A. COVER PAGE

Project Title: Bicoastal Marmoset Breeding Center	
Grant Number: 5U24MH123423-02	**Project/Grant Period:** 07/15/2020 - 05/31/2025
Reporting Period: 07/15/2020 - 05/31/2021	**Requested Budget Period:** 06/01/2021 - 05/31/2022
Report Term Frequency: Annual	**Date Submitted:** 04/07/2021
Program Director/Principal Investigator Information: XIAOQIN WANG , PHD **Phone Number:** (410) 614-4547 **Email:** xiaoqin.wang@jhu.edu	**Recipient Organization:** JOHNS HOPKINS UNIVERSITY 3400 N. Charles Street BALTIMORE, MD 212182680 **DUNS:** 001910777 **EIN:** 1520595110A1 **RECIPIENT ID:**
Change of Contact PD/PI: NA	
Administrative Official: MARISA BAILEY 733 N. Broadway, Suite 117 Baltimore, MD 21205 **Phone number:** 443-287-0982 **Email:** mabailey@jhu.edu	**Signing Official:** MARISA BAILEY 733 N. Broadway, Suite 117 Baltimore, MD 21205 **Phone number:** 443-287-0982 **Email:** mabailey@jhu.edu
Human Subjects: No	**Vertebrate Animals:** Yes
hESC: No	**Inventions/Patents:** No

B. ACCOMPLISHMENTS

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

The common marmoset (Callithrix jacchus) has experienced unprecedented growth in research across the United States and is rapidly emerging as a likely keystone biomedical model system in the next chapter of scientific discovery. Over the past decade, the number of marmoset laboratories in the US has quadrupled. There are now over 40 Principal Investigators who use marmoset as the model system in their research. Neuroscience is the primary engine driving marmoset research today, as nearly three quarters of marmoset researchers in the US use this model species to examine molecular, systems or cognitive functions in normal and diseased brains. Although these grassroots have been successfully forged new paths of scientific inquiry using marmosets in the U.S., critical bottlenecks have emerged that threaten to thwart the continued growth of this emerging model system. We propose to establish a Bicoastal Marmoset Breeding center, with two breeding colonies, one on the East Coast at Johns Hopkins University (JHU) and the other on the West Coast at University of California at San Diego (UCSD). The Center aims to produce a large number of marmosets to supply the marmoset research community in the U.S. Because of the non-availability of air transport of NHP in U.S. and prohibitively expensive ground transportation of NHP between the east and west coast, these two breeding colonies are strategically located to support the marmoset community in regions near each colony. We believe such a center is needed to address the national shortage of marmosets in order for the marmoset model to realize its full potential as a keystone species in the next chapter of neuroscience that serves to accelerate the rate of discovery and better understand human neurological disease.

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 : ProgressReport_MH123423_2021(B2).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?

No

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?

JHU colony:
In Year 2, we plan to purchase 8-10 additional breeding cages and will increase our total number of breeding pairs in the Bayview facility to 13-14 breeding pairs. In addition, we plan to complete the operating suite and to purchase a portable x-ray machine. Finally, we plan to initiate genetic testing and designated husbandry studies after further guidance from the Marmoset Coordination Center.

UCSD Colony:
Having completed this initial phase of the project, we placed an order for additional cages in anticipation of expanding the size of the colony in the second year of the project. These cages are due to be completed by May 2021. We plan to expand the breeding colony to an additional 4-5 breeding pairs during the upcoming project year. We also plan to initiate genetic testing to optimize the diversity of the breeding pairs following guidance from the Marmoset Coordination Center.

B.2 What was accomplished under these goals?

JHU Colony:

In Year 1, we established a new animal housing room with designated support spaces at our Bayview campus, as outlined in the original grant proposal. Support spaces include a clinical treatment area outfitted with a downdraft table, sink, refrigerator, portable exam light, Bair hugger heat support system, a controlled drug box, and additional clinical supplies (syringes, blood tubes, iSTAT blood analyzer, portable SPO2 monitor, microchip scanner, blood glucose monitor, etc). In addition to the clinical treatment area, we established a designated feed preparation room equipped with a refrigerator/freezer combo and necessary supplies for food storage, prep, enrichment storage and prep, and other common husbandry duties. A reverse osmosis (RO) water system was installed in order to keep husbandry practices consistent with our East Baltimore campus colony. Finally, we are in the process of outfitting an operating suite in order to support major operative procedures.

We purchased 10 breeding cages in preparation for moving animals into the new housing room and purchased a portable ultrasound machine to facilitate breeding colony management. We designated 7 breeding pairs to be transferred to the Bayview facility. Transfer is scheduled for April 2021. Of these breeding pairs, 4 pairs have produced a total of 7 viable offspring. The remaining 3 pairs are pregnant and due to give birth between April and June of 2021. Pre-transfer pathogen testing as outlined in the grant proposal was performed.

UCSD Colony:

The primary aim for the first year of the project was to establish the breeding colony at the UCSD Elliot Field Station (EFS). We ordered 10 new cages be built by the Scripps Institute of Oceanography machine shop, which were completed in September 2020. This shop has constructed all the marmoset cages for Miller lab since 2010. The building at EFS designated to house the marmoset breeding colony required construction modifications to accommodate the monkeys, which were completed by the end of September 2020. We received 8 animals from JHU and one from Arizona State University on October 21, 2020. All these animals were housed individually at EFS to undergo quarantine. At the conclusion of the quarantine period in Mid-December, we began transporting animals from the home research colony in Miller lab out to EFS to pair with the animals and establish the initial breeding pairs. We successfully paired 16 animals in total, or 8 breeding pairs. All breeding pairs have been undergone routine health monitoring since this time. At present, two breeding pairs are pregnant.

C. 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?

No

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

NOTHING TO REPORT

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

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

Have inventions, patent applications and/or licenses resulted from the award during the reporting period? No

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

C.5 OTHER PRODUCTS AND RESOURCE SHARING

NOTHING TO REPORT

D. PARTICIPANTS

D.1 WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

Commons ID	S/K	Name	Degree(s)	Role	Cal	Aca	Sum	Foreign Org	Country	SS
username	Y	WANG, XIAOQIN	PHD	PD/PI	percent effort					NA
	N	Hutchinson, Eric Kenneth	AB,DVM	Faculty						NA
	N	Schmidt, Zachary		Non-Student Research Assistant						NA
	N	Lynch, Jessica		Technician						NA
	N	BECK, SARAH	BS,DVM,PHD	Faculty						NA
	N	Miller, Samantha		Non-Student Research Assistant						NA
	Y	Miller, Corey Nicholas	BS,MD,PHD	Co-Investigator						NA
	N	Izzi, Jessica M	DVM,MOTH,BS	Co-Investigator						NA

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

D.2 PERSONNEL UPDATES

D.2.a Level of Effort

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

No

D.2.b New Senior/Key Personnel

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

No

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: Wang_Other Support_2021-03 Progress report update.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

OMB No. 0925 0001 (Rev. 09/17 Approved Through 03/31/2020)

For New and Renewal Applications – DO NOT SUBMIT UNLESS REQUESTED

PHS 398 OTHER SUPPORT

Wang, Xiaoqin

ACTIVE

R01 DC003180 (Wang) 2/25/2020-1/30/2025 [redacted]
NIH/NIDCD $421,899
Information Processing in Auditory Cortex
The major goals of this project are to understand neural mechanisms for representing species-specific vocalizations in auditory cortex of awake marmosets and fundamental neural mechanisms underlying cortical representations of these biologically important sounds.

R01 DC005808 (Wang) 3/1/2018-2/28/2023 [redacted]
NIH/NIDCD $339,515
Auditory-Vocal Interaction Mechanisms in Primates
The major goals of this project are to study behavioral and physiological mechanisms underlying auditory-vocal interactions in non-human primates, how the vocal production system modulates neural processing in auditory cortex, and whether marmoset vocalizations exhibit experience-based plasticity.

R01 DC014503 (Wang) 12/1/2015-11/30/2021 (NCE) [redacted]
NIH/NIDCD $268,173
Cortical Processing of Cochlear Implant Signals
The major goals of this project are to elucidate neural coding and plasticity mechanisms underlying cortical processing of cochlear implant (CI) signals in the context of vocal communication.

U24 MH123423 (Wang) 7/15/2020-5/31/2025 [redacted]
NIH BRAIN Initiative $850,197
Bicoastal Marmoset Breeding Center
The major goal of this project is to establish a bicoastal marmoset breeding center, with breeding colonies at JHU and UCSD, to supply marmosets to the research community in the U.S.

OVERLAP: There is no scientific or budgetary overlap.

E. IMPACT

E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES? Not Applicable
E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE? NOTHING TO REPORT
E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER? Not Applicable
E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)? NOTHING TO REPORT

F. 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 Subject

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. SPECIAL REPORTING REQUIREMENTS SPECIAL REPORTING REQUIREMENTS

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

NOTHING TO REPORT

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

Not Applicable

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: JOHNS HOPKINS UNIVERSITY	001910777	MD-007	Johns Hopkins University 733 N Broadway, Suite 117 Baltimore, MD 212051832
JOHNS HOPKINS UNIVERSITY	001910777	MD-007	720 Rutland Ave Traylor 410 BALTIMORE, MD 212052109

The Regents of the Univ. of Calif., U.C. Sand Diego	804355790	CA-049	University of California San Diego Office of Contract & Grant Admin, 0934 La Jolla, CA 920930934
JOHNS HOPKINS UNIVERSITY	001910777		3400 N. Charles Street BALTIMORE, MD 212182680
JOHNS HOPKINS UNIVERSITY	001910777	MD-007	Johns Hopkins University 733 N Broadway, Suite 117 Baltimore, MD 212051832
JOHNS HOPKINS UNIVERSITY	001910777	MD-007	720 Rutland Ave Traylor 410 BALTIMORE, MD 212052109
The Regents of the Univ. of Calif., U.C. Sand Diego	804355790	CA-049	University of California San Diego Office of Contract & Grant Admin, 0934 La Jolla, CA 920930934

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? No

G.12 F&A COSTS

Is there a change in performance sites that will affect F&A costs?

No

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

FINAL

RESEARCH & RELATED BUDGET - SECTION A & B

ORGANIZATIONAL DUNS*: 001910777

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: JOHNS HOPKINS UNIVERSITY

Start Date*: 06-01-2021 **End Date*:** 05-31-2022

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	Xiaoqin		Wang		Project Lead	base salary & percent effort				15,164.00	4,246.00	19,410.00
2.	Ms	Jessica		Izzi		Co Investigator					38,772.00	10,856.00	49,628.00

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

Additional Senior Key Persons: File Name:

Total Senior/Key Person **69,038.00**

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						
3	Veterinarian	percent effort			59,020.00	16,526.00	75,546.00
3	**Total Number Other Personnel**					**Total Other Personnel**	**75,546.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**144,584.00**

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

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

ORGANIZATIONAL DUNS*: 001910777

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: JOHNS HOPKINS UNIVERSITY

Start Date*: 06-01-2021 **End Date*:** 05-31-2022

C. Equipment Description

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

Equipment Item	Funds Requested ($)*
1. [equipment item 3] Marmoset caging designed by Tecniplast ($10,0	75,608.93
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**75,608.93**

Additional Equipment: File Name:

D. Travel	Funds Requested ($)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	2,336.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**2,336.00**

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*: 001910777

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: JOHNS HOPKINS UNIVERSITY

Start Date*: 06-01-2021 **End Date*:** 05-31-2022

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	24,418.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	433,118.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Animal Purchases	68,047.07
9. Animal Care	127,912.00
Total Other Direct Costs	**653,495.07**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**876,024.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. IDC	63.75	367,298.00	234,152.00
		Total Indirect Costs	**234,152.00**

Cognizant Federal Agency

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**1,110,176.00**

J. Fee	Funds Requested ($)*
	0.00

K. Budget Justification* File Name:

(Only attach one file.)

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

PI: **WANG, XIAOQIN**	Title: Bicoastal Marmoset Breeding Center	
Received: 10/16/2020	FOA: PA18-591	Council: 00/2021
Notice of Special Interest: NOT-AG-20-034		
Competition ID: FORMS-F-ADMINSUPP-RESEARCH	FOA Title: Administrative Supplements to Existing NIH Grants and Cooperative Agreements (Parent Admin Supp - Clinical Trial Optional)	
3 U24 MH123423-02S1	Dual: AA,AG,AT,DA,DC,DE,EB,ES,EY, HD,NS	Accession Number: 4509549
IPF: 4134401	Organization: JOHNS HOPKINS UNIVERSITY	
Former Number: 1U24MH123423-01	Department: Biomedical Engineering	
IRG/SRG: ZMH1 (03)	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 249,322	Animals: Y Humans: N Clinical Trial: N Current HS Code: 10 HESC: N HFT: N	New Investigator: Early Stage Investigator:
Senior/Key Personnel:	*Organization:*	*Role Category:*
XIAOQIN WANG	JOHNS HOPKINS UNIVERSITY	PD/PI

OMB Number 4040-0010
Expiration Date 12/31/2022

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	State Application Identifier

1. TYPE OF SUBMISSION*

❍ Pre-application ● Application ❍ Changed/Corrected Application

4.a. Federal Identifier
MH123423

b. Agency Routing Number
NOT-AG-20-034

2. DATE SUBMITTED

Application Identifier
00144082

c. Previous Grants.gov Tracking Number

5. APPLICANT INFORMATION

Organizational DUNS*: 001910777

Legal Name*: JOHNS HOPKINS UNIVERSITY
Department: Biomedical Engineering
Division: School of Medicine
Street1*: 733 N Broadway, Suite 117
Street2: Edward D. Miller Research Building
City*: Baltimore
County:
State*: MD: Maryland
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 212051832

Person to be contacted on matters involving this application
Prefix: First Name*: Marisa Middle Name: Last Name*: Bailey Suffix:
Position/Title: Grants Associate
Street1*: 733 N. Broadway
Street2: Suite 117
City*: Baltimore
County:
State*: MD: Maryland
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 21205-1832
Phone Number*: 443-287-0982 Fax Number: Email: mabailey@jhu.edu

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** 052595110

7. TYPE OF APPLICANT* O: Private Institution of Higher Education

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

8. TYPE OF APPLICATION*

❍ New ❍ Resubmission
❍ Renewal ❍ Continuation ● Revision

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

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

9. NAME OF FEDERAL AGENCY*
National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER
242
TITLE:

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Bicoastal Marmoset Breeding Center

12. PROPOSED PROJECT
Start Date* Ending Date*
04/01/2021 03/31/2022

13. CONGRESSIONAL DISTRICTS OF APPLICANT
MD-007

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: First Name*: XIAOQIN Middle Name: Last Name*: WANG Suffix:
Position/Title: Professor
Organization Name*: JOHNS HOPKINS UNIVERSITY
Department: Biomedical Engineering
Division: School of Medicine
Street1*: Johns Hopkins University
Street2: 720 Rutland Ave
City*: Baltimore
County:
State*: MD: Maryland
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 212052109
Phone Number*: (410) 614-4547 Fax Number: (410) 614-9599 Email*: xiaoqin.wang@jhu.edu

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	$298,186.00
b. Total Non-Federal Funds*	$0.00
c. Total Federal & Non-Federal Funds*	$298,186.00
d. Estimated Program Income*	$0.00

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

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

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

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

● I agree*

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

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: First Name*: Marisa Middle Name: Last Name*: Bailey Suffix:
Position/Title*: Grants Associate
Organization Name*: Johns Hopkins University
Department: Research Administration
Division: School of Medicine
Street1*: 733. N. Broadway
Street2: Suite 117
City*: Baltimore
County:
State*: MD: Maryland
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 212051832
Phone Number*: 443-287-0982 Fax Number: Email*: mabailey@jhu.edu

Signature of Authorized Representative*
Marisa Bailey

Date Signed*
10/16/2020

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:

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

OMB Number: 4040-0010
Expiration Date: 12/31/2022

Project/Performance Site Location(s)

Project/Performance Site Primary Location

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

Organization Name:	JOHNS HOPKINS UNIVERSITY
Duns Number:	001910777
Street1*:	Johns Hopkins University
Street2:	733 N Broadway, Suite 117
City*:	Baltimore
County:	BALTIMORE CITY
State*:	MD: Maryland
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	212051832
Project/Performance Site Congressional District*:	MD-007

Additional Location(s)

File Name:

Funding Opportunity Number: PA-18-591. Received Date: 2020-10-16T15:46:33.000-04:00

OMB Number: 4040-0010
Expiration Date: 12/31/2022

RESEARCH & RELATED Other Project Information

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

1.a. If YES to Human Subjects

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

If YES, check appropriate exemption number: _ 1 _ 2 _ 3 _ 4 _ 5 _ 6 _ 7 _ 8

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

IRB Approval Date:

Human Subject Assurance Number

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

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ● Yes ❍ No

IACUC Approval Date: 11-19-2018

Animal Welfare Assurance Number D16-00173

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

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

4.b. If yes, please explain:

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

4.d. If yes, please explain:

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

5.a. If yes, please explain:

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

6.a. If yes, identify countries:

6.b. Optional Explanation:

	Filename
7. Project Summary/Abstract*	AbstractSummary_U24_Supp_Oct2020.pdf
8. Project Narrative*	ProjectNarrative_U24_Supp_Oct2020.pdf
9. Bibliography & References Cited	ReferencesCited_U24_Oct2019.pdf
10.Facilities & Other Resources	Facilities_U24_Oct2019.pdf
11.Equipment	Equipment_U24_Supp_Oct2020.pdf

Tracking Number: GRANT13228921
Funding Opportunity Number: PA-18-591. Received Date: 2020-10-16T15:46:33.000-04:00

Nonhuman primates (NHP) are crucial animal models for research on Alzheimer's disease and its related dementias because of their closest evolutionary relatives of humans, with whom they share anatomical, physiological, and gene interactions features. The common marmoset (Callithrix jacchus) is a NHP model of increasing importance for aging research. This new world primate provides some unique advantages for the study of aging and aging-related disorders, including its relatively short lifespan among all the NHP used in biomedical research. There has been an increasing number of investigators who are currently using or would like to use marmosets as a model system to study aging and age-related diseases including Alzheimer's disease. However, there is a significant bottleneck for the research in this field. There are currently no reliable distributors of marmosets for biomedical research in the country. The situation is even direr for researchers who need access to aging marmosets. Recognizing such a bottleneck, NIH has recently funded two marmoset breeding programs including the parent award of this application ("Bicoastal Marmoset Breeding Center", U24-MH123423). The goal of the proposed project is to fill the gap in the availability of aging marmosets for the study of Alzheimer's disease and its related dementias. We could use this center to develop a resource of aging marmosets for Alzheimer's disease studies. This resource will be extremely valuable to the scientific community studying Alzheimer's disease and its related dementias.

Public Health Relevance Statement:

A proper model system is crucial to advance the studies of age-related diseases. The proposed project will contribute to the research in this field by making critical resource available to the research community that study brain mechanisms underlying Alzheimer's disease and its related dementias.

Laboratory: [From parent award]

Wang Lab: Dr. Wang's laboratory (~2000 sq. ft.) has several full-size soundproof chambers for conducting behavioral and single-unit recording studies in awake marmosets, a large RF/EMI/Acoustic shielded chamber for conducting wireless neural recording experiments in freely roaming marmosets, all fully equipped with computers and hardware, capable of generating well-controlled acoustic stimuli and performing neurophysiological recordings. The lab has acess to MRI scanners proprietary/confidential which houses a 11.4T small animal scanner that is suitable for marmosets.

Miller Lab: Dr. Miller's laboratory has 4 testing rooms, an observation area, a colony room, electronics workbench and a clean room for data analysis. Each testing room is equipped with multiple video cameras for monitoring subjects during testing. The lab is also equipped with a downdraft table for perfusing animals following the conclusion of experiments. The electronics bench is equipped with an electronics scope, moveable hood arm and all the necessary tools for constructing the microelectrode arrays. The lab has acess to the UCSD Histology Core and the UCSD Center for Functional MRI which houses a 7T small animal scanner that is suitable for marmosets. The Center provides space for short-term housing of the animals prior to and after scanning sessions.

Animal:

Johns Hopkins University (JHU)

The proprietary/confidential Johns Hopkins University contains 160,000 net square feet of research space. Animals housed in this building are used in laboratories within the building, and proprietary/confidential. The offices and laboratories of RAR are located on proprietary/confidential. There are four animal holding facilities in the building, which encompass a total of 18,977 net square feet of space. These holding areas are located proprietary/confidential hold both small and large animals, including mice, rats, rabbits, cats, dogs, swine, sheep and nonhuman primates including marmosets. Twelve of the rooms are in the north wing, and 8 in the south wing. All animal rooms are protected by a card-key security system. The marmosets are currently housed on proprietary/confidential large animal holding rooms (with a total of 1,728 Sq ft), with an anteroom and a dedicated procedure and husbandry room adjacent to the holding rooms. All animals are housed in USDA registered, AAALAC International accredited facilities and are maintained in rooms housing multiple breeding groups and social pairs. Additional animal holding rooms will be allocated to accommodate the proposed breeding colony.

University of California at San Diego (UCSD)

Marmoset breeding for this project will take place at the UC San Diego Elliot Field Station. This research facility located 10 miles east of the main UCSD campus. The site consists of 26.8 acres. There are 14 buildings which provide approximately 12000 sq ft of conditioned space, and 13,000 sq ft of unconditioned space. The facility includes large and small animal holding facilities, animal procedure/radiology facilities, surgical facilities, offices, storage and support space, resident caretaker trailers, large animal outdoor pens/corrals, kennels, and animal housing and procedure facilities. Nonhuman primates including marmoseta are routinely housed in the conditioned space, including marmosets. 3000 sq ft are available at the UCSD Elliot Field Station for this breeding project. We will be allocated 1000sq ft in year 1, 2000 in year 2 and the full space by year 3 to accommodate the growing colony size. Elliot Field Station has portable emergency generators available for long term power outages. Several layers of security are in place including 24-hour on-site staff, security cameras and biometric recognition access systems which is directly connected to our centralized security systems. Security fencing has three separate layers in order to gain access to the animal housing facilities. Each of those are locked and some are additionally secured with intrusion detectors. All the animal facilities at UCSD are AALAC accredited.

Computer:

Wang Lab: There are a total of ~20 computers in the laboratory; 10 are devoted for behavioral and electrophysiological experiments and the rest are available for data analyses.

Miller Lab: For data analysis, my laboratory consists of 4 iMac computers and 2 custom data analysis PCs (128GB RAM, 24TB Harddrive, Intel 16-core processor). Each of the 4 testing chambers also has a custom build PC for performing experiments (16GB RAM, 4TB Hard drive, Intel 4 or 8-core processor). The lab also has a 12-Core data server housed outside the lab that all data are backed up to each evening. Computers are equipped with all the necessary software (Matlab, Adobe CS4, RAVEN, etc).

Office:

Wang Lab: Adequate office space (~600 sq. ft.) for all personnel is located adjacent to the laboratory and colony rooms.

Miller Lab: Miller has an office outside the primary lab but in the same building as the main laboratory (McGill Hall) . Office space is provided by the Psychology department for UCSD graduate students and Post-docs. Research assistants have desk space in the main laboratory. A desk in a shared office will also be provided at Elliott Field Station to enable oversight of the breeding colony housed at that location.

Other:

Wang Lab: The P.I.'s laboratory is part of the Johns Hopkins University Center for Hearing and Balance. The P.I. has access to shared facilities (e.g. surgical suite, electronic shop, histology core facility) operated by the Center for Hearing and Balance. The Biomedical Engineering Department maintains a machine shop in the building, managed by a skilled machinist; some machines (lathe, mill, drill press, bandsaw, etc.) are available to the P.I. (pay-for-service at an hourly rate). The machine shop is experienced in making devices and parts used in chronic recording experiments. The P.I.'s laboratory has an active collaboration with Dr. Stewart Hendry's neuroanatomy laboratory at the Mind Brain Institute in Johns Hopkins University.

Miller Lab: The Miller lab is a part of the Cognitive Neural Systems group in the Department of Psychology and the Neurosciences Graduate Program. The former meets weeks to either hear talks from outside speakers or hear presentations of from students or post-docs from one of the 10 labs in this group (Anagnostaris, Aron, Gentner, Gremel, Miller, Reinagel, Serences, Voytek, Vul, Saygin). The Neuroscience Seminars provide weekly talks and opportunities for interactions with the broader neuroscience faculty across the campus. The machine shop at UCSD and Scripps Institute of Oceanography have each fabricated material for the laboratory. Both are available for any custom machining needed for this study.

Equipment [From parent award]

Wang Lab (JHU):

- Three full-size soundproof chambers (IAC-1204) for conducting neural recording experiments or combined behavior-physiology experiments, one of which is specifically configured to measure full-field spatial receptive fields using a 24-speaker free-field speaker array. Two small soundproof chambers for conducting behavioral training. Each of the soundproof chambers is equipped with computer-controlled stimulus generation and data acquisition systems (Tucker-Davis Technologies). All sound signals are generated using a customized Matlab program (Mathworks) and delivered at a nominal sampling rate of 100kHz at 16-bit through a DAQ card (National Instruments, PICe-6323), followed by a programmable attenuator (Tucker Davis Technologies, PA5), and an audio amplifier (Crown Audio, model D-75A).

- Several microdrives, amplifiers, oscilloscopes and other equipment for neural recording experiments.

- Two eye tracking systems (I-SCAN) for monitoring animal's behaviors.

OMB Number: 4040-0010
Expiration Date: 12/31/2022

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

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

Position/Title*: Professor
Organization Name*: JOHNS HOPKINS UNIVERSITY
Department: Biomedical Engineering
Division: School of Medicine
Street1*: Johns Hopkins University
Street2: 720 Rutland Ave
City*: Baltimore
County:
State*: MD: Maryland
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 212052109

Phone Number*: (410) 614-4547 Fax Number: (410) 614-9599

E-Mail*: xiaoqin.wang@jhu.edu

Credential, e.g., agency login: [redacted]

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

Degree Type: Degree Year:

Attach Biographical Sketch*: File Name: Biosketch_XiaoqinWang_U24_Supp_Oct2020.pdf

Attach Current & Pending Support: File Name:

Tracking Number: GRANT13228921
Funding Opportunity Number: PA-18-591 . Received Date: 2020-10-16T15:46:33.000-04:00

OMB No. 0925 0001/0002 (Rev. 08/12 Approved Through 8/31/2015)

BIOGRAPHICAL SKETCH

Prov de the fo ow ng nformat on for the Sen or/key personne and other s gn f cant contr butors.
Fo ow th s format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Wang, Xiaoqin

eRA COMMONS USER NAME (credential, e.g., agency login) [redacted]

POSITION TITLE: Professor of Biomedical Engineering and Neuroscience

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Sichuan University, Sichuan, China	B.S.	07/1984	Electrical Engineering
University of Michigan, Ann Arbor, MI	M.S.E.	05/1986	Electrical Engineering and Computer Science
Johns Hopkins University, Baltimore, MD	Ph.D.	05/1992	Biomedical Engineering & Auditory Neurosci.
University of California, San Francisco, CA	Postdoctoral	08/1995	Cortical Neurophysiol & Neural Plasticity

A. Personal Statement

I was initially trained as an electrical engineer with a strong background in mathematics and engineering. I became interested in how the brain processes sensory information in graduate school and have pursued this passion ever since. I have studied both auditory and somatosensory systems in a variety of animal models, from rodents to non-human primates, from the periphery to the cerebral cortex in a wide range of experiments utilizing innovative experimental, computational and engineering approaches. I have tackled challenging problems in auditory neuroscience and gained considerable experience in managing parallel research projects along multiple directions. My primary research interest is to understand neural mechanisms underlying perception and production of communication sounds (speech and vocalizations) and auditory-vocal interactions. My laboratory pioneered the common marmoset (*Callithrix jacchus*) as a model system to study neural basis of hearing and vocal communication and has maintained a large breeding colony since 1995. At Johns Hopkins University, I have mentored more than 30 graduate students and postdoctoral fellows. A number of my formal trainees have become independent investigators in academic positions.

1. Wang, X., M.M. Merzenich, K. Sameshima and W.M. Jenkins. Remodeling of Hand Representation in Adult Cortex Determined by Timing of Tactile Stimulation. *Nature*, 378: 71-75 (1995).
2. Wang, X., T. Lu, R.K. Snider and L. Liang. Sustained firing in auditory cortex evoked by preferred stimuli. *Nature* 435: 341-346 (2005). PMID: 15902257
3. Bendor, D. A. and X. Wang. The neuronal representation of pitch in primate auditory cortex. *Nature* 436:1161-1165 (2005). PMID: 16121182
4. Eliades, S.J. and X. Wang. Neural Substrates of Vocalization Feedback Monitoring in Primate Auditory Cortex. *Nature* 453: 1102-1106 (2008). PMID: 18454135

B. Positions and Honors

Positions and Employment

1995-2002 Assistant Professor, Departments of Biomedical Engineering and Neuroscience, Johns Hopkins University School of Medicine

2002-2005 Associate Professor, Departments of Biomedical Engineering and Neuroscience, Johns Hopkins University School of Medicine
2005-present Professor, Departments of Biomedical Engineering, Neuroscience and Otolaryngology, Johns Hopkins University School of Medicine

Other Experience and Professional Memberships

Reviewers: *NIH AUD Study Section (2006, Regular: 2007-2011), IFCN-8 Study Section (2001), NIDCD R21 &. R03 Study Sections (1998-2000), NSF Grant Review Panelists (2001, 2005, 2009, 2010, 2015)*

Reviewers: *Science, Nature, Nature Neuroscience, PNAS, Neuron, PLoS Biology, Journal of Neuroscience, Journal of Neurophysiology, Current Biology, Neuroscience, Cerebral Cortex, Brain Research, Journal of Comparative Neurology, Behavioral Neuroscience, Journal of Acoustic Society of America, Hearing Research, Journal of Association of Research in Otolaryngology, Neural Computation, Journal of Computational Neuroscience, Annals of Neurology, IEEE Transaction on Biomedical Engineering*.

Co-organizers of "Advances and Perspectives in Auditory Neuroscience (APAN)", an annual satellite symposium at Society for Neuroscience Annual Meeting (2003-present), "Beijing International Workshop on Auditory Neuroscience" (2009, 2012), "The Common Marmoset as a Transgenic Model of the Human Brain in Health and Disease" workshop at HHMI Janelia Research Campus (2015), "Primate Neuroscience Workshop" at Tsinghua University (2015), "Primate Neuroscience: perception, cognition, and disease models" conference at Cold Spring Harbor Asia, Suzhou, China (2017)

Honors

1992 The Kleberg Foundation Postdoctoral Fellowship
1999 Presidential Early Career Award for Scientists and Engineers (PECASE)
2013 Fellow, American Institute for Medical and Biological Engineering (AIMBE)

C. Contribution to Science

1. I pioneered the marmoset model for behavioral and neurophysiological studies of auditory and vocal functions. Marmoset is an especially interesting non-human primate species for neuroscience research because of its rich social behaviors and rapid reproduction rate. The latter is an important factor in creating transgenic animal models. The marmoset has not been widely used in brain research until recently. I began to study marmosets as a postdoctoral fellow at UCSF and have made important contributions to this growing field by developing key chronic neural recording techniques in my laboratory at Johns Hopkins University since 1995. My laboratory was the first to develop both extracellular and intracellular recording techniques in awake and behaving marmosets, the first to develop wireless neural recording technique with chronically implanted multi-channel electrode arrays in freely moving marmosets. My laboratory is also the first to develop an operant conditioning technique to study marmoset's perceptual behaviors. Other laboratories that study the marmoset are now using these techniques. In addition, my laboratory has systematically studied and quantified vocal repertoire in both adult and developing marmosets. We also developed computational models to synthesize marmoset vocalizations based on their statistics. These fundamental studies have paved the way for further studies on behavioral and neural mechanisms underlying vocal communication by marmosets.

    a. Eliades, S.J. and X. Wang. Chronic multi-electrode neural recording in free-roaming monkeys. *J Neurosci Methods.* 172(2):201-214 (2008). PMID: 18572250 PMCID: PMC2553366
    b. Roy S, Wang X. Wireless multi-channel single unit recording in freely moving and vocalizing primates. *J Neurosci Methods*. 203(1): 28-40 (2012). PMID: 21933683 PMCID: PMC3848526
    c. Agamaite, J.A., Chang, C-J, Osmanski, M. S., & Wang, X. A Quantitative Acoustic Analysis of the Vocal Repertoire of the Common Marmoset (*Callithrix jacchus*). *J Acoust Soc Am* 138: 2906-2928 (2015). PMID: 26627765 PMCID: PMC4644241
    d. Pistorio, A.L., B. Vintch, and X. Wang**,** Acoustical analysis of vocal development in a New World primate, the common marmoset (*Callithrix jacchus*). *J. Acoust. Soc. Am.* 120:1655-1670 (2006). PMID: 17004487

2. I have led important discoveries of neural coding mechanisms of auditory cortex. For several decades, the majority of studies of auditory cortex were conducted in anesthetized animals. The progress of the field was relatively slow comparing with the study of the visual system. This was in part due to the fact that

auditory cortex is severely suppressed under anesthesia and neurons in this brain region are highly non-linear. Through a series of quantitative and innovative experiments in alert marmosets, my laboratory has elucidated various neural coding mechanisms by auditory cortex, in particular, how rapidly time-varying sounds are represented by firing-rate based coding schemes. We also demonstrated spectral and spectro-temporal selectivity of auditory cortex neurons. One important observation we made was that the temporal firing pattern of an auditory cortex neuron is associated with the optimality of an acoustic stimulus.

a. Lu, T., L. Liang and X. Wang. Temporal and rate representations of time-varying signals in the auditory cortex of awake primates. *Nat Neurosci*, 4:1131-1138, (2001). PMID: 11593234
b. Barbour, D. and X. Wang. Contrast tuning in auditory cortex. *Science*, 299: 1073-1075 (2003). PMID: 12586943
c. Wang, X., T. Lu, R.K. Snider and L. Liang. Sustained firing in auditory cortex evoked by preferred stimuli. *Nature* 435: 341-346 (2005). PMID: 15902257
d. Bendor, D. A. and X. Wang. Differential neural coding of acoustic flutter within primate auditory cortex. *Nat Neurosci.* 10:763-771 (2007). PMID: 17468752

3. I have led important discoveries of neural representations of pitch and harmonicity in auditory cortex. This is an important area of research in auditory neuroscience because a fundamental structure of sounds encountered in the natural environment is the harmonicity. Harmonicity is an essential component of music found in all cultures. It is also a unique feature of vocal communication sounds such as human speech and animal vocalizations. Through a series of experiments, we have identified a special “pitch center” in marmoset auditory cortex that mirrors a seminar region found in human auditory cortex by other researchers. We also showed that marmosets could perceive and discriminate pitch of harmonic complex sounds and exhibit human-like pitch perception behaviors. Together, our findings suggest that a fundamental organizational principle of auditory cortex is based on the harmonicity. Such an organization likely plays an important role in music processing by the brain. It may also form the basis of the preference for particular classes of music and voice sounds.

a. Bendor, D. A. and X. Wang. The neuronal representation of pitch in primate auditory cortex. *Nature* 436:1161-1165 (2005). PMID: 16121182
b. Osmanski M. S., Song X. and X. Wang. The role of harmonic resolvability in pitch perception in a vocal non-human primate, the common marmoset (Callithrix jacchus). *J. Neurosci.* 33: 9161-9168 (2013). PMID: 23699526 PMCID: PMC3694575
c. Wang X. The harmonic organization of auditory cortex. *Front. Syst. Neurosci.* **7**:114 (2013). doi: 10.3389/fnsys.2013.00114. PMID: 24381544 PMCID: PMC3865599
d. Song, X., Osmanski, M. S., Guo, Y., & Wang, X. Complex pitch perception mechanisms are shared by humans and a New World monkey. *Proc Natl Acad Sci U S A.* 113(3): 781-6 (2016). PMID: 26712015 PMCID: PMC4725463

4. I have led important discoveries of behavioral and neural mechanisms for vocal control and vocal feedback processing in the non-human primate brain. These studies are highly relevant for understanding speech processing mechanisms in the human brain. Until recently, the vast majority of studies on vocal production and feedback processing have been based on songbird models. The marmoset model developed in my laboratory has provided a unique opportunity to study these questions in a primate brain. We have developed behavioral techniques to induce vocal behaviors in laboratory condition and identify regions in the frontal cortex that are involved in vocal production. We have observed for the first time neural activity in auditory cortex that signals vocal feedback perturbations.

a. Eliades, S.J. and X. Wang. Sensory-motor interaction in the primate auditory cortex during self-initiated vocalizations. *J. Neurophysiology*, 89: 2194-2207 (2003). PMID: 12612021
b. Miller, C. T. and X. Wang. Sensory-motor interactions modulate a primate vocal behavior: antiphonal calling in common marmosets. *J. Comp Neurobiol. A.* 192:27-38 (2006). PMID: 16133500
c. Eliades, S.J. and X. Wang. Neural Substrates of Vocalization Feedback Monitoring in Primate Auditory Cortex. *Nature* 453: 1102-1106 (2008). PMID: 18454135

d. Roy S, Miller C, Gottsch D, and Wang X. Vocal control by common marmoset in the presence of interfering noise. *The Journal of Experimental Biology* 214: 3619-3629 (2011). PMID: 21993791 PMCID: PMC3192021

5. My laboratory has developed a cochlear implant model using the marmoset, the first of its kind in this non-human primate species. We have used this unique model to study how the auditory cortex represents CI stimulation and discovered important neural coding properties.

a. Johnson LA, Della Santina CC, Wang X. Temporal bone characterization and cochlear implant feasibility in the common marmoset (Callithrix jacchus). *Hear Res.* 290(1-2): 37-44 (2012). PMID: 22583919 PMCID: PMC3394878
b. Johnson, L.A., Della Santina, C.C., Wang, X. Selective neuronal activation by cochlear implant stimulation in auditory cortex of awake primate. *J Neurosci.* 36(49):12468-12484 (2016). PMCID: PMC5148231
c. Johnson, L.A., Della Santina, C.C., Wang, X. Representations of time-varying cochlear implant stimulation in auditory cortex of awake marmosets (Callithrix jacchus). *J Neurosci.* 37(29): 7008-7022 (2017). PMID: 28634306 PMCID: PMC5518426

D. Research Support

U24-MH123423 Xiaoqin Wang (P.I.) 7/15/2020-5/31/2025
NIH
Bicoastal Marmoset Breeding Center
The overall goal of this project to produce a large number of marmosets to supply the marmoset research community in the U.S. Because of the non-availability of air transport of NHP in U.S. and prohibitively expensive ground transportation of NHP between the east and west coast, these two breeding colonies are strategically located to support the marmoset community in regions near each colony. This is the parent award of this supplement application.

R01-DC03180 Xiaoqin Wang (P.I.) 2/25/2020-1/31/2025
NIH
Information Processing in Auditory Cortex
The overall goal of this study is to understand neural mechanisms for representing species-specific vocalizations in auditory cortex of awake marmosets and the fundamental neural mechanisms that subserve cortical representations of these biologically important sounds. No overlap with the present application.

R01 DC005808 Xiaoqin Wang (P.I.) 3/1/2018-2/28/2023
NIH
Auditory-Vocal Interaction Mechanisms in Primates
The overall goal of this study is to reveal behavioral and physiological mechanisms underlying auditory-vocal interactions in non-human primates using the common marmoset as the model. The specific aims of this project are to study how the vocal production system modulates neural processing in auditory cortex, and whether marmoset vocalizations exhibit experience-based plasticity. No overlap with the present application.

R01 DC014503 Xiaoqin Wang (P.I.) Charles Della Santina (Co-PI) 12/1/2015-11/30/2020
NIH
Cortical processing of cochlear implant signals
The long-term goal of our research is to elucidate neural coding and plasticity mechanisms underlying cortical processing of cochlear implant (CI) signals in the context of vocal communication. We have established a new CI model (the common marmoset) to pursue these questions. The results of this research will help elucidate cortical processes involved in electric hearing and provide insights for improving current cochlear implant designs. No overlap with the present application.

N66001-17-2-4008 Xiaoqin Wang (Lead P.I.) 3/2/2017-3/1/2021
DARPA
Target Neuroplasticity Training (TNT)

The overall goal of this project is to develop a peripheral nerve stimulation training program that will enhance human perceptual and language learning. Laboratories from Johns Hopkins and UCSD will perform animal experiments to understand the neurophysiological basis of VNS-induced cortical plasticity and VNS-enhanced learning and to optimize stimulation parameters to increase the rate of peripheral nerve stimulation enhanced learning. Laboratories from Johns Hopkins, UCSF, University of Iowa and University of Texas - Austin, will perform human studies to understand the neurophysiological mechanisms for plasticity and improved learning with peripheral nerve stimulation. They will also develop invasive and non-invasive peripheral nerve stimulation training protocols to enhance language perception and learning. No overlap with the present application.

T32 EB003383 Xiaoqin Wang (P.I.) 7/1/2015-6/30/2021 (NCE)
NIH/NIDCD
Training Program in Neuroengineering

The central mission of this training program is to produce the next generation of engineers, scientists and educators and to groom the trainees into scientific and engineering leaders. The training program selects outstanding trainees through multi-departmental recruiting efforts and an institution-wide effort to recruit under-represented minority. The training program is structured to provide introductions to select laboratories, mentors and projects, including expanded internship opportunities to industry and the medical school, provide mentoring for career development and eventual career transition. The program includes six theme areas (Neurotechnology, Neuroimaging, Computational Neuroengineering, Systems Neuroscience, Neural Tissue Engineering, and Clinical Neuroengineering) and embraced a number of additional faculty preceptors across eight departments and two divisions. No overlap with the present application.

E. Representative Former Trainees (selected from >30 graduate students and postdocs)

Postdoctoral fellows:
Ross Snider, postdoc (current position: Associate Professor, Montana State University)
Poppy Crum, postdoc (current position: Senior Principal Scientist, Head Scientist at Dolby Laboratories)
Edward Bartlett, postdoc (current position: Associate Professor, Purdue University)
Cory Miller, postdoc (current position: Associate Professor, UCSD)
Yi Zhou, postdoc (current position: Assistant Professor, Arizona State University)
Michael Osmanski, postdoc (current position: Research Associate, Johns Hopkins University)
Lixia Gao, postdoc (current position: Assistant Professor, Zhejiang University, China)

Graduate students:
Dennis Barbour, MD/PhD student (current position: Associate Professor, Washington University)
Thomas Lu, PhD student (current position: Research Scientist, UC Irvine)
Siddhartha Kadia, PhD student (current position: CEO, Evans Analytical Group)
Simil Raghavan, PhD student (current position: Program Officer, National Academy of Engineering)
Daniel Bendor, PhD student (current position: Associate Professor, University College of London, UK)
Elias Issa, PhD student (current position: Assistant Professor, Columbia University)
Srivatsun Sadagopan, PhD student (current position: Assistant Professor, University of Pittsburg)
Steven Eliades, MD/PhD student (current position: Assistant Professor, University of Pennsylvania)
Luke Johnson, PhD student (current position: Assistant Professor, University of Minnesota)
Evan Remington, PhD student (current position: postdoc, MIT)
Lei Feng, PhD student (current position: postdoc, University of Minnesota)
Xindong Song, PhD student (current position: postdoc, Johns Hopkins University)

OMB Number: 4040-0010
Expiration Date: 12/31/2022

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

ORGANIZATIONAL DUNS*: 001910777

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: JOHNS HOPKINS UNIVERSITY

Start Date*: 04-01-2021 **End Date*:** 03-31-2022 **Budget Period: 1**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Xiaoqin		Want		PD/PI	base salary [redacted]				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)

Funding Opportunity Number: PA-18-591 . Received Date: 2020-10-16T15:46:33.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

ORGANIZATIONAL DUNS*: 001910777
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: JOHNS HOPKINS UNIVERSITY

Start Date*: 04-01-2021 **End Date*:** 03-31-2022 **Budget Period: 1**

C. Equipment Description

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

Equipment Item	**Funds Requested ($)***
1 . Marmoset caging designed by Tecniplast	172,672.00
Total funds requested for all equipment listed in the attached file	
Total Equipment	**172,672.00**

Additional Equipment: File Name:

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

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

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

Tracking Number: GRANT13228921
Funding Opportunity Number: PA-18-591 . Received Date: 2020-10-16T15:46:33.000-04:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1

ORGANIZATIONAL DUNS*: 001910777
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: JOHNS HOPKINS UNIVERSITY

Start Date*: 04-01-2021 **End Date*:** 03-31-2022 **Budget Period: 1**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Animal Care per diem	76,650.00
Total Other Direct Costs	**76,650.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**249,322.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	63.75	76,650.00	48,864.00
		Total Indirect Costs	**48,864.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number)	Department of Health and Human Services, Steven Zuraf, (301)492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**298,186.00**

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*
	298,186.00

L. Budget Justification*	File Name: BudgetJustification_U24_Supp_Oct2020.pdf (Only attach one file.)

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

Tracking Number: GRANT13228921
Funding Opportunity Number: PA-18-591 . Received Date: 2020-10-16T15:46:33.000-04:00

Budget Justification

Major Equipment:

1) Years 1 ($172,672): Customized marmoset caging system designed by Tecniplast. Our breeding colony currently use this type of housing cases. It's flexible and can be configured to accommodate the needs of both breeding families, their offspring and aging animals ([proprietary/pricing/estimated costs]).

Animal expenses:

Animal care per diem ($76,650): Housing 21 marmosets for one year at the per diem rate of $10 per animal per day.

Other Expenses: None.

TECNIPLAST

Customer:
Johns Hopkins Univ
Ba t more MD 21205

QUOTATION N° UQ2000230

Rev s on N°	1
C ent Serv ce D	CS 2019 0035737
ssue Date	08/24/2020
Prepared by	Anne e tham

Qty	Description	Unit Price	Disc.	Disc. Price	TOTAL
10 pcs	MARMRACKQFE - Ma mose Quad cages Fu y Equ pped nc udees fou 5" food bow s, fou Nes ng boxes, fou S/S bo e ho de s comp e e w h 700m Po yca bona e bo es and S/S caps, wo opaque cage d v de s A ve ca s d ng doo s w be made of SS Mesh	$	proprietary/pricing/estimated costs		
10 pcs	S DE PANE S (K T OF 4 PANE S TO COVER BOTH S DES OF THE CAGES) *(MARMQSP)*	$			
10 pcs	BACK PANE S (K T OF 4 PANE S TO COVER THE ENT RE BACK S DE OF THE CAGES) *(MARMQBP)*	$			

Sub o a	$	proprietary/pricing/ estimated costs
F e gh	$	
	$	
GRAND TOTAL	**$**	

SHIPMENT INFORMATION

Sh p	Bes Way
De ve y Te ms	FOB DEST, FRE GHT PREPA D & ADDED
ead T me	To Be De e m ned

Terms & Conditions

- Cu ency USD
- Taxes Taxes no nc uded
- Paymen Te ms 30% Down, Ba ance due NET 30
- Quo a on va d y 10/23/2020
- Refe o h ps //goo g /wC DRg fo a comp e e s ng of ou Te ms & Cond ons By ac ng on h s quo a on he cus ome acknow edges and conf ms ha he/she has ev ewed and ag eed o hese e ms

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals ($)	
Section A, Senior/Key Person		0.00
Section B, Other Personnel		0.00
Total Number Other Personnel	0	
Total Salary, Wages and Fringe Benefits (A+B)		0.00
Section C, Equipment		172,672.00
Section D, Travel		0.00
1. Domestic	0.00	
2. Foreign	0.00	
Section E, Participant/Trainee Support Costs		0.00
1. Tuition/Fees/Health Insurance	0.00	
2. Stipends	0.00	
3. Travel	0.00	
4. Subsistence	0.00	
5. Other	0.00	
6. Number of Participants/Trainees	0	
Section F, Other Direct Costs		76,650.00
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. Other 1	76,650.00	
9. Other 2	0.00	
10. Other 3	0.00	
Section G, Direct Costs (A thru F)		249,322.00
Section H, Indirect Costs		48,864.00
Section I, Total Direct and Indirect Costs (G + H)		298,186.00
Section J, Fee		0.00
Section K, Total Costs and Fee (I + J)		298,186.00

Funding Opportunity Number: PA-18-591 . Received Date: 2020-10-16T15:46:33.000-04:00

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

Expiration Date: 02/28/2023

1. Vertebrate Animals Section

Are vertebrate animals euthanized? ● Yes ○ No

If "Yes" to euthanasia

Is the method consistent with American Veterinary Medical Association (AVMA) guidelines?

● Yes ○ No

If "No" to AVMA guidelines, describe method and provide scientific justification

2. *Program Income Section

*Is program income anticipated during the periods for which the grant support is requested?

○ Yes ● No

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

*Budget Period	*Anticipated Amount ($)	*Source(s)

Tracking Number: GRANT13228921

Funding Opportunity Number: PA-18-591 . Received Date: 2020-10-16T15:46:33.000-04:00

PHS 398 Cover Page Supplement

3. Human Embryonic Stem Cells Section

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

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

❑ Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Cell Line(s) (Example: 0004):

4. Human Fetal Tissue Section

*Does the proposed project involve human fetal tissue obtained from elective abortions? ❍ Yes ● No

If "yes" then provide the HFT Compliance Assurance

If "yes" then provide the HFT Sample IRB Consent Form

5. Inventions and Patents Section (Renewal applications)

*Inventions and Patents: ❍ Yes ● No

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

*Previously Reported: ❍ Yes ❍ No

6. Change of Investigator/Change of Institution Section

❑ Change of Project Director/Principal Investigator

Name of former Project Director/Principal Investigator

Prefix:

*First Name:

Middle Name:

*Last Name:

Suffix:

❑ Change of Grantee Institution

*Name of former institution:

PHS 398 Research Plan

OMB Number: 0925-0001
Expiration Date: 02/28/2023

Introduction	
1. Introduction to Application (for Resubmission and Revision applications)	
Research Plan Section	
2. Specific Aims	SpecificAims_U24_Supp_Oct2020_Rev.pdf
3. Research Strategy*	ResearchStrategy_U24_Supp_Oct2020_Rev.pdf
4. Progress Report Publication List	
Other Research Plan Section	
5. Vertebrate Animals	VertebrateAnimals(JHU)_U24_Oct2019.pdf
6. Select Agent Research	
7. Multiple PD/PI Leadership Plan	
8. Consortium/Contractual Arrangements	
9. Letters of Support	
10. Resource Sharing Plan(s)	Resource_Sharing_Plan_U24_Oct2019.pdf
11. Authentication of Key Biological and/or Chemical Resources	
Appendix	
12. Appendix	

Tracking Number: GRANT13228921
Funding Opportunity Number: PA-18-591. Received Date: 2020-10-16T15:46:33.000-04:00

Specific Aims

Nonhuman primates (NHP) are crucial animal models for research on Alzheimer's disease and its related dementias because of their closest evolutionary relatives of humans, with whom they share anatomical, physiological, and gene interactions features. The common marmoset (Callithrix jacchus) is a NHP model of increasing importance for aging research. This new world primate provides some unique advantages for the study of aging and aging-related disorders, including its relatively short lifespan among all the NHP used in biomedical research. Marmosets are known to develop amyloidosis, a major biological marker for Alzheimer's disease, naturally at old age. Amyloidosis is also transmissible to this species, making it an extremely promising NHP model for Alzheimer's disease. There has been an increasing number of investigators who are currently using or would like to use marmosets as a model system to study aging and age-related diseases including Alzheimer's disease. However, there is a significant bottleneck for the research in this field. There are currently no reliable distributors of marmosets for biomedical research in the country. The situation is even direr for researchers who need access to aging marmosets. Recognizing such a bottleneck, NIH has recently funded two marmoset breeding programs including the parent award of this application ("Bicoastal Marmoset Breeding Center", U24-MH123423). The goal of this administrative supplement application is to fill the gap in the availability of aging marmosets for the study of Alzheimer's disease and its related dementias. Because our breeding center will be housing a sizable number of marmosets over all ages, we could use this center to develop a resource of aging marmosets for Alzheimer's disease studies if supported by additional funding through this supplement. This resource will be extremely valuable to the scientific community studying Alzheimer's disease and its related dementias.

Aim 1. Establish additional capacity of the Bicoastal Marmoset Breeding Center to maintain aging marmosets

We propose to use this administrative supplement to allow the Bicoastal Marmoset Breeding Center to maintain aging marmosets. In the parent U24 award, the center will house a number of breeders and their offspring. These offspring will be distributed to marmoset users as experimental subjects once they reach >1.5 years of ages. Our breeding colonies will have aging marmosets that can no longer be used as breeders and are not suitable for distribution as experimental animals to most marmoset users. However, these aging marmosets will be an important asset to the Alzheimer's disease researchers. Currently, there are no available sources for these researchers to obtain aging marmosets. This administrative supplement award would allow us to acquire additional housing cages and resources in order to maintain aging marmosets within our colonies till they can be distributed to Alzheimer's disease researchers. At the present funding level of the parent U24 award, we are not able to keep any animals once they are retired from breeding. This application is in response to NIH RFA NOT-AG-20-034 which states "The work may include pilot projects or resource development". The proposed aim is within the scope of the parent U24 award and this RFA.

Research Strategy

A. Significance

Nonhuman primates (NHP) are crucial animal models for research on Alzheimer's disease and its related dementias because of their closest evolutionary relatives of humans, with whom they share anatomical, physiological, and gene interactions features. The common marmoset (Callithrix jacchus) is a NHP model of increasing importance for aging research. This New World primate provides some unique advantages for the study of aging and aging-related disorders, including its relatively short lifespan among all the NHP used in biomedical research.

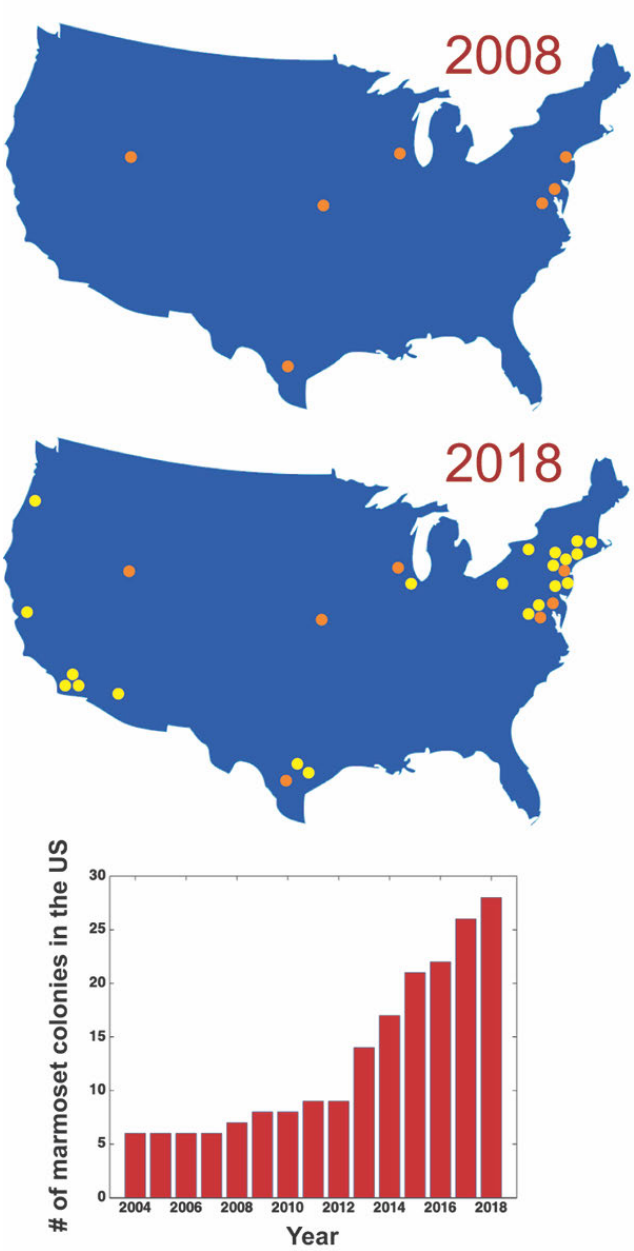

Figure 1. Growth of Marmoset Colonies in the United States. [Top] The schematic maps of the US show the marmoset research colonies [above] in 2008 in orange dots, while [Middle] plots the new colonies in yellow dots that have been established through 2018. [Bottom] Bar graph plots the # of marmoset colonies by year for the past 15 years. Notably, most of the growth in has occurred since 2013.

Although marmosets have been used as a model system in biomedical research for several decades, until recently it was generally regarded as a niche model system. In less than a decade, however, this landscape has dramatically changed in the United States. The number of marmoset colonies increased from 8 in 2008 to 28 in 2018 and the trend has continued (Figure 1). In addition, there has been an increasing number of investigators who are currently using or would like to use marmosets as a model system to study aging and age-related diseases including Alzheimer's disease. However, there is a significant bottleneck for the research in this field. There are currently no reliable distributors of marmosets for biomedical research in the country. The situation is even direr for researchers who need access to aging marmosets. Recognizing such a bottleneck, NIH has recently funded two marmoset breeding programs including the parent award of this application ("Bicoastal Marmoset Breeding Center).

The goal of this administrative supplement application is to fill the gap in the availability of aging marmosets for the study of Alzheimer's disease and its related dementias. Because our breeding center will be housing a sizable number of marmosets over all ages, we could use this center to develop a resource of aging marmosets for Alzheimer's disease studies if supported by additional funding through this supplement. This resource will be extremely valuable to the scientific community studying Alzheimer's disease and its related dementias.

We propose to use this administrative supplement to allow the Bicoastal Marmoset Breeding Center to maintain aging marmosets. In the parent U24 award, the center will house a number of breeders and their offspring. These offspring will be distributed to marmoset users as experimental subjects once they reach >1.5 years of ages. Our breeding colonies will have aging marmosets that can no longer be used as breeders and are not suitable for distribution as experimental animals to most marmoset users. However, these aging marmosets will be an important asset to the Alzheimer's disease researchers. Currently, there are no available sources for these researchers to obtain aging marmosets. This administrative supplement award would allow us to acquire additional housing cages and resources in order to maintain aging marmosets

within our colonies till they can be distributed to Alzheimer's disease researchers. At the present funding level of the parent U24 award, we are not able to keep any animals once they are retired from breeding. This application is in response to NIH RFA NOT-AG-20-034 which states "The work may include pilot projects or resource development". The proposed aim is within the scope of the parent U24 award and this RFA.

Marmosets as a model of Alzheimer's disease

Alzheimer's disease (AD) is a severe chronic neurodegenerative disorder with increasing prevalence with aging. A hallmark characteristic of AD is the accumulation in the brain of amyloid-β plaques (amyloidosis). The marmoset is suggested as a potential AD animal model as amyloidosis is transmissible to this species (Baker et al. 1993, Maclean et al. 2000, Ridley et al. 2006, Philippens et al. 2017). It has also been shown that marmosets can develop amyloidosis naturally at old age (Maclean et al. 2000, Ridley et al. 2006, Guela et al. 2002, Mansfield 2003). The amyloidosis is an important hallmark of AD and constructs the basis of the amyloid cascade hypothesis (Hardy and Higgins 1992). For patients with AD, a pro-inflammatory state is increasingly associated with amyloid-β (Aβ) aggregates, that characterizes AD pathogenesis.

The non-human primate of choice for studying mechanisms of brain function has traditionally been the macaque. However, the common marmoset represents a complementary species with advantageous characteristics for studying a range of human diseases. First, the marmoset has strong reproductive power and a relatively short lifespan. Macaques reach sexual maturity after ~5 years and give birth once a year to a single offspring. Rhesus and cynomolgus macaques typically live 25 years and can live up to 30 and 40 years in captivity, respectively. This lifespan presents a number of logistical challenges for longitudinal studies of age-related disorders, including neurodegenerative diseases. In contrast, marmosets reach sexual maturity at 18 months of age, and females give birth twice a year, usually to non-identical twins or triplets. Based on average birth rates, to obtain 400 offspring from 50 breeding females, it would take 6 years in marmosets and 20 years in rhesus macaques. Marmosets typically live about 10-14 years in captivity and are considered aged after only 8 years. Furthermore, the efficiency of *in vitro* fertilization of oocytes (100/collection/animal) is very high (>50%), making marmosets highly economical and scalable for generating the number of genetically modified marmosets needed for preclinical evaluation.

Second, because of marmosets' small body size, they can be housed in social groups consistent with the size and composition of groups in the wild. This is particularly important because the range of sophisticated social and cognitive behaviors that emerge naturally within social groups – and that are shared with humans (Miller et al. 2016, Mitchell and Leopold 2015) - can be effectively studied under more controlled laboratory conditions. This makes them ideal for modeling the broad range of human diseases associated with aging, especially neurodegenerative and psychiatric disorders including Alzheimer's disease, which ultimately require a primate model due to the idiosyncrasies of primate brain organization and function. Moreover, since marmosets can be housed in their natural social group, the anxiety, depression, and social withdrawal common amongst laboratory housed rhesus macaques (Camus et al. 2013) does not emerge. Because these behaviors are atypical of marmosets in laboratories, genetic models of psychiatric disorders will not be confounded by these environmental factors. Third, in contrast to rhesus macaques, marmosets are free of Herpes B viruses, making the species safer to work with. Finally, technologies for generating transgenic marmosets have already been developed, and their short generation time represents a distinct advantage for creating and expanding transgenic lines over larger nonhuman primate species.

Selected publications on amyloidosis (a hallmark of AD) and marmosets:

Baker HF, Ridley RM, Duchen LW, Crow TJ, Bruton CJ. 1993. Evidence for the experimental transmission of β-amyloidosis to primates. Int J Exp Path 74:441-454.

Guela C, Nagykery N, Wu C-K. 2002. Amyloid-β deposits in the cerebral cortex of the aged common marmoset (*Callithrix jacchus*): incidence and chemical composition. Acta Neuropathol 103:48-58.

Hardy J, Higgins G (1992) Alzheimer's disease: The amyloid cascade hypothesis. Science 256, 184-185.

Maclean CJ, Baker HF, Ridley RM, Mori H. 2000. Naturally occurring and experimentally induced β-amyloid deposits in the brains of marmosets (Callithrix jacchus). J Neural Transm 107:799-814.

Mansfield K. 2003. Marmoset models commonly used in biomedical research. Comp Med 53:383-392.

Philippens IH, Ormel PR, Baarends G, Johansson M, Remarque EJ, Doverskog M. 2017. Acceleration of amyloidosis by inflammation in the amyloid-beta marmoset monkey model of Alzheimer's disease. J Alzheimers Dis 55:101-113.

Ridley RM, Baker HF, Windle CP, Cummings RM. 2006. Very long term studies of the seeding of β-amyloidosis in primates. J Neural Transm 113:1243-1251.

The collective objective of the marmoset research community to leverage the benefits of this NHP model system in order to accelerate our knowledge of the genetic, physiological and environmental factors underlying human disease. While a diversity of animal models has significantly contributed to our general knowledge of the cellular and molecular basis of disease in biological systems, precisely how these processes unfold within the uniquely primate physiology remains sorely under studied. All of the Community Priorities and Recommendations focus on establishing essential resources and infrastructure necessary for marmosets to bridge this considerable gap and realize the model's potential as a keystone organism in biomedical research for the next generation.

B. Approach

B1) History of marmoset colony and research at JHU

Dr. Wang established the marmoset colony at Johns Hopkins University School of Medicine in 1995 and has been successfully breeding marmosets since then. Since the inception of our colony, we have maintained a well-managed breeding program and avoided in-breeding. Our breeding program has been highly successful over the past 24 years, with each breeding pair producing on average 3 live offspring per year. Dr. Wang's lab and veterinarians at Johns Hopkins University School of Medicine have worked with marmosets for over 20 years and gained considerable experience in caring this non-human primate species. Over the years, our breeding colony has produced animals used in a number of NIH-funded research projects. Dr. Wang's laboratory has pioneered the marmoset model for behavioral and neurophysiological studies of auditory and vocal functions and has made important contributions to this growing field by developing key behavioral, surgical, and neurophysiological techniques (Wang 2018). They are the first to develop both single neuron extracellular and intracellular recording techniques in awake and behaving marmosets (Lu et al. 2001, Wang et al. 2005), the first to develop wireless neural recording technique with chronically implanted multi-channel electrode arrays in freely moving marmosets (Eliades and Wang, 2008, Roy and Wang 2012) and the first to develop an operant conditioning technique to study marmoset's auditory perceptual behaviors (Remington et al. 2012).

B2) The marmoset colonies at JHU

- **The existing JHU marmoset colony** is located in the animal facility on [redacted] with a total of 1,728 Sq ft animal housing space.

- **The Bicoastal Marmoset Breeding Center colony**, funded by the parent U24 award, is located on [redacted], within an existing large-animal housing facility and serviced by Animal Care Services of JHU. Sufficient animal housing space has been allocated to the breeding center to accommodate the new breeding center's needs. The breeding colony will have 15 breeding pairs in Year-1, add 10 breeding pairs in Year-2 and 7 breeding pairs in Year-3, to reach a total of 32 breeding pairs by the end of Year-3. We plan to maintain 32 active breeding pairs for Year-4 and Year-5. We will obtain initial breeding pairs from the existing colony at JHU.

JHU Census. JHU existing colony currently has 210 marmosets, ~150 are 1.5 years or older. Over the past two years, we deliberately increased our colony size in anticipation of the national needs for the marmosets by the research community and to support our own growing transgenic marmoset program.

JHU Colony Distribution. There 50 active breeders (25 breeding pairs), 79 being on hold as potential future breeders, 45 experimental animals, 25 potential future experimental animals. The experimental animals are used in invasive or non-invasive protocols. Some of these animals will be transferred to the new breeding center colony to start the breeding program.

JHU Pedigree. The animals in the JHU colony are from different sources. Over the past 24 years, we have periodically purchased marmosets from various sources to diversify genetic background of the animals in the

colony. proprietary/confidential [redacted]

JHU has a large, well-established AAALAC-accredited animal care program. We have strong veterinary expertise from our leading department on Molecular and Comparative Pathobiology which will allow us to provide expert veterinary care for transgenic marmosets with disorders. Special care will be needed to care transgenic marmosets so veterinary expertise is essential. Dr. Jessica Izzi (co-I of this application) has extensive experience in working with marmosets both at NIH and JHU.

B3) Research plan for this supplement award

Our aim is to establish additional capacity of the Bicoastal Marmoset Breeding Center colony to maintain aging marmosets. The funding of the parent award only allows us to house breeding pairs and their offspring. These offspring will be distributed to marmoset users as experimental subjects once they reach >1.5 years of ages. Our breeding colonies will have aging marmosets that can no longer be used as breeders and are not suitable for distribution as experimental animals to most marmoset users. We plan to use the fund from this supplement award to purchase additional housing cages in order to maintain aging marmosets within our colony till they can be distributed to Alzheimer's disease researchers. At the present funding level of the parent U24 award, we are not able to keep any animals once they are retired from breeding. In addition, we have existing aged animals from our colony to commit to this new project.

Additional considerations for the proposed expansion of the breeding center capacity:

- We do not expect this supplement award to have any effects on the breeding and distribution of marmosets for the neuroscience community (parent award). We are fully committed to produce and distribute young adult marmosets to the neuroscience community. This supplement award (if funded) will allow us to add additional older animals to our breeding colony as well as allowing us to keep aging animals once they are retired from active breeding. At the present time, we do not have an "exit plan" for older animals and the parent award only pays for housing active breeders and their offspring.

- Although the use of marmosets as aging models is significantly expanding, their use as animal models of Alzheimer's diseases is still at an early stage. However, this is a catch-22 situation. Many researchers who would be interested in using marmosets for Alzheimer's studies have no access to aging marmosets. We have received many requests from such researchers in the past few years for obtaining aging marmosets including neuroscientists who are studying the aging brain affected by AD disorders.

- We envision using this one-year supplement award to build the additional capacity in our breeding center to house aging animals such as customized marmoset cages. After this funding period, the aging animals will be distributed to researchers for Alzheimer's studies. We plan to use this added capacity to continue housing aging animals in our colony and use the proceeds from animal distribution to pay for the cost of maintaining these animals after the supplement award ends.

Vertebrate Animals [From parent award]

1. Proposed use of animal

We propose to use common marmosets (*Callithrix jacchus*) in this study. The proposed research has been approved by the Johns Hopkins University Animal Use and Care Committee (Protocol# PR18M345). We plan to house up to 250 marmosets each year in the proposed breeding program.

2. Procedures

A breeding colony of marmosets has been maintained at JHMI Animal Facility since 1995. Marmosets reach sexual maturity around 18 months of age. We usually pair a male and a female as a breeder at 1.5-2 years of age. They typically begin breeding 6-12 months after being pair-housed (in a large family cage). Marmosets typically give births twice a year. The offspring usually stays with parents in the family cage till they are one year old. Breeding takes place naturally in the colony. Breeding pairs are housed in family cages where offspring stays with parents till they reach ~1 year of age. Young adult marmosets will be pair-housed with the same sex partner after they are removed from their natal families at approximately 1 year of age until they reach approximately 1.5-2 years of age when they are either pair-housed with an opposite sex partner to form a new breeding pair or pair-housed with a same sex partner if they are used in experimental protocols.

Descriptions of routine care, caging and husbandry, clinical monitoring, blood sampling, etc.

Animals in our colony are either singly-housed, pair-housed (as juveniles or breeding pairs), or in large family cages with up to 3 litters. Animals are pair-housed whenever possible. Singly-housed or pair-housed animals consist of study animals with protocol-related exemptions or animals that do not have a suitable conspecific available. Juveniles are weaned between 1.5-2 years of age. Visual health checks are conducted a minimum of once daily by animal care staff and any clinical concerns are reported directly to the veterinary staff. Animals are fed LabDiet 5LK6 Callitrichid Diet once daily and are offered a variety of feed enrichment at least 3x per week. Chlorinated water is provided in bottles that are changed daily. Non-edible enrichment consists of wooden sticks, huts, forage boards, and other toys. Non-edible enrichment and cages are sanitized every 2 weeks on alternating schedules.

All animals in the colony are weighed every two weeks and weights are recorded and tracked in an excel sheet. Any concerning weight trends are reported to the veterinary staff.

Animals receive a full routine physical examination with blood work (CBC and chemistry) and full body radiographs once per year. Additional clinical monitoring is performed when warranted based on health concerns noted by technical staff, care staff, or veterinarians when animals are scheduled to start on study or undergo surgery. Fecal samples are submitted as indicated to test for pathogens such as *Giardia spp., Klebsiella pneumonia, Salmonella,* and *Campylobacter spp.* Additional diagnostics are performed by veterinary staff as indicated, including but not limited to abdominal ultrasound, cystocentesis, and bone marrow biopsy. A veterinarian is present to either assist with or perform all surgical procedures.

Description of how large litters are managed:

Upon birth, the dam and infants are hand-caught and the infants are weighed and examined by a veterinarian for any congenital defects or other concerns. The dam is checked to confirm lactation and to confirm that the uterus is empty (no additional fetuses or placenta present). If the animal gives birth to more than 2 infants, the additional infants are either cross-fostered, hand-reared, or euthanized. Typically, the smallest infant is chosen and/or the infant is chosen based on sex (for instance, if 2 males and 1 female are born, 1 male may be chosen to remove from family group). The veterinarian will determine the fate for each infant based on available fosters in the colony or ability to hand-rear successfully. In most cases, hand-rearing is only chosen if the animal is extremely valuable (i.e. transgenic marmoset). A foster family is chosen based on good rearing history and having recently given birth (dam is actively nursing or lactating). Foster family should either have a singleton or no infants.

Birth control of the breeding females:

Because of considerations of a particular breeding family's health condition, we sometimes need to control the rate of births of certain breeding pairs. Estrumate, a synthetic prostaglandin analog structurally related to PGF2α, will be used to control reproduction in breeding pairs on a protocol adapted from one used by the Wisconsin Regional Primate Research Center for their colony of captive-bred common marmosets. Giving a PGF2α analog disrupts the corpus luteum in pregnant females, resulting in a loss of support for early

pregnancy. There are no documented long-term effects (physical or behavioral) and as soon as treatment is halted, normal pregnancy can occur at the next regular estrus cycle. Benefits include keeping the family units together, slowing down the increase in colony size, and allowing the breeding female's body to replenish itself. The PGF2α analog will be administered in early pregnancy, detected by manual uterine palpation and determined by uterine diameter standard measurements derived by WRPRC. The uterine palpation will be done in awake, hand restrained, breeding females and, if uterine diameter indicates early pregnancy, Estrumate will be administered via IM injection. The standard dose is 0.75μg PGF2α analog given once intramuscularly. The animal may be checked after 3 to 4 days for decrease in uterine diameter. For resistant pregnancies the dose is increased to 1.0μg PGF2α analog given IM once daily for two days. The process is repeated every 4 to 6 weeks. The considered alternatives to using a PGF2α analog included separation of mates, causing extreme stress among all group members; oophorectomy in breeding females, an permanent and invasive procedure with many possible physical complications and disruption of the family unit (breeding females inhibit estrus in submissive females through scent marking and it is unknown what effect lack of estrogen may have on this process); vasectomy in the breeding male, also a very invasive procedure, possibly permanent, which is difficult in such a small species; and an implant birth control device in the breeding female, a method used widely in captive nonhuman primate species but which is not feasible in the common marmoset because of the very small amount of proper tissue in which to place the implant.

3. Justification of the use of animals

The common marmoset is the ideal nonhuman model for neuroscience. The species is amenable to functional neuroimaging techniques commonly used in humans, but can also be studied with various invasive neurophysiological procedures. The marmoset is particularly suitable for the following reasons: 1) the species' exhibits a rich repertoire of cognitively sophisticated behaviors that typify primates, as well as social cognitive behaviors – such as imitation and prosociality - which are rare amongst nonhuman primates but characteristic of human sociality 2) it is one of a few primate species that can be easily bred in captivity (not an endangered species) and easy to handle (body weight 300-500g), and 3) the species has an almost entirely lissencephalic (smooth) cortex, making all areas of cortex much easier to access experimentally than many other primate species.

4. Veterinary Care

The veterinary care will be provided by the Research Animal Resources (RAR) department at JHU (AAALAC accredited), which is very experienced in caring primates including marmosets. RAR provides central support service for animal procurement, housing, clinical care, and veterinary research support and collaboration at Johns Hopkins University campuses, including the East Baltimore medical school campus, Homewood campus, and Bayview campus. The department is overseen by 4 faculty veterinarians with ACLAM board certification. In addition, RAR provides post-doctoral training for veterinarians specializing in laboratory animal medicine.

5. Procedure to Limit Pain and Discomfort

There are no experimental procedures to be performed to the animals in this project. If a surgery is needed for clinical reasons, a long acting anesthetic (0.5% Marcaine) will be used to infiltrate the wound. This will be helpful in reducing postprocedural pain. A continuous, powerful, short acting anesthetic (isoflurane) for titration of anesthesia to an areflexic level. The anesthetic level (withdraw and corneal reflexes) and heart and respiratory rates will be monitored continuously by a second experimenter not involved in surgery. Isoflurane administration will be adjusted to areflexia and to maintain the heart and respiratory rates at the baseline values. Postoperatively, Buprenorphine (0.005mg/kg) will be given subcutaneously to further minimize pain and discomfort. After the surgery, the animal will be evaluated daily by the veterinarians and lab staffs until it fully recovers. Veterinary consultation will be requested to advise treatment, should any problems arise.

6. Method of Euthanasia

When an animal needs be euthanized for clinical reasons, it will be first sedated by ketamine (IM, 20mg/kg) and then euthanized with a lethal dose of intravenous sodium pentobarbital (IP, 150mg/kg), followed by intracardial perfusion with a 4% paraformaldehyde (to preserve the brain tissue for histology). This is a fast and effective method that has been successfully used in many small New World primates, including marmosets, and is consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association (AVMA).

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Resource Sharing Plan: [From parent award]

The proposed Bicoastal Marmoset Breeding Center will produce large quantities of marmosets for distribution to the broader Neuroscientific community. There are two potential shared resources that will be available from this effort. First, are the animals themselves. We anticipate that by Year 2 of the project, we will be able to sell animals to researchers across the US, with an increased number of animals available in subsequent years. Because of the high demand for marmosets currently, we will distribute animals based on a combination of availability and the needs of individual researchers. Until demand has stabilized, we will commit equal numbers of animals annually to researchers in the following three categories: New Investigators, NIH funded neuroscience projects and large scale molecular neuroscience projects. Researchers within each of these categories can submit requests and will be filled in the order they are received. We will limit the number animals received by any one Investigator to 10 for the first two categories and 20 for the molecular neuroscience projects to ensure that animals are distributed broadly across the community until demand has stabilized. A second resource that will be generated by this project are the genetics of the population. All animals in the Center will be made available for genotyping under the direction of the Marmoset Coordination Center. The outcome of these results may then be utilized to optimize genetic diversity across the US marmoset population.