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CALIFORNIA NATIONAL PRIMATE RESEARCH CENTER

ANNUAL PROGRESS REPORT

5P51RR000169-44
5/1/2005-4/30/2006

withheld

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

5P51RR000169-44

CALIFORNIA NATIONAL PRIMATE RESEARCH CENTER

Final

UNIVERSITY OF CALIFORNIA - DAVIS

ANNUAL PROGRESS REPORT

Reporting From: 05/01/2005
Reporting To: 04/30/2006

43.365% AIDS Related

withheld

CALIFORNIA NATIONAL PRIMATE RESEARCH CENTER

Patent or Copyright was not awarded this grant year.

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RESEARCH SUBPROJECTS

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withheld

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withheld

withheld

withheld

withheld

RESPIRATORY DISEASES

withheld

withheld

withheld

withheld

VIROLOGY & IMMUNOLOGY

withheld

PERSONNEL ROSTER

Core Doctoral Scientists

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

Affiliated

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

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
withheld		UNIVERSITY OF MARYLAND: MD, USA
		Proprietary Info AND UC DAVIS: CA, USA
		UC SAN FRANCISCO: CA, USA
		UC SAN FRANCISCO: CA, USA
		Proprietary Info
		NCI: MD, USA
		UNIVERSITY OF COLORADO: CO, USA
		Proprietary Info
		UNIVERSITY OF ARIZONA: AZ, USA
		UC LOS ANGELES: CA, USA
		Proprietary Info
		UC SAN FRANCISCO: CA, USA
		UC SAN FRANCISCO: CA, USA
		Proprietary Info
		UC SAN FRANCISCO: CA, USA
		Proprietary Info
		Proprietary Info
		Proprietary Info
		TEMPLE UNIVERSITY, SCHOOL OF MEDICINE: PA, USA

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
withheld		UNIVERSITY OF MICHIGAN: MI, USA
		Proprietary Info
		UNIVERSITY OF MONTANA: MT, USA
		Proprietary Info
		UNIVERSITY OF ALABAMA: AL, USA
		Proprietary Info
		CDC MEASLES BRANCH: GA, USA
		UC IRVINE: CA, USA
		Proprietary Info
		UC SAN DIEGO: CA, USA
		Proprietary Info
		Proprietary Info

SUBPROJECT DESCRIPTIONS

NPRC MANAGEMENT SUBPROJECTS

AIDS RESEARCH FACILITY IMPROVEMENT GRANT (0258)

NPRC UNIT: MODERNIZE & IMPROVE - AID

%NPRC $: 0.000% **AIDS RELATED RESEARCH**

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

SUBPROJECT DESCRIPTION

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

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

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

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

SUBPROJECT PROGRESS

The project will provide space for 52 each, -80° Revco freezers. This project is currently in design review with NCRR. Projected completion date is June 1st, 2006.

PURCHASE AND INSTALLATION OF BIO-ISOLATION UNITS (0259)

NPRC UNIT: MODERNIZE & IMPROVE - AID

%NPRC $: 0.000% **AIDS RELATED RESEARCH**

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

SUBPROJECT DESCRIPTION

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

While the CNPRC has taken steps to increase available indoor space, the current limitations associated with separation of animals inoculated with different biological agents creates underutilization of current cage capacity in the infectious indoor housing areas. This proposal requests funds to purchase 25 bio-isolation cages. These cages would be placed in existing Personal Info and would immediately allow us to increase our indoor occupancy by 100 animals.

SUBPROJECT PROGRESS

This project was completed.

EXTRAMURAL RESEARCH FACILITIES CONSTRUCTION II (0344)

NPRC UNIT: MODERNIZE & IMPROVE - AID

%NPRC $: 0.000% **AIDS RELATED RESEARCH**

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

SUBPROJECT DESCRIPTION

Objective: To construct a new building, the Virology and Immunology Laboratory (VIL) 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

This project is currently undergoing budget and scope review. Due to delays pending resolution of available infrastructure, this project was impacted by construction cost escalations. Project scope will be reduced to match available funds. Design development is expected to be complete August, 2008.

G20 MODULAR ANIMAL HOUSING UNITS FOR PRIMATE NURSERY (0260)

NPRC UNIT: MODERNIZE & IMPROVEMENT

%NPRC $: 0.000% **AIDS RELATED RESEARCH**

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

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 infants cohorts that are either allergen naïve or have been exposed to both dust mite allergen and ozone. These units will be sited immediately Personal o 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

This project is at 95% construction documents and is currently in design review with NCRR.

EXTRAMURAL RESEARCH FACILITIES CONSTRUCTION (0290)

NPRC UNIT: MODERNIZE & IMPROVEMENT

%NPRC $: 0.000%

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

SUBPROJECT DESCRIPTION

Objective: To replace the building, designated Personal Info that currently houses the Brain, Mind and Behavior (BMB) Unit on the CNPRC campus with a new foundation and a metal frame building with overall dimensions of 7,433 sq. ft.

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

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

SUBPROJECT PROGRESS

This project has been impacted by unanticipated construction escalation costs and is currently in design development. The goal is to reduce scope to match available funds while still achieving program goals. Design development will be complete by June, 2006.

PRODUCTION OF PEDIGREED SPF RHESUS MACAQUES (0168)

NPRC UNIT: PRIMATE SERVICES

%NPRC $: 1.180% **AIDS RELATED RESEARCH**

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

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-relaed research. We have successfully established and maintained a long-term breeding colony of SPF, genetically characterized Indian origin rhesus macaques. To date, 99 animals produced in this colony 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. Animals are also typed for two MHC loci, MaMu A*01 and MaMu B*01. Macaques with the MaMuA*01 allele are thought to be important for research in vaccinology and the biology of cytotoxic lymphocytes. We have successfully demonstrated the feasibility of selective breeding to provide animals with specific MHC genotypes, including MaMu A*01.

SUBPROJECT PROGRESS

Currently, this SPF breeding colony numbers 165 animals. Future plans include the expansion of the Indian-origin SPF colony through natural breeding of the established population, and by nursery-derivation of SPF infants born to non-SPF Indian-origin breeders.

GENETICALLY DEFINED HERPES/RETROVIRUS SPF MACAQUES (0275)

NPRC UNIT: PRIMATE SERVICES

%NPRC $: 1.180% **AIDS RELATED RESEARCH**

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

SUBPROJECT DESCRIPTION

Objective: Since the start date of 9/30/02, 64 adult non-SPF rhesus macaques (8 males, 56 females) have been assigned to this project. All 64 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

Although not projected until 2004, 3 offspring were produced from these breeding groups in 2003. Sixteen offspring have been produced to date. All offspring from non-SPF breeders are taken at birth, nursery reared and eventually socialized for pair housing. Infants are tested for 7 persistent viral infections 4 times during the first year, and twice in the second year. All nursery derived infants have remained negative for SRV, STLV, SIV, SFV, B virus, CMV and RRV after one year of follow-up. With few exceptions, complete MHC haplotypes have been obtained for all non-SPF breeders and their nursery-derived SPF offspring.

RESEARCH SUBPROJECTS

HEIRARCHICAL PROCESSING IN THE MOTION SYSTEM (0272)

NPRC UNIT: AFFILIATE RES PROGRAM

%NPRC $: 0.295%

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

SUBPROJECT DESCRIPTION

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

SUBPROJECT PROGRESS

We have now quantitatively compared the tuning for "heading" stimuli, and the compensation for eye movements, in these two areas.

THE ROLE OF THE PULVINAR IN VISUAL ATTENTION (0375)

NPRC UNIT: AFFILIATE RES PROGRAM

%NPRC $: 0.590%

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

SUBPROJECT DESCRIPTION

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

METABOLIC ACTIVATION OF AIR TOXICS IN ASTHMATIC MONKEYS (0302)

NPRC UNIT: AFFILIATE RES PROGRAM

%NPRC $: 0.295%

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

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 PROGRESS

Naphthalene and 1-nitronaphthalene are ambient air pollutants which undergo P450-dependent bioactivation in the lung. Reactive metabolites of naphthalene and 1-nitronaphthalene covalently bind to proteins, and the formation of covalent adducts correlates with airway epithelial cell injury in rodent models. These studies were designed to identify protein adducts generated from these reactive metabolites within distal respiratory airways. Distal bronchioles and parenchyma from rhesus monkeys were incubated with ^14 C-naphthalene or ^14 C-1-nitronaphthalene. Proteins were separated by two-dimensional gel electrophoresis, blotted to polyvinylidene difluoride membranes, and adducted proteins imaged by storage phosphor analysis. Mass spectrometry of in-gel tryptic digests identified numerous adducted proteins including: 8 cytoskeletal proteins, 2 chaperone proteins, 7 metabolic enzymes, 1 redox protein, 2 proteins involved in ion balance and cell signaling, and 2 extracellular proteins. While many proteins are adducted by both naphthalene and 1-nitronaphthalene, some are unique to the individual toxicant and airway subcompartment. Although the role which adduction of these proteins plays in cytotoxicity was not evaluated, these studies provide candidate proteins for future work designed to determine the importance of protein adducts in the mechanisms of toxicity and for developing biomarkers useful in determining the relevance of findings in animal models to exposed human populations.

POSITRON EMISSION TOMOGRAPHY IN CYNOMOLGOUS MONKEYS (0374)

NPRC UNIT: AFFILIATE RES PROGRAM

%NPRC $: 0.885%

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

SUBPROJECT DESCRIPTION

Objective: This project is designed to utilize positron emission tomography (PET) imaging in conjunction with Cu-64 DOTA-conjugated monoclonal antibodies to screen potential new anti-cancer therapeutic agents. We are examining the biodistribution of selected antibodies and antibody fragments that are directed against human antigens and cross-react with cynomolgus monkeys. It is anticipated that these studies will lead to more clinically relevant characterization of potential new anti-cancer therapies, and that PET imaging will significantly reduce the number of animals necessary for pharmacokinetic studies.

SUBPROJECT PROGRESS

We have studied several animals with excellent success. Both expected (blood pool plus target tissue) and unexpected biodistributions have been observed. Some of the off-target distributions have explained toxicities observed at therapeutic doses (e.g., bone marrow), while others have given the first indication that certain organs accumulate the antibody. Subsequently, some unfavorable distributions have been manipulated by image-guided pre-dosing strategies.

PATHOGENESIS OF INTESTINAL DYSFUNCTION IN SIMIAN AIDS (0271)

NPRC UNIT: AFFILIATE RES PROGRAM

%NPRC $: 1.180% **AIDS RELATED RESEARCH**

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

SUBPROJECT DESCRIPTION

Objective: Simian immunodeficiency virus (SIV) and human immunodeficiency virus (HIV) infections lead to rapid depletion of CD4 T cells from gut-associated lymphoid tissue (GALT). Although the administration of antiretroviral therapy (ART) has been shown to increase CD4 T-cell levels in the peripheral blood in both SIV and HIV infections, its efficacy in restoring intestinal mucosal CD4 T cells has not been well investigated. To gain insights into the molecular mechanisms of virally induced disruptions in the mucosal immune system, we have evaluated longitudinal changes in viral burden, T-cell subsets, and mucosal gene expression profiles in SIV-infected rhesus macaques in the absence or presence of ART.

SUBPROJECT PROGRESS

Our results demonstrate a dramatic suppression of mucosal viral loads and rapid reconstitution of CD4 T cells in GALT in animals receiving ART that were not observed in untreated SIV-infected animals. DNA microarray-based gene expression profiling indicated that CD4 T-cell restoration in GALT was associated with up regulation of growth factors and genes involved in repair and regeneration of the mucosal epithelium. In contrast, untreated SIV-infected animals increased expression of lymphocyte activation and inflammatory response-associated genes and did not up regulate mucosal growth and repair associated transcription. In conclusion, these data indicate that initiating ART in primary SIV infection may lead to the restoration of the mucosal immune system through reduction of inflammation and promotion of epithelial repair in the intestinal mucosa.

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

NPRC UNIT: AFFILIATE RES PROGRAM

%NPRC $: 0.885% **AIDS RELATED RESEARCH**

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

SUBPROJECT DESCRIPTION

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

SUBPROJECT PROGRESS

Colony-bred rhesus macaques (Macaca mulatta) from the California National Primate Research Center were used to study the role of cytotoxic CD8+ T cells in animals with SIV infection while receiving antiretroviral therapy. After establishing SIV infection for 10 weeks, some animals were CD8 T cell depleted for 1 week. After 13 weeks of infection all animals received antiretroviral therapy for 2 weeks. Plasma viral load measurements were used to calculate plasma virus clearance rates (reflecting loss of productively infected cells). Data indicated that the elimination of productively infected cells after the establishment of SIV infection is largely due to antiretroviral therapy and independent of CD8+ T cell killing.

LINKING FUNCTIONAL IMAGING, NUEROPHYSIOLOGY & ANATOMY (0377)

NPRC UNIT: AFFILIATE RES PROGRAM

%NPRC $: 0.590%

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

SUBPROJECT DESCRIPTION

Objective: Brain imaging methods such as functional magnetic resonance imaging (fMRI), magnetic source imaging (MSI) and diffusion tensor imaging (DTI) are rapidly evolving as essential tools for assaying normal and abnormal brain function. The overall goal of this research is to enhance our understanding of the relationship between the signals measured using these imaging techniques and the underlying neural activity. We propose to conduct a series of experiments in anesthetized macaque monkeys to examine the correlation between functional brain imaging signals, specifically the BOLD signals of fMRI, the modeled current sources of MSI, and the imaging of white-matter tracts with DTI, with "gold standard" single and multi-unit electrophysiological recordings, and neuroanatomical tracing techniques. The specific aims are 1) To measure the stimulus evoked changes in magnitude, location and timing of functional brain imaging signals and relate them to changes in underlying neural activity, 2) To correlate non-invasive anatomic connectivity measures derived from tractography of DTI with connectivity derived using neuroanatomical techniques, and 3) To compare measures of functional connectivity based on the covariance of fMRI and MSI time-series with anatomic connectivity derived from DTI and neuroanatomic studies. These experiments represent a unique collaborative effort to combine several techniques in the same animal to generate a better understanding of the ability of modem 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.