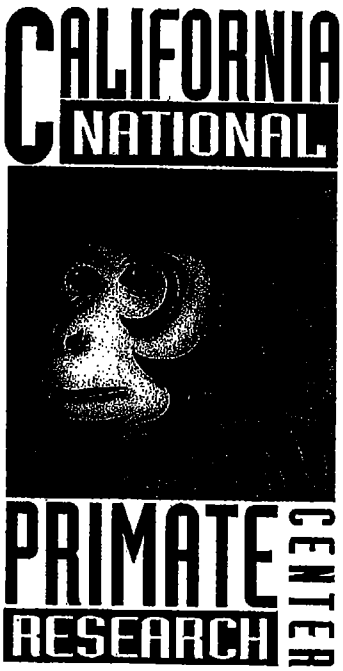
# CALIFORNIA NATIONAL PRIMATE RESEARCH CENTER




# ANNUAL PROGRESS REPORT

**5P51RR000169-45**
**05/01/2006-04/30/2007**

withheld

**Office of the Vice Chancellor for Research**
**University of California, Davis**
**Davis, CA 95616**

NATIONAL INSTITUTES OF HEALTH
DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL PRIMATE RESEARCH CENTERS (NPRC) PROGRAM
DIVISION OF COMPARATIVE MEDICINE
NATIONAL CENTER FOR RESEARCH RESOURCES

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2P51RR000169-45

# CALIFORNIA NATIONAL PRIMATE RESEARCH CENTER

Final

## UNIVERSITY OF CALIFORNIA - DAVIS

## ANNUAL PROGRESS REPORT

Reporting From: 05/01/2006

Reporting To: 04/30/2007

40.300% AIDS Related

withheld

3/29/07

CALIFORNIA NATIONAL PRIMATE RESEARCH CENTER

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withheld



withheld



RESEARCH CORES

withheld



withheld



withheld



withheld



withheld



withheld



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withheld



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withheld



withheld



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# PERSONNEL ROSTER

## Core Doctoral Scientists

| Name, Degree | Department | Non-Host Institution: State, Country |
|---|---|---|
| withheld | | |

## Affiliated

| Name, Degree | Department | Non-Host Institution: State, Country |
|---|---|---|
| withheld | | Proprietary Info USA |
| | | UNIVERSITY OF ARIZONA: AZ, USA |
| | | Proprietary Info |
| | | UNIVERSITY OF MARYLAND: MD, USA |

## Affiliated

| Name, Degree | Department | Non-Host Institution: State, Country |
|---|---|---|
| withheld | | Proprietary Info<br>AND UC DAVIS: CA, USA<br>UC SAN FRANCISCO: CA, USA<br>UC SAN FRANCISCO: CA, USA<br>Proprietary Info<br>NCI: MD, USA<br>UNIVERSITY OF COLORADO: CO, USA<br>Proprietary Info<br>UC SAN FRANCISCO: CA, USA<br>Proprietary Info<br>UC SAN FRANCISCO: CA, USA<br>Proprietary Info<br>UC SAN FRANCISCO: CA, USA<br>Proprietary Info<br>Proprietary Info<br>Proprietary Info<br>TEMPLE UNIVERSITY, SCHOOL OF MEDICINE: PA, USA<br>UNIVERSITY OF MICHIGAN: MI, USA<br>Proprietary Info |

## Affiliated

| Name, Degree | Department | Non-Host Institution: State, Country |
|---|---|---|
| withheld | | UC SAN FRANCISCO: CA, USA |
| | | UNIVERSITY OF MONTANA: MT, USA |
| | | Proprietary Info |
| | | UNIVERSITY OF ALABAMA: AL, USA |
| | | Proprietary Info |
| | | NATIONAL INSTITUTES OF HEALTH: MD, USA |
| | | UC SAN DIEGO: CA, USA |
| | | Proprietary Info |
| | | Proprietary Info |

## SUBPROJECT DESCRIPTIONS

# NPRC MANAGEMENT SUBPROJECTS

## AIDS RESEARCH FACILITY IMPROVEMENT GRANT (0258)

**NPRC UNIT:** MODERNIZE & IMPROV - AID

**%NPRC $:** AIDS RELATED RESEARCH

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
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### SUBPROJECT DESCRIPTION

Objective: The CNPRC has expanded animal facilities to support AIDS research. The expansion of projects and the increase of animals for these studies have resulted in a shortage of basic infrastructure to support AIDS investigators.

The proposed improvements can be classified into two categories: 1) short and long term storage of animal tissue and biological samples utilized directly and indirectly to support AIDS related research and 2) improvements and replacement of existing resources and equipment utilized in support of AIDS related research.

This proposal seeks to purchase equipment and perform renovations to improve the CNPRC as a resource for AIDS related biomedical research as follows:

1. Increasing -80°C freezer capacity
2. Improving animal housing with the installation of environmental monitoring sensors
3. Improving necropsy facility by replacing the tables and fume hood
4. Improving clinical laboratory support by replacing the blood cell counter.

### SUBPROJECT PROGRESS

The project provides space for 52 each, -80° Revco freezers. This project was completed on June 1st, 2006.

## PURCHASE AND INSTALLATION OF BIO-ISOLATION UNITS (0259)

**NPRC UNIT:** MODERNIZE & IMPROV - AID

**%NPRC $:** AIDS RELATED RESEARCH

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
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| withheld | | | | |

**SUBPROJECT DESCRIPTION**

Objective: The research program at the CNPRC is expanding in all areas and the demands for animals and animal housing have increased concurrently.

While the CNPRC has taken steps to increase available indoor space, the current limitations associated with separation of animals inoculated with different biological agents creates underutilization of current cage capacity in the infectious indoor housing areas. This proposal requests funds to purchase 25 bio-isolation cages.

**SUBPROJECT PROGRESS**

This project was completed.

## G20 MODULAR ANIMAL HOUSING UNITS FOR PRIMATE NURSERY (0260)

**NPRC UNIT:** MODERNIZE & IMPROV - AID

**%NPRC $:** AIDS RELATED RESEARCH

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
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### SUBPROJECT DESCRIPTION

Objective: This is a G20 grant to purchase two modular animal buildings for expansion of research programs using the infant rhesus model. The modular units will provide necessary separation of infant cohorts that are either allergen naïve or have been exposed to both dust mite allergen and ozone. These units will be sited immediately adjacent to the CNPRC Respiratory Exposure facility to optimize transport of infant monkeys to the exposure chambers. These modular units will allow necessary expansion of asthma research program targeting development of strategies for prevention and treatment of this debilitating disease.

### SUBPROJECT PROGRESS

The project is scheduled to be completed by May 1, 2007.

## EXTRAMURAL RESEARCH FACILITIES CONSTRUCTION II (0344)

**NPRC UNIT:** MODERNIZE & IMPROV - AID

**%NPRC $:** AIDS RELATED RESEARCH

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
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| withheld | | | | |

### SUBPROJECT DESCRIPTION

Objective: To construct a new building, the Virology and Immunology Laboratory that will house the Virology and Immunology (V&I) Unit on the CNPRC campus. The specific aims of this proposal are to: (1) address significant deficiencies of research space, forcing the CNPRC to situate Staff Scientists (mainly from the Respiratory Disease (RD) Unit) in six widely separated spaces on campus, (2) co-locate V&I researchers currently widely dispersed at the CNPRC and Center for Comparative Medicine (CCM, located on CNPRC property), (3) provide appropriate containment (e.g., level 3) facilities and other current technologies that enable researchers to investigate diseases that they are currently unable to study and (4) provide new space for recruitment of Staff Scientists in cell and gene based therapies.

### SUBPROJECT PROGRESS

Due to delays pending resolution of available infrastructure, this project was impacted by construction cost escalations. Project scope has been reduced to match available funds. The project is currently in campus review. Current schedule has a construction start date of January, 2008.

## EXTRAMURAL RESEARCH FACILITIES CONSTRUCTION (0290)

**NPRC UNIT:** MODERNIZE & IMPROVEMENT

**%NPRC $:**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
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**SUBPROJECT DESCRIPTION**

Objective: To provide approved animal testing and wet lab space currently housed in Personal Info

The new structure will accommodate several existing programs of research that are focused on Child Health and Disease.

All four Research Units at the CNPRC have research currently in progress in the area of Childhood Health, and this is an area of research focus that will continue to expand center-wide.

**SUBPROJECT PROGRESS**

This project has been impacted by unanticipated construction escalation costs and is currently in design development. The project's scope has been reduced to match existing budget. Construction is scheduled to begin June, 2007.

## PRODUCTION OF PEDIGREED SPF RHESUS MACAQUES (0168)

**NPRC UNIT:** PRIMATE SERVICES

**%NPRC $:** 1.300% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
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### SUBPROJECT DESCRIPTION

Objective: There is a continuing need for rhesus macaques of Indian-ancestry that are free of specific pathogens, particularly persistent viral infections, for use in AIDS-related research. We have successfully established and maintained a long-term breeding colony of SPF, genetically characterized Indian origin rhesus macaques. The current colony census is 193 animals. To date, 132 animals produced in this colony have been made available to AIDS researchers at various institutions.

Animals produced in this colony are SPF for Cercopithecine herpesvirus 1 (CHV1), simian type D retrovirus (SRV), simian immunodeficiency virus (SIV), simian T- lymphotropic Virus (STLV) and simian foamy virus (SFV). All animals are of known pedigree and geographic origin. Offspring produced are also haplotyped for several MHC class I (Mamu A*01, A*02, A*08, B*01, B*17) and class II (DPB, DQA, DQB) loci.

### SUBPROJECT PROGRESS

Currently, this SPF breeding colony numbers 193 animals. Future plans include the expansion of the Indian-origin SPF colony through natural breeding of the established population, and by nursery-derivation of SPF infants born to non-SPF Indian-origin breeders.

## GENETICALLY DEFINED HERPES/RETROVIRUS SPF MACAQUES (0275)

**NPRC UNIT:** PRIMATE SERVICES

**%NPRC $:** 1.300% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
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**SUBPROJECT DESCRIPTION**

Objective: Since the start date of 9/30/02, 87 adult non-SPF rhesus macaques (13 males, 74 females) have been assigned to this project. All 87 animals have completed a 90 day quarantine period and have been released to corn cribs for breeding. The objective of this project is to derive SPF animals from non-SPF founder stock.

**SUBPROJECT PROGRESS**

A total of 70 offspring have been produced on this project to date. All offspring from non-SPF breeders are taken at birth, nursery reared and eventually socialized for pair housing. Infants are tested for 7 persistent viral infections 4 times during the first year, and twice in the second year. All nursery derived infants have remained negative for SRV, STLV, SIV, SFV, B virus, CMV and RRV after one year of follow-up. With few exceptions, complete MHC haplotypes have been obtained for all non-SPF breeders and their nursery-derived SPF offspring.

# RESEARCH SUBPROJECTS

## SYNERGY BETWEEN SALMONELLA AND SIV INFECTION (0409)

**NPRC UNIT:** AFFILIATE RES PROGRAM

**%NPRC $:** 1.000% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
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### SUBPROJECT DESCRIPTION

Objective: Non-typhoidal Salmonella serotypes (NTS) are a leading cause of food-borne infections worldwide, with S. Typhimurium and S. Enteritidis being isolated most frequently. In immunocompetent individuals, NTS cause a localized gastroenteritis with low mortality rates. However, NTS cause bacteremia in patients with acquired immunodeficiency syndrome (AIDS). The high prevalence of HIV in sub-Saharan Africa has made NTS a leading cause of bacteremia in this region, resulting in considerable mortality (21 to 38%). AIDS patients acquiring an infection with NTS usually present with bacteremia while gastroenteritis is not observed. There is currently no information available on how human immunodeficiency virus (HIV) and NTS synergize to cause this atypical clinical picture.

Our long-range goal is to understand the pathogenesis of infections with NTS in HIV patients. The objectives of this project are to use a simian immunodeficiency virus (SIV)/NTS rhesus macaque model to determine how the innate immune response to NTS is altered in HIV patients. Our central hypothesis is that SIV infection reduces innate immune responses in the gut leading to inflammation, thus preventing the massive neutrophil influx, which prevents systemic dissemination of NTS and contributes to diarrhea. The rationale for the proposed research is that a better understanding of the mechanisms by which HIV impairs innate immune response to NTS infection will be relevant for the treatment or prevention of other opportunistic infections at mucosal surfaces.

We plan to test our hypothesis and fulfill the objectives of this application by pursuing the following specific aim:

1. Investigate the development of cytokine and inflammatory responses during NTS infection of ligated ileal loops in SIV negative and SIV positive rhesus macaques. We will use the a ligated ileal loop model, which is ideally suited to study innate immune responses, such as the events resulting in rapid neutrophil recruitment during NTS infection. We will monitor host responses and test the working hypothesis that the severity of neutrophil infiltration is inversely correlated to the ability of NTS to disseminate within host tissue. Most importantly, we will test several models by which SIV-infection reduces innate immune responses leading to IL17 and/or CXC chemokine production.

### SUBPROJECT PROGRESS

We successfully performed ligated ileal loop surgery on SIV infected and naïve Rhesus macaques. The data are currently being analyzed and we expect Submitted

## HEIRARCHICAL PROCESSING IN THE MOTION SYSTEM (0272)

**NPRC UNIT:** AFFILIATE RES PROGRAM

**%NPRC $:** 0.300%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
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**SUBPROJECT DESCRIPTION**

Objective: We have extended our investigations beyond areas MT and MST, to incorporate a polysensory cortical area in the parietal cortex, the ventral intraparietal area (VIP). We were specifically interested in the question of how activity in these areas was similar or different with respect to the encoding of self motion direction, when it is based on visual cues.

## THE ROLE OF THE PULVINAR IN VISUAL ATTENTION (0375)

**NPRC UNIT:** AFFILIATE RES PROGRAM

**%NPRC $:** 0.700%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
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**SUBPROJECT DESCRIPTION**

Objective: The pulvinar nucleus of the thalamus is one of the most enigmatic structures in the brain. Of thalamic nuclei, it shows the largest increase in size with evolution, keeping pace with the size of primate neocortex. Despite considerable effort, its function remains essentially completely unknown. Two related suggestions dominate current thinking about the pulvinar, and each has some experimental support. Neither, however, has been critically tested, and the present application is intended to provide this critical test of both ideas. The first idea is that the pulvinar controls the spatial location of directed attention. This idea has support - though not conclusive - from lesion studies and physiological recording studies. We plan to directly test this idea by perturbing activity in the pulvinar while recording in extrastriate cortex. We know that directed attention produces local changes in the gain of response of extrastriate neurons; activation of the pulvinar should mimic this change and reversible inactivation of the pulvinar should eliminate it. The other suggestion for the role of the pulvinar concerns the mechanism of such gain changes in sensory cortex. In particular, it has been suggested that recurrent projections between the pulvinar and cortical structures control the flow of information between cortical areas; this regulation might underlie any role in directing spatial attention. We plan to test this idea using multiple electrode recording in extrastriate cortex. Two dorsal extrastriate areas, the middle temporal (MT) and the medial superior temporal (MST) are both connected to the same subdivision of the pulvinar (Plm), and also connected with each other - MT provides a dominant source of feedforward input to MST. We will record from both structures simultaneously while again perturbing the activity in the pulvinar. If the connections with the pulvinar regulate information flow in visual cortex, we predict that such perturbation will modulate the cross-correlation of activity between MT and MST. Success on either aim will dramatically influence our thinking about the function of thalamocortical circuits.

## METABOLIC ACTIVATION OF AIR TOXICS IN ASTHMATIC MONKEYS (0302)

**NPRC UNIT:** AFFILIATE RES PROGRAM

**%NPRC $:** 0.300%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
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**SUBPROJECT DESCRIPTION**

Objective: Numerous epidemiologic studies have noted associations between exposures to ambient air pollutants (VOC, particulates, ozone) and asthma incidence and severity. Recent work in juvenile rhesus macaques has shown that a syndrome having many of the hallmark signs of allergic asthma can be induced by intermittent ozone and house dust mite allergen (HDMA) exposures. Several of the structural alterations observed in this model occur in the airways, a primary site for pulmonary xenobiotic metabolism. These studies were conducted to test the hypothesis that exposures resulting in fundamental alterations in the structure and function of the lung also alter the ability to metabolize xenobiotics, with a focus on bioactivated xenobiotics.

## DEVELOPMENT AND REORGANIZATION OF PRENATAL VISUAL SYSTEM (0405)

**NPRC UNIT:** AFFILIATE RES PROGRAM

**%NPRC $:** 0.700%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
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### SUBPROJECT DESCRIPTION

Objective: To determine the factors responsible for the formation of segregated eye-specific projections from the two eyes to the dorsal lateral geniculate nucleus of the thalamus.

### SUBPROJECT PROGRESS

We have made multi-array recordings from fetal retinas at different stages of development to define the type of neuronal activity that occurs spontaneously during the gestational period when eye-specific projections are being formed. These experiments have cast doubt on the prevalent notion that retinal waves of activity are responsible for the formation of segregated retinogeniculate projections.

## PRENATAL DEVELOPMENT OF VISUAL SYSTEM (0410)

**NPRC UNIT:** AFFILIATE RES PROGRAM

**%NPRC $:** 1.300%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
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**SUBPROJECT DESCRIPTION**

Objective: The objective of the proposed research program is to further our understanding of the cellular and molecular mechanisms underlying the formation of specific retinogeniculate projections in the primate visual system. The proposed research program will break new ground by increasing our understanding of the mechanisms underlying the formation of M and P pathways which are a distinguishing feature of the primate visual system.

## INTESTINAL CYTOKINE & T CELL HOMEOSTASIS IN SIV INFECTION (0387)

**NPRC UNIT:** AFFILIATE RES PROGRAM

**%NPRC $:** 1.000% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF | DEPARTMENT CODE | NON-HOST INSTITUTION: STATE, COUNTRY |
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| withheld | | | | |

**SUBPROJECT DESCRIPTION**

Objective: Efficacy of antiretroviral therapy (ARV) in HIV-1 infected individuals is determined by viral suppression and restoration of CD4 +T cell numbers in the peripheral blood, which represents only 2% of the total lymphocytes in the body; whereas, the gut associated lymphoid tissue (GALT) harbors 90% of the lymphocytes. The kinetics of CD4 +T cell restoration and function in GALT following ARV has not been fully determined. Our preliminary results showed a modest but incomplete restoration and function of intestinal CD4+T cells in SIV-infected animals during therapy. We propose that the alterations in composition of intestinal T lymphocyte subsets (increased prevalence of CD8+ T cells and inflammatory cytokines such as TNFalpha subsequent to CD4+ T cell depletion in primary SIV infection may have a negative impact on the restoration of intestinal CD4 +T cells during ARV. Immune activation and inflammatory cytokines such as TNFalpha may contribute to the delay in the CD4 + T cell restoration. The overall objective of this application is to develop strategies to improve or accelerate CD4 +T cell restoration in GALT during HIV infection and to identify potential mechanisms of CD4 + T cell repopulation by using the SIV-infected rhesus macaque model. There are three specific aims. (1) To determine the effects of TNFalpha inhibitor, RDP58, on intestinal CD4+ T cell restoration and function, T cell homeostasis, cell cycle stage and viral suppression in SIV-infected rhesus macaques during PMPA antiviral therapy. Therapy will be initiated in the primary or chronic stage of viral infection and longitudinal jejunal biopsy and peripheral blood samples analyzed for CD4+ T cell repopulation and function, changes in cell cycle and levels of apoptosis, viral suppression and evolution of genomic diversity. (2) To determine the effect of CD8 vT cell depletion on repopulation and function of CD4 + T cell subsets and intestinal T cell homeostasis and viral suppression and decay kinetics and genomic diversity in GALT of SIV-infected rhesus macaques receiving therapy. This study will examine the contribution of CD8+ T cells in killing of productively infected cells in SIV infected macaques during potent antiretroviral therapy. (3) To examine the progression of SIV-induced intestinal CD4+T cell depletion and CD4+ T cell restoration during therapy by gene expression analysis. Examination of gene expression profiles in GALT of SIV-infected animals with and without therapy will detect cellular and molecular mechanisms involved in the infection associated pathophysiologic process. The proposed studies may provide insights into mechanisms of CD4+T cell depletion during SIV infection and subsequent CD4+ T cell restoration in GALT following ARV in combination with an immunomodulator or CD8+ T cell depletion.

## LINKING FUNCTIONAL IMAGING, NUEROPHYSIOLOGY & ANATOMY (0377)

**NPRC UNIT:** AFFILIATE RES PROGRAM

**%NPRC $:** 0.700%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
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| withheld | | | | UC SAN FRANCISCO, CA USA |

**SUBPROJECT DESCRIPTION**

Objective: Brain imaging methods such as functional magnetic resonance imaging (fMRI), magnetic source imaging (MSI) and diffusion tensor imaging (DTI) are rapidly evolving as essential tools for assaying normal and abnormal brain function. The overall goal of this research is to enhance our understanding of the relationship between the signals measured using these imaging techniques and the underlying neural activity. We propose to conduct a series of experiments in anesthetized macaque monkeys to examine the correlation between functional brain imaging signals, specifically the BOLD signals of fMRI, the modeled current sources of MSI, and the imaging of white-matter tracts with DTI, with "gold standard" single and multi-unit electrophysiological recordings, and neuroanatomical tracing techniques. The specific aims are 1) To measure the stimulus evoked changes in magnitude, location and timing of functional brain imaging signals and relate them to changes in underlying neural activity, 2) To correlate non-invasive anatomic connectivity measures derived from tractography of DTI with connectivity derived using neuroanatomical techniques, and 3) To compare measures of functional connectivity based on the covariance of fMRI and MSI time-series with anatomic connectivity derived from DTI and neuroanatomic studies. These experiments represent a unique collaborative effort to combine several techniques in the same animal to generate a better understanding of the ability of modern imaging techniques to track changes in the nervous system under varying stimulus conditions and to uncover the circuitry necessary for complex sensory abilities. Our efforts are among the first to bridge the gap between imaging, neurophysiology and anatomy, an essential step in relating the wealth of electrophysiological recording data from macaque monkeys to the human cortex, and in understanding complex functions such as the sensory integration necessary for cognitive processes like object recognition and language.

## FLOW EFFECTS OF ENDOTHELIAL/TROPHOBLAST INTERACTION (0279)

**NPRC UNIT:** AFFILIATE RES PROGRAM

**%NPRC $:** 0.700%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
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| withheld | | | | |

### SUBPROJECT DESCRIPTION

Objectives:

1. Characterize the effect of shear stress on the directional migration of trophoblast cells
2. Determine the role of chemokines and endothelial adhesion molecules in shear stress-mediated trophoblast migration.
3. Determine the effect of shear stress and trophoblast-endothelial cell interaction on the induction of a migratory trophoblast phenotype.
4. Characterize the expression of CCR5, RANTES, proteoglycans, and integrins in invaded macaque uterine vessels.

### SUBPROJECT PROGRESS

We are interested in understanding the role of uterine endothelial cells during early pregnancy when placental trophoblast cells are invading uterine blood vessels and when vessel walls are being remodeled. Following on from our previously published studies which showed that trophoblast migration was regulated by RANTES and the chemokine receptor CCR5, we showed that tobacco smoke inhibits trophoblast migration as the result of dysregulation of the RANTES/CCR5 chemotactic axis. Early gestation macaque trophoblasts were incubated in the absence or presence of cigarette smoke-conditioned medium. Cell migration was quantified using migration chambers. CCR5 and G protein receptor kinase 2 (GRK2) expression were measured by immunofluorescence microscopy and Western blotting. cAMP levels were measured by ELISA. Trophoblast migration towards RANTES was reduced when cells were incubated in cigarette smoke-conditioned medium. Trophoblasts also showed reduced expression of CCR5, increased levels of cAMP, and increased expression of GRK2. Finally, the secretion of RANTES by uterine endothelial cells was reduced by exposing the cells to cigarette smoke-conditioned medium. These results support the idea that cigarette smoke constituents inhibit directional trophoblast migration by causing increased desensitization of trophoblast CCR5 and inhibiting the secretion of RANTES by endothelial cells. This work was published in Toxicol Sci.

## IN VIVO LEUKOCYTE TRAFFICKING IN THE SIMIAN MODEL FOR AIDS (0268)

**NPRC UNIT:** AFFILIATE RES PROGRAM

**%NPRC $:** 1.300% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
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**SUBPROJECT DESCRIPTION**

Objective: Infection of the central nervous system (CNS) with human immunodeficiency virus (HIV)-1 often causes the development of neurological complications, known as HIV-associated dementia, the basis of which is poorly defined. Infiltration of activated monocytes into the brain of HIV-infected individuals is thought to play a critical role in neuroinflammation and neuropathogenesis. However, it remains unclear if CNS tissue-specific signals are present that promote monocyte brain infiltration, if distinct monocyte subsets exhibit increased neuroinvasive potential (versus homing potential towards other sites of inflammation), and if a unique monocyte migratory program is triggered upon HIV infection (versus activation with other stimuli such as bacterial lipopolysaccharides).

## GRAVITY AND LIGHT AS COUNTERMEASURES FOR CIRCADIAN DYSF. IN ALTERED GRAVITY (0187)

**NPRC UNIT:** AFFILIATE RES PROGRAM

**%NPRC $:** 0.500%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
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### SUBPROJECT DESCRIPTION

Objective: The Circadian Timing System (CTS) coordinates the temporal aspects of physiology and behavior in animals. Disruptions in circadian timing have adverse effects on performance and health. Adaptation to altered acceleration environments, such as space flight, results in profound changes in many physiological systems, including the CTS and sleep regulation. Understanding responses to altered gravitational environments is critical to the development of effective countermeasures for astronauts on long duration space flights and planetary expeditions, as well as for our understanding of how gravity affects humans on Earth. Acute exposure to altered acceleration and light exposure are both capable of phase-shifting the circadian clock. Since artificial gravity produced by small centrifuges is a likely countermeasure for the adverse effects of spaceflight on skeletomuscular, cardiorespiratory and other systems, the interactions of this with light countermeasures for circadian dysfunction needs to be understood. Potential light countermeasures will need to be optimized to the properties of the newly described non-image forming photoreception system consisting of intrinsically photosensitive retinal ganglion cells and projections to key areas of the brain involved in regulation of sleep-wake cycles and circadian rhythms.

### SUBPROJECT PROGRESS

We have recently completed studies on the response of sleep and circadian rhythms to light of selective spectral content presented at different times of day as an initial part of understanding the basis for potential light countermeasures to deleterious changes produced by altered gravity. We have also completed studies examining the response of the immune system, a key target for spaceflight countermeasures, to altered sleep schedules, as a model for sleep and circadian changes in spaceflight. Initial findings from an ongoing analysis suggest a complex role for light in gating sleep-wake. A major finding is that while blue light can serve as an alerting stimulus, a reactive increase in sleep occurs following blue light exposure which appears to be independent of daily sleep drive and may act independently from the circadian rhythm of arousal and sleep timing. We are also in the process of renovating the centrifuge facility to better address light responses in altered acceleration environments.

## PHARMACOKINETIC STUDIES OF SELECT MILLENNIUM COMPOUNDS IN CYNOMOLGUS MONKEYS (0284)

**NPRC UNIT:** AFFILIATE RES PROGRAM

**%NPRC $:** 0.700%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
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**SUBPROJECT DESCRIPTION**

Objective: Determine PK profile of new compounds in rhesus monkeys.

**SUBPROJECT PROGRESS**

The project is ongoing.

## SCREEN FOR FRAGILE X MUTATIONS IN PRIMATES (0249)

**NPRC UNIT:** AFFILIATE RES PROGRAM

**%NPRC $:** 0.300%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
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### SUBPROJECT DESCRIPTION

Objective: Fragile X syndrome, the most common inherited form of mental retardation, arises in individuals with more than 200 CGG repeats in the 5' untranslated region of the fragile X mental retardation 1 (FMR1) gene. In humans, approximately 1 in 260 women, is a carrier of the expanded (55 to 200) CGG repeat. We have identified a rhesus macaque pedigree with 3 subject carriers of an expanded CGG region in the premutation range. Human subject carriers of fragile X premutations express higher levels of FMR1-mRNA, between 2 to 10 fold in blood samples. The increased FMR1 expression can lead to cell toxicity over the years and be the cause of Fragile X associated tremor ataxia syndrome (FXTAS) a newly described neurodegenerative disease. It has also been observed that premutation carriers often express lower levels of fragile X protein (FMRP) that presumably causes social phobia, autistic-like behavior, anxiety, OCD, psychotic traits and learning disability. This pedigree represents the first animal model that spontaneously carries an expanded repeat. FMR1 mRNA and protein levels have not yet been analyzed in macaque carriers of premutations (subjects MMU 24660, 34220, 35122). By examining FMR1 gene in this pedigree we expect to make progress in the understanding of the molecular mechanisms leading to the pathological expansion of the CGG repeats in succeeding generations, as well as identifying factors involved in transcriptional-translational regulation.

### SUBPROJECT PROGRESS

M. mulatta may be useful as an animal model for the study of fragile X syndrome: the allele distribution has been determined for FMR1 (homologue) CGG repeats of unrelated founder females of M. mulatta monkeys. All of these females with progeny were analyzed for FMR1 (homologue) allele size by PCR amplification and Southern blot analysis. Among 530 X chromosomes, at least 26 distinct repeat lengths were identified, ranging from 16 to 54 (mean is 28) CGG repeats. Three animals carried borderline premutation alleles with 54 CGG repeats, within the region of marginal instability for humans. They could become founders of a breeding population that would be of fundamental importance for fragile X mental retardation and FXTAS research.

## EFFECT OF CHROMIUM ON PROGRESSION OF INSULIN RESISTANCE (0348)

**NPRC UNIT:** AFFILIATE RES PROGRAM

**%NPRC $:** 1.000%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
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### SUBPROJECT DESCRIPTION

Objective: To determine the effect of long term supplementation with Chromium in the progression of Metabolic Syndrome in obese rhesus monkeys fed sugar sweetened beverages. Chromium supplementation has been demonstrated to improve insulin sensitivity in some, but not all, studies conducted in insulin-resistant subjects. Chromium has also been suggested to have effects to improve plasma lipid profiles. This study examines the long-term (1 year) effects of chromium supplementation to prevent or attenuate the progression of insulin resistance and dylipidemia in a nonhuman primate model of the Metabolic (insulin resistance) Syndrome. The development of insulin resistance in obese rhesus monkeys shares similar features with the progression of metabolic disease in humans. We have previously demonstrated that providing obese rhesus monkeys with a sugar-sweetened beverage daily in combination with ad libitum access to their normal diet for 1 year results in modest weight and body fat gain accompanied by a rapid progression of insulin resistance and dyslipidemia (elevated triglyceride and reduced HDL levels). The use of this model in which rigorous control and compliance with diet and chromium intake can be ensured will allow us to determine the effects of long-term chromium supplementation in the progression of the metabolic syndrome. In addition, we will assess the effects of chromium on a number of lipid and inflammatory parameters associated with insulin resistance and cardiovascular risk. We will also determine the effects of chromium on two parameters closely linked to muscle insulin action; muscle triglyceride content and whole body substrate oxidation (respiratory quotient). Although chromium picolinate is the most widely used form of chromium supplement, some studies suggest that the nicotinate form of chromium is more bioavailable and therefore more effective. Therefore, we will compare the bioavailability (tissue chromium status) and the efficacy of chromium picolinate and chromium nicotinate in the amelioration of diet-induced insulin resistance and dyslipidemia. The results of these studies will provide valuable information for the design and implementation of new clinical studies examining the effects of chromium supplements in the management of metabolic syndrome in humans.

### SUBPROJECT PROGRESS

The third year of this 3-year project began September 1, 2006. The last of these animals completed the study on March 16, 2007. At this time all of the data and samples collected are being analyzed. All samples from each animal are assayed in a single assay in order to minimize inter-assay variability. We will then be able to assess whether and how each chromium compound affects the progression of insulin resistance and dyslipidemia in obese rhesus monkeys consuming fructose.

## EFFECTS OF FISH OIL AND ALPHA-LIPOIC ACID ON THE PROGR. OF INSUL. RESIST. (0404)

**NPRC UNIT:** AFFILIATE RES PROGRAM

**%NPRC $:** 1.000%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
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### SUBPROJECT DESCRIPTION

Objective: The prevalence of obesity is increasing markedly. Even moderate obesity can contribute to the development of the pathological characteristics of the Metabolic Syndrome. Insulin resistance is the underlying characteristic of Metabolic Syndrome and, along with beta-cell dysfunction, results in Type 2 Diabetes Mellitus (T2DM). Due to the rising incidence of Metabolic Syndrome and T2DM and the limited ability of current treatments to prevent their long-term complications, it is clear that more attention needs to be focused on primary prevention of insulin resistance. In this application we propose to investigate the long-term (1 year) effects of fish oil and α-lipoic acid supplementation, alone and in combination, to prevent or attenuate the progression of insulin resistance and dyslipidemia in a nonhuman primate model of diet-induced insulin resistance. The development of insulin resistance in obese rhesus monkeys shares similar features with the progression of metabolic disease in humans. We have previously demonstrated that providing obese rhesus monkeys with a sugar-sweetened beverage daily in combination with ad libitum access to their normal diet for 1 year results in modest weight and body fat gain accompanied by a rapid progression of insulin resistance and dyslipidemia (elevated triglyceride and reduced HDL levels). The use of this model in which rigorous control and compliance with diet and supplement intake can be ensured will allow us to determine the effects of long-term administration of fish oil and α-lipoic acid on the progression of thedevelopment and progression of insulin resistance and dyslipidemia. We propose to determine the efficacy of two widely used nutritional supplements known to activate PPARs and/or target lipid dysregulation, inflammation (fish oil), and oxidative stress (alpha-lipoic acid) in this nonhuman primate model. We will pursue the following specific aims: Specific Aim 1: Test the hypothesis that supplementation with fish oil will activate PPARalpha, gamma and delta, increase plasma adiponectin levels, and prevent or attenuate the progression of insulin resistance. Specific Aim 2: Test the hypothesis that supplementation with the potent anti-oxidant, alpha-lipoic acid will reduce oxidative stress and prevent or attenuate the progression of insulin resistance. Specific Aim 3: Test the hypothesis that the effects fish oil in combination with alpha-lipoic acid will be greater than either fish oil or alpha-lipoic acid alone. In addition, we will determine the effects of the supplements on lipid, oxidative stress and inflammatory parameters associated with insulin resistance and cardiovascular risk including substrate oxidation, apolipoprotein-B, lipoprotein particle size, adiponectin, C-reactive protein, homocysteine, interleukin-6, tumor necrosis factor-alpha, monocyte-chemoattractant protein-1, soluble adhesion factors, and PAI-1.

### SUBPROJECT PROGRESS

The first year of this 3 year project began September 1, 2006. Baseline data has been collected and the animals are being administered fish oil, alpha-lipoic acid, a combination of the two supplements, or the placebo daily.

## STRUCTURAL BASIS OF AMBLYOPIA & STRABISMUS (0083)

**NPRC UNIT:** AFFILIATE RES PROGRAM

**%NPRC $:** 0.300%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
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### SUBPROJECT DESCRIPTION

Objective: Transmission of Burst Firing at the Retinogeniculate Synapse: In the visual system, output from the retina is filtered through a thalamic relay station called the lateral geniculate nucleus (LGN) before transmission to the cortex. The probability that a given retinal action potential generates an action potential in a geniculate neuron is usually much less than 100%. It is possible, however, for a single retinal spike to generate more than one geniculate spike, because LGN firing behavior exists in two modes: tonic and burst. Burst spikes are defined as those occurring after a 100 ms pause, with an interspike interval of less than 4 ms. During the silent period, the low-threshold Ca2+ current (IT) becomes de-inactivated. Subsequently, a single retinal EPSP can cause a burst of geniculate action potentials riding on a large depolarizing Ca2+ current. We tested what happens to efficacy when an LGN neuron fires in burst mode, rather than tonic mode, during natural stimulation.

### SUBPROJECT PROGRESS

Our approach was to record extracellular action potentials and retinal EPSPs ("S-potentials") of single LGN neurons in the macaque. EPSPs originated from a single retinal ganglion cell in most of the cells that we recorded. The overwhelming majority of LGN action potentials were triggered by a retinal EPSP. When retinal EPSPs failed to generate LGN spikes, a large fraction acted as "priming" EPSPs, leading to paired-spike facilitation. The occurrence of action potentials in LGN neurons therefore depends critically on the precise timing of EPSPs. Burst events were relatively uncommon, but when they occurred, nearly all of the LGN spikes in the burst train were driven by a retinal EPSP. This finding indicates that bursts in LGN cells usually originate from bursts in retinal ganglion cells, and are not generated by the LGN itself.

## XENOTRANSPLANTATION OF PORCINE ISLETS IN DIABETIC RHESUS MONKEYS (0361)

**NPRC UNIT:** AFFILIATE RES PROGRAM

**%NPRC $:** 1.000%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
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**SUBPROJECT DESCRIPTION**

Objective: To assess the efficacy of swine islet cell xenotransplantation using novel encapsulation strategy in chemically induced diabetic rhesus macaques.

**SUBPROJECT PROGRESS**

The study is ongoing.