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

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

3/29/07

CALIFORNIA NATIONAL PRIMATE RESEARCH CENTER
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  - USA
  - UNIVERSITY OF ARIZONA: AZ, USA

- Proprietary Info
  - UNIVERSITY OF MARYLAND: MD, USA

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UC SAN FRANCISCO: CA, USA

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NCI: MD, USA
UNIVERSITY OF COLORADO: CO, USA

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TEMPLE UNIVERSITY, SCHOOL OF MEDICINE: PA, USA
UNIVERSITY OF MICHIGAN: MI, USA

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SUBPROJECT DESCRIPTIONS

NPRC MANAGEMENT SUBPROJECTS
AIDS RESEARCH FACILITY IMPROVEMENT GRANT (0258)

NPBC UNIT: MODERNIZE & IMPROV - AID
%NPBC #: AIDS RELATED RESEARCH

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

SUBPROJECT DESCRIPTION

Objective: The CNPRC has expanded animal facilities to support AIDS research. The expansion of projects and the increase of animals for those 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°C Revco freezers. This project was completed on June 1st, 2006.
PURCHASE AND INSTALLATION OF BIO-ISOLATION UNITS (0259)

NPRI UNIT: MODERNIZE & IMPROV - AID
\%NPRI $: AIDS RELATED RESEARCH

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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.
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 naive 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)

NPFR UNIT: MODERNIZE & IMPROV - AIDS
%NPFR $: AIDS RELATED RESEARCH

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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.
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 CNFRC 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.
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 (DPB1, 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)

INVESTIGATOR: withheld

DEGREES: 

STAFF CODE: 

DEPARTMENT: 

NON-HOST INSTITUTION: STATE, COUNTRY: 

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, nursed 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 (8409)

INVESTIGATOR: Withheld

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 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 to...
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)

INVESTIGATOR: WITHHELD

SUBPROJECT DESCRIPTION

Objective: The pulvinar nucleus of the thalamus is one of the most enigmatic structures in the brain. 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 (PIm), 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.
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.
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.
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.
Objective: Efficacy of antiretroviral therapy (ART) 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 ART 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 ART. 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+ T 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 pathophysiological 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 ART in combination with an immunomodulator or CD8+ T cell depletion.
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 neuroanatomical 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)

INVESTIGATOR: 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.
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 DYSP. IN ALTERED GRAVITY (0187)

INVESTIGATOR

DEGREES

STAFF

DEPARTMENT

NON-HOST INSTITUTION: STATE, COUNTRY

withheld

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)

INVESTIGATOR             DEGREES        STAFF DEPARTMENT CODE

withheld

NON-HOST INSTITUTION: STATE, COUNTRY

SUBPROJECT DESCRIPTION

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

SUBPROJECT PROGRESS

The project is ongoing.
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 200 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 presumuably 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.
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 dyslipidemia in a non-human 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.
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 the development 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 (α-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 PPARα, the 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, α-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 α-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 factor, and PAI-1.

SUBPROJECT PROGRESS

The first year of this 2 year project began September 1, 2006. Baseline data has been collected and the animals are being administered fish oil, α-lipoic acid, a combination of the two supplements, or the placebo daily.
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.
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.
SUBPROJECT DESCRIPTION

Objective: The use of organs from nonhuman species (xenografts) such as pigs represents a solution for the acute shortage of organs currently available for human transplantation. Xenografts are rapidly rejected by antibodies that bind to the gal carbohydrate that is present on pig cells and absent in humans and Old World primates.

Xenoantibodies in humans exposed to pig cells following placement on a bioartificial liver containing pig hepatocytes are encoded by the IGHV3-11 and IGHV3-74 germline progenitors. The objectives of this study were to (1) identify the immunoglobulin VH genes used by rhesus monkeys to encode xenoaantibody responses to individual porcine hepatocytes and endothelial cells; (2) determine whether rhesus monkeys use the same Ig VH genes to encode xenoaantibody responses to both isolated hepatocytes and vascularized liver grafts from porcine donors; (3) compare the Ig VH genes that encode xenoaantibody responses to both isolated cells (hepatocytes and pancreatic islet cells) and vascularized organs (heart and liver) from porcine donors.

SUBPROJECT PROGRESS

The studies supported by this grant have shown that rhesus monkeys represent an appropriate preclinical model for testing novel reagents for the ability to prolong xenograft survival.
SUBPROJECT DESCRIPTION

Objective: While area 5 has been considered a posterior parietal field involved exclusively in processing somatic inputs, recent evidence from our laboratory in both New World and Old World monkeys, as well as work from other laboratories, indicate that this cortical area is also involved in processing visual inputs, and is closely associated with the motor system. Accumulating evidence indicates that area 5 may be a "central planner" critical for monitoring limb location during intended reaching and grasping, converting sensory locations into motor coordinates for intentional movement, and in perceiving the movements of the body in extra personal space. The goal of the present investigation is to determine the role of posterior parietal area 5 in visually guided and non-Visually guided reaching and grasping, object manipulation, bilateral coordination of the hands, and information transfer across the cerebral hemispheres. This study represents one of the first attempts to combine modern neuroanatomical, electrophysiological, and lesioning techniques to determine the contribution of a single cortical field involved in generating sophisticated hand use. Further, it is one of the few studies that utilizes electrophysiological and neuroanatomical techniques to examine the long-term cortical changes that occur after cortical damage, followed by behavioral training.
BRAIN AND BEHAVIOR IN EARLY IRON DEFICIENCY (0381)

INVESTIGATOR:

Non-Host Institution: State, Country
UNIVERSITY OF MICHIGAN, MI USA

SUBPROJECT DESCRIPTION
Objective: Identify developmental periods most sensitive to iron deficiency effects on brain development and to characterize these effects.

SUBPROJECT PROGRESS
All data gathering has been completed. Three research reports have been completed and published or accepted for publication. Work on the database continues as a basis for further publications. Pending Support Analysis to date supports the conclusion that iron deficiency produces different syndromes of behavioral impairment when it occurs during gestation than during infancy.
SUBPROJECT DESCRIPTION

Objective: The major goal of the NIEHS Center for Environmental Health Sciences at UCD is to maintain a strong program in the toxicology of agrochemicals and related xenobiotics, particularly relating to human health and the mechanistic aspects of toxicology.
SUBPROJECT DESCRIPTION

Objective: To determine the biophysical and cell biological factors associated with cell damage due to low temperature and osmotic stress.

SUBPROJECT PROGRESS

Our studies have demonstrated that rhesus sperm have unique biophysical characteristics including lipid composition and membrane phase transitions. In addition, ice formation does not appear to be a significant factor in reduced post-thaw sperm function, primarily because we have not seen evidence that cell integrity is damaged or that the cells are disrupted as part of the cryopreservation process.
A MONKEY MODEL FOR ANTI-CYTOMEGALOVIRUS THERAPY (0379)

INVESTIGATOR: withheld

DEGREES:

STAFF:

DEPARTMENT:

%NPJC #: 0.700%

REPORT PERIOD: 05/01/2006-04/30/2007

SUBPROJECT DESCRIPTION

Objective: The long-range goal of this project is to develop a non-human primate model to evaluate therapy for human cytomegalovirus (HCMV) that will 1) enable rapid in vivo evaluation of promising anti-HCMV drugs and 2) allow development of therapeutic strategies for HCMV under clinically relevant conditions. For these studies we are using Rhesus CMV (RhCMV) infection of rhesus macaques. We have previously established with in vitro studies that RhCMV and HCMV are nearly identical in susceptibility to the drugs that are approved for HCMV therapy in humans. In the past year we have evaluated the FDA approved drug cidofovir (CDV) for anti-RhCMV activity in macaques during acute infection. A pharmacokinetics study was performed to establish an appropriate dose and route of CDV administration. The optimal dose was 5 mg/kg given intravenously, once weekly, which is equivalent to the CDV dose used for HCMV therapy in humans. Ten RhCMV-infected macaques were treated with CDV and compared to ten mock-treated controls. Virus loads in the treated animals were reduced more than 99% relative to mock-treated controls. These studies validate the RhCMV model for in vivo studies of HCMV therapy.

SUBPROJECT PROGRESS

We are currently evaluating a novel drug candidate, maribivir, which appears to be much less toxic than CDV or other approved anti-CMV drugs.
FUNCTION OF MACAQUE SPERM PROTEINS IN FERTILIZATION (0018)

NPRC UNIT: AFFILIATE RES PROGRAM
%NPRC #: 0.700%

INVESTIGATOR:

DEGREES:

STAFF CODE:

DEPARTMENT:

NON-HOST INSTITUTION: STATE, COUNTRY:

withheld

SUBPROJECT DESCRIPTION

Objective: Our lab has had a long standing interest in identifying and characterizing sperm surface proteins that play a role in the interaction of sperm with the fluids and cells of the female reproductive tract. Our findings in non-human primates are relevant to issues in human reproduction, providing insights into causes of infertility as well as identifying possible targets for contraception. We previously reported that DEFB126 (formerly ESP13.2) coats the entire surface of macaque sperm and remains until sperm become capacitated. The release of DEFB126 from sperm during capacitation is required for sperm recognition and binding of the zona pellucida, suggesting that DEFB126 masks zona pellucida ligands on the sperm surface. Furthermore, DEFB126 appears to mask all sperm surface components and protects sperm from immune recognition. Immunoprotection appears to stem from the highly glycosylated carboxyl domain which is comprised of oligosaccharides that terminate in sialic acid. DEFB126 provides uniform negative charge over the surface of sperm that is significantly reduced as sperm release DEFB126 during capacitation.

SUBPROJECT PROGRESS

In the last year we have focused on evaluating the potential role of DEFB126 in sperm transport in the female reproductive tract. Preliminary studies in past years suggest that DEFB126 remains on the sperm surface as sperm migrate into the oviduct. We have recently demonstrated that sperm attach to oviductal epithelia with high affinity. The ability of sperm to bind to the luminal surface of the epithelium is dependent upon the presence of DEFB126. Treatments that either remove or modify DEFB126 significantly inhibit the ability of sperm to attach to oviductal epithelia. Non-capacitated sperm and as well as purified DEFB126 binds only to secretory cells which become more abundant in the isthmus of the oviduct during the follicular phase of the macaque cycle. Evidence supports a role for DEFB126 in the formation of a sperm reservoir in the macaque oviduct.

Simultaneously, we have been collaborating with an expert in tracheal epithelium physiology and the cellular mechanisms of cystic fibrosis to develop a long-term oviductal epithelial culture system that will be used for more mechanistic studies of sperm-epithelial interaction. We have recently published an initial report describing a novel culture system, which is vastly superior to prior attempts of other investigators in its ability to generate native-like oviductal epithelium. Over the years we have collaborated with several groups in the development of methods of semen cryopreservation and the assessment of cryodamage to mammalian sperm. Recently we worked on measuring the effects of conventional methods employing liquid nitrogen and cryoprotectants on damage of DNA and chromosomes in sperm. We determined that although cryopreservation can result in DNA and chromosomal damage in a large proportion of sperm, highly motile post thaw sperm have a low incidence of damage and thus can be selected for IVF techniques such as intra-cytoplasmic sperm injection (ICSI).
Objective: The focus of this Center is the gamete as a contraceptive target. Remarkable advances have occurred recently in genomics and proteomics, cell biology, fertilization research and drug discovery. These advances have combined to open new possibilities for contraceptive intervention, directed against gametes, that may have been previously imagined but were unattainable. Most of our projects target sperm, though one project proposes a potential egg target. Anti-sperm contraception can block sperm function or sperm development. Our Center's projects include both targets. A major theme of the Center is small molecule inhibitors to block sperm function. Our Center is actively studying sperm plasma membrane proteins that function in sperm-egg interaction and we propose screens for small molecules that inhibit these sperm proteins and thus prevent fertilization. A second theme is to block sperm development. Novel pharmacological strategies to derail the complex process of sperm production are proposed here. All of us who study sperm development are aware of important advances in spermatogenesis and realize that new, feasible contraceptive targets are being identified. Thus, we have proposed an expansion of our target list in spermatogenesis, increasing our scope and chances of developing new products for birth control.
SUBPROJECT DESCRIPTION

Objective: To define the cortical mechanisms of auditory-visual interactions that form unified percepts. We have determined that single neurons in the cerebral cortex are strongly modulated by two sensory stimuli in a manner consistent with the resulting perception.

SUBPROJECT PROGRESS

We are continuing to record the activity of single neurons. These studies are showing that neurons in previously considered 'unimodal' visual cortex are influenced by auditory stimuli as well. These results provide a significant contribution to our understanding of cortical processing of sensory stimuli, and provide insights into how perception can be altered in mental illnesses such as schizophrenia and autism. These are time intensive studies and will progress over the next funding year. The work, since its beginning, has led to two research publications as well as two review chapters in books. In Preparation
TRANSMISSION OF H. PYLORI IN THE RHECUS MONKEY (0193)

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

SUBPROJECT DESCRIPTION

Objective: Infection with Helicobacter pylori causes a histological gastritis that in some individuals is associated with the development of peptic ulcer disease or gastric malignancy. Although H. pylori may be the most common human bacterial infection, the mechanism by which it is transmitted remains unknown. Person to person transmission probably accounts for most infections. Yet one of the great paradoxes in the epidemiology of H. pylori is that when one examines the gastric lining, the bacterium is ubiquitous, but when fecal or oral secretions are studied it is often difficult to find. This may reflect the difficulty of studying in humans the role of acuity of infection, age of the host, and the possible effects of vomiting, diarrhea, and the CagA pathogenicity island on transmission. Rhesus monkeys are naturally infected with H. pylori which is very similar to strains that infect humans, and this animal model provides a unique opportunity to study experimentally the transmission of H. pylori in a naturally infected host. We hypothesize that scuity of infection, the presence of vomiting and diarrhea, and the CagA pathogenicity island are critical variables in transmission of H. pylori. Furthermore we propose that there may be a cooperativity between transmission of H. pylori and transmission of bacterial enteric diseases. Diarrheal and vomiting diseases may increase H. pylori transmission by increasing the shedding H. pylori in feces and vomitus, and in turn, H. pylori infection may cause increased gastric pH and thereby promote infection with enteric bacteria by reducing the gastric bactericidal barrier.

SUBPROJECT PROGRESS

Results suggest that acquisition of H. pylori infection is most consistent with oral-oral transmission.
SUBPROJECT DESCRIPTION

Objective. Helicobacter pylori causes an inflammatory infiltrate in gastric mucosa that in about 10% of cases progresses to peptic ulcer disease or gastric cancer. Disease results from an interaction between strain-specific bacterial virulence genes and the particular host response, neither of which is well understood. Since experimental inoculation of rhesus macaques with H. pylori causes gastritis that closely mimics human infection, this model provides a unique opportunity to further our understanding of H. pylori pathogenesis. Rapid progress in genomics and gene expression technologies makes it possible to use the macaque model to study the H. pylori host-pathogen interaction by in vivo analysis of gene expression. We propose to extend our work in the rhesus model of H. pylori into an analysis of bacterial (Specific Aim 1) and host (Specific Aim 2) gene expression during experimental infection.

Since the host immune response is increasingly recognized as a critical variable in the outcome of infection, we will also study host gene transcription after immunization with urease coupled with either CpG or alum adjuvant, in order to promote a Th1 or Th2 immune response, respectively (Specific Aim 3). These studies will provide a functional genomic understanding of the H. pylori host-pathogen relationship that may have implications for novel treatment or vaccine strategies.

SUBPROJECT PROGRESS

We infected groups of monkeys with either wild type (WT) H. pylori J166, Cag pathogenicity island isogenic knockout of H. pylori J166 (PAI-), or control. We hypothesize that Cag PAI+ H. pylori induce an antimicrobial environment in the gastric mucosa that serves to protect the gastric niche against competition from enteric microorganisms.
SUBPROJECT DESCRIPTION

Objective: The goal of this work is to elucidate the relationship between neural activity in auditory cortex and sound perception. The applicant will determine 1) the abilities of humans and nonhuman primates to perceive and integrate spectral and temporal features of sounds, and 2) the relationship of single neuron responses in auditory cortex to psychophysical performance.
SUBPROJECT DESCRIPTION

Objective: The long-term objectives of this proposal are to understand the functional organization of feedforward and feedback pathways between the lateral geniculate nucleus (LGN) and visual cortex. For sensory systems, feedforward projections from thalamic relay cells provide the cortex with information about the external environment. The cortex, in turn, sends extensive feedback to thalamic relay cells. The cortex thus functions both to process information supplied by the thalamus as well as to influence dynamically the transmission of thalamic input.

The proposed studies involve three sets of experiments. The first set of experiments deals with the issue of what role magnocellular and parvocellular LGN inputs play in the construction of postsynaptic receptive fields in layer 4C of visual cortex. Recordings will be made from monosynaptically connected neurons in the LGN and layer 4C in order to compare the organization of pre- and postsynaptic receptive fields as well as to assess the dynamics of synaptic transmission.

The second set of experiments deals with determining the physiology of corticogeniculate feedback neurons located in layer 6 of visual cortex. Neurons in layer 6 that provide feedback input to the LGN are located in the upper third and lower third of the layer. Neurons in the upper third project exclusively to the parvocellular geniculate layers; neurons in the lower third project primarily to the magnocellular layers. We will examine the physiological properties of these neurons to determine whether they are differentially sensitive to visual stimuli. If so, then it seems likely that neurons in the upper and lower regions of layer 6 should be able to differentially modulate activity traveling in the magno- and parvocellular streams.

The third set of experiments deals with the functional influence of cortical feedback on geniculate activity. By recording from ensembles of geniculate neurons, we will determine whether cortical feedback selectively influences the activity of neurons in the magno- and parvocellular layers of the LGN. If feedback is found to influence the temporal patterns of LGN activity, then we will examine data from the first set of experiments to determine the efficacy of these patterns in driving cortical responses.

SUBPROJECT PROGRESS

Results from this work will not only increase our understanding of how visual information is processed by the nervous system, but will provide a framework for understanding the functional relationship that exists between thalamus and cortex. Only by such a detailed understanding of the normal balance between feedforward and feedback interactions can disorders of this relationship, such as appear in many forms of epilepsy, be understood.
SUBPROJECT DESCRIPTION

Objective: This project is a core that is part of a Program Project (P01-AI058708) to characterize molecular mechanisms of HIV post-integration latency. For these studies we are using an animal model for highly active antiretroviral therapy (HAART) that mimics HAART therapy in HIV-infected humans. The model consists of rhesus macaques infected with a chimeric virus of simian immunodeficiency virus containing the reverse transcriptase from HIV-1 (RT-SHIV).

SUBPROJECT PROGRESS

During the past year we have been performing a comprehensive analysis of numerous tissues collected at necropsy from RT-SHIV-infected animals treated with suppressive HAART in order to identify viral reservoirs. We have developed methods for extraction and analysis of RT-SHIV DNA and RNA in tissues by PCR and RT-PCR. We have analyzed two RT-SHIV-infected control animal (no drug therapy) and animals that were treated with HAART. In the control animal, viral DNA and RNA were detected in nearly all tissues examined including lymphoid tissues, all regions of the gastrointestinal (GI) tract, brain, and genital tissues. In preliminary analyses of tissues from the HAART-treated animals (with plasma viral loads 50 copies of viral RNA per ml), we have identified potential sites of residual virus replication in some lymph node and the GI tract. We have also identified potential sites of latency in tissues from some of these animals. Work is in progress to characterize these reservoirs in more detail.
SUBPROJECT DESCRIPTION
Objective: To develop a safe and effective smallpox vaccine.

SUBPROJECT PROGRESS
We have made several clones of VV from the Dryvax preparation of the Wyeth strain of the virus. These clones have been tested extensively in vitro and in vivo in SCID mice to identify a clone that is as close as possible to the original uncleaved virus. We tested the final three candidates in macaques to evaluate primate responses to the clones. The macaques were inoculated by scarification with each of the three VV clones and the original uncleaved Wyeth strain virus. Pock lesion size was measured as a method of comparing the relative ability of each clone to replicate in primates. All inoculated macaques resolved the pock lesions by four weeks post-vaccination. Currently we are finishing the development of the recombinant vaccinia virus smallpox vaccine and will be testing it in macaques in the near future for immunogenicity and safety.
SUBPROJECT DESCRIPTION

Objective: The amygdaloid complex is a heterogeneous anatomical region located in the primate temporal lobe. It has been implicated in the mediation of emotional behavior, especially fear, and in the coordination of species typical social behavior. Our laboratory is conducting a multidisciplinary research program aimed at understanding the structure, physiology, and function of the nonhuman primate amygdala. We are using these data as the basis for understanding the pathology associated with disorders of social interaction such as autism.

SUBPROJECT PROGRESS

During this project period, we have completed an analysis of cortical inputs to the amygdala. This is the second of two papers that have defined all of the potential sensory inputs to the macaque monkey amygdala. We have also initiated a new series of studies designed to evaluate the development of these connections. This project has been renewed and we will now start a new series of studies to evaluate the development of the nonhuman primate amygdala. The first year of this project involves a longitudinal MRI analysis of the developing rhesus monkey brain. Thereafter, parallel histological and neuroimaging studies will be conducted.
NEUROBIOLOGY OF PRIMATE SOCIAL BEHAVIOR (0002)

NPSC UNIT: BRAIN, MIND, & BEHAVIOR

%NPSC: 1.000%

INVESTIGATOR

NON-HOST INSTITUTION: STATE, COUNTRY

withheld

DEGREES STAFF DEPARTMENT
CODE

SUBPROJECT DESCRIPTION

Objective: The primate amygdaloid complex is an important component of the brain system involved in mediating appropriate species-specific behaviors such as threat and defense. Large lesions of the inferior temporal lobe including the amygdala, produce the so-called "Kluver-Bucy Syndrome" which has been characterized as an inability to attribute emotional significance to perceived stimuli. Significant changes in social behavior have also been reported. Critical reading of the literature, however, indicates that the experimental basis for this characterization is tenuous. Previous studies have often suffered from the lack of discrete lesions, comprehensive histological analysis or ethologically appropriate and sophisticated behavioral assessment.

This project uses sophisticated neurobiological and behavioral methods to reassess the role of the primate amygdala in normal social interaction. The research is carried out in the context of a long-standing program of neuroanatomy which has demonstrated that the amygdala receives sensory information from widespread regions of the neocortex. The overarching hypothesis guiding this program is that the amygdala is a high level perceptual apparatus that interprets ongoing sensory information in order to orchestrate appropriate species-specific responses.

SUBPROJECT PROGRESS

These studies will provide important insights into the neurobiology of normal social behavior and may contribute to an understanding of the pathologies of social communication in disorders such as autism. An important new area has been the completion of amygdala lesions in neonatal macaques. The infants were returned to their mothers for rearing and their social development has been extensively studied. The infants with amygdala and hippocampal lesions have now been studied for 3 1/2 years. We have demonstrated that damage to the amygdala does not interrupt normal species typical social behavior. However, emotional systems for interpreting environmental dangers have been disrupted. Animals with hippocampal damage have demonstrated a remarkable sparing of memory impairment. This provides convincing evidence of brain adaptation after early neonatal injury.
SUBPROJECT DESCRIPTION

Objective: The hippocampal formation is an important component of the brain system involved in producing long term memories. It is clear that the system that carries out this function in the human brain is structured very similarly to the nonhuman primate brain but is different in important ways from the rodent brain. This program of research involves various types of morphological studies to evaluate the intrinsic organization as well as the extrinsic connections and chemical neuroanatomy of the macaque monkey and human hippocampal formation. These studies range from intracellular labeling of single neurons in the in vitro hippocampal slice preparation to connectional studies of the hippocampus and related regions to studies of the human hippocampal formation and related structures.

SUBPROJECT PROGRESS

Work in this project has focused on completing research into the connectivity of the primate retrosplenial cortex and beginning studies of the development of the primate hippocampal formation. We have also carried out behavioral studies following selective lesion of the money hippocampal formation.
SUBPROJECT DESCRIPTION

Objective: To determine whether social stress affects SIV disease progression and AIDS following establishment of viral set point, and the mechanisms involved, and to generate pilot data on whether drugs that block the action of stress-response systems can ameliorate the effects of social stress on SIV disease progression.

SUBPROJECT PROGRESS

We have found that, under conditions of social stress, personality factors, hormone concentrations, and cytokine gene expression are strongly correlated with each other and are related to measures of disease progression. In non-stressful conditions, however, these measures are not related.
SUBPROJECT DESCRIPTION

Objective: To implement a colony-wide assessment program that will identify animals differing in biobehavioral organization, and to provide this information to (a) colony managers to aid in decision-making in the areas of health, reproduction, and enrichment, and (b) investigators for use in scientific studies.

SUBPROJECT PROGRESS

Regulation of emotion is associated with specific genotypes for genes that impact monoamine neurotransmitter function, by early rearing, and by the interaction of genotype and rearing history. Moreover, aspects of early temperament are related to a variety of behavioral and health outcomes associated with impulsivity, social affiliation, and measures pertaining to asthma.
SUBPROJECT DESCRIPTION

Objective: To understand the neurobiology of social behavior by tracing transmission of somatosensory information from the body surface to neuronal regions concerned with processing tactile information essential for social behavior interactions.

The propensity to seek contact and to form strong positive relationships is exemplified in the extreme by the South American titi monkey. In nature and in the laboratory, these monogamous primates spend up to 90% of their day in physical contact with other members of their family group. Animals sit side-by-side with their lateral surface in close contact with another monkey. Contact between titi monkeys also includes active contact, such as grooming or grasping. A unique aspect of social contact in titi monkeys is tail-twining. Very often all members of a family group (3-5 individuals) sit in a row and combine their tails in a single twine.

Using multielectrode electrophysiological recording this research examines the role of several somatosensory cortical areas involved in social contact. The research involves two steps: The first is to map, in individual animals, the flow of somatosensory information from the body surface to regions of the neocortex that utilize somatosensory information in regulation of social behavior. This phase of the research relies on electrophysiological recording in anesthetized monkeys. To evaluate the extent to which cortical regions are involved in social behavior, focal lesions will be performed and the effects of the lesion on social motivation and social cognition will be evaluated. These studies are unique in that they take advantage of an overt behavior, directly mediated by the somatosensory system, to examine the role of cortical mechanisms.

SUBPROJECT PROGRESS

The results of our electrophysiological recordings indicate that somatosensory representation of body parts relevant to social behavior, such as the lateral surface of the body is magnified in titi monkeys. Bilateral lesions of a small region of the prefrontal cortex (defined by reciprocal connections with the primary somatosensory cortex) were performed in six titi males. Following lesion, the males increased the time spent interacting with their mate and offspring. The increased sociability of the lesioned males was specific to family members. Interactions with unfamiliar adults in a variety of circumstances does not change post-lesion or actually decreases. Neurochemical analysis indicated that these males also had higher levels of corticotin, a neurohormone implicated in affective relationships. PET scans indicated an overall increase in neural activity for the lesioned males as well as changes in neural activity in nuclei identified by rodent research as influential in social behavior. Our working hypothesis is that the lesions removed an inhibitory influence on mesolimbic dopaminergic pathways leading to increased reinforcement value for social contact with their mates.
GENETIC MANAGEMENT OF ANIMAL COLONIES (0392)

INVESTIGATOR: withheld

NON-HOST INSTITUTION: STATE, COUNTRY

DEGREES

STAFF

DEPARTMENT

CODE

SUBPROJECT DESCRIPTION

Objective: Identify genetic markers useful to genetically characterize genetic differences among regional populations of rhesus and long-tail macaques and provide genotyping and genetic management services to NIH investigators.

SUBPROJECT PROGRESS

We have genetically characterized regional populations of rhesus and long-tail macaques, conducted phylogenetic analyses to infer phylogenetic history and developed methodology and bioinformatics to identify many SNPs in rhesus genome.
SUBPROJECT DESCRIPTION

Objective: The Center for Fetal Monkey Gene Transfer conducts research on crucial questions in gene therapy in nonhuman primates and provides extensive outreach and services to NHLBI-funded investigators. The mission of the Gene Therapy Center is three-fold: (1) to use established monkey models to explore fetal approaches for heart, lung, and blood diseases; (2) to evaluate the safety and efficiency of gene-based strategies for potential human application; and (3) to provide NHLBI-funded investigators with essential expertise and services through an annual call for proposals. The Gene Therapy Center also provides training to investigators and their students, fellows, and staff, and develops new techniques and methodologies each year that are shared with the greater research community.

SUBPROJECT PROGRESS

Examples of published work that highlights the unique and important accomplishments of the program include: addressing the potential for germ cell transduction post-fetal gene delivery; evidence that direct organ-targeting approaches using ultrasound-guided techniques (heart, lung) are safe and do not alter prenatal or postnatal development or function; and new methods for imaging transgene expression in fetal and infant monkeys longitudinally and over time using microPET and optical imaging. Through the outreach program, a mechanism for clinical investigators to conduct preclinical studies is also in place, and has provided essential safety data prior to pediatric human clinical trials.
ANNUAL GENE THERAPY SYMPOSIUM FOR HEART, LUNG, AND BLOOD DISEASES (0232)

NPSC UNIT: REPRODUCTIVE SCIENCES

SUBPROJECT DESCRIPTION

Objective: The intent of these annual interdisciplinary scientific symposia is to provide a novel and informal scientific setting for the dissemination and exchange of ideas and research findings by bringing together students, fellows, and junior/senior investigators who do not typically interact at other meetings. Presentations focus on workshops on cutting edge technologies, and speakers who address key thematic issues. Each year, a competitive process supports the attendance and participation of approximately 20 students and postdoctoral or clinical fellows. Each student or fellow has the opportunity to present his or her work in a brief oral presentation followed by a poster session.

SUBPROJECT PROGRESS

The focus topic for the 5th Annual Gene Therapy Symposium was “Tissue Engineering and Regenerative Medicine.”
Rhesus mesenchymal stem cells for fetal gene delivery (0314)

NPRC UNIT: REPRODUCTIVE SCIENCES
%NPRC$: 1.300%

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

withheld

Subproject description
Objective: Mesenchymal stem cells can be expanded and induced to terminally differentiate into a variety of cell types of mesenchymal origin thus providing the potential to replace or restore tissues damaged by disease. In addition, the use of mesenchymal stem cells with inserted genes may be the ideal treatment strategy for a variety of congenital and acquired illnesses, since this approach could provide a means for integration of healthy cells into host tissue with gene products that can restore or enhance organ function.

Subproject progress
Studies have evaluated age-related differences in growth and differentiation potential. These studies showed significant differences in the growth and differentiation potential of mesenchymal stem cells when fetal and adult cells were compared. Studies also showed that adult monkey cells are typically infected with simian foamy virus, and that addition of an antiretroviral agent such as tenofovir to the cultures eliminates virus replication and enhances population doublings. The potential use of Raman spectroscopy to characterize mesenchymal stem cells has also been explored.
CENTER OF EXCELLENCE IN TRANSLATIONAL HUMAN STEM CELL RESEARCH (0395)

INVESTIGATOR

DEGREES

STAFF

DEPARTMENT

CODE

NON-HOST INSTITUTION: STATE, COUNTRY

Withheld

SUBPROJECT DESCRIPTION

Objective: The Center for Pediatric Stem/Progenitor Cell Translational Research is a partnership Center of Excellence that unifies research across basic science, translational, and medical disciplines for a common goal - the advancement of cellular therapies for the treatment of childhood diseases. The Center encompasses three research projects with central themes of cell expansion and reconstitution, transplantation and cell fate, pediatric nonhuman primate models, and in vivo imaging. Center projects are supported by four Cores (administrative, cell and vector, nonhuman primate, bioinformatics and biostatistics) and the Center includes a Pilot and Feasibility Program, with a focus on outreach to the greater research community.

SUBPROJECT PROGRESS

The Center will work towards bringing translational studies to clinical application. Recent accomplishments include the labeling of stem and progenitor cells with 64Cu for tracking cells post-transplant with microPET.
SUBPROJECT DESCRIPTION

Objective: To develop protocols for freezing and in vitro maturation of monkey oocytes. These methods will have direct relevance to human oocytes as well as allow preservation of genetically valuable and/or endangered nonhuman primates.

SUBPROJECT PROGRESS

We have made progress on developing methods for cryopreservation of oocytes. We attempted to cryopreserve immature oocytes to avoid the problem of spindle damage by cryopreservation. However, cumulus cell-oocyte connections are irreversibly damaged by slow-rate freezing. Therefore, we have now begun to develop a vitrification protocol. Oocytes will survive intact after vitrification, but must be inseminated immediately after thaw. Thus far, only limited embryonic development has been achieved. In parallel studies, we are making progress on media for in vitro maturation (IVM) of oocytes. The role of mineralcorticoids and growth hormone are being investigated. The overall efficiency of IVM of oocytes remains low in humans and non-human primates despite ongoing research in the field. At this point in time IVM is not a routinely feasible medical procedure. Growth hormone (GH) has been shown to have stimulatory effects on oocyte maturation in the rat, pig and rabbit while little research in the human or nonhuman primate has been done. Therefore, various concentrations of GH were added to IVM medium and cumulus expansion and nuclear maturation were examined after 24 hours. Cumulus expansion was analyzed as percent increase expansion after 24 hours of IVM. Images were taken using a heated Nikon microscope and cumulus oocyte complexes were measured using ImageJ software. Nuclear maturation was assessed using immunocytochemistry to analyze nuclear status. Classification of oocytes was broken down into four nuclear states: germinal vesicle, metaphase I, metaphase I to metaphase II transition and metaphase II (presence of a polar body).

Immunocytochemistry confirmed the presence of GH receptors on the oocyte and cumulus cells. Average percent cumulus expansion was highest in the presence of 1ng/ml recombinant human growth hormone (r-hGH), however, cumulus expansion with 10ng/ml and 100 ng/ml were still greater than cumulus expansion without any r-hGH present. Values were not found to be statistically significant, likely due to the low sample numbers. Nuclear maturation data shows a dose-response trend with increasing concentrations of r-hGH having higher average percentages of oocytes at the MII to MII transition and MII stage when the nuclear states are combined. The presence of GH receptors on the cumulus oocyte complex along with higher cumulus expansion and nuclear maturation rates suggest that r-hGH increases the ability of oocytes to mature in vitro and could further lead to an increase in developmental capacity of IVM oocytes. Similar studies are now being performed on the role of insulin and insulin receptor in IVM. The following publications are relevant to this project, but do not show up in PubMed: VandeVoort CA, Leibo SP. Effect of cooling and exposure to ethylene glycol on in vitro maturation and embryo development of rhesus oocytes. Cryoletters 26:5, 2006 pp.305-312. Leibo SP, Kabisch HM, Schramm RD, Harrison RM, VandeVoort CA. Male-to-male differences in post-thaw motility of rhesus spermatozoa after cryopreservation of replicate ejaculates. J Med Primatol, p. 1-13, 2006.
EFFECTS OF TABOCCO SMOKE ON PRIMATE SPERM FUNCTION AND GENETICS (0364)

INVESTIGATOR: withheld

SUBPROJECT DESCRIPTION
Objective: To determine the effects of environmental tobacco smoke on male reproductive function.

SUBPROJECT PROGRESS
Of the 1.3 billion people worldwide who smoke cigarettes or other tobacco products nearly 80% are men. Tobacco use increases the risk for various diseases, such as cancers, vascular diseases, and respiratory tract diseases, not only in smokers but also in those people exposed to environmental tobacco smoke (ETS - i.e. second-hand smoke). Effects of ETS on male reproduction have been investigated in men and rats; however, the lifestyle factors in men and physiological difference between primates and rats limit the application of the results. The objective of this study was to use a nonhuman primate model to examine the effect of ETS on sperm function. Our previous in vitro results showed that sperm exposed to ETS medium were affected in terms of motility, mitochondria integrity, and ability to display hyperactivation. In this study, four adult rhesus monkeys (Macaca mulatta) were housed within the environmental exposure chambers for three months to acclimatize to the environment. During this period, pre-treatment semen samples were collected and each monkey served as his own control prior to a 6 month ETS exposure. Sperm number, motility, viability, and percentage of acrosomal reacted sperm were evaluated. Computer assisted semen analysis (CASA) system was used to measure motility parameters including average path velocity (VAP), straight-line velocity (VSL), curvilinear velocity (VCL), amplitude of lateral head displacement (ALH), beat-cross frequency (BCF), and linearity (LIN). Sperm-zona binding assays were also performed to examine the ability of sperm to bind and acrosome react. The monkeys were exposed to ETS six hours a day, five days a week. During the exposure period, semen samples were collected each week and evaluated, and the health of the monkeys was carefully monitored. At the end of the exposure period, ETS showed no effect on semen volume, sperm concentration, sperm motility, sperm viability, or percentage of acrosome reacted sperm. We are continuing analyses on samples collected during the exposure period to determine if ETS affected x:y ratio of sperm, embryos generated by IVF with sperm from ETS exposed males and levels of DNA adducts.
SUBPROJECT DESCRIPTION

The Behavior Assessment Core provides a battery of standardized behavioral assessments, primarily focused on rhesus and cynomolgus monkey infants, to other CNPRC units and service cores as well as outside investigators. The core can provide equipment and protocols to investigators experienced in behavioral techniques, or can conduct the evaluations using experienced technical staff. Offsite projects can be accommodated via video recording of behaviors. Consultation in selecting tests, and data summary, analysis and interpretation are also provided on a recharge basis. Materials are made available to help investigators include core services in grant and contract proposals.

SUBPROJECT PROGRESS

During the past year, the core conducted an experiment for an investigator at University of California San Diego using behavioral methods to provide cognitive enrichment and measuring the effect on neural stem cells. Another project for a commercial laboratory is evaluating behavior in videotapes made offsite. Data from the first project were forwarded to the investigators; the second project is ongoing.
SUBPROJECT DESCRIPTION

Objective: Our facility provides light microscopy, stereology, digital imaging, histology, and consultation services.

Our goal is to assist faculty, staff, and students with their research needs for qualitative and quantitative applications. We can assist with the production of publication quality images and offer consultation on experimental approaches for use with our equipment. Instrumentation housed in our facility is available 24 hours a day, 7 days a week for trained CNPRC users. Consultation, training, and support service, along with access to the equipment for other departments, is available from 8-5 Monday through Friday.

The facility houses the following equipment:

- A Cryostat for frozen sections.
- Microtomes for paraffin or plastic sectioning.
- An Olympus BX61 research microscope with SIS image analysis software and Intelligent Imaging Innovations Slidebook software for stereology and data collection.
- A second Olympus BX61 microscope with Intelligent Imaging Innovations Slidebook software for stereology technique development by the Core's staff.
- A graphics workstation, a flatbed scanner, and a high-quality color printer.
- A Delta Vision Microscopy System for very high resolution multi-dimensional fluorescence imaging.
- A CAST Grid Stereology System for data collection.
- A computer workstation for offline analysis of stereology data.
- PhotoShop and Illustrator software.
- A fluorescence stereomicroscope.
- A dual-head brightfield stereomicroscope.

SUBPROJECT PROGRESS

New software has been developed in collaboration with Intelligent Imaging Innovations program "Slide Book". We are using the beta software to collect images in a stratified random fashion and with multiple channels of fluorescence. They are custom developing a counting module for us that will make the software fully functional for our purposes. New techniques have been developed for design-based sampling of heart tissue for pathology. The core has begun to collect whole slide-scan images of nonhuman primate pathology cases for sharing with pathologists from other primate center and training laboratory animal pathologists.
SUBPROJECT DESCRIPTION

Objective: The Endocrine Core provides hormone analyses services, evaluation of neuroendocrine processes, and consultation on neuroendocrine research to other CNPAC units and service cores as well as outside investigators.

The Core’s primary laboratory function is to measure hormones, metabolites, receptors and carrier proteins in a variety of biological samples including tissue, plasma, serum, cerebrospinal fluid (CSF), saliva, urine and feces. Secondary functions of the Core include providing guidance and training to Core Faculty, Staff Scientists, and Graduate Students in the performance of assays as well as the design of experiments requiring hormone measurements. Similar services are provided to non-Center research scientists. In addition, this core develops and validates steroid, monoamine, protein, and receptor assays for use in research conducted with nonhuman primates.

The Endocrine Core consists of two major components housed entirely at the CNPAC. The Reproductive Hormone component, overseen by (redacted), performs assays for gonadal function, and pregnancy detection with analyses of steroid hormones on serum, urine and fecal samples as well as development of automated methods for reproductive hormones with an emphasis on macaque-specific assays. The Stress Hormone component, overseen by (redacted), provides analyses of stress-related hormones as well as developing techniques for evaluating neuroendocrine function using hormonal measures to evaluate neurobehavioral processes, including responsiveness, regulation, and individual differences.

SUBPROJECT PROGRESS

The Endocrine Core continues to serve the dual purposes of service and development. Over the past funding period the Core has served over 170 scientists, processed over 12,000 samples and recharged approximately $11,000. This service provides mainly unique analyses that are not available elsewhere. Similarly, its assay development is directed towards providing assays that currently do not exist elsewhere. During the past year the Endocrine Core has extended its service from reproductive and stress-related hormones exclusively to include metabolic hormones and carrier proteins. It is our intent to provide in-house service for all assays requested through (proprietary info) and by individual investigators. New assays are being formatted on the ACS-180 automated chemiluminescence platform whenever possible in order to provide the most dependable and cost-effective service. A macaque thyroid panel as well as monkey chorionic gonadotropin (mCG), have been added to the list of hormones available for a new nation-wide service once this new technology is published. In addition to the assays being developed using chemiluminescence, additional assays for monoamines and their metabolites are being developed using HPLC and will be offered as they become available.
ADAPTING MICROTITER PLATE ASSAYS TO AN AUTOMATED PLATFORM (0341)

INVESTIGATOR: Proprietary Info

SUBPROJECT DESCRIPTION
Objective: The objective of the project is to simplify and standardize common analytical assays from the Endocrine Core in order to provide a fast, more reliable and more economical service to scientists and animal managers. Assays that have traditionally used a microtiter plate format were selected for adaptation to an automated platform, the ACS-180. Previously the immunoassays for estrone conjugates, pregnandiol-3-glucuronide, follicle stimulating hormone and monkey chorionic gonadotropin were adapted. In the past year, thyroid stimulating hormone, monkey chorionic gonadotropin and non-hormone analyses such as transferrin, and fibronectin were also adapted.

The result of this project is the current ability to perform all of the designated assay using the ACS-180 autoanalyzer. The advent will shorten turn-around time, reduce costs, provide increased reliability and provide service to a broader user base and a national service.

SUBPROJECT PROGRESS
Progress to date demonstrates proof of concept and a potential to provide a national or even international service for hormone measurements. Additional assays are now being identified including clinical assays that have previously been commissioned to outside laboratories. The following publication is relevant to this project, but does not appear in PubMed: Lohstroh P, Laughlin L, Gee N, Lasley B. Development, validation, and application of a chemiluminescent immunoassay for the measurement of circulating chorionic gonadotropin levels in the laboratory macaque. J Med Primatol, 1-6, 2006.
PATHOGEN DETECTION LAB CORE/SIMIAN RETROVIRUS LABORATORY (0223)

NPRC UNIT: RESEARCH CORES
%NPRC #: AIDS RELATED RESEARCH

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

Proprietary info

SUBPROJECT DESCRIPTION

Objective: Since 1986, the PDL Core has provided over 10,000 virological and serological analyses of nonhuman primate specimens annually. We provide services to more than 50 clinicians, researchers, and colony managers.

Services include:
• Specialty lab testing and expert consultation services to public and private sector local, regional, national, and international research colonies, zoological collections, and veterinary laboratories and practices of all sizes
• Methods and reagents validated, standardized, and controlled by in-laboratory studies and proficiency testing
• Maintenance of reference banks of characterized specimens
• All serological test results reviewed by personnel who are fully accredited by American Society for Clinical Pathology and Laboratory Field Services of the State of California
• Resource for development and maintenance of Specific Pathogen-free (SFF) colonies
• Resource for field or epidemiological studies
• Resource for laboratory baseline and monitoring of animals on research studies
• Resource for unusual or atypical diagnostic cases
• Staff committed to quality and client-oriented service
• Purpose is to facilitate laboratory needs of nonhuman primate clinicians and researchers

SUBPROJECT PROGRESS

Research efforts to develop, validate, and improve diagnostic assays are continuously on-going. PDL routinely offers antibody, antigen, virus, and DNA detection for a number of infectious agents. The PDL is in the process of changing from an individual ELISA format to a multiplex bead immunoassay format using Lumineq technology for all antibody testing. This new platform will allow simultaneous testing for antibodies to multiple viral agents in a single assay using very small volumes of serum, thus increasing the efficiency and cost-effectiveness of testing services offered by PDL.
IMMUNOLOGY CORE SERVICES (0286)

Proprietary Info

INVESTIGATOR

NON-HOST INSTITUTION: STATE, COUNTRY

DEGREES

STAFF

DEPARTMENT

CODE

SUBPROJECT DESCRIPTION

Objective: The Immunology Service Core is designed to provide 1) standardized measures of immune response in macaques, 2) advice to outside investigators on experimental design of primate immunology studies, 3) development of new technology for assessing immune responses in this animal model, 4) information on techniques and reagents that are useful for primate immunology, and 5) training of personnel in the use of immunology assays for work with macaques. Because of the large volume of AIDS-related research done by both staff and non-staff scientists at the CNPRC, the emphasis of this core was on antiviral immunity.

In addition, assays to nominal test antigens were available for other infectious and non-infectious research at the CNPRC. The Core, which began operation in August 2000, has four services or work areas corresponding to humoral immunity (requires BSL-2 only for initial sample processing), cellular immunity (requires BSL-2 containment throughout the time of assay), an allergy unit, and a molecular core unit. Humoral immune assays include the detection of antibodies to viral antigens by ELISA. In addition, antibody levels to the nominal antigens, tetanus toxoid, cholera toxin and keyhole limpet hemocyanin are measured by ELISA. Cellular assays include the detection of antiviral cytotoxic T lymphocytes (CTL) or natural killer cells (NK) and lymphocyte proliferation to viral and nominal antigens. A mixed lymphocyte reaction is available for genetics and transplantation. Cytokine/chemokine-secreting cells are assayed by ELISPOT.

The molecular core unit analyzes and quantitates cytokine/chemokine mRNA transcript levels by real-time PCR. Additional target gene amplification is available for certain apoptosis genes and some transcription factors. SIV DNA and RNA detection/quantitation and the provision of aliquots of SIVmac challenge stocks, titered for mucosal inoculation, have been added to the Core and will comprise a new component of the Molecular Immunology Division in the Core during the next base grant cycle.

The allergy unit is responsible for providing allergy and pulmonary related services, including characterization and preparation of allergens for aerosol delivery and systemic sensitization procedures. In addition, immunoassays to detect histamine and tryptase levels, as well as immunoassays to detect allergen-specific IgE/IgG have been developed. Support for preparation, analysis and archiving of collected blood and bronchoalveolar lavage samples is also available.

In the past year the Core has begun distributing the 2 infectious stocks of cell-free SIV. We have approx. 1 liter of SIVmac231 and 500ml of SIVmac239. The stocks are divided into 0.5 and 1 ml aliquots and frozen in LN2. The stocks have titers of 105 TCID50 and contain approx. 109 rRNA copies/ml. For both stocks, IV inoculation of 10 TCID50 infects 2 of 2 animals and the animals have sustained high plasma vRNA and declining CD4+ T cells. We also found that 1 TCID50 of both stocks infects 1 of 2 monkeys inoculated IV, although the plasma vRNA levels were lower in these infected animals. Approximately 10mmls of virus have been distributed thus far.
In addition the Core has developed and validated new lymphocyte phenotyping panels and a multicolor cytokine flow assay and as soon as rates are approved by UCD committees these will be offered. We currently have several outside investigators with frozen cells that are seeking this service. Pending Support

Finally, a number of additional gene targets have been added to the gene expression service of the Core and we are assisting outside UCD investigators develop laser capture microscopy and RNA extraction and recovering our costs based on time and materials.

SUBPROJECT PROGRESS

The services offered by the Immunology Core are summarized as follows: * Sample Processing * Total IgG, IgA, ELISA assays * Ag Specific IgG, IgA ELISA assays * Total IgG, IgA ELISPOT assays * Ag Specific IgG, IgA ELISPOT assays * Cytotoxic T Lymphocyte assay * T-cell Proliferation assay * Ag Specific IFN-g ELISPOT * B Cell Transformation * Mixed Lymphocyte Reaction * SIV RNA or DNA PCR * Nucleic acid extraction * Natural Killer Cell assay * Nucleic acid extraction * SIV RNA or DNA PCR * Real-time PCR to quantify cytokine/chemokine mRNA * SIVmac challenge stocks * House dust mite allergen preparation and characterization * Trypsin ELISA assays * Der p 1/Der f 1 and Der p 2 specific IgE amplified ELISA * Der p/Der f specific IgG ELISA
INHALATION EXPOSURE FACILITY (0226)

NPCC UNIT: RESEARCH CORES

INVESTIGATOR: WITHHELD

DEGREES: WITHHELD

STAFF: WITHHELD

DEPARTMENT: WITHHELD

CODE: WITHHELD

NON-HOST INSTITUTION: STATE, COUNTRY

SUBPROJECT DESCRIPTION

Objective: The Inhalation Exposure Facility permits unique human health-related pulmonary research opportunities using nonhuman primates.

Capabilities exist for in vivo or in vitro exposure to precisely characterized and controlled atmospheres of gases and aerosols. For health effects of air pollution research, the range of test subjects used for exposure studies can include animals, isolated and perfused lungs, tracheal explants and human or monkey lung cell cultures. This permits an integrated, comparative approach to defining mechanisms of respiratory system injury and repair.

A recent addition to the capabilities is a pulmonary function laboratory that offers a comprehensive array of testing for infant through adult nonhuman primates.

Services Offered:
- Special Exposures
- Ozone Generation and Monitoring
- Aerosol Generation and Analysis
- NOx Generation and Monitoring
- Allergen Generation and Analysis
- Filtered Air Exposure
- BTS Generation and Analysis
- Pulmonary Function Testing Laboratory
- Baseline Airway Resistance Testing
- Airway Responsiveness Testing
- Allergen Responsiveness Testing
- Static Lung Mechanics Testing
- Physiologic Monitoring - Aerosol Therapy

SUBPROJECT PROGRESS

Major emphasis in research activities was directed to further inhalation exposure studies of asthma and air pollution in non-human primates. Inhaled steroid aerosol delivery with plasma concentration measurements was developed for infant nonhuman primates. An exposure regimen was completed that includes groups exposed to house dust-mite allergen aerosol + ozone and filtered air control groups. Animals in each group were treated with the inhaled steroid, beclomethasone, or a placebo aerosol. Aerosol therapy studies with inhaled immunostimulatory sequence DNA aerosols continued with improved inhaled dose estimates for adult nonhuman primates. This aerosol delivery system now incorporates electronic flow controls to permit enhanced portability for operation in more remote locations. Other nonhuman primate projects included metabolic measurements using indirect calorimetry and prenatal and postnatal exposure to aged and diluted cigarette smoke.
SUBPROJECT DESCRIPTION

Objective: Identify specific gene expression signatures that are associated with asthma inflammation and pathogenesis by characterizing gene expression pattern in the airways of asthmatic rhesus monkeys during a year long progression of disease.

SUBPROJECT PROGRESS

During the induction and maturation of allergic airways disease (asthma) bronchoalveolar lavages, endobronchial biopsies and peripheral blood samples were used to explore the development of the immune response. Results confirmed the mixed nature of the response in that Th1 and Th2 cytokines were expressed at differing times as assayed by microarray analysis.
SUBPROJECT DESCRIPTION
Objective: Cloning, gene therapy, and stem cell technologies are rapidly developing in a variety of species that are models for human biology. Rhesus macaques and baboons are the animal models that most closely resemble humans, biologically, physiologically, and genetically, and are the most feasible for a variety of research applications. Simple gene or complex trait, infectious or environmental, the rhesus macaque plays an important role in research that is directly related to human health. But, genetic applications and resources for the rhesus macaque and other nonhuman primates (NHPs) have not been developed or used to their fullest capacities. Most primate holding facilities have not used genetics to assist with colony management, nor has animal relatedness been considered in research applications, such as vaccine or exposure studies. The genetic background clearly plays an important role in biological responses of an individual and should be more controlled in all animal and human studies. The central hypothesis is that the genetic background of an individual, particularly as an animal model, is vital to research study design. The investigators propose to develop and facilitate the genetic resources of NHPs, particularly rhesus macaque, and apply genetic information to colony management and study design.

SUBPROJECT PROGRESS
Our NCRR R24 on NHP genetic resources has been successful in a variety of applications. This funding has supported 2 graduate students with their research on the affects of genetic variation on animal behavior, particularly genes in the serotonin pathway. A major focus of the research has been to develop a high density genetic mapping resource for the macaque, a 10,000 Rad radiation hybrid panel. The genes mapped on this panel will augment the annotation of the genetic sequence of the rhesus macaque, supporting the correct assembly and comparison to humans and other species.
EARLY IMMUNE EVENTS IN CHILDHOOD ASTHMA (0412)

INVESTIGATOR: Withheld
DEGREES: Staff Department Code

NON-HOST INSTITUTION: State, Country

SUBPROJECT DESCRIPTION
The primary objective of this project is to determine the early pulmonary mechanisms that initiate development of clinical symptoms in childhood asthma, using a rhesus monkey model of allergic airways disease. We have hypothesized that pulmonary eosinophilia is a critical first step in the initiation of allergic airways disease during postnatal development.

SUBPROJECT PROGRESS
For our first year of funding, we have completed an experimental protocol to first test a revised sensitization strategy using Dermatophagoides pteronyssinus (Der p, house dust mite). Allergen sensitized animals developed non-specific airways hyperresponsiveness and airways eosinophilia. Experiments planned for the second funding year will utilize an anti-IL-5 drug treatment protocol to determine if inhibition of eosinophils will affect the development of clinical symptoms of asthma in this animal model.
SUBPROJECT DESCRIPTION

Objectives:
1. To characterize conditions of exposure to a common indoor air pollutant (ETS) in monkeys during critical windows of development (ranging from early gestation to 13 months postnatal age) correlated to measures from ultrasonography, amniotic fluid and blood samples of the mother and/or infant.
2. To determine the consequences in the lung of exposure to ETS in monkeys during critical perinatal periods of development (from early gestation to 13 months postnatal age) on immunological development of the Rhesus monkey.
3. To determine if the same perinatal ETS exposure enhances neurotrophin production in the lungs in association with increased production of substance P in C-fibers resulting in exaggerated CNS respiratory responses.
4. To determine if cessation of exposure to ETS after the perinatal period will ameliorate effects or be associated with persistent changes in the lung and its neural control.
5. To determine the effects of ETS on NF-kappaB signaling to increase apoptosis in infant monkey lungs
6. To evaluate the impact of perinatal exposure to ETS on brain development and cognitive function in the neonal Rhesus monkey.

SUBPROJECT PROGRESS

We can conclude that short-term exposure to ETS can induce an acute systemic inflammatory response in the neonate, and long-term exposure to ETS beginning in utero or at 6 months postnatal age can significantly alter immune effectors. Each of these consequences of exposure to ETS may compromise normal immune system development with potential implications for future onset of diseases.
Afferent Nerve Activ. in Isol. Trachea of Inf. Monkeys Exp. to Ozone & Allergen (0123)

INVESTIGATOR: WITHHELD

SUBPROJECT DESCRIPTION

Objective: In primates and humans, a substantial portion of lung development occurs postnatally, including proliferation and innervation of the developing respiratory tract. We documented that the airways of 6 month-old monkeys exposed to ozone (O3) plus allergen (HDMA) during postnatal development had significantly fewer intraepithelial nerves than animals raised in filtered air (FA). In addition, the nerves had an altered distribution in the epithelium. To determine whether inhaled corticosteroids could reverse these changes, 1-month-old rhesus monkeys were sensitized and then exposed for 5 months to FA or O3 (0.5 ppm, 6 hr/day, 5 days, every other wk) plus HDMA (2 hr/day, 3 days, every other wk). One half of the FA and O3/HDMA animals were given inhaled budesonide (BUD) (0.33 ng/5 minutes) daily from 3-6 months. The density and distribution of intraepithelial nerves in intrapulmonary airways was evaluated immunohistochemically using immunoreactivity for protein gene product (PGP) 9.5. In addition, significantly fewer intraepithelial nerves in the airways of O3/HDMA monkeys compared to FA monkeys, airways of O3/HDMA monkeys contained clusters of abnormal PGP 9.5-immunoreactive cells. Treatment with BUD did not promote re-innervation of epithelial mucosa. In addition, there was a significant increase in PGP 9.5-positive ciliated cells.

SUBPROJECT PROGRESS

We conclude that periodic cycles of acute injury and repair following episodic exposure to environmental inflammatory pollutants and allergens, during postnatal lung development, compromized the development of airway intraepithelial nerves leading to a loss of innervation and the presence of unidentified PGP 9.5-positive ciliated cells within the epithelium. Further, treatment with inhaled corticosteroids fails to reverse the aberrant innervation.
SUBPROJECT DESCRIPTION
Objective: Inhaled corticosteroids (ICS) are frequently used to treat persistent asthma in young children, however the safety and efficacy of this therapeutic modality during the first year of life is not known. We have previously reported that an exposure regimen of house dust mite (HDM) aerosol and ozone results in the development of airway hyperresponsiveness and eosinophilia in 6 month old infant rhesus monkeys. In the current study, we determined if ICS treatment can prevent or attenuate airways inflammation in this animal model of childhood asthma.

SUBPROJECT PROGRESS
We conclude that ICS treatment during infancy does not prevent the characteristic development of eosinophilia in allergic airways. Our findings further suggest that this process is mediated, in part, by the inability to inhibit eotaxin-3 expression in HDM-exposed infant airways.
SUBPROJECT DESCRIPTION

Objective: Airway smooth muscle has been implicated in the excessive bronchoconstriction of asthma. The present study addressed the question of whether the episodic nature of urban exposure to oxidant air pollutants contributes to the rise in childhood respiratory diseases by altering postnatal lung development.

SUBPROJECT PROGRESS

We conclude that the periodic cycles of acute injury and repair associated with the episodic nature of environmental patterns of ozone exposure alters postnatal morphogenesis and differentiation of airways in infant primates and that some of the alterations are not reversible with inhalation therapy once the process has started, but that others are modified by the therapy.
GLUTATHIONE LEVELS IN AIRWAYS OF INFANT MONKEYS EXP. TO O3 WITH & WITHOUT HDMA (0184)

NPSC UNIT: RESPIRATORY DISEASES
%NPSC #: 0.706%

INVESTIGATOR

DEGREES

STAFF

DEPARTMENT

CODE

NON-HOST INSTITUTION: STATE, COUNTRY

Withheld

SUBPROJECT DESCRIPTION

Objective: Naphthalene (NA) and 1-nitronaphthalene (1-NN) are ambient air pollutants which undergo bioactivation by pulmonary cytochrome P450 monoxygenases and deplete Glutathione. Reactive metabolites become bound covalently to cellular proteins and this process has been implicated in cellular injury associated with these agents in rodent models. The relevance of rodent models in assessing the importance of chemicals which require bioactivation is not clear because of the 10 to 100 fold lower activities of cytochrome P450 monoxygenases in primates compared to rodent lungs. Besides being a target for bioactivated toxicants, the airway is also one of the most susceptible sites for acute inflammatory response. Inflammation results in a strong suppression of cytochrome P450 dependent metabolism at least in extrahepatic tissues. Recent work has established and validated a primate model for human asthma which involves exposure to house dust mite antigen (HDMA) and ozone (O3). Accordingly these studies were designed to measure the formation of, and identity of reactive metabolite protein adducts in rhesus macaques and to determine whether treatments which produce an asthmatic response alter the rates and or nature of protein adducts generated.

SUBPROJECT PROGRESS

These studies show that many of the proteins which are targeted by reactive NA and NN metabolites in rodent models are also adducted in lungs of rhesus macaques, that while many of the proteins are adducted in common by the two toxicants some are unique to the separate agents. The overall levels of bound metabolite did not appear to change with allergen exposure. In a comparison with younger animals, it was determined that for the rhesus monkey age modifies the protein adduction profile. For young animals exposed for shorter periods during postnatal lung development, a larger, more complex mix of proteins was adducted.
SUBPROJECT DESCRIPTION

Objective: To determine the role of innate immunity in orally SIV-infected infant macaques.

SUBPROJECT PROGRESS

Infant macaques rapidly mount innate immune responses to SIV infection that seems to be similar in magnitude compared to adults. Thus, changes in pathogenesis between infants and adults are not due to differences in type I interferon responses, but are likely due to differences in adaptive responses.
A NON-HUMAN PRIMATE MODEL FOR CYTOMEGALOVIRUS VACCINES (0218)

NPRC UNIT: VIROLOGY & IMMUNOLOGY
%NPRC #: 1.000% AIDS RELATED RESEARCH

INVESTIGATOR

DEGREES

STAFF

DEPARTMENT

COUNTRY

withheld

NON-HOST INSTITUTION: STATE, COUNTRY

SUBPROJECT DESCRIPTION

Objective: To (a) characterize the roles of the RhCMV interleukin-10 and US28 proteins in the RhCMV replication cycle, and (b) develop novel vaccine designs against human cytomegalovirus by constructing RhCMV variants containing deletions in the viral interleukin-10 and US28 genes.

There are no licensed vaccines for human cytomegalovirus (HCMV). Limited clinical trials have been conducted with live attenuated and recombinant subunit vaccines. Despite partial success protecting from disease in renal transplant recipients, the goal of developing an HCMV vaccine that elicits protective immunity has not been achieved. There are impediments to the development of an HCMV vaccine. Design of an effective HCMV vaccine requires characterization of the correlates of protective immunity and a better understanding of HCMV natural history. Both aspects of HCMV are incompletely resolved and difficult to investigate in humans. Studies have suggested that two measures of humoral immunity, neutralizing antibodies and antibody avidity, and one measure of cellular immunity, CTL, are useful for assessing protective anti-HCMV immunity. The two HCMV proteins associated with protective immune responses, gB and pp65, represent starting points for any rational vaccine.

Recent data on HCMV and the closely related rhesus CMV (RhCMV) strongly implicate viral modulation of host immune responses as a critical component of CMV natural history. CMV appears to have evolved strategies that alter lymphoid cell signaling and trafficking. Based on sequence homologies, it is reasonable to infer that HCMV has targeted pro-inflammatory immune responses for disruption during infection. Attenuation of HCMV's ability to modulate host immune responses should limit viral replication and disease sequelae. Accordingly, HCMV vaccines must be directed against both structural and immune modulating ORF to reduce virologic parameters of infection and/or disease. In other words, protective immunity will be enhanced when vaccination is directed against identified immunogens, such as gB and pp65, together with novel vaccine targets represented by immune modulating ORF. A successful outcome of this approach will demonstrate that attenuation of the CMV immunomodulatory ORF by immunization represents a rational vaccine strategy. This would fundamentally alter the paradigm for vaccine approaches to HCMV.

SUBPROJECT PROGRESS

(a) A modified rhesus CMV (RhCMV) variant has been constructed in which the viral interleukin-10 gene has been deleted. Compared to animals inoculated with wild-type RhCMV, animals inoculated with the IL-10-deleted variant are characterized by (1) an increased inflammatory response at the site of inoculation, (2) a shift in the predominant inflammatory cell at the site of inoculation, (3) an increase in viral-specific antibodies, and (4) an increase in viral-specific T cells in the draining lymph node two weeks post infection. These results demonstrate that the absence of a single viral protein, IL-10, leads to profound increases in innate and adaptive immune responses to viral antigens. (b) Exposure of LPS-activated dendritic cells to either viral or cellular IL-10 significantly reduces their viability through an inhibition of an LPS-mediated increase in the transcription and translation of the anti-apoptotic proteins.
EVALUATION OF PROTECTIVE CMV VACCINES IN RHESUS MACAQUES (0486)

NPRL UNIT: VIROLOGY & IMMUNOLOGY
%NPRL S: 1.000% AIDS RELATED RESEARCH

INVESTIGATOR: withheld

DEGREES: š soften spacing
STAFF: š soften spacing
DEPARTMENT: š soften spacing
CODE: š soften spacing

NON-HOST INSTITUTION: STATE, COUNTRY

SUBPROJECT DESCRIPTION

Objective: Since human cytomegalovirus (HCMV) was first recognized as a threat to the developing fetus, there have been repeated calls for a vaccine that could protect from the damaging effects of HCMV infection in those at risk for HCMV disease. The long quest for a HCMV vaccine that could prevent congenital infection and fetal sequelae, as well as end-organ disease in immune compromised individuals, remains unfulfilled. The primary objective measure for evaluating the efficiency of any vaccine is whether protective levels of immunity are generated and sustained in the vaccinated. An important issue for HCMV is the definition of what constitutes protective immunity. Using a stringent threshold, an immune response can be considered protective only if the vaccinated are absolutely protected from infection following repeated exposure to virus. Alternatively, a vaccine could still be considered protective if the course of challenge virus infection was so dramatically altered that the potential for transmission (horizontal and vertical) and pathogenesis of challenge virus was essentially eliminated. The difference between the two involves the level of virus replication at the primary site of challenge and the extent of dissemination beyond. The former definition requires the generation and maintenance of sterilizing immunity with no spread of the virus. The latter does not, but it does require that the immune system maintain a lifelong restriction on replication of a virus with a complex natural history of persistence in immune competent hosts. The hypothesis is presented that immunization against CMV can generate protective immune responses although the degree of protection (sterilizing versus limited dissemination) will be dependent on both the titer of challenge virus and the frequency of exposure. According to this hypothesis, immunization can protect completely against frequent exposure to a low titer CMV challenge. Protection will become more variable as the titer and/or the frequency of exposure to challenge virus increases. Vaccination should shift the virus-host balance decidedly in favor of the host such that both reactivation and shedding are significantly diminished. The hypothesis will be tested in the rhesus macaque model of HCMV infection through the following Aims. (I) Genetic immunization of seronegative macaques with plasmid expression vectors for RhCMV gB, pp65, and IE1, followed by immunization with formalin-inactivated virus. (II) Subcutaneous challenge of vaccinees and controls by experimental inoculation with either high or low titters of RhCMV. (III) Immunization of macaques followed by challenge of vaccinees and controls by natural routes with natural titters of RhCMV by co-housing vaccinees with seropositive, virus-excreting macaques. (IV) Alterations of RhCMV gene expression patterns to induce novel protective immune responses. A CMV vaccine can be considered protective if it results in a dead-end infection. This proposal will stringently test whether a combination of genetic immunization and formalin-inactivated virus can effectively eliminate horizontal spread of RhCMV following either experimental or natural infection.

SUBPROJECT PROGRESS

Rhesus macaques seronegative for RhCMV infection were immunized against RhCMV antigens using a vaccine regimen consisting of DNA immunizations followed by proteins boosts. The vaccine cocktail consisted of antigens directly relevant to the development of vaccines against human CMV. All immunized animals developed robust immune responses, and the level of the immune responses far exceeded those observed with DNA immunization alone. Vaccinees and controls animals were challenged with RhCMV, and the vaccinees displayed acute and chronic immune responses consistent with effective control of the challenge virus infection. These results have direct implications for evaluation of human CMV vaccines. New collaborative efforts have been initiated to use the monkey model to conduct pre-clinical evaluation of novel vaccine strategies prior to clinical testing in humans.
SUBPROJECT DESCRIPTION

Objective: To maintain healthy nonhuman primates for use in biomedical research, animals are routinely screened at most primate facilities for several infectious agents. In current practice, monkey serum samples are tested by conventional immunoassays such as enzyme linked immunosorbent assay (ELISA) or Western blot for the detection of specific antibodies. For testing antibodies against multiple agents in each sample, conventional immunoassays are laborious and time consuming. The objective is to develop more efficient immunoassays for serosurveillance of nonhuman primates. Accordingly, we have developed a novel multiplex serodiagnostics system where individually identifiable, fluorescent microbeads are coated with purified whole viral antigens.

SUBPROJECT PROGRESS

This project is a continuation of our previous study reported in Khan et al. (2006) Simultaneous detection of antibodies to six nonhuman-primate viruses by multiplex microbead immunoassay. Clin Vaccine Immunol 13: 45-52. Uniquely-labeled microbead sets were each coated with simian immunodeficiency virus (SIV), simian type-D retrovirus (SRV), human T-lymphotropic virus (HTLV - for detection of simian T-lymphotropic virus), simian foamy virus (SFV), herpesvirus papio type 2 (HVP-2 - for detection of herpes B virus), or rhesus cytomegalovirus (RhCMV). The six microbead sets were mixed, a serum sample was added followed by reporter (biotinylated-anti-IgG and PE-streptavidin), and the binding of anti-viral antibody to each bead set was detected in the Luminex flow cytometer. A validation study, with about 1000 macaque serum samples, has been implemented for fully assess the utility of the multiplex microbead immunoassay for serosurveillance of non-human primate colonies. The multiplex microbead immunoassay results demonstrated a strong correlation with ELISA results.
PRIVATE Source will support a project that will evaluate novel anti-tuberculosis vaccine formulations for efficacy in rhesus macaques at UC Davis. Macaques experimentally inoculated with Mycobacterium tuberculosis (M. tb) show clinical signs of tuberculosis (TB). This project is organized into two phases.

Phase 1: Renovations will be done to (i) complete the biosafety level 3 (BSL-3) facility at CNPRC for housing nonhuman primates and (ii) modify the necropsy room for studies of Mycobacterium tuberculosis (M. tb). Phase 2 (subsequent 3 years): For the vaccine study, a total of 32 rhesus monkeys at CNPRC will be immunized with various vaccine formulations provided by Aeras. These include modified BCG vaccines and vaccines based on live adenovirus vectors expressing genetically engineered M. tb antigens.
COGNITIVE FUNCTION IN THE AGED MONKEY (0185)

INVESTIGATOR: Withheld

DEGREES: Staff

DEPARTMENT CODE: Proprietary Info

NON-HOST INSTITUTION: STATE, COUNTRY

SUBPROJECT DESCRIPTION

Objective: The overall aims of the project are to define the effects of normal, non-pathological aging on the component processes of memory, and to evaluate these changes in relation to markers of ovarian hormone impairment in rhesus monkeys. Groups of young and aged subjects are tested across a battery of well-studied, standardized neuropsychological task as well as newly developed procedures designed to provide a sensitive window on cognitive aging. Urinary hormone profiles are determined for all female monkeys periodically throughout the project in order to relate these parameters to individual differences in the status of age-related memory decline.

SUBPROJECT PROGRESS

During the current reporting period, the project has been supported by no-cost extension and bridging funds from the NIA, sustaining critical project activities during the review of a revised competitive continuation application. Under this arrangement, our efforts have focused on the continuation and completion of ongoing behavioral studies, rather than the initiation of new investigations.
SUBPROJECT DESCRIPTION

Objective: The Northwestern University Specialized Center of Research (SCOR) on Sex and Gender Factors Affecting Women's Health is a multidisciplinary NIH-funded program and includes investigators from two National Primate Research Centers, Pennsylvania State University Overall, projects are focused on the etiology of polycystic ovary syndrome, and include specific aims to determine the gene region associated with this syndrome, and how such genes result in reproductive abnormalities and an increased risk for diabetes. This SCOR encompasses human and nonhuman primate studies, and uses the monkey model to explore the syndrome proposed to be associated with prenatal androgen excess.

SUBPROJECT PROGRESS

The nonhuman primate research team has evaluated whether fetal androgen excess induces ovarian, hormonal, and beta-cell defects.
SUBPROJECT DESCRIPTION

Objective: To test whether an oligonucleotide CpG can stimulate innate immune mechanisms in the respiratory tract that can protect against an acute respiratory mucosal challenge with measles virus in the rhesus monkey. A secondary objective will be to determine whether CpG priming of innate immunity can augment the adaptive immune response to measles virus following a respiratory challenge.

SUBPROJECT PROGRESS

The CpG ODN used did not have a detectable effect on measles viremia in rhesus monkeys. However, induction of Type I interferons in the respiratory mucosa was achieved in by intratracheal administration of the CpG.
SUBPROJECT DESCRIPTION

Despite the near complete suppression of detectable virus in many HIV infected patients undergoing highly active antiretroviral therapy, viremia reemerges rapidly after interruption of treatment. Postintegration latency refers to latently infected resting memory CD4+ T cells containing transcriptionally silent integrated HIV-1 genomes. Postintegration latency contributes to the persistence of the virus under HAART and represents a known barrier to eradication of HIV infection.

SUBPROJECT PROGRESS

Four groups of investigators with extensive experience in the molecular virology and biology of HIV and SIV propose to address two major knowledge gaps in our understanding of post-integration latency: 1. Development of in vitro and in vivo models for HIV latency. This group has used a GFP-tagged virus to demonstrate that HIV infection reproducibly results in a state of postintegration latency after infection of a CD4+ cell line in vitro and propose to use the same strategy in primary human CD4 T cells. They have recently demonstrated that infection of rhesus macaques with a recombinant SIV virus (RT-SHIV) can be suppressed to undetectable levels using treatment with Emtricitabine+3TC+PMPA and that virus rapidly rebounds after cessation of therapy. This SIV model system is being used to define the reservoirs of SIV during infection in vivo. Quantitative PCR methods are being used to measure levels of viral RNA and DNA in over 30 tissues collected at necropsy in animals receiving HAART. Low levels of viral RNA are detected in numerous lymphoid tissues; this finding suggests residual replication in the presence of combination therapy of anti-viral drugs. This collaborative effort will culminate in the testing of biological agents aimed at reactivating latent SIV expression in infected macaques in an attempt to flush the latent pools. We anticipate that this effort will lead to increased understanding of molecular mechanisms responsible for postintegration latency and to the opening of new therapeutic opportunities aimed at eradicating HIV infection.
VACCINE EFFICACY OF VSV-SIV/MVA-SIV IN INFANT MACAQUES (0402)

INVESTIGATOR
withheld

DEGREES

STAFF

DEPARTMENT

CODE

NON-HOST INSTITUTION: STATE, COUNTRY
Proprietary Info

SUBPROJECT DESCRIPTION
Objective: To determine the immunogenicity and efficacy of a novel VSV-SIV/MVA-SIV vaccine regimen in infant macaques.

SUBPROJECT PROGRESS
The VSV-SIV/MVA-SIV vaccine is safe in infant macaques and shows no adverse reactions. The vaccine induces humoral and cellular SIV-specific responses.
## RESEARCH SERVICES

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PUBLISHED: JOURNALS


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<td>Neutralizing antibody responses against autologous and heterologous viruses in acute versus chronic human immunodeficiency virus (HIV) infection: evidence for a constraint on the ability of HIV to completely evade neutralizing antibody responses. J Virol 80 6155-64 2006</td>
<td>DeBias, Steven G; Schweighardt, Becky; Warner, Terril; Galovich, Justin; Ho, Rebecca; Sinclair, Elizabeth; Hunt, Peter; McCune, Joseph M; Martin, Jeffrey N; Petropoulos, Christos J; Hecht, Frederick M</td>
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### SOURCE OF INVESTIGATORS' SUPPORT

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**TOTAL FUNDING:**

$96,344,040
RESOURCE SUMMARY: SUBPROJECTS

The following only includes information associated with subprojects.

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RESOURCE SUMMARY: ADMINISTRATIVE

PERSONNEL:

Personnel Total: 54

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<td>MAINTENANCE</td>
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<td>REPRODUCTIVE SCIENCES</td>
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RESEARCH TABLE

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Total 60 47 107

INVESTIGATOR SUPPORT

NON-FEDERAL

| FOUNDATION | $888,362 |
| INDUSTRY   | $1,390,600 |

NON-FEDERAL $2,230,418

FEDERAL

NON-PHS

NASA $0

PHS

AA $826,112
AG $9,104,242
AI $19,223,202
AT $596,384
CA $257,210
CDC $0
DC $261,003
DE $189,375
DK $1,158,144
ES $8,182,568
BY $2,946,411
FDA $456,900
GM $147,609
HD $5,409,681
HL $6,006,008
MH $2,306,705
NS $4,917,877
OD $876,659
RR $31,144,532

PHS $94,013,322

TOTAL SUPPORT $96,344,040
# COLONY STATISTICS

Base Colony Only

*Note: These animals are supported by NCRR Comparative Medicine.*

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<tr>
<th>Genus Species</th>
<th>Breeding Colony</th>
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<th>Transferred</th>
<th>Total Colony Census</th>
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<td>M</td>
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Non-Base Colony Only

*Note: These animals are supported by NCRR Comparative Medicine.*

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1 - Total number of animals in breeding colony including adult breeding animals and designated juvenile replacements at time of report.
2 - Total number of animals assigned to experimental protocols at time of report.
3 - Total number of animals in Center's P51 supported colony.
4 - Sex undetermined.
5 - Total number of animals transferred into colony from outside sources during the reporting period.
6 - Total number of animals transferred to other facilities during the reporting period.
RESEARCH HIGHLIGHTS

AMYGDALA LESIONS LIMITS BEHAVIORAL EXPRESSION DIFFERENTLY IN ADULT AND YOUNG MACAQUES

SPID(s): 0002

In adult rhesus monkeys amygdala lesions resulted in animals that were more willing to approach and interact with animate and inanimate stimuli. In contrast, infant macaques with amygdala lesions animals are less likely to approach food incentives and engage socially in competitive situation.

Publications:

PubMed ID: 16893283

Bauman MD, Toscano JE, Mason WA, Lavenex P, Amaral DG. The expression of social dominance following neonatal lesions of the amygdala or hippocampus in rhesus monkeys (Macaca mulatta). Behav Neurosci 120 4, 2006 Aug pp.749-60

PubMed ID: 16637171

AUTOMATED ASSAY FOR MONKEY CHORIONIC GONADOTROPHIN

SPID(s): 0341

An automated assay for monkey chorionic gonadotropin (mCG) was adapted and optimized for the chemiluminescence platform of the Bayer ACS-180 autoanalyzer. This automated assay performs similarly to previous assays in terms of sensitivity and specificity but provides additional speed, reliability, and more easily accessible reagents compared to previous formats. The ability to perform high throughput analyses for pregnancy detection provides an extremely desirable and cost effective tool that has a myriad of applications for colony breeding programs and colony management.

The following publications is relevant to this project, but does not show up in PubMed:


Publications:

PubMed ID:
EFFECT OF MATERNAL ANTIBODIES ON MEASLES VACCINE IMMUNE RESPONSES

SPID(s): 0055

Measles virus infection is a major cause of infant morbidity and mortality in developing countries despite the fact that an effective vaccine exists. This is because the vaccine does not protect infants that have high titers of maternal anti-measles antibodies. So despite vaccination a large number of children are susceptible to infection as maternal antibody wanes and they become exposed. This study demonstrates that the presence of antibody effects the generation of both protective cellular and humoral immunity and characterized the levels of antibody that elicit this effect. These findings will be useful in designing new vaccines to work in the face of pre-existing maternal immunity.

Publications:

PubMed ID: 16569419

ENVIRONMENTAL INFLUENCES ON THE PERINATAL LUNG DEVELOPMENT

SPID(s): 0027

Low levels of environmental tobacco smoke during a critical window of maturation in neonatal nonhuman primates compromises lung development with potential implications for future lung growth and function. The findings of this study support a role for NF-kB in the regulation of apoptosis, with inhibition of NF-kB by environmental tobacco smoke resulting in increased lung parenchyma apoptosis.

Publications:

PubMed ID: 16876770

PubMed ID: 16466656

PubMed ID: 16709937

PubMed ID: 16487273

PubMed ID: 17012261

PubMed ID: 16393655

IMMUNE EFFECOR CD8+ T CELLS ACT THROUGH ANTIVIRAL ANTIBODIES TO ILL INFECTED CELLS

SPID(s): 0363, 0370

The immune effector mechanisms that contribute to control of HIV replication are poorly understood but many investigators have found that CD8+ lymphocytes are involved. Both T cells and NK cells are CD8a+ so defining the role of NK cells acting by ADCC to kill infected cells is a priority in HIV research. These studies demonstrate that antibodies contribute to CD8+ lymphocyte killing of virus infected cells and control of virus replication.

Publications:

PubMed ID: 16940533


PubMed ID: 16584561

Inhaled corticosteroids are frequently used to treat persistent asthma in young children, however the safety and efficacy of this therapeutic modality during the early development is not known. An exposure regimen of house dust mite aerosol and ozone results in the development of airway hyperresponsiveness and eosinophilia in 6 month old infant rhesus monkeys. This exposure regimen was used along with daily inhaled corticosteroids in filtered air and house dust mite aerosol and ozone-exposed infant rhesus monkeys over the first 6 months of life. Inhaled corticosteroids did not prevent the characteristic development of eosinophilia through the inability to inhibit eosinophil-3 expression or airways hyperresponsiveness. It also resulted in abnormal parenchymal development with increased alveolarization that was associated with increased lung compliance and residual lung volume in both the filtered air and house dust mite aerosol and ozone-exposed infant rhesus monkeys. Although there is no data relative to the permanence of these changes, the functional changes are usually associated with increased airways resistance and gas trapping in the lung, hallmarks of chronic obstructive lung disease.

Publications:
PubMed ID: 16648242
PubMed ID: 16698728
PubMed ID: 16616710
PubMed ID: 16931639
PubMed ID: 16309914
IN VIVO DETECTION OF GENE EXPRESSION BY MICROPET AND OPTICAL IMAGING IN FETAL AND INFANT MONKEYS

Significant advancements have been made in the use of noninvasive imaging techniques to monitor gene expression longitudinally and over time. These techniques include nuclear imaging such as positron emission tomography (PET) that utilize radioactively tagged tracers and optical techniques based on bioluminescence or fluorescence. Reporter genes for PET imaging include the mutant herpes simplex virus-thymidine kinase (HSV-tk), where the radiolabeled substrate for the enzyme is trapped only in cells that express the reporter gene. For bioluminescent approaches, the reporter gene produces an enzyme that can catalyze a bioluminescent reaction in the presence of the necessary substrate, leading to the emission of light. A common reporter gene used is firefly luciferase and its substrate, luciferin. The gene transfer efficiency of HIV-1-derived lentiviral vectors were used to monitor gene expression in vivo using these noninvasive imaging methods. These studies have clearly shown that the HIV-1-derived lentiviral vector with a dual reporter can efficiently be used to monitor gene expression longitudinally and over time in gravid and infant nonhuman primates, and without any adverse findings.

Publications:

PubMed ID: 16873720

PubMed ID: 17134373
MECHANISM OF SPECIES DEPENDENT ENVIRONMENTAL LUNG INJURY

SPID: 0389

Children who are raised in polluted areas of California have significantly lower pulmonary function than college freshmen growing up in unpolluted areas. Infant monkeys exposed to 5 months of repeated episodes of ozone, such as occurs in California during the summers, showed abnormal development of the conducting airways with significant narrowing of the bronchioles. This was correlated with increased airways resistance and implies that along with the human epidemiological data in California that children exposed to episodes of ozone during infancy may have a permanent change in lung structure and function that is evident in adulthood.

Publications:

PubMed ID: 16648242

PubMed ID: 17325971

Hyde Dallas M, Tyler Nancy K, Plopper Charles G. Morphometry of the respiratory tract: avoiding the sampling, size, orientation, and reference traps. Toxicol Pathol 35 1, 2007 pp.41-8
NURSERY REARING LEADS MORE ADULT-LIKE ENDOCRINE PROFILES IN INFANT MACAQUES

SPII(s): 0136

When tested at 3-4 months of age, rhesus macaques raised with their mothers in large or small social groups show levels of hypothalamic-pituitary-adrenal (HPA) activity that is substantially higher than adult HPA levels. Nursery rearing results in much lower HPA activity than age-matched mother-reared monkeys and hormonal levels and response profiles more similar to adult macaques. At least with respect to this endocrine parameter nursery rearing leads to early physiological maturation and/or bypasses a developmental epoch characterized by heightened HPA responsiveness. In mother raised infants an intact hippocampus is necessary to show suppression of HPA activity following administration of dexamethasone a potent agonist for Type II glucocorticoid receptors.

Publications:

PubMed ID: 16963810

ORAL-ORAL TRANSMISSION OF HELICOBACTER PYLORI IN RHESUS MONKEYS

SPI(s): 0193

Infection with H. pylori causes a gastritis that in some individuals is associated with development of peptic ulcer or gastric malignancy. H. pylori is one of the most common human bacterial infections, yet the mechanism by which it is transmitted is unknown. Evidence suggests that it is transmitted person-to-person during childhood, but because it is rarely cultivated from saliva, feces, or from environmental surfaces the mode of transmission has been unknown. Like humans, social housing of rhesus monkeys results in transmission of H. pylori. This study examined various mechanisms by which H. pylori could be transmitted from naturally or experimentally infected animals to uninfected animals. Concentrations of H. pylori in vomit were most compatible with what is needed for an infectious dose, and seems the likeliest mode of transmission in children.

Publications:

PubMed ID: 16790815


PubMed ID: 17021115

PERSISTENT BEHAVIORAL CHANGES WITH PRENATAL OR POSTNATAL IRON DEFICIENCY IN INFANT MACAQUES

SPID(s): 0381

Prenatal iron deficiency lead to reduced activity and lower inhibitory response in novel environments. Postnatal iron deficiency leads to greater emotionality and impaired cognitive performance on selected tasks. This study indicates that different syndromes of behavioral changes are associated with prenatal and postnatal iron deficiency. Moreover these effects can occur in the absence of concurrent iron deficiency.

Publications:

PubMed ID: 16522913

PubMed ID: 16343844
Golub Mari S, Hogrefe Casey E, German Stacey L, Capitanio John P, Lozoff Betsy. Behavioral consequences of developmental iron deficiency in infant rhesus monkeys. Neurotoxicol Teratol 28 1, 2006 Jan-Feb pp.3-17

PROTEIN-FREE MEDIUM THAT PREVENTS ZONA HARDENING IN CULTURE

SPID(s): 0132

Development of a protein-free medium for in vitro maturation of oocytes that prevents zona hardening is essential for the study of components that affect the maturation process. Immature macaque oocytes were cultured in modified medium with serum protein or without protein to determine the best conditions. Results indicated insemination dramatically improved in medium with the addition of polyvinyl alcohol. These results suggest that fertilization failure occurs when macaque oocytes are cultured in medium without protein, but this can be prevented with polyvinyl alcohol.

Publications:

PubMed ID:


PubMed ID:

VIRUS DISSEMINATION IN INFANT MACAQUES AFTER ORAL SIMIAN IMMUNODEFICIENCY VIRUS EXPOSURE

SPID(s): 0401

Understanding the routes of viral dissemination from portals of entry to lymphoid tissues is a major need in HIV research. This study defined the route and timing of viral dissemination after oral SIV inoculation of neonatal rhesus macaques. Viral dissemination occurs very rapidly, indicating that interventions designed to stop virus spread beyond the portal of entry must act quickly and be very effective or the virus will escape to disseminate.

Publications:

PubMed ID: 16775324

ADMINISTRATIVE INFORMATION

ALLOCATION OF RESOURCE ACCESS

Allocation of CNPRC resources is formally granted by the Director’s Office, with the concurrence of the CNPRC Research Advisory Committee. The criteria used for granting access to the Center’s resources include the following:

- Funding source
- Justification for using nonhuman primates
- Relevance of the study to the Center Program (fulfillment of the Center’s mission)
- Impact on the CNPRC program (ongoing commitments, staff expertise, and duration)
- Primate availability (species, age, sex, numbers, housing type)
- Space availability
- Procedures required

All investigators are required to submit a pre-proposal to the CNPRC’s Research Advisory Committee prior to the development of a grant proposal to assure that the Center is able to provide the necessary resources. This form provides information for evaluating the above criteria. For the period 5/1/05 to-date 49 pre-proposals were submitted to the Research Advisory Committee. Of these pre-proposal submissions, 46 were approved, two were revised and approved, and one was denied.

COMMITTEE REPORTS

CNPRC National Scientific Advisory Board (NSAB): Members of the NSAB are appointed by the Center’s Principal Investigator and are representative of the scientific community outside the Center. The NSAB provides advice and guidance to the Principal Investigator and Center director on planning and program activities to support continued and balanced scientific growth of the center, and assuring proper administrative organization.

UC Davis Organized Research Unit Advisory Committee: This committee, which reports to the Chancellor of the University and the Vice Chancellor for Research, evaluates the effectiveness of the CNPRC on an annual basis, particularly its effectiveness in relation to its interactions with the UC Davis campus.

CNPRC Research Advisory Committee: This committee is composed of the Director, the Associate Director for Research, the Associate Director for Primate Services, the Assistant Director for Administration, the Assistant Director for Colony Management and Research Services, and the Unit Leaders. To enhance translational research, the Director of the Clinical and Translational Science Center and the Director of the Center for Comparative Medicine at UC Davis are invited members of the committee. The committee meets biweekly to review and discuss proposed research projects and other matters relating to the Center’s research needs. All projects are discussed and evaluated in terms of scientific merit, resources available, availability of animals, need for use of nonhuman primates, priority, and humane treatment of animals.

Director’s Management Committee: This committee is composed of the Director, Associate Director for Research, Associate Director for Primate Services, Assistant Director for Administration, and Assistant Director for Colony Management and Research Services. The committee meets weekly to discuss administrative, facility, and colony management topics relating to the Center. Many of the issues discussed in this committee are brought in a more formal manner to the Research Advisory Committee for further discussion and consensus building.

Space Advisory Committee: This committee is comprised by a representative from each of the four research units, as well as Animal Care/Research Services and Primate Medicine. The committee is advisory to the Director on issues related to space allocation.

Colony Management Committee: This committee is comprised of the Associate Director for Primate Services and the Assistant Director for Colony Management and Research Services, Staff Scientists, and pertinent staff. This group meets on a monthly basis to review field cage issues in the outdoor breeding colony. This committee also provides input to the Environmental Enrichment Committee.

Administrative Services Management Committee: This committee is comprised of the Assistant Director for Administration and various members of the administrative staff. This committee meets weekly to discuss administrative issues relating to grants management, accounting, purchasing, facilities, and personnel/payroll.
Environmental Enrichment Committee: Composed of the Associate Director for Primate Services; a staff scientist with expertise in primate behavioral management; the Assistant Director for Colony Management and Research Services; and veterinary and research staff. This committee meets to discuss ongoing practices, new areas of focus/concern, suggestions/problem areas, and the efficacy of current environmental enrichment practices.

CNPRC Staff Council: This committee was organized to allow technical, administrative, and secretarial staff a direct avenue of communication with the Research Advisory Committee. The committee makes recommendations regarding working conditions, physical facilities, and social events. The committee includes 10 members who represent the CNPRC’s major employee units and geographic areas: Business Office/Administration — 1; Animal Care (indoor) — 1; Animal Care (outdoor) — 1; Staff Research Associates (one per research unit) — 4; Veterinary Pathology and Clinical Laboratories — 1; Research Services — 1; and the Center for Comparative Medicine — 1. The council also evaluates and selects quarterly nominations for the Employee of the Quarter award. Representatives of the Staff Council bring issues to the Research Advisory Committee on an ad hoc basis.

CNPRC Injury and Illness Prevention Program Safety Committee: Composed of the CNPRC safety officer as well as administrative and technical staff, this committee meets quarterly to review items of concern to the Center and disseminate information to units on such matters as illness/injury prevention plans, exposure-infection control plans, unit emergency action plans, HIV counseling/testing programs, and medical waste handling/treatment guidelines.

Infection Control Committee: This committee is composed of the Associate Director for Primate Services, the Assistant Director for Colony Management and Research Services, representatives of the Virology and Immunology Unit, and a physician from the UC Davis Medical Center. This committee meets to discuss, review, and establish practices and policies relating to the control of disease transmission between animals and humans.

DISSEMINATION

Our research results are disseminated through publications in scientific journals and presentation of papers, poster sessions, and seminars at scientific and professional meetings. The CNPRC also coordinates with the campus communications office for matters concerning the media. Enhancing and formalizing the communication efforts of the CNPRC continue to be a high priority.

The Center continued to formalize the role of the Research Advisory Committee to assure dissemination of information to collaborative and affiliate scientists. In addition, the external web site continues to be enhanced, providing information about the core services at the Center and promoting the Pilot Research Program. Our internal web site and employee newsletter continues to be a resource for staff.

The CNPRC also has an Education Outreach Program, the primary goal of which is to introduce K-6 students to nonhuman primates, general science concepts, animals in research, and biomedical research programs and careers. A class specific-curricula that meets the California State Standards for Science Content is presented 1-2 times per month at elementary schools in Davis and the surrounding communities. Future goals of the program include expanding to additional high-risk and low-income communities where careers in science and scientific concepts are not often presented.

In addition, tours and lectures were provided to further educate and inspire both high school and college students in the areas of biomedical and translational research, veterinary professions, and primate biology.

The Primate Center also continues to co-host, with the Center for Comparative Medicine, a weekly seminar series, inviting speakers from institutions around the country to present seminars on various topics of interest to the primate research community. This series continues to serve as an effective mechanism to increase awareness of our program and services.

TRAINING

The Primate Center offers job-related training on a day-to-day basis. Supplemental training and development opportunities are available at no or low cost through University Extension and the Staff Development Office.

UC Davis provides an annual allocation of staff development funds for off-campus education, and these are available by application to staff who work for the Primate Center or who provide effort on Center projects. Selection for off-campus training is made annually by the CNPRC Research Advisory Committee based upon availability of training funds and the benefit of the training to the Primate
Center and to the employee.

The Primate Center has an on-going training program for individuals who wish to obtain one of the following degrees: Assistant Laboratory Animal Technician (ALAT), Lab Animal Technician (LAT), and Laboratory Animal Technologist (LATG).

PATENTS, LICENSES, INVENTIONS AND COPYRIGHTS

None.

AWARDS, HONORS, SPECIAL RECOGNITIONS

withheld

California National Primate Research Center
American Association of Zoo Veterinarians
Duane Ulrey 2006 Achievement Award -
"For achievements in the science of wild animal health and service."

withheld

California National Primate Research Center
Harry Frank Guggenheim Foundation
Disertation Fellowship -
"Genetic and developmental risk factors for impulsivity and aggression in rhesus macaques."

INFRASTRUCTURE

***Physical Plant

Facilities Improvements

In the past twelve months several projects have been initiated or completed. These include the following:

- Freezer building: Provided monitored housing for up to 52 -80" freezers. These freezers are used for long term storage of viral stock. The building has both room and freezer temperature monitoring and includes back up power during electrical service interruptions.
- Animal Modular Buildings: This project includes 8 modular units suitable for housing Nonhuman Primates in a variety of configurations. Each unit provides over 1000 square feet (sf) and includes Chemical, Bacteriological, and Radiological filtration to the supply air. A back up generator provides power during service interruptions.
- North Corral Expansion: This includes the installation of four (4) each ½ acre corrals. Each corral includes upgrades to enhance round access and cage functionality. In addition to the corrals, four pads will be developed for future build out.
- CNPRC utility upgrades: This project provides required infrastructure for core utilities such as domestic water for fire protection, voice and data upgrades, and natural gas for supplemental heating within the outdoor colonies.
- Childhood Health Disease Facility: The 3600 sf project will include over 500 sf wet lab space and 1700 sf animal housing & testing space. The new space will replace and consolidate current space used by the Brain, Mind, and Behavior unit. The new building will be

Personal to the unit's office support and animal housing.

- Virology & Immunology Laboratory: This building will provide 5500 sf of wet lab and support space for the Virology & Immunology unit. The project will bring dispersed researchers to a centralized location. The laboratory space will meet standards for BSL-2 and -3 containment.
- Animal Wing BSL-3 Renovations: The project will provide final improvements to operate four (4) animal rooms at BSL-3 containment. The conversion of room Personal into a necropsy suite will eliminate the need for animal transport from the BSL-3 suite when necropsies are required. This will benefit infection control practices by removing the need for animal transport into the main colony area. The remaining rooms Personal Info will provide Animal Biosafety Level 3 (ABSL-3) housing suitable for work with animals infected with indigenous or exotic agents that present the potential of aerosol transmission and of causing serious or potentially lethal disease. ABSL-3 builds upon the standard practices, procedures, containment equipment, and facility requirements of ABSL-2.
- Upgraded HVAC system: Replacement and upgraded the heating & cooling system to Personal animal buildings. The increased capacity ensures proper animal room temperatures are maintained during extreme weather conditions.
- Various security improvements

Major projects completed or in progress during this reporting period include:
Freezer building. (completed)
$522,000 - NIH G20 grant funded

Animal Modular Buildings (in progress)
$2,104,110 - NIH SPF grants, $568,890 - NIH G20 grant funded

North Corral Expansion. (in progress)
$1,809,000 - UCD Campus funded

CNPRC utility upgrades. (in progress)
$4,083,000 - UCD campus funded

Childhood Health Disease Facility. (in progress)
$1,948,732 - NIH C06 grant funded, $487,182 - CNPRC match funds

Virology & Immunology Laboratory. (in progress)
$3,800,000 - NIH C06 grant funded, $1,024,040 - UCD funded, $538,025 - CNPRC match funds

Animal Wing BSL 3 Renovations (in progress)
$375,000 - Private Source, $200,000 - UCD funding

Upgraded HVAC system. (completed)
$24,000 - UCD campus funded

Card Access. (completed)
$365,000 - NIH Base grant funded

Additional Security Cameras. (completed)
$80,000 - NIH Base grant funded

Intrusion monitors. (completed)
$50,835 - NIH Base grant funded

Parking lot enclosure/Auto gate relocation. (completed)
$162,748 - NIH Base grant funded

Perimeter Fence cameras. (in progress)
$654,000 - NIH G20 grant funded

Security Kiosk. (in progress)
$189,000 - NIH Base grant funded

***Colony Management - The heavy demand for animals and the need for additional space continues to be a central focus for CNPRC colony management. Efforts towards expansion of SPF colony production continue, supported by both the base grant and support from NCCR for production of pedigreed Indian-origin rhesus macaques, as well as Chinese-origin rhesus. The expansion of SPF production is currently limited by a shortage of space for nurseries, SPF indoor housing, and separate hospital housing for both indoor and outdoor animals.

The Centers long term production colony consists of 17 half acre corrals. Of these 17, 4 corrals are in full SPF production with a total of 500 primates. In the next year the Center will finish construction of 4 additional corrals and the SPF production colony will continue to expand.

This past year we continued with the ongoing service in the nursery to provide 24-hour care for infants in seven research and one SPF colony nurseries. During 2006, approximately 300 infants were nursery reared for ongoing studies in asthma, autism, gene and stem cell therapy, pediatric AIDS, drug therapy and vaccine development.

The routine schedules used in Colony Management activities such as weighing, TB testing, vaccinations, and cage changing are now

posted on the Center's internal website to allow investigators to be kept up-to-date on routine Animal Care functions.

***Animal Care Unit - The Animal Care Staff provided husbandry, preventive health care and research support for approximately 4,700 animals. This included approximately 2,360 animals housed outdoors (Corn Cribs and 1/2 acre Corrals) and 2,340 animals indoors (non-infectious, infectious, nursery, and quarantine). Specialized areas of care and husbandry are continually emerging as new agents are used in infectious disease research, SPF derivation expands, clean rooms for immunosuppressed animals are required, and primate nurseries become more complex.

The "Training and Education Coordinator" has been in place for the second year, and has added extensively to the Animal Care Program. With 90+ staff members in Animal Care continued training and evaluation is essential. The Training Coordinator interacts with the Animal Resource Supervisors, and the staff members in a daily basis organizing group training and also providing one-on-one interaction. The new hire orientation program provides an excellent venue for employees' initial orientation and safety training. The Coordinator also conducts weekly classes for staff to prepare for the AAALAS assistant animal technician, and animal technician certification testing. The Center supports this program by covering the cost of the testing for all staff that qualify. As of March 2007, 31 staff members have passed the AAALAS exam and are now ALAT certified. Courses for the LAT exam are current in progress at the Center and we anticipate at least many staff members will take this test sometime this year. In addition, classes in Laboratory animal Laws and Regulations are provided to all Primate Center staff.

***Progress in Core Service Units

- Primate Services - Primate Services is the centralized research support unit that maintains the animal colony and its database as well as provides service and support to all investigators ranging from initial development of research protocols, to technical support and final collection of data. Our emphasis continues to be on increasing support for the specialized needs of Primate Center investigators. The Primate Services Unit is administered by the Associate Director of Primate Services and by supervisors from each of the support areas in Primate Services. The overall mission of Primate Services is to facilitate biomedical and behavioral research utilizing the nonhuman primate model.

- Primate Medicine - The demands on the Primate Medicine Service continued to increase in 2006 resulting from continued expansion of the colony population, expansion of SPF breeding colony development, and an increasing role of the veterinary staff in research support activities with an increasing interaction between investigators and members of the veterinary staff. The interest in increased interaction with investigators is driven by a greater need for project consultation and an interest in getting more detailed information regarding spontaneous health problems in the colony. Biweekly meetings with investigators continue to facilitate project management and anticipate problems before they occur. The recruitment of additional clinical staff (both veterinary and technical) has allowed the Primate Medicine service to meet the basic needs of veterinary care for the colony as well as to provide high quality research support to investigators. The continued expansion of SPF rhesus macaque production and animal housing for infectious disease studies continues to pose challenges for separate hospital space and support facilities.

Veterinary staff and residents conducted clinical studies in several areas, including an evaluation of the efficacy of tylosin in the treatment of chronic diarrhea. Specialized surgical and technical procedures continued to occupy significant professional time of the veterinary staff. These procedures included gastrointestinal biopsy, chronic electrophysiology implants, and intra-operative and post-operative support for animals on organ transplant studies. Over the last year, there has been a continued trend of increased demand for veterinary support for imaging procedures including MRI, CAT scan, bronchoscopy, endoscopy and laparoscopy.

Primate Medicine Service also continued its focus on teaching, both in the classroom and the clinic. Veterinary staff participated in laboratory animal medicine, pathology, and ultrasound rounds, and weekly seminars in laboratory animal science. Veterinary staff team-teach a didactic course in Primate Medicine, as part of the curriculum in the School of Veterinary Medicine. In addition there is an expanded coordination of the residency program between the Primate Center and the Center for Laboratory Animal Science on the UC Davis campus. The CNPRC also hosted visiting veterinarians and veterinary students from around the United States and Canada.

- Research Services - Research Services continues to experience growth in the number of ongoing projects that this Unit provides daily research support for. Over the past year, studies in transplantation, diabetes, neuroscience, asthma, nutrition and infectious disease have been very progressive and have presented unique support needs. Staff Research Associates are now on duty 7 days per week, and supply technical support for overnight projects as needed. The staff continues to provide investigators with project support in the areas of; animal selection and screening based on investigator criteria, daily project technical support, sample collection and processing and animal monitoring. SRA's routinely transport animals to offsite MRI and CT scanning sites including UCD campus, UCD Medical Center, as well as to the Bay Area.
With the increasing size of the Center's SPF colony, increasing efforts are spent in managing viral testing, harvesting, and overall management of these animals. Currently the Center has 4 production cages, and is well on its way to stocking a fifth cage by mid year 2007. Genetic screening of the colony continues to progress. Paternity data is available for all animals assigned to the Center's outdoor breeding cages, and infants are sampled routinely months after they are born. With project demands for animals very high, harvest activity continues to increase.

- Quality Assurance - The Quality Assurance Unit (QAU) continues to support the regulatory activities for projects at the Center that are conducted under GCP guidelines. The QAU provides on-going training to all staff members to standardize data recording and documentation of husbandry and research events. A focus of the QAU this year was the continued refinement of the controlled substance documentation program. New tracking procedures and documentation records were implemented. Extensive staff training was also completed.

QAU continues to monitor colony quality functions such as: water quality reports, feed analysis, and environmental monitoring. Quality assurance services also routinely provided of investigators on the UCD campus, on a fee for service basis. The unit has begun to post critical SOPs on the Primate Centers internal web site to make them more available for reference use.

- Pathology Services - The Pathology Service provides diagnostic service for the breeding colony and research groups both within and outside the CNPRC through necropsies and biopsies according to standard operating procedures that are reviewed and revised annually. Histologic processing for light microscopy is performed under contract with the UCD medical school on the UC Davis campus and for electron microscopy with the CNPRC Computational Imaging Core.

The Pathology Unit also performs special (terminal) procedures on a recharge basis for investigators at the CNPRC, as well as for investigators outside the facility either under contract or as part of the Biospecimen Request Program administered by the Pathology Unit. These procedures include perfusions of specified organs (brain, liver, lung, uterus, etc.) with specific fixatives, sterile collection of specific tissues (blood, CSF, and various organs) at euthanasia/necropsy, collection of tissues for specialized analyses such as immunohistochemistry or electron microscopy, GLP necropsies, and antemortem collection of tissues (blood, bone marrow, CSF, lymphoid tissues, and brain) for in vitro studies. Collaborative efforts are ongoing with neuroscientists to study the anatomic correlates of learning, memory, and aging in the central nervous system and with virologists/immunologists in an attempt to understand the pathophysiology of AIDS.

In addition, collaborative studies are in progress with investigators at the University of Nebraska to study colonic spirochetosis and with investigators at UCDMC, UC Davis Veterinary School, to study Helicobacter pylori induced gastritis, and age-related changes in gastric pH as a risk factor for H. pylori infection.

The Pathology Unit also handles the collection, organization, storage, and retrieval of wet tissues, tissue blocks, glass slides, kodachrome slides, and electronic images of pathologic lesions, and maintains these as a resource for researchers both here and around the world. The Pathology Unit provides consultation and collaboration to CNPRC and outside investigators in the development of experimental design, as well as in monitoring and evaluating animals on experimental protocols, and supervises the training of pathology residents, primate medicine residents, veterinary students, staff research associates, and laboratory assistants in the theory and practice of pathology as it applies to nonhuman primates in colony management and research applications.

- Data Services - The Data Services unit continued to provide information and computing services for the center. A number of enhancements were made to existing data systems. We completed numerous ad hoc queries for investigators and research staff.

Several new programming projects were completed or are in progress:
* Additional enhancements were made to WebVitals, including editable user preferences, inclusion of morning health signs by animal and updates to a number of existing pages. The move of the web portal to Oracle Application Server was completed, providing single sign on capability to WebVitals, the freezer databases and the Respiratory database.
* Significant progress was made in learning the Oracle Reports development environment. Work has continued on updating and re-writing our old legacy reports, as well as creating new reports where needed.
* The monthly billing system is being overhauled and expanded. The Central Supply and miscellaneous billing components have been completely rewritten, and all reports for the rest of the system have been rewritten using Oracle Reports. Printing of invoices, recharge notices and the billing detail is no longer done offline, and we are preparing to offer emailed statements to the clients and investigators.
* We are developing a web interface to allow payment of registration fees for CNPRC sponsored seminars and symposia. This will be expanded once the pilot version is complete and has been fully tested.
* Data Services has provided technical support for the installation and configuration of a new security camera system, and a card
access system for physical access to the center. We continue to provide technical, ongoing maintenance and support for these systems on the server side, and client software support and training to the specific users overseeing these systems.

We are preparing to move the production database to a faster, larger OpenVMS system. A database upgrade will be performed shortly afterward. We are also in the initial planning stages of the next database move, which will move us from the OpenVMS operating system to Linux.

We have maintained our desktop support for both the Macintosh and Intel based PC platforms. The current mix of systems supported is approximately 80 Macintoshs, 300 PCs, and 35 printers. Data Services desktop support staff handled approximately 1200 question, repair or upgrade calls. The domain, and file services were updated. We have continued our desktop server maintenance and upgrades. Maintenance additions and updates were performed on the public and internal web sites. The center network infrastructure continues to be maintained and upgraded as needed.

- Clinical Laboratories - The Clinical Laboratories primary function continues to be the diagnostic support for monitoring and defining the health status of the colony. In addition, it continues to provide clinical laboratory technical support to outside investigators on a recharge basis. The key services provided include hematology, parasitology, microbiology, urinalysis, chemistry, cytology, serology, reference serum and buffy coat bank, and flow cytometry. Closed to 27,000 samples were processed in all the above mentioned areas. The laboratory has continued to collaborate with in-house as well as outside investigators in the assessment for contamination of cultured cells as well as in vivo transplant cells. In addition, the laboratory has routinely used flow cytometry for evaluating its clinical and research samples. The laboratory participated in the nonhuman primate Reagent survey and will continue to participate in the future. In 2006, we began addressing the sorting of live cells in the flow facility. A biocontainment hood has been purchased to house the FACSAria for live cell sorting. The flow cytometry service offered by the clinical labs will continue to provide investigators with all the tools and instrumentation needed to obtain state of the art information of phenotyping cells as well as assessing cell activation and function.

The Clinical Laboratory has supported continuing education for all laboratory personnel. Laboratory personnel have been able to obtain continuing education to meet licensing criteria without travel expenses and time away from work. This was achieved by participation in American Society of Clinical Pathology (ASCP) audio teleconferences, medical laboratory online classes, and books offered through Anderson Continuing Education for Laboratory personnel. This participation has provided valuable and pertinent continuing education. In-house training has also continued primarily in safety. Safety seminars are routinely given for all new infectious disease projects to educate staff on the proper handling and processing of clinical laboratory specimens. The Clinical Laboratory continues to work towards the computerization of the laboratory data. SNOMED entries for microbiology and parasitology are performed on a daily basis. We continue to work with data services to find the best system for laboratory information management. In addition to all the current clinical laboratory data from chemistry and hematology there is an extensive data base generated by flow cytometry that needs to be stored for future retrieval.

***Science Cores

- Behavior Assessment Core - The Behavior Assessment Core provides a battery of standardized behavioral assessments, primarily focused on rhesus and cynomolgus monkey infants, to other CNPRC units and service cores as well as outside investigators. The core provides equipment and protocols to investigators experienced in behavioral techniques, or conducts the evaluations using experienced technical staff. Offsite projects can be accommodated via video recording of behaviors. Consultation in selecting tests, and data summary, analysis and interpretation are also provided on a recharge basis. Materials are made available to help investigators include core services in grant and contract proposals.

During the past year, the core conducted an experiment for an investigator at the University of California San Diego using behavioral methods to provide cognitive enrichment and measuring the effect on neural stem cells. Another project for a commercial laboratory is evaluating behavior in videotapes made offsite. Data from the first project were forwarded to the investigators; the second project is ongoing.

- Computational Imaging Core - This core facility provides light microscopy, stereology, digital imaging, histology, and consultation services, primarily for the CNPRC, and also for all campus departments on a recharge basis. The goal is to assist faculty, staff, and students with their research needs for qualitative and quantitative applications. This core assists with the production of publication quality images and offers consultation on experimental approaches for use with our equipment. Instrumentation housed in the Core is available 24 hours a day, 7 days a week for trained CNPRC users. Consultation, training, and support service, along with access to the equipment for other departments, is available from 8-5 Monday through Friday.
The facility houses the following equipment:
* A Cryostat for frozen sections.
* Microtomes for paraffin or plastic sectioning.
* Sample preparation equipment for histological paraffin and plastic processing and embedding.
* Data storage server (expandable multi-terabyte volume) for archiving client and facility data.
* Web-based calendar for instrument reservations.
* An Olympus BX61 research microscope with SIS image analysis software and Intelligent Imaging Innovations Slidebook software for stereology and data collection.
* A second Olympus BX61 microscope with Intelligent Imaging Innovations Slidebook software for stereology technique development by the Core's staff.
* A graphics workstation, a flased scanner, and a high-quality color corrected printer for publication quality prints.
* A Delta Vision Microscopy System and computer workstation for very high resolution multi-dimensional fluorescence imaging with deconvolution.
* A computer workstation for offline analysis of stereology data used for method development by Core staff.
* A CAST Grid Stereology System for quantitative data collection.
* PhotoShop and Illustrator software—all computers are outfitted with spectrophotometrical color balanced monitors.
* A fluorescence stereomicroscope outfitted with a high sensitivity camera coupled to a computer system.
* A dual-head brightfield stereomicroscope.

In the future, we hope to add the following equipment:
* A hyperspectral camera system with advanced image analysis software for microscopy and macro-photography.
* A confocal microscope with spectral separation. We are considering the possible addition of multiphoton imaging and Raman spectroscopy.

- Endocrine Core - The Endocrine Core continues to serve the dual purposes of service and development. Over the past funding period the core has served over a dozen scientists, processed over 3,500 samples and recharged approximately $36,000. This service provides mainly unique analyses that are not available elsewhere. Similarly, its assay development is directed towards providing assays that currently do not exist elsewhere. During the past year the Endocrine Core has extended its service from reproductive hormones exclusively to include metabolic hormones and carrier proteins. It is our intent to provide in-house service for all assays requested through Therapeutics, Research Services and by individual investigators. New assays are being formatted on the ACS-180 automated chemiluminescence platform whenever possible in order to provide the most dependable and cost-effective service. A macaque thyroid panel as well as monkey chorionic gonadotropin (mCG), have been added to the list of hormones available for a new nation-wide service once this new technology is published.

- Immunology Core - The Immunology Service Core is designed to provide 1) standardized measures of immune response in macaques, 2) advice to outside investigators on experimental design of primate immunology studies, 3) development of new technology for assessing immune responses in this animal model, 4) information on techniques and reagents that are useful for primate immunology, and 5) training of personnel in the use of immunology assays for work with macaques. Because of the large volume of AIDS-related research done by both staff and non-staff scientists at the CNPRC, the emphasis of this core was on antiviral immunity.

In addition, assays to nominal test antigens were available for other infectious and non-infectious research at the CNPRC. The Core, which began operation in August 2000, has four services or work areas corresponding to humoral immunity (requires BSL-2 only for initial sample processing), cellular immunity (requires BSL-2 containment throughout the time of assay), an allergy unit, and a molecular core unit. Humoral immune assays include the detection of antibodies to viral antigens by ELISA. In addition, antibody levels to the nominal antigens, tetanus toxoid, cholera toxin and keyhole limpet hemocyanin are measured by ELISA. Cellular assays include the detection of antiviral cytotoxic T lymphocytes (CTL) or natural killer cells (NK) and lymphocyte proliferation to viral and nominal antigens. A mixed lymphocyte reaction is available for genetics and transplantation. Cytokine/chemokine-secreting cells are assayed by ELISPOT.

The molecular core unit analyzes and quantitates cytokine/chemokine mRNA transcript levels by real-time PCR. Additional target gene amplification is available for certain apoptosis genes and some transcription factors. SIV DNA and RNA detection/quantitation and the provision of aliquots of SIVmac challenge stocks, titered for mucosal inoculation, have been added to the Core and will comprise a new component of the Molecular Immunology Division in the Core during the next base grant cycle.

The allergy unit is responsible for providing allergy and pulmonary related services, including characterization and preparation of allergens for aerosol delivery and systemic sensitization procedures. In addition, immunoassays to detect histamine and tryptase levels, as well as immunoassays to detect allergen-specific IgE/IgG have been developed. Support for preparation, analysis and
archiving of collected blood and bronchoalveolar lavage samples is also available.

In the past year the Core has begun distributing the 2 infectious stocks of cell-free SIV. We have approx. 1 liter of SIVmac251 and 500ml of SIVmac239. The stocks are divided into 0.5 and 1 ml aliquots and frozen in LN2. The stocks have titers of 105 TCID50 and contain approx. 109 vRNA copies/ml. For both stocks, IV inoculation of 10 TCID50 infects 2 of 2 animals and the animals have sustained high plasma vRNA and declining CD4+ T cells. We also found that 1 TCID50 of both stocks infects 1 of 2 monkeys inoculated IV, although the plasma vRNA levels were lower in these infected animals. Approximately 10mmls of virus have been distributed thus far.

In addition the Core has developed and validated new lymphocyte phenotyping panels and a multicolor cytokine flow assay and as soon as rates are approved by UCD committees these will be offered. We currently have several outside investigators with frozen cells that are seeking this service. We have also submitted a recharge rate for immunohistochemistry assays as proposed in the last base grant renewal. If approved, this service can be added to the Immunology Core in the near future. Finally, a number of additional gene targets have been added to the gene expression service of the Core and we are assisting outside UCD investigators develop laser capture microscopy and RNA extraction and recovering our costs based on time and materials.

The services offered by the Immunology Core are summarized as follows:
* Sample Processing
  * Total IgG, IgA ELISA assays
  * Ag Specific IgG, IgA ELISA assays
  * Total IgG, IgA ELISPOT assays
  * Ag Specific IgG, IgA ELISPOT assays
  * Cytotoxic T Lymphocyte assay
  * T-cell Proliferation assay
  * Ag Specific IFN-g ELISPOT
  * B Cell Transformation
  * Mixed Lymphocyte Reaction
  * SIV RNA or DNA PCR
  * Nucleic acid extraction
  * Natural Killer Cell assay
  * Nucleic acid extraction
  * SIV RNA or DNA PCR
  * Real-time PCR to quantify cytokine/chemokine mRNA
  * SIVmac challenge stocks
  * House dust mite allergen preparation and characterization
  * Tryptase ELISA assays
  * Der p 1/Der f1 and Der p 2 specific IgE amplified ELISA
  * Der p/Der f specific IgG ELISA

- Inhalation Exposure Core - The Inhalation Exposure Facility located at the CNPRC is one of the largest in existence on a university campus. It permits unique human health-related pulmonary research opportunities using nonhuman primates. Capabilities exist for in vivo or in vitro exposure to precisely characterized and controlled atmospheres of gases and aerosols. For health effects of air pollution research, the range of test subjects used for exposure studies can include animals, isolated and perfused lungs, tracheal explants and human or monkey lung cell cultures. This permits an integrated, comparative approach to defining mechanisms of respiratory system injury and repair. A relatively recent addition to the capabilities is a pulmonary function laboratory that offers a comprehensive array of testing for infant through adult nonhuman primates.

Services Offered:
* Special Exposures
  * Ozone Generation and Monitoring
  * Aerosol Generation and Analysis
  * NOx Generation and Monitoring
  * Allergen Generation and Analysis
  * Filtered Air Exposure
  * ETS Generation and Analysis

Pulmonary Function Testing Laboratory

Baseline Airway Resistance Testing
Airway Responsiveness Testing
Allergen Responsiveness Testing
Static Lung Mechanics Testing
Late Phase Allergen Responsiveness Testing

This facility continued to provide stable, well characterized exposures to air pollutants, allergens, therapeutic agents, aerosols and other test atmospheres as required by the research projects supported. As a Core service provider, the facility supported 14 research projects during the reporting period with some 33 major investigators.

In addition to UC Davis investigators, core services were provided to scientists at University of Alabama at Birmingham, Michigan State University, Pennsylvania State University, Louisiana State University, Proprietary Info J.S. EPA, Proprietary Info

Major emphasis in research activities was directed to further inhalation exposure studies of asthma and air pollution in nonhuman primates. Aerosol therapy studies with inhaled immunostimulatory sequence DNA aerosols continued with improved inhaled dose estimates for adult nonhuman primates. Other nonhuman primate projects included metabolic measurements using indirect calorimetry and exposure to aged and diluted cigarette smoke.

- Pathogen Detection Core - Since 1986, the Pathogen Detection Core (PDC) has provided over 10,000 virological and serological analyses of nonhuman primate specimens annually. We provide services to more than 50 clinicians, researchers, and colony managers.

Research efforts to develop, validate, and improve diagnostic assays are continuously on-going. PDC routinely offers antibody, antigen, virus, and nucleic acid detection for a number of infectious agents. PDC is in the process of moving all virus-specific antibody testing over to the multiplex microbead immunoassay (MMIA) platform using Luminex technology.

Services include:
* Specialty lab testing and expert consultation services to public and private sector local, regional, national, and international research colonies, zoological collections, and veterinary laboratories and practices of all sizes
* Methods and reagents validated, standardized, and controlled by in-laboratory studies and proficiency testing
* Maintenance of reference banks of characterized specimens
* All serological test results reviewed by personnel who are fully accredited by American Society for Clinical Pathology and Laboratory Field Services of the State of California
* Resource for development and maintenance of Specific Pathogen-free (SPF) colonies
* Resource for field or epidemiological studies
* Resource for laboratory baseline and monitoring of animals on research studies
* Resource for unusual or atypical diagnostic cases
* Staff committed to quality and client-oriented service
* Purpose is to provide for the diagnostic laboratory needs of nonhuman primate clinicians and researchers

**Changes in Operation and Committees

A new committee, the Space Advisory Committee was established. Members include representatives from each of the four research units, as well as Animal Care/Research Services, and Primate Medicine. The committee is advisory to the Director on issues related to space allocation.