels of viral RNA (high viral RNA showed low IFN-beta transcription; low viral RNA showed high IFN-beta transcription).
Next, we evaluated virus infectivity and DC activation by flow cytometry at 24 hours post-infection. We observed a dramatic difference in percent infectivity (as measured by E protein staining), viral RNA, and DC activation across all of the mouse lines. Most intriguingly, we found that the Oas1b flavivirus resistance gene mutation did not track with the ability of WNV to infect or replicate in these cells. We are now expanding our analysis to evaluate WNV replication across the 60 CC mouse lines.

PUBLICATIONS:

PMID	Title
29514902	Dynamics of Tissue-Specific CD8⁺ T Cell Responses during West Nile Virus Infection.
29499768	Editorial overview: Viral immunology: Generating immunity to diverse viral pathogens.
28867493	Taking the defensive: Immune control of Zika virus infection.
30626670	West Nile virus-inclusive single-cell RNA sequencing reveals heterogeneity in the type I interferon response within single cells.

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: RIG-I-LIKE RECEPTOR REGULATION OF T CELL IMMUNITY AGAINST FLAVIVIRUS INFECTION

SPID#: 13100

UNIT/DIVISION: Emory Vaccine Center

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: Infectious Disease

SUB-CATEGORY: Immunology

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: U19AI083019

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Emory Vaccine Center
Prin. NPRC Core Sci.		
Other Core and Affil.		Emory Vaccine Center

PROJECT DESCRIPTION:

This is a subcontract with the University of Washington on an NIH-funded U19 (see below).
The overall objective of Project 4 (Suthar) is to understand the crosstalk between innate immune sensing and the regulation of protective T cell immune responses following flavivirus infection. Our studies are divided into three specific aims:

Aim 1. To determine the role of RLR signaling and function in regulating T cell priming
Aim 2. To define the T-cell intrinsic function of MAVS and LGP2 in regulating effector and memory T cell responses
Aim 3. To determine how MAVS and LGP2 function to regulate memory T cell recall responses.

PROGRESS REPORT:

1) We have been making strides to understand how West Nile virus and Zika virus block human dendritic cell activation through inhibiting STAT5 signaling. This study is currently under review.

2) We recently developed a WNV-inclusive single cell mRNAseq assay to simultaneously evaluate WNV infection and host response at a single cell level. Through this study, we observed that only a few cells within the bulk population displayed robust transcription of IFN-β mRNA, and this did not appear to depend on viral RNA abundance within the same cell. Furthermore, we observed considerable transcriptional heterogeneity in the IFN-I response, with genes displaying high unimodal and bimodal expression patterns. Broadly, IFN-stimulated genes negatively correlated with viral RNA abundance, corresponding with a precipitous decline in expression in cells with high viral RNA levels. Altogether, we demonstrated the feasibility and utility of WNV-inclusive scRNA-seq as a high-throughput technique for single-cell transcriptomics and WNV RNA detection. This approach can be

implemented in other models to provide insights into the cellular features of protective immunity and identify novel therapeutic targets. This study was recently published in the Journal of Virology.

3) The mouse model presents a robust system in which to study disease and neuropathogenesis and has been used to describe WNV pathogenesis in three phases: early post-inoculation, visceral-organ dissemination, and neuroinvasion. As classically described, early events in the periphery are critical for control of viral replication and priming of adaptive immunity followed by the neuroinvasive stage characterized by central nervous system (CNS) infiltration, cortical neuron infection, neuroinflammation, and neuronal cell death. As central features of the neuro-immune axis, meningeal lymphatic vessels drain to the superficial and deep cervical lymph nodes (scLNs and dcLNs, respectively); however, an in-depth examination of viral RNA abundance and the immune responses within these compartments is notably lacking. We have been working to understand the kinetics of virus replication, infection of cells and subsequent immune response within the brain and the meningeal lymphatic system during WNV infection. We plan to submit a manuscript of this work over the next 6 months.

4) We have recently found that MAVS, the central adaptor for RIG-I like receptor (RLR) signaling plays an important role in promoting antigen-specific CD8+ T cell responses during WNV infection. In the absence of MAVS, we have observed reduced CD8+ T cell accumulation, poor cytokine secretion that corresponds with a lack of viral control within the periphery and brain during WNV infection. Mechanistically, we have found that MAVS functions to maintain mitochondrial homeostasis within CD8+ T cells. In the absence of MAVS, TCR activation leads to increased production of reactive oxygen species, lipid peroxidation and an increase in CD95 expression. Interestingly, we also observed that both ZAP70 and dLck, two important components of TCR signaling, displayed slower kinetics of activation in the absence of MAVS. This suggests that MAVS directly influences mitochondrial dynamics and TCR signaling within antigen-specific CD8+ T cells. We plan to submit a manuscript of this work over the next 3 months.

5) Previous studies have found that inflammasome signaling components, namely NLRP3, ASC, Caspase-1, are critical for promoting protective immunity during WNV infection in mice. However, the cell-specific roles of these inflammasome molecules are not well understood. Generation of effective antiviral CD8+ T cell responses are essential for limiting WNV replication, reducing pathology and protecting against lethal WNV infection. Control of CD8+ T cell functions are tightly regulated by a large signaling network, however the crosstalk between the inflammasome signaling pathway and CD8+ T cell function is largely unexplored. Here we investigate the role of the capsase-1 signaling network in antigen-specific CD8+ T cells during WNV infection. Following T cell-receptor stimulation of naïve CD8+ T cells, we observed rapid upregulation of active caspase-1 that persisted through 72 hours post-stimulation. Similarly, we found that active caspase-1 is induced in antigen-specific CD8+ T cells during WNV infection. In the absence of caspase-1 within CD8+ T cells, we observed reduced accumulation, dysregulated T cell differentiation and impaired cytokine production, demonstrating that caspase-1 directly controls CD8+ T cell function during virus infection. Mechanistically, we next found that CD3, but not CD28 stimulation, triggers active caspase-1 and this was dependent on p38 MAPK signaling. Our findings identify a novel, non-canonical CD8+ T cell intrinsic role for caspase-1 during viral infection.

PUBLICATIONS:

PMID	Title
30626670	West Nile virus-inclusive single-cell RNA sequencing reveals heterogeneity in the type I interferon response within single cells.
30439342	Cross-Reactive Dengue Virus Antibodies Augment Zika Virus Infection of Human Placental Macrophages.
28867493	Taking the defensive: Immune control of Zika virus infection.
29514902	Dynamics of Tissue-Specific CD8⁺ T Cell Responses during West Nile Virus Infection.
29499768	Editorial overview: Viral immunology: Generating immunity to diverse viral pathogens.

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: 0000021335 BURROUGHS WELLCOME FUND

SPID#: 13101

UNIT/DIVISION: Emory Vaccine Center

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: Infectious Disease

SUB-CATEGORY: Therapy

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER: Private Source

SUPPORTING ORGANIZATION:

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Emory Vaccine Center
Prin. NPRC Core Sci.		
Other Core and Affil.		

PROJECT DESCRIPTION:

Bacterial pathogens are a major cause of morbidity and mortality worldwide, and antibiotic-resistant bacteria threaten to send us back to the pre-antibiotic era. In order to cause disease, bacterial pathogens must rapidly adapt to the host environment and counteract immune defenses so they can survive and replicate. We have identified a novel regulatory system that is induced during infection of host cells by the intracellular pathogen Francisella novicida. The CRISPR (Clustered Regularly Interspaced Palindromic Repeats)-CAS (CRISPR-associated) system is a recently described bacterial defense against invading foreign DNA derived from bacteriophages or plasmids. It has been unclear if these systems have additional functions in bacterial physiology. We demonstrate a novel RNAi-like function of this system in targeting an endogenous mRNA, regulating the expression of a bacterial lipoprotein (BLP). We now propose to further elucidate critical mechanistic details of how Cas9 mediates degradation of endogenous mRNA. In addition, we will study the conditions in which the Cas9 regulatory system is induced during infection, and test its role in the virulence of the antibiotic-resistant pathogens Staphylococcus aureus and Enterococcus faecalis. This work will lead to a deeper understanding of host-pathogen interactions, and will also be applied for research and translational purposes. We will determine whether we can "program" this system to target the degradation of any endogenous bacterial mRNA, thus creating a bacterial RNAi-like knockdown system with numerous research and biotechnological applications. We will also further determine the potential of Cas9 system mutants to serve as attenuated vaccine strains, potentially providing a novel means by which to combat pathogenic bacteria including antibiotic-resistant strains

PROGRESS REPORT:

Cas9 has been expressed exogenously in eukaryotic cells and exploited to generate knockout cells, relying on its ability to site specifically introduce double strand breaks in DNA. This has led to a biotechnological revolution. Given our previous findings that Cas9 can target RNA in addition to DNA, we have explored whether Cas9 can be programmed to target specific RNAs in eukaryotic cells, which could represent a novel form of RNA silencing

with broad potential applications.

One potential application of the Cas9 machinery in targeting RNAs in eukaryotic cells would be to repress viral RNA. Some viruses inhibit RNA interference pathways, and the Cas9 system could represent an alternative approach to circumvent viral evasion. Working in collaboration with Redacted by agreement (Emory Vaccine Center, expert in hepatitis C virus; HCV), we tested whether Cas9 could be used to repress HCV genomic RNA and viral protein production.

Cas9 functions with small RNAs that determine the specificity of the nucleic acids to be targeted. We expressed Francisella novicida Cas9 (FnCas9) along with one such “RNA-targeting guide RNA” or “rgRNA” in eukaryotic cells. The rgRNA was designed with a sequence complementary to that of the HCV 5’ UTR (untranslated region) or 3’ UTR, or a control with a non-specific sequence. As shown in Figure 1, we observed significant repression of viral protein production (as measured by staining for the viral E2 protein) in cells expressing FnCas9 as well as either the rgRNA targeting the 5’ or 3’ UTR. The combination of FnCas9 and the non-specific, control rgRNA did not result in repression of viral E2 protein production. Importantly, the DNA targeting activity of Cas9 proteins was not a confounding factor since HCV is an RNA virus, and does not have a DNA stage. In addition, we targeted FnCas9 to the host cell cytosol, where it would not be in contact with DNA. Targeting of FnCas9 to the cytosol was required for inhibition of HCV protein production, and localization of FnCas9 to the nucleus abrogated this activity (data not shown).

In addition, we assayed for production of a virally-encoded luciferase protein. We observed similar results to those demonstrating inhibition of E2 protein. Viral luciferase was repressed in cells expressing FnCas9 as well as either the rgRNA targeting the 5’ or 3’ UTR (Figure 2). The combination of FnCas9 and the non-specific, control rgRNA did not result in repression of viral E2 protein production (Figure 2).

Taken together, these data demonstrated that the FnCas9 system can be reprogrammed in eukaryotic cells to target RNA. These exciting findings open the possibility to using the FnCas9 machinery as a novel means of RNA silencing, with very broad potential applications.

Intriguingly, we found that orthologous Cas9 proteins from diverse Type II CRISPR-Cas families, including Streptococcus pyogenes, S. thermophilus, and Neisseria meningitidis, are also capable of inhibiting HCV during cellular infection (Figure 3). This suggests a broader capability of diverse Cas9 proteins to target and associate with RNAs of interest.

Since the lifecycles of viruses with both RNA and DNA genomes require an RNA stage (generated during transcription, replication, or both), and FnCas9 can target both negative- and positive-sense strands of RNA (Figure 4), it is likely that the FnCas9:rgRNA machinery can be utilized to target diverse viruses, including both +ssRNA viruses (such as flavivirus, poliovirus, and rhinovirus) and –ssRNA virus (such as filovirus, paramyxovirus and orthomyxovirus). Furthermore, some eukaryotic viruses have mechanisms to circumvent eukaryotic RNA-targeting antiviral defenses, such as classical RNAi systems; however, these viruses have not evolved in the presence of Cas9, so it is unlikely that they have Cas9 evasion strategies. Thus, the FnCas9:rgRNA machinery could facilitate the targeting of viruses as soon as their genome sequences are available, without knowledge of the virus lifecycle or host receptors.

Given the vast success of Cas9 as a mediator of genome engineering in a multitude of species, our data suggest that FnCas9 could be used in a broad range of systems, representing a new paradigm in Cas9-mediated genetic engineering. This work demonstrates a portable, inter-domain machinery capable of viral inhibition, likely just one of myriad potential biotechnological and medical applications of Cas9-mediated RNA targeting.

PUBLICATIONS:

PMID	Title
30297362	Role of Capsule in Resistance to Disinfectants, Host Antimicrobials, and Desiccation in Acinetobacter baumannii.
30111627	Aminoglycoside Heteroresistance in Acinetobacter baumannii AB5075.
30092194	Bacterial Prison Break: A Host Protein Mimic Paves the Way.
29454797	Alterations in Intestinal Microbiota Lead to Production of Interleukin 17 by Intrahepatic γδ T-Cell Receptor-Positive Cells and Pathogenesis of Cholestatic Liver Disease.

PMID	Title
29693659	A high-frequency phenotypic switch links bacterial virulence and environmental survival in Acinetobacter baumannii.
29511071	Carbapenem-Resistant <i>Klebsiella pneumoniae</i> Exhibiting Clinically Undetected Colistin Heteroresistance Leads to Treatment Failure in a Murine Model of Infection.
29030138	Peculiar purulence: Hypervirulent Klebsiella pneumoniae causing pyomyositis.
27934695	Overview of CRISPR-Cas9 Biology.
27788983	MCR-1 confers cross-resistance to lysozyme.
27572838	Antibiotic failure mediated by a resistant subpopulation in Enterobacter cloacae.
26852268	Harnessing the Prokaryotic Adaptive Immune System as a Eukaryotic Antiviral Defense.
26459891	A PmrB-Regulated Deacetylase Required for Lipid A Modification and Polymyxin Resistance in Acinetobacter baumannii.
25723882	Disseminated emm Type 12 Group A Streptococcus and Review of Invasive Disease.
26060274	The Atypical Occurrence of Two Biotin Protein Ligases in Francisella novicida Is Due to Distinct Roles in Virulence and Biotin Metabolism.
25887612	I can see CRISPR now, even when phage are gone: a view on alternative CRISPR-Cas functions from the prokaryotic envelope.
25918406	Cas9-mediated targeting of viral RNA in eukaryotic cells.
25822986	Low doses of imatinib induce myelopoiesis and enhance host anti-microbial immunity.
25927010	Mechanisms of Antimicrobial Peptide Resistance in Gram-Negative Bacteria.
24982068	Colistin heteroresistance in Enterobacter cloacae is associated with cross-resistance to the host antimicrobial lysozyme.
25024199	A CRISPR-Cas system enhances envelope integrity mediating antibiotic resistance and inflammasome evasion.
24583361	Induction of human plasmablasts during infection with antibiotic-resistant nosocomial bacteria.
24772391	CRISPR-Cas systems: new players in gene regulation and bacterial physiology.
24310610	Vaccine activation of the nutrient sensor GCN2 in dendritic cells enhances antigen presentation.
24323919	Exploiting CRISPR/Cas systems for biotechnology.
24313380	A Francisella virulence factor catalyses an essential reaction of biotin synthesis.

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: CRISPR/CAS SYSTEMS IN BACTERIAL GENE REGULATION AND VIRULENCE

SPID#: 13102

UNIT/DIVISION: Emory Vaccine Center

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: Infectious Disease

SUB-CATEGORY: Therapy

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER: Private Source

SUPPORTING ORGANIZATION: NIAID

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Emory Vaccine Center
Prin. NPRC Core Sci.		
Other Core and Affil.		

PROJECT DESCRIPTION:

CRISPR-Cas systems have recently been described to mediate bacterial defense against invading foreign nucleic acid derived from bacteriophages or plasmids, which they target for degradation. These systems have not previously been shown to target mRNA or control endogenous gene expression. We demonstrate that the CRISPR-Cas protein Cas9 targets an endogenous mRNA, revealing a novel bacterial RNA silencing machinery and genetic regulatory paradigm. Since Cas9 targeting of a BLP mRNA in F. novicida is the only currently known example of CRISPR-Cas-mediated endogenous gene regulation, we will employ this model to answer fundamental questions about the mechanism of action of this system, as well as the parameters controlling its induction. This will lead to the elucidation of basic foundational principles governing Cas9 and CRISPR-Cas biology. The proposed research will have a sustained and powerful impact on our understanding of Cas9, CRISPR-Cas systems, RNA silencing, genetic regulatory mechanisms, bacterial virulence, and innate immune evasion, and lay the framework for a much broader knowledge of how diverse bacterial pathogens cause disease.

PROGRESS REPORT:

Our insights thus far into the requirements for Cas9 targeting of RNA, as well as the worldwide success of using Cas9 in genome engineering targeting DNA in eukaryotic cells, led us to hypothesize that Cas9 might be capable of targeting RNA when exogenously expressed in eukaryotic cells. Indeed, when expressed with a guide RNA (gRNA), Cas9 could target RNA in human cells. Specifically, we used Cas9 to target the genome of the RNA virus, hepatitis C virus (HCV). By targeting an RNA virus that has no DNA stage in its lifecycle, we were certain that Cas9-mediated targeting of DNA was not a confounding factor in these experiments. Cas9 targeting of HCV

RNA led to a significant inhibition of viral protein production (4). A similar effect was observed by targeting two distinct sequences on the viral genome. We demonstrated that Cas9 interacts with its gRNA within human cells, and that a mutant Cas9 protein that is deficient for RNA binding, is also deficient in viral inhibition. Importantly, distinct Cas9 mutants lacking endonuclease activity were fully functional in inhibiting viral protein production, indicating that Cas9 did not have to degrade the RNA target to mediate its effect. Subsequent in vitro translation experiments revealed that Cas9 targeting of RNA was sufficient to cause a block in translation. Furthermore, the inhibition of viral protein production required expression of Cas9 in the host cell cytosol, and did not require a PAM (proto-spacer adjacent motif), as is necessary when Cas9 targets DNA. Cas9 was also capable of being programmed to target both negative- and positive-sense strands of RNA. Intriguingly, we found that orthologous Cas9 proteins from diverse Type II CRISPR-Cas families, including Streptococcus pyogenes, S. thermophilus, and Neisseria meningitidis, were also capable of inhibiting HCV protein production during cellular infection. This suggests a broader capability of diverse Cas9 proteins to target and associate with RNAs of interest.

Cas9-mediated targeting of RNA in eukaryotic cells represents a new paradigm in Cas9 genome engineering, and highlights a novel tool that could be widely used to target RNAs of interest. As far as viral targeting, this is likely a broadly useful tool, beyond HCV. Since the lifecycles of viruses with both RNA and DNA genomes require an RNA stage (generated during transcription, replication, or both), and we found that FnCas9 can target both negative- and positive-sense strands of RNA, it is likely that the Cas9:gRNA machinery can be utilized to target diverse viruses, including both +ssRNA viruses (such as flavivirus, poliovirus, and rhinovirus) and -ssRNA virus (such as filovirus, paramyxovirus and orthomyxovirus). Furthermore, some eukaryotic viruses have mechanisms to circumvent eukaryotic RNA-targeting antiviral defenses, such as classical RNAi systems; however, these viruses have not evolved in the presence of Cas9, so it is unlikely that they have Cas9 evasion strategies. Thus, the Cas9:rgRNA machinery could facilitate the targeting of viruses as soon as their genome sequences are available, without knowledge of the virus lifecycle or host receptors. In addition to targeting of viral RNAs, these data also suggest the possibility of using Cas9 to target host RNAs of interest.

PUBLICATIONS:

PMID	Title
25024199	A CRISPR-Cas system enhances envelope integrity mediating antibiotic resistance and inflammasome evasion.
24772391	CRISPR-Cas systems: new players in gene regulation and bacterial physiology.
24146613	Alternative roles for CRISPR/Cas systems in bacterial pathogenesis.
24323919	Exploiting CRISPR/Cas systems for biotechnology.
25887612	I can see CRISPR now, even when phage are gone: a view on alternative CRISPR-Cas functions from the prokaryotic envelope.
25918406	Cas9-mediated targeting of viral RNA in eukaryotic cells.
26852268	Harnessing the Prokaryotic Adaptive Immune System as a Eukaryotic Antiviral Defense.
27934695	Overview of CRISPR-Cas9 Biology.

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: ARMR: A NOVEL DRUG TARGET AND MEDIATOR OF ANTIBIOTIC RESISTANCE

SPID#: 13103

UNIT/DIVISION: Emory Vaccine Center

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: Infectious Disease

SUB-CATEGORY: Therapy

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER: R33AI098800

SUPPORTING ORGANIZATION: NIAID

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Emory Vaccine Center
Prin. NPRC Core Sci.		
Other Core and Affil.		

PROJECT DESCRIPTION:

Drug resistant Gram-negative bacterial pathogens are an increasing cause of hospital-acquired infections, mortality, and a huge burden on healthcare costs. Acinetobacter baumannii is a major cause of such infections and strains have recently emerged which are resistant even to the last line of defense drugs, polymyxin B and colistin (polymyxin E), which target and disrupt the lipid A portion of lipopolysaccharide (LPS) in the outer membrane.

PROGRESS REPORT:

Virtual Screening
Our most potent in silico hit (#31) had selective activity against colistin resistant cells. The best scoring docking pose of hit #31 suggested a mechanism-specific pharmacophore that could be tested pharmacologically. Accordingly, we used 2D similarity searching, 3D pharmacophore mapping, and docking, to develop focused libraries of vendor compounds for experimental verification/validation of in silico predicted structure activity relations (SAR). The MCULE collection of ~4.5 million commercially available compounds was reduced to <1,000 ranked most interesting by 2D or 3D similarity to our interaction pharmacophore. The most potent hit from the HTS (below) had striking similarity to hit #31, but with even greater activity. These results provide further confidence for pursuing the hit #31 family, as this compound class was independently identified by two screening approaches.

High-throughput Screening (HTS)
A library of 138,000 compounds was initially screened and ~600 compounds, with >50% inhibition, were retested to determine IC50 and colistin selectivity. SAR evaluation of the 600 revealed two potent compounds that both demonstrated the combination of strong activity and specificity (colistin synergy) but with dissimilar chemical

structures; compound #50 with similarity to hit #31 from the in silico screen (IC50 = 680 nM), and compound #44 from a different compound class (IC50 = 840 nM). Both of the hit classes were used to select close analogs for SAR with results presented below (Figure 1). Each set represents close chemical analogs of a single chemotype and suggest a highly selective site of activity.

The hit #31 structure was modified and numerous alterations that abrogated activity were identified. This highlights residues that are essential for ArmR inhibitory activity. We determined the IC50 of hit #31 to be 180 nM, well within the range of compounds that have been developed into viable therapeutics. Furthermore, hit #31 had no activity against a strain of A. baumannii genetically engineered to lack ArmR, indicating that ArmR is the major, if not the only, target within the cells.

The colistin minimum inhibitory concentration (MIC) for our screening strain was measured to be 24 ug/ml. With the addition of hit #31, the MIC was reduced to 2 ug/ml, which is considered to represent bacterial susceptibility to colistin and indicates that the antibiotic will be effective against such a strain ~90% of the time. Therefore, hit #31 effectively reversed the colistin resistance of our screening strain.

Since ArmR is required for the modification of the lipid A portion of LPS with cationic sugars, we tested for the presence of absence of these sugars after treatment with hit #31. Consistent with its inhibitory activity, cationic lipid A modifications were absent when our screening strain was treated with hit #31, explaining the molecular basis for the ability of hit #31 to re-sensitize the strain to colistin.

Furthermore, hit #31 was tested for toxicity against human cells, using HEK293 cells as a model. Toxicity was not observed below a concentration of 20 uM, which is 100-fold higher than the IC50. This represents a large therapeutic window consistent with that observed for other inhibitors that have reached the clinic.

In addition, we tested the efficacy of hit #31 in reversing colistin resistance of a panel of A. baumannii clinical isolates with a range of MICs. Hit #31 reversed colistin resistance of 7 out of 8 isolates tested, including the one with the highest colistin MIC of 128 ug/ml. The MIC of this isolate was reduced to 2 ug/ml in the presence of hit #31, indicating a 64-fold reduction in MIC. Based on these findings, we conclude that hit #31 has robust activity against diverse clinical isolates of A. baumannii, and may be a critical component of our future arsenal to combat increasingly frequent colistin resistant strains.

PUBLICATIONS:

PMID	Title
24982068	Colistin heteroresistance in Enterobacter cloacae is associated with cross-resistance to the host antimicrobial lysozyme.
23695834	Clinical use of colistin induces cross-resistance to host antimicrobials in Acinetobacter baumannii.
22908157	Rapid killing of Acinetobacter baumannii by polymyxins is mediated by a hydroxyl radical death pathway.
25927010	Mechanisms of Antimicrobial Peptide Resistance in Gram-Negative Bacteria.
26459891	A PmrB-Regulated Deacetylase Required for Lipid A Modification and Polymyxin Resistance in Acinetobacter baumannii.
29693659	A high-frequency phenotypic switch links bacterial virulence and environmental survival in Acinetobacter baumannii.
30111627	Aminoglycoside Heteroresistance in Acinetobacter baumannii AB5075.

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE:	MATERNAL STRESS AND OBESITY, MILK IMMUNOBIOLOGY, INFANT GROWTH
SPID#:	13106
UNIT/DIVISION:	Animal Resources
TYPE:	Research
START DATE:	4/15/2014
END DATE:	12/31/2017
GENERAL CATEGORY:	Reproductive
SUB-CATEGORY:	Development
NIH GRANT:	☒ Yes ☐ No
GRANT NUMBER:	R21HD079969
SUPPORTING ORGANIZATION:	NIH
SPECIFIC INFORMATION:	

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Developmental and Cognitive Neuroscience / Animal Resources
Prin. NPRC Core Sci.		Developmental and Cognitive Neuroscience
Other Core and Affil.		

PROJECT DESCRIPTION:

Evidence from human and animal studies show that chronic stress exposure and obesity synergize to elevate circulating stress and pro-inflammatory signals. What is less clear and particularly important for nursing mothers, however, is whether these signals translate to milk and affect infant development. Human milk contains many hormonal and immunological signals including cytokines, adipokines, immunoglobulins (Ig), and growth factors that mediate infant health and development; however, it is not known whether and to what extent maternal stress and obesity may alter these and produce adverse growth trajectories for infants. To disentangle prepartum maternal stress from postpartum stress, fourty-three newborns were either cross-fostered to mothers of the same or different ranks or raised by their biological mothers. In addition, half of the mother-infant dyads were maintained on a low calorie diet through lactation while the other half were switched to a rich dietary condition. Aim 1 tested the hypothesis that chronic social stress and adiposity will synergize to increase stress and inflammatory signals in milk. This aim was accomplished by measuring cortisol, cytokine and adipokine markers in milk and serum from lactating rhesus monkeys of different social rank (dominant vs. subordinate) and postpartum diet exposure (high calorie vs. low calorie). Aim 2 tested the hypothesis that chronic social stress and adiposity will interact to decrease immune defense components in milk. Milk levels of sIgA in lactating dams were evaluated in parallel with stress and inflammatory markers studied in Aim 1. Finally, Aim 3 determined the contribution of milk signals studied in aims 1 and 2 to infant growth and health trajectories. Specifically, Aim 3 tested the hypothesis that pro-inflammatory cytokines and adipokines significantly predict infant growth in addition to milk energy in a rich dietary environment.

PROGRESS REPORT:

The final assays for the remaining milk hormonal and immunological markers as well as longitudinal measurements of milk macronutrient proximates are complete. Data analyses and manuscript preparation are

currently underway. It is anticipated that at least two manuscripts will be submitted for publication related to this project within the next 3-6 months.

This project employed significant Yerkes resources, including rhesus macaques and procedure rooms.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Redacted by agreement funded by NIH/NICHD (R21 HD 079969)

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: AUTOMATED FEEDERS, CLINICAL MONITORING, BREEDING RHESUS MACAQUES

SPID#: 13107

UNIT/DIVISION: Animal Resources

TYPE: Research

START DATE: 7/31/2016

END DATE: 7/31/2021

GENERAL CATEGORY: Animal

SUB-CATEGORY: Device

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER:

SUPPORTING ORGANIZATION: Yerkes NPRC

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Animal Resources / Vet Med
Prin. NPRC Core Sci.		
Other Core and Affil.		Animal Resources / Vet Med

PROJECT DESCRIPTION:

In 2015, thirty-two commercially-available automated feeding stations were successfully deployed in 8 outdoor compounds at the Yerkes National Primate Research Center (YNPRC) Field Station, housing a large portion of the rhesus macaque breeding colony. This project seeks to determine whether feeding data generated by computer-controlled automated feeding stations can be used to enhance the clinical monitoring and social stability of rhesus macaques living in large outdoor breeding groups. As animals obtain food pellets, the computer-controlled system records grams obtained in real-time by detecting RFID microchips implanted subcutaneously in each wrist of individual animals. The primary outcomes of this study include: 1) quantification of daily caloric intake according to sex, gender, and reproductive stage; 2) the association of various clinical conditions (e.g. trauma, diarrhea, retained placentas) with a significant reduction in caloric intake; 3) the association of select breeding and social behaviors with changes in caloric intake. This project employed significant Yerkes resources, including colony management staff, animal care staff, veterinary staff, and rhesus macaques.

PROGRESS REPORT:

Data collection for this project was recently completed and analyzed. In the past year, findings were presented at national meetings, including the American Association of Laboratory Animal Science 69th National Meeting, the Association of Primate Veterinarians 46th Workshop, and the 2018 Yerkes Research Symposium. A manuscript is currently under review in a peer-reviewed journal. At least two other manuscripts are expected in the next 12-18 months. This project is part of the veterinary resident training program in the Division of Animal Resources. This project is used to teach veterinary trainees how to summarize and analyze data using excel and select statistical programs.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

None

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: CHRONIC STRESS, ANTI-TETANUS IMMUNOGENICITY, FEMALE RHESUS MACAQUES

SPID#: 13108

UNIT/DIVISION: Animal Resources

TYPE: Research

START DATE: 7/1/2015

END DATE: 6/30/2018

GENERAL CATEGORY: Immunology

SUB-CATEGORY: Vaccine

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER:

SUPPORTING ORGANIZATION: Yerkes NPRC

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Animal Resources / Vet Med
Prin. NPRC Core Sci.		
Other Core and Affil.		Animal Resources / Vet Med

PROJECT DESCRIPTION:

This project sought to evaluate how chronic stress may negatively affect anti-tetanus immunity among breeding female rhesus macaques (Macaca mulatta) and their offspring. Using rhesus macaques in large breeding troops at Yerkes National Primate Research Center (NPRC) Field Station, the aim of this project was to determine whether and to what extent social subordination impairs the durability and prenatal transfer of anti-tetanus immunity in breeding female rhesus macaques.

PROGRESS REPORT:

This study is completed and results have been published in the Journal of the American Association for the Laboratory Animal Science (July 2018). Findings from this study have also been presented at several national conferences and local seminars in the past 24 months, including the American Association of Laboratory Animal Science 68th National Meeting, the Association of Primate Veterinarians 45th Workshop, the 2017 Yerkes Research Symposium, and in the 2017 Yerkes Comparative Medicine Seminar series.

This project employed significant Yerkes resources, including colony management staff, veterinary staff, and rhesus macaques.

PUBLICATIONS:

PMID	Title
29764539	Effect of Chronic Social Stress on Prenatal Transfer of Antitetanus Immunity in Captive Breeding Rhesus Macaques (<i>Macaca mulatta</i>).

FUNDING SOURCES:

Redacted by agreement supported by departmental funds.

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: CENTRAL MEMORY CD4 T CELL INFECTION: KEY ROLE IN ART RESPONSE AND HIV PERSISTENCE

SPID#: 13112

UNIT/DIVISION: Microbiology Immunology

TYPE: Research

START DATE: 9/20/2013

END DATE: 8/31/2019

GENERAL CATEGORY: AIDS

SUB-CATEGORY: Immunology

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R01AI110334

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Microbiology Immunology
Prin. NPRC Core Sci.		Microbiology Immunology
Other Core and Affil.		Infectious Disease

PROJECT DESCRIPTION:

A major obstacle to cure HIV infection is our incomplete understanding of what factors regulate the immunologic response to antiretroviral therapy (ART) and the persistence of the latent HIV reservoir. Although it is well established that HIV preferentially infect memory CD4 T cells, it is still unclear to what extent the relative distribution of HIV infection within the various CD4 T cell subsets influences: (i) the magnitude of CD4 T cell reconstitution, (ii) the extent of residual activation and (iii) the size of the persistent HIV reservoir during ART. Recent evidence generated in nonhuman primate models of HIV infection implicates the infection of CD4 T central memory (TCM) as a key factor determining the outcome of infection. In the pathogenic SIV-infection of rhesus macaques, the levels of infection of CD4 TCM dictate the tempo of progression to AIDS, and the preservation of CD4 TCM in vaccinated animals associates with resistance to SIV infection. Furthermore, in nonpathogenic SIV infection of sooty mangabeys, low level of CD4 TCM infection is a key mechanism of AIDS resistance. Based on these findings, we propose that the pattern of infected CD4 T cells is more important than the overall level of virus replication and the total number of infected cells in dictating the magnitude of CD4 T cell reconstitution and the size of the virus reservoir during ART. Here, we will test the hypotheses that, in blood and lymph nodes, CD4 TCM infection (i) critically contributes to the extent of immunologic restoration and residual immune activation and (ii) is a prognostic factor for both the size and stability of the HIV reservoir following ART. If our hypothesis is confirmed, these studies will suggest that novel strategies aimed at protecting CD4 TCM from infection should be a critical component of interventions aimed at curing HIV infection

PROGRESS REPORT:

We completed all the proposed analyses, including: (i) the recruitment to additional participants for fresh blood and LN biopsy collections; (ii) sorting of highly purified CD4 T cell subsets from blood and LN; (iii) quantification

of cell-associated and integrated HIV from blood and LN purified CD4 T cell subsets; (iv) immunophenotyping of blood and LN derived cells; (v) determining the main signaling pathways regulating susceptibility to HIV infection and cell survival in the different CD4 T cell subsets. Specifically, to determined if differential infection of CD4 T-cell subsets contributes to divergent CD4 recovery and maintenance of the reservoir during ART, the frequency of cells harboring HIV-DNA was measured in naïve (N), central-memory (CM), transitional-memory (TM), and effector-memory (EM) CD4 T-cells from blood and LN of virologically suppressed immunologic responders (IR; CD4 counts >500 cells/μL <2 years on-ART) and non-responders (INR; CD4 counts <500 cells/μL >2 years on-ART). When compared to IR, INR demonstrated higher levels of total and integrated HIV-DNA in all memory CD4 T-cell subsets, both prior to and on-ART. Remarkably, HIV-DNA levels were significantly more stable during ART in CM and TM, but not in N or EM CD4 T-cells of INR as compared to IR. Furthermore, INR showed higher expression of co-inhibitory receptors previously associated with HIV persistence (PD-1 and TIGIT) exclusively on CM and TM CD4 T-cells pre-ART. The frequency of CM CD4 T-cells expressing PD-1 or TIGIT pre-ART predicted HIV-DNA content on-ART among all patients. These data link infection and expression of PD-1 and TIGIT in long-lived CD4 T-cell subsets prior to ART with CD4 recovery and HIV persistence on-ART, and highlight protection of CM and TM CD4 T-cell infection as a strategy to limit residual disease.

PUBLICATIONS:

PMID	Title
30585798	Role of cytokine agonists and immune checkpoint inhibitors toward HIV remission.
30305357	Bone Marrow-Derived CD4⁺ T Cells Are Depleted in Simian Immunodeficiency Virus-Infected Macaques and Contribute to the Size of the Replication-Competent Reservoir.
29987877	Systemic DPP4 activity is reduced during primary HIV-1 infection and is associated with intestinal RORC⁺ CD4⁺ cell levels: a surrogate marker candidate of HIV-induced intestinal damage.
29889662	Progress in achieving long-term HIV remission.
29669853	CD32 is expressed on cells with transcriptionally active HIV but does not enrich for HIV DNA in resting T cells.
29045906	CTLA-4<sup>+</sup&gtPD-1⁻ Memory CD4⁺ T Cells Critically Contribute to Viral Persistence in Antiretroviral Therapy-Suppressed, SIV-Infected Rhesus Macaques.
27387885	Follicular T helper cells: hotspots for HIV-1 persistence.
25167059	Limited HIV infection of central memory and stem cell memory CD4+ T cells is associated with lack of progression in viremic individuals.

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: IMMUNE BASED INTERVENTIONS FOR HIV ERADICATION

SPID#: 13113

UNIT/DIVISION: Microbiology Immunology

TYPE: Research

START DATE: 2/6/2015

END DATE: 1/31/2020

GENERAL CATEGORY: AIDS

SUB-CATEGORY: Immunology

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R01AI116379

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Microbiology Immunology
Prin. NPRC Core Sci.		
Other Core and Affil.		

PROJECT DESCRIPTION:

We previously showed that supplementation of ART with IL-21, an immunomodulatory cytokine with anti-inflammatory properties, reduced immune activation and SIV persistence in the highly translational model of SIV-infected Rhesus Macaques (RMs). Despite the beneficial effects of IL-21 on reduction of inflammation and viral persistence during ART, latent sources of viral burden persist and virus replication rebound after structured treatment interruption (STI), thus suggesting that more efficient anti-viral responses are required to control viral rebound even in the context of reduced inflammation and size of the persistent viral reservoir. Therefore, we now propose to tackle ineffective antiviral response by addition of IFN, a potent antiviral molecule, in a novel combination therapy in the context of IL-21 supplemented ART. We hypothesize that supplementation of ART therapy with a combined IL-21 and IFN regimen will reduce inflammation, reinvigorate antiviral immunity and lessen persistent viral burden

PROGRESS REPORT:

During the fourth year of this project, we have completed the assays and analyses concerning the SIV reservoir content in tissues, IFN□-mediated enhancement of immune function, and virological rebound following the anti-retroviral therapy interruption (ATI). Specifically, during ART the viral reservoir content was quantified by a quantitative viral outgrowth assay (qVOA) using purified CD4+ cells from lymph node (LN) and cell-associated SIV-RNA/DNA was quantified by qRT-PCR in cryopreserved peripheral blood mononuclear cells (PBMC). Furthermore, the modulation of antiviral responses by rhesusized (rh)-IFN□ during suppressive ART were accessed in PBMCs by ELISpots against SIV-Gag and –Env. Following ATI, treated RMs either continued treatment with rh-IFN□ (n=6) or switched to human pegylated (peg)-IFN□ (n=8) and responsiveness was monitored by RNA-seq per the stimulation of interferon stimulated genes (ISGs); whereas, the viral burden was quantified with plasma viral loads and cell-associated SIV-DNA/RNA in PBMCs. A manuscript covering the performed work is currently in preparation.

PUBLICATIONS:

PMID	Title
30305357	Bone Marrow-Derived CD4⁺ T Cells Are Depleted in Simian Immunodeficiency Virus-Infected Macaques and Contribute to the Size of the Replication-Competent Reservoir.
30262807	Hallmarks of primate lentiviral immunodeficiency infection recapitulate loss of innate lymphoid cells.
29987877	Systemic DPP4 activity is reduced during primary HIV-1 infection and is associated with intestinal RORC⁺ CD4⁺ cell levels: a surrogate marker candidate of HIV-induced intestinal damage.
29045906	CTLA-4⁺PD-1⁻ Memory CD4⁺ T Cells Critically Contribute to Viral Persistence in Antiretroviral Therapy-Suppressed, SIV-Infected Rhesus Macaques.
28051083	The loss of CCR6⁺ and CD161⁺ CD4⁺ T-cell homeostasis contributes to disease progression in SIV-infected rhesus macaques.
26551680	Interleukin-21 combined with ART reduces inflammation and viral reservoir in SIV-infected macaques.

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE:	TARGETING CYTOLYTIC CELLS TO LYMPHOID SITES OF HIV PERSISTENCE
SPID#:	13114
UNIT/DIVISION:	Microbiology Immunology
TYPE:	Research
START DATE:	9/1/2016
END DATE:	8/31/2019
GENERAL CATEGORY:	AIDS
SUB-CATEGORY:	Immunology
NIH GRANT:	☒ Yes ☐ No
GRANT NUMBER:	R33AI116171
SUPPORTING ORGANIZATION:	NIH
SPECIFIC INFORMATION:	

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Case Western
Prin. NPRC Core Sci.		Microbiology Immunology
Other Core and Affil.		

PROJECT DESCRIPTION:

Any strategy aimed at HIV eradication in chronic infection will need to address the persistence of virus in secondary lymphoid organs. Lymph nodes (LN) are rapidly infected in early infection, and maintain residual level of activation/inflammation during ART that may potentiate infection of susceptible cells to sustain the latent reservoir. Furthermore, cytolytic effector T cells are typically excluded from LN by their movement across a concentration gradient of the lysophospholipid sphingosine-1 phosphate (S1P). As a result, lymphoid tissues that constitute critical sites of HIV persistence are relatively protected from HIV-specific cytolytic cells. Based on these findings, we propose a novel approach to retain cytolytic cells in lymphoid tissues by administration of the S1P receptor agonist FTY720. We hypothesized that sustained exposure to cytolytic cells will promote a more inflammatory LN environment, will accelerate the stochastic bursts of SIV replication that play a role in sustaining HIV reservoirs, and will allow cytolytic cells to recognize and destroy virus expressing cells directly in lymphoid tissues. We will test this model in the well-established model of SIV infection of rhesus macaques (RMs) using the S1P receptor agonist FTY720, a molecule approved by the FDA for the treatment of multiple sclerosis that blocks the interaction of S1P with its receptors and results in significant circulating lymphopenia as a consequence of lymphocyte sequestration in LN. In the R21 phase of this proposal, we will assess the safety and activity of two different doses of FTY720 in retaining cytolytic cells in lymphoid tissues in ART-suppressed SIV-infected RMs. If successful, these studies will pave the way for the R33 phase, in which we will determine how FTY720 affects (i) antiviral cytotoxic responses and residual inflammation and (ii) HIV persistence in lymphoid tissues.

PROGRESS REPORT:

During the second year of the R33 phase of the grant we have made significant progress in our proposed studies aimed at testing the effects of lysophospholipid sphingosine-1 phosphate (S1P) receptor agonist FTY720

administration in ART-suppressed, SIV-infected rhesus macaques (RMs). Specifically, all 22 RMs assigned to this study have been infected with SIVmac239 and treated for up to 8 months with a very effective three-drug ART regimen. Furthermore, one of the experimental groups have received FTY720 administration, started at ART initiation. During the study, numerous collections have been performed at key experimental points in blood, bone marrow (BM), lymph node (LN), and rectal biopsies (RB). Cells collected from these sites have been used for flow cytometry analyses as well as cryopreserved for reservoir and T cell function measurements to be performed at completion of the study. We infected all 22 animals with SIVmac239 (i.v.; 300 TCID50) and performed longitudinal collections at several experimental points post infection in blood and tissues. Infection was successful, with all 22 RMs showing peak viremia at day 14 p.i. between 107 to 108 and set point viremia at day 42 p.i. between 106 to 107. ART was initiated at day 42 p.i.; with all 22 animals achieving undetectable viral loads (<30 copies/mL). Initiation of FTY720 administration for 58 days in Group #3 (ART + Late FTY720; n=8 animals) was started at the end of August. All 22 animals underwent ART interruption, and will be longitudinally monitored for the following 4 months.

PUBLICATIONS:

PMID	Title
29045906	CTLA-4⁺PD-1⁻ Memory CD4⁺ T Cells Critically Contribute to Viral Persistence in Antiretroviral Therapy-Suppressed, SIV-Infected Rhesus Macaques.
26829644	Loss of Function of Intestinal IL-17 and IL-22 Producing Cells Contributes to Inflammation and Viral Persistence in SIV-Infected Rhesus Macaques.
30305357	Bone Marrow-Derived CD4⁺ T Cells Are Depleted in Simian Immunodeficiency Virus-Infected Macaques and Contribute to the Size of the Replication-Competent Reservoir.

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: SINGLE CELL TRANSCRIPTIONAL PROFILING REVEALS A NOVEL POPULATION OF MUCOSAL TFH CELLS

SPID#: 13115

UNIT/DIVISION: Microbiology Immunology

TYPE: Research

START DATE: 5/1/2018

END DATE: 4/30/2019

GENERAL CATEGORY: AIDS

SUB-CATEGORY: Immunology

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER:

SUPPORTING ORGANIZATION: Yerkes NPRC

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Microbiology Immunology
Prin. NPRC Core Sci.		Microbiology Immunology
Other Core and Affil.		Microbiology Immunology

PROJECT DESCRIPTION:

Despite extensive study, our understanding of the molecular events that determine the susceptibility of CD4+ T cells to SIV/HIV infection and the cellular events that follow lentiviral infection have been limited by our ability to track events that occur in single cells and analyze gene expression, including viral gene expression, on a single cell basis. New techniques that permit high-throughput analysis of gene expression in single cells can be used to deconvolute cell types in apparently homogenous populations of bulk cells.

PROGRESS REPORT:

Using high-throughput microfluidic quantitative real-time PCR of single intestinal CD4+ T cells of SIV-infected macaques, we measured expression of five viral transcripts used to define SIV-infected cells along with 91 cellular genes chosen for potential relevance in the viral replication cycle. Single cell analysis of over 300 single jejunal CD4+ T cells revealed that approximately 20% of these cells were SIV-infected. Comparison of gene expression using multiple statistical methods identified PD-1 and CXCR5 as being the most significantly differentially expressed genes between infected and uninfected cells. The coexpression of PD-1 and CXCR5 on CD4+ T cells defines T follicular helper (Tfh) cells. However, Tfh have been classically associated with secondary lymphoid tissue. Flow cytometric analysis of jejunal samples from uninfected macaques identified a distinct population of PD-1+ CXCR5+ CD4+ T cells, with multiple phenotypic characteristics of classical Tfh cells, including expression of BCL-6 and IL-21. Transcriptional profiling of a panel of 70 Tfh-associated genes verified the similarity of this novel population to classical Tfh. PD-1+ CXCR5+ cells from the small intestine were highly infected with SIV in vivo. This study is the first single cell gene expression analysis of primate lentivirus-infected cells, and identified a novel and highly susceptible target cell population in vivo during acute infection. These results are currently being prepared for publication.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: MONITORING SIV RESERVOIRS WITH WHOLE BODY IMMUNOPET

SPID#: 13116

UNIT/DIVISION: Pathology

TYPE: Research

START DATE: 7/15/2014

END DATE: 6/30/2019

GENERAL CATEGORY: AIDS

SUB-CATEGORY: Imaging

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R01AI111907

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	NIRC / Microbiology Immunology
Prin. NPRC Core Sci.		
Other Core and Affil.		Pathology

PROJECT DESCRIPTION:

The project aims to optimize novel PET/CT imaging technologies for the mapping of virus replication in total body scans as well as immune determinants to interrogate host/pathogen interactions in real time at the macroscopic level. These optimized techniques will then be utilized to understand the viral dynamics during acute SIV infection via the IV, rectal and vaginal route and the dynamics of viral reservoirs in SIV infected monkeys that are subjected to extended ART followed by ART interruption (ATI).

PROGRESS REPORT:

During the past year, we have documented that mapping of viral replication during the first 3 weeks of SIV infection showed a saturation of upper body lymphoid tissues and lung during the first week while the GI tract and spleen SIV signal levels culminated at 2 weeks post infection irrespective of the route of infection. During the chronic phase on infection, monkeys showed a high level of individual variation in the repartition of their signal but much of the signal was seen in the large intestine. Prolonged ART almost fully extinguished these signals albeit residual PET signal was observed in discrete areas of the abdomen primarily in transverse colon and other GI sites. Upon ART interruption, interestingly, the lung signal was again saturated at 5 days post interruption while other lymphoid tissues including GI showed increases of signal over the following 3 weeks post ATI.

PUBLICATIONS:

PMID	Title

None.

FUNDING SOURCES:

Principal Investigator, NIH/NIAID [Redacted by agreement] Microbiology and Immunology, New Iberia Research Center

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: DEVELOPMENT OF RECTAL ENEMA AS MICROBICIDE

SPID#: 13117

UNIT/DIVISION: Pathology

TYPE: Research

START DATE: 9/1/2014

END DATE: 6/30/2019

GENERAL CATEGORY: AIDS

SUB-CATEGORY: Therapy

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: U19AI113127

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Clin Path / Johns Hopkins University
Prin. NPRC Core Sci.		
Other Core and Affil.		Pathology

PROJECT DESCRIPTION:

Oral pre-exposure prophylaxis (PrEP) with tenofovir disoproxil fumarate/ emtricitabine (TDF/FTC) has been approved for prophylaxis of HIV-1 transmission, but is associated with systemic adverse effects, high cost, and low adherence in some populations. Protection from rectal transmission of HIV using topical microbicides that are congruent with sexual behavior, e.g., medicated lubricants and douches, offer the promise of improved adherence and lower cost while limiting systemic toxicity. Sodium based hypo-osmolar enemas have been shown to protect the colon epithelium while at the same time promote the uptake of hydrophilic drugs by the tissue. We have therefore incorporated tenofovir (TFV) into two enema formulations and tested whether these formulations protect macaques from rectal SHIV acquisition.

PROGRESS REPORT:

During the current reporting period, sodium based iso (IOsm) and hypo-osmolar (HOsm) intrarectal douches were tested for their ability to promote uptake of TFV into the tissue and circulation and their ability to protect rhesus macaques from weekly low-dose SHIV challenges. Daily PrEP with TDF alone or with TDF/FTC failed to protect half monkeys (3/6) during 8 repeated rectal SHIV challenges. IOsm rectal delivery failed to deliver protective levels of TDF even at high dose. By comparison, HOsm rectal douche delivery of TFV protected 6/6 monkeys during repeated SHIV challenges, with gradual loss of protection when challenges were delayed relative to douching. The study demonstrates the ability to rapidly deliver protective doses of TFV via the mucosal route and portal of viral entry as a potential affordable alternative to oral PrEP.

PUBLICATIONS:

PMID	Title
29802984	Development of rectal enema as microbicide (DREAM): Preclinical progressive selection of a tenofovir prodrug enema.

FUNDING SOURCES:

Redacted by agreement Clinical Pharmacology, Johns Hopkins University
NIH/NIAID

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: ANTIBODY FUNCTION AND VIRAL DIVERSITY CORE

SPID#: 13118

UNIT/DIVISION: Emory Vaccine Center

TYPE: Research

START DATE: 6/1/2016

END DATE: 5/31/2021

GENERAL CATEGORY: AIDS

SUB-CATEGORY: Vaccine

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: UM1AI124436

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Emory Vaccine Center
Prin. NPRC Core Sci.		
Other Core and Affil.		Emory Vaccine Center

PROJECT DESCRIPTION:

The Antibody Function and Viral Diversity Core will perform a thorough characterization of the antigen specific B cells, antibody effector functions, and antibody specificities elicited by the trimeric BG505 SOSIP-based HIV-1 envelope immunogens in rhesus macaques. We will also determine how vaccine elicited antibodies contribute to protection against an autologous SHIV challenge, and also assess viral determinants that mediate breakthrough of vaccine-mediated protection.

PROGRESS REPORT:

Immunizations are complete for one set of trials and challenges are close to completion. The immunizations are still underway for the second set. We have analyzed post-immunization neutralizing antibody responses in serum, and sorting of antigen-specific memory B cells from immunized rhesus macaques and production of monoclonal antibodies is in progress.

PUBLICATIONS:

PMID	Title

None.

FUNDING SOURCES:

Redacted by agreement funded by NIAID.

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE:	MATERNAL HIGH-FAT DIET, MILK FATTY ACIDS, INFANT BRAIN DEVELOPMENT
SPID#:	13119
UNIT/DIVISION:	Developmental and Cognitive Neuroscience
TYPE:	Research
START DATE:	5/1/2017
END DATE:	4/30/2018
GENERAL CATEGORY:	Neural
SUB-CATEGORY:	Development
NIH GRANT:	☐ Yes ☒ No
GRANT NUMBER:	OD011132
SUPPORTING ORGANIZATION:	Yerkes NPRC
SPECIFIC INFORMATION:	

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Developmental and Cognitive Neuroscience
Prin. NPRC Core Sci.		Developmental and Cognitive Neuroscience
Other Core and Affil.		

PROJECT DESCRIPTION:

Breastfeeding is linked to numerous health benefits for human infants including normal growth trajectories and optimal immune development. Yet the beneficial effects of breastfeeding on general cognitive abilities and behavioral development is still controversial, particularly for full-term infants. Preliminary findings from an on-going rhesus macaque study (R01) at the Yerkes NPRC showed that infants raised by mothers consuming a high-fat diet (HFD) during lactation had reduced pre-frontal cortex functional connectivity and higher circulating proinflammatory cytokines levels by 6 months of age compared to infants raised by mothers consuming a low-fat diet (LCD). Previous rodent studies show pro-inflammatory n-6 fatty acids such as arachidonic acid (AA) may affect synaptogenesis and myelination by changing the cell membrane composition. The HFD used in this monkey study had an excess of n-6 fatty acids compared to the LFD; therefore, these findings indicate a role for n-6 fatty acids derived from the lard and soybean oil in the HFD. Without lipid metabolomic analyses, however, it is currently unknown whether the infants were exposed to these pro-inflammatory fatty acids via mother's milk or during weaning, which occurs between 4-6 months of age in this species. Using maternal milk and plasma samples as well as infant plasma samples collected across lactation and weaning, the following aims are being examined in order to begin to understand how maternal consumption of a HFD and diet-induced obesity can impair infant neurodevelopment via milk: 1) determine optimal extraction protocol to perform liquid-chromatograph mass-spectrometry (LC/MS) lipidomics using rhesus macaque milk; 2) determine whether maternal consumption of a TAD and diet-induced obesity results in higher n-6 fatty acids and lower n-3 fatty acid levels in breast milk; 3) determine whether the milk fatty acid profiles studies in aim 2 predict increased systemic inflammation and impair brain development in the nursing infants of TAD-fed mothers at 6 months of age and whether maternal milk lipid metabolome studied in aim 2 correlate with infant plasma lipid metabolome across weaning. Milk and plasma fatty acid compositions and global lipidomics are being assessed by LC/MS

PROGRESS REPORT:

As of 1/24/19, sample collection and optimal protocols for extraction of long-chain fatty acids and global lipidomics using rhesus macaque milk has been completed. The data analyses regarding this metabolomic study is on-going. We are currently in search of a biostatistician to assist in these analyses.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Redacted by agreement Supported by the 2017 Yerkes NPRC P51 Pilot Study Program

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: DEVELOPMENT OF HIPPOCAMPAL-PREFRONTAL INTERACTIONS IN ADOLESCENT MONKEYS

SPID#: 13121

UNIT/DIVISION: Developmental and Cognitive Neuroscience

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: Behavior

SUB-CATEGORY: Neural

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R01HD090925

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Developmental and Cognitive Neuroscience
Prin. NPRC Core Sci.		Developmental and Cognitive Neuroscience
Other Core and Affil.		

PROJECT DESCRIPTION:

We propose to develop a cutting edge and clinically relevant nonhuman primate (NHP) model to trace the development of hippocampal-prefrontal interactions in monkeys from pre-adolescence to early adulthood, focusing on critical cognitive functions, i.e. relational (episodic) and working memory (WM) mediated by the hippocampus and dorsolateral prefrontal cortex, respectively. We will use a combination of cognitive tasks, noninvasive in vivo neuroimaging techniques, selective transient disconnection experiments, and measure of gonadal hormone status. These studies are proposed because impaired memory is an important component of many developmental neuropsychiatric disorders in humans, i.e. schizophrenia, autism, ADHD, Fragile X, Down's and Williams syndromes and their emergence and severity differ in males and females. Hence, the study of the hippocampus and of its interactions with the prefrontal cortex has become of major clinical interest to further our understanding of the memory deficits that are associated with these developmental neuropsychiatric disorders.

PROGRESS REPORT:

During the reporting period, we acquired 4 juvenile male monkeys that went through quarantine and then began training on the working memory task for the pre-adolescent time point. We started by using a computerized testing apparatus for this task, but after 4 months of acclimation to the testing box it became evident that these young animals were too anxious to even use the touchscreen, so we decided to continue testing them using a manual version of the task with a Wisconsin General Testing Apparatus. Three of the 4 juvenile monkeys acclimated very well and rapidly to the testing and completed the task, the remaining one did not adapt to the testing box and needed to be discontinued due to persistent behavioral problems. The three monkeys were then tested on the spatial recognition task without issues and blood samples to measure testosterone levels as well

as brain scans (structural T1, DTI and rsFMRI) were also collected in these same animals. These animals will be re-tested on the tasks at the next time point (early adolescent time point) in the Spring 2019. In the fall of 2018, we acquired another cohort of 7 juvenile male monkeys that are just finishing quarantine and that will be tested on the working memory and spatial recognition tasks and received blood collection and brain scans at the same time points (pre-adolescent period) as the first cohort of juvenile monkeys.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: METABOLIC DYSFUNCTION IN TRANSGENIC HUNTINGTON'S DISEASE MONKEYS

SPID#: 13122

UNIT/DIVISION: Developmental and Cognitive Neuroscience

TYPE: Research

START DATE: 5/1/2017

END DATE: 4/30/2018

GENERAL CATEGORY: Metabolic

SUB-CATEGORY: Huntington's Disease

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER:

SUPPORTING ORGANIZATION: Emory University

SPECIFIC INFORMATION: Pilot funded by Private Source

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Developmental and Cognitive Neuroscience
Prin. NPRC Core Sci.		Neuropharmacology and Neurologic Diseases
Other Core and Affil.		

PROJECT DESCRIPTION:

Pilot grant was supported by Private Source
Huntington's disease (HD) is a fatal neurodegenerative disease with an autosomal dominant inheritance. Although the mutation for this monogenic disease was identified for two decades, there is still no cure or treatment. A significant limiting factor in this field is the lack of a well-characterized animal model that progressively develops the full spectrum of clinical symptoms seen in HD patients. Although the most notable clinical symptoms of HD are motor disturbances and brain atrophy, other symptoms include cognitive dysfunction, emotional dysregulation, increased inflammation, and metabolic dysfunction. Moreover, there is evidence that these symptoms are present prior to onset of motor symptoms, indicating that they are key features of HD and not side effects of the disease. While motor and cognitive symptoms can be easily studied in rodents, there are limitations to using rodents to study other HD symptoms. The rhesus macaque represents a more translational animal model due to numerous anatomical and physiological similarities to humans. For these reasons, a transgenic Huntington's Disease (tHD) monkey was developed at the Yerkes National Primate Research Center. Recent research shows that tHD monkeys exhibit subtle cognitive deficits, fine motor control impairments, emotional dysregulation, and increased inflammation; However, the metabolic function of tHD monkeys has not been previously characterized.

PROGRESS REPORT:

As of 1/25/19, sample collection and immunoassays for the characterization of metabolic dysfunction in the transgenic HD monkey model are completed. Changes in body condition were determined by DEXA scan and morphometry. Fasted blood samples were collected in post-prandial tests in which plasma levels of leptin and ghrelin were used to assess total body energy homeostasis. Additionally, intravenous glucose tolerance tests were conducted to determine whether the tHD monkey model has impaired glucose tolerance and insulin

insensitivity compared to unaffected controls. Plasma lipids and fatty acid profiles were evaluated for differences in lipid metabolism between tHD and control monkeys. Preliminary data show no significant differences in the study parameters measured in this small pilot study. Additional longitudinal samples will be collected if additional funding is available to increase statistical power.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Redacted by agreement Pilot grant funded by Private Source
Private Source Emory University

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE:	ANTICIPATORY ANXIETY: MAPPING FUNCTIONAL MICROCIRCUITS IN THE BNST
SPID#:	13123
UNIT/DIVISION:	Behavioral Neuroscience and Psychiatric Disorders
TYPE:	Research
START DATE:	5/1/2018
END DATE:	12/31/2020
GENERAL CATEGORY:	Neural
SUB-CATEGORY:	Psychiatric
NIH GRANT:	☐ Yes ☒ No
GRANT NUMBER:	R01MH072908
SUPPORTING ORGANIZATION:	NIH/NIMH
SPECIFIC INFORMATION:	

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Behavioral Neuroscience and Psychiatric Disorders
Prin. NPRC Core Sci.		Behavioral Neuroscience and Psychiatric Disorders
Other Core and Affil.		

PROJECT DESCRIPTION:

The major goals of this study are to identify the cellular and neuroanatomical pathways that contribute to the induction and expression of anticipatory anxiety.

PROGRESS REPORT:

In our previous reporting period, we had shown that a systemic intraperitoneal injection of Nk3R antagonist Osanetant (Osa) decreased the effects of chronic stress. Because Nk3r is also expressed in the central amygdala, we decided to use local infusion of Osanetant in the BNST to decipher the specific role of the tac2 pathway in BNST neurons. We showed that intra BNST infusion of Osanetant decreases the long-term behavioral consequences of chronic stress while the actute stress response remain unaffected. It also prevents in some extent the effects of chronic stress on the mRNA expression of genes associated with anxiety. Moreover, we examined the effects of intra BNST infusion Nk3R agonist senktide (Senk). Chronic activation of Nk3R in the BNST led to an enhanced anxiety in the open field and the passive avoidance task, like what is observed after chronic stress. Interestingly, 7 days of Senktide infusion also partially recapitulates the molecular changes induced by chronic stress exposure. We showed an increased expression of Tac 2, Nk3r and Pac1R as well as a decrease in Ptpn5 expression. However, Crf expression was not affected, suggesting an independent regulatory pathway.

Another goal of our proposal was to examine the role of the stress-induced increased acetylcholine release and its modulation in chronic stress induced anxiety behavior. In the previous funding period, we showed that carbachol could induce transient inward current exclusively in CRF+ type III neurons. Our previous study also showed that the oval nucleus of BNST express the mRNA for muscarinic receptor M1-M5 (Guo et al 2012), however the distribution of muscarinic receptors in three cell types remains unknown. We firstly examined the expression of muscarinic M1-M5 in the three BNST cell types. Our result found that all cell types of BNSTov

neurons express mRNAs for all five muscarinic receptors subtypes. However, the level of expressions seems specific for each cell types with, for example, the expression of M1 receptor in type II significantly higher than in type III neurons. Then using our CSS model, we examined the effects of chronic stress on the mRNA expression of M1-M5 in each cell types. We showed that CSS affected muscarinic receptor expression in a cell type dependent manner: no changes were observed in type I neurons, while type II neurons showed a significant increase of the inhibitory muscarinic receptor subtypes (M2, M4) and type III neurons exhibited an increase of excitatory muscarinic receptors (M1, M3). We found these results are extremely interesting, as we previously proposed that type II neurons are potentially anxiolytic and type III neurons are anxiogenic, and type II neurons potentially inhibit the activity of type III neurons (Daniel & Rainnie, 2016). The CSS induced increase of inhibitory muscarinic receptor subtypes will decrease activity of type II neurons and subsequently cause disinhibition of type III neurons whereas in the type III neurons, the increase of excitatory muscarinic receptor will increase the activity of these neurons. The overall changes of muscarinic receptor expression in the BNSTov lead to the increase of excitability of CRF+neurons after CSS, which may underlie the molecular mechanism of anxiety-like behavior.
Another major objective of this award is to investigate factors that contribute to susceptibility or resilience to chronic stress, which are of great interest in understanding the etiology of PTSD. In the previous reporting period, using our chronic social defeat (CSD) model, we discovered that there is a stress-incubation period during which mice develop depressive behaviors roughly after 7 but before 10 days of social defeat stress, and about 30% of the population exhibit resilience to the stress. We were able to recapitulate this behavior with the pattern of activation of CRF+ neurons in the BNSTov. Using Cav2 retrograde tracing, we also showed that those neurons received glutamatergic inputs from the PVT.
Our findings unveil a conceptually innovative avenue to explore the relationship between chronic stress and depression. BNSTov CRF neurons have a unique property in that they encode the duration of stress and once surpassed a certain amount of stress, their pattern of activation and their molecular profiles change, which promotes a dramatic change in behavior. We have shown the key role of the neurokinin B pathway in the expression of chronic stress induced anxiety. We have demonstrated that Nk3R antagonist Osanetant significantly prevents the anxiogenic effects of a chronic stress exposure but we also showed that while this molecule is approved for human clinical trial, an chronic administration might prevent the expression of coping mechanisms.

PUBLICATIONS:

PMID	Title
29660417	RDoC-based categorization of amygdala functions and its implications in autism.

FUNDING SOURCES:

Redacted by agreement funded by NIMH

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: VIRAL VECTOR MEDIATED CRISPER EDITING OF VOLE OXYTOCIN RECEPTOR

SPID#: 13124

UNIT/DIVISION: Behavioral Neuroscience and Psychiatric Disorders

TYPE: Research

START DATE: 7/1/2017

END DATE: 6/30/2019

GENERAL CATEGORY: Neural

SUB-CATEGORY: Genetic

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R21MH114151

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Behavioral Neuroscience and Psychiatric Disorders
Prin. NPRC Core Sci.		Behavioral Neuroscience and Psychiatric Disorders
Other Core and Affil.		

PROJECT DESCRIPTION:

Oxytocin receptors in the nucleus accumbens, a reward center of the brain, are involved in social attachment and resilience to early life social neglect in prairie voles. Among prairie voles there is remarkable individual variation in the density of oxytocin receptor in the nucleus accumbens. This variation in receptor density predicts social behavior, including how neonatal social neglect influences adult social bonding. We have identified 14 single nucleotide polymorphisms (SNPs) that predict 80% of the variation in oxytocin receptor expression in the nucleus accumbens. The goal of this project is to develop a viral vector mediated CRISPR approach to edit individual candidate SNPs in the adult brain to determine which SNP is the functional SNP influencing expression. The results from these studies will provide insights into how single base pair changes in behavioral relevant genes can robustly influences expression in specific brain regions.

PROGRESS REPORT:

Specific Aim 1: Validation of AAV-mediated CRISPR-Cas9 editing of the prairie vole genome.
As proposed, we plan to use two already validated sgRNAs (by our collaborator Prof. Redacted by agreement) in our AAV-CRISPR-Cas9 system to knockdown prairie vole OXTR expression in the nucleus accumbens. We are in the process of validating these sgRNAs for use in AAVs. We performed a PCR-based assay in which recombinant Cas9 and synthesized sgRNAs are used to cleave a PCR amplicon of the Oxtr gene. In this assay, both sgRNAs were functional. At the same time, we designed and synthesized two sgRNAs that target the LacZ gene (as a negative control) and confirmed that these sgRNAs do not result in Cas9-mediated cleavage of the Oxtr PCR amplicon. Next, we cloned both the Oxtr and LacZ sgRNAs into AAV-U6-sgRNA-CMV-eGFP (AAV-sgRNA) and co-transfected HEK293T cells with AAV-sgRNA-Oxtr or AAV-sgRNA-LacZ, with the coding sequence of the prairie vole Oxtr, and with AAV-RSV-Cas9. By means of a T7 endonuclease assay that cleaves DNA strands harboring mismatches, we observed that transfection of AAV-sgRNA-OXTR, but not AAV-sgRNA-LacZ resulted

in the cleavage of PCR-amplicons surrounding sgRNA target sites, indicating indel formation in the Oxtr CDS.

We have generated AAV vectors of the Cas9/sgRNA and injected them into the nucleus accumbens of prairie voles and our preliminary results indicates that there is a reduction in binding, however this is just an N=2 at this time. We are injecting more animals now and will vary variables (time after injection before taking brain, titer) to determine the optimum conditions for CRISPR editing.

Specific Aim 2: Identifying the functional SNP responsible for the brain-region specific variation in prairie vole OXTR binding. We have not perform any experiments under this aim yet.

Our results so far demonstrate that our sgRNA's are effective at targeting the praire vole oxytocin receptor gene and that our plasmids are working.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Redacted by agreement funding by NIMH.

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE:	PRIMATE EXTERNAL GLOBUS PALLIDUS IN NORMAL AND PARKINSONIAN
SPID#:	13126
UNIT/DIVISION:	Neuropharmacology and Neurologic Diseases
TYPE:	Research
START DATE:	9/28/2017
END DATE:	7/31/2022
GENERAL CATEGORY:	Neural
SUB-CATEGORY:	Brain Structure/Function
NIH GRANT:	☒ Yes ☐ No
GRANT NUMBER:	R01NS100908
SUPPORTING ORGANIZATION:	NIH
SPECIFIC INFORMATION:	

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Neuropharmacology and Neurologic Diseases
Prin. NPRC Core Sci.		Neuropharmacology and Neurologic Diseases
Other Core and Affil.		Neuropharmacology and Neurologic Diseases

PROJECT DESCRIPTION:

Patients with Parkinson's disease (PD) experience motor impairments that lead to severe disability. These impairments are associated with abnormal neuronal activity in the basal ganglia.The long-term goal of our research is to elucidate how the abnormal activity of the basal ganglia relates to the motor deficits in PD, with the goal of developing novel therapies to treat parkinsonism with improved specificity and fewer unwanted side effects. This project studies the external segment of the globus pallidus (GPe), a key structure in the basal ganglia circuitry. In rodent models of PD, there is evidence that PD-related abnormalities occur selectively in specific types of GPe neurons, raising the possibility that different GPe neuron populations might make distinct contributions to the normal and pathological roles of the GPe. However, the translational relevance of these findings is limited by functional and anatomical differences between the rodent and primate GPe. Our experiments will define functional differences between classes of GPe neurons in normal rhesus monkeys and in monkeys rendered parkinsonian by treatment with the neurotoxin MPTP. Monkeys are an excellent animal model for studying PD-related changes in brain activity, because their basal ganglia and connected brain structures closely resemble those in humans, and because MPTP-treated monkeys show the majority of the motor impairments seen in PD patients. We will use electrophysiological in vivo recordings to evaluate differences in the firing rates and patterns of GPe neuron subpopulations. Our studies will begin to determine how the activities of primate GPe neuron subtypes differ, how they regulate the spiking activity in other basal ganglia neurons in the normal and parkinsonian states, and whether they are involved in the pathophysiology of parkinsonism. The knowledge gained from these studies may enable us to develop new treatments for PD that harness functional and anatomical differences of GPe neuron types.

PROGRESS REPORT:

Two rhesus monkeys have been studied so far in this project. In both of them we have completed all the functional experiments (electrophysiological recordings and optogenetic manipulations) in the normal state. Both monkeys are currently undergoing treatment with MPTP to develop parkinsonism. We expect to continue the experiments in the parkinsonian state in the following month. A third monkey for this project has been received and we will start habituating this animal to be handled by the experimenters and to sit on a primate chair. Preliminary results from this project were presented at the Society for Neuroscience 2018 meeting

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Redacted by agreement (PI), funded by NINH/NINDS R01NS100908

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: OPTOGENETIC THERAPY FOR PARKINSON'S DISEASE

SPID#: 13127

UNIT/DIVISION: Neuropharmacology and Neurologic Diseases

TYPE: Research

START DATE: 1/1/2018

END DATE: 12/31/2018

GENERAL CATEGORY: Neural

SUB-CATEGORY: Therapy

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER:

SUPPORTING ORGANIZATION: Private Source

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Neuropharmacology and Neurologic Diseases
Prin. NPRC Core Sci.		
Other Core and Affil.	Redacted by agreement	Neuropharmacology and Neurologic Diseases

PROJECT DESCRIPTION:

This project is aimed at examining the potential of optical stimulation of the subthalamic nucleus (STN) for the therapy of Parkinson's disease. The main objective of the study is to determine the behavioral effects of optical inactivation of STN neurons in parkinsonian non-human primates in order to assess the potential antiparkinsonian efficacy of this technology in patients. The planned studies use optogenetics with the transgenic expression of inhibitory opsins in the STN and optical stimulation for physiological and behavioral effects. Experiments are performed in parkinsonian non-human primates injected with viral vector in the STN for recordings of neral activity and behavioral assessments after illumination of the STN.

PROGRESS REPORT:

The project has been advanced to the stabilization of an animal after the virus injection in the STN for optical stimulation. The next experiments will test the neural effect of STN illumination to move forward to the final tests of behavioral effects. If results are positive in this pilot study, a complete study with the appropriate sample size will be designed.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Private Source

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: HUMAN MINIPROMOTERS FOR BRAIN GENE THERAPY

SPID#: 13128

UNIT/DIVISION: Neuropharmacology and Neurologic Diseases

TYPE: Research

START DATE: 10/1/2016

END DATE: 12/1/2019

GENERAL CATEGORY: Neural

SUB-CATEGORY: Viral

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER:

SUPPORTING ORGANIZATION: Private Source

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Neuropharmacology and Neurologic Diseases
Prin. NPRC Core Sci.		
Other Core and Affil.		Neuropharmacology and Neurologic Diseases

PROJECT DESCRIPTION:

The goal of this project is to develop Mini-promoters that could be put into AAV viral vectors to transfect specific populations of neurons in the monkey central nervous system. This is an interdisciplinary project led by Dr Redacted by agreement from University of British Columbia. Work achieved at the Yerkes Primate Center is focused on the testing of viral vectors specificity and sensitivity for neuronal populations in the rhesus monkey brain.

PROGRESS REPORT:

The progress made in the monkey experiemnts proposed in this project during the past year can be summarized as follows:
Five adult (4-11 years old) rhesus monkeys (2 males, 3 females) from the Yerkes Primate Center breeding colony were used. All animals were screened for AAV9 sero-negativity before being assigned to the project. All animals underwent structural MRI to help determine stereotaxic coordinates for intracerebral injections. The five monkeys received bilateral injections of AAV9-Ple356-EmGFP (N=3) or AAV9-Syn1-EmGFP (N=2) through burr holes in the skull using Hamilton microsyringes. All surgical procedures were approved by the Institutional Animal Care and Use Committee of Emory University. In each animal, the brain tissue was processed as follows. After perfusion with aldehydes, the brain was taken out from the skull, post-fixed for 24 hours, immersed in 30% sucrose for 1-2 weeks and then cut in serial 50 um-thick sections with a freezing microtome. Series of 1/10 sections through the injection sites were processed to localize the viral vector with a GFP antibody using the immunoperoxidase method. Adjacent sections were prepared for either tyrosine hydroxylase immunoperoxidase or double immunofluorescence to assess the co-localization of GFP and TH in single neurons of the locus coeruleus (LC). After processing, the sections were mounted on slides, coverslipped and analyzed under the light or confocal microscope. Digital images of immunoperoxidase-stained sections were collected using a ScanScope light microscope. Data obtained from these animals indicate: (1) The GFP labeling following AAV9-Ple356 injections was exclusively confined to neuronal elements, and was strongly expressed in TH-positive neurons of LC (2) The volume of GFP labeling in the cerebellar cortex overlying the LC region was minimal (~1

mm3) when the Ple356 Mini-promoter was used, compared with the strong cerebellar labeling generated by the pan-neuronal hSyn1 promoter (~90-100 mm3). (3) Altogether, data from the 5 monkeys used in this aim revealed that the extent of neuronal labeling generated by the pan-neuronal hSyn1 promoter was far greater (~60-100 mm3) than that induced by the Ple356 Mini-promoter (~1-12 mm3). (4) Double immunofluorescence experiments confirmed the co-localization of GFP and TH within single LC neurons. (5) In small groups of TH-negative neurons of the cerebellar cortex, lateral parabrachial region (LPB), laterodorsal tegmental nucleus and pedunculopontine nucleus, GFP expression was transduced by the Ple356 Mini-promoter. The chemical phenotype of these neurons is currently being studied.
Overall, these results extend the murine data showing that the Mini-promoter Ple356 targets preferentially noradrenergic neurons in the LC.

PUBLICATIONS:

PMID	Title

None

FUNDING SOURCES:

Redacted by agreement is the subcontract PI at the Yerkes Primate Center, Emory University; Redacted by agreement from University British Columbia, Canada, is the Project PI. The project is funded by the Private Source in Canada.

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: THE THALAMOSTRIATAL SYSTEM AND COGNITION

SPID#: 13129

UNIT/DIVISION: Neuropharmacology and Neurologic Diseases

TYPE: Research

START DATE: 8/1/2017

END DATE: 7/31/2019

GENERAL CATEGORY: Neural

SUB-CATEGORY: Brain Structure/Function

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R03NS103155

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Neuropharmacology and Neurologic Diseases
Prin. NPRC Core Sci.		Developmental and Cognitive Neuroscience
Other Core and Affil.		

PROJECT DESCRIPTION:

This grant, in collaboration with Redacted by agreement aims at testing the effects of lesion of the thalamostriatal projections from the caudal intralaminar thalamic nuclei, namely the centromedian and parafascicular nuclei (CM/Pf), on cognition in adult rhesus monkeys. The rationale for this project relies on previous evidence that the CM/Pf complex undergoes severe degeneration in Parkinson's disease. Based on rodent behavioral data and electrophysiology studies of CM/Pf neuronal responses to attention-related stimuli in monkeys, the overall hypothesis of this project is that selective lesion of the thalamostriatal projection from CM or Pf neurons induce cognitive impairments in monkeys.

PROGRESS REPORT:

The progress made in this project over the past year is summarized as follows:
A. Specific Aim: The specific aim of this project is to test whether parafascicular (PF)-caudate or centromedian (CM)-putamen lesions has any impact on cognitive behaviors related to selective attention, attentional set-shifting or habits in monkeys.
Our goal is to use of a novel retrograde immunotoxin approach to selectively ablate the PF-caudate nucleus or CM-putamen projection, and determine the impact of such lesion on various cognitive behaviors related to selective attention, attention set shifting or habits in rhesus monkeys. Macaque monkeys are used because the organization of their cognitive skills and the neural systems underlying this organization are sufficiently close to those of humans to make the necessary cross-species comparisons.
Over the past year, we have written computer programs to run the AutoShaping and Intradimentional/extradimentional (ID/ED) attention shift task and have prepared all the stimuli necessary to run the Visual Paired Comparison (VPC) task. Three adult female rhesus monkeys (5 years of age) are used in this project. These three animals were tested in the behavioral AutoShaping protocol . All behavioral tasks performed in this project were in an automated testing apparatus with a touch screen on which stimuli will appear. Animals were first progressively habituated to sit in the transported cage for around 30 minutes. Positive

reinforcement is provided in the form of food treats delivered by hand.
The animals were then brought to the automated apparatus in the experimental lab and acclimated with the testing environment. Animals were habituated to touch stimuli on the screen to receive food rewards (Primate Product flavored pellets). The aim was to train the monkey to touch filled shapes that appeared in the computer touch screen. We used an approximation procedure that consists of the presentation of a large picture on the screen and any touch within the picture results in a reward. After the pre-training was completed, the animals were subjected to the cognitive ID/ED task. In this task, the stimuli consist of pictures of blue-filled shapes (32 X 32mm) and red lines (38 mm high) and the task has three stages. Stage 1 (ST1): The animals first received a series of simple visual discriminations in which a response to one of the two stimuli results in a food reward, followed by a simple reversal (SR) during which the same two stimuli were presented, but the reinforcement contingencies reversed. ST 2: A compound discrimination was given in which the shape stimuli of the last reversal was used but red lines are added over the shape. Animals continue to respond to the shape and should ignore the red lines to be correct. After reaching criterion, the reinforcement contingencies between the two compounds were again reversed. ST 3: Intra-dimensional shift stage: a new pair of compound stimuli (new blue shape, new red line) was presented, with one of the shape stimuli associated with reinforcement, (despite new examples of shape and line stimuli, the same dimension of the stimulus, i.e. “shape remains relevant for reinforcement). This stage was followed by the intra-dimensional reversal. ST 4: Extra-dimensional shift, novel shape and line stimuli were introduced, but this time responding to one of the two line stimuli was reinforced (shapes are irrelevant). Again, the extra-dimensional shift was followed by a reversal. Two of the monkeys have completed four stages of the ID/ED task and have been injected with the retrograde lentiviral vector [HiRet-IL-2Rα-GFP vector (8.5 X 107 i.units/ml)] in the striatum and the immunotoxin in the CM/Pf complex on both sides of the brain. The other monkey is performing in stage 3 and will complete the stage 4 in February. Behavioral testing in lesioned animals will start early February 2019.

PUBLICATIONS:

PMID	Title

None

FUNDING SOURCES:

Redacted by agreement and Redacted by agreement (MPI). Funded by NINDS.

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: PATHOPHYSIOLOGY OF THE PEDUNCULOPONTINE NUCLEUS IN PARKINSON'S DISEASE

SPID#: 13130

UNIT/DIVISION: Neuropharmacology and Neurologic Diseases

TYPE: Research

START DATE: 9/15/2017

END DATE: 7/31/2022

GENERAL CATEGORY: Neural

SUB-CATEGORY: Brain Structure/Function

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R01NS098441

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Neuropharmacology and Neurologic Diseases
Prin. NPRC Core Sci.		Neuropharmacology and Neurologic Diseases
Other Core and Affil.		

PROJECT DESCRIPTION:

This grant supports work to better understand the functional anatomy, synaptic organization and pathophysiology of the pedunculopontine tegmental nucleus (PPN), and its ascending and descending projections in normal and parkinsonian monkeys. A multidisciplinary approach that includes in vivo electrophysiology in awake monkeys, viral vector tracing methods, three dimensional reconstruction electron microscopy techniques and optogenetic methods will be used in this project of which the main goals are: 1) to characterize the synaptic relationships between descending projections from the internal globus pallidus (GPi) and specific populations of PPN neurons that project either to the lower brainstem/spinal cord or the substantia nigra pars compacta and 2) to examine parkinsonism-related changes in spontaneous firing rates and patterns of primate PPN neurons, and to test the hypothesis that GPi deep brain stimulation ameliorates these changes.

PROGRESS REPORT:

The progress made in this project during the past year for each specific aim is as follows:
Aim 1: To study the synaptic relationships between functionally specific GABAergic GPi terminals and PPNd neurons that project to the cervical spinal cord or the SN.
During the past year, postmortem tissue from two rhesus monkeys (1 control, 1 MPTP-treated) that received injections of AAV5 vector in the GPi was prepared for electron microscopic analysis of the synaptic connections oAf pallido-tegmental GABAergic terminals between control and MPTP-treated parkinsonian monkeys. We found that GPi injections of AAV5 in the sensorimotor region of the GPi led to profuse anterograde labeling of pallidal axons and terminals in the PPN region. The postsynaptic targets of a total of 64 GPi terminals from a control monkey and 47 GPi terminals from a parkinsonian monkey have been determined at the EM level. Material from 2-3 additional control and parkinsonian monkeys will be added to this portion of the study in the coming years to further assess possible changes in the pattern of synaptic connections of GPi terminals in the parkinsonian state.

Aim 2: To test the hypothesis that the function and ultrastructure of GABAergic GPi terminals on PPNd neurons is altered in MPTP-treated parkinsonian monkeys.
During the past year, we started experiments in a rhesus monkey in the normal state. A second monkey is currently being trained to accept handling by the experimenters, and the surgery to implant recording chambers is scheduled for late summer 2018.
In the first monkey, we electrophysiologically mapped both recording chambers and identified, based on the neuronal firing patterns and surrounding landmarks, the internal segment of the globus pallidus (GPi), the substantia nigra and the PPN. Then, in one GPi we injected AAV vectors carrying the genomic sequences for the excitatory opsin C1V1, while in the other GPi we injected AAVs carrying the sequences for the inhibitory opsin Jaws. We are currently in the waiting period to allow for robust expression of the opsins on the GPi somata and along the axons and on terminals of GPi neurons that project to the PPN. This will be followed by testing of the responses of PPN neurons to the activation of excitatory or inhibitory opsins. Once the experiments in the normal state are completed, the animal will be treated with MPTP to induce parkinsonism, followed by additional testing of optical stimulation responses in the parkinsonian state.
In related experiments that extend the experiments under aim 1, we injected AAVs carrying the sequence of the excitatory opsin ChR2 in one PPN in this monkey, and examined the responses of ipsilateral SN neurons to light stimulation of PPN terminals. These experiments shed light on the physiologic effects of activating PPN inputs to the SNc. We have recorded from 82 SN neurons (75 likely representing SNc) while activating ChR2 with single pulses (500 ms) or trains of pulses (10 ms each, 10 pulses, 20 Hz). We are currently analyzing the data from these experiments.
Electron microscopic studies to determine if pallidal terminals in the PPN undergo ultrastructural changes in the parkinsonian state have also been undertaken. So far, brain tissue used for these studies has been gathered from 2 control and 2 MPTP-treated parkinsonian monkeys stored in the bank of monkey brain tissue supported by the Emory Udall Center of Excellence of Parkinson's disease. Each of the monkeys used in these experiments received injections of AAV2/5 vectors in the GPi and displayed robust anterograde labeling in the PPN region, as visualized on vibratome-cut light microscopy slides. Blocks of PPN tissue from areas enriched in AAV-containing terminals were then removed from the slides and processed for Single Block Facing/Scanning Electron Microscopy (SBF/SEM). The SBF/SEM processing of four blocks of tissue (2 control, 2 MPTP) is now completed. We aim to reconstruct a total of 5-10 labeled GPi terminals and their post¬synaptic targets/blocks of tissue. From each reconstructed terminal, we will collect morphometric measurements, including the volume and the number of synapses formed by each terminal, the surface area of each synapse, and the inter-synapse distance (i.e., the distance between the two nearest points of adjacent reconstructed synapses). Because each of these features were found to be critical regulators of the strength and physiological properties of morphologically similar terminals in other brain regions, their assessment may lead to new information about neuroplastic changes GPi terminals undergo in the parkinsonian state. The measurements will be statistically compared using 2-way ANOVAs, with appropriate post-hoc comparisons with Student's t-tests between normal and parkinsonian monkeys (or the corresponding non-parametric tests if data are not normally distributed).

PUBLICATIONS:

PMID	Title

None

FUNDING SOURCES:

Redacted by agreement and Redacted by agreement (MPIs). Funded by NINDS

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: IMPROVING STABILITY AND REPRODUCTION IN RHESUS COLONIES BY MANIPULATING SEX RATIO

SPID#: 13131

UNIT/DIVISION: Animal Resources

TYPE: Research

START DATE: 9/1/2016

END DATE: 6/30/2020

GENERAL CATEGORY: Animal

SUB-CATEGORY: Behavior

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R24OD020349

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Animal Resources
Prin. NPRC Core Sci.		Developmental and Cognitive Neuroscience
Other Core and Affil.		Animal Resources
		CNPRC
		CNPRC

PROJECT DESCRIPTION:

A common problem in captive breeding groups of rhesus macaques is high rates of contact aggression and wounding. High rates of contact aggression and resulting injuries can negatively impact the health, welfare, and the reproductive success of the animals, as it may be a symptom of underlying instability and likely reflects increased stress reactivity at the individual level. Group stability can be enhanced by increasing the proportion of non-natal adult males in breeding groups. Our main objective is to determine the relative efficacy of different introduction techniques on male retention in a new group and the effects of each technique on social network measures of group stability. We will also investigate the characteristics of adult males, behavioral patterns in breeding groups, and demographic variables that are associated with successfully increasing male proportions within groups. Since our collaborators at the CNPRC have developed an innovative, data-driven social network approach to examine underlying mechanisms of group stability in rhesus, we have a unique opportunity to directly compare results between two NPRC facilities. Ultimately, this research has potential to improve welfare, production, and research value in captive rhesus colonies, as well as reduce the need for veterinary interventions and the associated expenses.

PROGRESS REPORT:

Behavioral observations have been conducted on six large social groups of rhesus macaques, before and after the introduction of a group of adult males to each of these groups of females. Post-introduction observations will be on-going for three of these groups over the next several months. Three introduction cages were constructed

and were used for some of these group introductions, to allow the comparison of two introduction approaches. Behavioral observations were conducted on the adult males prior to group introductions, and personality assessments were conducted. These and other factors will be used to predict a male's ability to successfully integrate into new breeding groups. Hair samples were collected from adult females for assays of cortisol, as a measure of chronic stress. The behavioral data, along with records on wounding and infant births, will allow the evaluation of interrelationships among sex ratio, group stability, wounding rates, stress, and reproductive success.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Redacted by agreement funded by Office of Research Infrastructure Programs

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: USING DNA/MVA/PROTEIN IMMUNIZATION OF RHESUS MACAQUES TO INVESTIGATE HOW THE BACKGROUND OF THE HIV-1 ENVELOPE AND NATURE OF THE PROTEIN BOOST SHAPE THE GENETIC AND FUNCTIONAL ANTIBODY LANDSCAPE

SPID#: 13132

UNIT/DIVISION: Emory Vaccine Center

TYPE: Research

START DATE: 7/1/2017

END DATE: 6/30/2022

GENERAL CATEGORY: AIDS

SUB-CATEGORY: Immunology

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R01AI128837

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Emory Vaccine Center
Prin. NPRC Core Sci.		
Other Core and Affil.		Emory Vaccine Center

PROJECT DESCRIPTION:

Despite a strong and lengthy effort focused on developing an HIV vaccine, immune correlates necessary to achieve robust and sustained protection remain unknown. We propose to study the humoral immune response elicited by novel envelope immunogen sets derived from two HIV-1 infected individuals, chosen due to the disparate nature of their early antibody responses and subsequent development of very high or extremely low neutralizing antibody breadth. We will use a vaccination strategy that has shown promise in human volunteers, DNA and modified vaccinia Ankara (MVA), in the well-established rhesus macaque animal model, to determine how the natural history of these envelope immunogens, and presentation of the immunogens in different molecular forms, impacts the genetic and functional antibody landscape

PROGRESS REPORT:

We successfully generated the DNA and MVA vaccine vectors and the two patient-derived envelope gp120 protein immunogens. We have also generated stable gp140 trimers for one of the patient-derived envelope immunogens and are still optimizing the other trimer. DNA immunizations of rhesus macaques began in October of 2018 and immunizations and sample collections are ongoing.

PUBLICATIONS:

PMID	Title

None.

FUNDING SOURCES:

Redacted by agreement funded by NIAID.

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: VACCINE IMMUNOLOGY SCIENCE AND TECHNOLOGY FOR AFRICA (VISTA)

SPID#: 13133

UNIT/DIVISION: Emory Vaccine Center

TYPE: Research

START DATE: 7/1/2018

END DATE: 6/30/2019

GENERAL CATEGORY: Infectious Disease

SUB-CATEGORY: Vaccine

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER:

SUPPORTING ORGANIZATION: Private Source

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Emory Vaccine Center
Prin. NPRC Core Sci.		
Other Core and Affil.		Emory Vaccine Center
		IAVI
		IAVI
		UAB

PROJECT DESCRIPTION:

This VISTA project is one of several vaccine related efforts underway at the International AIDS Vaccine Initiative (IAVI). Its intent is to enhance African research capacity and leadership, particularly with respect to HIV vaccine design. This is important because most cases of HIV infection occur within Africa, especially in the sub Saharan region. VISTA aims to identify vulnerable sites on HIV to inform vaccine design toward candidates that elicit strong cytotoxic T cell responses. VISTA includes traineeships for African scientists in molecular virology (in Dr. Redacted by agreement laboratory at the Emory Vaccine Center at Yerkes) and immunology (in IAVI's Human Immunology Laboratory at the Imperial College London and at African CRCs).

PROGRESS REPORT:

During the past reporting period, individuals in Redacted by agreement laboratory, under the guidance of Redacted by agreement have continued to sequence entire HIV-1 genomes from plasma isolated virus collected near the time of transmission. We have relied heavily on PacBio next generation sequencing techniques coupled with in-house-developed data processing algorithms. We have then cloned viral DNA regions to create infectious molecular clones (IMCs) using conventional methods as well as by using synthesized DNA segments produced by the GenScript company. These IMCs were then tested for infectivity and then transferred to the laboratory of Dr. Redacted by agreement at the University of Alabama at Birmingham. Here the luciferase reporter gene is added to IMCs for eventual use of these constructs in viral inhibition assays performed at the Human Immunology

Laboratory in the U.K. Approximately 22 IMCs from Rwandan subjects have been completed in the past year. However, a couple of these clones have been found to be nonfunctional, prompting us to investigate why a potential transmitted founder (TF) virus might not appear infectious in our system. We have also completed two IMCs from Ugandan subjects.
In addition to the above efforts, we continue our efforts to train African scientists several African nations in advanced molecular and virological techniques. In the past we have had visitors from Kenya, South Africa, Rwanda, Zambia, and Uganda. We are currently hosting one scientist from Uganda and are anticipating the arrival of a second scientist from this nation in the weeks to come. Here the goal is to ensure that these scientists possess the advanced skills required to conduct similar laboratory procedures once they return to their home nations. These many efforts are designed to promote vaccine research aimed at countering the spread of HIV-1. Since the bulk of worldwide infections occurs on the African continent, having scientists on the ground in these affected nations is important in accelerating efforts to combat this disease.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Redacted by agreement (Co-Investigator); Funded by Private Source
Support from the Emory Center for AIDS Research (P30 AI050409)
Yerkes National Primate Research Center base grant through the Office of Research Infrastructure Programs/OD P51OD11132

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: INNATE-ADAPTIVE CROSSTALK IN PROTECTIVE AND VACCINE-INDUCED IMMUNITY TO TB HOST RESPONSES BY MYCOBACTERIUM TUBERCULOSIS

SPID#: 13135

UNIT/DIVISION: Emory Vaccine Center

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: Infectious Disease

SUB-CATEGORY: Immunology

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R01AI134244

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Emory Vaccine Center
Prin. NPRC Core Sci.		
Other Core and Affil.		Emory Vaccine Center

PROJECT DESCRIPTION:

Developing an effective vaccine for tuberculosis (TB) remains challenging because we do not understand how to improve protective immunity to Mycobacterium tuberculosis (Mtb) infection. CD4 T cells and IFN-g responses are are not sufficient for conferring protective immunity and Mtb impairs DC functions, leading to antigen-specific CD4 T cells that are ineffective in controlling infection. Therefore we need to design vaccines that induce additional DC-T cell responses that confer better protection. There is accumulating evidence that Th17 responses are important for protective immunity to TB but the molecular mechanisms for Th17 generation in TB are not well defined. We previously showed that an avirulent hip1 mutant Mtb strain induces earlier and higher IL-17 responses and attenuated disease, suggesting that Mtb restricts optimal Th17 responses in the lung. Here we present novel data that links the CD40-costimulatory capacity of DCs with Th17 generation during Mtb infection. We propose to test the hypothesis that boosting the CD40-CD40L interaction and enhancing Th17 responses will improve protection against TB and contribute to immune control. Using a mucosal DC vaccination model, we will test whether boosting CD40-CD40L interactions improves protection and define the Mtb-specific T cell memory responses associated with protective immunity (Aim 1). We will use a BCG hip1 deletion strain, which induces higher CD40 expression and increased Th1 and Th17 responses, to assess its vaccine efficacy compared to BCG (Aim 2). To expand insights from mice to human TB, we will determine whether the capacity of DCs to promote IL-17 is greater in individuals who latently control infection compared to those who develop active TB. (Aim 3). Our studies will provide important mechanistic insights into how Mtb modulates DC-T crosstalk in animal models and human cells and open new avenues to target host pathways that can boost protective immunity and improve vaccine efficacy.

PROGRESS REPORT:

We have carried out experiments focusing on on Aims 1 and 2 and have laid the foundation for testing the hypotheses proposed in this project.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: THE ORIGIN, PREDICTORS AND IMMUNE CORRELATES OF VIRAL REBOUND IN ORALLY SHIV-INFECTED INFANT MACAQUES

SPID#: 13136

UNIT/DIVISION: Microbiology Immunology

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: AIDS

SUB-CATEGORY: AIDS

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER: P01AI131276

SUPPORTING ORGANIZATION: NIAID

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Duke Univ.
Prin. NPRC Core Sci.		Microbiology Immunology
Other Core and Affil.		

PROJECT DESCRIPTION:

Almost 2 million children are infected with HIV worldwide, and every year more than 150,000 new pediatric HIV infections occur. Postnatal breast milk transmission accounts for at least half of these new infections. Current standard of care commits HIV-infected children to lifelong, daily antiretroviral treatment (ART). A cure is needed to provide HIV-infected children a life without the medical complications, pharmacological burden, and social stigma associated with HIV-1 infection. While early initiation of ART leads to prolonged virus suppression, the virus rebounds after treatment cessation due to the persistence of virus reservoirs. However, there is hope that strategies to reduce or eliminate virus reservoirs could lead to long-term remission, as demonstrated by the over two-year ART-free remission that was demonstrated in the case known as `the Mississippi baby'. Using a highly relevant animal model, the overall goal of our Program is to define the origin, kinetics, and predictors of viral rebound in postnatally-infected infants, as well as assess the potential impact of immune-based interventions to eradicate pediatric HIV reservoirs. Our central hypothesis is that the origin and kinetics of viral rebound in postnatally infected infants can be predicted through biomarker measurement (Project 1) and can be extended through the enhancement of antiviral humoral and T cell immunity (Project 2). Specifically, we will use a highly translational animal model of pediatric HIV infection and long-term ART treatment to accomplish the following Specific Aims: 1) Define the origin, kinetics, and predictors of viral rebound following long term ART treatment in our animal model of postnatal infection; 2) Define the impact of passive immunization with broadly-neutralizing antibodies and T cell-based vaccine on viral rebound in our animal model of postnatal infection; and 3) Develop a mathematical model that will define the primary contributing factors and the potential efficacy of immune-based interventions on viral rebound following postnatal infection. Successfully completed, this Program will use our highly translational animal model to uniquely define the tissue origin, kinetics, and viral sequences of viral rebound, guiding development and evaluation of pediatric-specific HIV cure strategies; define biomarkers that

can be used to clinically predict viral rebound; and evaluate the impact of immune-based interventions on viral rebound. Together, these results will help guide the design of passive and active vaccine strategies to achieve long-term remission or cure in human infants.

PROGRESS REPORT:

Since this project was awarded, we have worked to achieve our objectives, specifically focusing on Aim 1 as the in vivo studies of this Program are initiated. The overall P01 was awarded on July 22nd, 2017 and the Notice of Award for the Emory Subcontract for Core 1 was received on November 20th, 2017. Since that time, we have also completed all of the relevant administrative procedures to identify and assign infant rhesus macaques to this study. The IACUC protocol (YER-1000513) was approved by Emory on 7/12/2017 and the Animal Request Form was reviewed by the Research Allocation Advisory Committee in December 2017. It should be noted that a reduction in the Award Budget necessitated a reduction in the number of animals able to be studied and supported by the Core (from 61 to 59). This reduction prompted us to re-assess the animal groups included in the original proposal and modifications were made that reflect allocation of what were previously 4 groups of animals into 2 groups of animals, while still maintaining adequate numbers of animals within each group to answer the important scientific questions posed by the leaders of Projects 1 & 2. We therefore combined groups A1 and B2 and well as B2 and C1. A1 and B2 combine the infant oral challenge model optimization with the control on-ART euthanasia for tissue reservoirs groups. B2 and C1 were previously treated the same, with ART initiation at week 8 after SHIV infection and ART interruption after 1 year, and now 6/10 in the new combined group will undergo immuno-PET/CT imaging (that was previously included in the experimental design for group B2). These revisions make the best use of both animal and budgetary resources. Due to the standard YNPRC rhesus macaque breeding season, infants were not available to be assigned to this protocol until the start of the birthing season (~March/April 2018). Since the start of the birthing season, 4 out of the 16 animals budgeted in Year 1 have been assigned (3 male and 1 female) and additional animals are being screened to meet our requirements, with exclusion of Mamu-B*08 and Mamu-B*17 positive animals due to their association with natural virus control. Currently assigned animals have been transferred to the YNPRC nursery at the Main Center from the Field Station and are under expert veterinarian care. They were infected the week of April 22nd, 2018. Based on feedback from the initial grant reviewers and developments in the field, we have selected the SHIV.CH505.375H.dCT, kindly provided by Redacted by agreement as the virus challenge for this study (rather than the SHIV1157ipd3N4 as originally proposed). The advantage of the SHIV.CH505 is that it contains a T/F Env from subtype C HIV and has been modified for enhanced binding to rhesus CD4. Furthermore, the groups of both Redacted by agreement and Redacted by agreement have extensive experience with mucosal challenge with this virus. Consideration was given to a similarly constructed SHIV.CH848 virus; however, the CH505 Env has a more favorable antibody binding and neutralization profile, that will be relevant for the activities of Project 2. The Materials Transfer Agreement for the antiretroviral drugs to be used in the study is now completed, with final signatures and drug shipment as expected.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

P01 AI131276

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: DURABLE ANTIBODY MEDIATED PROTECTION AGAINST HIV

SPID#: 13137

UNIT/DIVISION: Microbiology Immunology

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: AIDS

SUB-CATEGORY: AIDS

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER: P01AI124912

SUPPORTING ORGANIZATION: NIAID

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	University of Maryland / Institute for Human Virology
Prin. NPRC Core Sci.		Microbiology Immunology
Other Core and Affil.		

PROJECT DESCRIPTION:

The quest for a prophylactic AIDS vaccine is ongoing and it is probable that the successful vaccine must elicit protective antibody responses. Regardless of the mechanism of antibody-mediated protection, antibody persistence and appropriate T cell help are emerging as significant problems in AIDS vaccine development. The problem of antibody persistence is seen clearly in the RV144 trial. Protection was as highest in the first year but waned rapidly to background in parallel with anti-V2 antibodies that were associated with reduced risk of infection. Poor antibody persistence is not unique to RV144. It occurred in the VAX003/VAX004 efficacy trials, also using gp120 immunogens, and it has been observed repeatedly in gp120 vaccine trials in humans and non-human primates. Poor antibody persistence to gp120 is entwined with a second major problem. How to elicit necessary CD4+ T cell help without establishing fertile fields for increased HIV replication at sites of exposure, blunting protection, or increasing acquisition. It appears that vaccine-elicited CD4+ T cell and innate immune responses are associated with increased acquisition in the Step/Phambili trials that used an Ad5Hu- HIV “T-cell vaccine” as the immunogen. There are reports of vaccine-associated increased acquisition in non- human primate (NHP) models using other vectors and immunogens in addition to AdHu5. Taken together, the conjoint problems of antibody persistence and T cell “balance” must be solved for any antibody-based HIV vaccine to be effective. This requirement introduces a new concept for HIV vaccine development based on achieving “balanced” T cell and humoral responses, contrasting sharply with current approaches that focus on one arm or the other, or that seek to maximize both arms in parallel. Exploration of this concept forms the foundation of the proposed program that will test the central hypothesis that an HIV vaccine candidate can elicit durable antibody responses supported by a balanced CD4+ T cell profile that favors protection. This hypothesis is based on published work from the investigators and on solid preliminary data in RM models. This hypothesis will be tested via three highly interactive projects. Redacted by agreement (IHV) will lead the program Redacted by agreement IHV) will lead Project 1 that exploits DNA/Protein co-immunization protocols to test hypotheses regarding the disposition of plasma cell subsets and how they determine the unusually poor durability of anti-gp120 antibody responses Redacted by agreement (IHV) will lead Project 2 to determine how vaccine elicited CD4+ T cells attenuate antibody-mediated protection Redacted by agreement (Emory) will lead Project 3 to determine the

phenotypes of vaccine-elicited CD4+ T cells and innate immune signatures that favor durable protection. In terms of major outcomes, this work is expected to fully identify the mechanism of poor anti-Env antibody persistence and to overcome this problem while maintaining “safe” levels of CD4+ T cells that don’t blunt protection. These results are expected to fundamentally advance AIDS vaccine development for which broad durable protection is the Holy Grail.

PROGRESS REPORT:

During the last year of this project we have identified and assigned a total of 49 Indian origin rhesus macaques (RM) that were divided as follows: 34 animals for the studies included in Project #1 (led by Redacted by agreement which focuses on exploiting innovative DNA/Protein co-immunization protocols to improve the usually poor durability of anti-gp120 antibody responses) and 15 animals included in Project #2 (led by Redacted by agreement which focuses on determining how vaccine elicited mucosal CD4+ T cell responses may attenuate the protection from SHIV acquisition conferred by passive transfer of neutralizing antibodies. For Project #1, we conducted a series of in vitro studies of the immune responses generated by the used immunogens in terms of Envelope-specific plasmablasts responses in peripheral blood as detected by EliSPOT specific for IgG, IgM, and IgA. We found that the animals included in group 1 (receiving DNA-FLSCgp120+IL-12 together with FLSC gp120 protein) showed stronger pasmablasts responses both at day 4 post-boost immunization and one week after the third immunization as compared to the rhesus macaques that received FLSC gp120 protein only. In a subgroup of 6 animals (three per group) necropsy was conducted at week 28 after immunization, and plasma blast specific for the HIV Envelope proteins were in the bone marrow, draining and non-draining lymph nodes. In addition, germinal center follicular T helper (Tfh) responses wer also evaluated in draining and non-draining lymph nodes as well as overall T cell phenotyping. Finally, we banked and cryopreserved serum, plasma as well mononuclear cells from all harvested tissues. The results of this in-depth tissue analysis confirma more robust plasma blast and plasma cell response in macaques vaccinated with DNA + protein (as compared to protein alone). Additional analyses are currently ongoing to evaluate the T cell phenotype, including the possible increased level of activated CCR5+ CD4+ T cells in mucosal tissues that may enhance virus transmission, as well as a longitudinal evaluation of the levels of HI-Env-specific neutralizing and binding antibody in the serum.

PUBLICATIONS:

PMID	Title

None

FUNDING SOURCES:

NIAID P01AI124912

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: HIV REBOUND

SPID#: 13139

UNIT/DIVISION: Microbiology Immunology

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: AIDS

SUB-CATEGORY: Immunology

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: P01AI131338

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	University of Pennsylvania School of Medicine
Prin. NPRC Core Sci.		Microbiology Immunology
Other Core and Affil.		

PROJECT DESCRIPTION:

The majority of ART treated HIV-infected individuals experience detectable rebound in HIV plasma viremia within weeks following interruption of ART. Recent mathematical estimates suggest that virus reactivation events occur every 5-8 days following ART removal. Immunologic strategies to prevent or extend the time to virus reactivation and HIV rebound are critically needed to enable durable control or eradication of HIV within infected individuals. This P01 proposal will explore and model two immunologic strategies to prevent, limit, or delay viral rebound by (1) directly targeting rebounding virus through passive nAb therapy in transmitted founder-SHIV infected rhesus macaques (Project 1) and (2) inhibiting lymphocyte egress from LT to both prevent infected CD4+ T cell redistribution and enable the interaction between reactivated infected CD4+ T cells and protective CD8+ T cells in lymphoid tissue after ART interruption in SIV infected rhesus macaques (Project 2). Together these studies will provide novel insights into immunological strategies to delay or prevent viral rebound after ART interruption.

PROGRESS REPORT:

We have made significant progress in our proposed study aimed at testing immunological strategies to modulate viral rebound. In vivo studies of year 2 focused on project 2, i.e. at determining how administration of FTY720 impact on viral persistence during ART and viral rebound after ART treatment interruption (ATI). Specifically, 14 RMs became available for the study in March after completing mandatory quarantine. We have (i) optimized the complex flow cytometry panels that will be used longitudinally throughout the study; (ii) performed the baseline blood and tissue collections; (iii) infected all 14 animals with SIVmac239M; (iv) performed longitudinal collections at several experimental points post-infection in blood and tissues of the SIV-infected macaques; and (v) began the three-drug ART regimen in all 14 RMs. All 14 animals achieved undetectable plasma viremia while on ART. In 7 of these animals, we initiated the proposed treatment with FTY720 in the last 30 days of ART. Animals will interrupt ART and will be longitudinally followed for viral rebound.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: LIMITING HIV ESTABLISHMENT AND MAINTENANCE BY PRESERVING INTESTINAL IMMUNITY

SPID#: 13140

UNIT/DIVISION: Microbiology Immunology

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: AIDS

SUB-CATEGORY: Immunology

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER: R01AI129745

SUPPORTING ORGANIZATION: NIAID

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	University of Nebraska Medical Center
Prin. NPRC Core Sci.		Microbiology Immunology
Other Core and Affil.		

PROJECT DESCRIPTION:

Developing novel interventions aimed at limiting inflammation and improving immune responses is a key priority for HIV cure strategies. In this proposal we will investigate the effects of a combined interleukin (IL)-21 and anti-α4β7 monoclonal antibody (mAb) administration on inflammation, antiviral immune responses, and virus persistence in cART-suppressed SIV-infected rhesus macaques (RMs). The rationale for this combined intervention comes from our previous studies. First, we showed that IL-21 reduces inflammation, improves T cell immune function, and limits viral persistence – particularly in lymph nodes (LN) - when administered in acute or chronic, cART-treated SIV-infected RMs. Next, we showed that administration of anti-α4β7 mAb to ART-treated SIV-infected RMs resulted in a highly significant, unprecedent suppression of plasma and gut viral loads even after ART treatment interruption. While controlling viral rebound, anti-α4β7 treated RMs still maintain replication competent virus in their PBMCs and did not reduce the SIV reservoir in LN. Furthermore, anti-α4β7 mAb did not improve T cell immune responses. Thus, IL-21 supplementation has the potential to strongly synergize with anti-α4β7 in targeting SIV persistence.

PROGRESS REPORT:

We have made significant progress in our proposed studies aimed at testing the effects of the combined IL-21 and anti-□4ß7 monoclonal antibody (mAb) treatment in ART-treated, SIV-infected rhesus macaques (RMs). Specifically, we (i) performed a pilot study with 4 uninfected RMs to examine the safety and tolerability of the combined IL-21 and anti-□4ß7 treatment, (ii) optimized the complex flow cytometry panels that will be used longitudinally throughout the study; (iii) performed the baseline blood and tissue collections; (iv) infected all the remaining twenty-six animals with SIVmac239; (v) started ART in all 26 animals, with all of them achieving undetectable plasma viremia; (vi) performed longitudinal collections at several experimental points post-infection. At present, animals have been on ART for approximately 10 months. We will soon start the proposed immune

based interventions, including IL-21 and anti-□4ß7 administration.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: PERSISTENT VIRUS RESERVOIRS IN SIV-INFECTED MACAQUES

SPID#: 13141

UNIT/DIVISION: Microbiology Immunology

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: AIDS

SUB-CATEGORY: Immunology

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R33AI104278

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Microbiology Immunology
Prin. NPRC Core Sci.		
Other Core and Affil.		

PROJECT DESCRIPTION:

This project has two main Aims: (1) the identification of the anatomic location and precise cellular nature of the persistent HIV reservoir and (2) to design and monitor the effect of novel therapeutic strategies aimed at eliminating this reservoir. During the R21 phase of our R21/R33 TaPHIR grant, we developed and validated the rhesus macaque (RM) model of SIV infection for the study of viral reservoirs, by achieving prolonged clinically relevant suppression of plasma viral replication with a potent ART regimen. Using this model, we then defined the relationship between the expression of co-inhibitory receptors on memory CD4+ T cells and the level of infection of these cells in vivo under suppressive ART.

PROGRESS REPORT:

In the R21 part and in the first year of the R33 grant we (i) completed the analyses aimed at determining the contribution of memory CD4+ T cells expressing PD-1 and CTLA-4 to SIV persistence across all tissues sampled; (ii) investigated whether PD-1 and CTLA-4-expressing CD4+ T cells shared phenotypic and functional characteristics with functional CD4+ T cell subsets; (iii) investigated in the lymph node the establishment and maintenance of viral infection in PD-1 and CTLA-4 expressing T cells in situ; and (iv) compared the levels of SIV DNA in each of the PD-1 and/or CTLA-4-expressing or non-expressing memory CD4+ T cell subsets across the different tissue compartments at necropsy, in order to identify anatomic sites harboring heightened levels of SIV-infected cells. A manuscript summarizing these main findings has been published in Immunity (McGary et al, 2017). Furthermore, and in collaboration with Qura Therapeutics (partnership between UNC and GSK), human-macaque chimeric Abs antibodies that effectively target PD-1 and CTLA-4 expressing cells have been developed and tested for in vivo studies in ART-treated RMs. In the most recent period, we infected with SIVmac239 and treated with ART for 12 months the animals assigned to this study. Furthermore, after 1 year of ART we have started and completed the dual blockade of PD-1 and CTLA-4 administered to reduce or eliminate the persistent reservoir of latently infected memory CD4+ T cells. After completing the combined immune checkpoint blockade we stopped ART and longitudinally followed the kinetics of viral rebound after ART interruption. A manuscript

summarizing these data is in preparation; a preliminary version of our finding will be presented at CROI 2019 (Oral presentation, Seattle).

PUBLICATIONS:

PMID	Title
30305357	Bone Marrow-Derived CD4⁺ T Cells Are Depleted in Simian Immunodeficiency Virus-Infected Macaques and Contribute to the Size of the Replication-Competent Reservoir.
29045906	CTLA-4⁺PD-1⁻ Memory CD4⁺ T Cells Critically Contribute to Viral Persistence in Antiretroviral Therapy-Suppressed, SIV-Infected Rhesus Macaques.
28051083	The loss of CCR6⁺ and CD161⁺ CD4⁺ T-cell homeostasis contributes to disease progression in SIV-infected rhesus macaques.
27387885	Follicular T helper cells: hotspots for HIV-1 persistence.
26829644	Loss of Function of Intestinal IL-17 and IL-22 Producing Cells Contributes to Inflammation and Viral Persistence in SIV-Infected Rhesus Macaques.
27482392	Animal models in HIV cure research.
25023622	Animal models for viral infection and cell exhaustion.

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: IMPACT OF CONCURRENT HIV AND LATENT TB THERAPIES ON MTB-SPECIFIC IMMUNE FUNCTION

SPID#: 13143

UNIT/DIVISION: Emory Vaccine Center

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: Infectious Disease

SUB-CATEGORY: Immunology

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R01AI123047

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Emory Vaccine Center
Prin. NPRC Core Sci.		
Other Core and Affil.		Emory Vaccine Center

PROJECT DESCRIPTION:

Tuberculosis (TB) is the leading cause of death in Human Immunodeficiency Virus (HIV)-infected individuals globally. The majority of HIV-negative individuals infected with Mycobacterium tuberculosis (Mtb) are asymptomatic, and are considered to have latent TB infection (LTBI). Co-infection with HIV increases the risk of progressing to active TB disease (ATB) by over 20 fold but the underlying immune mechanisms remain unclear. Antiretroviral therapy (ART) decreases the incidence of ATB in HIV-infected individuals but the incidence of TB in HIV-coinfected individuals remains 4- to 7-fold higher after ART than in HIV-uninfected people in TB-endemic settings. Recent clinical trials have shown that regimens that concurrently administer Isoniazid Preventive Treatment (IPT) and ART are significantly better than ART alone in reducing TB incidence among individuals with LTBI. However, uptake of concurrent ART and IPT regimens remains poor and the immune mechanisms underlying the benefits of concurrent ART and IPT have not been defined. We propose to identify the components of TB immunity in the blood and lung compartments that remain impaired after ART, versus those that are restored by concurrent ART and IPT, in the rhesus macaque nonhuman primate (NHP) aerosol model of LTBI and Simian Immunodeficiency Virus (SIV) co-infection. We hypothesize that co-infection with SIV increases Mtb burden within alveolar macrophages in the lung and progressively impairs the functional capacities of tissue-resident Mtb-specific CD4 and CD8 T cells in the lung; ART only partially restores these functions. We further hypothesize that IPT-mediated reduction in Mtb burden, in conjunction with ART, enhances protective Mtb-specific T cell immunity compared to ART alone. We will model these concurrent regimens in a highly faithful model of Mtb/HIV co-infection in rhesus macaques to study the kinetics of lung-specific CD4 and CD8 T cell responses by longitudinal sampling of blood, bronchoalveolar lavage (BAL) and lung biopsy tissue. By identifying mechanisms underlying restoration of Mtb-specific immune function after concurrent ART and IPT, our studies have the potential to provide new insights into immune pathways that can be targeted for host-directed adjunctive therapies for TB/HIV co-infection and incorporated into designing better vaccines for TB.

PROGRESS REPORT:

We focused on optimizing flow cytometry assays to study tissue resident memory responses in the lung which is a central component of our proposal. Moreover since animal experiments were only able to begin in June 2018, we wanted to use this time to get all the assays ready. Overall, we have optimized flow cytometry panels for blood and lung specimens from Rhesus macaques to characterize tissue resident memory T cells.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: DETERMINING HOW MACROPHAGES REGULATE IMMUNITY TO ZIKA VIRUS INFECTION AT THE MATERNAL-FETAL INTERFACE

SPID#: 13144

UNIT/DIVISION: Emory Vaccine Center

TYPE: Research

START DATE: 3/1/2017

END DATE: 2/28/2022

GENERAL CATEGORY: Infectious Disease

SUB-CATEGORY: Immunology

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: U01AI131566

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Emory Vaccine Center / Pediatrics
Prin. NPRC Core Sci.		
Other Core and Affil.		Emory Vaccine Center / Pediatrics

PROJECT DESCRIPTION:

The placenta is characterized by intimate contact between the maternal blood and fetal chorionic villi. This organ is a target for rubella, cytomegalovirus, herpes simplex, HIV-1, hepatitis B and C viruses and parvovirus B19 infection, by either direct or contiguous infection of placental cell layers, virion passage through a breach or by cell-associated transport. Most recently, Zika virus (ZIKV), a mosquito-borne flavivirus of significant public health concern in the Americas, was found to transmit from an infected mother to the developing fetus in utero, resulting in adverse pregnancy outcomes characterized by fetal brain abnormalities and microcephaly. The greatest risk of serious fetal sequelae is associated with ZIKV infection early in pregnancy, suggesting enhanced tropism for placental cells during the first- and second-trimester. However the mechanism by which ZIKV establishes placental and fetal infection is poorly understood. We seek to fill this gap in knowledge and develop a deeper mechanistic understanding for how macrophages in the maternal-fetal compartment maintain immune homeostasis and restrict ZIKV transmission to the developing fetus. Given the increased risk of fetal demise associated with ZIKV infection early during pregnancy, we hypothesize that macrophages in the maternal-fetal compartment (decidual, placental and fetal) in early gestation are more permissive for ZIKV infection and replication as compared to late-gestation macrophages, directly corresponding to reduced potency of cell autonomous antiviral immune signaling. The major goals of our proposal are: 1) To define the dynamics of innate immune signaling in macrophages at the maternal-fetal interface during pregnancy; 2) To determine how macrophages in the maternal-fetal compartment control ZIKV infection during pregnancy.

PROGRESS REPORT:

The Redacted by agreement laboratory currently has three ongoing projects that are aligned with our proposed research:

1) During this reporting period, we established that dengue cross-reactive antibodies facilitate ZIKV infection of the placenta. This is a very important achievement as this now defines a mechanism by which ZIKV uses to cross the placental barrier and also highlights the impact that cross-reactive dengue antibodies can have on vertical transmission of a flavivirus. These findings were published in Cell Host Microbe in November 2018.

2) We have been characterizing the pattern recognition receptor (PRR) signaling pathways as described in Aim 1 of our grant. We have now treated Hofbauer cells with a panel of Toll-like receptors (TLRs), RIG-I-like receptors (RLRs) and cGAS ligands to better understand the ability of Hofbauer cells to respond to pathogen associated molecular patterns (PAMPs).
Hofbauer cells (HCs) are placental-resident macrophages (MΦ) derived from the fetal yolk-sac and implicated in placental homeostasis, immune regulation, and protein transfer at the maternal-fetal barrier. Several studies have demonstrated that HCs are targets of viral infection, including Zika virus (ZIKV) which is transmitted from an infected mother and can result in adverse pregnancy outcomes ranging from congenital brain abnormalities and microcephaly to miscarriage and stillbirth. Interestingly, decidual MΦ (maternal-derived and in an immune-competent environment) are not permissive to ZIKV infection, suggesting that divergent ontogeny/phenotype and microenvironment may contribute to cellular tropism. However, much of the immunobiology and responsiveness of HCs to invading pathogens within the immune privileged villous stroma remains largely unexplored. In this project, we focused on elucidating the phenotypic and functional plasticity of these cells at steady state and in response to viral pathogens. To evaluate HC immunophenotype, HCs were isolated from 2nd trimester and term placenta (N=5 ea.), then RNA isolated for bulk RNAseq analyses. We will perform comparative transcriptomic and pathway analyses on: 1) freshly isolated HCs (i.e. those at steady state); 2) ZIKV-affected HCs; and 3) monocyte-derived macrophages (MDMΦ) polarized to conventional M1/M2 phenotypes (N=5 ea.). To determine HC functional response to invading viral pathogens, HCs from the same donors (indicated above) were stimulated with multiple pattern recognition receptor agonists and their response evaluated by 25-plex Luminex assays and qPCR analyses for induction of immune and anti-viral effectors. Here we focus on the cytosolic helicases RIG-I and MDA5 along with STING, which are known to recognize viral RNA and DNA, respectively. In another set of experiments, we treated HCs from term placenta with TLR agonists (TLR1/2- Pam3CSK4, TLR2-HKLM, TLR3- Poly-I:C, TLR4- LPS TLR5- FLA-ST (Flagellin), TLR2/6- FSL-1, TLR7- Imiquimod and TLR8-ssRNA40/LyoVec). While ZIKV fails to induce a pro-inflammatory cytokine response (at the protein level) in HCs, we found that each of these agonists trigger a potent cytokine response, with some variation between treatments.

3) We have also focused on our efforts to better understand the virus-host interactions that regulate ZIKV infection of Hofbauer cells. In a previous study, we made a couple of observations that have identified targets of ZIKV antagonism of the innate immune response using human monocyte derived dendritic cells and human cell lines. We have now extended these observations into our HCs using either normal ZIKV infection conditions or under ZIKV enhancing conditions (ADE). Our efforts are now focused on identifying the mechanisms by which ZIKV blocks type I IFN induction and STAT5 activation, which is a transcription factor critical in promoting costimulatory molecule expression.

PUBLICATIONS:

PMID	Title
29860306	Human Cytomegalovirus Enhances Placental Susceptibility and Replication of Human Immunodeficiency Virus Type 1 (HIV-1), Which May Facilitate In Utero HIV-1 Transmission.
28776046	Jak Inhibitors Modulate Production of Replication-Competent Zika Virus in Human Hofbauer, Trophoblasts, and Neuroblastoma cells.
30439342	Cross-Reactive Dengue Virus Antibodies Augment Zika Virus Infection of Human Placental Macrophages.

FUNDING SOURCES:

Redacted by agreement NIH/NIAID Grant # U01AI131566

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE:	EFFECTS OF HORMONAL CONTRACEPTIVES ON GENITAL IMMUNITY AND HIV SUSCEPTIBILITY
SPID#:	13145
UNIT/DIVISION:	Microbiology Immunology
TYPE:	Research
START DATE:	9/1/2018
END DATE:	8/31/2019
GENERAL CATEGORY:	AIDS
SUB-CATEGORY:	Women's Health
NIH GRANT:	☒ Yes ☐ No
GRANT NUMBER:	R01HD089831
SUPPORTING ORGANIZATION:	NIH
SPECIFIC INFORMATION:	

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	U. Washington
Prin. NPRC Core Sci.		
Other Core and Affil.	Redacted by agreement	Microbiology Immunology

PROJECT DESCRIPTION:

The results from this study will inform contraceptive recommendations for women with HIV risk, including international recommendations by the World Health Organization, the normative body that convenes annual reviews of the emerging data on contraceptives and HIV risk.

PROGRESS REPORT:

In the past year we have completed RNA preparation from approximately 30 samples from the female genital tract of Kenyan and South African women. We ran RNA-Seq on 15 samples as a pilot to establish the optimal library preparation method. These results were presented by webinar at a meeting of the investigators in Madrid Spain prior to the R4P meeting in October 2018.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE:	GENETIC REGULATION OF VARIABILITY IN BRAIN OXYTOCIN RECEPTORS
SPID#:	13146
UNIT/DIVISION:	Behavioral Neuroscience and Psychiatric Disorders
TYPE:	Research
START DATE:	5/24/2018
END DATE:	2/28/2023
GENERAL CATEGORY:	Genetic
SUB-CATEGORY:	Neural
NIH GRANT:	☒ Yes ☐ No
GRANT NUMBER:	R01MH112788
SUPPORTING ORGANIZATION:	NIH
SPECIFIC INFORMATION:	

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Behavioral Neuroscience and Psychiatric Disorders
Prin. NPRC Core Sci.		Behavioral Neuroscience and Psychiatric Disorders
Other Core and Affil.		

PROJECT DESCRIPTION:

Oxytocin (OT) regulates many aspects of social behavior, including parental nurturing, social information processing, and social attachment. OT is thought to influence social behaviors by enhancing the salience and reinforcing value of social stimuli. Intranasal administration of OT in humans increases attention to social cues, emotion detection and socially reinforced learning. Intranasal OT enhances some aspects of social functioning in individuals with autism spectrum disorder (ASD), and the OT system is a leading pharmacological target for enhancing social function in ASD. Single nucleotide polymorphisms (SNPs) in noncoding regions of the human OT receptor gene (OXTR) are associated with core symptoms of ASD, altered brain activity patterns, and diagnosis of ASD. However, human gene association studies do not provide insights into how polymorphisms in OXTR lead to variation in brain function or social behavior. The socially monogamous prairie vole is an ideal model organism to explore the precise molecular mechanisms by which variation in the OXTR gene can lead to alterations in brain phenotype, and downstream social behaviors. OXTR signaling in the nucleus accumbans (NAcc) is critically involved in alloparental nurturing and social bond formation in prairie voles. There is remarkable individual variation in the density of OXTR in the NAcc of prairie voles that is associated with variation in social behavior and with resilience to early life social neglect. A set of 14 SNPs in the prairie vole OXTR gene (Oxtr) explains up to 80% of the variation in OXTR density in the NAcc, but not in other brain areas. The goal of this proposal is to use prairie voles to explore how variation in Oxtr influences molecular processes and brain phenotypes that are part of machinery hypothesized to affect downstream behavioral phenotypes. Since the 14 SNPs strongly associated with NAcc OXTR density were in perfect linkage disequilibrium in the samples studied thus far, it is not possible to determine which of those SNPs is most likely to be influencing Oxtr expression. The first Aim will examine the association of the candidate SNPs with NAcc OXTR density in 230 genetically diverse prairie voles to identify the SNPs most strongly associated with OXTR density in the NAcc. The second Aim will examine the influence of the candidate SNPs and their associated molecular phenotype on coordinated brain activity during sociosexual interactions. The third Aim will use chromatin immunoprecipitation

(ChIP) to characterize the regulatory landscape of the Oxtr in NAcc and other brain regions in order to further refine the list of SNPs most likely to be influencing brain phenotype. Finally, the CRISPR/Cas9 genome editing system will be used to edit the SNPs most likely to be functional in order to identify those with the greatest influence on OXTR density in the NAcc. Characterization of the regulatory status of the SNP most likely to be influencing OXTR expression and the consequences on brain function will provide important insights that will guide future human genetic studies investigating the potential influence of OXTR SNPs on brain phenotype, social cognition and psychopathology.

PROGRESS REPORT:

Major activities

With respect to Aim 1, we have made a major effort and progress to diversity the genetics of our prairie vole colony by introducing completely unrelated animals that are F1 from wild caught stock. We anticipate that the wild caught animals (who are unrelated to each other as far as we know) will have a different LD structure at the Oxtr gene than the animals in our colony. We imported 14 adult F1 from wild animals into our colony from Redacted by agreement at Cornell University. We created new breeder pairs at Emory consisting of 14 breeders from our original colony, each paired with a wild derived partner. Those animals have since produced multiple litters of offspring. We have now collected brains and DNA from 80 animals (40 male and 40 females). I addition, Redacted by agreement provided us with 20 brains from wild caught animals. We have now cut all but 15 of these brains from the olfactory bulb to the hindbrain. The remaining 15 will be cut in the next two weeks. We have also used PCR and DNA sequencing to genotype 40 kbp of the Oxtr from each of these animals. We have devised new wells using 3D printing that will allow us to do large scale autoradiography assays with >200 slides at a time. We should have the autoradiography done by mid-February and then we can begin to quantify OXTR binding in various brain regions and relate binding to the SNPs to identify which SNPs remain highly associated with binding density. We will be able to get additional animals from the wild in coming years if this appears to be useful. Redacted by agreement postdoctoral fellow who contributed significantly to writing the grant and was going to be in charge of Aim, unfortunately left the lab because of uncertainty in funding after Council. I have hired a technician in his place. He is still at Yerkes and I am hopeful that he will be able to return to this project after his current commitment.

With respect to Aim 3, based on advice from a chromatin expert, we decided focus on ATAC-seq for our initial chromatin studies. We microdissected tissue from the striatum (expresses Oxtr in a SNP dependent way), the insular cortex (INS; expresses Oxtr independently of the SNP) and the superior colliculus (does not express Oxtr) and then performed ATAC-seq. In our first experiment we got data only for the NAc and INS. Peaks in the ATAC-seq data indicate locations of open chromatin, which are areas that may be regulatory and SNPs in those areas are potentially affecting expression.

In this preliminary study, we see consistent peaks in the 5' flanking region (e.g. promoter) of the Oxtr. We also see peaks in the intron that are more robust in the striatum than in the insular cortex, and one of these aligns with one of our candidate SNPs. Now that we have worked out the technique and the pipeline for analyzing the data we will repeat this with all 3 brain regions and include 6 replicates (3 male and 3 female) for each area so that we can be confident that any differences we see are real.

We have made progress technical progress in relation to Aim 4, which used CRISPR to create germline mutations in the Oxtr. Redacted by agreement was able to use CRISPR to create null mutations in the prairie vole Oxtr gene. He has worked out the procedure so that he has very efficient gene editing rates. We published the generation of these Oxtr knockout voles along with a preliminary analysis of their behavioral phenotype in Hormones and Behavior. This gives us confidence that we will be able to edit the candidate SNPs using CRISPR once we have a better idea of which SNP is most likely to be active.

Rigor and Reproducibility: A power analysis was conducted beforehand to ensure that the experiments group was sufficiently powered to meet statistical significance at $p < 0.05$ based on estimated effect sizes. Moreover, throughout the course of these studies experimenters were blinded to the treatment condition/genotype until all data had been collected and analyzed.

Key Outcomes: We have increased the genetic diversity of our breeding colony in order to break up the LD structure and collected brains and DNA from a large number of animals and are ready to begin autoradiography. We have developed an ATAC-seq assay for vole brain tissue and established a pipeline for analyzing chromatin structure for Oxtr from this data. We have optimized CRISPR for mutation the Oxtr in prairie vole embryo.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Redacted by agreement Funded by NIMH.

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: MODULATION OF TYPE 1 IFN SIGNALING TO REDUCE THE IMMUNOGENICITY OF RECOMBINANT AAV VECTORS

SPID#: 13147

UNIT/DIVISION: Microbiology Immunology

TYPE: Pilot

START DATE:

END DATE:

GENERAL CATEGORY: AIDS

SUB-CATEGORY: Immunology

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: P51OD011132

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	University of Miami, Pathology
Prin. NPRC Core Sci.		
Other Core and Affil.		Microbiology Immunology

PROJECT DESCRIPTION:

Infusions of HIV-1-specific broadly neutralizing antibodies (bNAbs) have been shown to suppress viremia in infected individuals, and clinical trials are ongoing to assess the prophylactic potential of bNAbs. Although these results are very promising, passive immunization is impractical to prevent or treat HIV infection in millions of people. In view of these obstacles, rAAV-mediated transfer of genes encoding bNAbs offers an attractive, cost-effective, and safe alternative to passive delivery of bNAbs. The utility of AAV as a gene therapy vector stems from its non-pathogenicity and ability to transduce both dividing and non-dividing cells. Additionally, the only protein expressed from rAAV vectors is the transgene product and, as long as it is viewed as “self” by the immune system, transgene expression can persist for long periods of time. Since muscle cells undergo little or no turnover, they are a preferred target for rAAV-mediated gene transfer. Little or no integration occurs in rAAV-transduced cells and rAAV vectors have been well tolerated in past clinical trials. Unfortunately, harnessing the full potential of rAAV as a vector platform for delivering bNAbs genes faces important hurdles, including the development of anti-drug antibodies (ADAs). As expected, the immunogenicity of mAbs increases proportionately with the degree of species mismatch between the mAb molecule and the host13. However, even in cases of complete species match, delivery of mAbs by either passive infusion or rAAV-mediated gene transfer can elicit ADAs2. Indeed, rhesus macaques treated with rAAV vectors encoding SIV-specific mAbs of rhesus origin have been shown to mount ADAs4. Additionally, preliminary analyses of the IAVI-sponsored clinical trial of a rAAV vector encoding the anti-HIV-1 bNAbs PG9 have revealed ADAs in 7/16 AAV-treated subjects total, and in 7/9 individuals in the highest dose groups. Although pharmacological immunosuppression and in vivo B-cell depletion have been shown to prevent the elicitation of ADAs in humans, the high risk and cost associated with these approaches make them impractical for large scale clinical implementation. Thus, the development of short term interventions for suppressing ADAs without immunocompromising the host would greatly improve the utility

of rAAV-based gene therapies.

PROGRESS REPORT:

Initial efforts have focused on production of the production of the type I IFN inhibitor by our collaborator in Israel and obtaining IACUC approval. We now have the type I IFN inhibitor in the lab and the animal protocol is almost complete. We have also selected the AAV-seronegative animals for this project. We expect to start this experiment in the first half of February.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: DEVELOPMENT AND COMPARISON OF TECHNOLOGY FOR AUTOMATED HIGH-THROUGHPUT COGNITIVE PHENOTYPING IN LARGE SOCIAL GROUPS OF RHESUS MONKEYS

SPID#: 13148

UNIT/DIVISION: Developmental and Cognitive Neuroscience

TYPE: Pilot

START DATE:

END DATE:

GENERAL CATEGORY: Animal

SUB-CATEGORY: Behavior

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: P51OD011132

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Developmental and Cognitive Neuroscience
Prin. NPRC Core Sci.		Developmental and Cognitive Neuroscience
Other Core and Affil.		Animal Resource

PROJECT DESCRIPTION:

Because of the rising costs of keeping nonhuman primates for biomedical research, it is increasingly important to make efficient use of all available animals. We can increase the value of our national primate resources by both using the largest proportion of subjects in research at all times, and by implementing technology that allows us to use animals to advance science in new ways, without compromising reproduction. We propose to develop and compare technologies that will leverage the animal resources at the Yerkes Field Station to enable whole colony cognitive phenotyping. We will assess the feasibility of this new technology by scaling up cognitive tests developed in the laboratory for use with small numbers of subjects, to the field station scale involving ten times as many animals. Our objective with this application is to develop new techniques for cognitive testing that allow cognitive phenotyping at the colony scale. Our rationale is that such whole-colony cognitive phenotyping will make possible a new generation of studies of the genetic, developmental, dietary, physiological, and social determinants of cognitive function. We will achieve this goal without affecting our ability to carry out the range of studies, and monkey production, that depend on our current animal resources.

PROGRESS REPORT:

We have developed, built, and tested a prototype. Testing was conducted in a large social cage. We are currently building another unit based on this experience, and we will deploy it at the Yerkes Field station shortly for full testing in a group compound.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Redacted by agreement Co-PI (with Redacted by agreement NICHD T-32 Training Grant, Co-PI with Redacted by agreement Mechanisms of learning across development and species

Redacted by agreement PI, National Science Foundation, Function and evolution of cognitive monitoring and cognitive control in monkeys.

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: ELECTROPHYSIOLOGICAL EFFECTS OF ELECTRICAL AND CHEMICAL INHIBITION OF THE THALAMIC BURST IN A NON-HUMAN PRIMATE MODEL OF FOCAL MOTOR SEIZURES

SPID#: 13149

UNIT/DIVISION: Neuropharmacology and Neurologic Diseases

TYPE: Pilot

START DATE:

END DATE:

GENERAL CATEGORY: Neural

SUB-CATEGORY: Therapy

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: P51OD011132

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Neuropharmacology and Neurologic Diseases
Prin. NPRC Core Sci.		Neuropharmacology and Neurologic Diseases
Other Core and Affil.		

PROJECT DESCRIPTION:

Epilepsy is a common and devastating medical problem, which remains insufficiently treated in 30% of patients. It is understood that seizures commonly arise in cortical regions or the temporal lobe but also involve subcortical circuits that frequently include the basal ganglia and thalamus. However, our understanding of the brain mechanisms that maintain and propagate seizure activity remains incomplete, at least in part because of the lack of animal models of seizure activity that would represent the anatomical complexity that is at play in seizures in humans. A particularly poorly understood component of the propagation of seizure activity in the thalamus is the involvement in seizure activity of neurons within the basal ganglia receiving ventral motor thalamus. This portion of the thalamus receives basal ganglia input, and is engaged in reciprocal connections with the cerebral cortex. It is important to study activity patterns of these ventral thalamic neurons and their projections in primates, because its circuitry has undergone significant evolutionary changes, such as the emergence of interneurons in primates whose activity (presumably) shapes the activity of thalamic and cortical neurons. We therefore propose to analyze the activity of neurons in this area in a primate model of focal motor seizures. A very prominent seizure-related abnormality of neuronal discharge in most brain regions is an increase of the incidence of synchronized burst discharges, which occur concomitant to ictal activity in simultaneously recorded electroencephalographic (EEG) records. This phenomenon has been well described in the basal ganglia in several seizure models, as well as in some areas of the thalamus (mostly anterior dorsal nucleus) in epileptic patients, and in rat models of temporal lobe epilepsy. Intra-cellular and extracellular recordings in the existing animal studies have demonstrated that the activation of T-type calcium channels in thalamic neurons is critical for the generation of

burst firing patterns and the emergence of neuronal synchrony affecting thalamocortical interactions. These channels are abundant in the thalamus, and pharmacologic blockade of T-type calcium channels is known to have anti-epileptic properties. However, the available T-type calcium channel active drugs (such as ethosuximide or zonisamide) are non-specific, and can induce significant side effects such as psychosis, or sleep disturbances, which limit their usefulness. Recently, a family of highly specific T-type calcium channel blockers has become available. Here we propose to study the effects of focal motor seizures and potentially therapeutic modulation of thalamic bursting activities on the cortico-thalamic network.

PROGRESS REPORT:

Two monkeys have been assigned to this project. The coordinate of the target have been identified and baseline recordings of unit and local field potentials (LFPs) have been performed. We successfully recorded the approximately 20 cells and their respective LFPs during seizures and interictal activity. We will pursue the thalamic recordings during seizures and test the effect of GPi stimulation in coming weeks.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: CIFAR GLOBAL SCHOLAR PROGRAM

SPID#: 13150

UNIT/DIVISION: Behavioral Neuroscience and Psychiatric Disorders

TYPE: Research

START DATE: 10/1/2017

END DATE: 9/30/2019

GENERAL CATEGORY: Genetic

SUB-CATEGORY: Psychiatric

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER:

SUPPORTING ORGANIZATION: Private Source

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Behavioral Neuroscience and Psychiatric Disorders
Prin. NPRC Core Sci.		
Other Core and Affil.		Behavioral Neuroscience and Psychiatric Disorders

PROJECT DESCRIPTION:

The Private Source program provides funding and support to help Scholars build their network and develop essential skills to become the next generation of research leaders. I was 1 of 15 early stage investigators across the world that was selected for this honor in 2017. This award was used to fund research expenses for all projects in my laboratory. This included the role of a sub-thalamic brain region, the zona incerta, in fear-related behavior and using olfaction to follow intergenerational imprints of stress. In addition, Private Source provided me with professional development funds to "attend" an online grant-writing workshop.

PROGRESS REPORT:

During this time, thanks to Private Source support:
1. I attended an online grant-writing workshop.
2. I presented my work at 2 CIFAR meetings: the CIFAR Global Scholar Meeting and a CIFAR Child & Brain Development Program meeting.
3. we published one paper in Biological Psychiatry (Aoued et al.)
4. we have deposited two papers on bioRxiv and are seeking publication for these manuscripts.

PUBLICATIONS:

PMID	Title
30292395	Reversing Behavioral, Neuroanatomical, and Germline Influences of Intergenerational Stress.

FUNDING SOURCES:

Private Source

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: FRONTIERS IN ADDICTION RESEARCH AND PREGNANCY

SPID#: 13151

UNIT/DIVISION: Behavioral Neuroscience and Psychiatric Disorders

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: Reproductive

SUB-CATEGORY: Addiction

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER: R25DA043880

SUPPORTING ORGANIZATION: NIDA

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	University of Pissburgh
Prin. NPRC Core Sci.		
Other Core and Affil.		Behavioral Neuroscience and Psychiatric Disorders

PROJECT DESCRIPTION:

Frontiers in Addiction Research and Pregnancy is a week long course focusing on the topic of addiction and pregnancy. Because of the opioid epidemic, this is a very timely course that informs scientists early in their career on the fundamentals of the problem and its treatment. The participants are diverse and are exposed to didactic lectures, discussion groups and laboratory exercises.

PROGRESS REPORT:

The Frontiers in Addiction Research & Pregnancy (FrARP) teaching/training course was held in Atlanta from Oct 12 to 18 and was a significant success. The meeting venues were the Ellis Hotel and Morehouse School of Medicine. Shuttle transport between the two was timely and efficient. There were 16 trainee/participants from several countries and at several training levels. The lecturers, all expert in their area and from outstanding institutions, were also quite diverse coming from many places in the USA. The lecture topics focused on the topic of addiction and pregnancy. The workshop demonstrations were in laboratories at Morehouse and were highly interactive. The participants were involved and there was lively discussion. There was an emphasis on mentoring and career development information was given by the experienced faculty. The participants especially enjoyed and participated in this. Overall, the program provided clear presentations with enough time to permit questions from the participants. Plans were made for the next course on the west coast in San Diego.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Redacted by agreement NIDA

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: HARNESSING IL-10 IN CART TREATED SIV INFECTED MACAQUES TO RESTORE IMMUNITY AND TO ERADICATE HIV

SPID#: 13152

UNIT/DIVISION: Microbiology Immunology

TYPE: Research

START DATE: 7/1/2018

END DATE: 6/30/2023

GENERAL CATEGORY: AIDS

SUB-CATEGORY: Immunology

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R37AI141258

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Case WEstern
Prin. NPRC Core Sci.		Microbiology Immunology
Other Core and Affil.		

PROJECT DESCRIPTION:

While current ART has prevented AIDS and reduced HIV-related morbidities and mortality for the majority of infected individuals, a therapeutic regimen able to eradicate or functionally cure HIV infection does not exist. Persistence of HIV in a small pool of latently infected cells remains the major obstacle for HIV eradication largely because the mechanisms that underlie viral persistence are still unknown. Our group has generated significant and convincing results in cART treated HIV infected humans and SIV infected rhesus macaques (RMs) suggesting that Interleukin(IL)-10 plays an important role in the establishment and maintenance of the HIV reservoir by (i) impeding the early antiviral innate and the HIV/SIV specific adaptive immune response and (ii) promoting the differentiation of Tfh and Tr1 cells that are major HIV/SIV reservoirs. The importance of IL-10 in the establishment and maintenance of HIV has prompted Merck to successfully develop a Rhesus form of an anti-human IL-10 Ab that is currently being tested in clinic; administration of this Ab in a proof of concept study to SIV infected RMs was safe and well tolerated; it also recapitulated several of the biological activities of the human Ab as it showed a negative impact on Tfh frequencies which could translate in a smaller reservoir. In this proposal, we will test the hypothesis that neutralization of IL-10 activity systemically and in lymphoid tissues will lead to restoration of cellular immune responses, decreased Tfh and Tr1 numbers, and a decay in HIV reservoir. Biomarkers that predict successful clinical interventions involving anti-IL-10 and leading to HIV eradication are not available. In Aim 1, we will perform an unbiased OMICs integrated approach to identify cell subsets, soluble effector molecules, metabolites and molecular pathways, which underlie the modulation of HIV reservoirs by IL-10 in cell subsets isolated from PBMCs and tissues from cART treated HIV infected subjects. We will identify markers that are associated to low levels of IL-10 and conversely to lower HIV reservoir in Tfh and Tr1 cells and efficient innate antiviral and cell mediated immunity. These markers will be used to monitor the impact of the anti-IL-10 intervention that aims at restoring innate antiviral immunity and cell mediated immunity for HIV eradication.

Direct demonstration that IL-10 regulates HIV persistence will be provided by examining the impact of IL-10 blockade on virus persistence in a large study of ART-treated, SIV-infected RMs. Preclinical trial of Aim 2 will allow us to determine the restoration of innate immunity by early IL-10 blockade as this intervention should inhibit the upregulation of NLRX-1, a molecule we have shown to play a critical role in the early HIV/SIV dissemination and conversely in the seeding of the HIV/SIV reservoir. Pre-clinical trial of Aim 3 should allow the restoration of the adaptive immune response by preventing the development of IL-10 producing Tr1 cells; IL-10 blockade will also trigger the HIV/SIV reservoir decay in Tfh cells which depend on IL-10 for their survival and differentiation. Achievement of these goals will lead to the development of a much-needed strategy aimed at eradicating HIV.

PROGRESS REPORT:

HIV eradication have become a realistic possibility as was shown by the Berlin patient who was cured of HIV by bone marrow transplantation of cells that cannot be infected by HIV. Therapeutic interventions which are less invasive must be explored and tested. We present here a novel strategy that targets IL-10, a cytokine that enhances the number of cells that can become reservoirs for HIV and inhibits antiviral immune responses. We expect that our approach will restore immune responses and decrease the reservoir size, thus promoting HIV remission. During the 7 month period of this project, we have made significant progress in our proposed studies aimed at testing the effects of anti-IL-10 monoclonal antibody (mAb) treatment in ART-treated, SIV-infected rhesus macaques (RMs). Specifically, we completed all the relevant documents for animal assignation to the study and finalized the MTAs for the antiretroviral drugs (ART). Fifteen RMs have been assigned to this study. Since assignation, we (i) optimized the complex flow cytometry panels that will be used longitudinally throughout the study and (ii) performed the baseline blood and tissue collections. All animals will be experimentally infected with SIVmac239 in the next two months and will start ART at 6 weeks post infection. In the meantime, we have continued the PK/PD study on the anti-IL-10 antibody to further define the dose with the best balance between safety and activity in blocking IL-10 in blood and tissues.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: INACTIVATION OF THE INTERNAL GLOBUS PALLIDUS IN MONKEYS BY CHEMOGENETIC MODULATION OF LIGAND-GATED ION CHANNELS

SPID#: 13153

UNIT/DIVISION: Neuropharmacology and Neurologic Diseases

TYPE: Research

START DATE: 7/1/2018

END DATE: 6/30/2020

GENERAL CATEGORY: Neural

SUB-CATEGORY: Brain Structure/Function

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R21NS106346

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Neuropharmacology and Neurologic Diseases
Prin. NPRC Core Sci.		Neuropharmacology and Neurologic Diseases
Other Core and Affil.		Developmental and Cognitive Neuroscience

PROJECT DESCRIPTION:

Abnormal activity patterns in specific neuron networks may underlie dysfunction in many brain diseases. It is therefore a goal of translational research to manipulate the activity of specific brain pathways in an effort to restore normal function. Current clinical neuromodulation methods (such as deep brain stimulation) are relatively non-specific, and can lead to significant side effects. Novel genetically based neuromodulation techniques have made it possible to more precisely target specific neuron populations. Among these, chemogenetic techniques have gained attention because of their high translational potential. These methods involve the use of engineered receptors that are introduced into specific neuron types using genetic manipulations. The receptors will not be activated by endogenous neurotransmitters, but only by exogenously applied compounds. Thus, a systemically administered drug can elicit specific actions in genetically targeted neuron populations. While widely used in rodents, chemogenetic methods in primates remains in their infancy. We are interested in the use of chemogenetic tools to control ligand-gated ion channels (LGICs) in primates. These channels can directly influence the electrical properties of neurons and increase or decrease the neuronal activity depending on the ion channel. A recently developed subtype of LGICs, termed “pharmacologically selective actuator molecules” (PSAMs), is based on nicotinic receptors which are engineered to not recognize their endogenous activator, acetylcholine, but to be selectively activated by a “pharmacologically selective effector molecule” (PSEM), or by very small doses of the clinically approved drug varenicline. The fact that the PSAM approach re-purposes a clinically used drug makes it highly attractive for translation into therapy for human diseases. However, PSAMs have not yet been used in primates (human or non-human). It is therefore essential to examine the expression and function of these receptors in monkeys. In this project, we plan to study whether PSAMs can be used in monkeys to manipulate neuron activities and behavior. It is our long-term goal to test the potential of PSAMs as an antiparkinsonian treatment. In the proposed experiments, we will express PSAMs in the internal pallidum

(GPi) of monkeys using viral vectors. We have chosen GPi as a target because GPi activity is abnormal in various movement disorders, including Parkinson's disease (PD), and manipulation of GPi activity (such as pallidotomy procedures) has antiparkinsonian properties. Once the (inhibitory) PSAMs are expressed in GPi, we will systemically administer varenicline or PSEM, expecting to induce a reduction of the activity of GPi neurons and slow movement. The expression of PSAMs will be verified by in vivo PET imaging, as well as post-mortem histology. Data generated by this project will be used for a subsequent R01 proposal in which we will examine the effects of PSAM-mediated inactivation of GPi in MPTP-treated parkinsonian monkeys. If we find that this technique has antiparkinsonian properties without inducing adverse effects, it could be developed into a new therapy for treating PD symptoms with fewer side effects than the currently available methods.

PROGRESS REPORT:

This project started on July 2018. We have requested 2 rhesus monkeys, and the animals were recently assigned to the project. In the next few months, the animals will be habituated to the experimental setting. Yerkes Imaging Core is in the process of preparing [18F]-ASEM for the imaging portion of the study.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: INHIBITING P13K P110B TO BLOCK COCAINE-INDUCED HABITS AND DRUG SEEKING

SPID#: 13154

UNIT/DIVISION: Behavioral Neuroscience and Psychiatric Disorders

TYPE: Research

START DATE:

END DATE:

GENERAL CATEGORY: Neural

SUB-CATEGORY: Behavior

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R01DA044297

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Behavioral Neuroscience and Psychiatric Disorders
Prin. NPRC Core Sci.		
Other Core and Affil.		Behavioral Neuroscience and Psychiatric Disorders

PROJECT DESCRIPTION:

PI3-kinase (PI3K) is a membrane-associated signaling complex that phosphorylates phosphoinositides, second messengers that regulate neuronal development, survival, and plasticity. In 2002, Izzo et al. reported that intraventricular PI3K inhibition blocks the expression of cocaine-induced psychomotor sensitization (Nature Neurosci.). Subsequent studies indicated that repeated cocaine exposure can increase PI3K activity in the medial prefrontal cortex (mPFC). Nevertheless, causal relationships between mPFC PI3K and cocaine-induced behavioral sequelae remain unconfirmed. We will directly manipulate the PI3K subunit p110β to mitigate stimulus-elicited habits following cocaine.

p110β is one of the four PI3K catalytic subunits, and it is highly expressed throughout postnatal development and in adulthood. We find that reduction of Pik3cb, encoding p110β, broadly throughout the mPFC blocks stimulus-elicited habits and locomotor sensitization following cocaine exposure during adolescence or young adulthood. These are periods of considerable drug experimentation in humans. In Aim 1, we will use viral-mediated gene silencing to identify specific mPFC subregions responsible for the “protective” consequences of Pik3cb inhibition.

One widely-reported consequence of repeated cocaine exposure is an imbalance in dopamine receptor-mediated signaling, favoring D1-family Gs-coupled, at the expense of D2-family Gi-coupled, systems. D1 stimulation activates PI3K and is a likely mechanism by which psychostimulants strengthen habit-based behavior. Overexpression of Drd1 in the mPFC decreases D2 expression in the downstream striatum, suggesting that normalization of mPFC D1-mediated signaling following cocaine could engage striatal D2 systems. In Aim 2, we will test the hypothesis that Pik3cb inhibition in the mPFC creates a permissive environment for dorsomedial striatal D2-dependent goal-directed response strategies.

Cocaine can induce activity-dependent dendritic spine proliferation in the mPFC. Meanwhile, inhibiting PI3K p110β can normalize aberrant dendritic spine proliferation in models of Fragile X Syndrome. Thus, inhibiting p110β could conceivably correct cocaine-induced spinogenesis. Further, PI3K p110δ and γ regulate RhoA

GTPase-dependent neuronal contraction and NMDA receptor-dependent long-term depression, respectively. In Aim 3, we will test the hypothesis that inhibiting p110β and δ will correct dendritic spine densities and block habits following cocaine, while p110γ inhibition could exacerbate cocaine's influence.

Our findings indicate that p110β blockade confers certain behavioral resiliencies to cocaine. The proposed studies will crystallize anatomical mechanisms and cyto-structural consequences. Knowledge gained from these experiments could advance treatment strategies for drug use disorders, given that subunit-selective inhibitors may have more favorable clinical profiles than broad-spectrum PI3K blockade.

PROGRESS REPORT:

Phosphoinositide 3-kinase (PI3K) is a membrane-associated signaling complex that phosphorylates phosphoinositides, second messengers that regulate neuronal development, survival, and plasticity. PI3K is composed of p110 catalytic subunits that determine the intracellular positioning and activation properties of PI3K and are also aligned with specific signaling pathways. In year 1, we focused on establishing and validating key tools necessary for ascertaining whether and how inhibiting PI3K p110β is "protective" against cocaine-induced decision-making abnormalities (Aims 1-2). We also expanded our studies to manipulate other p110 subunits (Aim 3). We concentrated on p110δ, generating key discoveries that will propel us into year 2.

Specific Outcomes. With regards to Aims 1-2, a key objective for year 1 (which we accomplished) was to develop and validate viral vectors by which to manipulate PI3K p110β in excitatory neurons. In addition to in vitro confirmation, we have initiated in vivo confirmation, and we have also confirmed that fluorescent tags are sufficiently robust for dendritic spine imaging, a component of Aim 3.

Also with regards to Aim 3, we aimed to generate foundational results that would guide investigations into the behavioral functions of less well-characterized PI3K p110 subunits. We approached this goal by: 1) assessing whether upstream signaling partners of the PI3K p110δ subunit are associated with goal-directed action vs. habit-based response strategies throughout cortico-limbic structures in mice; 2) developing and validating viral vectors to reduce p110δ in excitatory neurons; and 3) assessing whether viral-mediated knockdown of Pik3cd, which encodes p110δ, in excitatory neurons impacts the ability of mice to engage in goal-directed actions.

PUBLICATIONS:

PMID	Title
30477984	Prefrontal cortical trkB, glucocorticoids, and their interactions in stress and developmental contexts.

FUNDING SOURCES:

Redacted by agreement funded by NIDA

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: ORBITOFRONTAL CORTICAL COORDINATION OF ACTION-CONSEQUENCE DECISION MAKING

SPID#: 13155

UNIT/DIVISION: Behavioral Neuroscience and Psychiatric Disorders

TYPE: Research

START DATE: 7/1/2018

END DATE: 6/30/2023

GENERAL CATEGORY: Neural

SUB-CATEGORY: Behavior

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R01MH117103

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Behavioral Neuroscience and Psychiatric Disorders
Prin. NPRC Core Sci.		
Other Core and Affil.		Behavioral Neuroscience and Psychiatric Disorders

PROJECT DESCRIPTION:

Elevated glucocorticoids, particularly during specific developmental periods, cause long-term biases towards habit-based behaviors that are linked with depression, obesity, and other maladaptive outcomes in adulthood. Neurobiological mechanisms remain largely unclear. Integrin receptors are cell adhesion factors linked with the stress response system and genetic risk for neurodevelopmental disease. Composed of an α subunit responsible for ligand binding and a β subunit that activates intracellular signaling, integrins respond to extracellular matrix proteins, influencing cell structure through downstream cytoskeletal signaling factors. Integrin-mediated signaling stabilizes cell structure in the transition from adolescence to adulthood, such that genetic ablation of the β1 subunit, highly expressed in the cortex and hippocampus, causes dendritic spine loss starting in adolescence. In humans, ITGB1, encoding β1-integrin, is identified in genome-wide association studies of depression and schizophrenia, diseases characterized by deficits in PFC-dependent planning and action.

Despite connections with neurodevelopmental disease, β1-integrin involvement in PFC-dependent action selection remains opaque. We will test the hypothesis that a β1-integrin-Abl2/Arg-cortactin-ROCK2 signaling axis coordinates goal-directed action selection and thus, is a sensible target for blocking habits due to glucocorticoid and stressor exposure. Aligned with RDoC-defined positive valence domains, specific aims are:

Aim 1. To identify how the β1-integrin-Arg-cortactin-ROCK2 signaling axis influences oPFC-dependent action selection. We will use a combination of viral-mediated gene silencing and pharmacological manipulations to test the hypothesis that β1-integrin-Arg-cortactin-ROCK2 interactions in the oPFC coordinate goal-directed response choice, countering inflexible habits. Next, we will test the hypothesis that β1-integrin-dependent oPFC interactions with the basolateral amygdala support goal-directed response choice. Last, we will test the hypothesis that site-selective Itgb1 silencing structurally phenocopies glucocorticoid exposure, eliminating dendritic spines on excitatory neurons within the oPFC.

Aim 2. To mitigate stressor-related habits and dendritic spine abnormalities in the oPFC. Next, we will test the hypothesis that stimulation of Arg and cortactin will block habits and changes in dendritic spine densities and

morphologies following developmental corticosterone or exposure to social isolation. This aim will reveal strategies by which to correct cyto-structural change and habit biases following adversity.

Aim 3. To reveal functional interactions with tyrosine receptor kinase B (trkB). Activation of β1-integrin-mediated signaling events that inhibit ROCK2 stimulates BDNF, which binds to its high-affinity receptor trkB. ROCK2 inhibition also modifies the ratio of full-length/truncated trkB in the PFC, favoring the active full-length isoform, and it enhances action-outcome memory in multiple contexts. Our final aim will test the hypothesis that the enrichment of action-outcome decision making (blocking habits) via ROCK2 inhibition is trkB-dependent.

PROGRESS REPORT:

Significant progress was made this year in particular on aim 1, which was aimed at identifying what, if anything, is the relationship between β1-integrin and complex decision-making behavior, in particular the ability to prospectively select actions based on their consequences, particularly when those consequences are not immediately observable. Selecting actions based on anticipated consequences requires the orbitofrontal cortex (OFC). We hypothesized that cell adhesion β1-integrin receptors are essential to OFC function, and we anticipated developmental windows during which β1-integrins might be more influential than others. We discovered that OFC-selective β1-integrin silencing prior to adolescence, but not later, impaired the ability of mice to extinguish conditioned fear and update reward-related expectations. Early-life knockdown eliminated dendritic spines, the primary sites of excitatory plasticity in the brain, and weakened sensitivity to cortical inputs. Notwithstanding these defects in male mice, females were resilient to OFC (but not hippocampal) β1-integrin loss. Existing literature suggests that resilience may be explained by estradiol-mediated transactivation of β1-integrins and tyrosine receptor kinase B (trkB). Accordingly, we administered a trkB agonist administered during adolescence, which corrected reward-related decision making in adult β1-integrin-deficient males. In sum, we find that developmental β1-integrins are indispensable for expectancy updating later in life. Unpublished Unpublished

Additional accomplishments supported by this award include: 1) the publication of a review article in Neuroscience and Biobehavioral Reviews (current impact factor 9.44), and 2) the publication of our discovery that inhibiting the protein ROCK2 (and thus amplifying the neurobiological effects of Arg kinase – see our Aims description above for further explanation) expedites dendritic spine pruning during adolescence. Dendritic spine elimination occurs in a regionally selective fashion that maps on to temporal differences between prefrontal cortical brain regions in their postnatal development. We include in this report evidence of interaction between Arg-ROCK2 signaling and trkB. We discussed early evidence of these interactions in our original proposal, and we have now replicated and reported them: Specifically, inhibiting ROCK2 causes a change in the ratio of active/inactive (truncated) trkB, favoring the active, full-length trkB isoform. This scenario would favor “pro-survival” neurotrophic signaling. These findings are reported in Shapiro et al., 2019, Neurobiol Dis.

PUBLICATIONS:

PMID	Title
30477984	Prefrontal cortical trkB, glucocorticoids, and their interactions in stress and developmental contexts.
30593834	Rho-kinase inhibition has antidepressant-like efficacy and expedites dendritic spine pruning in adolescent mice.

FUNDING SOURCES:

Redacted by agreement funded by NIMH

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: THE CEREBELLUM IN PARKINSON'S DISEASE (PD): MORPHOLOGICAL AND ULTRASTRUCTURAL ANALYSIS OF THE CEREBELLUM AND THE GLUTAMATERGIC OLIVO-CEREBELLAR INPUTS IN THE NON-HUMAN PRIMATE MPTP-MODEL OF PD

SPID#: 13156

UNIT/DIVISION: Neuropharmacology and Neurologic Diseases

TYPE: Pilot

START DATE: 5/1/2018

END DATE: 4/30/2019

GENERAL CATEGORY: Neural

SUB-CATEGORY: Brain Structure/Function

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER:

SUPPORTING ORGANIZATION: Private Source

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Neuropharmacology and Neurologic Diseases
Prin. NPRC Core Sci.		
Other Core and Affil.		Supv, Research Specialist, YRK: NND-Neuroscience

PROJECT DESCRIPTION:

Parkinson's disease is classically synonymous with basal ganglia dysfunction, which is secondary to the dopaminergic denervation that follows the loss of nigrostriatal dopamine neurons. Although the cerebellum has long been known to control the coordination of voluntary movement, gait, posture and motor functions, its influence in PD has been often overlooked. Recently, pathological changes in the cerebellum following dopaminergic degeneration have been reported in patients with PD and in animal models of the disease, suggesting that those conditions may affect the functional connectivity within the cerebellum and between the cerebellum and large-scale cortical networks. Functional data in PD patients have demonstrated cerebellar atrophy that is related to both increases and decreases in cerebellar-cortical connectivity, and that may be drive disease processes and symptoms. Although such findings clearly suggest cerebellar involvement in PD, the nature of the pathological changes in the cerebellum following dopaminergic degeneration remains unclear. Anatomical and ultrastructural studies are needed to elucidate pathological changes of the neuronal and synaptic circuits in the cerebellum that are associated with parkinsonism. To address this need, we will apply state-of-the art three-dimensional analysis to study quantitative morphological and ultrastructural changes in the MPTP-treated rhesus monkey, a well-established non-human primate model of PD. The data we will obtain will help us to better understand of the synaptic organization of the cerebellar cortex, as well as the potential pathological alterations in this structure. We will also study the pattern of excitatory glutamatergic inputs from the inferior olive (olivo-cerebellar pathway) and compare these in the normal and parkinsonian state. By providing a deeper understanding of the cerebellar networks affected in parkinsonism, our study will spur the development of new

strategies and targets for alternative PD treatments.

PROGRESS REPORT:

The aim 1 of the project, anatomical study of the cerebellum volume and the number of Purkinje (PK) cells (using cerebellum serial sections and stereological approach), and the study of Purkinje (PK) cell morphology and glutamatergic olivo-cerebellar inputs (climbing fibers, CF) in the cerebellar cortex (using stacks of confocal images and 3D reconstructed models of PK cells and CF fibers traced with Neurolucida360) in control and MPTP-treated parkinsonian monkeys it being completed. The aim 2, quantitative 3D-ultrastructural analysis (serial block face scanning electron microscopy-SBF/SEM and Reconstruct software) of the CF on the PK cells of motor-related areas of cerebellum from control and MPTP-treated parkinsonian monkeys will be completed during the next two months.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Redacted by agreement	Private Source

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: ESTABLISHMENT OF FAST PH MRI FOR IMAGING METABOLIC INJURY DURING ACUTE STROKE

SPID#: 13159

UNIT/DIVISION: Neuropharmacology and Neurologic Diseases

TYPE: Research

START DATE: 7/1/2013

END DATE: 4/30/2019

GENERAL CATEGORY: Imaging

SUB-CATEGORY: Stroke

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R01NS083654

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Neuropharmacology and Neurologic Diseases
Prin. NPRC Core Sci.		
Other Core and Affil.		Neuropharmacology and Neurologic Diseases

PROJECT DESCRIPTION:

Stroke is a debilitating neurological disorder that is associated with tremendous socioeconomic burden. Whereas FDA-approved tissue plasminogen activator (tPA) is a potent thrombolytic agent for treating acute ischemic stroke, few patients present for treatment within its therapeutic window. There remains substantial interest in developing strategies to extend the thrombolytic therapy into subpopulations who may benefit from late intervention. MRI has become an essential clinical tool for the triage and management of acute ischemic stroke patients, yet the conventional stroke MRI is inadequate to fully characterize the heterogeneous ischemic tissue injury and effectively guide treatment in late-presenting stroke patients. The approximation of diffusion/perfusion MRI (DWI/PWI) mismatch as ischemic penumbra, despite its initial enthusiasm, has been recognized to be oversimplified. PWI lesion contains tissue at no risk to infarction, while DWI lesion may recover if promptly reperfused. Besides falsely characterizing some salvageable tissue as ischemic core, DWI may also fail to identify tissue that has already suffered irreversible injury, as the eventual infarction is often larger than acute DWI lesion. As noted in the report of NIH/NINDS Stroke Progress Review Group (SPRG) in 2011, the number one priority for stroke imaging is to understand the impact of hemodynamics, collateral flow, oxygen and brain metabolism upon tissue survival and function. Tissue acidosis is closely associated with tissue oxygen/glucose metabolism, and may provide a metabolic biomarker for defining ischemic penumbra. However, currently available in vivo pH measurement techniques have significant limitations. Our proposal aims to develop endogenous amide proton chemical exchange saturation transfer (CEST) MRI for fast and non-invasive pH imaging. We will first develop novel acquisition and post-processing strategies to enhance the sensitivity of CEST imaging (Aim1). We will then develop quantitative analysis that transform pH-weighted MRI to tissue pH mapping in experimental stroke model (Aim 2). We will then evaluate pH imaging, a novel metabolic imaging marker, to guide tPA thrombolysis in an embolic stroke model that closely mimics human ischemic stroke and therapy (Aim 3). In summary, our proposal establishes fast and quantitative pH stroke imaging in experimental

stroke models, and once the sensitivity and specificity of pH MRI in defining metabolic penumbra are confirmed, we will translate it to clinic and evaluate its utility in late-presenting stroke patients.

PROGRESS REPORT:

We just upgraded our rat imaging gradient coil on 01/04/2019, and are currently running test scans to establish multi-parametric MRI at 7 T. We are testing spin echo EPI based CEST imaging sequence that mitigates gradient echo CEST MRI that we have been using.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: DEVELOPMENT OF GLYCOGEN CEST MRI FOR ASSESSMENT OF POMPE DISORDER

SPID#: 13160

UNIT/DIVISION: Neuropharmacology and Neurologic Diseases

TYPE: Research

START DATE: 6/1/2018

END DATE: 5/31/2020

GENERAL CATEGORY: Imaging

SUB-CATEGORY: Imaging

NIH GRANT: ☒ Yes ☐ No

GRANT NUMBER: R21AR071529

SUPPORTING ORGANIZATION: NIH

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Neuropharmacology and Neurologic Diseases
Prin. NPRC Core Sci.		
Other Core and Affil.		Neuropharmacology and Neurologic Diseases

PROJECT DESCRIPTION:

Pompe Disease is an inherited metabolic neuromyopathy caused by acid α-glucosidase (GAA) deficiency/absence, which results in lysosomal glycogen accumulation and extensive tissue damage, especially in muscles. Alglucosidase alfa, an enzyme replacement therapy (ERT), has been approved for treating all patients with Pompe disease. Unfortunately, the patient population with Pompe disease is heterogeneous, with many patients not developing clear symptoms until the muscle pathology has advanced beyond glycogen accumulation, reducing the efficacy of ERT. There is a lack of means to map glycogen distribution in Pompe patients, characterize its progressive buildup and, more importantly, guide ERT treatment. The present project proposes to develop non-invasive and quantitative muscle glycogen MRI, addressing an unmet need in Pompe research. The central hypothesis is that optimized glycogen MRI enables non-invasive and quantitative imaging of muscle glycogen accumulation, a key feature of Pompe disease. Specifically, aim 1 will develop and improve the sensitivity of glycogen CEST imaging in tissue-mimicking glycogen-gel phantoms. Aim 2 will validate glycogen MRI as an imaging biomarker of Pompe disease progression by longitudinally monitoring muscle glycogen accumulation in GAAKO mice before symptom onset. The goal is to establish muscle glycogen MRI as a unique imaging technique for Pompe disease and ultimately, may be applied to guide ERT treatment.

PROGRESS REPORT:

We have collected magic angle spinning glycogen NMR data from 14 T. We are currently optimizing CEST scans on 7 T, in particular, identifying fast means to correct for field inhomogeneity artifact in CEST MRI. We are also building a mouse MRI-compatible cradle for 7 T.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: PRODUCTION OF P. CYNOMOLGI SPOROZOITES FOR OPTIMIZING INFECTION CONDITIONS OF PRIMARY MACAQUE HEPATOCYTE CULTURES

SPID#: 13161

UNIT/DIVISION: Emory Vaccine Center

TYPE: Research

START DATE: 1/1/2018

END DATE: 12/31/2019

GENERAL CATEGORY: Infectious Disease

SUB-CATEGORY: Malaria

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER: RR374139/Private Source

SUPPORTING ORGANIZATION: UGA Private Source

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Emory Vaccine Center
Prin. NPRC Core Sci.		
Other Core and Affil.		Emory Vaccine Center

PROJECT DESCRIPTION:

Goal is to infect M. mulatta with P. cynomolgi, feed mosquitoes on the infected blood, and obtain infectious sporozoites from the salivary glands for the purpose of infecting liver cell cultures. Goals also include establishing blood stage cultures.

PROGRESS REPORT:

We coordinated and performed planned experiments and submitted proposals with the UGA team, and Redacted by agreement Redacted by agreement presented work accomplished at a BMGF sponsored meeting in New Zealand.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Subcontract from UGA / Private Source support

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: PRODUCTION OF P. FALCIPARUM GAMETOCYTE CULTURES FOR TRANSMISSION STUDIES

SPID#: 13162

UNIT/DIVISION: Emory Vaccine Center

TYPE: Research

START DATE: 6/1/2018

END DATE: 6/30/2019

GENERAL CATEGORY: Infectious Disease

SUB-CATEGORY: Malaria

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER: Private Source

SUPPORTING ORGANIZATION:

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Emory Vaccine Center
Prin. NPRC Core Sci.		
Other Core and Affil.		Emory Vaccine Center

PROJECT DESCRIPTION:

Goal is to generate P. falciparum gametocytes in culture, show these are infectious to mosquitoes, and transport the parasites to CDC for feeding experiments involving wildtype and transgenic mosquitoes.

PROGRESS REPORT:

A series of experiments have been performed with successes reaching the project goals, and optimization work performed.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Emory Subcontract from Private Source

Yerkes National Primate Research Center
2017 Annual Progress Report SPID Form

TITLE: OPTIMIZATION OF P. VIVAX SPOROZOITES PRODUCTION USING SQUIRREL MONKEYS

SPID#: 13163

UNIT/DIVISION: Emory Vaccine Center

TYPE: Research

START DATE: 9/1/2017

END DATE: 6/1/2019

GENERAL CATEGORY: Infectious Disease

SUB-CATEGORY: Malaria

NIH GRANT: ☐ Yes ☒ No

GRANT NUMBER: Private Source

SUPPORTING ORGANIZATION:

SPECIFIC INFORMATION:

INVESTIGATORS:

	Name	Dept
Principal Investigator	Redacted by agreement	Emory Vaccine Center
Prin. NPRC Core Sci.		
Other Core and Affil.		Emory Vaccine Center

PROJECT DESCRIPTION:

Goal is to infect Saimiri boliviensis with P. vivax, feed mosquitoes on the infected blood, and obtain infectious sporozoites from the salivary glands for the purpose of infecting liver cell cultures.

PROGRESS REPORT:

Progress has been made infecting Saimiri boliviensis with P. vivax, feeding mosquitoes on the infected blood, and obtaining infectious sporozoites from the salivary glands for the purpose of infecting liver cell cultures. Optimization steps are being taken and a new proposal is being planned for submission.

PUBLICATIONS:

PMID	Title

FUNDING SOURCES:

Emory Subcontract from Private Source support

10. Outreach. Provide a brief statement describing outreach activities including how the research community is informed about the capabilities of the NPRC, as well as other items related to outreach (e.g., community relations).

Description: The Yerkes National Primate Research Center informs scientists about our role as a resource to researchers by publishing in peer-reviewed scientific journals, making presentations to the scientific community at local, national and international scientific meetings, manning an exhibit booth on behalf of all NPRCs at the annual Society for Neuroscience meeting and providing information to the NPRCresearch.org and NPRC.org websites.

The center is also proactive in informing our employees, the Emory community, national organizations and the general public about our role to discover causes, preventions, treatments and cures to improve human health and lives worldwide. We distribute a bi-monthly employee newsletter as well as distribute news releases internally and to media, maintain the Yerkes.emory.edu website, give presentations at community meetings and to junior, high school and college students, offer tours of our center, keep other Emory communicators informed about our research successes and animal care program, and work with national organizations to extend the reach of NPRC information.

The Yerkes Research Center continues to manage the public relations agency working on behalf of the seven NPRCs. Using our new brand foundation and visual identity, we launched NPRC.org and the Twitter account @nprcnews to provide the latest NPRC research information.

11. Comments. Provide information showing (in dollars) how the Resource was supported during the reporting period, broken down by: 1) Direct Costs of the ORIP grant, 2) Program Income, 3) Other Sources of support, including cost sharing by the grantee Institution and contribution of F&A costs from the ORIP grant or other grants. If program income is reported, the amount in this table must be the same as the amount reported in Section G.11, “Program Income” of the RPPR. Do not include support (e.g., individual R01 grants) for the PIs or other investigators that does not contribute directly to the NPRC. Describe any limitations of this information.

Direct Costs of the ORIP Grant	Program Income	Other Sources of Support	Total Support for the Resource
$7,936,218	$3,021,217	$32,764,442	$43,721,877
Includes Year 58 supplement which does not include F&A	Estimated program income as the current budget period is still ongoing	Includes F&A cost recovery, internal funds, etc.	

12. Feedback from Users. Provide a brief statement discussing how feedback is solicited and the topics that are covered (e.g. quality of: the web site, the ordering process, service delivered, etc.). If feedback has been solicited, include a brief summary of the most significant results, lessons learned and changes made in response to feedback.

- N/A

13. Infrastructure Improvements. Provide a list of major infrastructure improvements and capital equipment (as defined by the Institution) purchased during the reporting period. For NIH sources of support, report the Institute or Center from which support was derived.

Type of Improvement	Source of support
MS Seminar Room AV Upgrade	ORIP P51 I/M FUnds
FS M6/M7 HVAC Upgrade	ORIP P51 I/M Funds
FS G13 Trailer Replacement	ORIP P51 I/M Funds

Type of Improvement	Source of support
MS Air Handler	ORIP P51 I/M Funds
RD Renovation	ORIP P51 I/M Funds/Program Income
FS Propane Plant	ORIP P51 Yr58 Supplement
FS Emergency Generator	ORIP P51 Yr58 Supplement
MS Emergency Water Well	ORIP P51 Yr58 Supplement

Description: The infrastructure improvements listed above represent the major projects undertaken during the current reporting period. These projects support P51 activities and related research efforts.

Composite Application Budget Summary

Categories	Budget Period
Salary, Wages and Fringe Benefits	4,863,346
Equipment	584,305
Travel	43,706
Participant/Trainee Support Costs	0
Other Direct Costs (excluding Consortium)	1,959,360
Consortium Costs	0
Direct Costs	7,450,717
Indirect Costs	3,089,885
Total Direct and Indirect Costs	10,540,602

Component Budget Summary

Components	Categories	Budget Period
8504-001 (Admin Core)	Salary, Wages and Fringe Benefits	123,910
	Equipment	0
	Travel	2,000
	Participant/Trainee Support Costs	0
	Other Direct Costs (excluding Consortium)	4,000
	Consortium Costs	0
	Direct Costs	129,910
	Indirect Costs	58,459
TOTALS	Total Direct and Indirect Costs	188,369
8510-002 (Admin Core)	Salary, Wages and Fringe Benefits	120,483
	Equipment	0
	Travel	0
	Participant/Trainee Support Costs	0
	Other Direct Costs (excluding Consortium)	0
	Consortium Costs	0
	Direct Costs	120,483
	Indirect Costs	54,217
TOTALS	Total Direct and Indirect Costs	174,700
8509-003 (Admin Core)	Salary, Wages and Fringe Benefits	9,052
	Equipment	0
	Travel	0

	Participant/Trainee Support Costs	0
	Other Direct Costs (excluding Consortium)	0
	Consortium Costs	0
	Direct Costs	9,052
	Indirect Costs	4,073
TOTALS	Total Direct and Indirect Costs	13,125
8511-004 (Admin Core)	Salary, Wages and Fringe Benefits	0
	Equipment	584,305
	Travel	0
	Participant/Trainee Support Costs	0
	Other Direct Costs (excluding Consortium)	0
	Consortium Costs	0
	Direct Costs	584,305
	Indirect Costs	0
TOTALS	Total Direct and Indirect Costs	584,305
8506-005 (Admin Core)	Salary, Wages and Fringe Benefits	20,262
	Equipment	0
	Travel	2,000
	Participant/Trainee Support Costs	0
	Other Direct Costs (excluding Consortium)	0
	Consortium Costs	0
	Direct Costs	22,262
	Indirect Costs	10,018
TOTALS	Total Direct and Indirect Costs	32,280

8505-006 (Admin Core)	Salary, Wages and Fringe Benefits	7,167
	Equipment	0
	Travel	2,000
	Participant/Trainee Support Costs	0
	Other Direct Costs (excluding Consortium)	0
	Consortium Costs	0
	Direct Costs	9,167
	Indirect Costs	4,125
TOTALS	Total Direct and Indirect Costs	13,292
8508-007 (Admin Core)	Salary, Wages and Fringe Benefits	17,236
	Equipment	0
	Travel	0
	Participant/Trainee Support Costs	0
	Other Direct Costs (excluding Consortium)	4,000
	Consortium Costs	0
	Direct Costs	21,236
	Indirect Costs	9,556
TOTALS	Total Direct and Indirect Costs	30,792
8507-008 (Admin Core)	Salary, Wages and Fringe Benefits	7,365
	Equipment	0
	Travel	0
	Participant/Trainee Support Costs	0
	Other Direct Costs (excluding Consortium)	0
	Consortium Costs	0

	Direct Costs	7,365
	Indirect Costs	3,314
TOTALS	Total Direct and Indirect Costs	10,679
8525-001 (Core)	Salary, Wages and Fringe Benefits	65,826
	Equipment	0
	Travel	0
	Participant/Trainee Support Costs	0
	Other Direct Costs (excluding Consortium)	16,000
	Consortium Costs	0
	Direct Costs	81,826
	Indirect Costs	36,822
TOTALS	Total Direct and Indirect Costs	118,648
8522-002 (Core)	Salary, Wages and Fringe Benefits	47,102
	Equipment	0
	Travel	0
	Participant/Trainee Support Costs	0
	Other Direct Costs (excluding Consortium)	452,898
	Consortium Costs	0
	Direct Costs	500,000
	Indirect Costs	225,000
TOTALS	Total Direct and Indirect Costs	725,000
8521-003 (Core)	Salary, Wages and Fringe Benefits	18,145
	Equipment	0
	Travel	0

	Participant/Trainee Support Costs	0
	Other Direct Costs (excluding Consortium)	4,000
	Consortium Costs	0
	Direct Costs	22,145
	Indirect Costs	9,965
TOTALS	Total Direct and Indirect Costs	32,110
8524-004 (Core)	Salary, Wages and Fringe Benefits	17,065
	Equipment	0
	Travel	0
	Participant/Trainee Support Costs	0
	Other Direct Costs (excluding Consortium)	4,000
	Consortium Costs	0
	Direct Costs	21,065
	Indirect Costs	9,479
TOTALS	Total Direct and Indirect Costs	30,544
8523-005 (Core)	Salary, Wages and Fringe Benefits	91,148
	Equipment	0
	Travel	0
	Participant/Trainee Support Costs	0
	Other Direct Costs (excluding Consortium)	6,000
	Consortium Costs	0
	Direct Costs	97,148
	Indirect Costs	43,716
TOTALS	Total Direct and Indirect Costs	140,864

8518-001 (Other)	Salary, Wages and Fringe Benefits	150,765
	Equipment	0
	Travel	2,000
	Participant/Trainee Support Costs	0
	Other Direct Costs (excluding Consortium)	20,000
	Consortium Costs	0
	Direct Costs	172,765
	Indirect Costs	77,744
TOTALS	Total Direct and Indirect Costs	250,509
8517-002 (Other)	Salary, Wages and Fringe Benefits	33,095
	Equipment	0
	Travel	2,000
	Participant/Trainee Support Costs	0
	Other Direct Costs (excluding Consortium)	0
	Consortium Costs	0
	Direct Costs	35,095
	Indirect Costs	15,793
TOTALS	Total Direct and Indirect Costs	50,888
8520-003 (Other)	Salary, Wages and Fringe Benefits	568,544
	Equipment	0
	Travel	5,000
	Participant/Trainee Support Costs	0
	Other Direct Costs (excluding Consortium)	93,000
	Consortium Costs	0

	Direct Costs	666,544
	Indirect Costs	299,946
TOTALS	Total Direct and Indirect Costs	966,490
8519-004 (Other)	Salary, Wages and Fringe Benefits	124,080
	Equipment	0
	Travel	2,000
	Participant/Trainee Support Costs	0
	Other Direct Costs (excluding Consortium)	150,000
	Consortium Costs	0
	Direct Costs	276,080
	Indirect Costs	124,236
TOTALS	Total Direct and Indirect Costs	400,316
8514-005 (Other)	Salary, Wages and Fringe Benefits	1,946,057
	Equipment	0
	Travel	2,000
	Participant/Trainee Support Costs	0
	Other Direct Costs (excluding Consortium)	442,492
	Consortium Costs	0
	Direct Costs	2,390,549
	Indirect Costs	1,075,747
TOTALS	Total Direct and Indirect Costs	3,466,296
8513-006 (Other)	Salary, Wages and Fringe Benefits	742,751
	Equipment	0
	Travel	2,000

	Participant/Trainee Support Costs	0
	Other Direct Costs (excluding Consortium)	158,209
	Consortium Costs	0
	Direct Costs	902,960
	Indirect Costs	406,332
TOTALS	Total Direct and Indirect Costs	1,309,292
8516-007 (Other)	Salary, Wages and Fringe Benefits	295,296
	Equipment	0
	Travel	2,000
	Participant/Trainee Support Costs	0
	Other Direct Costs (excluding Consortium)	50,000
	Consortium Costs	0
	Direct Costs	347,296
	Indirect Costs	156,283
TOTALS	Total Direct and Indirect Costs	503,579
8515-008 (Other)	Salary, Wages and Fringe Benefits	288,857
	Equipment	0
	Travel	2,000
	Participant/Trainee Support Costs	0
	Other Direct Costs (excluding Consortium)	343,511
	Consortium Costs	0
	Direct Costs	634,368
	Indirect Costs	285,466
TOTALS	Total Direct and Indirect Costs	919,834

8526-009 (Other)	Salary, Wages and Fringe Benefits	15,686
	Equipment	0
	Travel	0
	Participant/Trainee Support Costs	0
	Other Direct Costs (excluding Consortium)	0
	Consortium Costs	0
	Direct Costs	15,686
	Indirect Costs	7,059
TOTALS	Total Direct and Indirect Costs	22,745
8528-010 (Other)	Salary, Wages and Fringe Benefits	29,617
	Equipment	0
	Travel	0
	Participant/Trainee Support Costs	0
	Other Direct Costs (excluding Consortium)	0
	Consortium Costs	0
	Direct Costs	29,617
	Indirect Costs	13,328
TOTALS	Total Direct and Indirect Costs	42,945
8527-011 (Other)	Salary, Wages and Fringe Benefits	38,299
	Equipment	0
	Travel	0
	Participant/Trainee Support Costs	0
	Other Direct Costs (excluding Consortium)	0
	Consortium Costs	0

	Direct Costs	38,299
	Indirect Costs	17,235
TOTALS	Total Direct and Indirect Costs	55,534
8529-012 (Other)	Salary, Wages and Fringe Benefits	39,250
	Equipment	0
	Travel	0
	Participant/Trainee Support Costs	0
	Other Direct Costs (excluding Consortium)	0
	Consortium Costs	0
	Direct Costs	39,250
	Indirect Costs	17,662
TOTALS	Total Direct and Indirect Costs	56,912
8532-013 (Other)	Salary, Wages and Fringe Benefits	0
	Equipment	0
	Travel	10,894
	Participant/Trainee Support Costs	0
	Other Direct Costs (excluding Consortium)	1,250
	Consortium Costs	0
	Direct Costs	12,144
	Indirect Costs	5,465
TOTALS	Total Direct and Indirect Costs	17,609
8531-014 (Other)	Salary, Wages and Fringe Benefits	0
	Equipment	0
	Travel	5,812

	Participant/Trainee Support Costs	0
	Other Direct Costs (excluding Consortium)	0
	Consortium Costs	0
	Direct Costs	5,812
	Indirect Costs	2,615
TOTALS	Total Direct and Indirect Costs	8,427
8512-015 (Other)	Salary, Wages and Fringe Benefits	46,288
	Equipment	0
	Travel	2,000
	Participant/Trainee Support Costs	0
	Other Direct Costs (excluding Consortium)	0
	Consortium Costs	0
	Direct Costs	48,288
	Indirect Costs	21,730
TOTALS	Total Direct and Indirect Costs	70,018
8530-001 (Project)	Salary, Wages and Fringe Benefits	0
	Equipment	0
	Travel	0
	Participant/Trainee Support Costs	0
	Other Direct Costs (excluding Consortium)	210,000
	Consortium Costs	0
	Direct Costs	210,000
	Indirect Costs	94,500
TOTALS	Total Direct and Indirect Costs	304,500

TOTALS		**10,540,602**

Categories Budget Summary

Categories	Components	Budget Period
R&R Budget - Senior/Key Person Funds Requested	8504-001 (Admin Core)	119,448
	8510-002 (Admin Core)	0
	8509-003 (Admin Core)	0
	8511-004 (Admin Core)	0
	8506-005 (Admin Core)	11,945
	8505-006 (Admin Core)	7,167
	8508-007 (Admin Core)	0
	8507-008 (Admin Core)	0
	8525-001 (Core)	12,465
	8522-002 (Core)	27,596
	8521-003 (Core)	4,449
	8524-004 (Core)	4,449
	8523-005 (Core)	33,509
	8518-001 (Other)	0
	8517-002 (Other)	0
	8520-003 (Other)	80,357
	8519-004 (Other)	0
	8514-005 (Other)	0
	8513-006 (Other)	358,580
	8516-007 (Other)	37,060
	8515-008 (Other)	29,661

	8526-009 (Other)	11,945
	8528-010 (Other)	26,279
	8527-011 (Other)	33,559
	8529-012 (Other)	34,795
	8532-013 (Other)	0
	8531-014 (Other)	0
	8512-015 (Other)	21,343
	8530-001 (Project)	0
TOTALS		854,607
R&R Budget - Other Personnel Funds Requested	8504-001 (Admin Core)	4,462
	8510-002 (Admin Core)	120,483
	8509-003 (Admin Core)	9,052
	8511-004 (Admin Core)	0
	8506-005 (Admin Core)	8,317
	8505-006 (Admin Core)	0
	8508-007 (Admin Core)	17,236
	8507-008 (Admin Core)	7,365
	8525-001 (Core)	53,361
	8522-002 (Core)	19,506
	8521-003 (Core)	13,696
	8524-004 (Core)	12,616
	8523-005 (Core)	57,639
	8518-001 (Other)	150,765
	8517-002 (Other)	33,095

	8520-003 (Other)	488,187
	8519-004 (Other)	124,080
	8514-005 (Other)	1,946,057
	8513-006 (Other)	384,171
	8516-007 (Other)	258,236
	8515-008 (Other)	259,196
	8526-009 (Other)	3,741
	8528-010 (Other)	3,338
	8527-011 (Other)	4,740
	8529-012 (Other)	4,455
	8532-013 (Other)	0
	8531-014 (Other)	0
	8512-015 (Other)	24,945
	8530-001 (Project)	0
TOTALS		4,008,739
R&R Budget - Section A & B. Total Salary, Wages and Fringe Benefits (A+B)	8504-001 (Admin Core)	123,910
	8510-002 (Admin Core)	120,483
	8509-003 (Admin Core)	9,052
	8511-004 (Admin Core)	0
	8506-005 (Admin Core)	20,262
	8505-006 (Admin Core)	7,167
	8508-007 (Admin Core)	17,236
	8507-008 (Admin Core)	7,365
	8525-001 (Core)	65,826

	8522-002 (Core)	47,102
	8521-003 (Core)	18,145
	8524-004 (Core)	17,065
	8523-005 (Core)	91,148
	8518-001 (Other)	150,765
	8517-002 (Other)	33,095
	8520-003 (Other)	568,544
	8519-004 (Other)	124,080
	8514-005 (Other)	1,946,057
	8513-006 (Other)	742,751
	8516-007 (Other)	295,296
	8515-008 (Other)	288,857
	8526-009 (Other)	15,686
	8528-010 (Other)	29,617
	8527-011 (Other)	38,299
	8529-012 (Other)	39,250
	8532-013 (Other)	0
	8531-014 (Other)	0
	8512-015 (Other)	46,288
	8530-001 (Project)	0
TOTALS		4,863,346
R&R Budget - Section C. Total Equipment	8504-001 (Admin Core)	0
	8510-002 (Admin Core)	0
	8509-003 (Admin Core)	0

	8511-004 (Admin Core)	584,305
	8506-005 (Admin Core)	0
	8505-006 (Admin Core)	0
	8508-007 (Admin Core)	0
	8507-008 (Admin Core)	0
	8525-001 (Core)	0
	8522-002 (Core)	0
	8521-003 (Core)	0
	8524-004 (Core)	0
	8523-005 (Core)	0
	8518-001 (Other)	0
	8517-002 (Other)	0
	8520-003 (Other)	0
	8519-004 (Other)	0
	8514-005 (Other)	0
	8513-006 (Other)	0
	8516-007 (Other)	0
	8515-008 (Other)	0
	8526-009 (Other)	0
	8528-010 (Other)	0
	8527-011 (Other)	0
	8529-012 (Other)	0
	8532-013 (Other)	0
	8531-014 (Other)	0

	8512-015 (Other)	0
	8530-001 (Project)	0
TOTALS		584,305
R&R Budget - Domestic Travel	8504-001 (Admin Core)	2,000
	8510-002 (Admin Core)	0
	8509-003 (Admin Core)	0
	8511-004 (Admin Core)	0
	8506-005 (Admin Core)	2,000
	8505-006 (Admin Core)	2,000
	8508-007 (Admin Core)	0
	8507-008 (Admin Core)	0
	8525-001 (Core)	0
	8522-002 (Core)	0
	8521-003 (Core)	0
	8524-004 (Core)	0
	8523-005 (Core)	0
	8518-001 (Other)	2,000
	8517-002 (Other)	2,000
	8520-003 (Other)	5,000
	8519-004 (Other)	2,000
	8514-005 (Other)	2,000
	8513-006 (Other)	2,000
	8516-007 (Other)	2,000
	8515-008 (Other)	2,000

	8526-009 (Other)	0
	8528-010 (Other)	0
	8527-011 (Other)	0
	8529-012 (Other)	0
	8532-013 (Other)	10,894
	8531-014 (Other)	5,812
	8512-015 (Other)	2,000
	8530-001 (Project)	0
TOTALS		43,706
R&R Budget - Foreign Travel	8504-001 (Admin Core)	0
	8510-002 (Admin Core)	0
	8509-003 (Admin Core)	0
	8511-004 (Admin Core)	0
	8506-005 (Admin Core)	0
	8505-006 (Admin Core)	0
	8508-007 (Admin Core)	0
	8507-008 (Admin Core)	0
	8525-001 (Core)	0
	8522-002 (Core)	0
	8521-003 (Core)	0
	8524-004 (Core)	0
	8523-005 (Core)	0
	8518-001 (Other)	0
	8517-002 (Other)	0

	8520-003 (Other)	0
	8519-004 (Other)	0
	8514-005 (Other)	0
	8513-006 (Other)	0
	8516-007 (Other)	0
	8515-008 (Other)	0
	8526-009 (Other)	0
	8528-010 (Other)	0
	8527-011 (Other)	0
	8529-012 (Other)	0
	8532-013 (Other)	0
	8531-014 (Other)	0
	8512-015 (Other)	0
	8530-001 (Project)	0
TOTALS		0
R&R Budget - Section D. Total Travel	8504-001 (Admin Core)	2,000
	8510-002 (Admin Core)	0
	8509-003 (Admin Core)	0
	8511-004 (Admin Core)	0
	8506-005 (Admin Core)	2,000
	8505-006 (Admin Core)	2,000
	8508-007 (Admin Core)	0
	8507-008 (Admin Core)	0
	8525-001 (Core)	0

	8522-002 (Core)	0
	8521-003 (Core)	0
	8524-004 (Core)	0
	8523-005 (Core)	0
	8518-001 (Other)	2,000
	8517-002 (Other)	2,000
	8520-003 (Other)	5,000
	8519-004 (Other)	2,000
	8514-005 (Other)	2,000
	8513-006 (Other)	2,000
	8516-007 (Other)	2,000
	8515-008 (Other)	2,000
	8526-009 (Other)	0
	8528-010 (Other)	0
	8527-011 (Other)	0
	8529-012 (Other)	0
	8532-013 (Other)	10,894
	8531-014 (Other)	5,812
	8512-015 (Other)	2,000
	8530-001 (Project)	0
TOTALS		43,706
R&R Budget - Tuition/Fees/Health Insurance	8504-001 (Admin Core)	0
	8510-002 (Admin Core)	0
	8509-003 (Admin Core)	0

	8511-004 (Admin Core)	0
	8506-005 (Admin Core)	0
	8505-006 (Admin Core)	0
	8508-007 (Admin Core)	0
	8507-008 (Admin Core)	0
	8525-001 (Core)	0
	8522-002 (Core)	0
	8521-003 (Core)	0
	8524-004 (Core)	0
	8523-005 (Core)	0
	8518-001 (Other)	0
	8517-002 (Other)	0
	8520-003 (Other)	0
	8519-004 (Other)	0
	8514-005 (Other)	0
	8513-006 (Other)	0
	8516-007 (Other)	0
	8515-008 (Other)	0
	8526-009 (Other)	0
	8528-010 (Other)	0
	8527-011 (Other)	0
	8529-012 (Other)	0
	8532-013 (Other)	0
	8531-014 (Other)	0

	8512-015 (Other)	0
	8530-001 (Project)	0
TOTALS		0
R&R Budget - Stipends	8504-001 (Admin Core)	0
	8510-002 (Admin Core)	0
	8509-003 (Admin Core)	0
	8511-004 (Admin Core)	0
	8506-005 (Admin Core)	0
	8505-006 (Admin Core)	0
	8508-007 (Admin Core)	0
	8507-008 (Admin Core)	0
	8525-001 (Core)	0
	8522-002 (Core)	0
	8521-003 (Core)	0
	8524-004 (Core)	0
	8523-005 (Core)	0
	8518-001 (Other)	0
	8517-002 (Other)	0
	8520-003 (Other)	0
	8519-004 (Other)	0
	8514-005 (Other)	0
	8513-006 (Other)	0
	8516-007 (Other)	0
	8515-008 (Other)	0

	8526-009 (Other)	0
	8528-010 (Other)	0
	8527-011 (Other)	0
	8529-012 (Other)	0
	8532-013 (Other)	0
	8531-014 (Other)	0
	8512-015 (Other)	0
	8530-001 (Project)	0
TOTALS		0
R&R Budget - Trainee Travel	8504-001 (Admin Core)	0
	8510-002 (Admin Core)	0
	8509-003 (Admin Core)	0
	8511-004 (Admin Core)	0
	8506-005 (Admin Core)	0
	8505-006 (Admin Core)	0
	8508-007 (Admin Core)	0
	8507-008 (Admin Core)	0
	8525-001 (Core)	0
	8522-002 (Core)	0
	8521-003 (Core)	0
	8524-004 (Core)	0
	8523-005 (Core)	0
	8518-001 (Other)	0
	8517-002 (Other)	0

	8520-003 (Other)	0
	8519-004 (Other)	0
	8514-005 (Other)	0
	8513-006 (Other)	0
	8516-007 (Other)	0
	8515-008 (Other)	0
	8526-009 (Other)	0
	8528-010 (Other)	0
	8527-011 (Other)	0
	8529-012 (Other)	0
	8532-013 (Other)	0
	8531-014 (Other)	0
	8512-015 (Other)	0
	8530-001 (Project)	0
TOTALS		0
R&R Budget - Subsistence	8504-001 (Admin Core)	0
	8510-002 (Admin Core)	0
	8509-003 (Admin Core)	0
	8511-004 (Admin Core)	0
	8506-005 (Admin Core)	0
	8505-006 (Admin Core)	0
	8508-007 (Admin Core)	0
	8507-008 (Admin Core)	0
	8525-001 (Core)	0

	8522-002 (Core)	0
	8521-003 (Core)	0
	8524-004 (Core)	0
	8523-005 (Core)	0
	8518-001 (Other)	0
	8517-002 (Other)	0
	8520-003 (Other)	0
	8519-004 (Other)	0
	8514-005 (Other)	0
	8513-006 (Other)	0
	8516-007 (Other)	0
	8515-008 (Other)	0
	8526-009 (Other)	0
	8528-010 (Other)	0
	8527-011 (Other)	0
	8529-012 (Other)	0
	8532-013 (Other)	0
	8531-014 (Other)	0
	8512-015 (Other)	0
	8530-001 (Project)	0
TOTALS		0
R&R Budget - Other Participants/Trainee Support Costs	8504-001 (Admin Core)	0
	8510-002 (Admin Core)	0
	8509-003 (Admin Core)	0

	8511-004 (Admin Core)	0
	8506-005 (Admin Core)	0
	8505-006 (Admin Core)	0
	8508-007 (Admin Core)	0
	8507-008 (Admin Core)	0
	8525-001 (Core)	0
	8522-002 (Core)	0
	8521-003 (Core)	0
	8524-004 (Core)	0
	8523-005 (Core)	0
	8518-001 (Other)	0
	8517-002 (Other)	0
	8520-003 (Other)	0
	8519-004 (Other)	0
	8514-005 (Other)	0
	8513-006 (Other)	0
	8516-007 (Other)	0
	8515-008 (Other)	0
	8526-009 (Other)	0
	8528-010 (Other)	0
	8527-011 (Other)	0
	8529-012 (Other)	0
	8532-013 (Other)	0
	8531-014 (Other)	0

	8512-015 (Other)	0
	8530-001 (Project)	0
TOTALS		0
R&R Budget - Section E. Total Participants/Trainee Support Costs	8504-001 (Admin Core)	0
	8510-002 (Admin Core)	0
	8509-003 (Admin Core)	0
	8511-004 (Admin Core)	0
	8506-005 (Admin Core)	0
	8505-006 (Admin Core)	0
	8508-007 (Admin Core)	0
	8507-008 (Admin Core)	0
	8525-001 (Core)	0
	8522-002 (Core)	0
	8521-003 (Core)	0
	8524-004 (Core)	0
	8523-005 (Core)	0
	8518-001 (Other)	0
	8517-002 (Other)	0
	8520-003 (Other)	0
	8519-004 (Other)	0
	8514-005 (Other)	0
	8513-006 (Other)	0
	8516-007 (Other)	0
	8515-008 (Other)	0

	8526-009 (Other)	0
	8528-010 (Other)	0
	8527-011 (Other)	0
	8529-012 (Other)	0
	8532-013 (Other)	0
	8531-014 (Other)	0
	8512-015 (Other)	0
	8530-001 (Project)	0
TOTALS		0
R&R Budget - Materials and Supplies	8504-001 (Admin Core)	0
	8510-002 (Admin Core)	0
	8509-003 (Admin Core)	0
	8511-004 (Admin Core)	0
	8506-005 (Admin Core)	0
	8505-006 (Admin Core)	0
	8508-007 (Admin Core)	0
	8507-008 (Admin Core)	0
	8525-001 (Core)	15,000
	8522-002 (Core)	48,135
	8521-003 (Core)	3,000
	8524-004 (Core)	3,000
	8523-005 (Core)	3,000
	8518-001 (Other)	20,000
	8517-002 (Other)	0

	8520-003 (Other)	90,000
	8519-004 (Other)	150,000
	8514-005 (Other)	440,492
	8513-006 (Other)	156,209
	8516-007 (Other)	50,000
	8515-008 (Other)	20,000
	8526-009 (Other)	0
	8528-010 (Other)	0
	8527-011 (Other)	0
	8529-012 (Other)	0
	8532-013 (Other)	1,250
	8531-014 (Other)	0
	8512-015 (Other)	0
	8530-001 (Project)	0
TOTALS		1,000,086
R&R Budget - Publication Costs	8504-001 (Admin Core)	0
	8510-002 (Admin Core)	0
	8509-003 (Admin Core)	0
	8511-004 (Admin Core)	0
	8506-005 (Admin Core)	0
	8505-006 (Admin Core)	0
	8508-007 (Admin Core)	0
	8507-008 (Admin Core)	0
	8525-001 (Core)	0

	8522-002 (Core)	0
	8521-003 (Core)	0
	8524-004 (Core)	0
	8523-005 (Core)	0
	8518-001 (Other)	0
	8517-002 (Other)	0
	8520-003 (Other)	0
	8519-004 (Other)	0
	8514-005 (Other)	0
	8513-006 (Other)	0
	8516-007 (Other)	0
	8515-008 (Other)	0
	8526-009 (Other)	0
	8528-010 (Other)	0
	8527-011 (Other)	0
	8529-012 (Other)	0
	8532-013 (Other)	0
	8531-014 (Other)	0
	8512-015 (Other)	0
	8530-001 (Project)	0
TOTALS		0
R&R Budget - Consultant Services	8504-001 (Admin Core)	4,000
	8510-002 (Admin Core)	0
	8509-003 (Admin Core)	0

	8511-004 (Admin Core)	0
	8506-005 (Admin Core)	0
	8505-006 (Admin Core)	0
	8508-007 (Admin Core)	4,000
	8507-008 (Admin Core)	0
	8525-001 (Core)	0
	8522-002 (Core)	0
	8521-003 (Core)	0
	8524-004 (Core)	0
	8523-005 (Core)	0
	8518-001 (Other)	0
	8517-002 (Other)	0
	8520-003 (Other)	0
	8519-004 (Other)	0
	8514-005 (Other)	0
	8513-006 (Other)	0
	8516-007 (Other)	0
	8515-008 (Other)	0
	8526-009 (Other)	0
	8528-010 (Other)	0
	8527-011 (Other)	0
	8529-012 (Other)	0
	8532-013 (Other)	0
	8531-014 (Other)	0

	8512-015 (Other)	0
	8530-001 (Project)	0
TOTALS		8,000
R&R Budget - ADP/Computer Services	8504-001 (Admin Core)	0
	8510-002 (Admin Core)	0
	8509-003 (Admin Core)	0
	8511-004 (Admin Core)	0
	8506-005 (Admin Core)	0
	8505-006 (Admin Core)	0
	8508-007 (Admin Core)	0
	8507-008 (Admin Core)	0
	8525-001 (Core)	0
	8522-002 (Core)	0
	8521-003 (Core)	0
	8524-004 (Core)	0
	8523-005 (Core)	0
	8518-001 (Other)	0
	8517-002 (Other)	0
	8520-003 (Other)	0
	8519-004 (Other)	0
	8514-005 (Other)	0
	8513-006 (Other)	0
	8516-007 (Other)	0
	8515-008 (Other)	0

	8526-009 (Other)	0
	8528-010 (Other)	0
	8527-011 (Other)	0
	8529-012 (Other)	0
	8532-013 (Other)	0
	8531-014 (Other)	0
	8512-015 (Other)	0
	8530-001 (Project)	0
TOTALS		0
R&R Budget - Subawards/Consortium/Contractual Costs	8504-001 (Admin Core)	0
	8510-002 (Admin Core)	0
	8509-003 (Admin Core)	0
	8511-004 (Admin Core)	0
	8506-005 (Admin Core)	0
	8505-006 (Admin Core)	0
	8508-007 (Admin Core)	0
	8507-008 (Admin Core)	0
	8525-001 (Core)	0
	8522-002 (Core)	0
	8521-003 (Core)	0
	8524-004 (Core)	0
	8523-005 (Core)	0
	8518-001 (Other)	0
	8517-002 (Other)	0

	8520-003 (Other)	0
	8519-004 (Other)	0
	8514-005 (Other)	0
	8513-006 (Other)	0
	8516-007 (Other)	0
	8515-008 (Other)	0
	8526-009 (Other)	0
	8528-010 (Other)	0
	8527-011 (Other)	0
	8529-012 (Other)	0
	8532-013 (Other)	0
	8531-014 (Other)	0
	8512-015 (Other)	0
	8530-001 (Project)	0
TOTALS		0
R&R Budget - Equipment or Facility Rental User Fees	8504-001 (Admin Core)	0
	8510-002 (Admin Core)	0
	8509-003 (Admin Core)	0
	8511-004 (Admin Core)	0
	8506-005 (Admin Core)	0
	8505-006 (Admin Core)	0
	8508-007 (Admin Core)	0
	8507-008 (Admin Core)	0
	8525-001 (Core)	0

	8522-002 (Core)	0
	8521-003 (Core)	0
	8524-004 (Core)	0
	8523-005 (Core)	0
	8518-001 (Other)	0
	8517-002 (Other)	0
	8520-003 (Other)	0
	8519-004 (Other)	0
	8514-005 (Other)	0
	8513-006 (Other)	0
	8516-007 (Other)	0
	8515-008 (Other)	0
	8526-009 (Other)	0
	8528-010 (Other)	0
	8527-011 (Other)	0
	8529-012 (Other)	0
	8532-013 (Other)	0
	8531-014 (Other)	0
	8512-015 (Other)	0
	8530-001 (Project)	0
TOTALS		0
R&R Budget - Alterations and Renovations	8504-001 (Admin Core)	0
	8510-002 (Admin Core)	0
	8509-003 (Admin Core)	0

	8511-004 (Admin Core)	0
	8506-005 (Admin Core)	0
	8505-006 (Admin Core)	0
	8508-007 (Admin Core)	0
	8507-008 (Admin Core)	0
	8525-001 (Core)	0
	8522-002 (Core)	0
	8521-003 (Core)	0
	8524-004 (Core)	0
	8523-005 (Core)	0
	8518-001 (Other)	0
	8517-002 (Other)	0
	8520-003 (Other)	0
	8519-004 (Other)	0
	8514-005 (Other)	0
	8513-006 (Other)	0
	8516-007 (Other)	0
	8515-008 (Other)	0
	8526-009 (Other)	0
	8528-010 (Other)	0
	8527-011 (Other)	0
	8529-012 (Other)	0
	8532-013 (Other)	0
	8531-014 (Other)	0

	8512-015 (Other)	0
	8530-001 (Project)	0
TOTALS		0
R&R Budget - Other Direct Cost 1	8504-001 (Admin Core)	0
	8510-002 (Admin Core)	0
	8509-003 (Admin Core)	0
	8511-004 (Admin Core)	0
	8506-005 (Admin Core)	0
	8505-006 (Admin Core)	0
	8508-007 (Admin Core)	0
	8507-008 (Admin Core)	0
	8525-001 (Core)	1,000
	8522-002 (Core)	404,763
	8521-003 (Core)	1,000
	8524-004 (Core)	1,000
	8523-005 (Core)	3,000
	8518-001 (Other)	0
	8517-002 (Other)	0
	8520-003 (Other)	3,000
	8519-004 (Other)	0
	8514-005 (Other)	2,000
	8513-006 (Other)	2,000
	8516-007 (Other)	0
	8515-008 (Other)	322,511

	8526-009 (Other)	0
	8528-010 (Other)	0
	8527-011 (Other)	0
	8529-012 (Other)	0
	8532-013 (Other)	0
	8531-014 (Other)	0
	8512-015 (Other)	0
	8530-001 (Project)	210,000
TOTALS		950,274
R&R Budget - Other Direct Cost 2	8504-001 (Admin Core)	0
	8510-002 (Admin Core)	0
	8509-003 (Admin Core)	0
	8511-004 (Admin Core)	0
	8506-005 (Admin Core)	0
	8505-006 (Admin Core)	0
	8508-007 (Admin Core)	0
	8507-008 (Admin Core)	0
	8525-001 (Core)	0
	8522-002 (Core)	0
	8521-003 (Core)	0
	8524-004 (Core)	0
	8523-005 (Core)	0
	8518-001 (Other)	0
	8517-002 (Other)	0

	8520-003 (Other)	0
	8519-004 (Other)	0
	8514-005 (Other)	0
	8513-006 (Other)	0
	8516-007 (Other)	0
	8515-008 (Other)	1,000
	8526-009 (Other)	0
	8528-010 (Other)	0
	8527-011 (Other)	0
	8529-012 (Other)	0
	8532-013 (Other)	0
	8531-014 (Other)	0
	8512-015 (Other)	0
	8530-001 (Project)	0
TOTALS		1,000
R&R Budget - Other Direct Cost 3	8504-001 (Admin Core)	0
	8510-002 (Admin Core)	0
	8509-003 (Admin Core)	0
	8511-004 (Admin Core)	0
	8506-005 (Admin Core)	0
	8505-006 (Admin Core)	0
	8508-007 (Admin Core)	0
	8507-008 (Admin Core)	0
	8525-001 (Core)	0

	8522-002 (Core)	0
	8521-003 (Core)	0
	8524-004 (Core)	0
	8523-005 (Core)	0
	8518-001 (Other)	0
	8517-002 (Other)	0
	8520-003 (Other)	0
	8519-004 (Other)	0
	8514-005 (Other)	0
	8513-006 (Other)	0
	8516-007 (Other)	0
	8515-008 (Other)	0
	8526-009 (Other)	0
	8528-010 (Other)	0
	8527-011 (Other)	0
	8529-012 (Other)	0
	8532-013 (Other)	0
	8531-014 (Other)	0
	8512-015 (Other)	0
	8530-001 (Project)	0
TOTALS		0
R&R Budget - Section F. Total Other Direct Cost	8504-001 (Admin Core)	4,000
	8510-002 (Admin Core)	0
	8509-003 (Admin Core)	0

	8511-004 (Admin Core)	0
	8506-005 (Admin Core)	0
	8505-006 (Admin Core)	0
	8508-007 (Admin Core)	4,000
	8507-008 (Admin Core)	0
	8525-001 (Core)	16,000
	8522-002 (Core)	452,898
	8521-003 (Core)	4,000
	8524-004 (Core)	4,000
	8523-005 (Core)	6,000
	8518-001 (Other)	20,000
	8517-002 (Other)	0
	8520-003 (Other)	93,000
	8519-004 (Other)	150,000
	8514-005 (Other)	442,492
	8513-006 (Other)	158,209
	8516-007 (Other)	50,000
	8515-008 (Other)	343,511
	8526-009 (Other)	0
	8528-010 (Other)	0
	8527-011 (Other)	0
	8529-012 (Other)	0
	8532-013 (Other)	1,250
	8531-014 (Other)	0

	8512-015 (Other)	0
	8530-001 (Project)	210,000
TOTALS		1,959,360
R&R Budget - Section G. Total Direct Cost (A thru F)	8504-001 (Admin Core)	129,910
	8510-002 (Admin Core)	120,483
	8509-003 (Admin Core)	9,052
	8511-004 (Admin Core)	584,305
	8506-005 (Admin Core)	22,262
	8505-006 (Admin Core)	9,167
	8508-007 (Admin Core)	21,236
	8507-008 (Admin Core)	7,365
	8525-001 (Core)	81,826
	8522-002 (Core)	500,000
	8521-003 (Core)	22,145
	8524-004 (Core)	21,065
	8523-005 (Core)	97,148
	8518-001 (Other)	172,765
	8517-002 (Other)	35,095
	8520-003 (Other)	666,544
	8519-004 (Other)	276,080
	8514-005 (Other)	2,390,549
	8513-006 (Other)	902,960
	8516-007 (Other)	347,296
	8515-008 (Other)	634,368

	8526-009 (Other)	15,686
	8528-010 (Other)	29,617
	8527-011 (Other)	38,299
	8529-012 (Other)	39,250
	8532-013 (Other)	12,144
	8531-014 (Other)	5,812
	8512-015 (Other)	48,288
	8530-001 (Project)	210,000
TOTALS		7,450,717
R&R Budget - Section H. Indirect Costs	8504-001 (Admin Core)	58,459
	8510-002 (Admin Core)	54,217
	8509-003 (Admin Core)	4,073
	8511-004 (Admin Core)	0
	8506-005 (Admin Core)	10,018
	8505-006 (Admin Core)	4,125
	8508-007 (Admin Core)	9,556
	8507-008 (Admin Core)	3,314
	8525-001 (Core)	36,822
	8522-002 (Core)	225,000
	8521-003 (Core)	9,965
	8524-004 (Core)	9,479
	8523-005 (Core)	43,716
	8518-001 (Other)	77,744
	8517-002 (Other)	15,793

	8520-003 (Other)	299,946
	8519-004 (Other)	124,236
	8514-005 (Other)	1,075,747
	8513-006 (Other)	406,332
	8516-007 (Other)	156,283
	8515-008 (Other)	285,466
	8526-009 (Other)	7,059
	8528-010 (Other)	13,328
	8527-011 (Other)	17,235
	8529-012 (Other)	17,662
	8532-013 (Other)	5,465
	8531-014 (Other)	2,615
	8512-015 (Other)	21,730
	8530-001 (Project)	94,500
TOTALS		3,089,885
R&R Budget - Section I. Total Direct and Indirect Costs (G +H)	8504-001 (Admin Core)	188,369
	8510-002 (Admin Core)	174,700
	8509-003 (Admin Core)	13,125
	8511-004 (Admin Core)	584,305
	8506-005 (Admin Core)	32,280
	8505-006 (Admin Core)	13,292
	8508-007 (Admin Core)	30,792
	8507-008 (Admin Core)	10,679
	8525-001 (Core)	118,648

	8522-002 (Core)	725,000
	8521-003 (Core)	32,110
	8524-004 (Core)	30,544
	8523-005 (Core)	140,864
	8518-001 (Other)	250,509
	8517-002 (Other)	50,888
	8520-003 (Other)	966,490
	8519-004 (Other)	400,316
	8514-005 (Other)	3,466,296
	8513-006 (Other)	1,309,292
	8516-007 (Other)	503,579
	8515-008 (Other)	919,834
	8526-009 (Other)	22,745
	8528-010 (Other)	42,945
	8527-011 (Other)	55,534
	8529-012 (Other)	56,912
	8532-013 (Other)	17,609
	8531-014 (Other)	8,427
	8512-015 (Other)	70,018
	8530-001 (Project)	304,500
TOTALS		10,540,602

A. COMPONENT COVER PAGE

Project Title: Office of the Director

Component Project Lead Information:

Redacted by agreement

B. COMPONENT ACCOMPLISHMENTS

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

The Yerkes Director's Office serves to establish key strategic objectives and to coordinate the overall management of the Center. The guideposts for our management of the Center include the strategic objectives of the NIH, as well as the outcomes of strategic planning exercises within the Emory University Woodruff Health Sciences Center (WHSC) and within Yerkes. Strategic planning is conducted in close collaboration with the Associate Director for Scientific Programs (ADSP), and is a unified process that reflects not only our structured internal planning efforts but also the integration of these internal strategic plans with those of our affiliates, including the other NPRCs, Office of Research Infrastructure Programs (ORIP) and the WHSC. The Director also works closely with the ADSP on recruitment, retention and promotion of faculty. In collaboration with the Chief Business Officer (CBO), the Director works to ensure effective fiscal and administrative oversight of funds used for both sponsored research activities and operations of the Center in compliance with University and Federal guidelines. The Director also works closely with the CBO and other members of the Yerkes leadership team to identify new sources of support for the Center. Finally, the Director works in concert with the Chief of Public Affairs to communicate the results of key scientific studies, not only to our scientific colleagues but also, to our Center employees and the public at large. The Director will also ensure the coordination and communication of plans with appropriate counterparts in WHSC, as well as in the ORIP and with other NPRCs.

The Specific Aims are:

1. To establish scientific and strategic priorities for the Yerkes Center and to orchestrate efforts to achieve these goals within the Center, WHSC, and nationwide;

2. To work collaboratively with the ADSP to recruit outstanding scientists, retain our faculty, and support their promotion in rank at Emory University;

3. To work in concert with the Yerkes CBO and other members of the Yerkes leadership team to ensure equitable and strategic allocation of financial resources and to identify new sources of support for the Center;

4. To provide effective communication regarding Center activities and priorities to the Yerkes community, WHSC and the national biomedical research and lay communities.

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

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: B2_8504 Director.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

Not Applicable

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

File uploaded: B4_c Training.pdf

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

NOTHING TO REPORT

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

Strategic Planning

Strategic planning at Yerkes plays a central role in the establishment of short-term and long-term goals to advance nonhuman primate translational research. Strategic planning is conducted in close collaboration with the ADSP, and is a cohesive process that reflects not only the structured internal planning efforts but also the integration of these internal strategic plans with those of our affiliates, including the other NPRCs, ORIP and the WHSC. Working with the ADSP, as well as the Scientific Division Chiefs, the CBO, the other Associate Directors, and the Yerkes faculty, the Director will help identify short-term and long-term goals that will guide the recruitment of new faculty, allocation of resources, and the future directions of the Center's Core services. Of particular interest are efforts to leverage advances in genomics to advance our scientific programs and the opportunities to create greater synergy between our neuroscience and microbiology/immunology communities. These strategic goals will be reevaluated on at least an annual basis, and aligned with the strategic objectives of the WHSC and University, as well as ORIP and the NIH.

Faculty Recruitment

The Center Director will continue to work closely with the ADSP in coordinating faculty recruitment and promotion activities. Structured

faculty recruitments will be based on specific needs in focused research areas and will be initiated in close cooperation with the Science Divisions. These recruitment efforts will also be coordinated with other units of the University, typically departments within the School of Medicine, based on research program relevance. Retention efforts will occur as both proactive and reactive steps to retain our most productive faculty but will be guided by the overarching objectives of the strategic planning process to ensure that there is an alignment of resource commitments to overall strategic goals.

Specific areas of faculty recruitment in the upcoming funding period include: 1. The Associate Director for Pathology; and 2. An additional faculty position for the ERASE AIDS initiative, which is focused on nonhuman primate models of HIV cure research; and 3. Bringing a joint search with the Emory College of Arts and Sciences Department of Psychology in comparative behavioral neuroscience to successful completion.

B.2. Accomplishments—Director's Office

A robust, integrated and effective leadership team is essential for the short-term and long-term success of the Yerkes National Primate Research Center (NPRC) and its ability to achieve its operating and strategic goals. The Center Director provides overall leadership for the Center, establishing scientific and administrative priorities that are guided by the Center's strategic plans. The Director is ultimately responsible for the oversight of all activities at the Center, including establishment of scientific priorities, strategic planning, coordination of new faculty recruits, financial management and business planning, human resources and public communications. In order to efficiently and effectively manage these diverse responsibilities, the Director of the Yerkes Center works closely with the Associate Director for Scientific Programs (ADSP), the Chief Business Officer (CBO), the Associate Director for Animal Resources, the Associate Director for Pathology, the four Chiefs of the Scientific Divisions, the Director of Human Resources and the Chief of Public Affairs.

The Specific Aims of the Director's Office, which are unchanged, are:

1. To establish scientific and strategic priorities for the Yerkes Center and to orchestrate efforts to achieve these goals within the Center, WHSC, and nationwide;

2. To work collaboratively with the ADSP to recruit outstanding scientists, retain our faculty, and support their promotion in rank at Emory University.

3. To work in concert with the Yerkes CBO and other members of the Yerkes leadership team to ensure equitable and strategic allocation of financial resources and to identify new sources of support for the Center;

4. To provide effective communication regarding Center activities and priorities to the Yerkes community, WHSC and the national biomedical research and lay communities.

The Yerkes Director's Office has demonstrated significant progress in meeting each of our key objectives during the reporting period (5/1/18 to 4/30/19), and in particular, has made key progress in strategic planning and in faculty recruitment. Specific progress in each of these areas includes:

Strategic Planning:

The Center Director has worked closely with the Associate Director for Scientific Programs (ADSP), Dr. Redacted by agreement to coordinate our implementation of this plan. The Yerkes strategic plan was developed from 2014 to 2016 following a series of strategic planning sessions involving each of the four scientific divisions, as well as the Division of Animal Resources and Pathology. In 2017, a final document was prepared and presented to and approved by all Yerkes faculty. This document identifies priorities for faculty recruitment and allocation of resources through 2021. These key strategic priorities align with the new Woodruff Health Sciences Strategic Plan, especially for the Innovative Discovery initiative, as well as Emory University's strategic framework (Faculty Excellence, Academic Community of Choice, and Innovation).

Ongoing progress towards achieving the goals of the strategic plan follows:

Near-term Initiatives

- Faculty recruitment of Associate Director of Pathology, Director of Imaging Center and a geneticist (*two of three completed*, *recruitment of Pathology AD ongoing*)
- Initiate rhesus colony phenotyping program to include 150 animals; collaborate with Marcus Autism Center to support genomic analyses and expand animal resources committed to long-term autism studies effective (*phenotyping of >100 animals completed to date; whole exome or whole genome data now available for >100 animals; analysis to date has yielded several genetic variants associated with autism in humans*)
- Faculty recruitment for the ERASE AIDS initiative in nonhuman primate HIV cure research (*first recruitment completed, to join Yerkes in March 2019*)

Medium and Long-term Initiatives

- Expand pilot projects to include at least one additional project per year based on high-priority, targeted research areas (*one additional pilot funded in FY17 in partnership with CFAR, pilot funding identified as priority area for fundraising*)
- Recruit new DCN senior scientist (*ongoing, see below regarding Psychology Department search*)
- Initiate new collaborative studies with Pediatrics Department, especially in the area of autism (*see summary above under rhesus colony phenotyping*)
- Pursue joint effort with the Psychology Department to recruit faculty with strong interest in nonhuman primate cognitive and social neuroscience (*interviews completed and lead candidate identified, offer currently being prepared*)
- Expand imaging focus on infectious diseases and transplantation by investing in novel PET tracer development for immunoPET and neuroinflammation; initiate collaboration with CSI to pursue nanoparticle MRI and obtain whole-body PET/CT (*underway with new Imaging Director,* Redacted by agreement
- Expand nonhuman primate transgenic Huntington's disease program; establish program for expanded phenotyping of Huntington's disease colony (*on hold, efforts to obtain funding unsuccessful to date*)
- Expand nonhuman primate transgenic program to include other applications (e.g. optogenetics) (*initial experiments under way, funding options being pursued*)
- Develop nonhuman primate TB program via Private Source other foundation, or NIH support (*one major funding proposal under consideration at present*)
- Expand whole genome (WGS) and whole exome (WES) data from Yerkes rhesus macaque SPF colony to 500-1000 animals over next 5 years (*whole genome and whole exome data currently available for >100 Yerkes animals, funding included in SPF grant renewal for WGS/WES of ~40 additional animals*)
- Support bioinformatics and big data analyses via recruitment of Yerkes faculty with expertise in bioinformatics and actively participate in WHSC efforts to embrace big data science; ensure access to adequate data storage and support concierge model for Yerkes IT (*ongoing*)
- Increase quarantine space and run housing; consider expansion of SPF colony (*three renovation/construction projects completed or near completion, $3M NIH C06 proposal planned for submission in March 2019*)
- Enhance collaboration between Animal Resources and research scientists; facilitate involvement of veterinarians in research projects and at multiple stages (*ongoing*)
- Expand educational opportunities; development of a collaborative pathology residency program (*on hold pending recruitment of new Pathology AD*).
- Expand collaborative and independent research funding base of Pathology Division (*on hold pending recruitment of new Pathology AD*).

Faculty recruitment:

- Redacted by agreement was recruited as part of the ERASE AIDS Initiative and will have a joint appointment with the SOM Department of Pathology and Laboratory Medicine. Redacted by agreement has studied the role of antibodies to prevent HIV infection and facilitate HIV cure-related therapeutic strategies.
- Comparative Behavioral Neuroscience: A joint faculty search between the ECAS Department of Psychology and Yerkes has led to the identification of four highly qualified candidates, and an offer has recently been extended to the lead candidate, who is anticipated to start in Q1 2020.
- Redacted by agreement was hired as an Associate Pathologist in the Yerkes Division of Pathology.
- Redacted by agreement was hired as an Associate Veterinarian in the Yerkes Division of Animal Resources.

B.4. Training and Professional Development Opportunities

Please see the overall component for response.

C. COMPONENT PRODUCTS

C.1 PUBLICATIONS

Not Applicable

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

Not Applicable

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

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

Not Applicable

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Nothing to report

D. COMPONENT PARTICIPANTS

Not Applicable

E. COMPONENT IMPACT

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

Not Applicable

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

Not Applicable

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

NOTHING TO REPORT

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?
Not Applicable

F. COMPONENT CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

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

NOTHING TO REPORT

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

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. COMPONENT SPECIAL REPORTING REQUIREMENTS

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

Not Applicable

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

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

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

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

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Not Applicable

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

RPPR - Admin Core-8504

RESEARCH & RELATED BUDGET - SECTION A & B **FINAL**

ORGANIZATIONAL DUNS*: 066469933

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

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.	Dr	Jonathan		Lewin		PI	Institutional Base Salary	EFFORT			0.00	0.00	0.00
2.	Redacted by agreement					Project Lead					94,800.00	24,648.00	119,448.00

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

Additional Senior Key Persons: File Name:

Total Senior/Key Person **119,448.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
1	Secretarial/Clerical	0.6			3,541.00	921.00	4,462.00
1	**Total Number Other Personnel**					**Total Other Personnel**	**4,462.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**123,910.00**

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

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

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	Funds Requested ($)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	2,000.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**2,000.00**

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

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

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	0.00
2. Publication Costs	0.00
3. Consultant Services	4,000.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
Total Other Direct Costs	**4,000.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**129,910.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. MTDC	45.0	129,910.00	58,459.00
		Total Indirect Costs	**58,459.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, Steven Zuraf, (301) 492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**188,369.00**

J. Fee	Funds Requested ($)*
	0.00

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

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

Budget Justification

The budget request for the upcoming period is submitted in accordance with the peer reviewed P51 renewal approved in 2016. Justification for each budget category was also peer reviewed and approved at that time, and there is no significant change in this budget request from previously approved levels.

A. COMPONENT COVER PAGE

Project Title: Asc. Dir. for Scientific Programs

Component Project Lead Information:

Redacted by agreement

B. COMPONENT ACCOMPLISHMENTS

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

The Associate Director for Scientific Programs (ADSP) provides assistance to the Director in all aspects of scientific programs of the Center, including formulating short-term and long-range goals and strategic planning, establishing specific objectives and implementing steps for promoting the scientific programs and resource enhancements of the Center. The ADSP serves as Acting Director during the Director's absence. The responsibilities of the office are accomplished in conjunction with the Director, Science Division Chiefs, Science Core Directors and with affiliate and collaborating scientists, to identify needs and establish priorities. Specifically, the ADSP promotes the further development of the Center's core, affiliate and collaborative research programs, and assists the Director in guiding the Center's research and management activities while participating in the development and implementation of a strategic research plan. Additionally, the ADSP works closely with the Director by participating in the Consortium of NPRCs and through promoting the NPRC mission to key individuals in NIH and elsewhere in government. Specific activities encompassed by this leadership position include taking a lead role in the organization of the 2020 P51 Base Grant application, organizing strategic planning for research programs, serving as Chair of the Yerkes Space Committee, coordinating faculty recruitment and promotion activities as Chair of the Appointment and Promotions Committee, enhancing the mentoring programs for junior scientists, serving as Chair of the Research Advisory Committee, reviewing the research utilization of animal resources at the Center, exploring new collaborative research opportunities, as well as taking on other activities as needed that will support scientific research at Yerkes. Redacted by agreement has appropriate scientific expertise and leadership experience to meet the challenges of these multiple roles at the Center.

The Specific Aims are:

1.To enhance the scientific programs of the Center through the development and application of innovative technologies and collaborative efforts among Center scientists and outside investigators at the national and international level;

2.To provide leadership and oversight in strategic planning, promotion of scientific programs, and expansion of the Center infrastructure, including the evaluation of research programs for mission relevance and scientific merit to ensure that required state-of-the-art resources are available;

3.To coordinate faculty recruitment and promotion and to enhance mentoring activities for junior scientists.

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

Yes

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: B2_8505 ADSR.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

Not Applicable

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

File uploaded: B4_c Training.pdf

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

NOTHING TO REPORT

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

The continued success of the Center will depend largely on the ability to strengthen its scientific programs and its leadership position within Emory University, and at the national and international levels. Genetics and genomics have become essential in many aspects of biomedical research, and the importance of genomic analysis of nonhuman primates will assume increasing significance in multiple fields, ranging from microbiology/immunology studies to studies of addiction, autism and other neuropsychiatric diseases. The Yerkes Center is well positioned, with its outstanding programs in molecular biology and immunology, infectious diseases, and neuroscience, to take a leadership role in this regard by initiating genomic characterization of specific groups of monkeys, as recently done by Yerkes HIV/AIDS researchers and others, sequencing the sooty mangabey genome, or in ongoing work to characterize the pheno- and genotype of large groups of rhesus macaques in the colony. The latter program has made significant progress during the last year and will continue for the current year. While primarily carried out by scientists at the Field Station, the ADSP will remain closely involved, providing oversight and helping to shape the future direction of the phenotyping program. Future efforts also will emphasize the importance of developing complex, multi-dimensional phenotyping information related to normal and abnormal behavior and physiology that is highly relevant to human disease, pathology, and behavior.
Further, the Yerkes Center has the expertise and initiative to move techniques that allow for genetic manipulation of targeted brain circuits and other tissues through the use of optogenetics or chemogenetics. These techniques are commonplace in rodents, but have yet to become mainstream in primate experimentation. While optogenetic technology has been in use at the Center for several years, Yerkes scientists Redacted by agreement have only recently made significant progress towards the use of chemogenetics in monkeys.

Further advancing this technology will be highly important, since it will allow for relatively non-invasive mechanistic studies linking brain circuits to function and pathology. Chemogenetic techniques also have significant translational relevance, as they may lead to new treatments for human diseases, such as Parkinson's disease or dystonia. Development of these techniques remains an obvious priority, as is the need to generate the first use cases of applying the new techniques to models of neuropsychiatric diseases.
Development of the Yerkes Imaging Core will remain a significant activity in the coming funding period. The new Imaging Center director Redacted by agreement is an expert in stroke imaging. This fact, together with the recent move of Emory stroke researcher Redacted by agreement to the Center, brings with it the prospect of an expanded role of the Yerkes Imaging Core in research on cerebrovascular diseases, in addition to providing continued help with other lines of research. The primary task of the coming months and years will be to help the Imaging Center to overcome some of its significant challenges, including the need to modernize aging equipment, and the need to expand its user base.
Finally, successful recruitment and retention of research faculty are essential to the mission of the Center. We have filled some of the key open positions at Yerkes (Assistant Director of the Genetics Core and Director of the Imaging Center), and continue efforts to retain junior faculty by providing them effective research and professional mentorship, as well as the resources to succeed. The new recruitments will provide many exciting opportunities to develop research collaborations at the Center and with scientists outside of the center.

B.2. Accomplishments—Associate Director for Scientific Programs

The Associate Director for Scientific Programs (ADSP) works closely with the Center Director in all aspects of scientific programs of the Center, including formulating short-term and long-range goals and strategic planning, establishing specific objectives, and promoting the scientific programs and resource enhancements of the Center.

In the last funding period, the ADSP continued his activities with the research scientists at the Yerkes Field Station, working to enhance the unique research opportunities provided by our large groups of socially-housed rhesus monkeys. A major ongoing project that has now completed its second successful year at the Yerkes Field Station is a phenotyping effort, consisting of the collection of behavioral data and biospecimens from a large number of animals. The effort will continue in the coming year(s), with plans to add further animals in subsequent years. The ADSP is also involved in many of the ongoing discussions about major projects planned by Field Station investigators, several of which involve plans to utilize the phenotyping (and genotyping) data.

The ADSP works closely with the Center Director in coordinating faculty recruitment and promotion activities. The ADSP serves as Chair of the Faculty Promotion Committee, which is comprised of the Chiefs of the four Science Divisions, and the Associate Director of Animal Resources (who also serves as the Interim Associate Director of Pathology). The ADSP participated actively in the ongoing recruitment of a faculty member who will jointly be hired by the Department of Psychology and the Yerkes Center. After interviews of multiple highly talented researchers, hiring discussions are now underway with one of them. In addition, the ADSP participated in the successful searches for a staff pathologist, as well as that for the Assistant Division Chief and the Chief of Clinical Operations in the Division of Animal Resources.

Faculty recruitment and promotion guidelines were revised for further clarification. The ADSP oversaw the process of promotion of two faculty members Redacted by agreement during the course of the last year. The ADSP also provides oversight of the Yerkes Center Mentoring Program. The annual career review guidelines and forms were revised and appropriate annual reviews of junior faculty were conducted (including follow-up meetings with several faculty to provide additional discussions).

The ADSP is head of the Yerkes Space Committee, which is charged with facilitating research by managing space requests (in a generally space-constrained environment). The space committee handled multiple requests during the last year and accomplished a short turn-around time of these requests (2-3 weeks).

Finally, the ADSP chairs the Research Advisory Committee, charged with evaluating requests for the use of Yerkes resources or expertise for collaborative research projects. The agenda of RAC meetings was revised to now include a regular update on available resources and all outstanding requests for nonhuman primates. We also introduced a new pre-proposal process to prevent resource shortfalls. Such pre-proposals are only needed for grant applications with a substantial impact on animal resources, and are used to trigger discussion with the veterinary leadership. All pre-proposals are also discussed at weekly Associate Directors meetings, and summarized at the monthly meeting of the Research Advisory Committee.

B.4. Training and Professional Development Opportunities

Please see the overall component for response.

C. COMPONENT PRODUCTS

C.1 PUBLICATIONS

Not Applicable

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

Not Applicable

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

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

Not Applicable

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Nothing to report

D. COMPONENT PARTICIPANTS

Not Applicable

E. COMPONENT IMPACT

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

Not Applicable

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

Not Applicable

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

NOTHING TO REPORT

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?
Not Applicable

F. COMPONENT CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

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

NOTHING TO REPORT

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

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. COMPONENT SPECIAL REPORTING REQUIREMENTS

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

Not Applicable

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

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

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

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

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Not Applicable

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

RPPR - Admin Core-8505

RESEARCH & RELATED BUDGET - SECTION A & B **FINAL**

ORGANIZATIONAL DUNS*: 066469933

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

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		Redacted by agreement				Project Lead	Institutional Base Salary	EFFORT			5,688.00	1,479.00	7,167.00

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

Additional Senior Key Persons: File Name:

Total Senior/Key Person **7,167.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	**Total Number Other Personnel**					**Total Other Personnel**	**0.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**7,167.00**

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

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

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	Funds Requested ($)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	2,000.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**2,000.00**

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

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

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	0.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
Total Other Direct Costs	**0.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**9,167.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. MTDC	45.0	9,167.00	4,125.00
		Total Indirect Costs	**4,125.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, Steven Zuraf, (301) 492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**13,292.00**

J. Fee	Funds Requested ($)*
	0.00

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

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

Budget Justification

The budget request for the upcoming period is submitted in accordance with the peer reviewed P51 renewal approved in 2016. Justification for each budget category was also peer reviewed and approved at that time, and there is no significant change in this budget request from previously approved levels.

A. COMPONENT COVER PAGE

Project Title: Business Services

Component Project Lead Information:

Redacted by agreement

B. COMPONENT ACCOMPLISHMENTS

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

The Business Services Office (also referred to as Business and Finance) is responsible for an array of services required for the day-to-day operations of the Center. It is responsible for budgeting and financial management, to assist in grant proposal preparation, for financial review of grant proposals, post-award administration of grants, procurement of goods and services, billing and recharge recovery, shipping, bi-weekly payroll, labor distribution, effort certification and other research compliance issues, and reception of visitors to the Center. The business functions are centrally organized and provided to all laboratories and service units at Yerkes. Because so much of the activity is grant-driven, the staff must focus on compliance issues as well as service aspects. The Business Services Office is esponsible for all of the above activities relating to the Yerkes P51 Base Grant as well as for the other approximately $64M in sponsored research funding at Yerkes. This office must safeguard the resources of the Yerkes Center. Business Services is responsible for the financial management and accounting of the Emory-designated Unrestricted Operating Budget (UOB) funds, designated funds, endowment funds, all discretionary funds used by faculty and staff, and for the financial and compliance activities relating to extramural support for investigators. The Chief Business Officer, who reports to he Yerkes Director, Chief University Financial Officer, and the Chief University Budget Officer, heads this office.

The Specific Aims are:

1. To continue to provide comprehensive and effective financial management and oversight of all funds used in support of both the operations and sponsored research associated with the Yerkes Center including, most importantly, the management of the P51 award;

2. To provide high level customer service to our cohort of faculty, staff, and students in each Division within Yerkes by outlining and adhering to established internal policies as well as university-level policies and providing operational support on all activities;

3. To continue to provide financial oversight, rate setting, and cost recovery for our numerous service center activities at Yerkes;

4. To represent Yerkes on university-level committees and initiatives to ensure that the needs and interests of Yerkes are taken into consideration when policies and strategic plans are developed.

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

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: B2_8506 Bus Svs.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

Not Applicable

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

File uploaded: B4_c Training.pdf

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

NOTHING TO REPORT

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

Continue to provide comprehensive and effective financial management and oversight of all funds used in support of both the operations and sponsored research associated with the Yerkes Center including, most importantly, the management of the P51 award.

Business Services will work with faculty, leadership and central offices such as Emory's Office of Sponsored Research (OSP) and Research: Grants and Contracts (RGC) to provide information and acquire training and updates to more effectively manage the P51 as well as our numerous other externally-funded grants.

Provide high level customer service to our cohort of faculty, staff, and students in each Division within Yerkes by outlining and adhering to established internal policies as well as university-level policies and providing operational support on all activities. As noted in our Accomplishments section, our staff are provided with training sessions from various entities including NIH, NCURA, and SRAI. In-house training sessions will be held as opportunities arise.

Continue to provide financial oversight, rate setting, and cost recovery for our numerous service center activities at Yerkes. The CBO and the Director of Business and Finance will continue to work with the leaders of Animal Resources, Pathology, and the other Service Cores to conduct regular, comprehensive reviews of expenses and recharge recovery. These reviews will include annual rate setting analyses and projections. New rates will be posted on the Yerkes website and will be disseminated to faculty at the regular faculty meetings and by email using the faculty listserv. The financial performance of Service Cores and units providing experimental clinical

services will continue to receive financial reports on a regular basis and these include annualized projections for the fiscal year.

Represent Yerkes on university-level committees and initiatives to ensure that the needs and interests of Yerkes are taken into consideration when policies and strategic plans are developed.

B.2. Accomplishments—Business Services

The Business Services Office, primarily through its Research Administration Services (RAS) component, managed nearly $75M in sponsored research funding in FY18, which was nearly the same level of funding as FY17. FY16 had reflected an increase of nearly 19% over the prior year without any increase in FTE levels. This FTE level has been maintained, in part, by a frequent review of workload distribution and reassigning portfolios between existing staff when warranted. Our staff reviewed and approved total grant expenditures of $76.6M, a slight decrease of 1.67% over the previous year.

Led by Redacted by agreement our Director of Business and Finance, the Business Services unit worked with Service Centers to update their rates for FY19 and to continue to improve their utilization tracking. Service units recovered recharge funding at nearly equal to FY17 at $11.9M. Indirect Cost Recovery remains nearly stable at roughly $27.5M. FY19 trends are slightly lower than FY18 thus far. This unit manages our operating budget of $47.8M excluding the research grants of $63,630,246 that are managed by the RAS group, led by Redacted by agreement Redacted by agreement

Our Research Administration Services group and Redacted by agreement Chief Business Officer (CBO), reviewed and submitted 196 grant proposals from Yerkes-based faculty for a total of $104,630,156 in requested funding. There were also numerous collaborative proposals for which our input was necessary but for which Yerkes would not be the prime awardee. Redacted by agreement Director of the Yerkes RAS unit, attended the Society of Research Administrators International's Research Intensive Leadership Training at the end of February 2018. Redacted by agreement Director of Business and Finance, was invited to participate in Emory University's in depth review of the procurement process and is now a member of the Emory Procurement Network. She, Redacted by agreement Redacted by agreement are active members of the university's Enterprise Finance Network/FON. Ms. Redacted by agreement serves on the NPRC Costing Model Working Group, Redacted by agreement is a member of the NPRC COO/CFO group. Redacted by agreement s an active member of the RAS Directors' Committee. Redacted by agreement was nominated for and accepted into this year's cohort of the highly successful Excellence Through Leadership program at Emory.

The two security guards continue to manage security for the Center's main campus with one at the front desk reception for screening visitors and vendors to enhance security and the other circulating throughout the multiple buildings on our Main Station campus. Video surveillance continues to be enhanced and expanded where deemed necessary. Our security guards have real-time access to all surveillance cameras at the Main Station.

Redacted by agreement continues to serve as a member of the Emory Finance Steering Committee which oversees the upgrades and modifications to the PeopleSoft Financial System referred to as Compass as well as to the Oracle-based Emory Business Intelligence financial reporting data warehouse both of which are used for all financial transactions and financial reporting at Emory. She continues to serve as a member of Emory's HR Leadership Committee as well as a member of the Emory Finance Network Systems Committee.

Redacted by agreement completed her service on the Provost-initiated Research Administrative Services (RAS) Task Force Improvement Committee. This committee was formed in response to a Faculty Council request to address weaknesses and inconsistencies among the School of Medicine's RAS units. The Committee developed and submitted a final 108-page report to the Provost on March 26, 2018. We were pleased to know that the Yerkes and School of Public Health RAS units were deemed to be effective and thus not part of this review.

B.4. Training and Professional Development Opportunities

Please see the overall component for response.

C. COMPONENT PRODUCTS

C.1 PUBLICATIONS

Not Applicable

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

Not Applicable

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

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

Not Applicable

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Nothing to report

D. COMPONENT PARTICIPANTS

Not Applicable

E. COMPONENT IMPACT

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

Not Applicable

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

Not Applicable

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

NOTHING TO REPORT

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?
Not Applicable

F. COMPONENT CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

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

NOTHING TO REPORT

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

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. COMPONENT SPECIAL REPORTING REQUIREMENTS

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

Not Applicable

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

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

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

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

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Not Applicable

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

RPPR - Admin Core-8506

RESEARCH & RELATED BUDGET - SECTION A & B **FINAL**

ORGANIZATIONAL DUNS*: 066469933

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

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		Redacted by agreement				Project Lead	Institutional Base Salary	EFFORT			9,480.00	2,465.00	11,945.00

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

Additional Senior Key Persons: File Name:

Total Senior/Key Person **11,945.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Business/Finance Director	0.6			6,601.00	1,716.00	8,317.00
1	**Total Number Other Personnel**					**Total Other Personnel**	**8,317.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**20,262.00**

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

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

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	Funds Requested ($)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	2,000.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**2,000.00**

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

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

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	0.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
Total Other Direct Costs	**0.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**22,262.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. MTDC	45.0	22,262.00	10,018.00
		Total Indirect Costs	**10,018.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, Steven Zuraf, (301) 492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**32,280.00**

J. Fee	Funds Requested ($)*
	0.00

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

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

Budget Justification

The budget request for the upcoming period is submitted in accordance with the peer reviewed P51 renewal approved in 2016. Justification for each budget category was also peer reviewed and approved at that time, and there is no significant change in this budget request from previously approved levels.

A. COMPONENT COVER PAGE

Project Title: Human Resources

Component Project Lead Information:

Redacted by agreement

B. COMPONENT ACCOMPLISHMENTS

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

The Yerkes Human Resources (HR) Office is comprised of three employees, each responsible for working with various components within Emory's Central Human Resources. Policies and procedures related to benefits, compensation, recruitment, learning and development, and employee relations, are administered through Yerkes Human Resources. In addition, this office interacts with Emory's International Student and Scholar Services unit with visa related matters as well as providing orientation and information to new faculty, staff and students at the Center. The Human Resources office works in conjunction with the Office of General Counsel on the student and scholar liability agreements for unpaid individuals who participate in research at the Center. We also work together with the Office of Equity and Inclusion on equal employment opportunity, disability, and compliance services. Working with our internal committee, the well-established Yerkes Staff and Wellness Council, the HR office sponsors several special events throughout the year for our staff employees. These activities are designed to create a balance between their job duties and the opportunity to interact with other departments on a social level. With a greater focus on health and well-being and positive lifestyle changes, the establishment of our Yerkes Staff and Wellness Council has been met with great enthusiasm by all Center employees. The members of this committee also work with the wellness component of the campus Faculty Staff Assistance Program (FSAP) to provide our employees with programs that include healthy changes in their diets, nutrition and daily exercise routines so that living healthier becomes a lifestyle change.

Goals for this unit are:

1.To continue to work efficiently and effectively with all our employees to provide the best service in all aspects of human resources;

2.To build upon our already established, collaborative efforts with Central Human Resources and other departments within Emory and work together to provide enhanced support in the services we provide to our overseas scholars in both legal and equal opportunity initiatives;

3.To enhance our operations by utilizing technology to streamline processes and become more efficient and effective in our day to day work;

4.Provide cultural awareness by continued onsite Equity and Inclusion programs for faculty, staff managers and general staff at Yerkes.

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

Yes

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: B2_8507 HR.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

Not Applicable

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

File uploaded: B4_c Training.pdf

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

NOTHING TO REPORT

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

We have worked and will continue to collaborate with the Office of Equity and Inclusion at Emory to provide opportunities for our faculty and staff to receive continuing education on various topics relevant to that office such as Preventing Discrimination and Harassment in the Workplace.

The new Director of Human Resources will be meeting with employees to establish relationships and determine human resource needs for the different units within the Center in order to enhance the work experience and culture of the Center.

We will also continue the Center Mentor Program Plan, which will make mentorship opportunities available to employees at Yerkes to assist with career development.

We have and will continue to collaborate with the Office of General Council to provide enhanced support in the services we provide to our overseas scholars in both legal and equal opportunity initiatives.

We will begin digitizing files and process mapping to improve efficiency and reduce waste in our day-to-day functions.

B.2 Accomplishments—Human Resources

The Yerkes Human Resources Office, currently staffed with three employees, continues to be the onsite resource office for all Human Resources functions, i.e. recruitment and employment, compensation, benefits, learning and development, and employee relations. In addition, relative to the HR functions, the Human Resources Office interacts with other departments within Emory University: International Student and Scholar Services (for visa and visa related matters), Office of General Counsel (for unpaid non-Emory students and other personnel liability agreements), the Office of Equity and Inclusion (for compliance and diversity issues) and with the Faculty Staff Assistance Program (for wellness and other matters).

Following the retirement of the long-standing Yerkes HR Director Redacted by agreement in January 2019, we hired Redacted by agreement to assume this critical role at Yerkes. Redacted by agreement obtained an M.B.A. from St. Leo University and an M.Ed. from Arizona State, and previously served as the HR Manager for the WP Carey School of Business at Arizona State University.

The Yerkes Staff and Wellness Council continues to work with the HR Office to provide social and wellness events and programs in addition to community projects throughout the year, in conjunction with Emory Wellness Office and its Faculty Staff Assistance Program.

During the past year, the Human Resources Office has continued to endeavor to provide an excellent level of service to all faculty, staff, students and collaborators as has been done in the past. As a result of the Engagement Survey conducted in June 2016, the Center established a Mentor Program. The objective of this program is to assist the mentee in an area of interest, not necessarily related to the mentee's current position at the Center. The program helps the mentee in communication, goal setting, career planning and developing other soft skills. As we concluded the first year, two employees successfully completed the program. We also continue to work on the development of a Rewards and Recognition Program for staff employees within the Center.

Yerkes HR Office participated in an Emory initiative to review the current Orientation and Onboarding program at the University and institute changes that will make that process more welcoming and informative for new employees. As a result, the University has instituted a New Employee Orientation program with sessions every other Monday.

Together with the University, the Center transitioned from IBM Kenexa Brassring to a new internet-based recruitment applicant tracking system powered by iCIMS (Internet Collaborative Information Management Systems), which is designed to change how Emory sources candidates, posts jobs, communicates with candidates, schedules interviews, makes job offers and pre-starts the new employee. This system has changed the user experience for job applicants, making the process more seamless and easier to use for potential employees at Emory.

B.4. Training and Professional Development Opportunities

Please see the overall component for response.

C. COMPONENT PRODUCTS

C.1 PUBLICATIONS

Not Applicable

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

Not Applicable

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

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

Not Applicable

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Nothing to report

D. COMPONENT PARTICIPANTS

Not Applicable

E. COMPONENT IMPACT

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

Not Applicable

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

Not Applicable

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

NOTHING TO REPORT

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?
Not Applicable

F. COMPONENT CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

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

NOTHING TO REPORT

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

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. COMPONENT SPECIAL REPORTING REQUIREMENTS

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

Not Applicable

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

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

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

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

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Not Applicable

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

RPPR - Admin Core-8507

RESEARCH & RELATED BUDGET - SECTION A & B **FINAL**

ORGANIZATIONAL DUNS*: 066469933

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

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		Redacted by agreement				Project Lead	0.00	0.0			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** **0.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	HR Division Director	0.6			5,845.00	1,520.00	7,365.00
1	**Total Number Other Personnel**					**Total Other Personnel**	**7,365.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**7,365.00**

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

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

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

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

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

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

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	0.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
Total Other Direct Costs	**0.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**7,365.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. MTDC	45.0	7,365.00	3,314.00
		Total Indirect Costs	**3,314.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, Steven Zuraf, (301) 492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**10,679.00**

J. Fee	Funds Requested ($)*
	0.00

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

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

Budget Justification

The budget request for the upcoming period is submitted in accordance with the peer reviewed P51 renewal approved in 2016. Justification for each budget category was also peer reviewed and approved at that time, and there is no significant change in this budget request from previously approved levels.

A. COMPONENT COVER PAGE

Project Title: Information Technology

Component Project Lead Information:

Redacted by agreement

B. COMPONENT ACCOMPLISHMENTS

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

The Yerkes Information Technology Department (YITD) promotes a user-centric environment that enables researchers, students, and staff to be more effective in their roles as they work to accomplish the Center's mission in alignment with that of Woodruff Health Sciences Center and the NIH. YITD's primary mission is to apply IT-related principles and practices to assist programs that produce healthcare and industry leaders whose research results in the innovation of human and animal health. The department has spent the last five years improving its enterprise level service offerings, operational capacity, and a framework to best meet that mission. We continue to enhance our capabilities by creating efficiency in the routine core services and freeing up the staff to support the growing interests of our researchers. The IT department has worked over the last four years to address several core operational issues that had critical impact to the Center in areas of administration and research. We are now able to better focus on process improvement and new technologies that will have beneficial impact to specific research programs and administrative workflow. We are working with ONPRC and WaNPRC on models to distribute animal data through federated resources and shared repositories of reporting tools. A partnership is underway with Library Information Technology Services (LITS) to consider expanding data sharing capabilities between universities for LIMS-related services. This is being done in an effort to provide greater clarity on functional requirements, scheduling of deliverables, and consistency in product improvements and changes. The Animal Research Management System (ARMS) and the Electronic Animal Search (EAS) web service were the first application development projects to introduce this methodology. As other Center services are evaluated for enhanced functionality, this model will be implemented. In an effort to facilitate and accelerate the creation of new research services, an evaluation will take place to determine a common set of data elements that can be readily provided to secondary systems. This data offering will also reduce the possibility of error when creating a combined data view for a subject from the secondary system.

The Specific Aims are:

1. To increase YITD staff presence in divisional areas to implement strategic planning processes in an effort to accurately understand the needs and translate them into sustainable IT solutions;

2. To investigate and encourage scalable technologies in informatics and animal resources that will optimize the research endeavors beyond the Center to Emory University and the NPRCs;

3.To implement application development with an Software Development Life Cycle (SDLC) model;

4.To perform an assessment of current research data sources around the Center combined with the data in ARMS for the possibility of a data warehouse.

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

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: B2_8508_IT.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

Not Applicable

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

File uploaded: B4_c Training.pdf

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

NOTHING TO REPORT

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

1.YITD is in the process of receiving vendor responses from an RFP to address a backlog of hardcopy clinical case data at the Field Station. The next steps are to select a vendor with the appropriate skill set to digitize the hardcopies into PDF and create an interface to the electronic medical records system.

2.YITD Operations is still working to fill a vacancy for the junior systems admin role. The vacancy has affected our ability to implement some services that give us enhanced visibility into our desktop and server environment for asset control and security. We still plan to move ahead with central IT to build out a process for data exchange between our service and the central IT ticketing system.

3.The YITD Systems Group has created POC financial reports in Oracle Business Intelligence to duplicate the functionality of our existing reports in Business Objects based on ARMS data. The next steps will be to validate with the finance department that the reports are accurate and reliable for eventual migration into production.

4.The RAAC/EAS faceted search engine capability will be replicated into a POC in Tableau and OBIEE to address the age and functional limitations of the existing Drupal 6 instance of the service.

5.The database architect in YITD has determined some key data for the data model of a clinical data warehouse from previous research project work with Redacted by agreement The next step will be to work with the clinicians on this set of data elements to create an initial repository of data definitions. This effort will have an ongoing input and validation component from the Yerkes research community.

B.2. Accomplishments—Information Technology

1. The Yerkes IT Department (YITD) Systems Group hired a business analytics person in mid-January of 2018. This hiring was done in preparation for the retirement of the senior team member in the first week of April 2018. Since that time, the new hire has been working with the remaining member of the team to become acclimated to the Center's processes and building relationships on campus. She has mocked up new finance reports in Oracle Business Intelligence and is going through the process of data validation at this time. If the functionality and accuracy of the existing billing reports in Business Objects can be duplicated in Oracle BI, then the next step will be to address a migration path for the clinical reports in Business Objects to Oracle BI.

2. The three external vendors presented on executing a discovery phase and a resulting development phase for UI improvements to ARMS. The internal university research IT application development office declined to move forward with a presentation. A decision was made to use one of the external vendors, and a SOW was prepared to execute the discovery phase. They vendor decided to change the terms of the engagement, and we moved forward with evaluating other vendors for a viable partner. One vendor is currently under consideration to perform the discovery phase for future UI development to improve ARMS data entry.

3. The university research IT application development office has fully incorporated LabKey into their service catalog. They have taken our feedback specifically in the areas of a communication and implementation plan and improved the project management and business analysis areas for the customer.

4. The latest version of the Research Animal Allocation Committee application Electronic Animal Search (RAAC/EAS) was placed into production over the last year and is operational with positive responses from the user community on functionality, reliability, and availability.

5. YITD has implemented a new cluster in the campus data center for the Imaging Core. This decision was based on the cost projections from working with Amazon on a cloud based solution, and current limitations in an application used for image reconstruction. We will be gathering metrics on the new cluster for peak, mean and duration on utilization for several months. These data will assist Amazon and us in making a more precise cost estimate for the next improvements in the cluster, when the application is refactored to better work in a cloud based environment.

6. YITD worked with Redacted by agreement and the Emory University research IT application development office to create an application that will display available phenotype information on a cohort of animals at the Field Station. The application referred to as PhenX is in production and currently receives data from ARMS. The core application of the service is Tableau, and since it has been in production, interest has been expressed by another colleague, Redacted by agreement for a Tableau sandbox to build a POC for genetics determination based of multiple data sources.

7. The Sr. IT Manager communicated his findings from the conversations with the Division Chiefs and SMEs. The main area of focus has been on improving cross training among the Client Services group. This effort is still underway and has resulted in improved response times on services that have been historically under a single support member.

B.4. Training and Professional Development Opportunities

Please see the overall component for response.

C. COMPONENT PRODUCTS

C.1 PUBLICATIONS

Not Applicable

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

Not Applicable

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

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

Not Applicable

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Nothing to report

D. COMPONENT PARTICIPANTS

Not Applicable

E. COMPONENT IMPACT

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

Not Applicable

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

Not Applicable

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

NOTHING TO REPORT

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?
Not Applicable

F. COMPONENT CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

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

NOTHING TO REPORT

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

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. COMPONENT SPECIAL REPORTING REQUIREMENTS

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

Not Applicable

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

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

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

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

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Not Applicable

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

RPPR - Admin Core-8508

RESEARCH & RELATED BUDGET - SECTION A & B **FINAL**

ORGANIZATIONAL DUNS*: 066469933

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

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		Redacted by agreement				Project Lead	0.00	0.0			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 **0.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
2	IT Director/Sr. Mgr	1.2			13,679.00	3,557.00	17,236.00
2	**Total Number Other Personnel**					**Total Other Personnel**	**17,236.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**17,236.00**

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

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

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

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

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

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

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	0.00
2. Publication Costs	0.00
3. Consultant Services	4,000.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
Total Other Direct Costs	**4,000.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**21,236.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. MTDC	45.0	21,236.00	9,556.00
		Total Indirect Costs	**9,556.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, Steven Zuraf, (301) 492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**30,792.00**

J. Fee	Funds Requested ($)*
	0.00

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

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

Budget Justification

The budget request for the upcoming period is submitted in accordance with the peer reviewed P51 renewal approved in 2016. Justification for each budget category was also peer reviewed and approved at that time, and there is no significant change in this budget request from previously approved levels.

A. COMPONENT COVER PAGE

Project Title: Public Affairs

Component Project Lead Information:

Redacted by agreement

B. COMPONENT ACCOMPLISHMENTS

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

The Yerkes Public Affairs (PA) Office directs the Yerkes Research Center's Public Affairs Unit as well as its Outreach and Community Engagement activities. For the purpose of this P51 Base Grant submission, there will be two related components: this Public Affairs section under the Administration component and a separate Outreach component. The Yerkes PA Office is responsible for the increasing recognition of Yerkes as a premier research center dedicated to conducting essential basic science and translational research to advance scientific understanding and to improve human health and wellbeing. To achieve this mission, PA works proactively in the multiple, complementary areas of Public Relations and Outreach. Specific activities that fall under Public Affairs are:

•Media Relations
•Issues Management
•Emergency Preparedness (in collaboration with Facilities Management)
•Special Projects as strategically determined and/or requested by the Center Director

For Media Relations, PA develops key messages and documents with background information, promotes published studies and awards via news releases and research video clips, coordinates media interviews and on-site filming, serves as an information resource and trains researchers to speak with media. In the area of Issues Management, PA proactively monitors diverse media sources for issues of concern, such as animal rights, frames these in perspective, develops strategic messages and serves as a spokesperson. To emergency preparedness issues relevant to Public Affairs, PA again monitors Public media for issues of concern, works with Emory's Office of Critical Event Preparedness and Response, and serves as a Risk Management Process Owner for the University's Risk Management team for the animal rights risk. Other responsibilities that fall to the PA unit include managing the Center's National Scientific Advisory Board and coordinating fund-raising initiatives.

The Specific Aims are:

1. To maintain a proactive approach to public relations;

2. To continue distributing news releases about published studies, connecting the research whenever possible to improvements in human health and facilitating interviews between researchers and media;

3.To continue monitoring issues of concern and determine how we can strategically share information that presents accurate and balanced information with key audiences.

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

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: B2_8509 Public Affairs.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

Not Applicable

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

File uploaded: B4_c Training.pdf

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

NOTHING TO REPORT

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

During the next year, the Yerkes National Primate Research Center PA Office will continue to be proactive in its public relations, including promoting our research successes via media relations. In addition, the office will continue managing issues, monitoring animal rights and taking on special projects as requested by the Director.

For the fifth year, Yerkes PA will continue to lead the national public relations efforts on behalf of the seven NPRCs, which will include maintaining nprc.org and @nprcnews, building out the animal welfare and education sections of nprc.org, and coordinating a visioning session for the NPRC directors to determine next steps in our PR outreach.

We will continue to work collaboratively with Americans for Medical Progress, Foundation for Biomedical Research and other organizations in order to further the reach of information about our scientific advancements and AAALAC International-accredited animal care program. One such opportunity is partnering with seven other organizations to sponsor an exhibit booth for and otherwise interact with the more than 1,000 attendees at the 11th World Conference of Science Journalists in July 2019.

B.2. Accomplishments—Public Affairs

The Yerkes Public Affairs (PA) Office is responsible for increasing recognition of Yerkes as one of the seven National Primate Research Centers fighting disease and improving human health by making breakthrough discoveries possible. To achieve this, the PA office directs the center's media relations; issues management; emergency preparedness and special projects as strategically determined by the Center Director, and coordinates a national online PR presence on behalf of the seven NPRC. PA staff also works in the area of outreach and community engagement, which is reported in another section within this progress report.

A continuing strategic PA project has been leading the collaborative public relations effort on behalf of all seven NPRCs. A priority project the past year was launching a new website, NPRC.org, as well as a Twitter handle, @nprcnews. The website launch included finalizing the content management system and site design, editing and securing approval for all information posted on the site (e.g., research stories, evergreen copy, individual NPRC descriptions and contact information, and historical highlights), and preparing launch materials for internal and external distribution. The Twitter launch included securing the handle, writing profile information, determining who to follow and writing tweets and selecting images. For both, we worked with national organizations to extend our distribution reach about the new educational resources. In addition, PA staff continued overseeing the PR agency and managed the contract, billings and payments. Yerkes staff continued to chair the PR Working Group, whose members recommended and reviewed information for NPRC.org and @nprcnews.

In addition, PA staff distributed news releases and responded to media requests, continued monitoring animal rights activities and other related issues, helped with the center's 2018 National Scientific Advisory Board meeting and spoke at two national meetings regarding Yerkes and NPRC public relations.

B.4. Training and Professional Development Opportunities

Please see the overall component for response.

C. COMPONENT PRODUCTS

C.1 PUBLICATIONS

Not Applicable

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

Not Applicable

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

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

Not Applicable

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Nothing to report

D. COMPONENT PARTICIPANTS

Not Applicable

E. COMPONENT IMPACT

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

Not Applicable

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

Not Applicable

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

NOTHING TO REPORT

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?
Not Applicable

F. COMPONENT CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

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

NOTHING TO REPORT

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

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. COMPONENT SPECIAL REPORTING REQUIREMENTS

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

Not Applicable

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

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

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

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

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Not Applicable

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

RPPR - Admin Core-8509

RESEARCH & RELATED BUDGET - SECTION A & B **FINAL**

ORGANIZATIONAL DUNS*: 066469933

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

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	Redacted by agreement				Project Lead	0.00	0.0			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 **0.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Sr. Communications Director	0.6			7,184.00	1,868.00	9,052.00
1	**Total Number Other Personnel**					**Total Other Personnel**	**9,052.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**9,052.00**

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

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

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

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

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

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

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	0.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
Total Other Direct Costs	**0.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**9,052.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. MTDC	45.0	9,052.00	4,073.00
		Total Indirect Costs	**4,073.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS, Steven Zuraf, (301) 492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**13,125.00**

J. Fee	Funds Requested ($)*
	0.00

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

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

Budget Justification

The budget request for the upcoming period is submitted in accordance with the peer reviewed P51 renewal approved in 2016. Justification for each budget category was also peer reviewed and approved at that time, and there is no significant change in this budget request from previously approved levels.

A. COMPONENT COVER PAGE

Project Title: Facilities Management

Component Project Lead Information:

Redacted by agreement

B. COMPONENT ACCOMPLISHMENTS

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

Facilities Management is responsible for providing and maintaining a safe and efficient physical environment that supports scientific discovery, humane animal care, and productive administrative services. Along with providing operations and maintenance of buildings and grounds, the facilities unit is responsible for security, as well as operating a Main Station shuttle service, daily transportation to/from the Field Station, package delivery and distribution, project management for new construction and major repairs and renovations, and fabrication shop operations. Ongoing and past efforts to improve the physical environment and services provided by Facilities Management have focused on emergency preparedness, lifecycle replacement of the physical plant, and improving finishes and systems in animal housing rooms. While making improvements in these areas will remain part of the efforts of Facilities Management, specific aims for the next five-year period will include improving customer service, reducing energy consumption and continuing to improve security. Facilities work requests and preventive maintenance tasks are managed by a work order management system implemented by Emory University. Yerkes began using the Emory system in 2013 when a 14-year old work order management system was retired. When fully implemented, the system will contain features that will improve service delivery to our customers. Energy conservation is a second focus of facilities for the next budget period. Past progress in our efforts to consume less energy includes light fixture replacements and installation of high efficiency building equipment when end-of-life replacements occur. In addition to continuing those efforts, focus will include water and natural gas conservation and increased efforts to reduce electricity consumption. Continuing to improve security is the third focus of facilities for the next budget period. Installation of a new high security fence at the Field Station and employing contract security personnel at the Main Station are two recent, significant accomplishments related to security. Increasing the number and quality of video cameras and continuing to raise awareness of security issues among employees are two areas of security enhancement that will be addressed during the next budget period.

The specific aims are:

1. To continually improve service delivery by maximizing the work order and preventive maintenance systems;

2. To research and implement strategies that reduce energy consumption;

3. To sustain ongoing efforts to improve security.

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

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: B2_8510 Fac Mgt.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

Not Applicable

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

File uploaded: B4_c Training.pdf

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

NOTHING TO REPORT

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

Plans for the next budget year include upgrades of the video surveillance and card access security systems, continued efforts to reduce power consumption by replacing lighting with LED fixtures and implementing energy saving features of the building automation system, and identify potential strategies for water conservation.

B.2. Accomplishments—Facilities Management

Facilities Management provides comprehensive facilities services in support of the Center's central mission of scientific discovery and quality care of nonhuman primates. The team of facilities personnel interacts with every unit of the Yerkes Center and is responsible for providing a safe, efficient physical environment for research and animal husbandry. Services and responsibilities of the facilities department include operations and maintenance of the physical plant, fabrication of research and enrichment devices, transportation services, receiving and distribution of parcels, security, and management of new construction and alterations and renovations. The facilities unit aims to continually improve service delivery, reduce energy consumption, improve security, and improve emergency preparedness.

Significant progress made in 2018 includes:

Main Station

- Several high definition cameras were added to the video surveillance system.
- Numerous lighting fixtures in animal housing, administrative, mechanical, and exterior spaces were replaced or retrofitted with LED lamps.
- Numerous modifications to electrical systems were made to accommodate new laboratory equipment.
- Several animal housing rooms were recoated with epoxy or acrylic flooring.
- Three area controllers serving the card access security system were upgraded.
- The vehicle gate serving the Redacted by agreement area was replaced.
- The deaerator tank in the Redacted by agreement was replaced.
- The furniture serving the Redacted by agreement was replaced.
- A section of the Redacted by agreement was renovated to house rhesus macaques.
- The Redacted by agreement was converted from office space to animal housing space.

Field Station

- Several animal housing rooms were recoated with epoxy or acrylic flooring.
- Several compound walls and observation towers were painted.
- Several trees were removed from the Field Station grounds.
- Numerous lighting fixtures in animal housing and administrative spaces were replaced or retrofitted with LED lamps.
- Extensive site work was performed to improve rodent control and erosion control.
- Two new vehicles were purchased for use in the facilities unit.
- One of the two vehicle entry gates was replaced.
- A new animal housing building and two adjoining compounds were built.
- Significant progress was made in redistributing emergency power service to the Field Station campus.

The following projects are supported through the Year 58 supplement and we have reported their progress in section B3 under the overall component; however, we are also reporting them in this section as they pertain to Yerkes overall facilities management:

- FS Emergency Power: the generator has been ordered; installation completion expected in April 2019.
- FS Propane Plant: We selected a vendor after the minimum gas pressure requirements and bidding process. We expect to obtain Gwinnett County permit in February, installation of vaporizing system equipment in March, and connection completion in April 2019.
- MS Emergency Potable Water: feasibility report completed on the best locations and probability of success, selected an installation contractor based on a minimum of 3 bids, and obtained DeKalb County approval. We expect to obtain Ga EPD approval in February, installation completion in March, and connection completion in April 2019.

B.4. Training and Professional Development Opportunities

Please see the overall component for response.

C. COMPONENT PRODUCTS

C.1 PUBLICATIONS

Not Applicable

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

Not Applicable

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

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

Not Applicable

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Nothing to report

D. COMPONENT PARTICIPANTS

Not Applicable

E. COMPONENT IMPACT

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

Not Applicable

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

Not Applicable

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

NOTHING TO REPORT

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?
Not Applicable

F. COMPONENT CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

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

NOTHING TO REPORT

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

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. COMPONENT SPECIAL REPORTING REQUIREMENTS

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

Not Applicable

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

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

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

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

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Not Applicable

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

RPPR - Admin Core-8510

RESEARCH & RELATED BUDGET - SECTION A & B **FINAL**

ORGANIZATIONAL DUNS*: 066469933

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

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		Redacted by agreement				Project Lead	0.00	0.0			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 **0.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
18	O/M Director, AD, Proj. Mgr, Supervisors, and Technicians	19.8			95,622.00	24,861.00	120,483.00
18	**Total Number Other Personnel**					**Total Other Personnel**	**120,483.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**120,483.00**

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

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

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

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

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

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

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	0.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
Total Other Direct Costs	**0.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**120,483.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. MTDC	45.0	120,483.00	54,217.00
		Total Indirect Costs	**54,217.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, Steven Zuraf, (301) 492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**174,700.00**

J. Fee	Funds Requested ($)*
	0.00

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

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

Budget Justification

The budget request for the upcoming period is submitted in accordance with the peer reviewed P51 renewal approved in 2016. Justification for each budget category was also peer reviewed and approved at that time, and there is no significant change in this budget request from previously approved levels.

A. COMPONENT COVER PAGE

Project Title: Facilities Improvement (I/M)

Component Project Lead Information:

Redacted by agreement

B. COMPONENT ACCOMPLISHMENTS

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

Facilities Improvement, previously referred to as Improvement and Modernization, is a substantial source of funding for facilities upgrades and improvement and modernization of equipment. Providing a modern, relevant physical environment for housing animals and conducting research is essential in recruiting and maintaining the best and brightest researchers. Facilities Improvement funds are critical to the Center's ability to provide facilities and equipment that are compliant, modern, efficient, and contribute to scientific discovery. Yerkes experienced continued growth during the current funding period, which included the addition of two significant buildings: the Redacted by agreement and the Redacted by agreement Growth in physical assets provides opportunities for new programs. Facilities Improvement funds are used to ensure the relevance and efficiency of existing infrastructure and the availability of modern equipment to support ongoing programs as well as those in their nascent stage.

The list of proposed equipment and projects represents a set of needs that have been determined to be our priority areas for the achievement of the Center's mission during the proposed funding period. They represent three general categories. The first is a focus on enhancing and modernizing security systems. The second is providing a humane and enriching environment for our research animals. The third is a focus on providing modern and efficient equipment for building systems, diagnostic laboratories, clinical services, and information technology.

The Specific Aims are:

1. To continually improve security infrastructure;

2. To provide the most humane and enriching environment for research animals;

3. To maintain modern and efficient building and research equipment.

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

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: B2_8511 IM.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

Not Applicable

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

NOTHING TO REPORT

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

NOTHING TO REPORT

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

Continued improvement in infrastructure is planned for the next budget year with Improvement and Modernization funds. Planned equipment and projects represent our ongoing commitment to providing facilities that are modern and efficient and allow the Center to recruit and retain the brightest and most talented researchers. Providing a humane and compliant environment for our research animals is vital to our continued success and is demonstrated by the planned projects for the upcoming budget year.

•Redacted by agreement building - $61,528: Primate chow for use at the Main Station is currently stored in a shipping container outfitted with lighting, electrical outlets, and a wall-mounted air-conditioning unit. Replacing the shipping container with a concrete structure will provide for greater storage capacity, smoother surfaces for improved sanitation, better climate control and improved resistance to pests.
•Air Handler replacement Redacted by agreement - $128,354: The air handler serving a portion of the Redacted by agreement of the Redacted by agreement has reached the end of its expected life cycle and is in need of replacement. Replacement of the unit will include connection to the Redacted by agreement building automation system.
•Boiler burner assembly replacement - $71,548: The burner assembly for the high-pressure steam boiler serving the Redacted by agreement Redacted by needs to be replaced. The new burner assembly will provide greater reliability of the boiler operations as well as cleaner exhaust of the boiler.
•Main Station propane backup system upgrade - $322,875: The vaporizer serving the propane-air mixing station needs to be replaced with a larger unit. The propane-air system provides a backup fuel source for natural gas-burning heating systems such as furnaces, boilers and hot water systems. The original system was installed in 2005. Since then, several new facilities have been added at the Main Station. The additional fuel burning equipment in the new facilities has prevented the propane backup system from providing enough fuel to serve the entire campus. The new vaporizer will provide enough capacity for the current heating load and will provide enough excess capacity for the foreseeable future.

B.2. Accomplishments—Facilities Improvement (I/M)

Improvement and Modernization provides vital funds for maintaining a modern and efficient infrastructure in support of the Center's mission of scientific discovery and health and well-being of primates and nonhuman primates. Projects and equipment funded by Improvement and Modernization funds aim to continually improve security infrastructure, provide the most humane and enriching environment for research animals, and maintain modern and efficient building and research equipment. Significant progress in achieving these aims has been accomplished in this budget year with the equipment purchased and projects completed.

- The audio/visual system serving the Redacted by agreement room was replaced. New components include projector, screen, podium, PC system, audio and visual control systems. The Redacted by agreement room is one of two large, primary meeting rooms for faculty & staff meetings, scientific lectures, undergraduate classes, and activities such as health screenings, blood donation and special events. The upgraded audio and visual systems significantly enhanced the presentation capabilities of this space.
- The heating, ventilation and air-conditioning (HVAC) systems serving the Redacted by agreement facilities at the Field Station were replaced. The new systems provide more efficient and reliable temperature and air flow to these animal housing facilities.
- The Redacted by agreement at the Field Station was replaced. This trailer provides space for lockers, showers, and dining. The old trailer had significant structural damage caused by age and water damage. The new trailer provides more shower and locker capacity while providing adequate space for breaks/lunch.
- The HVAC system serving the Redacted by agreement at the Main Station was replaced. The old unit had reached end-of-life expectancy and had become unreliable.
- The Redacted by agreement at the Main Station was renovated and converted from office space to animal housing space. Renovation included a complete reconfiguration of the interior space, new HVAC system, new plumbing fixtures, new electrical systems and new finishes throughout. The design allows for three animal housing rooms and a treatment room. One of the animal housing rooms was designed for use as either an animal housing room or additional treatment room with mobile casework which allows for maximum flexibility for programming of the interior space. Additionally, the facility was designed to allow for runs housing and/or individual cage housing.

Please see section E.2 of the Overall component for a list of major infrastructure improvements made during the current budget period.

C. COMPONENT PRODUCTS

C.1 PUBLICATIONS

Not Applicable

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

Not Applicable

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

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

Not Applicable

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Nothing to report

D. COMPONENT PARTICIPANTS

Not Applicable

E. COMPONENT IMPACT

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

Not Applicable

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

Not Applicable

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

NOTHING TO REPORT

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?
Not Applicable

F. COMPONENT CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

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

NOTHING TO REPORT

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

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. COMPONENT SPECIAL REPORTING REQUIREMENTS

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

Not Applicable

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

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

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

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

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Not Applicable

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

RPPR - Admin Core-8511

RESEARCH & RELATED BUDGET - SECTION A & B **FINAL**

ORGANIZATIONAL DUNS*: 066469933

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

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		Redacted by agreement				Project Lead	0.00	0.0			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 **0.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	**Total Number Other Personnel**					**Total Other Personnel**	**0.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**0.00**

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

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

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

C. Equipment Description

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

Equipment Item	Funds Requested ($)*
1. MS Propane Backup System Upgrade	322,875.00
2. AHU3 Main Building Replacement with Siemens Controls	128,354.00
3. Cinderblock Central Chow Storage	61,528.00
4. Boiler Burner Assembly Replacement	71,548.00
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**584,305.00**

Additional Equipment: File Name:

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

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

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

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	0.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
Total Other Direct Costs	**0.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**584,305.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. MTDC	45.0	0.00	0.00
		Total Indirect Costs	**0.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, Steven Zuraf, (301) 492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**584,305.00**

J. Fee	Funds Requested ($)*
	0.00

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

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

Budget Justification

The budget request for the upcoming period is submitted in accordance with the peer reviewed P51 renewal approved in 2016. Justification for each budget category was also peer reviewed and approved at that time, and there is no significant change in this budget request from previously approved levels.

A. COMPONENT COVER PAGE

Project Title: Asc. Dir. for Animal Resources

Component Project Lead Information:

Redacted by agreement

B. COMPONENT ACCOMPLISHMENTS

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

The Associate Director for Animal Resources (ADAR), Redacted by agreement provides centralized administration for the Division of Animal Resources including the Center's Animal Cores and other animal-based resources. The ADAR reports directly to the Center Director and works closely with him to ensure that Center priorities are met. She liaises with the Associate Directors for Scientific Programs and Pathology, as well as Finance and Research Administration in providing high quality resource management and service. The ADAR is responsible for regulatory compliance and manages the Center's reporting for USDA, OLAW, AAALAC and other regulatory agencies. She takes a leadership role in projecting Yerkes' future animal and facility needs, including identification of funding sources and preparation of resource grant proposals. She guides the Division's independent and collaborative research priorities. The mission of this office is to ensure that the Division of Animal Resources provides the highest standards of care for all colony animals, and that these standards are maintained throughout the Center. The ADAR must work closely with other NPRCs to ensure the best management, care and use of all nonhuman primate resources and actively participates in NPRC consortia activities. Redacted by agreement monitors Yerkes' Animal Care and Use Programs and Facilities Management to ensure regulatory compliance (USDA, OLAW, IACUC, AAALAC and USFWS). She is a member of the Emory University IACUC and serves as Yerkes Attending Veterinarian and IACUC Executive Committee member. The ADAR chairs the Yerkes Resource Allocation and Advisory Committee (RAAC) and helps project animal assignment needs working closely with the investigators to facilitate research. The ADAR liaises closely with the Yerkes Director, the Vice President for Research Administration and appointed Institutional Official for Yerkes as well as the IACUC on animal welfare and compliance issues. The future priorities and plans for the ADAR and the Division of Animal Resources will build upon the successes of the last five years focusing on the continued refinement and expansion of the Division's research support for internal and external investigators and the expansion of our collaborative and independent research activities. As a Division, it will continue to build its growing clinical research program while encouraging its clinicians and other divisional scientists to pursue clinical and collaborative research opportunities. The Division's members expect to become increasingly active research partners through their service oriented work and, to this end, one of the major priorities will be continuing the genetic and phenotypic definition of our nonhuman primate colonies in order to offer superior animal models to the research community.

The Specific Aims are:

1. To ensure animal welfare and regulatory compliance by managing all of the units in the division including; Veterinary Medicine, Animal Care, Behavioral Management, Research Services, Colony Management, Animal Records and Environmental Health and Safety Office for both the Main Station and the Field Station;

2.To facilitate research and collaboration between investigators and Animal Resource units and advance the scientific mission of the Center in concert with developing the careers of staff in the units;

3.To work closely with other internal divisions including Information Technology, Facilities Management, Public Affairs and Business Services as well as external divisions including IACUC, Office of Research Compliance, and the School of Medicine's (SOM) Division of Animal Resources to ensure communication and a global strategy for the Center.

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

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: B2_8512 ADAR.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

Not Applicable

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

File uploaded: B4_c Training.pdf

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

NOTHING TO REPORT

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

The Division of Animal Resources will continue to implement the aims described in the Research Strategy of each individual unit. Overall, each unit will continue to provide service to facilitate research at Yerkes as well as provide veterinary care, husbandry, behavioral and colony management to promote animal welfare and personnel safety. Each unit will continue to facilitate collaboration with other units both within the Division of Animal Resources and with other support and research divisions. The DAR will continue to maintain the high standards of animal care at Yerkes.

B.2. Accomplishments—Associate Director of Animal Resources (ADAR)

The ADAR, in collaboration with Colony Management, the Virology Core and the Genetics Core, successfully renewed the U42 SPF grant to support the SPF breeding colony at the Yerkes Field Station. The ADAR worked closely with facilities management and administration to complete renovations funded through former grant mechanisms and commission the newly renovated Redacted by agreement These new animal housing areas provide indoor caging that communicates directly with outdoor run space. This novel design facilitates research access indoors while still providing outdoor social space to enhance animal welfare. The ADAR has worked closely with the IACUC office in implementing a new IACUC management software program (eHuron) and development of a new protocol submission form. The ADAR has worked with the Training Coordinator to set up a Compassion Fatigue program at Yerkes that will take place in March 2019. For this program, YNPRC is bringing in a company Specific Private Vendor who will develop a specialized program for Yerkes to manage the challenges that laboratory animal and research personnel confront.

The ADAR was elected to a four-year term serving the Association of Primate Veterinarians from vice presidentelect through president of the organization. She continues to serve on two APV committees (Government and Regulatory Affairs and as past Chair of the Website Committee) as well as on the Government Affairs Committee of the American College of Laboratory Animal Medicine (ACLAM). The ADAR gave an invited talk at an ACLAM Forum meeting in April 2018 on chimpanzee retirement. The ADAR also served as a symposium organizer and presenter at the International Society of Primatology meeting in Kenya in August 2018. This symposium was titled “Surveillance of Pathogens and Genetics in Captive and Wild Nonhuman Primates and Their Impact on Primate Health” and covered a blend of captive and field techniques.

The ADAR served as a collaborator on a Zika virus research project examining the impact of Zika on cognitive function and brain development in infants that was published during the last reporting period. The ADAR worked with the veterinary fellow on a Rhesus tetanus antibody project that was published in February 2018. The ADAR is also mentoring a veterinary resident in collaboration with Redacted by agreement on characterizing the microbiome of the captive Sooty mangabey and its relationship to SIV status. This resident’s project will complement an ongoing project to characterize the wild Sooty mangabey microbiome and relationship to SIV status in comparison with the captive population.

Presentations

Cohen JK. Chimpanzees and the Path to Retirement. Presentation at American College of Laboratory Animal Medicine (ACLAM). Lake Tahoe, NV. 2018

Cohen JK*, Bochart R, Ericsen A & Bosinger S. An overview of the sooty mangabey (*Cercocebus atys*) microbiome and relation to Simian Immunodeficiency Virus (SIV) infection. International Society of Primatology Conference, Nairobi, Kenya August 2018 (Abstract for Oral Presentation)

Johnston JR*, Stovall MI, Crane MM, **Cohen JK**, Ethun KF. Use of automated feeders to detect clinical inappetence in socially-housed rhesus macaques (Macaca mulatta). Association of Primate Veterinarians 46th Workshop, Baltimore, MD, October 2018 (Abstract for Poster Presentation)

Johnston JR*, Stovall MI, Crane MM, **Cohen JK**, Ethun KF. Use of automated feeders to monitor food intake prior to trauma incidence among groups of socially-stable rhesus macaques. Association of Primate Veterinarians 46th Workshop, Baltimore, MD, October 2018 (Abstract for Oral Presentation)

Publications

Mavigner M, Habib J, Deleage C, Rosen E, Mattingly C, Kashuba, Amblard AF, Schinazi R, Jean S, **Cohen JK**, McGary C, Paiardini M, Wood M, Sodora D, Silvestri G, Estes J, Chahroudi A. SIV persistence in cellular and anatomic reservoirs in ART-suppressed infant rhesus macaques. Journal of Virology. 2018, Aug 29. 92(18). PMID: 29997216

Mavigner M, Raper J, Kovacs-Balint Z, Gumber S, O'Neal JT, Bhaumik SK, Zhang X, Habib J, Mattingly C, McDonald CE, Avanzato V, Burke MW, Magnani DM, Bailey VK, Watkins DI, Vanderford TH, Fair D, Earl E, Feczko E, Styner M, Jean SM, **Cohen JK,** Silvestri G, Johnson RP, O'Connor DH, Wrammert J, Suthar MS, Sanchez MM, Alvarado MC, Chahroudi A. Postnatal Zika virus infection is associated with persistent abnormalities in brain structure, function, and behavior in infant macaques. *Science Translational Medicine*. 2018, Vol. 10, Issue 435, eaao6975

Stammen R, **Cohen JK**, Crane M, Meeker T, Amara RR, Hicks SL, Meyer JS, Ethun K. Impact of chronic social stress on the prenatal transfer of anti-tetanus immunity in captive breeding female rhesus macaques (*Macaca mulatta*). *J. Am Assoc Lab Anim Sci.* 2018: 74 (4): 357-367.

B.4. Training and Professional Development Opportunities

Please see the overall component for response.

C. COMPONENT PRODUCTS

C.1 PUBLICATIONS

Not Applicable

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

Not Applicable

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

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

Not Applicable

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Nothing to report

D. COMPONENT PARTICIPANTS

Not Applicable

E. COMPONENT IMPACT

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

Not Applicable

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

Not Applicable

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

NOTHING TO REPORT

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?
Not Applicable

F. COMPONENT CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

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

NOTHING TO REPORT

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

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. COMPONENT SPECIAL REPORTING REQUIREMENTS

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

Not Applicable

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

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

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

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

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Not Applicable

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

RPPR - Other-8512

RESEARCH & RELATED BUDGET - SECTION A & B **FINAL**

ORGANIZATIONAL DUNS*: 066469933

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

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.		Redacted by agreement				Project Lead	Institutional Base Salary	EFFORT			9,480.00	2,465.00	11,945.00
2.						Asst Dir, Animal Resources					7,459.00	1,939.00	9,398.00

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

Additional Senior Key Persons: File Name:

Total Senior/Key Person **21,343.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
2	Secretarial/Clerical	1.2			5,531.00	1,438.00	6,969.00
1	Training Coordinator	2.4			14,267.00	3,709.00	17,976.00
3	**Total Number Other Personnel**					**Total Other Personnel**	**24,945.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**46,288.00**

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

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

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	Funds Requested ($)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	2,000.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**2,000.00**

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

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

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	0.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
Total Other Direct Costs	**0.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**48,288.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. MTDC	45.0	48,288.00	21,730.00
		Total Indirect Costs	**21,730.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, Steven Zuraf, (301) 492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**70,018.00**

J. Fee	Funds Requested ($)*
	0.00

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

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

Budget Justification

The budget request for the upcoming period is submitted in accordance with the peer reviewed P51 renewal approved in 2016. Justification for each budget category was also peer reviewed and approved at that time, and there is no significant change in this budget request from previously approved levels.

A. COMPONENT COVER PAGE

Project Title: Veterinary Medicine

Component Project Lead Information:

Redacted by agreement

B. COMPONENT ACCOMPLISHMENTS

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

The Veterinary Medicine Unit provides preventive medicine and clinical care for nonhuman primate colonies at the Main Station and Field Station, as well as management of the rodent sentinel program and treatment of clinical cases of rodents at the Main Station. In collaboration with investigators and the Research Resources Unit, the veterinary unit continues to provide research support by performing experimental interventions and imaging procedures. With continued collaboration of Field Station research and support units on the Colony Management Committee run by the Lead Veterinarian, colony breeding and management issues are addressed. Additional support and guidance are provided to investigators during the process of veterinary consultations when IACUC proposals or modifications are submitted for review. Throughout the conduct of all tasks and procedures, the unit continues to train two veterinary residents and one veterinary fellow each year to better prepare the next class of laboratory animal veterinarians. Additional involvement in research programs for veterinarians will continue as will faculty development by alternating memberships to key Emory and Yerkes committees and through faculty appointments in the Emory School of Medicine. Training programs for residents and fellows will continue to grow, as will all research and support personnel training programs. The mission of the Veterinary Medicine Unit is to ensure the health and wellbeing of the animals in compliance with IACUC approval and in compliance with regulatory agencies including USDA, PHS, and US Fish and Wildlife Service. Members of the unit work closely with the Emory Institutional Animal Care and Use Committee, either as a member or consultant, as well as with all units within the Division of Animal Resources at Yerkes, Yerkes Facilities Management, the Yerkes Resource Allocation and Advisory Committee, administrative offices at Yerkes, and representatives of all research units at Yerkes. With the increased requirement for training of research personnel as mandated by the eighth edition of the Guide For the Care and Use of Laboratory Animals, the Veterinary Medicine Unit participates in this training and documentation as well as training veterinary residents and fellows to work in the field of laboratory medicine. The veterinarians provide consultation and support not only to investigators at Yerkes but also to outside investigators/veterinarians.

These Specific Aims are:

1. To monitor and support the health and well-being of all nonhuman primate (and rodent) colonies at Yerkes as the research portfolio develops and expands. The expansion will include development of special training and procedures for the new Biosafety Level 3 nonhuman primate facility;

2. To provide evidence-based preventive care and veterinary care to the NHP breeding colonies through annual physical examinations, reproductive health monitoring, and weight management protocols. In support of these endeavors, the veterinary unit will work closely with IT personnel to maximize the clinical utilization of Animal Research Management System (ARMS);

3. To collaborate with investigators in the fields of infectious disease, transplant medicine, reproductive medicine, and neuroscience in tandem with research support. Additionally, to enable veterinarians to serve as co-investigators and co-principal investigators for NIH sponsored grants and obtain faculty appointments within the Emory University School of Medicine;

4.To serve as a resource for the education and training of pre- and post-graduate veterinarians and veterinary technicians in the field of laboratory animal medicine.

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

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: B2_8513 Vet Med.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

Not Applicable

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

File uploaded: B4_c Training.pdf

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

NOTHING TO REPORT

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

The Division of Animal Resources will continue to implement the aims described in the Research Strategy of each individual unit. Overall, each unit will continue to provide service to facilitate research at Yerkes as well as provide veterinary care, husbandry, behavioral and colony management to promote animal welfare and personnel safety. Each unit will continue to facilitate collaboration with other units both within the Division of Animal Resources and with other support and research divisions. The DAR will continue to maintain the high standards of animal care at Yerkes.

B.2. Accomplishments—Veterinary Medicine

Colony Accomplishments

During the 2018-2019 reporting period, the Veterinary Medicine Unit managed a colony of over 3,000 nonhuman primates. Clinical care and research support was provided for five species of nonhuman primates assigned to 67 active research projects at the Yerkes Main Station and Field Station. Approximately 3,200 animals were individually evaluated and/or treated for clinical health issues. The most common clinical health problems encountered included diarrhea and trauma. The Veterinary Medicine Unit is responsible for reviewing all medical records for nonhuman primates entering the Yerkes colony for assignment to multiple infectious disease, transplantation and neuroscience protocols. During the 2018-2019 reporting year, the veterinary staff assisted in evaluating and quarantining all nonhuman primates entering the colony from other facilities. A total of 6 Bolivian squirrel monkeys entered the colony on one shipment date as specified by the research needs of the investigator. Another 76 rhesus macaques entered quarantine from a total of two different facilities on three separate shipment dates in order to attempt to fulfill nonhuman primate requests for numerous IACUC-approved projects. Rhesus macaques also transfer from the Field Station to the Main Station facilities on an ongoing basis in order to meet investigator requests.

Research Accomplishments

Project 1: Effects of Pair Housing on Clinical Outcomes, Cortisol, and Stress-related Behaviors During Intrafacility Transfer and Acclimation Procedures in *Macaca mulatta*

Redacted by agreement

Transportation and relocation of nonhuman primates within facilities is often necessary to meet research and colony management objectives, but it can be very stressful for the animals. This recently developed project will evaluate the effects of pair housing on clinical outcomes, cortisol levels, and stress-related behaviors during intrafacility transfer and acclimation periods in rhesus macaques. To investigate these questions, rhesus macaques transferring to the Main Station from the Field Station will either be housed individually or paired immediately following transport, based on availability of suitable social partners as determined by Field Station Colony Management and Behavioral Management data. Subjects will be followed for 4 weeks after relocation and assessed for abnormal behaviors, anxiety, fear-related behaviors, hair coat scores, and the presence of diarrhea, anorexia, and/or weight loss. Fecal cortisol samples will be collected once weekly during the experiment. Results will be compared between groups. Data from this study will help determine best practices to enhance rhesus macaque psychological well-being during intrafacility transfers.

Project 2: A Comparison of Gastrointestinal Microbiome and SIV Status of the Sooty Mangabey (*Cercocebus atys*) and Rhesus Macaque (*Macaca mulatta*)

Redacted by agreement

Recent discoveries in gastrointestinal microbiome research have shown specific bacterial classes can be immune stimulatory, uphold mucosal integrity, and prevent disease. Furthermore, it is known that the gastrointestinal tract immune cells have an integrated role in SIV pathogenesis. This study will examine two objectives. First we will look at the gastrointestinal microbiome differences in SIV native and nonnative hosts. This portion of the project compares SIV viral status with the gastrointestinal microbiome in sooty mangabeys, a SIV native host, and rhesus macaques, a SIV nonnative host to determine if there is a bacterial class shift that may lead to protection against SIV disease progression. This project seeks to address two experimental unknowns: 1) When comparing SIV status in sooty mangabeys, is there a beneficial gastrointestinal microbial shift in SIV positive animals that leads to immune resistance? and 2) When comparing nonnative and native SIV hosts, is there a microbial shift that shows evidence of how the native host becomes a chronic SIV controller? The second component of this study will determine if there are substantial differences in the gastrointestinal microbiome of nonhuman primates exposed to different captive lifestyles. We hope to address the question of whether or not there is an intraspecies gastrointestinal microbiome difference between animals that live exclusively indoors versus outdoor-indoors. To do this we are comparing the microbiome of sooty mangabeys living in indoor-outdoor enclosures at the field station with indoor-only housing at the main center

at Yerkes National Primate Research Center. This data will provide valuable information about how different research lifestyles may influence the gastrointestinal microbiome. Data collection for this project is complete and data analysis is on-going. Preliminary findings were presented at the International Primatological Society 27th Meeting in August 2018.

Project 3: Automated Feeders and Clinical Monitoring in Breeding Rhesus Macaques

Redacted by agreement

In 2014-2015, thirty-two commercially-available automated feeding stations were successfully deployed in 8 outdoor compounds at the Yerkes National Primate Research Center (YNPRC) Field Station, housing a large portion of the rhesus macaque breeding colony. This project seeks to determine whether feeding data generated by computer-controlled automated feeding stations can be used to enhance the clinical monitoring and social stability of rhesus macaques living in large outdoor breeding groups. As animals obtain food pellets, the computer-controlled system records grams obtained in real-time by detecting RFID microchips implanted subcutaneously in each wrist of individual animals. The primary outcomes of this study include: 1) quantification of daily caloric intake according to sex, gender, and reproductive stage; 2) the association of various clinical conditions (e.g. trauma, diarrhea, retained placentas) with a significant reduction in caloric intake; 3) the association of select breeding and social behaviors with changes in caloric intake. This project employed significant Yerkes resources, including colony management staff, animal care staff, veterinary staff, and rhesus macaques. Data collection for this project was recently completed and analyzed. In the past year, findings were presented at national meetings, including the American Association of Laboratory Animal Science 69th National Meeting, the Association of Primate Veterinarians 46th Workshop, and the 2018 Yerkes Research Symposium. A manuscript is currently under review in a peer-reviewed journal. At least two other manuscripts are expected in the next 12-18 months. This project is part of the veterinary resident training program in the Division of Animal Resources. This project is used to teach veterinary trainees how to summarize and analyze data using Excel and select statistical programs.

Project 4: Chronic Stress and Anti-tetanus Immunogenicity in Female Rhesus Macaques

Redacted by agreement

This project sought to evaluate how chronic stress may negatively affect anti-tetanus immunity among breeding female rhesus macaques (*Macaca mulatta*) and their offspring. Using rhesus macaques in large breeding troops at Yerkes National Primate Research Center (NPRC) Field Station, the aim of this project was to determine whether and to what extent social subordination impairs the durability and prenatal transfer of anti-tetanus immunity in breeding female rhesus macaques. This study is completed and results have recently been published in the Journal of the American Association for the Laboratory Animal Science.

Project 5: The Role of Milk Immune Proteins and Oligosaccharides in Acute Enteritis in Rhesus Macaque Infants

Redacted by agreement

Diarrhea is an important health problem in captive rhesus macaque colonies particularly among infant and juvenile animals. Similar to humans, breast milk of rhesus macaques contains several immune defense components including oligosaccharides, secretory immunoglobulin A (sIgA), lactoferrin, lysozyme, and a variety of cytokines. Deficient levels of these key milk immunological constituents may then predispose the nursing infants to enteritis. Milk immunological constituents are also thought to aid in the development of a 'healthy' neonatal innate immune system by establishing a 'healthy' GI microbiome and stimulating the development of a robust intestinal immune defense system. Thus, the primary goal of this clinical project is to determine whether milk from dams of nursing infants with and without diarrhea contain different levels of immune defense proteins and oligosaccharides. In the past year, a subset of milk samples for this project have been collected. Additional samples will be collected.

Project 6: Establishing the Gut Microbiome in the Yerkes Rhesus Macaque Breeding Colony- Enhancing Clinical Care for the Treatment of Chronic Diarrhea

Redacted by agreement

Diarrhea is recognized as a major cause of morbidity in captive nonhuman primates and can be a significant management concern due to economic burdens associated with increased veterinary care as well as its impact to colony management, assignment eligibility and research outcomes. While it can occur at any age, there are multiple causes ranging from enteric pathogens, diet, genetic predisposition, neoplasia, and environment. A key factor to understanding the causes of acute and chronic diarrhea may lie in the role of the gut microbiome in a state of health and in disease. The primary goal of this clinical project is to establishing the gut microbiome within the rhesus macaque breeding colony maintained at the Yerkes NPRC Field Station. This will provide a unique opportunity to establish a long-term, population-based study of microbiome analysis, which may lead to insights in refining clinical care for acute and chronic diarrhea. In the past year, fecal samples were collected during annual physical exams and banked for future analysis. Additional samples will be collected.

Presentations

Jackson MN, Wood JS, Pinelli C. Solitary trichoepithelioma in a squirrel monkey (*Saimiri scuireus*). Association of Primate Veterinarians 46th Workshop, Baltimore, MD, October 2018 (POSTER)

Cantara S, Wood JS, Stammen RL, Pinelli C. Abdominal distention in a Rhesus macaque. American Association of Laboratory Animal Science 69th National Meeting, Baltimore, MD, October 2018 (ORAL PRESENTATION)

Cohen JK, Bochart R, Bosinger S. An overview of the sooty mangabey (*Cercocebus atys*) microbiome and relation to simian immunodeficiency virus infection. International Primatological Society 27th Congress, Nairobi, Kenya, August 2018 (ORAL PRESENTATION)

Johnston, J, Meeker T, Ramsey J, Stovall M, Crane, MM, Cohen JK, Ethun K. Use of automated feeders to monitor group stability in captive breeding colonies of rhesus macaques (*Macaca mulatta*). American Association of Laboratory Animal Science 69th National Meeting, Baltimore, MD, October 2018 (TWO POSTERS); Association of Primate Veterinarians 46th Workshop, Baltimore, MD, October 2018 (TWO POSTERS); Yerkes National Primate Research Symposium, Atlanta, GA, November 2018 (TWO POSTERS)

Owens DC, Bochart R, Pinelli CJ, Crane MM. Monodiscoid Placenta and Severe Placental Abruption in a Rhesus Macaque (*Macaca mulatta*). American Association of Laboratory Animal Science 69th National Meeting, Baltimore, MD, October 2018 (POSTER)

Publications

Stammen R, Cohen JK, Crane M, Meeker T, Amara RR, Hicks SL, Meyer JS, Ethun K. Impact of chronic social stress on the prenataltransfer of anti-tetanus immunity in captive breeding female rhesus macaques (*Macaca mulatta*). J. Am Assoc Lab Anim Sci. July 2018 57(4): 357-367.

B.4. Training and Professional Development Opportunities

Please see the overall component for response.

C. COMPONENT PRODUCTS

C.1 PUBLICATIONS

Not Applicable

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

Not Applicable

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

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

Not Applicable

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Nothing to report

D. COMPONENT PARTICIPANTS

Not Applicable

E. COMPONENT IMPACT

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

Not Applicable

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

Not Applicable

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

NOTHING TO REPORT

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?
Not Applicable

F. COMPONENT CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

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

NOTHING TO REPORT

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

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. COMPONENT SPECIAL REPORTING REQUIREMENTS

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

Not Applicable

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

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

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

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

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Not Applicable

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

RPPR - Other-8513

RESEARCH & RELATED BUDGET - SECTION A & B **FINAL**

ORGANIZATIONAL DUNS*: 066469933

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

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		Redacted by agreement				Project Lead	Institutional Base Salary	EFFORT			28,440.00	7,394.00	35,834.00
2						Sr. Veterinarian					28,056.00	7,295.00	35,351.00
3						Asc Veterinarian					25,077.00	6,520.00	31,597.00
4						Asc Veterinarian					25,959.00	6,749.00	32,708.00
5						Asc Veterinarian					12,069.00	3,138.00	15,207.00
6						Asc Veterinarian					29,644.00	7,707.00	37,351.00
7						Asc Veterinarian					22,145.00	5,758.00	27,903.00
8						Chief Veterinarian					23,190.00	6,029.00	29,219.00
9						Asst Dir, Animal Resources					22,377.00	5,818.00	28,195.00
10						Asc Veterinarian					25,352.00	6,592.00	31,944.00
11						Asc Veterinarian					21,399.00	5,564.00	26,963.00
12						Asc Veterinarian					20,879.00	5,429.00	26,308.00

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

Additional Senior Key Persons: File Name:

Total Senior/Key Person **358,580.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
1	Secretarial/Clerical	0.6			2,628.00	683.00	3,311.00
14	Surgery Specialist, Supervisor, Technicians	76.8			302,269.00	78,591.00	380,860.00
15	**Total Number Other Personnel**					**Total Other Personnel**	**384,171.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**742,751.00**

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

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

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	Funds Requested ($)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	2,000.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**2,000.00**

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

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

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	156,209.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Maintenance/Repair	2,000.00
Total Other Direct Costs	**158,209.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**902,960.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. MTDC	45.0	902,960.00	406,332.00
		Total Indirect Costs	**406,332.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS, Steven Zuraf, (301) 492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**1,309,292.00**

J. Fee	Funds Requested ($)*
	0.00

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

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

Budget Justification

The budget request for the upcoming period is submitted in accordance with the peer reviewed P51 renewal approved in 2016. Justification for each budget category was also peer reviewed and approved at that time, and there is no significant change in this budget request from previously approved levels.

A. COMPONENT COVER PAGE

Project Title: Animal Care

Component Project Lead Information:

Redacted by agreement

B. COMPONENT ACCOMPLISHMENTS

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

The Animal Care Unit provides husbandry and care services for the animal colony, as well as assistance to Veterinary, Colony Management, Behavioral and Research units. These groups work together in a well-coordinated, cohesive effort to provide quality animal care. This care and management program meets and often exceeds animal welfare standards and regulations while attaining colony management and research objectives. The goals will be to increase the effectiveness and efficiency of these efforts. The mission of the Animal Care Unit is to provide for the daily care of the animals including husbandry, observing, documenting, reporting, and monitoring the general health and wellbeing, and social stability of the groups and individual animals. Another goal is for Animal Care staff to effectively and proactively communicate abnormal findings to Veterinary, Colony Management, and Behavioral Management staff for further observation and treatment. This work is critical to the overall mission of the Center. An increased focus on training of animal care staff is clearly beneficial and an important priority. As animal welfare is continually being improved with emphasis on increased socialization efforts, enrichment modifications and facility renovations for enhancing welfare, animal care staff must adapt to accomplishing their husbandry procedures with the changes in environment. Animal care staff enthusiastically supports changes for improved animal welfare and continually modify practices to meet growth and changes. Lastly, the Animal Care Unit supports the Center's educational and public outreach efforts. There are opportunities for students to gain insights and experience into laboratory animal care and facility management. Animal care technicians also provide assistance during tours and interact with neighbors during Open House events.

The Specific Aims are:

1. To continue to attain the highest standards of animal care and animal welfare as demonstrated by successful institutional and regulatory reviews and inspections;

2. To invest in educational and training resources, as well as in professional training and development opportunities for the care staff. These investments include participation through membership in national and local laboratory animal professional organizations, and through training available at the AALAS Learning Library, as well as continued and ongoing involvement with a departmental cross training program and in a behavioral management certification program. All of these programs are extremely important aspects of animal care technician training and to developing a streamlined approach to colony care and management;

3. To ensure that the care technicians have the knowledge and experience to assist with a variety of techniques and procedures that improve the health and wellbeing of the animals, thus increasing efficiency overall, integrating care technicians seamlessly in assisting Veterinary, Colony Management Research units. Select staff members at the Main Station will be trained to work in the Animal Biosafety Level 3 (ABSL3) nonhuman primate facility in order to provide highly specialized animal care support when animals are assigned to that facility;

4. To continue to monitor and enhance the security and safety of the facilities in part by continuing to receive training in disaster and emergency preparedness through participation in disaster drills and preparedness assessments.

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

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: B2_8514 Animal Care.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

Not Applicable

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

File uploaded: B4_c Training.pdf

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

NOTHING TO REPORT

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

The Division of Animal Resources will continue to implement the aims described in the Research Strategy of each individual unit. Overall, each unit will continue to provide service to facilitate research at Yerkes as well as provide veterinary care, husbandry, behavioral and colony management to promote animal welfare and personnel safety. Each unit will continue to facilitate collaboration with other units both within the Division of Animal Resources and with other support and research divisions. The DAR will continue to maintain the high standards of animal care at Yerkes.

B.2. Accomplishments—Animal Care

Animal Care staff at both the Main Station and the Field Station continue to provide daily husbandry and care services as well as to provide support and assistance to veterinary, colony management, and research staff. Managers, supervisors and trainers have placed emphasis on enhancing the program of training and development for animal care staff. AALAS certification classes expanded to include all levels of the AALAS technician certification programs. In addition, more frequent class periods were offered (including a webinar format held in conjunction with other local research animal facilities) along with additional test taking opportunities. These efforts have resulted in increased participation in both classes and with accessing the online learning library by animal care staff.

The Division of Animal Resources Training and Education Committee is dedicated to providing cross training within the Division of Animal Resources. Newly hired animal care staff go through the new training developed by this committee and are better oriented to the functions of other units in the Division of Animal Resources as part of the onboarding process. This has improved communications and operations within the Division.

There has been continued emphasis on the incorporation of more Positive Reinforcement Training into regular husbandry activities such as water lixit training for monkeys, shift and gate training, and boxing and accessing training. Team building and effective communication exercises have been built into the annual care staff training program and regular staff meetings. At the Main Station, a specific training program was developed for the new IOC housing, which is unique in its capacity to house research nonhuman primates in indoor cages with access to outdoor runs. In addition, a room at the Main Station has been dedicated to training activities including annual training of animal care staff, AALAS certification courses, team building exercises, tech week activities and hands-on training. This space enhances the commitment to developing the technicians at a higher level. Animal care staff also received some specialized training throughout each quarter on topics such as ergonomics, hazard communications, risk assessment and PPE selection. The overall effectiveness of staff training now involves increased assessments and consultations with the DAR training coordinator.

Animal Care Technicians at both the Main Station and the Field Station participated in AALAS Certification Courses organized by the DAR Training Coordinator. Currently 36% of AC Staff at the Main Station and 44% of AC Staff at the Field Station are AALAS Certified.

A member of the management team at the Main Station successfully completed the Emerging Leaders Program at Emory University. Several Animal Care technicians attended the South Eastern AALAS Branch meeting in Decatur GA in March 2018. A presentation regarding efficient and effective communications was given by one of the animal care managers. Managers, supervisors, and care staff have been engaged professionally throughout the year with membership in various animal welfare and animal management organizations such as AALAS, SEAALAS, LAWTE, and LAMA. A member of the management team serves on the AALAS Board of Trustees. Animal care staff from both facilities also attended the National AALAS meeting in Baltimore MD in 2018. A member of the care staff management team participated in a panel discussion sponsored by the Academy for Veterinary Technicians and Nurses. The Yerkes Center celebrated International Laboratory Animal Technician Week in 2018 with activities that included presentations by research staff, interactive training games and recognition events. The Animal Care unit coordinated the internship of a Drexel University MLAS student, providing insight and direction into the operations of both facilities.

Animal care staff members from both campuses have also participated in education, public outreach and community service projects throughout the past year. Animal care technicians also provided support during two of the Center's biannual weekend Open House events by leading tour groups, talking to neighbors, distributing enrichment, and performing some animal training techniques. Care technicians assisted with numerous tours year round, many of which are for local elementary, high school and college groups. The animal care staff also participated in Gwinnett Chamber of Commerce events like the annual Gwinnett County Science Fair. Animal care technicians have also contributed during community events such as Red Cross blood drives and Adopt-A-Road roadside clean up events.

B.4. Training and Professional Development Opportunities

Please see the overall component for response.

C. COMPONENT PRODUCTS

C.1 PUBLICATIONS

Not Applicable

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

Not Applicable

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

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

Not Applicable

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Nothing to report

D. COMPONENT PARTICIPANTS

Not Applicable

E. COMPONENT IMPACT

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

Not Applicable

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

Not Applicable

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

NOTHING TO REPORT

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?
Not Applicable

F. COMPONENT CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

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

NOTHING TO REPORT

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

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. COMPONENT SPECIAL REPORTING REQUIREMENTS

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

Not Applicable

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

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

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

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

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Not Applicable

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

RPPR - Other-8514

RESEARCH & RELATED BUDGET - SECTION A & B **FINAL**

ORGANIZATIONAL DUNS*: 066469933

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

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.		Redacted by agreement				Project Lead	0.00	0.0			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 **0.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
2	Secretarial/Clerical	1.2			3,550.00	923.00	4,473.00
89	Operations Managers, Supervisors, Technicians	511.8			1,540,934.00	400,650.00	1,941,584.00
91	**Total Number Other Personnel**					**Total Other Personnel**	**1,946,057.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**1,946,057.00**

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

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

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	Funds Requested ($)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	2,000.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**2,000.00**

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

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

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	440,492.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Maint/Repair	2,000.00
Total Other Direct Costs	**442,492.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**2,390,549.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. MTDC	45.0	2,390,549.00	1,075,747.00
		Total Indirect Costs	**1,075,747.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, Steven Zuraf, (301) 492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**3,466,296.00**

J. Fee	Funds Requested ($)*
	0.00

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

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

Budget Justification

The budget request for the upcoming period is submitted in accordance with the peer reviewed P51 renewal approved in 2016. Justification for each budget category was also peer reviewed and approved at that time, and there is no significant change in this budget request from previously approved levels.

A. COMPONENT COVER PAGE

Project Title: Colony Management

Component Project Lead Information:

Redacted by agreement

B. COMPONENT ACCOMPLISHMENTS

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

The mission of the Colony Management Unit, based at the Yerkes Field Station, is to oversee the nonhuman primate colonies in order to meet the Yerkes Center management, production and scientific needs. These responsibilities include the implementation of a colony management plan that matches resources with projected colony and research needs, ongoing genetic characterization/pedigree analysis, development and implementation of breeding plans, acquisition and disposition of animals and animal housing allocation. The Colony Management unit is charged with working closely with the Veterinary Unit, Animal Care, Research Services and the investigators to provide defined experimental animals and biological samples.

The Colony Management Unit participates in annual health surveys and quarantine procedures, reporting and tracking births, animal accessibility training, sample collection for genetic testing, viral screening and pre-screening for research protocols, contraception and immunization administration, tattooing and microchip insertion and the development of housing allocation plans to meet breeding and research needs. The group oversees the specific pathogen free (SPF) rhesus breeding program. Colony management personnel are responsible for observation and charting the complex social dynamics that exist within each social group, through both opportunistic and formal observations of behavioral interactions within the social setting and recording and plotting these data to obtain hierarchical order. This information is essential to help maintain social group stability, the formation of new groups and the introduction of animals, including breeding aged males.

The Specific Aims are:

1. To manage the established SPF breeding colony of rhesus macaques to meet the needs of researchers and maximize genetic variability of the population, as well as the continuation of collecting genetic information on parentage and phenotypes;

2. To maintain the sooty mangabey population, a natural SIV host species, with substantial value in studies aimed at the prevention and treatment of AIDS. This includes the oversight of the Breeding Plan that has been adapted to facilitate the formation of new breeding groups to maintain population growth and genetic diversity in this closed population;

3. To implement and utilize a database for enhanced access to and manipulation of genetic information;

4. To foster personnel education and training programs;

5. To publish data on primate colony management.

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

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: B2_8515 Col Mgt.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

Not Applicable

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

File uploaded: B4_c Training.pdf

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

NOTHING TO REPORT

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

The Division of Animal Resources will continue to implement the aims described in the Research Strategy of each individual unit. Overall, each unit will continue to provide service to facilitate research at Yerkes as well as provide veterinary care, husbandry, behavioral and colony management to promote animal welfare and personnel safety. Each unit will continue to facilitate collaboration with other units both within the Division of Animal Resources and with other support and research divisions. The DAR will continue to maintain the high standards of animal care at Yerkes.

B.2. Accomplishments—Colony Management

Over the last reporting period, the colony produced 532 offspring, which is an increase of 9% over last year. Of these, 502 (94.4%) survived to at least four months of age. Breeding male milestones were met in 2018 with one multi-male bachelor group going into their first social group and a second group advancing to a more socially complex social group than they had previously experienced. An additional six males were put into their first breeding groups (two pairs and two harem breeding males), expanding the number of breeding groups and experienced breeder males in the colony. Large cages, attached to existing outdoor compounds to facilitate male introductions were built and utilized at the Redacted by agreement. Construction of the fencing has begun on two new compounds Redacted by agreement and each will have the capacity to house a SPF breeding group of up to 75 macaques. Eleven offspring from the first cohort of reproductively mature nursery raised females were born in 2018 representing a 79% live birth success rate. Overall, the growth in production has increased the availability of animals for research assignment, especially infants for pediatric AIDS research projects. Colony genetics continued with the characterization of parentage and MHC status. New tools, including an inbreeding avoidance calculator and a matriline calculator facilitated the selection of animals for the breeding colony and research assignment. Colony Management staff provided support for two studies at the Yerkes Field Station. A project examining male introductions and social networks required both management and technical support, while a pediatric AIDS vaccine study performed in social groups required significant technical support throughout the year.

Representatives from the Colony Management Unit participated at the American Society of Primatologists annual meeting, (San Antonio, TX, August 2018). Talks were presented on 1) the characterization and life history of SPF rhesus macaque breeder males at the Yerkes Field Station and 2) feeder use and patterns of feeding among young rhesus monkeys living in large breeding groups in outdoor compounds. In addition, Colony Management personnel were co-authors on a poster that described how breeding age rhesus macaques impact male dominance, trauma and grooming during breeder male introductions. A representative from Colony Genetics participated in the 27th International Primatological Society Congress in Nairobi, Kenya and presented a talk focused on the integration of host and microbial genetic sequencing into our effort to improve the clinical care of our rhesus macaque (*Macaca mulatta*) colonies. The establishment of genetic models in captive rhesus macaques was primarily discussed.

Presentations:

Conference paper: Characterization of breeding males in a SPF Rhesus Macaque colony: A life history approach. R.C. Stavisky, T. Meeker, J.K. Ramsey, M.M.Crane. American Society of Primatologists Annual Meeting, San Antonio, 2018.

Conference paper: Feeding patterns of infant and juvenile Rhesus Macaques (Macaca mulatta) living in large outdoor captive breeding groups. J.K. Ramsey, M.E. Wilson, T. Meeker, R.C. Stavisky, K. Cummings, M.M. Crane, J.K. Cohen, K. Ethun. American Society of Primatologists Annual Meeting, San Antonio, 2018.

Conference paper: Host and microbial genetics in caring for captive macaques. Patel N, Wu Y, Meeker T, Ramsey J, Stavisky R, Crane MM, Bosinger SE, Ericsen AJ. 27th International Primatological Society Congress, Nairobi, Kenya 2018.

Poster: Effects of breeding age Rhesus Macaque females on male-to-male dominance, trauma rates and grooming during large group introductions. M.A. Bloomsmith, S. Moss, M. Wilson, R. Stavisky, T. Meeker, C. Long. American Society of Primatologists Annual Meeting, San Antonio, 2018.

B.4. Training and Professional Development Opportunities

Please see the overall component for response.

C. COMPONENT PRODUCTS

C.1 PUBLICATIONS

Not Applicable

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

Not Applicable

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

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

Not Applicable

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Nothing to report

D. COMPONENT PARTICIPANTS

Not Applicable

E. COMPONENT IMPACT

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

Not Applicable

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

Not Applicable

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

NOTHING TO REPORT

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?
Not Applicable

F. COMPONENT CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

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

NOTHING TO REPORT

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

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. COMPONENT SPECIAL REPORTING REQUIREMENTS

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

Not Applicable

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

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

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

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

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Not Applicable

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

RPPR - Other-8515

RESEARCH & RELATED BUDGET - SECTION A & B **FINAL**

ORGANIZATIONAL DUNS*: 066469933

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

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		Redacted by agreement				Project Lead	Institutional Base Salary	EFFORT			0.00	0.00	0.00
2						Geneticist					4,728.00	1,229.00	5,957.00
3						Colony Director					18,813.00	4,891.00	23,704.00

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

Additional Senior Key Persons: File Name:

Total Senior/Key Person **29,661.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
11	Manager, Supervisor, Technicians	55.8			205,712.00	53,484.00	259,196.00
11	**Total Number Other Personnel**					**Total Other Personnel**	**259,196.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**288,857.00**

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

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

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	Funds Requested ($)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	2,000.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**2,000.00**

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

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

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	20,000.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Animal Per Diem	322,511.00
9. Maint/Repair	1,000.00
Total Other Direct Costs	**343,511.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**634,368.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. MTDC	45.0	634,368.00	285,466.00
		Total Indirect Costs	**285,466.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS, Steven Zuraf, (301) 492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**919,834.00**

J. Fee	Funds Requested ($)*
	0.00

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

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

Budget Justification

The budget request for the upcoming period is submitted in accordance with the peer reviewed P51 renewal approved in 2016. Justification for each budget category was also peer reviewed and approved at that time, and there is no significant change in this budget request from previously approved levels.

A. COMPONENT COVER PAGE

Project Title: Behavioral Management

Component Project Lead Information:

Redacted by agreement

B. COMPONENT ACCOMPLISHMENTS

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

The mission of the Behavioral Management Unit is to promote, maintain and measure primate wellbeing through collaboration among the Behavioral Management, Veterinary Medicine, Animal Care, and Research units. The Behavioral Management program includes daily implementation of animal welfare activities, the conduct of scientific investigation to advance knowledge, and responsibilities for regulatory aspects of primate welfare. Major elements of the daily program include: socialization of primates, providing environmental enrichment, applying animal training methods, and assessing behavior. Social housing throughout the lifespan of primates is the primary method to support their welfare and is the cornerstone of our mission. Enrichment methods emphasize feeding enrichment (devices, fresh produce), physical enrichment (objects, climbing structures, release into activity cages), and sensory enrichment (music, videotape viewing). A positive reinforcement animal training program facilitates animal care, research and veterinary care by reducing distress associated with common procedures, and increasing the ease of working with primates. Behavioral monitoring is done according to a defined schedule to identify behaviors of concern and to track outcomes of treatments implemented to address particular problems. Animals exhibiting psychological distress may be treated through an amplification of enrichment, training, adjustment of social dynamics, and pharmacological means, and additional behavioral monitoring is performed on these animals. The Behavioral Management program is dynamic and techniques are modified in accordance with in-house assessments and findings from the scientific literature. Behavioral research on a variety of topics is ongoing and this research contributes to the Center's strong scientific foundation that underlies improvements in primate behavioral management. Recent published studies relate to pair housing, abnormal behavior, animal training, and enrichment. Regulatory responsibilities of the Behavioral Management Unit include a review of welfare issues for each Yerkes research protocol using nonhuman primates as part of the Institutional Animal Care and Use Committee (IACUC) process. The Unit also addresses issues related to USDA and OLAW oversight, IACUC inspections, and the AAALAC accreditation process. Behavioral Management is continually striving to raise the bar for animal welfare with novel enrichment strategies, improved behavioral assessments and plans to increase socialization opportunities. Development of new strategies may require additional resources such as enrichment supplies, novel caging, new housing, and additional staff. Improvements to the program can be accomplished by staying active in the welfare science field, by frequent re-evaluation of the program to increase its efficiency, by development of enhanced record keeping systems within ARMS, by emphasizing the prevention of behavioral problems, and by seeking grant opportunities to explore behavioral issues in the colony.

The Specific Aims are:

1. To expand the daily social housing, environmental enrichment, and positive reinforcement training programs at the Yerkes Main Station and the Field Station, and improve these activities based on new research findings;

2. To enhance behavioral management education programs within and outside of Yerkes to teach others about integrating behavioral management principles into primate care programs;

3. To improve our behavioral monitoring program through enhanced automation of data collection and compilation, formal evaluation of the program, use of data for internal evaluations, and scientific assessments for publication;

4. To conduct and publish research on primate welfare to improve animal care and wellbeing;

5. To remain engaged in regulatory aspects of Behavioral Management and involved with the Behavioral Management Consortium to advance collaboration and exchange of information across NPRCs;

6. To enhance Behavioral Management staff development.

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

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: B2_8516 BMU.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

Not Applicable

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

File uploaded: B4_c Training.pdf

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

NOTHING TO REPORT

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

The Division of Animal Resources will continue to implement the aims described in the Research Strategy of each individual unit. Overall, each unit will continue to provide service to facilitate research at Yerkes as well as provide veterinary care, husbandry, behavioral and colony management to promote animal welfare and personnel safety. Each unit will continue to facilitate collaboration with other units both within the Division of Animal Resources and with other support and research divisions. The DAR will continue to maintain the high standards of animal care at Yerkes.

B.2. Accomplishments—Behavioral Management

Educational Programs by the Behavioral Management Unit (BMU) (April 1, 2018 - March 31, 2019)
The BMU continues to work on programs to educate others at the Yerkes Center about primate behavior, as well as teaching people from outside of Yerkes. Our Animal Care Technician training program includes a day-long orientation to behavioral management of primates, early in their tenure at Yerkes. This comprises information on behavior, reporting behaviors of concern, enrichment at Yerkes, feeding techniques, social housing and caging, and includes making enrichment and shadowing behavioral management specialists.

We have also continued with our "Behavioral Management Certification Course" for Yerkes Animal Care staff members, which is aimed to expand their understanding of primate behavior, enrichment, animal training, social housing and animal welfare by completing modules in each of these topics. For each module, BMU staff members teach one-hour sessions weekly, for eight weeks. Information is presented through lecture, discussion, demonstrations, and group exercises which may include hands-on skill development. Tests are given following each section. Upon passing, individual module certifications are earned for each topic of instruction. Once all areas are completed, a "Behavioral Management Certification" will be earned. To date, 82 Animal Care staff members have completed the primate behavior module (8 hours of information on the natural and captive behavior of common laboratory primate species, etc.). This helps to satisfy *The Guide* recommendation (page 53) that, "Personnel responsible for animal care and husbandry should receive training in the behavioral biology of the species they work with to appropriately monitor the effects of enrichment as well as identify the development of adverse or abnormal behaviors." To date, 22 Animal Care staff members have completed the enrichment module (8 hours of information on the five categories of enrichment, why it is important to use a variety of types of enrichment, the role of Animal Care staff members in the environmental enrichment program, etc.).

The BMU has a behavioral management "rotation" for the Yerkes veterinary residents consisting of a 3-week focus on behavioral observation, normal and abnormal behavior, positive reinforcement training methods, environmental enrichment techniques and assessment, social housing and managing social behavior. We worked with two veterinary residents during this period of time. One additional veterinary resident completed a 3-week focus period with BMU focusing on preparing primates for chair restraint and managing abnormal behavior cases as well asmedical treatments for self-injurious behavior in macaques. The BMU has an internship program for undergraduate students to get experience with primate welfare research and other aspects of behavioral management. In this period, we hosted five students for periods of 3 to 9 months each.

The BMU also designed and taught three workshops during this time period. The "Workshop on Macaque Pair Housing" was a four-day course offered at the Oregon National Primate Research Center in July 2018. Participants came from across the country representing other NPRCs, federal agencies, universities, and research hospitals. At the national AALAS conference (October 2018), the BMU taught an 8-hour workshop on "Teaching Monkeys to Cooperate with Restraint: Using Positive Reinforcement Training and Temperament Testing Methods" which focused on teaching research and veterinary staff members techniques for minimizing monkey stress associated with restraint. A third workshop was in August 2018, on "Positive Reinforcement Training for Primate Veterinary Care." This 8-hour workshop taught attendees about the range of behaviors with which primates can be trained to cooperate, to facilitate their health care.

Research Completed by the Behavioral Management Unit (April 1, 2018 - March 31, 2019)

Behavioral research conducted by Behavioral Management Unit (BMU) staff members led to journal articles and a scientific book chapter. One article evaluated how systematic preference assessments can enhance positive reinforcement training with rhesus macaques (Martin et al, in press). We found that the "multiple stimulus without replacement" technique identified rhesus food preferences, and the highly preferred items increased subjects' engagement with the training task as compared to low preference items. More effective reinforcers identified through this assessment have potential to increase animal performance and to improve their welfare. A co-edited volume on optimal animal welfare was published, and the introduction described the science and practice of optimal animal welfare (Maple and Bloomsmith, 2018).

Unpublished

The chapter reviewed basic training concepts, first steps in using positive training methods with nonhuman primates, a description of the types of training being conducted in research settings, and the impact of training on animal welfare. Examples were provided for how positive reinforcement training helps people working with the primates, as well as how it improves the scientific research being conducted. There was also a summary of how to develop an animal training program, and thoughts about how to further advance the field by employing Behavior Analysis approaches.

Publications

Unpublished

Maple, T.L. and Bloomsmith, M.A. (2018). Introduction: The Science and Practice of Optimal Animal Welfare. Behavioural Processes 156:1-2.

Unpublished

B.4. Training and Professional Development Opportunities

Please see the overall component for response.

C. COMPONENT PRODUCTS

C.1 PUBLICATIONS

Not Applicable

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

Not Applicable

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

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

Not Applicable

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Nothing to report

D. COMPONENT PARTICIPANTS

Not Applicable

E. COMPONENT IMPACT

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

Not Applicable

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

Not Applicable

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

NOTHING TO REPORT

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?
Not Applicable

F. COMPONENT CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

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

NOTHING TO REPORT

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

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. COMPONENT SPECIAL REPORTING REQUIREMENTS

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

Not Applicable

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

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

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

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

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Not Applicable

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

RPPR - Other-8516

RESEARCH & RELATED BUDGET - SECTION A & B **FINAL**

ORGANIZATIONAL DUNS*: 066469933

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

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		Redacted by agreement				Project Lead	Institutional Base Salary	EFFORT			0.00	0.00	0.00
2						Behavioral Management Head					29,413.00	7,647.00	37,060.00

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

Additional Senior Key Persons: File Name:

Total Senior/Key Person **37,060.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
10	Manager, Supervisor, Technicians	51.6			204,949.00	53,287.00	258,236.00
10	**Total Number Other Personnel**					**Total Other Personnel**	**258,236.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**295,296.00**

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

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

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	Funds Requested ($)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	2,000.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**2,000.00**

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

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

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	50,000.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
Total Other Direct Costs	**50,000.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**347,296.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. MTDC	45.0	347,296.00	156,283.00
		Total Indirect Costs	**156,283.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, Steven Zuraf, (301) 492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**503,579.00**

J. Fee	Funds Requested ($)*
	0.00

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

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

Budget Justification

The budget request for the upcoming period is submitted in accordance with the peer reviewed P51 renewal approved in 2016. Justification for each budget category was also peer reviewed and approved at that time, and there is no significant change in this budget request from previously approved levels.

A. COMPONENT COVER PAGE

Project Title: Animal Records

Component Project Lead Information:

Redacted by agreement

B. COMPONENT ACCOMPLISHMENTS

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

The Animal Records Unit is responsible for the entry and maintenance of data documenting clinical, research, and regulatory records for all animals at the Yerkes Center. The mission of the Animal Records Unit is primarily to ensure the accuracy, reliability and sustainability of animal records. The information maintained includes animal history, research assignment history, colony statistics and laboratory data including select genetic profiles. Accurate animal inventory and population is a priority, and the information is maintained so as to be current and readily available to personnel. Information concerning animal assignments to research projects is maintained along with relevant Institutional Animal Care and Use Committee (IACUC) information to ensure compliance with regulatory agencies and Center policies. The recently implemented Animal Research Management System (ARMS) maintains a comprehensive animal medical record and research history with enhanced tracking and capability of performing searches. Since the fall 2013 implementation of ARMS, record keeping is an evolving process that requires the Animal Records Supervisor to liaise with other departments such as Information Technology (IT), Veterinary Medicine, Business Services, Behavioral Management, Colony Management, and Pathology, to address necessary enhancements to maintain reliability, integrity and improve efficiency. Pertinent record information is provided as required for reporting purposes to regulatory agencies such as AAALAC, USDA, USFWS and OLAW. Personnel from the unit also prepare detailed reports as needed by the Animal Resources Division, IACUC and upon request by Center personnel or by outside investigators. The information maintained in ARMS is essential for veterinary, husbandry and behavioral management of the colony and to ensure compliance with animal welfare regulations. In addition, the information contained in ARMS is critical for investigators to maintain the integrity of the research and regulatory compliance. The unit works closely with IT to develop, implement, and utilize valuable applications in an electronic environment that is conducive to sustaining operations. Quality data input is critical for reporting to USDA, AAALAC, OLAW, and other regulatory agencies. The future priorities and plans for the Animal Records Unit focus on continued utilization of ARMS. We will continue to work with IT to enhance methods for data entry. The format of information input into ARMS is designed for optimal retrieval of information in search functions. This searchable format of information is greatly beneficial for tracking and managing data and useful for all divisions. The transition to this format has required the staff to evaluate ways to streamline data input. Animal Records and IT are developing innovative solutions to address this challenge and improve efficiency. In addition to ARMS, the IACUC Topaz software will be upgrading to Elements, which will provide easier access to IACUC data in Animal Records. The unit will continue to work closely with the IACUC Office, Topaz Enterprises and Emory's School of Medicine's (SOM) Division of Animal Resources to implement this new system.

The Specific Aims are:

1. To continue to maintain an accurate record keeping system in ARMS to provide data that both facilitate daily operations and research at the Center as well as track pertinent information to maintain compliance with regulatory agencies;

2. To work closely with IT to develop innovative applications to more efficiently input information into ARMS. Real-time information is critical to the management of the colony;

3. To develop systems that allow the most up to date entry of information into ARMS, including working closely with the Research Allocation and Advisory Committee (RAAC) to maintain accurate information for animal assignments as well as participating in the upgrade process for Topaz Elements and ensuring compliance with all regulations.

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

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: B2_8517 Animal Records.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

Not Applicable

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

File uploaded: B4_c Training.pdf

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

NOTHING TO REPORT

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

The Division of Animal Resources will continue to implement the aims described in the Research Strategy of each individual unit. Overall, each unit will continue to provide service to facilitate research at Yerkes as well as provide veterinary care, husbandry, behavioral and colony management to promote animal welfare and personnel safety. Each unit will continue to facilitate collaboration with other units both within the Division of Animal Resources and with other support and research divisions. The DAR will continue to maintain the high standards of animal care at Yerkes.

B.2 Accomplishments—Animal Records

The Animal Records Unit (ARU) supports the Division of Animal Resources by entering and managing the animal data for research, clinical care, animal census and billing. This includes preparing, storing, and retrieving patient health records from the Animal Resource Management System (ARMs). The ARU continues to assist with providing data for reporting to regulatory agencies, such as the USDA, AAALAC and NIH. The ARU is also involved with preparation of information for the AAALAC Program Description.
The current system, ARMs, has been operational for five years and while it has enhanced how we view and store animal information for reporting, users have encountered challenges with the user interface and integrating the application for real time data entry. Yerkes is seeking and has met with a few vendors to develop an interface to be used to improve entering real time data related to assessment, observation, housing, treatment, sample requests and obtaining lab results.

The ARU continues to provide vital information to the Information Technology Department (ITD) to increase the efficiency of entering and retrieving data from the ARMs system. There have been scripts developed to help alleviate the amount of time it takes to enter an animal record. A bulk template feature was developed and implemented. This feature reduced the amount of time that it takes to enter data for surveys by half. The ARU also worked with ITD to facilitate a way to streamline entering surgical statistics, which has eased entry challenges. There have been six applications developed to aid in the entry of data into the ARMs and more than 10,000 entries made into the electronic health record system over the last reporting period.
As of March 2018, ARU transitioned from using Elements for IACUC protocol retrieval to Huron (eIACUC). Since implementing ARMs, tracking the number of authorized animals assigned and used on an approved IACUC protocol is more efficient.

Although not funded through the P51 mechanism, the rodent animal records system, TOPAZ Elements (eBiz), was rolled out in September in of 2018 and since its application, the system is more transparent and can easily track animal movement within the system. Related to this effort, in November 2018, a representative from Animal Records had the opportunity to attend the TOPAZ Annual Conference in Baltimore, MD. This conference provided the opportunity to examine modifications that could potentially be problem solvers for the Elements system. The Yerkes ARU also had the privilege of going to Vanderbilt University, Nashville, TN to meet with their Animal Resources Department in order to establish a more streamlined process for Yerkes Animal Records to work within Elements. The visit proved to be rewarding and provided valuable insight that could enhance some of our processes as we continually work providing quality information.

B.4. Training and Professional Development Opportunities

Please see the overall component for response.

C. COMPONENT PRODUCTS

C.1 PUBLICATIONS

Not Applicable

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

Not Applicable

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

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

Not Applicable

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Nothing to report

D. COMPONENT PARTICIPANTS

Not Applicable

E. COMPONENT IMPACT

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

Not Applicable

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

Not Applicable

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

NOTHING TO REPORT

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?
Not Applicable

F. COMPONENT CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

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

NOTHING TO REPORT

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

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. COMPONENT SPECIAL REPORTING REQUIREMENTS

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

Not Applicable

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

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

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

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

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Not Applicable

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

RESEARCH & RELATED BUDGET - SECTION A & B FINAL

ORGANIZATIONAL DUNS*: 066469933

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

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.		Redacted by agreement				Project Lead	0.00	0.0			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 **0.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
6	Supervisor, Records Support Staff	7.2			26,266.00	6,829.00	33,095.00
6	**Total Number Other Personnel**					**Total Other Personnel**	**33,095.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**33,095.00**

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

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

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	Funds Requested ($)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	2,000.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**2,000.00**

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

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

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	0.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
Total Other Direct Costs	**0.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**35,095.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. MTDC	45.0	35,095.00	15,793.00
		Total Indirect Costs	**15,793.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, Steven Zuraf, (301) 492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**50,888.00**

J. Fee	Funds Requested ($)*
	0.00

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

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

Budget Justification

The budget request for the upcoming period is submitted in accordance with the peer reviewed P51 renewal approved in 2016. Justification for each budget category was also peer reviewed and approved at that time, and there is no significant change in this budget request from previously approved levels.

A. COMPONENT COVER PAGE

Project Title: Research Services

Component Project Lead Information:

Redacted by agreement

B. COMPONENT ACCOMPLISHMENTS

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

The Research Services Unit provides support for funded research studies through performing experimental interventions on behalf of investigators and facilitating the development of Scientific Advisory Committee (SAC) approved research proposals. A primary goal is to streamline the research process from outline to implementation for Core and Affiliate Investigators by providing a necessary service to researchers, which consists of well-trained personnel who perform the procedures to conduct research and move scientific knowledge forward. Research Services also ensures that compliance with Institutional Animal Care and Use Committee (IACUC) approved protocols is maintained. In order to fulfill these functions, the Research Services Unit liaises with Veterinary Medicine, Colony Management, Business Services and the investigators. The mission of Research Services is to provide administrative assistance as well as implementation of IACUC approved research proposals. Administrative assistance may include consultation to determine the details of project design, scheduling, budgeting, and providing assistance with protocol submissions to IACUC. This unit also coordinates the collection and delivery of specimens from colony animals in response to requests received through the Division of Pathology's Specimen Distribution Program. Research Services personnel provide a range of services and implement experimental interventions on behalf of investigators including: administration of vaccines, antiretroviral treatments and infectious agents by multiple routes; collection of biological specimens such as blood, bone marrow, CSF, and tissue biopsies; monitoring animals during minor experimental procedures; and assisting Veterinary Medicine with minor surgeries and other experimental interventions. All requested procedural interventions are referenced against the approved IACUC for that study to ensure regulatory compliance. As the research portfolio at Yerkes continues to grow, Research Services will continue to identify methods to improve efficiencies in order to maintain support for research. Lastly, Research Services will continue to expand the educational opportunities for personnel and build engagement and collaboration between staff and researchers.

The Specific Aims are:

1. To continue to provide excellent service to researchers and manage any increase in research support that is provided to internal and external investigators as Yerkes research programs continue to expand;

2. To continue close collaboration and training with Veterinary Medicine and investigators in anticipation of the need for more sophisticated procedures and to improve clinical observational skills and increase the services the unit can provide independently;

3. To continue ongoing efforts to foster communication and collaboration directly with investigators and increase the dissemination of knowledge about their research projects.

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

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: B2_8518 Res Svs.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

Not Applicable

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

File uploaded: B4_c Training.pdf

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

NOTHING TO REPORT

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

The Division of Animal Resources will continue to implement the aims described in the Research Strategy of each individual unit. Overall, each unit will continue to provide service to facilitate research at Yerkes as well as provide veterinary care, husbandry, behavioral and colony management to promote animal welfare and personnel safety. Each unit will continue to facilitate collaboration with other units both within the Division of Animal Resources and with other support and research divisions. The DAR will continue to maintain the high standards of animal care at Yerkes.

B.2. Accomplishments—Research Services

Research Services is the division that furthers the goals of numerous grants by providing support with sample collections and the care and treatment of the research animals. They also assist Principal Investigators with creating animal budgets needed for grant proposals. Over the past reporting period, Research Services (RS) participated in over 44 individual study schedules supporting 30 IACUC protocols for over 12 different Principal Investigators.

Research procedures and sample collections are performed by the Research Services staff. During this reporting period, there were 13,548 animal accesses, up 24% from last year. These accesses included 12,789 blood collections, which is a 31% increase from last year. In addition to blood collections, RS performed 829 bone marrow collections, 434 ear sticks for blood smears, 1408 rectal and vaginal secretion collections, and 80 fecal collections. RS also administered infectious agents to 984 nonhuman primates and vaccines to 1,021. Antiretroviral treatments continue to comprise a large amount of RS's time and resources, with 46,293 treatments administered this period. RS assisted veterinarians with 707 lymph node biopsies, 2,391 lymph node fine needle aspirate collections, 393 infusions, 1,159 rectal and vaginal biopsies, 87 osmotic pump placements, and the malaria team with 39 mosquito feedings.

In February 2018, Research Services posted a position for an additional Research Specialist in order to efficiently manage the increase in workload. This additional person was hired in March. Also in October 2018, Research Services hired a new Supervisor for the division.

B.4. Training and Professional Development Opportunities

Please see the overall component for response.

C. COMPONENT PRODUCTS

C.1 PUBLICATIONS

Not Applicable

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

Not Applicable

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

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

Not Applicable

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Nothing to report

D. COMPONENT PARTICIPANTS

Not Applicable

E. COMPONENT IMPACT

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

Not Applicable

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

Not Applicable

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

NOTHING TO REPORT

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?
Not Applicable

F. COMPONENT CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

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

NOTHING TO REPORT

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

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. COMPONENT SPECIAL REPORTING REQUIREMENTS

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

Not Applicable

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

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

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

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

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Not Applicable

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

RPPR - Other-8518

RESEARCH & RELATED BUDGET - SECTION A & B **FINAL**

ORGANIZATIONAL DUNS*: 066469933

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

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		Redacted by agreement				Project Lead	0.00	0.0			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 **0.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
10	Manager, Coordinator, Supervisor, Technicians	27.6			119,656.00	31,109.00	150,765.00
10	**Total Number Other Personnel**					**Total Other Personnel**	**150,765.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**150,765.00**

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

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

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	Funds Requested ($)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	2,000.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**2,000.00**

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

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

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	20,000.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
Total Other Direct Costs	**20,000.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**172,765.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. MTDC	45.0	172,765.00	77,744.00
		Total Indirect Costs	**77,744.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, Steven Zuraf, (301) 492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**250,509.00**

J. Fee	Funds Requested ($)*
	0.00

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

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

Budget Justification

The budget request for the upcoming period is submitted in accordance with the peer reviewed P51 renewal approved in 2016. Justification for each budget category was also peer reviewed and approved at that time, and there is no significant change in this budget request from previously approved levels.

A. COMPONENT COVER PAGE

Project Title: Env. Health and Safety

Component Project Lead Information:

Redacted by agreement

B. COMPONENT ACCOMPLISHMENTS

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

The mission of the Yerkes Environmental Health and Safety Office (Yerkes EHSO) is to provide oversight for the occupational health and safety programs at the Center. The primary goals of the Yerkes EHSO include creating a work environment that minimizes hazards, that reduces the risk of human illness and injury, provides comprehensive programs that support health and safety, promotes a culture of safety and accountability and assures compliance with local, state and federal regulations. The Yerkes Environmental Health and Safety Officer (Yerkes EHS Officer) reports to the Yerkes Associate Director of Animal Resources and to the Emory University Environmental Health and Safety Director. Recognizing that health and safety are critical elements in the vision and success of the organization, the Yerkes EHSO unit is responsible for ensuring that the highest standard of safety practices for all employees, students and visitors are realized. As a component of this goal, the Yerkes EHS Officer serves as Chairperson of the NIH Health and Safety Consortium group and collaborates with other NPRC colleagues via the NPRC Consortium to assure best practices. Additionally, the Yerkes EHS Officer participates with various Emory University committees to implement safety practices, is a voting member of the Institutional Biosafety (IBC) and the Research Health and Safety (RHSC) Committees, serves as a member of the University Compliance Committee and is the Environmental Health and Safety Office liaison to the Institutional Animal Care and Use Committee. Priorities for the Yerkes EHSO are to continue to strengthen our programs, monitor for opportunities for improvement and continue to strive for excellence. We will work with the University team to address challenges with the Emory Learning Management System in PeopleSoft. We will expand upon our already robust Biosafety Level 3 containment work to include the fulltime engagement of the Level 3 containment manager. We will continue to strengthen the Occupational Health Program components by moving data to the PeopleSoft system to provide employees with access to their Occupational Health data as well as add efficiency and accuracy to the documentation process.

The Specific Aims are:

1. To train employees, students and visitors in all relevant areas of Health and Safety, providing opportunities for learning via live didactic, computer based and participatory experiences;

2. To transition towards the University-supported PeopleSoft Emory Learning Management System to stream line processes and capture system-wide efficiencies;

3. To maintain a comprehensive Occupational Health Program that includes employees, students and visitors, as an indispensable objective of the Health and Safety Program;

4. To review and revise Standard Operating Procedures and Compliance monitoring to meet Yerkes EHSO goals and objectives;

5. To build upon existing programs to maintain and improve Biosafety Level 3 laboratories and Animal Biosafety Level 3 facilities to meet or exceed industry standards.

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

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: B2_8519 EHSO.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

Not Applicable

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

File uploaded: B4_c Training.pdf

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

NOTHING TO REPORT

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

The Division of Animal Resources will continue to implement the aims described in the Research Strategy of each individual unit. Overall, each unit will continue to provide service to facilitate research at Yerkes as well as provide veterinary care, husbandry, behavioral and colony management to promote animal welfare and personnel safety. Each unit will continue to facilitate collaboration with other units both within the Division of Animal Resources and with other support and research divisions. The DAR will continue to maintain the high standards of animal care at Yerkes.

B.2. Accomplishments—Yerkes Environmental Health and Safety Office

The mission of the Yerkes Environmental Health and Safety Office (Yerkes EHSO) is to provide oversight for the occupational health and safety programs at the Center. The primary goals of the Yerkes EHSO are to create a work environment that minimizes hazards, reduce the risk of human illness and injury, provide comprehensive programs that support health and safety, promote a culture of safety and accountability and assure compliance with local, state and federal regulations.

Accomplishments:

- Redacted by agreement – Promoted to Associate Director, Emory University Environmental Health and Safety Office.
- Redacted by agreement – Conducted comprehensive risk assessment for storage and safe use of husbandry chemicals
- Redacted by agreement – Completed requirement for Registered Biosafety Professional certification, Elected Southeastern Biological Safety Association(SEBSA) Councilor for 2018-2019, serves as the SEBSA Membership Chair 2019
- Redacted by agreement Streamlined health assessment process and is now responsible for scheduling all Yerkes EHSO trainings.
- Redacted by agreement – Added stocking PPE, biohazardous waste pickup and eye wash testings in new animal housing space.

Training:

The Yerkes EHSO provided training for employees, students and visitors in all relevant areas of health and safety. Learning opportunities are provided via didactic, computer-based and participatory experiences. In late 2017, computer-based training was fully transitioned into the Emory University Learning Management System (ELMS). The intent was to streamline data management and training into one system; however, there are still inefficiencies with ELMS. To address these inefficiencies, the University Research Safety Program has initiated their own learning management system, Bioraft.

- The Yerkes EHSO provides over 40 safety-related trainings that include, but are not limited to, agent specific information, personal protective equipment, hazard communications, bloodborne pathogens, ergonomics, biosafety level 3, respirator training, and radiation safety.
    - Completed 249 new employee, student, visitor, and contractor orientations.
    - Conducted over 4,033 training sessions for Yerkes personnel via didactic, computer based and participatory training.
    - Provided B-virus training for 683 personnel
    - Provided 5 B-virus training classes on the Emory University campus for 74 non-Yerkes personnel who work with nonhuman primate samples.
    - Conducted 3 hazmat tours of the Center for the DeKalb County Fire Department and HazMat Team
    - Worked with Emory's EHSO to identify and address Facilities Management Department training gaps. 5 additional training requirements were added.

Occupational Health:

The Yerkes EHSO maintains a comprehensive Occupational Health Program that includes employees, students and visitors. The on-site Occupational Health Nurse worked in collaboration with the University's Employee Health and Office of Injury Management to address work place injuries and exposures. Yerkes EHSO was part of the development and transition team for the new Enterprise-wide Occupational Health software "Enterprise Health". Occupational health program components related to Yerkes and nonhuman primates are part of the new system and include base line health assessments, annual health checks, TB testing, immunizations, serum banking, incident reporting, and respirator medical clearance. The system will serve employees and non-employees and provide them with access to occupational health documents. Enterprise Health will replace the current in-house Yerkes Occupational Health system that has reached the end of its service life. The Enterprise Health System is scheduled to go live in early 2019.

- Provided on site seasonal flu vaccinations to 100 employees

- Completed 163 health assessments for new employee, students, and visitors.
- Conducted 76 respiratory medical clearances.
- Placed 706 TSTs, 103 TB surveillance questionnaires, 16 T-Spots
- Collected 143 samples for the serum bank

Standard Operating Procedures (SOPs):
The Yerkes EHSO developed, reviewed and revised Standard Operating Procedures to meet Yerkes EHSO goals and objectives. Working with malaria researchers, Yerkes EHSO assisted in developing SOPs for the new mosquito insectary. Yerkes EHSO collaborated with Facilities Management and Insurance representatives to develop a Main Station Flood Disaster Plan.

- All SOPs (63) and addenda (16) due for their 3-year review were reviewed and published.

Containment Facilities:
The Yerkes EHSO continues to build upon existing programs to maintain and improve the Animal Biosafety Level 3 and other containment facilities to meet or exceed industry standards. Yerkes EHSO collaborated with malaria researchers, Animal Resources and Facilities Management in the construction and opening of the Yerkes Arthropod Containment level 2 mosquito insectary. The containment manager also began inspections of the MPTP suite.

- ABSL-3 containment failure testing completed.
- Conducted weekly inspections of the rodent ABSL-3 facility (51).
- Conducted weekly inspections of the mosquito insectary (22).
- Conducted weekly inspection of the BSL-3 laboratories (4 suites, 10 labs) (204 inspections).
- Conducted weekly inspection of the MPTP suite. (15 inspections)
- Provided annual training for all ABSL-3 users (62) and safety training for insectary access (31)

Biohazardous Waste Management:
Completed Biohazard Shipping training for all members of Yerkes EHSO to meet DOT requirements for packaging and shipping biohazardous materials.

- Collected, packaged and shipped 76,777 pounds of biomedical waste for treatment and disposal with vendor at off-site location.
- 5,051 pounds of pathological waste disposed via the Yerkes' alkaline hydrolysis thermal tissue digester

Eye Wash Testing:

- Total of 243 eye washes inspected weekly, 12,636 eye inspections completed.

Presentations:
Redacted by agreement

- Clinical Laboratory Work Practices and Procedures, 2-day workshop, PPE, Emergency Plans and Drills, Risk Assessments and Occupational Health sponsored by the Egleson Institute, North Carolina State Laboratory
- Clinical Laboratory Work Practices and Procedures, 2-day workshop for Clinical Laboratorians and Infection Preventionist, PPE, Emergency Plans and Drills, Risk Assessments and Occupational Health sponsored by the Egleson Institute, South Dakota State Laboratory
- Emory University Veterinarian Residency program, Safety Challenges working with Nonhuman Primates, Atlanta GA
- Emory University School of Public Health, Occupational Safety lecture to the Emory MPH injury prevention class
- Steering Committee member for annual conference: "Preventing and Treating Biological Exposures Colloquium" held in Huntington Beach CA
- NIH National Primate Research Center Occupational Health and Safety Consortium annual meeting at the Tulane National Primate Research Center. Occupational health and safety representatives shared experiences related to training, illness/injuries, and personal protective equipment.

Redacted by agreement

- "Chemical Control Measures for Husbandry Chemicals at an Animal Research Facility". American Association of Laboratory Animal Science 69th National Meeting, Baltimore, MD, October 2018. POSTER.
- "Chapter 7: Occupational Health & Safety", LATG prep course for Yerkes Animal Resources

Redacted by agreement

- "From ABSL-2 to ACL-2: Creation of an Insectary at Yerkes National Primate Research Center" presentation at 2018 SEBSA Biosafety Symposium in Knoxville, Tennessee
- "Seriously, an insectary at a primate center?" Poster at 2018 ABSA Annual Conference in Charleston, South Carolina

Publications:

Carnathan D, Lawson B, Yu J, Patel K, Billingsley JM, Tharp GK, Delmas OM, Dawoud R, Wilkinson P, Nicolette C, Cameron MJ, Sekaly RP, Bosinger SE, Silvestri G, Vanderford TH. Reduced Chronic Lymphocyte Activation following Interferon Alpha Blockade during the Acute Phase of Simian Immunodeficiency Virus Infection in Rhesus Macaques. J Virol. 2018 Apr 13;92(9). pii: e01760-17. doi: 10.1128/JVI.01760-17.

B.4. Training and Professional Development Opportunities

Please see the overall component for response.

C. COMPONENT PRODUCTS

C.1 PUBLICATIONS

Not Applicable

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

Not Applicable

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

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

Not Applicable

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Nothing to report

D. COMPONENT PARTICIPANTS

Not Applicable

E. COMPONENT IMPACT

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

Not Applicable

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

Not Applicable

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

NOTHING TO REPORT

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?
Not Applicable

F. COMPONENT CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

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

NOTHING TO REPORT

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

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. COMPONENT SPECIAL REPORTING REQUIREMENTS

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

Not Applicable

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

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

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

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

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Not Applicable

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

RPPR - Other-8519

RESEARCH & RELATED BUDGET - SECTION A & B **FINAL**

ORGANIZATIONAL DUNS*: 066469933

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

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		Redacted by agreement				Project Lead	0.00	0.0			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 **0.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
1	Secretarial/Clerical	0.6			2,281.00	593.00	2,874.00
4	Manager, EHSO Staff	16.8			96,195.00	25,011.00	121,206.00
5	**Total Number Other Personnel**					**Total Other Personnel**	**124,080.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**124,080.00**

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

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

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	Funds Requested ($)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	2,000.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**2,000.00**

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

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

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	150,000.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
Total Other Direct Costs	**150,000.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**276,080.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. MTDC	45.0	276,080.00	124,236.00
		Total Indirect Costs	**124,236.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS, Steven Zuraf, (301) 492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**400,316.00**

J. Fee	Funds Requested ($)*
	0.00

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

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

Budget Justification

The budget request for the upcoming period is submitted in accordance with the peer reviewed P51 renewal approved in 2016. Justification for each budget category was also peer reviewed and approved at that time, and there is no significant change in this budget request from previously approved levels.

A. COMPONENT COVER PAGE

Project Title: Division of Pathology

Component Project Lead Information:

Redacted by agreement

B. COMPONENT ACCOMPLISHMENTS

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

The Division of Pathology has two main roles: 1) to provide support to the research community of the Yerkes Center, as well as to external requestors and collaborators and 2) to contribute to colony health surveillance by providing diagnostic support to the Division of Animal Resources. As such, the Division promotes an open exchange of ideas, interdepartmental and interdisciplinary collaborations, the establishment and refinement of animal models of human disease and the support of projects from external collaborators in need of nonhuman primate experimentation. There are five major units within the Division: Anatomic Pathology (includes the Necropsy/Gross Pathology and Histopathology/Electron Microscopy Laboratories), Clinical Pathology, Molecular Pathology, Biological Material Procurement Program, and Biological Material Shipping Program.

The Specific Aims are:

1. To provide outstanding technical support to Center investigators in support of their research projects including, but not limited to, postmortem examination with collection and processing of tissues, electron microscopy, in situ hybridization, fluorescence in situ hybridization and immunohistochemistry services;

2. To provide diagnostic support to the Division of Animal Resources for clinical and experimental cases involving the colony animals, promoting colony health and disease surveillance to ensure the highest level of health in our animal colony;

3. To distribute valuable resources through the Biological Material Procurement Program. The collection and distribution of these specimens make it possible for scientists to take full advantage of the materials available and allows external investigators to work with cells and tissues to which they would otherwise not have access;

4. To develop and implement scientific protocols by applying current molecular pathology, clinical pathology, electron microscopy and histological assays;

5. To maintain and enhance training opportunities for veterinary and graduate students, veterinarians, pathologists and other scientists.

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

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: B2_8520 Pathology.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

Not Applicable

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

File uploaded: B4_c Training.pdf

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

NOTHING TO REPORT

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

The Division of Pathology will continue to implement the aims described in the Research Strategy. Overall, this unit will continue to provide service to facilitate research at Yerkes as well as provide veterinary care, husbandry, behavioral and colony management to promote animal welfare and personnel safety. It will continue to facilitate collaboration with other units both within the Division of Pathology and with other support and research divisions. The Division of Pathology will continue to maintain the high standards of animal care at Yerkes.

B.2. Accomplishments—Division of Pathology

The Division of Pathology provides diagnostic support to investigators from the Yerkes and Emory research communities as well as external investigators from academic institutions and the private sector working with laboratory animals in multiple and diverse research studies.

Service Pathology

The Service Pathology section contributes to colony surveillance, provides diagnostic support to the Yerkes Division of Animal Resources, and provides tissues and diagnostic services for scientific investigators (i.e., postmortem examinations, histopathology services, clinical pathology testing, etc.). It encompasses all aspects of diagnostic pathology, and includes the necropsy laboratory, histology and electron microscopy laboratory, molecular pathology and clinical pathology laboratory. During this reporting period, a new veterinary pathologist was hired, making a total of three certified pathologists in the unit. The veterinary pathologists continue to participate in the training of the laboratory animal medicine residents at Yerkes, as well as the veterinary medicine students selected to participate in the McClure Comparative Pathology Externship at the Center. They provide formal laboratory animal pathology instruction through several formal courses, and through direct training and supervision of veterinary students and residents emphasizing gross pathology and histopathological findings relevant to accurately diagnosing clinical and experimental cases.

Necropsy

The number of nonhuman primate necropsies performed during this reporting period totaled 597, of which 376 were in support of experimental research protocols and 221 were clinical necropsies in support of the health and maintenance of the Yerkes colony. In addition, 129 necropsies were completed on other laboratory species (predominantly mice and rats) at the Center. In addition, the staff is actively involved in the procurement of nonhuman primate specimens for investigators from Yerkes, Emory and other research institutions in the U.S.

Histology and Molecular Pathology

During the reporting period, the Histology and Electron Microscopy Laboratory processed 9,439 submissions, which included nonhuman primate and rodent necropsies, biopsies, and various cases from investigators at Yerkes, Emory and outside the University. The number of paraffin blocks processed was 6,462 and 4,113 microscopic slides. There were 512 special stains prepared as well as 2,558 slides sectioned for other procedures. In the same period, the Molecular Pathology Laboratory processed 297 slides for immunohistochemistry and *in situ* hybridization from nonhuman primates and rodents submitted by both Yerkes, Emory and external investigators.

Clinical Pathology

The Clinical Pathology Laboratory received 31,370 nonhuman primate and rodent specimens during the reporting period. There were 18,283 hematology examinations. These included CBCs, reticulocytes, differentials, and white blood cell and platelet counts, as well as coagulation tests, bone marrow and malaria examinations. There were 3,206 microbiology tests done. These included both clinical and experimental cultures, necropsy, and sterility specimens. A total of 5,161 chemistry panels were done, these included I-stat panels as well as comprehensive chemistry profiles (super chemistries) which were completed in-house. Parasitology testing included 2,070 fecal and body fluid examinations. In addition, 2,650 miscellaneous tests including serology, virology, thyroid hormone testing, rodent mite and pinworm tests were performed. Medical Technologists and Technicians from the Clinical Pathology Laboratory also support human donor phlebotomy for Emory Employee Health and Safety (EHSO) and Emory Research Blood Donor Program. Phlebotomy support for EHSO is performed for exposure and post exposure follow up testing, and on occasion for new employees. Research Blood Donor Program collections are performed to support human blood research requests. There are approximately 500 active human donors registered to provide blood to Emory investigators as part of the Research Blood Donor Phlebotomy Program. Clinical Pathology performed

phlebotomy for 280 healthy donor volunteers and 29 exposure blood collections. In addition, the Center's animal and human serum bank inventory is maintained by Clinical Pathology Laboratory staff.
Clinical Pathology Technologists and Technicians also aid in employee health infection control. All team members are certified by the Georgia Department of Public Health to administer and read Tuberculin Skin Testing for Yerkes/Emory staff. During the reporting period, staff members administered approximately 493 TB skin tests.

Biological Material Procurement Services

An important contribution to biomedical research is the provision of biological specimens to investigators at Yerkes and other regional, national and international institutions. The Senior Program Coordinator within the Division of Pathology manages and provides oversight for biological specimen requests from internal and external investigators through the Yerkes Biological Materials Procurement Program. During the reporting period, the Yerkes Center processed 63 specimen requests that resulted in the collection and provision of 1,124 samples. These samples were provided to 26 investigators of which 16 were located at Yerkes, 3 at Emory and 7 investigators at institutions within the U.S. During this time period, 24 articles were published in peer-reviewed journals, all resulting, in part, from the receipt of specimens from the Yerkes Center.

The Division also provides shipping services for the Center and its investigators, including shipment of clinical samples and hazardous (infectious) samples by IATA-certified shipping/research technicians. During this reporting period, Yerkes' Shipping Unit packaged and shipped 374 packages of biological samples, shipping to investigators and laboratories in the United States and Canada.

Research Program and Research Project Support

Division of Pathology faculty collaborated with internal and external investigators in development of new protocols. This includes assistance with scientific expertise, preparation of experimental protocols, budget development, preparation and submission of IACUC and Environmental Health and Safety protocols. Working with Yerkes' Division of Animal Resources, the Division of Pathology also provides laboratory and scientific support during the entire performance of an experimental protocol, analysis of data and publication of results. Division of Pathology faculty members contribute to multiple research programs such as renal/bone marrow/liver transplant, SIV/AIDS infection, the optimization of novel malaria models, causes of diarrhea in infant macaques, the testing of experimental vaccine platforms for HIV, malaria and influenza, cancer and diabetes in aging monkeys, immune activation in transgenic monkeys and cardiovascular diseases.

B.4. Training and Professional Development Opportunities

Please see the overall component for response.

C. COMPONENT PRODUCTS

C.1 PUBLICATIONS

Not Applicable

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

Not Applicable

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

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

Not Applicable

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Nothing to report

D. COMPONENT PARTICIPANTS

Not Applicable

E. COMPONENT IMPACT

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

Not Applicable

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

Not Applicable

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

NOTHING TO REPORT

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?
Not Applicable

F. COMPONENT CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

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

NOTHING TO REPORT

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

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. COMPONENT SPECIAL REPORTING REQUIREMENTS

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

Not Applicable

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

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

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

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

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Not Applicable

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

RPPR - Other-8520

RESEARCH & RELATED BUDGET - SECTION A & B **FINAL**

ORGANIZATIONAL DUNS*: 066469933

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

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		Redacted by agreement				Project Lead	Institutional Base Salary	EFFORT			9,480.00	2,465.00	11,945.00
2						Veterinary Pathologist					19,400.00	5,044.00	24,444.00
3						Veterinary Pathologist					17,072.00	4,439.00	21,511.00
4						Veterinary Pathologist					17,823.00	4,634.00	22,457.00

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

Additional Senior Key Persons: File Name:

Total Senior/Key Person **80,357.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
2	Secretarial/Clerical	1.2			6,170.00	1,604.00	7,774.00
15	Supervisors, Technicians	79.2			381,280.00	99,133.00	480,413.00
17	**Total Number Other Personnel**					**Total Other Personnel**	**488,187.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**568,544.00**

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

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

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	Funds Requested ($)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	5,000.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**5,000.00**

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

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

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	90,000.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Maint/Repair	3,000.00
Total Other Direct Costs	**93,000.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**666,544.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. MTDC	45.0	666,544.00	299,946.00
		Total Indirect Costs	**299,946.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS, Steven Zuraf, (301) 492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**966,490.00**

J. Fee	Funds Requested ($)*
	0.00

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

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

Budget Justification

The budget request for the upcoming period is submitted in accordance with the peer reviewed P51 renewal approved in 2016. Justification for each budget category was also peer reviewed and approved at that time, and there is no significant change in this budget request from previously approved levels.

A. COMPONENT COVER PAGE

Project Title: Biomarkers Core

Component Project Lead Information:

Redacted by agreement

B. COMPONENT ACCOMPLISHMENTS

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

The primary mission of the Yerkes Biomarkers Core is to develop, validate and execute steroid, protein and other biologically relevant assays in support of translational and clinical research performed at the Yerkes National Primate Research Center and by outside investigators. The Core has been continuously operating since the early 1980s and currently provides assays for reproductive function, stress physiology, growth, metabolism, circadian physiology, pituitary function, neuropeptides and neurotransmitters. The Core currently performs these assays though the use of ELISA, radioimmunoassay (RIA), and liquid chromatography mass spectrometry (LCMS) assays in multiple species. Assays are done for investigators and clinicians on a per sample basis in which the Core recovers cost for personnel, reagents, service contracts, and miscellaneous supplies. The facility Redacted by agreement and contains Thermo Fisher HPLC coupled to Orbitrap Classic mass spectrometer, Shimadzu UPLC system in tandem with an AB Sciex 6500 triple quadrupole mass spectrometer, and multiple gamma and plate readers. We perform all necessary sample processing and data analysis to provide investigators with usable data. In addition to the service work, the Core also strives to develop, implement, and validate new assays to meet new research needs. Furthermore, we strive to lower the cost and turnaround time of existing assays by validating ELISA and RIA assays on our multiple LCMS platforms whenever possible.

The Specific Aims are:

1. To develop, validate and implement an oxytocin and vasopressin LCMS assay for use in plasma, CSF and whole blood;

2. To continue to reduce cost and assay turnaround time of existing ELISA and RIA assays by implementing and validation them on LCMS platforms;

3. To provide users with robust collections of related assays such as a full thyroid panel (TSH, T4, free T4 and free T3) or a more comprehensive metabolic panel for only a slightly increased cost compared to individual LCMS assays.

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

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: B2_8521 Biomarkers.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

Not Applicable

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

File uploaded: B4_c Training.pdf

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

NOTHING TO REPORT

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

Over the next funding period we will be working to increase the intensity of MS output detection in order to begin validation of this oxytocin assay for several critical complex substrates, including cerebrospinal fluid, serum, saliva, and urine. We have been working to reach out to researchers to emphasize the importance of flash-freezing and consistent storage of any sample that will be used in a future oxytocin assay.

B.2. Accomplishments—Biomarkers Core

Over the past year of funding, the Core has provided 2442 immunoassay and 369 LC/MS tests using our standardized assays in support of research with our collaborators at Yerkes, Emory University and throughout the United States. Additionally, we have developed and validated a new LC/MS assay to measure cortisol in rhesus macaque breast milk. Measurement of milk cortisol allows researchers to evaluate stress levels in breast feeding mothers of various social ranks and, combining these results with cortisol levels in nursing infants, to understand how early life stressors in both mother and fetus impact growth and cognitive development. Finally, we continue to work on the development and validation of a highly sensitive LC/MS assay for oxytocin. This critical and difficult-to-quantify biomarker is a high priority for several researchers at Yerkes and Emory. In the past few months, the Core has had a significant breakthrough, and is able to accurately quantify oxytocin at 1 pg/mL to 500 pg/mL concentrations by LC/MS, which encompasses the biologically relevant range of oxytocin expected from most samples.

B.4. Training and Professional Development Opportunities

Please see the overall component for response.

C. COMPONENT PRODUCTS

C.1 PUBLICATIONS

Not Applicable

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

Not Applicable

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

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

Not Applicable

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Nothing to report

D. COMPONENT PARTICIPANTS

Not Applicable

E. COMPONENT IMPACT

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

Not Applicable

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

Not Applicable

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

NOTHING TO REPORT

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?
Not Applicable

F. COMPONENT CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

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

NOTHING TO REPORT

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

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. COMPONENT SPECIAL REPORTING REQUIREMENTS

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

Not Applicable

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

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

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

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

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Not Applicable

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

RPPR - Core-8521

RESEARCH & RELATED BUDGET - SECTION A & B **FINAL**

ORGANIZATIONAL DUNS*: 066469933

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

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 ($)*	Funds Requested ($)*
	Redacted by agreement				Project Lead	Institutional Base Salary	EFFORT			3,531.00	918.00	4,449.00

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

Additional Senior Key Persons: File Name:

Total Senior/Key Person **4,449.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
2	Supervisor, Technician	2.4			10,870.00	2,826.00	13,696.00
2	**Total Number Other Personnel**					**Total Other Personnel**	**13,696.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**18,145.00**

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

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

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

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

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

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

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	3,000.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Maint/Repair	1,000.00
Total Other Direct Costs	**4,000.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**22,145.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. MTDC	45.0	22,145.00	9,965.00
		Total Indirect Costs	**9,965.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS, Steven Zuraf, (301) 492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**32,110.00**

J. Fee	Funds Requested ($)*
	0.00

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

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

Budget Justification

The budget request for the upcoming period is submitted in accordance with the peer reviewed P51 renewal approved in 2016. Justification for each budget category was also peer reviewed and approved at that time, and there is no significant change in this budget request from previously approved levels.

A. COMPONENT COVER PAGE

Project Title: Comparative AIDS Core

Component Project Lead Information:

Redacted by agreement

B. COMPONENT ACCOMPLISHMENTS

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

The purpose of the Comparative AIDS Core (CAC) is to provide resources and technical support for studies of AIDS pathogenesis, prevention, and treatment using the well-established comparative models of pathogenic simian immunodeficiency virus (SIV) infection of rhesus macaques, an Asian “non-natural” host species that develops AIDS upon experimental infection with SIV, and non-pathogenic SIV infection of sooty mangabeys, an African “natural” host species in which the infection is typically benign despite high levels of virus replication. In particular, the Core has been a unique source of SIV-infected and uninfected mangabey samples for a large number of investigators in the field, as the Yerkes colony remains the only source of such samples for the biomedical research community in the entire world. We plan to maintain the colony size at a target number of ~175 individuals, which represents the historical size of the colony and allows us to manage the population in a manner that protects both the behavioral integrity and the existing genetic diversity of the colony. Overall, the CAC is a vital component of the highly successful Yerkes research program in AIDS-related studies, and is established and designed to provide oversight and coordination for these studies, as well as the necessary technical, laboratory and animal research support.

The Core staff includes scientists, veterinarians, pathologists, and animal care technicians who work closely with Yerkes Core Scientists, Affiliate Scientists and outside collaborators to design and carry out in vivo and in vitro experiments involving specimens collected from SIV-infected and uninfected mangabeys and rhesus macaques. Currently, the Core includes all the non-investigator assigned mangabeys, as well as a large number of rhesus macaques. All donor animals have known serologic and clinical health status with weights that permit routine collections of such specimens as blood, skin, milk, gastrointestinal biopsies, bone marrow aspirates and cerebrospinal fluid in accordance with approved Emory IACUC guidelines. Of note, a pre-existing cost accounting system permits appropriate recharges to be made for the collections of requested tissue specimens. The availability and distribution of these samples has resulted in many papers in high-impact journals and has been often critical in the provision of preliminary results that were used to acquire a number of large federal and non-federal grants. Finally, the Core provides formal training as needed to scientists, staff, postdoctoral fellows and students involved in AIDS research studies using nonhuman primates.

The Specific Aims are:

1. To continue to provide partial support for the maintenance of the Yerkes sooty mangabey colony as well as dedicated groups of rhesus macaques;

2. To continue to collect and store a large number of biological samples from the assigned animals that are then provided to intramural and extramural investigators for studies of AIDS pathogenesis, prevention, and treatment;

3. To expand our focus to include a strong program of research in novel approaches to HIV/AIDS prevention and treatment, including studies in which rhesus macaques and sooty mangabeys are treated chronically with antiretroviral therapy.

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

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: B2_8522 CAC.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

Not Applicable

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

File uploaded: B4_c Training.pdf

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

NOTHING TO REPORT

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

The Comparative AIDS Core will continue to function as a core resource of animals available to facilitate AIDS research. The core will continue to maintain rhesus macaques and sooty mangabeys assigned to the CAC and available to fill specimen requests for both internal and external investigators doing AIDS research.

B.2. Accomplishments—Comparative AIDS Core

During the reporting period, 70 biological samples were provided to investigators through our Tissue Distribution Program from the Comparative AIDS Core (CAC). Of these investigators, six are internal investigators at Yerkes, one at Emory and six are external from other institutions within the United States. In addition, 258 animals were assigned to externally-funded AIDS related studies during the reporting period. The sooty mangabey colony continues to be maintained at a steady population of approximately 170 animals with managed breeding. The CAC continues to maintain a population of animals available for AIDS research specimen requests as needed.

Publications during the reporting period related to the AIDS Core:

Scinto HB, Gupta S, Thorat S, Mukhtar MM, Griffiths A, Delgado J, Plake E, Vyas HK, Strickland A, Byrareddy SN, Montefiori DC, LaBranche C, Pal R, Treece J, Orndorff S, Ferrari MG, Weiss D, Chenine A-L, McLinden R, Michael N, Kim JH, Robb ML, Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, Ruprecht RM (2018). Novel strategy to adapt simian human immunodeficiency virus E1 carrying env from an RV144 volunteer to rhesus macaques: coreceptor switch and final recovery of a pathogenic virus with exclusive R5 tropism. J Virol. Jun 29; 92 (14). pii: e02222-17. doi: 10.1128/JVI.02222-17. PMID: 29743361 PMCID: PMC6026739.

Mylvaganam GH, Chea LS, Tharp GK, Hicks S, Velu V, Iyer SS, Deleage C, Estes JD, Bosinger SE, Freeman GJ, Ahmed R, Amara RR. Combination anti-PD-1 and antiretroviral therapy provides therapeutic benefit against SIV. JCI Insight. 2018 Sep 20;3(18). pii: 122940. doi: 10.1172/jci.insight.122940. [Epub ahead of print] PubMed PMID: 30232277.

Kumar NA, McBrien JB, Carnathan DG, Mavigner M, Mattingly C, White ER, Viviano F, Bosinger SE, Chahroudi A, Silvestri G, Paiardini M, Vanderford TH. (2018). Antibody-Mediated CD4 Depletion Induces Homeostatic CD4+ T Cell Proliferation without Detectable Virus Reactivation in Antiretroviral Therapy-Treated Simian Immunodeficiency Virus-Infected Macaques. J Virol. 92(22). pii: e01235-18. doi: 10.1128/JVI.01235-18. Print 2018 Nov 15. PMID: 30185596

Palesch D, Bosinger SE, Mavigner M, Billingsley JM, Mattingly C, Carnathan DG, Paiardini M, Chahroudi A, Vanderford TH, Silvestri G. Short-Term Pegylated Interferon α2a Treatment Does Not Significantly Reduce the Viral Reservoir of Simian Immunodeficiency Virus-Infected, Antiretroviral Therapy-Treated Rhesus Macaques. J Virol. 2018 Jun 29;92(14). pii: e00279-18. doi: 10.1128/JVI.00279-18. Print 2018 Jul 15. PubMed PMID: 29720521; PubMed Central PMsCID: PMC6026735.

Hoang TN, Harper JL, Pino M, Wang H, Micci L, King CT, McGary CS, McBrien JB, Cervasi B, Silvestri G, Paiardini M. (2018). Bone Marrow-Derived CD4+ T Cells Are Depleted in Simian Immunodeficiency Virus-Infected Macaques and Contribute to the Size of the Replication-Competent Reservoir. J Virol. pii: e01344-18. doi: 10.1128/JVI.01344-18. Print 2019 Jan 1. PMID: 30305357

Mudd JC, Busman-Sahay K, DiNapoli SR, Lai S, Sheik V, Lisco A, Deleage C, Richardson B, Palesch DJ, Paiardini M, Cameron M, Sereti I, Reeves RK, Estes JD, Brenchley JM. (2018). Hallmarks of primate lentiviral immunodeficiency infection recapitulate loss of innate lymphoid cells. Nat Commun. 9(1):3967. doi: 10.1038/s41467-018-05528-3. PMID: 30262807

Ploquin MJ, Casrouge A, Madec Y, Noël N, Jacquelin B, Huot N, Duffy D, Jochems SP, Micci L, Lécuroux C, Boufassa F, Booiman T, Garcia-Tellez T, Ghislain M, Grand RL, Lambotte O, Kootstra N, Meyer L, Goujard C, Paiardini M, Albert ML, Müller-Trutwin M. (2018). Systemic DPP4 activity is reduced during primary HIV-1 infection and is associated with intestinal RORC+ CD4+ cell levels: a surrogate marker candidate of HIV-induced intestinal damage. J Int AIDS Soc. 21(7):e25144. doi: 10.1002/jia2.25144. PMID: 29987877

Abdel-Mohsen M, Kuri-Cervantes L, Grau-Exposito J, Spivak AM, Nell RA, Tomescu C, Vadrevu SK, Giron LB, Serra-Peinado C, Genescà M, Castellví J, Wu G, Del Rio Estrada PM, González-Navarro M, Lynn K, King CT, Vemula S, Cox K, Wan Y, Li Q, Mounzer K, Kostman J, Frank I, Paiardini M, Hazuda D, Reyes-Terán G,

Richman D, Howell B, Tebas P, Martinez-Picado J, Planelles V, Buzon MJ, Betts MR, Montaner LJ. (2018). CD32 is expressed on cells with transcriptionally active HIV but does not enrich for HIV DNA in resting T cells. Sci Transl Med. 10(437). pii: eaar6759. doi: 10.1126/scitranslmed.aar6759. PMID: 29669853

Ferrando-Martinez S, Moysi E, Pegu A, Andrews S, Nganou Makamdop K, Ambrozak D, McDermott AB, Palesch D, Paiardini M, Pavlakis GN, Brenchley JM, Douek D, Mascola JR, Petrovas C, Koup RA. (2018). Accumulation of follicular CD8+ T cells in pathogenic SIV infection. J Clin Invest. 128(5):2089-2103. doi: 10.1172/JCI96207. Epub 2018 Apr 16. PMID: 29664020

S Burton, LM Spicer, TP Charles, S Gangadhara, PBJ Reddy, T Styles, V Velu, S Kasturi, T Legere, E Hunter, B Pulendran, R Amara, P Hraber, CA Derdeyn (2019). Clade C HIV-1 envelope vaccination regimens differ in their ability to elicit antibodies with moderate neutralization breadth against genetically diverse tier 2 HIV-1 envelope variants. Journal of Virology 2019 Jan 16. pii: JVI.01846-18. doi: 10.1128/JVI.01846-18. [Epub ahead of print] PMID:30651354

B.4. Training and Professional Development Opportunities

Please see the overall component for response.

C. COMPONENT PRODUCTS

C.1 PUBLICATIONS

Not Applicable

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

Not Applicable

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

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

Not Applicable

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Nothing to report

D. COMPONENT PARTICIPANTS

Not Applicable

E. COMPONENT IMPACT

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

Not Applicable

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

Not Applicable

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

NOTHING TO REPORT

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?
Not Applicable

F. COMPONENT CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

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

NOTHING TO REPORT

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

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. COMPONENT SPECIAL REPORTING REQUIREMENTS

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

Not Applicable

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

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

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

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

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Not Applicable

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

RPPR - Core-8522

RESEARCH & RELATED BUDGET - SECTION A & B **FINAL**

ORGANIZATIONAL DUNS*: 066469933

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

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.		Redacted by agreement				Project Lead	Institutional Base Salary	EFFORT			1,896.00	493.00	2,389.00
2.						Asc Dir, Animal Resources					9,480.00	2,465.00	11,945.00
3.						Geneticist					4,728.00	1,229.00	5,957.00
4.						Chief Veterinarian					5,798.00	1,507.00	7,305.00

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

Additional Senior Key Persons: File Name:

Total Senior/Key Person **27,596.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Laboratory Manager	2.4			15,481.00	4,025.00	19,506.00
1	**Total Number Other Personnel**					**Total Other Personnel**	**19,506.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**47,102.00**

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

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

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

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

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

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

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	48,135.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Animal Per Diem	404,763.00
Total Other Direct Costs	**452,898.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**500,000.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. MTDC	45.0	500,000.00	225,000.00
		Total Indirect Costs	**225,000.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, Steven Zuraf, (301) 492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**725,000.00**

J. Fee	Funds Requested ($)*
	0.00

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

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

Budget Justification

The budget request for the upcoming period is submitted in accordance with the peer reviewed P51 renewal approved in 2016. Justification for each budget category was also peer reviewed and approved at that time, and there is no significant change in this budget request from previously approved levels.

A. COMPONENT COVER PAGE

Project Title: Imaging Core

Component Project Lead Information:

Redacted by agreement

B. COMPONENT ACCOMPLISHMENTS

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

The primary mission of the Yerkes Imaging Core is to provide resources and technical support for performing magnetic resonance imaging (MRI), spectroscopy (MRS) and positron emission tomography (PET), all of which are capable of visualizing high-resolution anatomical, physiological, functional and biochemical information in vivo in a non-invasive and longitudinal fashion. The main facility Redacted by agreement occupies two floors attached to the Redacted by agreement at the Yerkes Main Station. There is an additional PET imaging facility Redacted by agreement located in the Redacted by agreement at the Yerkes Field Station. Hardware resources include 7T animal size and 3T human size MRI scanners, a cyclotron, two microPET scanners, computation resources and MR-compatible physiological monitoring equipment. Our staff works closely with Yerkes Core Scientists, Affiliate Scientists, and outside collaborators to design and carry out imaging experiments, and to collect, analyze and interpret imaging and spectroscopic data. Our computational support includes data analysis, implementation and development of software for data analysis, and data management and storage. In addition to its service component, the Imaging Core has its own active research programs. These include ongoing implementation and development of basic and novel pulse sequences, hardware and software support for data acquisition, construction of coils/detectors, head-holders and immobilization devices, and MR-compatible physiological monitoring equipment. These resources are made available to all users. The Imaging Core provides formal training as needed to scientists, staff, postdoctoral fellows, and students. Training includes lectures on basic MR and PET physics, radiochemistry, and applications as well as hands-on MR and PET experiments and data analysis. Furthermore, the Imaging Core works closely with the Emory Center for Systems Imaging (CSI), an integrated organizational structure designed to provide synergy for various aspects of imaging research and make imaging resources easily available to the greater university community. The CSI encompasses complementary resources based at specialized imaging facilities across Emory University including Emory University Hospital, Wesley Woods, the Winship Cancer Institute and the Psychology Department on the Emory College campus.

The Specific Aims are:

1.To establish the Yerkes Imaging Core as a premiere resource in nonhuman primate diffusion and perfusion MRI and resting state functional MRI (rsfMRI);

2.To expand our focus to include a strong program of research in stroke and neurovascular function in the context of functional brain imaging through the relatively recent hire of an endowed faculty appointment in stroke imaging;

3.To develop novel PET tracers and MRI contrast agents to support emerging research programs with particular emphasis on partnering with the Emory Vaccine Center and the Division of Microbiology and Immunology.

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

Yes

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: B2_8523 Imaging.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

Not Applicable

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

File uploaded: B4_c Training.pdf

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

NOTHING TO REPORT

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

We will continue to establish the Yerkes Imaging Core as a premiere resource in nonhuman primate diffusion, perfusion, metabolic MRI and resting state fMRI. The Imaging Core has made significant progress in the development of diffusion MRI techniques (including diffusion tensor imaging (DTI), high-angular resolution diffusion imaging (HARDI), diffusion spectrum imaging (DSI)) and perfusion MRI techniques (including continuous arterial spin-labeling techniques and dynamic susceptibility contrast MRI) as part of our studies in stroke imaging and nonhuman primate neurodevelopment. We have also developed standardized protocols for evaluating resting state functional connectivity in both anesthetized and fully conscious rhesus monkeys. These are two areas of in vivo imaging with significant potential across a broad range of research programs. In addition, the Yerkes Imaging Core will implement and optimize novel MRI techniques, such as chemical exchange saturation transfer (CEST) imaging, diffusion kurtosis imaging (DKI), susceptibility weighted imaging (SWI), quantitative susceptibility mapping (QSM), hardware and software support for data acquisition and processing, and construction of RF probes/detectors. These resources will be available to all users of the Imaging Core.

We will also expand our focus to include a strong program of research in stroke and neurovascular function in the context of functional

brain imaging. The major goal is to establish a preclinical program on novel stroke interventions and therapeutics that successfully translates to human use. These efforts will be supported by the recruitment of Redacted by as the Yerkes Center's first endowed chair in the area of stroke and neuroimaging. In addition, Redacted by agreement is investigating the role of vascular disease in the development of dementia by determining, in aged nonhuman primates, the relationship between imaging anomalies in MRI and cerebral amyloid angiopathy. His research program is well positioned to complement our nonhuman primate stroke research and enhance our understanding of neurovascular function. Moreover Redacted by the new imaging director, has expertise in DKI and CEST MRI, in particular imaging tissue pH change following stroke. His group is also actively pursuing novel MRI in studying transient ischemic attack (TIA), spreading depression, epilepsy, and brain tumor. Redacted by will work closely with investigators at Yerkes and Emory University Hospital to keep up the momentum and develop advanced neuroimaging.

Lastly, we will develop novel PET tracers and MRI contrast agents to support emerging research programs with particular emphasis on partnering with the Emory Vaccine Center and the Yerkes Division of Microbiology and Immunology. We are currently validating the use of biomarkers for evaluating neuroinflammation in the context of research on Parkinson's disease. These biomarkers, including F-18 labeled FEPPA, will have direct application in the study of neuroAIDS and cognitive dysfunction. In addition, we are also interested in superparamagnetic iron oxide nanoparticles (SPIONs) as they have emerged as a unique contrast agent to improve the sensitivity and specificity of MRI in detecting the abnormality of tissues or cell tracking. In particular, the exploratory studies of SPIONs for tracking HIV-specific cytotoxic T lymphocytes suggest the SPIONs may be a novel approach in in vivo monitoring of T cells and play a critical role in development of T cell-based therapies.

B.2. Accomplishments—Imaging Core

The Yerkes Imaging Core is part of the Yerkes National Primate Research Center at Emory University and focuses on the development of *in vivo* magnetic resonance imaging (MRI) and positron emission tomography (PET) to study anatomy, physiology and function non-invasively to address questions in neuroscience, neuropharmacology and neurodegenerative diseases. Research at the Imaging Core includes high-resolution structural, perfusion and functional imaging of nonhuman primates, diffusion-tensor imaging (DTI), awake monkey functional MRI (fMRI), quantitative perfusion imaging, quantitation of monoamine transporters and receptors, brain metabolic mapping, diffusion, perfusion and functional imaging of stroke, and image data analysis and visualization. The Imaging Core continues to support internal and external investigators with MRI and PET imaging as part of their individual research programs. In addition, we continued to commit significant resources to the development of a nonhuman primate model of ischemic stroke. Anendowed chair of stroke imaging Redacted by agreement joined the Imaging Core in 2017. In addition Redacted by agreement has been recruited as the new director of the Yerkes Imaging Center to succeed Redacted by agreement who retired at the end of 2017. We have expanded our use of diffusion tensor imaging DTI to characterize brain development in longitudinal studies conducted at the Yerkes Field Station. We have also made significant progress in establishing technical approaches that will be applicable to research programs in immunology and vaccine development. With the implementation of PET imaging, we have quantified the distribution of SIV virus *in vivo* and have validated biomarkers of neuroinflammation.

Significant progress has been made in imaging ischemic stroke in a clinically relevant monkey model. The long-term goal is to identify and characterize tissue at risk and functional remodeling after stroke and to cross validate against histology and behavioral assessments, to develop a mathematical model to predict outcome of stroke tissue fates using acute MRI data and to cross validate the prediction with histology, and to test pharmacological treatments in collaboration with Emory collaborators. We continue to make major advances in the neuropharmacology of abused stimulants in the context of medication development to treat stimulant addiction. As part of these efforts, we are able to routinely image fully conscious rhesus monkeys using fMRI. These advancements in awake monkey imaging will serve to enhance a variety of research programs at the Yerkes Imaging Core. Additional areas of significant interest include brain metabolic effects of neonatal medial temporal lobe lesions to characterize the neurobiology of learning and memory, the influence of psychosocial stress on the emergence of behavioral problems including anxiety, depression and socially motivated behaviors, and the discovery of pharmacological interventions to slow the progression and alleviate the symptoms of Parkinsonism. More general areas of interest include anatomical imaging for placement of recording electrodes and dialysis probes, imaging neurodegenerative diseases, functional MRI of memory and cognition, PET and fMRI imaging of drug abuse, fMRI of developing monkeys, structural imaging and diffusion tensor imaging of development and aging, PET imaging of monoamine transporters and receptors associated with early life experiences and social behavior and obesity. The Yerkes Field Station offers major advantages to our imaging program including social housing, and a large number of infants and juveniles needed for developmental studies. Onsite capability to conduct PET studies without either significant disruption to the animals located at the Field Station markedly enhances the quality of science and provides unique opportunities to investigators.

B.4. Training and Professional Development Opportunities

Please see the overall component for response.

C. COMPONENT PRODUCTS

C.1 PUBLICATIONS

Not Applicable

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

Not Applicable

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

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

Not Applicable

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Nothing to report

D. COMPONENT PARTICIPANTS

Not Applicable

E. COMPONENT IMPACT

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

Not Applicable

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

Not Applicable

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

NOTHING TO REPORT

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?
Not Applicable

F. COMPONENT CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

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

NOTHING TO REPORT

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

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. COMPONENT SPECIAL REPORTING REQUIREMENTS

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

Not Applicable

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

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

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

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

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Not Applicable

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

RPPR - Core-8523

RESEARCH & RELATED BUDGET - SECTION A & B **FINAL**

ORGANIZATIONAL DUNS*: 066469933

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

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.		Redacted by agreement				Project Lead	Institutional Base Salary	EFFORT			3,783.00	984.00	4,767.00
2.						Asc Veterinarian					14,482.00	3,766.00	18,248.00
3.						Imaging Core Asst Director					8,328.00	2,166.00	10,494.00

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

Additional Senior Key Persons: File Name:

Total Senior/Key Person **33,509.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
5	Staff Scientists, Technicians	9.6			45,745.00	11,894.00	57,639.00
5	**Total Number Other Personnel**					**Total Other Personnel**	**57,639.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**91,148.00**

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

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

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

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

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

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

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	3,000.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Maint/Repair	3,000.00
Total Other Direct Costs	**6,000.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**97,148.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. MTDC	45.0	97,148.00	43,716.00
		Total Indirect Costs	**43,716.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS, Steven Zuraf, (301) 492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**140,864.00**

J. Fee	Funds Requested ($)*
	0.00

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

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

Budget Justification

The budget request for the upcoming period is submitted in accordance with the peer reviewed P51 renewal approved in 2016. Justification for each budget category was also peer reviewed and approved at that time, and there is no significant change in this budget request from previously approved levels.

A. COMPONENT COVER PAGE

Project Title: Virology Core

Component Project Lead Information:

Redacted by agreement

B. COMPONENT ACCOMPLISHMENTS

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

The primary purpose of the Yerkes Virology Core is to provide serological and molecular viral diagnostic testing in support of Yerkes Research Services and Colony Management. The Core has developed a pipeline of diagnostic screens and tests which provide definitive diagnoses for the presence of infection by Simian Immunodeficiency Virus (SIV), Simian T Lymphotropic Virus (STLV), Simian type D retroviruses (SRV), and Simian Herpes B virus (Herpes-B). The presence of these viruses in rhesus macaques could confound the results of HIV vaccine and pathogenesis studies, present critical risks to human investigators accidentally exposed to rhesus macaque tissues, and could present significant health risks to the rhesus macaque colony as well. The screening pipeline consists of several tiers of increasingly stringent and sensitive tests. First, animals are screened for virus-specific antibodies using a cytometric bead array (CBA) based platform. Any animal with a positive or borderline CBA result is then tested by Western blot for the presence of antigen-specific antibodies. An inconclusive Western blot results in a third downstream virus-dependent test. For SIV and STLV, DNA is extracted from frozen peripheral blood mononuclear cells (PBMC) and a polymerase chain reaction (PCR) test is performed to detect integrated viral genomes. For SRV, a real-time, quantitative PCR is performed (currently outsourced to the California National Primate Research Center). For Herpes-B, samples are sent to the B-virus National Laboratory for analysis via competitive and recombinant ELISA. Additionally, the Yerkes Virology Core performs both custom virological assays (virus titration and growth) and kit-based CBA assays (e.g. rhesus cytokine assays) for clients across Emory University. Through the combined expertise of the leadership and technicians within this lab, and a close collaboration with the CFAR Virology and Molecular Biomarkers Core pre-clinical laboratory, the Yerkes Virology Core is extremely well-positioned to be the primary hub of virological and molecular diagnostic services across Emory University.

The Specific Aims are:

1. To continue to provide state-of-the-art viral diagnostic assays in support of the Specific Pathogen Free rhesus macaque colony (breeding) and Yerkes Animal Resources (study assignment), and expand the menu of virological services through the development, validation, and implementation of a Simian type D retrovirus quantitative real-time PCR;

2. To expand the menu of services provided for viral preparation, characterization, and diagnosis, including the growth and genetic characterization of standardized virus stocks for use in nonhuman primate studies of AIDS;

3. To develop and implement new assays to test for pre-existing immunity to viruses which could be used in pre-clinical trials of gene therapy delivery systems (AAV), candidate vaccines (CMV) or impact the health and immunological status of the primates housed at Yerkes (measles, etc.).

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

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: B2_8524 Virology.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

Not Applicable

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

File uploaded: B4_c Training.pdf

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

NOTHING TO REPORT

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

Over the next funding period, the Virology Core will continue the yearlong process of validating the in-house SRV qPCR by testing side-by-side with the CNPRC. After this testing period is over, we plan to review all data regarding the qPCR's performance after a full year of testing. Upon successful discernment of all positive and negative samples, we will shift to in-house SRV testing using this new assay. We will rely on the CNPRC Pathogen Detection Lab only for confirmation of putative qPCR-positive samples that may happen. Additionally, we plan to perform testing of the identified ~200 breeding age females in the SPF colony for Zika and West Nile Virus. Identification of Zika virus is most important in breeding females due to the documented neurocognitive deficits of infected newborns and the increased propensity for still-births and miscarriages in Zika infected pregnant dams. Likewise, West Nile Virus (which is endemic in Georgia) could potentially contribute to clinical morbidity in the SPF colony at large.

B.2. Accomplishments—Virology Core

During the course of this funding period, the Virology Core has tested over 1600 animals by Luminex, the multiplexed first step in our testing algorithm. Over 2600 confirmatory Western blots were performed for B-virus, SIV, STLV, and SRV combined. Indeterminate Western blots for SIV and STLV were confirmed negative via 376 PCRs. No animal was confirmed positive for any SPF pathogen, although several animals were tested monthly due to persistent indeterminate follow-up B-virus testing. For SRV confirmatory molecular testing, the Core has begun validating an SRV quantitative real-time PCR by testing samples side-by-side with the CNPRC's Pathogen Detection Lab. This is a multiplex real-time PCR that simultaneously quantifies SRV as well as a cellular gene with a constant copy number, oncostatin-M (OSM), as a positive control. A preliminary test of its ability to detect positive samples with low background was performed using a battery of blinded proficiency testing samples sent from the CNPRC that contained SRV positive, indeterminate, and negative samples. Our implementation of the SRV qPCR successfully detected the positive samples with no false positives or false negatives. After this initial success, we have performed a real-time PCR on 69 of the 94 samples that have been identified as SRV indeterminant in our confirmatory Western blots. All samples have been confirmed SRV-negative. We have discussed with Redacted by agreement at the CNPRC Pathogen Detection Lab about the provision of more SRV-positive samples for spot testing the sensitivity and specificity of our SRV qPCR implementation. In addition, the Virology Core has screened 93 animals at Yerkes and outside facilities for pre-existing immunity to AAV serotypes 2, 5, and 9 using our in-house developed AAV neutralization assay. Finally, in order to address the potential for flavivirus infection (Zika and West Nile Virus, specifically) of the rhesus macaque SPF breeding colony we have begun identification of ~200 breeding age females for detection of anti-Zika and anti-West Nile Virus antibodies.

B.4. Training and Professional Development Opportunities

Please see the overall component for response.

C. COMPONENT PRODUCTS

C.1 PUBLICATIONS

Not Applicable

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

Not Applicable

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

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

Not Applicable

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Nothing to report

D. COMPONENT PARTICIPANTS

Not Applicable

E. COMPONENT IMPACT

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

Not Applicable

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

Not Applicable

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

NOTHING TO REPORT

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?
Not Applicable

F. COMPONENT CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

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

NOTHING TO REPORT

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

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. COMPONENT SPECIAL REPORTING REQUIREMENTS

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

Not Applicable

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

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

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

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

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Not Applicable

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

RPPR - Core-8524

RESEARCH & RELATED BUDGET - SECTION A & B **FINAL**

ORGANIZATIONAL DUNS*: 066469933

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

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.		Redacted by agreement				Project Lead	Institutional Base Salary	EFFORT			3,531.00	918.00	4,449.00

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

Additional Senior Key Persons: File Name:

Total Senior/Key Person **4,449.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
2	Technicians	2.4			10,013.00	2,603.00	12,616.00
2	**Total Number Other Personnel**					**Total Other Personnel**	**12,616.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**17,065.00**

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

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

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

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

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

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

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	3,000.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Maint/Repair	1,000.00
Total Other Direct Costs	**4,000.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**21,065.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. MTDC	45.0	21,065.00	9,479.00
		Total Indirect Costs	**9,479.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, Steven Zuraf, (301) 492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**30,544.00**

J. Fee	Funds Requested ($)*
	0.00

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

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

Budget Justification

The budget request for the upcoming period is submitted in accordance with the peer reviewed P51 renewal approved in 2016. Justification for each budget category was also peer reviewed and approved at that time, and there is no significant change in this budget request from previously approved levels.

A. COMPONENT COVER PAGE

Project Title: Genomics Core

Component Project Lead Information:

Redacted by agreement

B. COMPONENT ACCOMPLISHMENTS

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

The primary mission of the Yerkes Genomics Core (GenCore) is to provide researchers in the Emory community with access to cutting-edge high throughput genomic technologies and bioinformatics. The facility [Redacted by agreement] is located in the [Redacted by agreement] at the Yerkes Main Station and the primary computing infrastructure is housed in the Emory central IT computing racks. The primary hardware housed by the GenCore includes an Illumina HiSeq 1000 next-generation sequencing system, an Affymetrix 3000 Gene Chip Scanner, and a Fluidigm Biomark microfluidic single-cell analysis real-time PCR platform. Supporting bioinformatics and computation is a dedicated IlluminaCompute Server and Isilon storage system. Through a partnership with the Center for AIDS Research (CFAR) Virology Core, the GenCore also utilizes an Illumina MiSeq system for applications that require long read technology. The GenCore laboratory is the only core facility on the Emory campus that conducts next-gen sequencing. The Yerkes GenCore was established in 2012 with the mandate to support nonhuman primate (NHP)-based and immunology-based research. The primary users of the GenCore are monkey model researchers at the Yerkes Center and immunologists within the Emory Vaccine Center; however, the GenCore is also utilized by members of the greater Emory community. The services offered by the GenCore include RNA-Seq and array-based transcriptomics, DNA-Seq, miRNA-sequencing, microbiome 16s rRNA sequencing and sample preparation. The GenCore staff also includes a dedicated bioinformaticist and provides a wide variety of analysis and computational services. Ongoing and completed projects in the GenCore laboratory include transcriptomic profiling of several pre-clinical vaccine candidates, expression monitoring of clinical trials samples undergoing novel anti-HIV therapies, and multiple small-scale RNAseq experiments in humans and several NHP species. The GenCore is the dedicated sequencing provider for the NIAID-sponsored Malaria-Host Pathogen Interaction Consortium (MaPHIC) contract [Redacted by agreement] [Redacted by agreement] The GenCore also has an active internal research program, primarily focused on improving genomic resources and assays for NHP applications. This has included a large-scale collaboration with the Baylor Genome Sequencing Center to sequence the genome of the sooty mangabey monkey – a species housed by the Yerkes Center and used to study HIV pathogenesis. Lastly, the GenCore has provided verification analyses for the generation of a novel rhesus macaque genome sequence.

The Specific Aims are:

1. To translate protocols for genomic profiling of the B- and T- lymphocyte receptor repertoire (TCR-Seq and Ig-Seq) for use in the rhesus macaque, and offer repertoire sequencing technology for use in SIV-vaccine studies;

2. To translate microbiome sequencing analyses to monkey models, and integrate microbiome studies into NHP applications including nutritional studies, veterinary monitoring, and SIV-vaccine trials;

3. To establish single-cell transcriptomics (scRNA-Seq) for application in monkey models and offer single-cell technology to the NHP research community, and to develop specialized scRNA-Seq for SIV/HIV latently infected cells;

4. To increase throughput, streamline project submission, billing and data retrieval for users;

5. To expand bioinformatics accessibility to the Yerkes community.

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

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: B2_8525 Genomics.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

Not Applicable

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

File uploaded: B4_c Training.pdf

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

NOTHING TO REPORT

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

1.Offer single-cell RNA-Seq via 10X Genomics Sequencing.

In the previous period, we had set a goal to improve cost and throughput for single-cell RNA-Seq. We were able to dramatically reduce the cost by establishing an “in house” SOP that minimally relies on commercial reagents. We also identified a robotic platform – a Mosquito HV – that accurately and precisely handles nanoliter pipetting. We purchased the device in the summer of 2017, largely using funds available to [Redacted by agreement] In 2018 however, we were able to procure a 10X Genomics Chromium Controller device for droplet based sequencing applications, including single-cell RNA-Seq. We have prioritized implementing the 10X device for users – and since its

implementation in the GenCore in January 2019 – have run assays for 7 users, and are aiming at a full launch to all users by June 2019. We have also secured a commitment from Illumina, from 10X Genomics and from BioLegend to provide financial support for a full-day symposium on 10X Genomics sequencing applications in August 2019.

2.Reduce cost of sequencing and NGS services

Our costs for services have remained essentially the same over the past two reporting periods, during which we have invested in capital equipment, staff and analysts so that we could maximize accessibility and turn-around time. In the upcoming period we hope to reduce sequencing services costs in two ways: (1) taking advantage of liquid handling platforms to reduce use of commercial reagents, but more importantly (2) obtain an Illumina NovaSeq to replace the Illumina HiSeq3000 as the 3000 comes to the end of its useful cycle. The NovaSeq has significantly reduced cost per base sequenced than the 3000 at higher densities Pending Support

Pending Support

3.Offer competitive Whole-Genome Sequencing (WGS) services to users.

In recent years, the GenCore has gained significant expertise in whole-genome sequencing of NHPs, gained through the experience of Redacted by project to sequence the sooty mangabey genome (Bosinger, Nature 2018) and the recruitment of Redacted by who has focused on whole-genome sequencing of macaques for discovery of novel alleles to control SIV infection (Ericsen A, Genome Biol 2014). Previously, whole genome sequencing had been largely relegated to the realm of large genome centers. With the advent of the Illumina NovaSeq, sequencing of this scale is now possible in traditional cores. Thus, the pursuit of the NovaSeq will enable the GenCore to offer WGS services to local users – we are awaiting a funding decision – however we have also acquired a 10X Genomics Chromium controller which allows for long-read sequencing and enables WGS projects. Should the NovaSeq be funded, we expect to implement WGS as a core service.

4.Continue to improve resources for characterizing the rhesus macaque immunoglobulin (Ig) loci for supporting HIV vaccine research.

An accurate Ig assembly, and an estimate of Ig gene segment allelic representation within the NPRC SPF colonies is an urgent need for testing of novel immunogens aimed at developing broadly neutralizing antibodies against HIV. Over the prior reporting period, we collaborated with Redacted by agreement and Pacific BioSciences to obtain long-read sequence assemblies of the Indian Macaca mulatta immunoglobulin loci. The sequencing and assembly have been completed and the Ig gene segments are currently being annotated. Over this period, we will continue these efforts by (i) performing repertoire sequencing of a set of hub breeder animals in the SPF colony. These efforts have been delayed as we are awaiting completion of genotyping and parentage efforts of the SPF colony. We will also contribute to these efforts by (ii) applying our novel bioinformatics algorithm BALDR that reconstructs immunoglobulin antibody sequences using short read data, and (iii) applying repertoire sequencing to vaccinated monkeys to identify usage of germ-line alleles.

5.Offer access to Macaca mulatta WGS genetic variant data.

Redacted by agreement are both members of the ORIP-supported NHP Genetic & Genomic Working Group (GGWG). One of the efforts of the GGWG group is to increase accessibility to NHP genomics datasets generated across the NPRCs. In addition to depositing raw sequences into publicly-accessible resources, such as NCBI SRA, we encourage local investigators and their collaborators to contribute macaque genomics data to the ONPRC-curated monkey genotype and phenotype (mGAP) repository, which currently hosts genomic data for approximately 1,522 macaques. Since mGAP entries are de-identified, it is unclear how many analyzed YNPRC datasets are currently listed on the resource, but approximately 120 datasets have been deposited thus far.

6.Incorporate long-read sequencing technology for users.

The ability to sequence long-fragments of DNA is becoming more common-place and has demonstrated utility in several applications, particularly for genome assembly. Towards these aims, the GenCore has acquired a 10X Genomics Chromium controller – which enables “synthetic long-reads” by barcoding DNA fragments in cis that can be reconstructed informatically. We have budgeted towards the purchase of an Oxford NanoPore MinIon, which allows ultralong reads. Lastly, over the past year, we have demonstrated the superiority of long-reads generated by PacBio technology by generating a de novo genome assembly of a Yerkes rhesus macaque, and used this for improved annotation of monkey immunoglobulin genes. While we do not have plans to purchase a PacBio instrument in the short-term, we are exploring a partnership with the Mt. Sinai Icahn School of Medicine Genomics Core to pursue additional PacBio sequencing aims utilizing rhesus macaques.

B.2. Accomplishments—Genomics Core

The Goals/Aims and Achievements for the Yerkes NHP Genomics Core over the prior reporting period were:

1. To translate protocols for genomic profiling of the B- and T- lymphocyte receptor repertoire (TCR-Seq and Ig-Seq) for use in the rhesus macaque, and offer repertoire sequencing technology for use in SIV-vaccine studies.

We have developed and implemented a non-commercial protocol for sequencing of rhesus macaque IgG, IgA, IgD, IgM, IgK and IgL immunoglobulin (antibody genes) in B cells. This protocol uses a template-switch protocol, and does not rely on prior knowledge of monkey variable (V) genes, which remain largely uncharacterized. This protocol has been run for several users of the Genomics Core, and has been published in large-scale study of macaque vaccination Unpublished The Genomics Core runs a large Project on a consortium grant (UM1 AI124436) to conduct B cell repertoire analysis and understand mechanisms driving bone marrow retention of antibody-producing B cells.

2. To translate microbiome sequencing analyses to monkey models, and integrate microbiome studies into NHP applications including nutritional studies, veterinary monitoring, and SIV-vaccine trials.

We have conducted several microbiome studies for clients of the GenCore. We now have adapted microbiome sequencing to rhesus macaques and sooty mangabeys from Yerkes and are finalizing a manuscript on this work, and have begun analyses on African wild mangabeys. We have also been awarded an Emory Synergy award to conduct sequencing of host transcripts from wild-caught lemurs in Madagascar with the Emory Dept. of Environmental Science.

3. To establish single-cell transcriptomics (scRNA-Seq) for application in monkey models and offer single-cell technology to the NHP research community, and to develop specialized scRNA-Seq for SIV/HIV latently infected cells;

The Yerkes NHP Genomics Core has emerged as a leader in conducting single-cell RNA-Seq in NHP studies. We have developed and published novel bioinformatics methodology to reconstruct single-cell RNA-seq data into accurate antibody sequences for humans and rhesus macaques (Upadhyay 2018, https://doi.org/10.1186/s13073-018-0528-3). We have produced single-cell RNA-Seq data for several groups, and our work has resulted in several grants being funded featuring GenCore single-cell RNA-Seq and bioinformatics (U24 AI120134; R01 AI136533; R01 AI128837; renewal of U19 AI057266; UM1 AI124436) and several co-authored manuscripts (Havenar-Daughton 2018; bioRxiv 549014). The GenCore continues to invest in this area, and the Genomics Core has procured a Mosquito HV system and 10X Genomics Chromium platform to extend these services. We hosted a symposium on single-cell RNA-Seq in 2016, and have acquired funds to do the same in 2019.

4. To increase throughput, streamline project submission, billing and data retrieval for users;

Through recharges, we have acquired robotics systems (Agilent Bravo; expanded our suite of QIACube DNA/RNA prep stations) and expanded our technical staff to a peak of four bench technicians. We introduced cloud-based software for project management (SmartSheet) and for LIMS (Clarity). This reduced turnaround times to an average of 3 weeks in 2018.

5. To expand bioinformatics accessibility to the Yerkes community.

We have expanded to two full-time FTE bioinformaticists. During the period from 2015 to now, our lead bioinformaticist has been an author on 20 publications for GenCore clients.

B.4. Training and Professional Development Opportunities

Please see the overall component for response.

C. COMPONENT PRODUCTS

C.1 PUBLICATIONS

Not Applicable

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

Not Applicable

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

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

Not Applicable

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Nothing to report

D. COMPONENT PARTICIPANTS

Not Applicable

E. COMPONENT IMPACT

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

Not Applicable

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

Not Applicable

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

NOTHING TO REPORT

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?
Not Applicable

F. COMPONENT CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

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

NOTHING TO REPORT

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

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. COMPONENT SPECIAL REPORTING REQUIREMENTS

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

Not Applicable

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

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

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

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

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Not Applicable

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

RPPR - Core-8525

RESEARCH & RELATED BUDGET - SECTION A & B **FINAL**

ORGANIZATIONAL DUNS*: 066469933

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

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		Redacted by agreement				Project Lead	Institutional Base Salary	EFFORT			5,165.00	1,343.00	6,508.00
2						Genomics Core Asst Director					4,728.00	1,229.00	5,957.00

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

Additional Senior Key Persons: File Name:

Total Senior/Key Person **12,465.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
4	Staff Scientist, Informatics Specialist, Technician	7.2			42,350.00	11,011.00	53,361.00
4	**Total Number Other Personnel**					**Total Other Personnel**	**53,361.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**65,826.00**

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

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

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

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

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

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

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	15,000.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Maint/Repair	1,000.00
Total Other Direct Costs	**16,000.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**81,826.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. MTDC	45.0	81,826.00	36,822.00
		Total Indirect Costs	**36,822.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS, Steven Zuraf, (301) 492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**118,648.00**

J. Fee	Funds Requested ($)*
	0.00

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

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

Budget Justification

The budget request for the upcoming period is submitted in accordance with the peer reviewed P51 renewal approved in 2016. Justification for each budget category was also peer reviewed and approved at that time, and there is no significant change in this budget request from previously approved levels.

A. COMPONENT COVER PAGE

Project Title: BNPD

Component Project Lead Information:

Redacted by agreement

B. COMPONENT ACCOMPLISHMENTS

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

The mission of the Division of Behavioral Neuroscience and Psychiatric Disorders (BNPD) is to conduct basic and translational research to better understand the neurobiological mechanisms underlying behaviors relevant to developmental and psychiatric disorders, including autism spectrum disorders, anxiety-related disorders, depression, post-traumatic stress disorders, and addiction. Faculty in BNPD use a wide range of state-of-the-art approaches in rodent and nonhuman primate (NHP) models, including rhesus macaques and new world monkeys, as well as humans to make basic science discoveries with the ultimate goal of translating these discoveries into novel therapeutic strategies to improve mental health. Investigators in BNPD use techniques that include electrophysiology, molecular genetics, epigenetics, chemogenetics (DREADDs), optogenetics, and behavioral genetics to explore the neural mechanisms underlying behaviors relevant to psychiatric disorders. All investigators in the division use rodent models, including transgenic mice, voles, and rats for high throughput rapid discoveries with the ultimate goal of translating both the discoveries and technologies to NHPs. Investigators in BNPD collaborate closely with investigators in other divisions at Yerkes as well as other National Primate Research Centers and research institutions to facilitate translating novel discoveries and technology from rodent models to NHPs. BNPD is the home of two Centers that exemplify the flow of technology and discovery from rodents to NHPs and humans. The Center for Translational Social Neuroscience is an Emory-wide Center that brings together many investigators at Yerkes across all of the neuroscience divisions as well as across Emory whose research is focused on the behavioral and neurobiological bases of social behavior or on psychiatric disorders that are characterized by deficits in social cognition. Pilot project grants, seminars and journal clubs facilitate interaction and collaboration and create a vibrant intellectual and training environment. The Silvio O. Conte Center for Oxytocin and Social Cognition is more focused on the neural mechanisms by which oxytocin enhances social cognition in voles, rats, and rhesus macaques as well as healthy and autistic human subjects. This NIH-funded center involves several highly integrative projects using parallel approaches across species to understand how oxytocin influences social cognition. The Division is led by Redacted by [illegible] who is the only Core Scientist in the division. All other investigators in the division are Affiliate Scientists with appointments in the School of Medicine's Departments of Psychiatry, Pediatrics, or Pharmacology. All research projects involving rodents or humans are funded by investigator-initiated federal or private foundation sources. Division scientists are highly invested in training and outreach activities, ranging from training postdoctoral fellows and PhD students to public outreach and K-12 outreach.

The Specific Aims are:

1. To enhance our scientific programs of excellence in basic and translational behavioral neuroscience relevant to psychiatry through the use of state-of-the-art technology using animal models that allow rapid scientific discovery;

2. To facilitate collaborations across Yerkes divisions, at other National Primate Research Centers and research institutions across the nation to facilitate the translation of discoveries made within BNPD to novel research in nonhuman primates;

3. To continue our significant commitment to training the next generation of scientists through undergraduate, graduate, and postdoctoral programs and to foster community outreach educational efforts.

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

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: B2_8526 BNPD.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

Not Applicable

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

File uploaded: B4_c Training.pdf

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

Please see the Overall component for response.

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

Redacted by agreement

•Continue to validate and methodologically characterize a viral vector-based CRISPR approach to mutate the oxytocin receptor gene in the adult vole brain. We hope to submit a methods papers describing these results.
•Submit two manuscripts describing the association of single nucleotide polymorphisms or methylation patterns in the oxytocin receptor and social or affective behaviors in rhesus macaques.
•Continue to examine how oxytocin influences neural communication between the basolateral amygdala, nucleus accumbens and prefrontal cortex during social bonding in prairie voles using simultaneous electrophysiological and pharmacological techniques.
•Import oxytocin receptor knockout and oxytocin receptor CRE voles from Redacted by agreement in Japan and begin to utilize these genetically

engineered voles to manipulate specific populations of oxytocin receptor neurons to explore their role in social behaviors.
•Complete the analysis of the relationship between oxytocin receptor SNPs of outbred prairie voles to identify the SNP that has the greatest influence on nucleus accumbens oxytocin receptor expression.
•To submit manuscripts describing the distribution of oxytocin and vasopressin receptors in the brains of two species of baboons and of chimpanzees.
•Finalize the ATAC-Seq and Chromatin Immunoprecipitation (ChIP) assays to characterize the transcriptional landscape of the prairie vole oxytocin receptor gene.
•Submit several manuscripts describing the fMRI data from the intranasal oxytocin study in autistic subjects from the Conte grant.
•Develop viral vector methods to analyze social engrams in voles and to map connectivity of oxytocin receptor expressing neurons that are involved in social bonding or empathy.
•To determine the effect of oxytocin receptor signaling in synaptic plasticity processes in the nucleus accumbens and BLA of prairie voles using in vivo electrophysiology.

Redacted by agreement
•In the coming year, we will continue to develop a line of research aimed at understanding how regulation of the actin cytoskeleton – the structural lattice that forms the shape and motility of neurons and their dendritic spines – can impact complex decision making. We will be focusing intensively on b1-integrin, a cell adhesion receptor that forms an endogenous brake on cellular structural lability. We have characterized the behavioral significance of b1-integrin in the medial and lateral prefrontal cortex, particularly during adolescence, when neuronal structure is quite dynamic. We aim to finalize and publish reports describing our findings and identify whether and how cortico-amygdalar and cortico-striatal connections are impacted by b1-integrin.
•My NIMH R01 awards also support efforts aimed at understanding how the neurotrophin receptor trkB in the orbitofrontal cortex impacts experience-dependent dendritic spine plasticity, and understanding whether this plasticity is relevant to behavioral decision making and expectancy updating. In 2019, we will focus our efforts on the medial structure of the orbitofrontal cortex, interfering with trkB activity by over-expressing an inactive form of the receptor to sequester its ligand.
•In 2018, Redacted by agreement teamed with Yerkes investigator and Division Chief Redacted by agreement and became a Principal Investigator on Dr. Redacted by agreement NIH-funded Conte Center award. In 2019, we will test the hypothesis that prelimbic prefrontal cortical neurons are essential in transferring reward value derived from social interaction to external rewards, and that prelimbic neurons act by transferring value information to the basolateral amygdala, ultimately coordinating goal-oriented behavior.
•We find that cocaine decreases levels of NMDA receptor NR2B subunit, as well as the PI3-kinase catalytic subunit p110b, in the prefrontal cortex. Interestingly, experimental manipulations that inhibit their activities or levels, respectively, confer resilience to cocaine, suggesting that these modifications represent a manner in which the brain attempts to protect itself against the drug. We aim to publish reports describing these findings in 2019. We are also expanding our efforts to studying the behavioral functions of another PI3K catalytic subunit, p110d.

Redacted by agreement
•Using a mouse model of paternal stress Redacted Laboratory), two models of social stress in the non-human primate (NHP) Redacted by agreement and Redacted by agreement Laboratories), and in collaboration with the Yerkes Genomics Core, Redacted by agreement has been examining how stress experienced by mice and rhesus macaques alters miRNA in circulating exosomes, and sperm. We exposed mice to olfactory stress and sequenced RNA present in circulating exosomes and sperm. In addition, we isolated and sequenced RNA found in exosomes and sperm obtained from NHP that had been subjected to infant maltreatment and social subordination. We are in the process of analyzing these data and we are trying to replicate our sequencing results using qPCR. In so doing, we will illuminate conserved signatures of stress across species. We plan to submit manuscripts to report the results of this work.
•Examine how parental legacies of stress influence offspring at an epigenetic level using our mouse model of paternal stress. We are beginning to uncover the mechanisms via which stress exposure leaves imprints in the male germ-line.
Redacted by agreement will continue to work on examining the contribution of sub-thalamic influences on fear-related responses and examine whether the efficacy of exposure-based therapies can be increased, or catalyzed, by manipulating the activity of sub-thalamic circuitry. Redacted by agreement has written an NIH R01 grant to help fund this work and is waiting to hear about the outcome of this grant.

BNPD will initiate the process to recruit an additional faculty in collaboration with the Department of Psychiatry.

Each faculty will continue to be involved in training undergraduates, graduate students and postdoctoral fellows from a diverse background. These trainees will be encouraged to engage K-12 students through outreach programs in collaboration with the Atlanta Chapter of the Society for Neuroscience. PI's will seek out outreach opportunities to engage with the public about the importance of neuroscience research in mental health.

B.2. Accomplishments—BNPD

BNDP faculty have continued to be successful at our mission of conducting basic and translational research to better understand the neurobiological mechanisms underlying behaviors relevant to psychiatric disorders using state of the art technology, including DREADDs, optogenetics, and electrophysiology. We have continued to collaborate with other faculty at Yerkes and other institutions to translate our findings in rodents into primate research. We continue to have an excellent record training a diverse group of undergraduates, graduate students and postdoctoral fellows. A brief overview of each faculty's activities and accomplishment is provided below.

Redacted by agreement

Redacted by agreement has continued to explore the prospects of using CRISPR technology to edit the genome of prairie voles. In collaboration with Redacted by agreement in Japan, Redacted by agreement co-authored a manuscript describing the generation and partial characterization of the first CRISPR edited prairie vole. This report on behavioral phenotype of the oxytocin receptor knockout vole was published in *Hormones and Behavior*. In addition, Dr. Redacted by agreement laboratory has made progress in developing viral vector mediated CRISPR approaches to edit genomic DNA in the brains of adult prairie voles. Using AAV vectors to deliver *Cas9* and a guide RNA targeting the oxytocin receptor gene, Redacted by agreement group has promising data demonstrating that infected brain tissue has a reduction in oxytocin receptor binding two weeks after infection. Further validation of this approach is underway.

Redacted by agreement was awarded a new NIH R01 that provides funding to examine the role of single nucleotide polymorphisms in vole oxytocin receptor on variation in receptor expression in the brain. His group has made progress on two Aims in the grant. First, the Redacted by agreement lab obtained 14 new unrelated breeders derived from wild caught prairie voles in order to increase the diversity in their vole colony. The lab has collected brains and performed oxytocin receptor autoradiography on 40 male and 40 female offspring from breeder pairs consisting of the new outbred animals and our original colony. The oxytocin receptor gene from these animals has also been sequenced to identify SNPs. The lab is now analyzing oxytocin receptor binding in the social salience network and will determine which SNPs in the oxytocin receptor most strongly predict expression in the striatum. In addition, the lab has performed ATAC-seq in order to determine which SNPs are in open regions of the chromatin to help identify the SNPs that are most likely affecting expression. The lab is currently replicating this experiment to increase sample size and reliability.

Redacted by agreement successfully renewed the NIMH Conte Center for Oxytocin and Social Cognition. Resources from this grant were used to purchase badly needed equipment for the Division to meet the goals of this grant, including a new fluorescent microscope, a cryostat, centrifuge, microtome, etc. The lab has also purchased equipment necessary for fiber photometry analysis of calcium influx to monitor neural activity. Redacted by agreement upgraded equipment to enhance their electrophysiological analysis of the circuits underlying pair bonding in voles. Redacted by agreement published a new review article in *Nature Reviews Neuroscience* synthesizing recent papers from his lab and others on the neurobiology pair bonding and the role of oxytocin in social cognition. In collaboration with Redacted by agreement and Redacted by agreement co-authored a paper in *American Journal of Primatology* describing the distribution of oxytocin and vasopressin fibers in the cortex of rhesus macaques, chimpanzees and humans. Redacted by agreement also coauthored another paper in *American Journal of Primatology* with Redacted by agreement (a Conte Center faculty member) entitled "Bridging the gap between rodents and humans: The role of non-human primates in oxytocin research." Redacted by agreement co-mentors a PhD student with Redacted by agreement Redacted by agreement at Yerkes and together are investigating whether polymorphisms in, or epigenetic markers of, oxytocin receptors in the rhesus macaque are associated with variation in social behavior. The manuscript describing these results has been written and will be submitted soon. Redacted by agreement lab has made progress in mapping oxytocin and vasopressin receptors in the brains of baboons and chimpanzees and will make direct comparisons to rhesus macaques. Finally, Redacted by agreement has continued to make progress in a project, in collaboration with the Emory Autism Center and Redacted by agreement in which fMRI will be used to examine the effects of intranasal oxytocin on functional connectivity in the brain of autistic subjects. All of the brain imaging data from autistic and control subjects have been collected, and Redacted by agreement group is in the process of analyzing the imaging data and writing manuscripts describing the results.

Redacted by agreement became the PI of two R01's for which Redacted by agreement (a former BNPD Affiliate Scientist) was PI before he left the Division last year. These grants focus on the role of the bed nucleus of the stria terminalis and the basolateral amygdala on anxiety related behaviors. The transition is now complete and those projects are running smoothly under Redacted by agreement leadership. Lab members have used inhibitory DREADDs and optogentics to show that selective inhibition of BNST CRF neurons confers susceptibility to chronic social defeat stress, suggesting that activity of these neurons promotes resilience to chronic stressors.

Redacted by agreement

The majority of Redacted by agreement research in the last >10 years has focused on how the prefrontal cortex develops during adolescence, and how pathological events such as cocaine or stressors or social adversities can alter the trajectory of prefrontal cortical development. In 2018, Redacted by agreement was awarded the following awards to continue this research: A National Institute of Drug Abuse R01, a National Institute of Mental Health R01, and a pilot project grant from the Emory University Research Council. Redacted by agreement also became the Principal Investigator on a Project of Redacted by agreement NIH Conte Center grant. Her project aims to reveal the manner in which social experience influences instrumental (goal-oriented) decision-making. Social interactions undeniably influence complex decision making in adolescence, perhaps more so than at any other time in life; thus, the Redacted by agreement lab's work on this project again coheres with the lab's overall goal: To understand how the postnatal development and stabilization of specific cortico-limbic circuits impact complex, reward-related decision making during and after adolescence.

The lab's efforts in 2018 combined operant conditioning in young and adult mice with high-resolution single cell imaging (both *ex vivo* and *in vivo*) to identify how dendritic and dendritic spine plasticity associates with reward-related expectation and behavior. The lab also used biochemical techniques and viral-mediated gene manipulations to identify causal relationships between key proteins in the prefrontal cortex (and other structures) and their impact on reward-related decision making. The Redacted by agreement lab utilized chemogenetic strategies (DREADDs) to identify specific projections and cell types involved in reward-related decision making. Notably, combining strategies allowed Redacted by agreement for example, to identify the effects of key proteins involved in prefrontal cortical development on experience-dependent dendritic spine plasticity in specific brain regions and circuits, and whether this dendritic spine plasticity is functionally relevant to an animal's ability to navigate a complex environment.

In 2018, Redacted by agreement published the following manuscripts: Shapiro et al., 2018, *Neurobiol Dis*; Barfield and Gourley, 2018, *Neurosci Biobehav Rev*; Pitts et al., 2018, *Sci Rep*; Zimmermann et al., 2018, *Neuropsychopharmacology*; and Gross et al., 2019, *Neuropsychopharmacology*. Redacted by agreement team also Unpublished

Redacted by agreement

Redacted by agreement was selected as a CIFAR Azrieli Global Scholar – a global competition held by the Canadian Institute for Advanced Research that selected 15 exceptional early career researchers from across the globe for this award. He also received a FAPESP-SPRINT Award from University of São Paolo in collaboration with the Halle Institute of Global Learning to collaborate with Redacted by agreement - a world-renowned expert in the study of unconditioned fear responses. Using a mouse model of paternal stress, Redacted by agreement and his team discovered that it is possible to reverse the effects of F0 parental stress in F1 offspring at the level of structure and function in the offspring brain and in the sperm of the F0 generation. This manuscript was recently published in *Biological Psychiatry*. Using a mouse model of paternal stress Redacted by agreement and his team discovered that RNA contained in sperm of stressed males is sufficient to alter olfactory-related neuroanatomy and behavior in offspring. Additionally, the team discovered that parental stress can have adaptive influences on the behavior of offspring. This work has been deposited on bioRxiv and is currently under peer-review. Redacted by agreement (Yerkes Core Scientist) is a collaborator and co-author on the paper. Using auditory fear conditioning, Redacted by agreement and his team discovered that manipulating activity of a sub-thalamic brain region called the zona incerta can be used to suppress fear generalization, a pathological dimension of PTSD. This work has been deposited on bioRxiv and is currently under peer-review. Redacted by agreement is in his fourth year as faculty and Pending Support

Training/Outreach:

The three active laboratories in BNPD have trained 12 graduate students, 6 postdoctoral fellows and 7 undergraduates in the current funding period. These trainees include several URMs, at each level of training. BNPD trainees are actively involved in outreach activities to help generate an interest in neuroscience in K-12 students in the Atlanta Community. PhD students have organized the Atlanta Brain Bee as well as a booth at the Atlanta Science Festival, in collaboration with the Atlanta Chapter of the Society for Neuroscience. BNPD students manage a Lending Library of teaching materials in support of Brain Awareness activities in Atlanta Schools. Redacted by agreement has participated in multiple public lectures highlighting the science of the Division.

B.4. Training and Professional Development Opportunities

Please see the overall component for response.

C. COMPONENT PRODUCTS

C.1 PUBLICATIONS

Not Applicable

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

Not Applicable

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

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

Not Applicable

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Nothing to report

D. COMPONENT PARTICIPANTS

Not Applicable

E. COMPONENT IMPACT

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

Not Applicable

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

Not Applicable

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

NOTHING TO REPORT

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?
Not Applicable

F. COMPONENT CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

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

NOTHING TO REPORT

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

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. COMPONENT SPECIAL REPORTING REQUIREMENTS

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

Not Applicable

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

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

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

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

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Not Applicable

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

RPPR - Other-8526

RESEARCH & RELATED BUDGET - SECTION A & B **FINAL**

ORGANIZATIONAL DUNS*: 066469933

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

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		Redacted by agreement				Project Lead	Institutional Base Salary	EFFORT			9,480.00	2,465.00	11,945.00

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

Additional Senior Key Persons: File Name:

Total Senior/Key Person **11,945.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
1	Secretarial/Clerical	0.6			2,969.00	772.00	3,741.00
1	**Total Number Other Personnel**					**Total Other Personnel**	**3,741.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**15,686.00**

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

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

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

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

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

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

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	0.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
Total Other Direct Costs	**0.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**15,686.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. MTDC	45.0	15,686.00	7,059.00
		Total Indirect Costs	**7,059.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, Steven Zuraf, (301) 492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**22,745.00**

J. Fee	Funds Requested ($)*
	0.00

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

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

Budget Justification

The budget request for the upcoming period is submitted in accordance with the peer reviewed P51 renewal approved in 2016. Justification for each budget category was also peer reviewed and approved at that time, and there is no significant change in this budget request from previously approved levels.

A. COMPONENT COVER PAGE

Project Title: DCN

Component Project Lead Information:

Redacted by agreement

B. COMPONENT ACCOMPLISHMENTS

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

Faculty in the Division of Developmental and Cognitive Neuroscience (DCN) will continue their investigator-initiated, collaborative research programs focused on the neurobiology of social behavior and cognition across the life span, providing nonhuman primate models for various neuropsychiatric disorders, including developmental disorders such as stress and anxiety, depression, schizophrenia, autism spectrum disorders, ADHD, and obesity. The faculty use state-of-the-art technology (behavior, cognition, genetics, transient inactivation, and neuroimaging, including PET) to both manipulate neurobiology and capture resulting changes in complex social and cognitive behavior. Importantly, Core Scientists within the Division will continue to serve as an intellectual resource on the psychobiology of nonhuman primates for local, regional, national and international investigators. Each Core Scientist will provide expertise to outside investigators wanting to use Center resources and those who need advice and consultation. In addition, the Core Scientists will continue to be an integral part of the training and scientific community at Emory University, with their commitments to undergraduate and graduate education, and to foster productive and successful collaborative relationships with investigators throughout the Emory campus. Importantly, the Affiliate Scientists within the Division, whose academic appointments are elsewhere, also contribute actively to the mission of the Center. The ability of the Core Scientists within the Division to provide this expertise is derived from their successful individual, extramural-funded research programs that, as detailed in the following section of peer-reviewed projects, will continue in the next five-year funding period.

The Specific Aims are:

1. To use neural inactivation methodologies (permanent lesions, pharmacological or viral-vector inactivation) coupled with neuroimaging to understand the neural connections serving memory and cognition as well as socio-emotional behavior;

2. To expand the assessment of the importance of candidate genes in the expression of a range of phenotypes including regulation of emotion and stress, cognition, adolescent brain maturation, food preference and risk for obesity, and reproductive compromise;

3. To expand use of neuroimaging tools to better understand changes in neurochemistry and neural connectivity throughout the life span in response to a number of social contexts or endocrinological manipulations;

4. To implement new standardized testing (e.g. eye tracking) to more fully examine behavioral effects of interventions; increase ad libitum testing of a number of cognitive modalities of socially housed monkeys using automated testing kiosks; and pursue the development of video capture of spontaneous social behavior of corral-housed monkeys using high-resolution IP cameras;

5. To continue our strong commitment to mentor junior faculty, graduate and undergraduate students, and postdoctoral fellows pursuing a career in behavioral neuroscience and foster productive and successful collaborative relationships with investigators throughout the Emory campus and to remain active in community outreach by conducting tours of Yerkes facilities and speaking at Center-approved community seminars.

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

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: B2_8527 DCN.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

Not Applicable

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

File uploaded: B4_c Training.pdf

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

Please see the Overall component for response.

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

Aim 1: All funded developmental projects in the DCN require neurobehavioral follow-ups of the animals from birth to early adulthood, thus within each project further investigation of the animals at different time points and using different procedures will continue during the next funded period. We will also pursue our measurement of higher cognitive processes in monkeys and gather data on individual variation in memory performance within a large rhesus macaque population to examine what role genetic variation plays in these memory phenotypes.

Aim 2: We will pursue studies on genotyping for dopamine, serotonin, monoamine-oxidase and FoxP2 and renewals of grant on the effects of anesthesia on neurobehavioral development as well as on the impact of post-natal Zika infection on neurobehavioral

development have been submitted.

Aim 3: Studies are underway to determine the role of variation in individual genes that influences complex behavioral and metabolic phenotypes using both univariate and multivariate analysis to examine the interplay between genetic variation and age on metabolism, inflammation, oxidative stress and physiological phenotypes. Our goals is to continue behavioral phenotyping, collection of biological samples, and genotyping of another cohort of juvenile monkeys as well as building a web-based data warehouse to store all related data so that users may search and access data that has been collected to date. Grants are also being written to support the phenotyping/genotyping studies of the PhenX project at the Field Station.

Aim 4: New procedures we have developed using eye-tracking of infant monkeys and detailed ethograms to study mother-infant interactions are being used in our new studies of the P50 Autism Center of Excellence grant. This project is a unique translational initiative to perform simultaneous longitudinal studies of development of social contingency in both humans and NHPs infant-mother pairs, with a focus on identifying early sociovisual engagement alterations and their neural correlates that result in deficits in social function of relevance for ASD. The Division will also pursue its efforts on the development and adaptation of behavioral testing paradigms in infant monkeys of relevance to pediatric human psychopathology. The development of video capture of spontaneous social behavior of corral-housed monkeys using high-resolution IP cameras will be continued. Studies are underway to pilot new chemogenetic techniques using the inhibitory PSAMs for studying the neural substrate of diverse cognitive functions as well as social behavior while the animals are maintained in social groups and across developmental periods. Almost all active and pending grants in DCN involve a neuroimaging component and we will continue to use the state-of-the-art neuroimaging tools we have developed in projects initiated in the next funding period.

Aim 5: Faculty in the DCN will continue their extensive collaboration between the DCN members as well as Faculty from the NND and BNPD as well as with Faculty from the Microbiology and Immunology Division. All DCN faculty will dedicate strong commitment in mentoring and collaborations with junior faculty, graduate and undergraduate students and postdoctoral fellows pursuing a career in behavioral neuroscience and foster productive and successful collaborative relationships with investigators throughout the Emory campus; they will also remain active in community outreach by conducting tours of Yerkes facilities and speaking at Center-approved community seminars.

B.2. Accomplishments—DCN

Aim 1: ***Non-human primate models of neurobehavioral development using brain manipulations and neonatal behavioral perturbations***: Faculty have pursued several developmental models during this funding period that are relevant to human normal and abnormal neurobehavioral development. Redacted by agreement received funding (NICHD 5-years renewal; MPI: Redacted by agreement to initiate a new project assessing the critical developmental periods of hippocampal-prefrontal interactions and the consequences of their dysfunction during the adolescent period in male monkeys. These interactions have become of major interest to further understand the neurobiology of developmental neuropsychiatric disorders, such as schizophrenia, in which both neural regions are affected and associated with memory impairment that are generally refractory to treatment. During the first year of current funding,10 juvenile male monkeys were added to the study and have started the cognitive testing at the pre-pubertal time point. These animals received neuroimaging scans (sMRI, DTI and rsfMRI) and morphometric squeletal measurements, as well as regular blood samples to estimate the onset of puberty. Redacted by agreement has also received funding for the renewal of the Autism Center for Excellence NIH grant (P50, PI: Redacted by agreement to further characterize early cycles of social contingency with a strong focus on mother-infant reciprocal behaviors, early social predictors shaping later social development/competence and detect potential outlier cases for follow up studies, and map the unfolding maturation of neural networks mediating the behavioral changes. This year, four newborn male monkeys were added to the project and received eye-tracking to follow visual social attention, motor and sensory reflexes, mother-infant contingency cycles, and neuroimaging scans (sMRI, DTI and rsfMRI) at several time points between 1-24 weeks of age. The data provide a critically needed NHP model of early social development for Autism Spectrum Disorders (ASD) that will be used in further investigations targeting gene-behavior relationships and therapeutic interventions for ASD. Using translational NHP models of early life stress (ELS: adverse caregiving, social subordination stress) Redacted by agreement studies neurodevelopmental and biological mechanisms that translate early adversity/stress into developmental psychopathology, including anxiety disorders, drug addiction and social and cognitive deficits. During the last year, her studies (NIH NIDA DA038588 and NICHD HD077623 R01s) showed that ELS leads not only to persistent activation of stress endocrine systems from infancy through adolescence, but derails emotional development and underlying cortico-limbic brain networks regulating social, emotional and reward functions. In particular, weaker prefrontal cortex connectivity with amygdala and ventral striatum (detected using DTI and resting state fMRI) and alterations in serotonin (5HT) receptor binding in those brain regions (using PET imaging) are being tested as ELS neurobiological vulnerabilities to psychostimulant addiction using a cocaine self-administration paradigm during adolescence. The findings suggest that ELS animals are, indeed, more sensitive to cocaine, most likely due to alterations in reward and emotional/stress regulation neurocircuits. But, more importantly, pharmacological interventions targeting the 5HT2C receptor dose-dependently reduce cocaine intake, particularly in the ELS animals, offering a potential effective treatment for ELS individuals with increased sensitivity to psychostimulants, particularly during adolescence. The findings are important, as there is no current treatment for psychostimulant addiction in humans. Redacted by agreement has pursued her developmental studies assessing how maternal factors, such as stress and obesity (both known to alter glucocorticoid signaling and yield pro-inflammatory condition), influence the integrity of milk throughout lactation, leading to alteration of infant growth and health. In collaboration with Redacted by agreement her lab also identified additive impact of postnatal exposure to social subordination stress and highly caloric, obesogenic, diets on primate brain development, which worsens with age (NIH/NICHD R01 HD077623). Interestingly, these effects seem mediated by elevations in stress hormones and inflammatory markers. In an ongoing project (NIMH 2016 – 2021), Redacted by agreement (now retired)and collaborator Redacted by agreement (Georgia State University) are investigating whether social dominance is differently regulated in males and females. Within the subjectstudy, they tested the hypothesis that increasing central serotonin (5HT) concentrations via chronic fluoxetine administration will increase rates of aggression and reduce measures of stress reactivity in female monkeys. Preliminary data suggest that although fluoxetine treatment has a significant effect on specific behaviors (aggression and anxiety-like behaviors decreased) in subordinate females, the SSRI treatment has no effect on acute stress hormone regulation in response to social stressor in both dominant or subordinate female monkeys. Preliminary 5HT1AR PET data from this fluoxetine study show an increased 5HT activity following fluoxetine treatment in female monkeys prefrontal 5HT1A-BP in a status-dependent manner. **Dr.** Redacted by agreement and his team have determined that damage to the primate hippocampus does not affect spatial memory, as long as navigation is not required, and they are preparing for publication a large body of tests

assessing hippocampal function across many additional cognitive functions. They found that monkeys retroactively exert cognitive control over memory, and that monkeys can actively rehearse entirely novel images in working memory. His team is continuing to develop infrastructure for cognitive testing of large groups of animals at the Yerkes Field Station.

Aim 2: ***Non-human primate models of neurobiological development using perinatal drug administration and infection.*** Using resting-state fMRI, Redacted by agreement showed that acute intranasal oxytocin administration in adult male monkeys increased functional connectivity between the amygdala and brain regions involved in processing emotion and reward, but decreased the functional connectivity with other regions involved generally in social cognition. Chronic administration of intranasal oxytocin given between 2 and 24 months of age also showed some developmental changes between the connectivity of brain regions involved in social cognition using resting state fMRI. However, these neural changes were not correlated with any overt measurable changes in social behavior, nor was chronic intranasal oxytocin administration associated with structural changes in brain connectivity as measured using DTI. Redacted by agreement pursued her studies exploring the impact of early anesthesia, with another publication in British Journal of Anesthesia on impacts on socioemotional development and has used pilot data from an Emory URC- funded pilot study showing the early exposure to propofol in infant macaques also yields lasting socioemotional impairments. These data all contributed to preliminary results for the renewal of her NIMH grant (MPI with Redacted by agreement at Mt. Sinai SOM) studying the impact of early sevoflurane exposure and potential preventative treatments (to be reviewed Feb-March, 2019). Redacted by agreement from DCN Division and Redacted by agreement from the Microbiology & Immunology Division received funding from a Yerkes-P51 pilot to explore the impact of postnatal Zika virus exposure on behavioral and brain development. Their preliminary findings showed changes in socioemotional behavior at 6 months of age (Science Translational Medicine, 2018) that remain evident at 12 months of age Unpublished These socioemotional changes were also associated with memory impairment and persistent brain structural and functional alterations (sMRI and rsFMRI), including enlarged ventricles and altered functional connectivity between amygdala and hippocampus, areas involved in emotional and arousal regulation. These findings suggest the need for long-term clinical monitoring of postnatal Zika pediatric cases and have been used as preliminary results for a collaborative R01 submission with these same collaborators to investigate the window of postnatal vulnerability as well as test the utility of post-exposure prophylaxis with Zika hyperimmune globulin to prevent adverse neurodevelopmental consequences.

Aim 3: ***Assessment of the importance of candidate genes in the expression of a range of phenotypes***: In studies funded by NIA (2017 – 2022), Redacted by agreement with collaborators Redacted by agreement Duke Univ. and Barreiro, University of Chicago) began studies in Fall of 2017 to investigate how genotypic differences, endogenous signals (gonadal steroids, leptin), and exogenous signals (isoflavones) modify social-rank dependent immune response and whether the response to vaccination is affected by subordination induced chronic stress. This study is currently underway and there are no preliminary data to report. **Dr.** Redacted by agreement has also identified molecular markers of ELS exposure. In addition to a recent publication showing accelerated telomere length (TL) shortening during development -a molecular marker of cellular damage linked to negative health outcomes- her lab has recently discovered longitudinal epigenetic (methylation, non-coding RNA) changes in stress regulatory genes (FKBP5 and GR) caused by ELS and examined their association with stress reactivity and physiological and behavioral and drug abuse phenotypes, as well as transgenerational transmission from parents to offspring (funded by a NIH/NICHD R21 grant –HD088931- with Redacted by agreement McLean Hospital). Further research efforts in Biobehavioral Genetics/Epigenetics are targeting the epigenetic basis of transgenerational transmission of ELS-related phenotypes of relevance to affective/behavioral disorders and drug addiction. This involves a recently funded collaboration with Redacted by agreement Redacted by (BNPD Division) to examine ELS-related epigenetic changes (microRNAs) in the sperm of ELS males. Finally, Redacted by agreement has continued directing the initiative called “PhenX Identification of Unique Phenotypes at the Yerkes Breeding Colony”, spearheaded by the office of the YNPRC director) together with colleagues from the DCN division Redacted by agreement to perform a systematic and comprehensive characterization of behavioral, physiological and neurobiological phenotypes from the Yerkes breeding colony in order to enhance the development of NHP models of human health-related disorders and diseases, and to facilitate subject assignments to breeding programs and research projects. During this last year, two hours of behavioral observations were collected on 119 juvenile rhesus monkeys living in the breeding colony at the Field Station in parallel to blood samples collected and frozen for DNA and RNA expression patterns and genotyping as well as identify biomarkers. We have also collected two hours of

behavioral observations on all the sires of these 119 animals, as well sires from last year's cohort of 94 juveniles. Preliminary behavioral findings indicated the presence of extreme social and emotional phenotypes in a small group of animals investigated. In addition, DCN division faculty Redacted by agreement Redacted by agreement teamed up with researchers at the Marcus Autism Center Redacted by agreement and at Baylor School of Medicine Redacted by agreement to build a genetic NHP model of Autism Spectrum Disorder (ASD)-related social deficits utilizing the behavioral data and DNA from blood samples generated by the Yerkes PhenX initiative. These additional studies will help identify and catalog genetic variants in this clinically-relevant developmental macaque model for ASD, where extremes social phenotypes are being identified. With a Yerkes P51 pilot grant, we examined during the current year the associations of social behavior data with damaging genetic variants in published genes of risk for ASD in humans (using whole exome and whole genome sequencing). Intriguing preliminary findings suggest the presence of genetic variants in juvenile macaques in several genes linked to ASD in the Simons Foundation (SFARI) list, which were associated with extreme low social behavior in macaques (in particular with breaking social contact with other animals). A publication of the findings is underway, and submission of new grants has been initiated to pursue the phenotyping and genotyping of the colony.

Aim 4: ***Implementation of new technologies***. Several new technologies have been piloted and implemented during the last period. (a) Eye-tracking procedures have been developed to capture the development of visual social engagement in infant monkeys. b) Studies are ongoing to investigate the cost-saving potential and clinical application of automated feeders compared to the traditional bin system; (c) Redacted by agreement and collaborators have implemented an RFID-based automated tracking system for monkeys in social groups. Currently 28 monkeys are wearing 3D-printed collars (13 for more than a year without problems) containing 4 active RFID tags in a large social group at the Yerkes Field Station. Their housing compound has been instrumented with RFID sensors and automated tracking data. Four 4K-resolution video cameras controlled by the RFID system allows video tracking of individual collared monkeys coordinated with their RFID tracking data. We are currently working on identifying 'tracking signatures' for social behaviors from the tracking data; (d) Redacted by agreement has continued to develop chemogenetic tools in nonhuman primates (NHPs) and has recently published a preprint in BioRXiv (doi: https://doi.org/10.1101/534214; also under review at Journal of Neuroscience) demonstrating that inhibitory DREADDs (designer receptors exclusively activated by designer drugs) injected into the amygdala of infant monkeys can transiently inhibit amygdala neurons and impact socioemotional behavior on two tasks using two different ligands. Yet, more work is greatly needed on improving the DREADDs technique, since clozapine-N-oxide and low dose clozapine (current ligands available for DREADD activation) have great potential for off-target side effects. Therefore, Redacted by agreement is working toward NIH funding (June 2019 submission date) to investigate new DREADD ligands developed by Redacted by agreement at NIDA and is serving as a Co-I on an NINDS R21 with Redacted by agreement (PI) to investigate an artificial ion channel receptor (PSAMs, pharmacologically selective affector molecules) in NHPs, as an alternative efficient chemogenetic tool.

Aim 5: A new joint faculty position at Yerkes/Psychology Department has been initiated during the current year to hire a young scientist (tenure-track) with expertise in Nonhuman Primate Behavioral Neuroscience. Potential candidates have been selected and interviewed, an offer is in process. Core and Affiliate Scientists in the Division have remained active in the mentoring of junior faculty, graduate and undergraduate students, and postdoctoral fellows pursuing a career in behavioral neuroscience and foster productive and continued successful collaborative relationships with investigators throughout the Emory campus. During the current year, Redacted by agreement have initiated a monthly seminar series titled "Work in Progress" that brings together faculty, post-docs and students to discuss ongoing projects. In addition, all faculty remained active in community outreach by conducting tours of Yerkes facilities and speaking at Center-approved community seminars.

B.4. Training and Professional Development Opportunities

Please see the overall component for response.

C. COMPONENT PRODUCTS

C.1 PUBLICATIONS

Not Applicable

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

Not Applicable

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

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

Not Applicable

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Nothing to report

D. COMPONENT PARTICIPANTS

Not Applicable

E. COMPONENT IMPACT

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

Not Applicable

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

Not Applicable

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

NOTHING TO REPORT

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?
Not Applicable

F. COMPONENT CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

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

NOTHING TO REPORT

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

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. COMPONENT SPECIAL REPORTING REQUIREMENTS

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

Not Applicable

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

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

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

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

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Not Applicable

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

RPPR - Other-8527

RESEARCH & RELATED BUDGET - SECTION A & B **FINAL**

ORGANIZATIONAL DUNS*: 066469933

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

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		Redacted by agreement				Project Lead	Institutional Base Salary	EFFORT			9,480.00	2,465.00	11,945.00
2						Core Faculty					7,674.00	1,995.00	9,669.00
3						Core Faculty					9,480.00	2,465.00	11,945.00

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

Additional Senior Key Persons: File Name:

Total Senior/Key Person **33,559.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
1	Secretarial/Clerical	0.6			3,762.00	978.00	4,740.00
1	**Total Number Other Personnel**					**Total Other Personnel**	**4,740.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**38,299.00**

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

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

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

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

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

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

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	0.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
Total Other Direct Costs	**0.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**38,299.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. MTDC	45.0	38,299.00	17,235.00
		Total Indirect Costs	**17,235.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS, Steven Zuraf, (301) 492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**55,534.00**

J. Fee	Funds Requested ($)*
	0.00

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

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

Budget Justification

The budget request for the upcoming period is submitted in accordance with the peer reviewed P51 renewal approved in 2016. Justification for each budget category was also peer reviewed and approved at that time, and there is no significant change in this budget request from previously approved levels.

A. COMPONENT COVER PAGE

Project Title: M&I

Component Project Lead Information:

Redacted by agreement

B. COMPONENT ACCOMPLISHMENTS

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

Faculty in the Division of Microbiology and Immunology (M&I) apply a wide number of cutting-edge, interdisciplinary approaches in nonhuman primate (NHP) models to studies of the pathogenesis, prevention, and treatment of infectious diseases such as HIV & AIDS, hepatitis C, tuberculosis, group A streptococcus infection, and others. Scientists in M&I direct NIH-funded independent research programs and are heavily involved in productive and successful collaborative relationships with several research centers on the Emory campus, including the Emory Vaccine Center (EVC), the Center for AIDS Research (CFAR), and the Emory Transplant Center (ETC). In addition, faculty in M&I are very active in collaborative studies with extramural scientific institutions, both national and international (Scripps, Harvard, Penn, Rockefeller, Pasteur, and many others), to which they provide specific expertise and resources, mainly regarding the use of NHP models for studies of infectious diseases. Scientists within M&I also direct or advise a number of key core services, which include: (i) the Yerkes Virology Core, that plays a fundamental role in the colony management by testing the animals for agents such as Herpes B virus, STLV, SRV, SIV, and others; (ii) the Yerkes Genomics Core, which supports studies of NHP gene sequencing, expression and profiling by microarray as well as next-generation sequencing technology; and (iii) the CFAR Virology Core, that provides a broad range of virology assays for studies of HIV and SIV infections. Finally, scientists in M&I are an integral part of the training community at Emory University, with commitments to provide undergraduate, graduate and postdoctoral training and education, as well as community outreach efforts. In particular, they serve as members of the graduate faculty and as thesis advisors to students in the immunology, microbiology, and molecular pathogenesis programs at Emory University. The overarching goal of the M&I is to continue to develop new knowledge necessary to improve the prevention and treatment of infectious diseases that represent major threats to human health. To this end, the M&I faculty will continue to use and pioneer research techniques in the areas of cellular immunology, flow cytometry, basic virology, histology and immunohistochemistry, molecular biology, and genomics and genetics.

The Specific Aims are:

1. To enhance our scientific programs of excellence in the pathogenesis, prevention, and treatment of infectious diseases through the development and application of transformative scientific concepts, innovative technologies, and collaborative efforts with outside investigators at the national and international level;

2. To expand our focus to include a strong program in the area of tuberculosis, and to expand our current program in the area of HIV functional cure and eradication. This expansion will be conducted through active recruitment of several new faculty members for which significant resources have already been allocated;

3. To continue our significant commitment to training the next generation of scientists through undergraduate, graduate and postdoctoral programs and to foster community outreach educational efforts.

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

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: B2_8528 MI.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

Not Applicable

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

File uploaded: B4_c Training.pdf

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

Please see the Overall component for response.

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

M&I scientists will continue to pursue and further expand their highly productive, cutting-edge research programs through the development of innovative scientific concepts, state-of-the-art technologies (including cell and molecular biology, flow cytometry, histology and immunohistochemistry, confocal microscopy, basic virology, transcriptome analysis, and in vivo imaging), and collaborative efforts to address key questions on the host-pathogen interaction occurring during infectious diseases such as HIV infection and AIDS, hepatitis C virus (HCV), Zika virus, malaria, tuberculosis, group A streptococcus, and others. This research effort will continue to fully leverage the unique NHP resources of the Yerkes Center to directly test in vivo a range of concepts and products that are ultimately aimed at the prevention and therapy of these disease. In addition, M&I scientists will remain active at the national and international level with a wide range of collaborations with extramural colleagues, thus fulfilling the core mission of the Yerkes Center in terms of research resources and infrastructure. We do not anticipate any major problem in accomplishing this overarching set of goals given the well-established combination of expertise, technologies, and collaborations that is represented in the current portfolio of funded projects, or will hopefully be soon available for studies planned for the next funding period.

In addition, we will continue to enhance our scientific programs of excellence in the key areas of interest for M&I Core and Affiliate Scientists, which will continue to include: (i) studies of candidate HIV/AIDS vaccines, that will be conducted mainly as part of large collaborative program project grants and center grants; (ii) studies of novel approaches for HIV/AIDS eradication, that we envision will continue to be highly productive in terms of high profile publications and funding of NIH grant applications; (iii) studies of AIDS pathogenesis using the comparative models of pathogenic and non-pathogenic SIV infection of natural and non-natural SIV hosts; (iv) studies of HCV pathogenesis and prevention; and (iv) studies of other infectious agents/diseases, such as Zika virus, group A streptococcus, and others. M&I scientists will also continue to serve as a resource for outside investigators who wish to establish collaborations to pursue hypothesis-driven studies in the areas of microbiology and immunology using NHP models.

We anticipate that scientists in M&I will maintain the strong scientific production that has consistently characterized the activity of the Division over the previous funding cycle (2011-2015). In this regard, we wish to emphasize that M&I is currently very well balanced in terms of experience and career stages of its Core and Affiliate scientists, with a roster that includes established, world-class investigators with large extramurally-funded programs together with very promising early stage and mid career investigators. The upcoming addition of Redacted by agreement who will join the M&I Division in March 2019 as an Assistant Professor will further strengthen the Division. Further, Core Scientists within M&I will continue to direct or be actively involved in key core services with the Emory/Yerkes scientific community, including the Yerkes Virology Core, Genomics Core, and Biomarkers Core, as well as the Virology Core of the Emory Center for AIDS Research (CFAR). Finally, scientists in M&I will continue their significant commitment to training the next generation of scientists through undergraduate, graduate and postdoctoral programs and to foster community outreach educational efforts.

B.2. Accomplishments—M&I

Researchers in the Yerkes Division of Microbiology and Immunology (M&I) conduct studies in nonhuman primates (NHPs) that are focused on understanding the pathogenic mechanisms of infectious diseases to then explore and develop novel strategies to prevent and treat these infections. These studies use outstanding scientific expertise, cutting-edge technology, and state-of-the-art experimental models to ultimately improve our ability to prevent and treat diseases such as HIV/AIDS, hepatitis C, Zika virus, Group A streptococcus infection, and others. Scientists in M&I also hold faculty appointments at the Emory University School of Medicine, and at the Emory Vaccine Center (EVC), which is partly based within the Yerkes campus. The strong and productive interaction between M&I and EVC is emphasized by the fact that numerous EVC scientists are affiliated with M&I, and by the large number of funded projects and published articles featuring M&I and EVC scientists together. Finally, M&I scientists provide expertise to many national and international investigators seeking consultation or requesting use of Yerkes Center NHP resources for studies of infectious diseases.

Ongoing studies within M&I are focusing on the following key areas:

1. Preclinical and clinical development of novel HIV/AIDS vaccine candidates (effort led by Redacted by agreement & Redacted by agreement which include: (i) studies of novel adjuvanted DNA/MVA vaccines used in conjunction with native form of SIV or HIV envelope (Env), including newly designed gp120-trimers that induces very strong antibodies against the V1-V2 loop of HIV envelope and may confer enhanced protection from SHIVsf162p3 challenge; (ii) studies of the immunogenicity of novel HIV envelope-based candidate HIV vaccines in conjunction with novel adjuvants and novel immunogen delivery platforms; (iii) studies of novel immunogens designed to improve the durability of HIV-Env specific antibody responses. These accomplishments are conducted with the following awards: Consortium for Innovative AIDS Research in Non-Human Primates, NIH/NIAID UM1-AI1214436 (B and T Cell Biology of Protection from and Eradication of SIV/SHIV Infection); U19 AI109633 “Integrated Preclinical and Clinical AIDS Vaccine development (IPCAVD)”; U19 AI109646 “Synthetic DNA & Novel Env Vaccine for HIV” (collaboration with Wistar Institute, U. Penn); P01AI124912 “Durable Antibody Mediated Protection Against HIV” (collaboration with IHV & University of Maryland); UM1 AI100663 Center for HIV/AIDS Vaccine Immunology and Immunogen Design (CHAVI-ID, collaboration with Scripps); R01 AI25068 Maximizing germinal centers and somatic hypermutation to HIV Env immunogens” (collaboration with La Jolla Institute for Allergy and Immunology); and Private Source “Evaluate and compare the immunogenicity and safety of different homologous prime-boost regimens combining NYVAC-KC, NYVAC, DNA and protein/ASOI” (collaboration with CHUV Lausanne, Switzerland).

2. Basic discovery and preclinical development of novel approaches for HIV/AIDS eradication. These studies are led by Redacted by agreement and Redacted by agreement in collaborations with Redacted by agreement and affiliated scientists Redacted by agreement and Redacted by agreement as well as a number of external collaborators from University of North Carolina Chapel Hill, University of Pennsylvania, Harvard University, Duke University, and Case Western Reserve University, and are conducted under the umbrella of several NIH R01, R21/R33, and UM1 awards that were awarded in the past 1-3 years. The key projects focus on (i) targeting immunological pathways to achieve a functional cure for HIV infection, including the role of co-inhibitory molecules such as PD-1, CTLA4, LAG-3; cytokines such as Interleukin-21, Interleukin-15, Interferon-α, and molecular pathways such as SMC and STINGa; (ii) defining the role of CD8+ T cells in suppressing virus production and virus reactivation in the setting of long-term ART

3. Studies of AIDS pathogenesis using the comparative models of pathogenic and non-pathogenic SIV infection of rhesus macaques (RM) and sooty mangabeys (SM). These studies led to the completion—for the first time—of a high quality whole genome sequencing and assembly of the SM, with validation via RNA sequencing, and then a genome-wide comparative analyses of transcript assemblies with RM and humans. This analysis identified a C-terminal frameshift in the SM TLR4 gene, associated with blunted *in vitro* response to TLR4 ligands, and a major structural change in exons 3-4 of ICAM-2, which abrogates its cell surface expression. These data provide a novel resource for comparative genomic studies of HIV/SIV pathogenesis and may elucidate the mechanisms by which SIV-infected SMs avoid AIDS. We are now extending this work

by targeting ICAM-2 and TLR4 in SIV-infected macaques and the de novo genomic sequencing of three additional non-human primate species.

4. Studies of Hepatitis C Virus (HCV) pathogenesis and prevention, led by Redacted by agreement with a major focus on the dynamics of antigen-specific B and Tfh responses during acute and chronic infection, remain a key areas of research effort with the M&I Division. His laboratory developed a novel tetrameric form of the HCV E2 glycoprotein ectodomain to enable visualization and isolation of E2-specific B cells from HCV patients with separate infection outcomes. This work led to the hypothesis that a rapid induction of Tfh responses accelerates the expansion of HCV-specific B cell clones producing broadly neutralizing antibodies that contribute to resolution of infection Redacted by agreement lab was awarded two new NIH R01 proposals on the dynamics of antigen-specific B cell responses during acute and chronic HCV, and on the persistence of HCV replication and T cell immunity in pregnancy (total of five active NIH R01s studying the interaction between chronic viral infection and the immune system.). Of note, recent research efforts on elucidating the role of T and B cell responses during pathogenesis of hepatitis E virus in non-human primates were conducted in collaboration with Redacted by agreement (OSU). The use of the non-human primates at Yerkes provided the preliminary data for a multiple PI NIH proposal submission in the near future.

5. Studies of Zika virus infection in infant rhesus macaques, with focus on the development of persistent neurocognitive abnormalities and neuropathology and testing the protective efficacy of Zika virus-specific neutralizing antibodies and candidate vaccines.

B.4. Training and Professional Development Opportunities

Please see the overall component for response.

C. COMPONENT PRODUCTS

C.1 PUBLICATIONS

Not Applicable

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

Not Applicable

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

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

Not Applicable

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Nothing to report

D. COMPONENT PARTICIPANTS

Not Applicable

E. COMPONENT IMPACT

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

Not Applicable

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

Not Applicable

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

NOTHING TO REPORT

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?
Not Applicable

F. COMPONENT CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

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

NOTHING TO REPORT

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

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. COMPONENT SPECIAL REPORTING REQUIREMENTS

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

Not Applicable

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

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

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

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

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Not Applicable

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

RPPR - Other-8528

RESEARCH & RELATED BUDGET - SECTION A & B **FINAL**

ORGANIZATIONAL DUNS*: 066469933

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

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		Redacted by agreement				Project Lead	Institutional Base Salary	EFFORT			1,896.00	493.00	2,389.00
2						Core Faculty					1,896.00	493.00	2,389.00
3						Core Faculty					9,480.00	2,465.00	11,945.00
4						Core Faculty					7,584.00	1,972.00	9,556.00

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

Additional Senior Key Persons: File Name:

Total Senior/Key Person **26,279.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
1	Secretarial/Clerical	0.6			2,649.00	689.00	3,338.00
1	**Total Number Other Personnel**					**Total Other Personnel**	**3,338.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**29,617.00**

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

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

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

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

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

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

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	0.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
Total Other Direct Costs	**0.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**29,617.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. MTDC	45.0	29,617.00	13,328.00
		Total Indirect Costs	**13,328.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, Steven Zuraf, (301) 492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**42,945.00**

J. Fee	Funds Requested ($)*
	0.00

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

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

Budget Justification

The budget request for the upcoming period is submitted in accordance with the peer reviewed P51 renewal approved in 2016. Justification for each budget category was also peer reviewed and approved at that time, and there is no significant change in this budget request from previously approved levels.

A. COMPONENT COVER PAGE

Project Title: NND

Component Project Lead Information:

Redacted by agreement

B. COMPONENT ACCOMPLISHMENTS

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

Faculty in the Division of Neuropharmacology and Neurologic Diseases (NND) use interdisciplinary approaches in nonhuman primate models to study a variety of translational problems in neuroscience including neurodegenerative diseases (Parkinson's, Huntington's, Alzheimer's), basal ganglia and motor function, neurobiology of drug addiction, and evolutionary biology. Our long-term goal is to develop new knowledge necessary for improved treatment of specific neurological and psychiatric disorders. Research techniques include behavioral models, neuropharmacology, neurochemistry, neuroanatomical mapping, electrophysiology, in vivo microdialysis, gene expression and profiling, transgenic models, optogenetics and functional brain imaging. The Yerkes Imaging Core plays a fundamental role in the NND, and faculty within the Imaging Core have appointments as Core Scientists or Affiliate Scientists within NND. Core Scientists within NND serve as an intellectual resource for the study of neuroscience in nonhuman primates for local, regional, national, and international investigators. Each staff scientist provides expertise to outside investigators seeking consultation or requesting use of the Yerkes Center resources. In addition, the Core Scientists are an integral part of the training and scientific community at Emory University with commitments to provide undergraduate, graduate, and postdoctoral training and education and foster productive and successful collaborative relationships with other investigators on the Emory campus. Most research scientists in NND are members of the graduate faculty at Emory University and serve as thesis advisors to students in the neuroscience and the molecular and systems pharmacology training programs. Lastly, there is a strong commitment to community outreach efforts at local area schools and educational organizations.

The Specific Aims are:

1. To enhance our scientific programs of excellence in neurodegenerative diseases, drug addiction and evolutionary biology through the development and application of innovative technologies and collaborative efforts with outside investigators at the national and international level;

2. To expand our focus to include a strong program of research in stroke and neurovascular function in the context of functional brain imaging through the active recruitment of an endowed faculty appointment;

3. To continue our significant commitment to training the next generation of scientists through undergraduate, graduate, and postdoctoral programs and to foster community outreach educational efforts.

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

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: B2_8529 NND.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

Not Applicable

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

File uploaded: B4_c Training.pdf

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

Please see the Overall component for response.

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

DNND scientists will continue to enhance their research programs through the development of innovative technologies and collaborative efforts. Optogenetic and chemogenetic techniques will be further refined and employed to interrogate specific neuronal subtypes and projection systems in normal and MPTP-treated parkinsonian rhesus monkeys. Along the same line, ongoing work will continue to develop new viral vector-based approaches that allow selective targeting of neuronal subpopulations in the basal ganglia, cortex, brainstem and thalamus of rhesus monkeys. Redacted by and her colleagues will advance optogenetic, pharmacological and gene therapy studies using new tools with high selectivity for AMPA and NMDA receptor subunits or auxiliary proteins to regulate overactive glutamatergic transmission that impinges upon specific neuron subtypes in the striatum of parkinsonian monkeys. We will also pursue our efforts in the development of new monkey models of PD based on the overexpression of alpha-synuclein, hoping that such models can provide us a tool to assess neuroprotective interventions towards the loss of midbrain dopaminergic neurons in rhesus monkeys. Members of the Emory Udall Parkinson's Disease Center Redacted by agreement will continue to play a significant role in fostering collaborations with outside investigators. Additional studies will focus on the development of transgenic reporter cells for noninvasive MRI, and the development of personal stem cells for cell therapy. Redacted by and his colleagues will continue their in vitro spermatogenesis work to provide new alternate methods to create transgenic nonhuman primates and innovative male fertility treatments. We will further support Redacted by objective in developing a new nonhuman primate model of ischemia, which could place the Yerkes Center at the forefront of research on cerebral ischemia in the world. The main goal of Redacted by agreement team over the coming year is to

begin a research program on neurorepair using a nonhuman primate model of cerebral ischemia and to launch an new area of inquiry focused on dementia and cerebrovascular diseases. Redacted by team has just completed a significant upgrade of the 7T scanner which will allow him to test new stroke imaging protocols using new gradient with high order shims Redacted by will expand his anatomical work on the localization of oxytocin and vasopressin projection systems to forebrain regions of various primate species and will apply for new funding to support his national resource of NHP tissue and MRI scans Redacted by research goals for the coming year are to develop advanced and fast multi-shell diffusion MRI techniques for examining the grey matter and white matter integrity and structural connectivity of NHP brains with neurodegenerative diseases and study neuroprotective effects of hypothermia treatement on NHP brains with stroke. He also plans to develop MRI techniques for monitoring physiological and functional alteration of the brain with mild traumatic brain injury (TBI).

NND faculty will continue their significant commitment to training the next generation of scientists through undergraduate, graduate, and postdoctoral programs and to foster community outreach educational efforts. As noted above, DNND Core Scientists and Affiliate Scientists are an integral part of the training and scientific community at Emory University with commitments to provide undergraduate, graduate, and postdoctoral training and education. Our faculty are highly engaged in seminars, lectures in ethics, student retreats and other program activities. Our faculty also host undergraduate students through various mechanisms to gain research experience during the summer months. There is also a strong commitment to community outreach efforts at local area schools and educational organizations. Many of these activities are coordinated through the Yerkes Office of Public Affairs and focus on educating the public on the importance of animal and nonhuman primate research in science and medicine. Our faculty are committed to continue these efforts in training and community outreach.

B.2. Accomplishments—Division of Neuropharmacology and Neurologic Diseases (DNND)

Researchers in the Yerkes Division of Neuropharmacology and Neurologic Diseases (DNND) are working to advance the understanding of brain function through studies focusing on the development and function of the nervous system and anatomical differences seen when neurological disorders are present. Faculty in the Division use interdisciplinary approaches in nonhuman primate models to study a variety of translational problems in neuroscience, including neurodegenerative diseases (Parkinson's, Huntington's and Alzheimer's), basal ganglia and motor function, neurobiology of drug addiction, stroke biology and therapeutics, anti-seizure therapies, and evolutionary biology. Our long-term goal is to develop the knowledge necessary for improved treatment of specific neurological and psychiatric disorders. Our scientists are highly collaborative with researchers in other Yerkes Divisions, and they provide expertise to regional, national and international investigators seeking consultation or requesting use of Yerkes Center resources.

Three DNND faculty members Redacted by agreement are part of the Udall Parkinson's Disease Center at Emory University (NIH/NINDS P50, PI: Redacted by agreement 2016-2021), which focuses on translational studies of the basal ganglia-thalamocortical circuitry and the development of new medication therapies for Parkinson's disease. During the past funding period, they used cutting edge anatomical, electrophysiological and optogenetic approaches to further study the neuroplastic changes that the thalamocortical cand corticothalamic systems undergo in the parkinsonian state. At the anatomical level, they provided direct evidence for significant thalamic denervation of deep cortical layers of motor cortices in parkinsonisn monkeys accompanied with significant remodeling of remaining corticothalamic afferents. In addition, they demonstrated pruning and morphological changes of corticothalamic terminals in the ventral motor thalamus of parkinsonian animals. These structural changes were associated with aberrant physiological responses of cortical and thalamic neurons to their synaptic afferents, thereby providing evidence that pathological changes of motor thalamo-cortico-thalamic loops may contribute to the pathophysiology of the basal ganglia-thalamocortical systems in Parkinson's disease. Some of these findings were presented at the 2108 Society for Neuroscience meeting in San Diego. Another main interest of this group has been to optimize optogenetic and chemogenetic approaches to modulate specific motor-related neural circuits in the monkey brain. These efforts recently led to the submission of a manuscript showing that the plasma membrane expression of Designer-Receptors Exclusively Activated by Designer Drugs (DREADDs) in monkey, but not in rodent, neurons depends on the DREADD/tag combination. These findings are critical to the interpretation of findings gathered by investigators who use chemogenetic approaches in primates. In addition to their Udall Center-related work Redacted by agreement have also pursued work funded through two additional NIH R01 grants, namely the characterization of the functional anatomy and neuroplasticity of the relationships between the brainstem pedunculopontine nucleus, basal ganglia and lower brainstem motor centers, and the characterization of the anatomical and functional cellular heterogeneity of the external globus pallidus (GPe) in control and MPTP-treated parkinsonian monkeys. Redacted by agreement (Yerkes core scientist) continued their analysis of the behavioral consequences of thalamic lesion in rhesus monkeys supported by a R03 NIH grant. The rationale of this project relies on pathological evidence that a specific group of caudal intralaminar thalamic nuclei in humans undergoes profound neuronal loss in Parkinson's disease (PD), and that this pathology may contribute to early cognitive impairments in PD. Three rhesus monkeys that have undergone selective lesion of the thalamostriatal system are currently being used in this project. Overall, Drs. Redacted by agreement have authored twelve peer-reviewed publications in 2018.

During the past year, Redacted by agreement has continued her work on the characterization of changes in neuronal activity the striatum undergoes in MPTP-treated parkinsonian monkeys. Her most recent studies focused on the study of cortical glutamatergic dysregulation of afferents to specific striatal neuron subtypes in parkinsonian monkeys. In the past year, she generated preliminary data required for the renewal of her NIH R01 grant and the application of a new R21 grant (in collaboration with Redacted by agreement to assess new gene therapy approaches that could dampen the abnormal increase in striatal glutamatergic transmission in the parkinsonian state. Results of these studies will contribute to developing therapies that target selective glutamatergic mechanisms and improve motor function in Parkinson's disease. Redacted by agreement and her colleagues published four peer-reviewed manuscripts related to this work during the past year.

Through financial support from his R24 grant, Redacted by agreement continued his work on the behavioral and pathological characterization of the nonhuman primate transgenic model of Huntington's disease (HD) developed in his laboratory. One of his most recent works, achieved in collaboration with Redacted by agreement (Yerkes core scientist), showed that the pattern of cell loss that affects projection neurons and interneurons in the striatum of transgenic HD monkeys is reminiscent of what has been reported in HD patients. These

findings were recently published in Scientific Reports. Redacted by agreement also pursued his R21-funded work to develop alternative fertility treatment for males who cannot produce sperm or those that may have cancer and receive chemo or radiation therapy that might impact their fertility. The results of this new in vitro spermatogenesis program may impact upon a broad range of therapeutic and research interventions (alternative fertility treatment, transgenerational paternal inheritance model, paternal genome instability, alternate methods to create transgenic animals, etc.) Redacted by agreement and his colleagues published four peer-reviewed manuscripts related to this work in 2018.

Redacted by agreement and his team continued his comparative neuroanatomy work among monkeys, chimpanzees and humans. During the past year, he and his colleagues completed a comparative study of oxytocin (OT)- and vasopressin (AVP)-containing neurons and fiber distribution in humans and nonhuman primates, which provided the first evidence that OT- and AVP-containing fibers innervate the cerebral cortex in primates. They also continued to develop and promote the collection of postmortem brain tissue and archived MRIs, along with a web-based inventory workers can browse to identify and request materials. Supported by a R24 (NS092988) grant, this tissue bank has become an important resource for the scientific community, being used in 24 published papers, with others in the pipeline. He also continued collaborations with external investigators on comparative methylomics and comparative connectivity.

Redacted by agreement recent achievements in the use of MRI to study brain network pathology in various diseased states include evidence that the mean diffusivity (MD) of fiber tracts may be a sensitive marker to monitor the early white matter changes following stroke insult. They also showed that Neuregulin-1 may have neuroprotective effects on white matter fibers using a rat model of stroke and that changes in Diffusion Tensor Imaging (DTI) indices are correlated with the reduction of the corpus callosum area and memory impairment in rhesus monkeys with neonatal hippocampus lesion. Redacted by agreement authored six original manuscripts in 2018.

Redacted by agreement who recently jolined the Yerkes Primate Center as Director of the Imaging Center, has collected large amount of preclinical stroke imaging data before the transition from Harvard to Emory. Using calibrated pH-weighted MRI toward absolute tissue pH Imaging during acute stroke, he and his colleagues showed graded and heterogeneous tissue pH change in ischemic core, penumbra and benign oligemia region. Unpublished In addition Redacted by agreement and Redacted by agreement (Dept. Radiology, Emory) were recently awarded a collaborative Emory Synergy grant to implement and test Diffusion Kurtosis Imaging (DKI) in stroke patients. Redacted by agreement authored eleven stroke and MRI-related peer-reviewed manuscripts in 2018.

Redacted by agreement the Yerkes Center's first endowed chair in the field of stroke, holds a joint academic appointment between Neurology and the Yerkes Center. He moved his research laboratory to the Yerkes Center in 2017 to launch a new program to develop a reproducible nonhuman primate model of cerebral ischemia in which the ischemic tissue is accessible to neuroprotective agents administered through the intravascular compartments. During the past year, he and his team discovered that binding of a protease, known as urokinase-type plasminogen activator, to its receptor induces the regrowth of axons that have been harmed by an ischemic injury. They have found that this improves the neurological outcome following an ischemic stroke. Another important finding that his work led to is evidence that the plasminogen system protects synapses in the ischemic brain by maintaining its structure and function. Redacted by agreement and his colleagues have published ten stroke-related peer-reviewed manuscripts in 2018.

Redacted by agreement main research interests are to characterize the behavioral consequences of neocortical or temporal seizures, and to assess the therapeutic effects of hippocampal asynchronous stimulation on temporal lobe seizures in monkeys. During the past year, she recorded and stimulated from the hippocampus and evaluated the effect of seizures induction and interictal activity on short-term memory in her rhesus monkey model of mesial temporal epilepsy. She also obtained preliminary data about the implication of the substantia nigra pars reticulata in medial temporal lobe epilepsy in this model. Furthermore, she collected new exciting data showing a strong implication of the thalamo-cortical loop in neocortical seizures.

Lastly, DNND Core and Affiliate Scientists are an integral part of the training and scientific community at Emory University with commitments to provide undergraduate, graduate, and postdoctoral training and education. Most scientists in DNND are members of the graduate faculty at Emory University and serve as thesis advisors to students in the neuroscience and pharmacology training programs. This has proven to be an excellent opportunity for students to interact with well-known researchers in their field of interest. Moreover, the Udall Center provides educational opportunities for students, postdoctoral fellows, and neurology/neurosurgery residents and fellows, such as lectures and hands-on training. Members of DNND are also heavily involved in public outreach efforts to discuss the relevance of their work to help advance knowledge and treatment of human brain diseases.

B.4. Training and Professional Development Opportunities

Please see the overall component for response.

C. COMPONENT PRODUCTS

C.1 PUBLICATIONS

Not Applicable

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

Not Applicable

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

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

Not Applicable

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Nothing to report

D. COMPONENT PARTICIPANTS

Not Applicable

E. COMPONENT IMPACT

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

Not Applicable

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

Not Applicable

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

NOTHING TO REPORT

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?
Not Applicable

F. COMPONENT CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

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

NOTHING TO REPORT

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

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. COMPONENT SPECIAL REPORTING REQUIREMENTS

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

Not Applicable

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

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

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

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

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Not Applicable

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

RPPR - Other-8529

RESEARCH & RELATED BUDGET - SECTION A & B **FINAL**

ORGANIZATIONAL DUNS*: 066469933

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

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		Redacted by agreement				Project Lead	Institutional Base Salary	EFFORT			9,480.00	2,465.00	11,945.00
2						Core Faculty					8,077.00	2,100.00	10,177.00
3						Core Faculty					6,266.00	1,629.00	7,895.00
4						Asc Dir, Scientific Programs					3,792.00	986.00	4,778.00

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

Additional Senior Key Persons: File Name:

Total Senior/Key Person **34,795.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
1	Secretarial/Clerical	0.6			3,536.00	919.00	4,455.00
1	**Total Number Other Personnel**					**Total Other Personnel**	**4,455.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**39,250.00**

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

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

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

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

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

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

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	0.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
Total Other Direct Costs	**0.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**39,250.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. MTDC	45.0	39,250.00	17,662.00
		Total Indirect Costs	**17,662.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS, Steven Zuraf, (301) 492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**56,912.00**

J. Fee	Funds Requested ($)*
	0.00

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

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

Budget Justification

The budget request for the upcoming period is submitted in accordance with the peer reviewed P51 renewal approved in 2016. Justification for each budget category was also peer reviewed and approved at that time, and there is no significant change in this budget request from previously approved levels.

A. COMPONENT COVER PAGE

Project Title: Pilot Projects

Component Project Lead Information:

Redacted by agreement

B. COMPONENT ACCOMPLISHMENTS

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

The overarching goal of the Yerkes Pilot Research Project Program is to support innovative biomedical or behavioral pilot research projects involving nonhuman primates. The process of obtaining NIH funding for translational research projects involving nonhuman primates in today's funding environment is extremely challenging. The success rates of NIH proposals remain quite low and without preliminary data, the prospects for funding are negligible. Moreover, the barriers to generate preliminary data for research projects involving nonhuman primates, especially for investigators not previously experienced in nonhuman primate research, are considerable. However, the continued advancement of translational research requires a sustained influx of new ideas, new approaches and new investigators. The goal of the Yerkes Pilot Research Program is to facilitate the translation of new ideas and new approaches, as well as the involvement of new investigators into NIH-funded research proposals involving nonhuman primates. These projects, by their nature, are developmental and higher risk, but also high reward, in that they form the foundation for future grant proposals and for future advances in the use of nonhuman primate models to address basic and translational problems in human health.

The Specific Aims are:

1. To promote basic and translational biomedical and behavioral pilot research projects involving nonhuman primates;

2. To promote these developmental projects by providing both seed funding and the critical expertise of Yerkes Core Scientists in the conduct of nonhuman primate research and the development and optimization of nonhuman primate disease models;

3. To support the career development of young investigators by prioritizing the funding of young investigators without prior R01-equivalent funding.

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

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: B2_8530 Pilots.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

Not Applicable

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

File uploaded: B4_c Training.pdf

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

Please see the Overall component for response.

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

The Pilot Research Program RFA for the next project period will be released in December 2019. The RFA will be broadly distributed, both within the Emory community and beyond, as described in detail under the Accomplishments section (B2). In addition, the announcement will be distributed nationally by posting on the Yerkes website as well as the NPRC Consortium website hosted by Redacted by Redacted by agreement

Following the receipt of applications, the review of applications will be carried out by the Yerkes National Scientific Advisory Board (NSAB). Each application will be reviewed by at least 3 NSAB members, who are asked to provide an overall impact factor using the standard NIH 1-9 scale, and using the standard review criteria, along with brief written comments. The collated scores and comments will be reviewed by the Center Director and the Associate Director for Scientific Programs for the selection of final projects. Applications from early career investigators will be given particular consideration. Applicants will be notified and projects initiated in May 2020.

We will continue to explore ways to increase the breadth of distribution of the Yerkes Pilot Project RFA, especially to engage investigators outside Yerkes and those who have not previously used nonhuman primates.

B.2. Accomplishments—Pilot Research Program

Overview

The goal of the Yerkes Pilot Research Program is to facilitate the translation of new ideas and new approaches, as well as the involvement of new investigators into NIH-funded research proposals involving nonhuman primates. These projects, by their nature, are developmental and higher risk, but also high reward, in that they form the foundation for future grant proposals and for future advances in the use of nonhuman primate models to address basic and translational problems in human health.

The Specific Aims, which are unchanged, include:

1. To promote basic and translational biomedical and behavioral pilot research projects involving nonhuman primates.
2. To promote these developmental projects by providing both seed funding and the critical expertise of Yerkes Core Scientists in the conduct of nonhuman primate research and the development and optimization of nonhuman primate disease models.
3. To support the career development of young investigators by prioritizing the funding of young investigators without prior R01-equivalent funding.

Description of the Pilot Project Program

The Yerkes Pilot Project Program is operated in accordance with the Office of Research Infrastructure Programs (ORIP) guidelines and designed to fund projects that aim to solve problems related to human health, as well as paving the way for subsequent independent grant support. The Yerkes Pilot Research awards each currently provide one year of support, up to $70,000 in direct costs. In addition, projects must meet the following criteria:

- Pilot research funds may not be used to provide interim support for established projects or for investigations funded from other sources;
- All Pilot Research Projects must be planned, conducted, and carried out under the supervision of at least one Core Scientist at the NPRC. A Core Scientist must assume responsibility for overall management, coordination and progress reports;
- All activities related to the use of NHPs must be conducted on-site at Yerkes. Other activities can be performed at other sites, depending on the nature of the pilot project.

The Pilot Research Program RFA is released in December. The RFA is broadly distributed, both within the Emory community and beyond. The RFA is distributed to the Emory School of Medicine Faculty listserv, the Yerkes Faculty listserv, the Emory CFAR listserv, the listserv for the Georgia CTSA, as well as the listserv for the Woodruff Health Science Research Administrators (which includes the School of Medicine, the Rollins School of Public Health, the School of Nursing and the Winship Cancer Center) and also to the Research Deans of the Laney Graduate School and the Emory College of Arts and Sciences for distribution to their faculty. These research administrators and/or Deans in turn distribute to their internal and external distribution lists. It is also distributed to the Atlanta Veterans Affairs Medical Center. In addition, the announcement is distributed nationally by posting on the Yerkes website as well as the NPRC Consortium website hosted by Redacted by agreement

Following the receipt of applications, the review of applications is carried out by the Yerkes National Scientific Advisory Board (NSAB). Each application is reviewed by at least 3 NSAB members, who are asked to provide an overall impact factor using the standard NIH 1-9 scale, and using the standard review criteria (Significance, Approach, Innovation, Investigator, Environment), along with brief written comments. The collated scores and comments are reviewed by the Center Director and the Associate Director for Scientific Programs for the selection of final projects. Applicants are then notified and projects are typically initiated in May.

We received 12 applications for our 2018 cycle of pilot projects. Following review by our NSAB, the three projects below (which include two PIs outside of Yerkes), were selected for funding. Project summaries for each of these projects follow.

Modulation of type I IFN signaling to reduce the immunogenicity of recombinant AAV vectors

PI: Redacted by agreement University of Miami Core Scientist: Redacted by agreement

Infusions of HIV-1-specific broadly neutralizing antibodies (bNAbs) have been shown to suppress viremia in infected individuals, and clinical trials are ongoing to assess the prophylactic potential of bNAbs. Although these results are very promising, passive immunization is impractical to prevent or treat HIV infection in millions of people. In view of these obstacles, rAAV-mediated transfer of genes encoding bNAbs offers an attractive, cost-effective, and safe alternative to passive delivery of bNAbs. The utility of AAV as a gene therapy vector stems from its non-pathogenicity and ability to transduce both dividing and non-dividing cells. Additionally, the only protein expressed from rAAV vectors is the transgene product and, as long as it is viewed as “self” by the immune system, transgene expression can persist for long periods of time. Since muscle cells undergo little or no turnover, they are a preferred target for rAAV-mediated gene transfer. Little or no integration occurs in rAAV-transduced cells and rAAV vectors have been well tolerated in past clinical trials. Unfortunately, harnessing the full potential of rAAV as a vector platform for delivering bNAbs genes faces important hurdles, including the development of anti-drug antibodies (ADAs). As expected, the immunogenicity of mAbs increases proportionately with the degree of species mismatch between the mAb molecule and the host13. However, even in cases of complete species match, delivery of mAbs by either passive infusion or rAAV-mediated gene transfer can elicit ADAs2. Indeed, rhesus macaques treated with rAAV vectors encoding SIV-specific mAbs of rhesus origin have been shown to mount ADAs4. Additionally, preliminary analyses of the IAVI-sponsored clinical trial of a rAAV vector encoding the anti-HIV-1 bNAbs PG9 have revealed ADAs in 7/16 AAV-treated subjects total, and in 7/9 individuals in the highest dose groups. Although pharmacological immunosuppression and in vivo B-cell depletion have been shown to prevent the elicitation of ADAs in humans, the high risk and cost associated with these approaches make them impractical for large scale clinical implementation. Thus, the development of short term interventions for suppressing ADAs without immunocompromising the host would greatly improve the utility of rAAV-based gene therapies.

Initial efforts have focused on production of the type I IFN inhibitor by our collaborator in Israel and obtaining IACUC approval. We now have the type I IFN inhibitor in the lab and the animal protocol is almost complete. We have also selected the AAV-seronegative animals for this project. We expect to start this experiment in the first half of February.

Electrophysiological effects of electrical and chemical inhibition of the thalamic burst in a non-human primate model of focal motor seizures

PI: Redacted by agreement Core Scientist: Redacted by agreement

Epilepsy is a common and devastating medical problem, which remains insufficiently treated in 30% of patients. It is understood that seizures commonly arise in cortical regions or the temporal lobe but also involve subcortical circuits that frequently include the basal ganglia and thalamus. However, our understanding of the brain mechanisms that maintain and propagate seizure activity remains incomplete, at least in part because of the lack of animal models of seizure activity that would represent the anatomical complexity that is at play in seizures in humans. A particularly poorly understood component of the propagation of seizure activity in the thalamus is the involvement in seizure activity of neurons within the basal ganglia receiving ventral motor thalamus. This portion of the thalamus receives basal ganglia input, and is engaged in reciprocal connections with the cerebral cortex. It is important to study activity patterns of these ventral thalamic neurons and their projections in primates, because its circuitry has undergone significant evolutionary changes, such as the emergence of interneurons in primates whose activity (presumably) shapes the activity of thalamic and cortical neurons. We therefore propose to analyze the activity of neurons in this area in a primate model of focal motor seizures. A very prominent seizure-related abnormality of neuronal discharge in most brain regions is an increase of the incidence of synchronized burst discharges, which occur concomitant to ictal activity in simultaneously recorded electroencephalographic (EEG) records. This phenomenon has been well described in the basal ganglia in several seizure models, as well as in some areas of the thalamus (mostly anterior dorsal nucleus) in epileptic patients, and in rat models of temporal lobe epilepsy. Intra-cellular and extracellular

recordings in the existing animal studies have demonstrated that the activation of T-type calcium channels in thalamic neurons is critical for the generation of burst firing patterns and the emergence of neuronal synchrony affecting thalamocortical interactions. These channels are abundant in the thalamus, and pharmacologic blockade of T-type calcium channels is known to have anti-epileptic properties. However, the available T-type calcium channel active drugs (such as ethosuximide or zonisamide) are non-specific, and can induce significant side effects such as psychosis, or sleep disturbances, which limit their usefulness. Recently, a family of highly specific T-type calcium channel blockers has become available. Here we propose to study the effects of focal motor seizures and potentially therapeutic modulation of thalamic bursting activities on the cortico-thalamic network.

Two monkeys have been assigned to this project. The coordinate of the target has been identified and baseline recordings of unit and local field potentials (LFPs) have been performed. We successfully recorded the approximately 20 cells and their respective LFPs during seizures and interictal activity. We will pursue the thalamic recordings during seizures and test the effect of GPi stimulation in coming weeks.

Development and comparison of technology for automated high-throughput cognitive phenotyping in large social groups of rhesus monkeys

PI: Redacted by agreement Core Scientist: Redacted by agreement

Because of the rising costs of keeping nonhuman primates for biomedical research, it is increasingly important to make efficient use of all available animals. We can increase the value of our national primate resources by both using the largest proportion of subjects in research at all times, and by implementing technology that allows us to use animals to advance science in new ways, without compromising reproduction. We propose to develop and compare technologies that will leverage the animal resources at the Yerkes Field Station to enable whole colony cognitive phenotyping. We will assess the feasibility of this new technology by scaling up cognitive tests developed in the laboratory for use with small numbers of subjects, to the Field Station scale involving ten times as many animals. Our objective with this application is to develop new techniques for cognitive testing that allow cognitive phenotyping at the colony scale. Our rationale is that such whole-colony cognitive phenotyping will make possible a new generation of studies of the genetic, developmental, dietary, physiological, and social determinants of cognitive function. We will achieve this goal without affecting our ability to carry out the range of studies, and monkey production, that depend on our current animal resources.

We have developed, built, and tested a prototype. Testing was conducted in a large social cage. We are currently building another unit based on this experience, and we will deploy it at the Yerkes Field station shortly for full testing in a group compound.

B.4. Training and Professional Development Opportunities

Please see the overall component for response.

C. COMPONENT PRODUCTS

C.1 PUBLICATIONS

Not Applicable

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

Not Applicable

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

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

Not Applicable

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Nothing to report

D. COMPONENT PARTICIPANTS

Not Applicable

E. COMPONENT IMPACT

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

Not Applicable

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

Not Applicable

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

NOTHING TO REPORT

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?
Not Applicable

F. COMPONENT CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

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

NOTHING TO REPORT

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

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. COMPONENT SPECIAL REPORTING REQUIREMENTS

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

Not Applicable

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

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

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

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

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Not Applicable

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

RESEARCH & RELATED BUDGET - SECTION A & B FINAL

ORGANIZATIONAL DUNS*: 066469933

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

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		Redacted by agreement				Project Lead	0.00	0.0			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 **0.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	**Total Number Other Personnel**					**Total Other Personnel**	**0.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**0.00**

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

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

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

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

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

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

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	0.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Pilot Projects $70,000 x 3	210,000.00
Total Other Direct Costs	**210,000.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**210,000.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. MTDC	45.0	210,000.00	94,500.00
		Total Indirect Costs	**94,500.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS, Steven Zuraf, (301) 492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**304,500.00**

J. Fee	Funds Requested ($)*
	0.00

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

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

Budget Justification

The budget request for the upcoming period is submitted in accordance with the peer reviewed P51 renewal approved in 2016. Justification for each budget category was also peer reviewed and approved at that time, and there is no significant change in this budget request from previously approved levels.

A. COMPONENT COVER PAGE

Project Title: Outreach

Component Project Lead Information:

Redacted by agreement

B. COMPONENT ACCOMPLISHMENTS

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

The Yerkes Public Affairs (PA) Office directs the Yerkes Research Center's Outreach and Community Engagement as well as its Public Relations. For the purpose of this P51 Base Grant submission, there will be two related components: this Outreach component and a separate component for Public Affairs/Public Relations under the Administrative component.

The PA Office is responsible for increasing recognition of Yerkes as a premier research center dedicated to conducting essential basic science and translational research to advance scientific understanding and to improve human health and wellbeing. To achieve this mission, the PA Office works proactively in the multiple, complementary areas of Outreach and Public Relations. Specific activities that fall under Outreach include:

•Tours
•Community and Educational Outreach, including speakers' bureau placements
•Educational internships
•Yerkes website
•Lunch and Learn programs
•Special Events, Meetings and Presentations
•Publications
•Government Relations
•Special Projects as strategically determined and/or requested by the Center Director

In the arena of educational initiatives, PA coordinates tours of the Main Station and Field Station for educational, community and other groups as appropriate, and offers at least two Field Station Open Houses annually for neighbors, community talk participants and others. In addition, PA facilitates approval of tour requests Yerkes employees submit for their family, friends, colleagues and others. PA also places speakers in the community and at schools, coordinates educational internships at the Center, manages the Yerkes website and also educates employees about Center research and other topics via the Lunch and Learn program. Each year, the Yerkes PA Office coordinates National Primate Research Center representation at the annual Society for Neuroscience meeting to educate researchers about the expertise and resources that the National Primate Research Centers offer. The Yerkes PA Office provides information to Emory publications to educate the greater Emory community about the Yerkes Research Center and provides information to elected officials to keep them informed about our Center.

The Specific Aims are:

1. To maintain a proactive approach to outreach;

2. To continue organizing community and educational outreach opportunities, and to use those opportunities to connect the Center's research whenever possible to improvements in human health;

3. To partner with other National Primate Research Centers, organizations and others strategically identified to extend the reach of Yerkes-related information.

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

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: B2_8531 Outreach.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

Not Applicable

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

NOTHING TO REPORT

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

Please see the Overall component for response.

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

During the next year, the Yerkes National Primate Research Center PA Office will continue to be proactive in its approach to educating employees, the Emory community, the greater metro Atlanta community and others about the Yerkes Research Center as well as the NPRC program.

At the time of this report, we are busy coordinating spring and summer tours, including our next Field Station Open House, and are planning an exhibit booth with the Emory Vaccine Center and Emory graduate students at the 2019 Atlanta Science Festival Expo.

We will continue to partner with other organizations to extend the reach of Yerkes information. These include Americans for Medical Progress (for which the Yerkes Chief of Public Affairs serves as an executive committee member of the organization's board), Foundation for Biomedical Research, Society for Neuroscience and FASEB, for which Yerkes Public Affairs staff has worked with the organization to feature a Yerkes veterinarian in an upcoming webinar. Also, the Yerkes Chief of Public Affairs has been invited to speak on a panel at the national AALAS meeting, making this the second year in a row for such a panel presentation.

B.2. Accomplishments—Outreach

The Yerkes Public Affairs (PA) Office is responsible for increasing recognition of Yerkes as one of the seven National Primate Research Centers fighting disease and improving human health by making breakthrough discoveries possible. To achieve this, the PA Office directs the center's outreach and community engagement. PA staff also works in the areas of media relations, issues management, emergency preparedness and special projects, and coordinates a national online PR presence on behalf of the seven NPRCs. Information about these initiatives is reported in another section within this progress report.

Falling under outreach and community engagement are: internal/employee communication; tours; community and educational outreach, including speakers' bureau placements and educational internships; Yerkes website; special events, meetings and presentations; and publications.

This year, we continued distributing an employee newsletter to ensure our employees have the most recent information about our center and distributed other information via our center's listserv. We reached approximately 2,000 people via our tour program, including our two Field Station Open Houses and educational tours for school groups and family, friends and colleagues. We also coordinated another eight-part continuing education series featuring Yerkes researchers and again partnered with Georgia State University and Emory University to offer the Institute on Neuroscience, which gives high school students and middle and high school teachers hands-on research experience during the summer. We posted information to our website, yerkes.emory.edu, as well as ensured we were represented on NPRC.org. In addition, we worked with Emory graduate students and Emory Vaccine Center employees to host a booth at the Atlanta Science Festival Expo, helped man the 2018 AALAS booth at the National Science Teacher Association meeting, helped coordinate the AALAS AREA program in Atlanta for veterinary tech students and hosted a group of 50 Emory VIPs for a presentation by Yerkes researcher Redacted by agreement Also, Yerkes PA staff provided information to Emory publications to educate the greater Emory community about the Yerkes Research Center.

Again this year, the Yerkes PA Office coordinated the National Primate Research Center's participation in the annual Society for Neuroscience meeting, including managing our sponsorship of the Animals in Research panel.

C. COMPONENT PRODUCTS

C.1 PUBLICATIONS

Not Applicable

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

Not Applicable

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

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

Not Applicable

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Nothing to report

D. COMPONENT PARTICIPANTS

Not Applicable

E. COMPONENT IMPACT

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

Not Applicable

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

Not Applicable

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

NOTHING TO REPORT

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?
Not Applicable

F. COMPONENT CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

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

NOTHING TO REPORT

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

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. COMPONENT SPECIAL REPORTING REQUIREMENTS

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

Not Applicable

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

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

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

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

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Not Applicable

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

RPPR - Other-8531

RESEARCH & RELATED BUDGET - SECTION A & B **FINAL**

ORGANIZATIONAL DUNS*: 066469933

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

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.		Redacted by agreement				Project Lead	0.00	0.0			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 **0.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	**Total Number Other Personnel**					**Total Other Personnel**	**0.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**0.00**

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

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

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	Funds Requested ($)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	5,812.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**5,812.00**

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

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

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	0.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
Total Other Direct Costs	**0.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**5,812.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. MTDC	45.0	5,812.00	2,615.00
		Total Indirect Costs	**2,615.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS, Steven Zuraf, (301) 492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**8,427.00**

J. Fee	Funds Requested ($)*
	0.00

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

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

Budget Justification

The budget request for the upcoming period is submitted in accordance with the peer reviewed P51 renewal approved in 2016. Justification for each budget category was also peer reviewed and approved at that time, and there is no significant change in this budget request from previously approved levels.

A. COMPONENT COVER PAGE

Project Title: Consortium

Component Project Lead Information:

Redacted by agreement

B. COMPONENT ACCOMPLISHMENTS

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

The mission of the Nonhuman Primate Research Centers Consortium is to strengthen communications, leverage system-wide resources and facilitate sharing of information and best practices. The Consortium Working Groups comprise experts from major disciplines within each center who collaborate to address priority issues, challenges and opportunities that the National Primate Research Center Directors identify at national and local levels.

The Nonhuman Primate Research Centers Consortium began in 2007 to enhance cooperation between the National Primate Research Centers and the NIH Office of Research Infrastructure Programs. The Consortium now has nine Working Groups with representation from all of the National Primate Research Centers and two additional Working Groups with focused representation.

The National Primate Research Center Directors oversee the Consortium in conjunction with the NIH Division of Program Coordination, Planning, and Strategic Initiatives. This oversight includes monitoring progress and reviewing and approving annual budgets.

The Specific Aim is:

1. To continue to strengthen the NPRC Consortium and each of its Working Groups as resources to National Primate Research Center faculty and staff, the NIH and researchers nationwide.

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

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: B2_8532 Consortium.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

Not Applicable

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

NOTHING TO REPORT

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

NOTHING TO REPORT

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

Our overarching goal continues to be to strengthen the NPRC Consortium and each of its Working Groups as resources to National Primate Research Center faculty and staff, the NIH and researchers nationwide.

Each Working Group submits annual plans to the NIH Division of Program Coordination, Planning, and Strategic Initiatives. Portions of those plans specific to the Yerkes Research Center are listed below.

Behavioral Management
The Yerkes Behavioral Management unit will continue to contribute to the Behavioral Management Working Group by writing joint publications, conducting grant-supported, collaborative research on animal management, sharing staff training information, finalizing the welfare report and working to ensure that this Consortium Working Group is a national resource.

Breeding Colony Management
The Yerkes Colony Management unit will continue to contribute to the ongoing efforts of the Breeding Colony Management Working Group. In addition, Yerkes will collaborate with the Behavioral Management Working Group to help prioritize future projects and provide information as requested.

Clinical and Surgical Techniques
Yerkes veterinary personnel will continue helping develop the lecture schedule, participating in monthly conferences and discussions, and developing guidelines through the use of surveys, questionnaires and discussions. Yerkes will also continue to provide written narratives and presentations for the Working Group's library.

Computational Methods and Resources Group
Yerkes representatives Redacted by agreement will continue to work with the expanded membership of the CMRG to review the scope of activities and to ensure that the efforts of this group are in fact serving all of the seven NPRCs.

Genetics & Genomics

The Yerkes team will continue to optimize the Fluidigm SNP genotyping platform to improve throughput and decrease cost for these analyses. They will also continue to facilitate the distribution of nonhuman primate genetic material.

Integrity-Compliance
The Yerkes Veterinary Medicine unit will contribute to the Integrity and Compliance Working Group by continuing to participate in quarterly calls, sharing information about the topics discussed and participating in discussions about the role of a training program in maintaining and monitoring compliance.

New Model Development
Yerkes participants in the NMD Redacted by agreement will help advance NHP model development by coordinating the discussion and comparison of common NHP traits documented at the NPRCs. Specific phenotypes being examined on a cross-center basis include Behavioral Inhibition/Anxiety, Left Ventricular Hypertrophy (LVH), and SIV Elite Controllers.

Occupational Health & Safety
The Yerkes Environmental Health and Safety unit will continue to chair the Occupational Health & Safety Working Group. This responsibility includes developing meeting agendas, chairing calls and the annual meeting, and taking minutes. Yerkes personnel will also continue to maintain contact with the B-virus lab at Georgia State University and share SOPs, data about injury and illness, and costs for supplies.

Outreach
The Yerkes Public Affairs unit will contribute to the Outreach Working Group by continuing to participate in monthly calls and the annual meeting, sharing information, representing all National Primate Research Centers at the annual Society for Neuroscience meeting and managing the Centers' two-year sponsorship of its Animals in Research panel, and continuing to provide information to and promote the nprcresearch.org website.

Pathogen Detection Working Group
Our representative to the newly formed PDWG Redacted by agreement is working with the group to review the scope of assays for pathogen detection being performed at each of the NPRCs and to review current standards for these assays, to ensure rigor and reproducibility among all the centers.

Public Relations
The Yerkes Public Affairs unit, which chairs the Public Relations Working Group, will continue to participate in monthly calls and the annual meeting, leading efforts to coordinate national public relations activities, and providing information to and promoting the nprcresearch.org website, as well as the public-facing website, which is currently in development.

Pathology
The Yerkes Division of Pathology will continue fulfilling and supporting the Working Group's goals to: provide instruction to lab animal and pathology residents, as well as veterinary students enrolled in the McClure Training Program; facilitate collaboration with and provide support to veterinary pathologists from the other National Primate Research Centers and schools of veterinary medicine; facilitate consultation with other veterinary pathologists and researchers; and serve as a repository of digital slides from classic pathological conditions of nonhuman primates.

Rigor and Reproducibility Working Group
Members of the Rigor and Reproducibility Working Group will participate to help identify best practices across the NPRCs that will help support the NIH's goal of ensuring the highest degree of rigor and reproducibility for NHP research.

Specialized Breeding Working Group
The Yerkes representatives to this newly formed group, Redacted by agreement will work with the rest of the SBWG to establish points to consider for the directed breeding of nonhuman primates that have been selected for specific genotypes or phenotypes.

Training
The two residents currently in training within the Yerkes Veterinary Medicine unit will continue to present to their colleagues, focusing on either a clinical case or the results of their research projects with nonhuman primates. Clinicians will continue to participate in the monthly Virtual Grand Rounds.

Zika
Yerkes members of the Zika Working Group will continue to work together with the other members to assure data sharing; coordinate Zika research projects among Centers; discuss the potential for sample storage and sample sharing, both ongoing and at necropsy; promote the sharing of SOPs for diagnostic assays; and promote the harmonizing of Zika virus diagnostic assays.

B.2. Accomplishments—Consortium

The Nonhuman Primate Research Centers Consortium began in 2007 to enhance cooperation between the National Primate Research Centers and the NIH Office of Research Infrastructure Programs. The Consortium now has 16 Working Groups. The overall mission of the Nonhuman Primate Research Centers Consortium is to strengthen communications, leverage system-wide resources and facilitate sharing of information and best practices among the NPRCs. The Consortium Working Groups comprise experts from major disciplines within each center who collaborate to address priority issues, challenges and opportunities that the National Primate Research Center Directors identify at national and local levels. The National Primate Research Center Directors oversee the Consortium in conjunction with the NIH Division of Program Coordination, Planning, and Strategic Initiatives. This oversight includes monitoring progress and reviewing and approving annual budgets.

The overall Specific Aim, which is unchanged, is to continue to strengthen the NPRC Consortium and each of its Working Groups as resources to National Primate Research Center faculty and staff, the NIH and researchers nationwide.

Yerkes employees participate in a number of the NPRC Consortium Working Groups; specific members for each of the groups are listed below.

Behavioral Management Consortium (BMC) – Redacted by agreement

Biomarkers Working Group (BWG) - Redacted by agreement

Breeding Colony Management Consortium (BCMC) – Redacted by agreement Redacted by agreement

Clinical and Surgical Techniques (CAST) - Redacted by agreement Redacted by agreement

Computational Methods and Resources Group (CMRG) – Redacted by agreement

Genetics and Genomics Working Group (GGWG) - Redacted by agreement

Integrity/Compliance Working Group (ICWG) – Redacted by agreement

New Model Development (NMD) – Redacted by agreement

Occupational Health and Safety (OHS) - Redacted by agreement

Outreach Working Group (OWG) - Redacted by agreement

Pathogen Detection Working Group (PDWG) Redacted by agreement

Pathology Working Group (PWG) - Redacted by agreement Redacted by

Public Relations Working Group (PRWG) – Redacted by agreement

Rigor and Reproducibility Working Group (RRWG) - Redacted by agreement

Specialized Breeding Working Group (SBWG) - Redacted by agreement

Training Consortium – Redacted by agreement

Zika Working Group (ZWG) - Redacted by agreement

C. COMPONENT PRODUCTS

C.1 PUBLICATIONS

Not Applicable

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

Not Applicable

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

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

Not Applicable

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Nothing to report

D. COMPONENT PARTICIPANTS

Not Applicable

E. COMPONENT IMPACT

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

Not Applicable

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

Not Applicable

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

NOTHING TO REPORT

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?
Not Applicable

F. COMPONENT CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

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

NOTHING TO REPORT

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

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. COMPONENT SPECIAL REPORTING REQUIREMENTS

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

Not Applicable

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

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

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Not Applicable

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

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

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

Not Applicable

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

RESEARCH & RELATED BUDGET - SECTION A & B FINAL

ORGANIZATIONAL DUNS*: 066469933

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

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		Redacted by agreement				Project Lead	0.00	0.0			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 **0.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	**Total Number Other Personnel**					**Total Other Personnel**	**0.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**0.00**

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

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

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	Funds Requested ($)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	10,894.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**10,894.00**

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

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

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 066469933
Budget Type*: ● Project ❍ Subaward/Consortium
Enter name of Organization: EMORY UNIVERSITY

Start Date*: 05-01-2019 **End Date*:** 04-30-2020

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	1,250.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
Total Other Direct Costs	**1,250.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**12,144.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. MTDC	45.0	12,144.00	5,465.00
		Total Indirect Costs	**5,465.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, Steven Zuraf, (301) 492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**17,609.00**

J. Fee	Funds Requested ($)*
	0.00

K. Budget Justification* File Name: H_8532 Budget Justification.pdf
(Only attach one file.)

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

Budget Justification—Consortium

The budget request for the upcoming period for this component includes the following working group budgets:

- Behavioral Management Consortium (BMC)
- Biomarkers Working Group (BWG)
- Breeding Colony Management Consortium (BCMC)
- Genetics and Genomics Working Group (GGWG)
- Integrity/Compliance Working Group (ICWG)
- Occupational Health and Safety (OHS)
- Pathogen Detection Working Group (PDWG)
- Pathology Working Group (PWG)
- Rigor and Reproducibility Working Group (RRWG)
- Zika Working Group (ZWG)

There is no significant change in this budget request from previously approved levels.