102 pgs

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

5P51RR013986-06
SOUTHWEST NATIONAL PRIMATE RESEARCH CENTER

Final

SOUTHWEST NATIONAL PRIMATE RESEARCH CENTER

ANNUAL PROGRESS REPORT

Reporting From: 05/01/2003
Reporting To: 04/29/2004

27.420% AIDS Related

John L VandeBerg 5/13/04
Signature Date

JOHN D VANDEBERG, PHD
DIRECTOR
Phone: 210-258-9430
Fax: 210-670-3309
e-mail: jlv@sfbr.org

Patent or Copyright was not awarded this grant year.

THIS PAGE LEFT INTENTIONALLY BLANK

TABLE OF CONTENTS

Printed on: 5/13/2004 11:03:44AM

COLLABORATIVE SUBPROJECTS

PERSONNEL ROSTER

Core Doctoral Scientists

Name, Degree	Department	Non-Host Institution: State, Country
ALLAN, JONATHAN S, DVM		
CAREY, K DEE, DVM, PHD	COMPARATIVE MEDICINE	SFBR: TX, USA
CUMMINS, L. BILL, DVM		
GIAVEDONI, LUIS D, PHD	VIROLOGY AND IMMUNOLOGY	SFBR: TX, USA
HUBBARD, GENE B, DVM, MS		
LANFORD, ROBERT E, PHD	VIROLOGY AND IMMUNOLOGY	SFBR: TX, USA
MAHANEY, MICHAEL C, PHD	GENETICS GROUP	
RICE, KAREN S, PHD		
ROGERS, JEFFREY, PHD	GENETICS	SFBR: TX, USA
SHARP, R MARK, PHD		
TARDIF, SUZETTE D., PHD	DIRECTOR'S OFFICE	SNPRC: TX, USA
VANDEBERG, JOHN D, PHD	DIRECTOR'S OFFICE	SNPRC: TX, USA

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
ALBRECHT, EUGENE D., PHD		NEW YORK UNIVERSITY: NY, USA UNIVERSITY OF MARYLAND: MD, USA
ATOR, NANCY A., PHD		NHLBI: MD, USA JOHNS HOPKINS UNIVERSITY: MD, USA
BIGGER, CATHERINE B, PHD, MD		UNIVERSITY OF PITTSBURGH: PA, USA
BRASKY, KATHLEEN M, MS, VMD		U MELBORNE, AUSTRALIA
BRENNA, JAMES THOMAS, PHD		
BRENT, LINDA Y, PHD		CORNELL UNIVERSITY: NY, USA
CAMERON, JUDY L, PHD		U PENNSYLVANIA: PA, USA UNIV TX HEALTH SCIENCE CENTER, SAN ANTONIO: TX, USA UNIVERSITY OF PITTSBURGH: PA, USA
CASHMAN, JOHN R., PHD		UNIVERSITY OF TEXAS HEALTH SCIENCES CENTER, SAN ANTONIO: TX, USA HUMAN BIOMOLECULAR RESEARCH INSTITUTE: CA, USA
CHAN, LAWRENCE, PHD		BAYLOR COL MED: TX, USA LAWRENCE BERKELEY NATIONAL LABORATORY: CA, USA

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
CLYMAN, RONALD I, MD		UNIV CA, SF: CA, USA
COALSON, JACQUELINE J, PHD		UNIV TX HEALTH SCIENCE CENTER SAN ANTONIO: TX, USA
[Names]		OREGON REGIONAL PRIMATE RESEARCH CENTER: OR, USA
COMUZZIE, ANTHONY G, PHD		
COUNTER, CHRISTOPHER M., PHD		DUKE UNIVERSITY: NC, USA
COX, LAURA A, PHD		
CRAPO, JAMES D, MD		NATIONAL JEWISH CENTER: CO, USA
[name]		UNIVERSITY OF PITTSBURGH: PA, USA
DAVIS, RONALD W., PHD		STANFORD UNIVERSITY: CA, USA
[name]		HOWARD FLOREY INSTITUTE, AUSTRALIA
[name]		UNIVERSITY OF PITTSBURGH: PA, USA
[name]	GENETICS	SFBR: TX, USA
EBERSOLE, JEFFREY, DDS		UNIVERSITY OF KENTUCKY: KY, USA
[name]		UNIV TX HEALTH SCIENCE CENTER, SAN ANTONIO: TX, USA
EICHLER, EVAN, PHD		CASE WESTERN RESERVE UNIVERSITY: OH, USA
FIGURSKI, DAVID H., PHD		COLUMBIA UNIVERSITY: NY, USA
[name]		UNIV TX HEALTH SCIENCE CENTER SAN ANTONIO: TX, USA
[name]		UNIVERSITY OF NEBRASKA: NE, USA
[name]		HOWARD HUGHES MEDICAL INSTITUTE: NY, USA
FROST, PATRICE A III, DVM		
[Names]		UNIV WA: WA, USA
		NATIONAL INSTITUTES OF HEALTH: MD, USA
HANLEY, FRANK L., MD		STANFORD UNIVERSITY: CA, USA
HILLIARD, JULIA K., PHD		GEORGIA STATE UNIVERSITY: GA, USA
HODARA, VIDA, PHD		
HONORE, ERIKA K, PHD		
[name]		MASSACHUSETTS GENERAL HOSPITAL: MA, USA
[ ]		WAKE FOREST UNIVERSITY: NC, USA
KHAN, FIRYAL, MD		MOOREHOUSE SCHOOL OF MEDICINE: GA, USA
KIMATA, JASON T, PHD		

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
[name]		BAYLOR COLLEGE OF MEDICINE: TX, USA
KRAUSS, RONALD, MD		LAWRENCE BERKELEY NATIONAL LABORATORY: CA, USA
[name]		
[name]		U ILLINOIS: IL, USA
LELAND, M MICHELLE, DVM		
LEMON, STANLEY M, MD		UNIV TX MEDICAL BRANCH, GALVESTON: TX, USA
[name]		NIDDK, NIH: MD, USA
LOCKWOOD, CHARLES, MD		YALE UNIVERSITY: CT, USA
MANISCALCO, WILLIAM M, MD		UNIV ROCHESTER: NY, USA
MARSHAK, DAVID, PHD		UNIVERSITY OF TEXAS MEDICAL SCHOOL, HOUSTON: TX, USA
MARTIN, DAVID W, PHD		
[name]		TEXAS A&M UNIVERSITY HEALTH SCIENCES CENTER: TX, USA
MCCARREY, JOHN R, PHD		UNIVERSITY OF TEXAS, SAN ANTONIO: TX, USA
MCDONALD, THOMAS, PHD		NEW YORK UNIVERSITY: NY, USA
MENDELSON, CAROLE R, PHD		UNIV TX SW MED CENTER, DALLAS: TX, USA
[name]		HOWARD FLOREY INSTITUTE, AUSTRALIA
MURASE, NORKO, MD		UNIVERSITY OF PITTSBURGH: PA, USA
MURTHY, KRISHNA K, DVM, PHD		
NATHANIELSZ, PETER W, MD, PHD		NEW YORK UNIVERSITY: NY, USA
[Names]		NEW YORK UNIVERSITY: NY, USA
PIANTODOSI, CLAUDE A., MD		EASTER VIRGINIA MEDICAL SCHOOL: VA, USA
PIERCE, RICHARD A, PHD		NATIONAL JEWISH MEDICAL AND RESEARCH CENTER: CO, USA
PLATT, ORAH S., MD		BARNES-JEWISH HOSPITAL: MO, USA
[name]		HARVARD CHILDREN'S HOSPITAL: MA, USA
RAPER, JAYNE, PHD		
RINJBRAND, CORNELIUS, PHD		NEW YORK UNIVERSITY: NV, USA
[name]		UNIVERSITY OF TEXAS MEDICAL BRANCH-GALVESTON: TX, USA
		LAWRENCE BERKELEY NATIONAL LABORATORY: CA, USA

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
[name]		UNIVERSITY OF PITTSBURGH: PA, USA
SCANU, ANGELO M., PHD		UNIVERSITY OF CHICAGO: IL, USA
[Names]		NEW YORK UNIVERSITY: NY, USA
SHADE, ROBERT E, PHD	PHYSIOLOGY AND MEDICINE	SFBR: TX, USA
SHAUL, PHILIP W, MD		UNIV TX SW MED CENTER DALLAS: TX, USA
SMITH, JAMES R., PHD		UNIVERSITY OF TEXAS HEALTH SCIENCES CENTER, SAN ANTONIO: TX, USA
[ ]		UNIVERSITY OF FLORIDA: FL, USA
STARZL, THOMAS, MD		UNIVERSITY OF PITTSBURGH: PA, USA
STRAUSS, WILLIAM M., PHD		UNIVERSITY OF COLORADO: CO, USA
SUNDAY, MARY E, MD, PHD		BRIGHAM AND WOMEN'S HOSPITAL: MI, USA
SZABO, AKOS, MD		UNIVERSITY OF TEXAS HEALTH SCIENCES CENTER, SAN ANTONIO: TX, USA
THOMAS, DAVID L, MD		JOHNS HOPKINS UNIV, BALTIMORE: MD, USA
TROILO, DAVID, OD		NEW ENGLAND COLLEGE OF OPTOMETRY: MA, USA
[name]		SALK INST: CA, USA
WALKER, CHRISTOPHER M, PHD		OHIO STATE UNIV-CHILDREN'S RESEARCH INSTITUTE: OH, USA
WALKER, DAVID, MD		UNIVERSITY OF TEXAS MEDICAL BRANCH, GALVESTON: TX, USA
WANG, JIAN, PHD, MD		
WANG, XING LI, PHD, MD		
[name]		HOWARD FLOREY INSTITUTE, AUSTRALIA
WHITE, CARL, MD		NATIONAL JEWISH MEDICAL AND RESEARCH CENTER: CO, USA
WILLIAMS, JEFF T, PHD		
[Names]		UNIVERSITY OF PITTSBURGH: PA, USA
WONG, DEAN F., PHD		JOHNS HOPKINS UNIVERSITY: MD, USA
WOODRUFF, TERESA K., PHD		NORTHWESTERN UNIVERSITY: IL, USA
[ ]		UNIV TX HEALTH SCIENCE CENTER SAN ANTONIO: TX, USA

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
ZAHORSKY-REEVES, JOANNE L., PHD		UNIVERSITY OF SOUTHERN CALIFORNIA: CA, USA
ZHOU, PAUL, PHD		

Graduate Student/Postdoctoral Scientists

Name, Degree	Department	Non-Host Institution: State, Country
C		UNIV TEXAS HEALTH SCIENCE CENTER, SAN ANTONIO: TX, USA
Names	GENETICS GROUP	
		UNIV TEXAS HEALTH SCIENCE CENTER, SAN ANTONIO: TX, USA
		UNIV TEXAS HEALTH SCIENCE CENTER, SAN ANTONIO: TX, USA
	GENETICS GROUP	
>		UNIV OF MINNESOTA: MN, USA
		UNIV OF TEXAS HEALTH SCIENCE CENTER, SAN ANTONIO: TX, USA

THIS PAGE LEFT INTENTIONALLY BLANK

SUBPROJECT DESCRIPTIONS

NPRC MANAGEMENT SUBPROJECTS

ABSL2 CHIMPANZEE FACILITY IMPROVEMENT (0246)

NPRC UNIT: ADMINISTRATIVE

%NPRC $: 0.100% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
VANDEBERG, JOHN D.	PHD	C	DIRECTOR'S OFFICE	SNPRC, TX USA

AXIS I CODES: 1A, 11 **AXIS II CODES:** 31, 66

ABSTRACT

We plan to modify existing chimpanzee facilities in order to fulfill the following long-term objectives: (1) to enable an increase in the number of chimpanzees that can be actively maintained and used in infectious disease research at any point in time, (2) to expand the capacity for maintaining chimpanzees being held for future protocols, (3) to provide access to outdoor enclosures for chimpanzees used in research protocols or held for future experiments, and (4) to establish emergency power capability for ABSL-2 chimpanzee research facilities. Specifically, we plan to (1) renovate nine ABSL-2 chimpanzee housing buildings by creating 40 outdoor runs, and (2) install an emergency power system for 18 ABSL-2 chimpanzee research buildings. The nine buildings that will be renovated contain indoor, built-in individual cages (total of 47 cages) for animals used for infectious disease studies. We propose to renovate the buildings so that an outdoor portion is created for each cage, thereby providing the chimpanzees the opportunity to go outdoors when research criteria permit. The additions also will provide greater flexibility for housing chimpanzees by enabling some animals to be pair-housed. This capability will increase the number of chimpanzees that can be used in ABSL-2 studies simultaneously, and the number that can be held for future studies. The net result of the proposed renovations is to increase our capacity for infectious disease studies that require the use of chimpanzees in ABSL-2 containment, to bring our chimpanzee facilities up to generally accepted standards, and to protect against catastrophic loss of animals and research results consequent to power outages.

EMERGENCY ELECTRICAL POWER FOR ABSL 2/3 FACILITIES (0248)

NPRC UNIT: ADMINISTRATIVE

%NPRC $: 0.100% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
VANDEBERG, JOHN D	PHD	C	DIRECTOR'S OFFICE	SNPRC, TX USA

AXIS I CODES: 1A, 11 **AXIS II CODES:** 31, 66

ABSTRACT

The primary objective of this project is to provide emergency electrical power capability for ABSL-2/3 facilities used to conduct AIDS-related research as well as other infectious disease research such as West Nile and hepatitis viruses. A secondary objective is to provide two portable, hydraulic lift tables to reduce injuries to veterinary personnel working with sedated chimpanzees. Three emergency power generators, each driven by a diesel engine, will be installed and electrically connected to three power circuits. These circuits provide electricity to [illegible] sq. ft. of ABSL-2/3 space used to house chimpanzees and monkeys and associated procedure space. Obtaining emergency power capability will respond to an AAALAC, Int. finding but, more importantly, will protect against a potential catastrophic loss of animals and research results consequent to power outages. Additionally, the emergency power will prevent a compromise in biocontainment conditions due to loss of power for HVAC units. The lift tables will be used for sedated adult chimpanzees used in AIDS-related and other infectious disease research and will prevent or reduce back, shoulder and arm injuries to personnel. This project is expected to bid soon.

RESEARCH FACILITIES CONSTRUCTION - HOUSING FACILITY FOR CHIMPANZEES (0249)

NPRC UNIT: ADMINISTRATIVE

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
VANDEBERG, JOHN D	PHD	C	DIRECTOR'S OFFICE	SNPRC, TX USA

AXIS I CODES: 1A, 1I **AXIS II CODES:** 31

ABSTRACT

The proposed construction will provide a [illegible] nsf indoor/outdoor long-term housing facility for chimpanzees. This facility, which will be for the exclusive use of the Southwest National Primate Research Center (SRPRC) at the Southwest Foundation for Biomedical Research, will provide 16 cages each with an outdoor and a protected indoor section that will house up to 6 chimpanzees per cage. Construction of this facility is needed to provide cost-effective long-term housing for up to 72 chimpanzees that are not currently participating in research projects. Transfer of a portion of the existing chimpanzee colony to new facilities will reduce the cost of current and future projects for NIH-funded researchers by reducing per diem fees, and will make available valuable research space currently used to house animals that are not participating in research projects. The proposed construction will also accommodate an increase in the chimpanzee population that is projected to occur with the relocation of animals from other facilities, thereby increasing the number and diversity of chimpanzees available to researchers through the SNPRC and enhancing the national effort to maintain chimpanzees for ready use by the biomedical research community. Concept drawings have been prepared and are being reviewed. Plat application has been approved by the city.

RESEARCH FACILITIES CONSTRUCTION - HOUSING FACILITIES FOR BABOONS (0250)

NPRC UNIT: ADMINISTRATIVE

%NPRC $: 1.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
VANDEBERG, JOHN D	PHD	C	DIRECTOR'S OFFICE	SNPRC, TX USA

AXIS I CODES: 1A, 11 **AXIS II CODES:** 58

ABSTRACT

This is a proposed renovation of [illegible] gsf of outdoor housing facilities for baboons maintained by the Southwest National Primate Research Center (SNPRC) at the Southwest Foundation for Biomedical Research. These cage facilities, B-,C- and D- cages, range in age from 36 to 21 years. The general condition of each of these buildings has deteriorated to the point that normal maintenance and repair procedures can no longer maintain these facilities in a condition adequate to ensure the health and safety of their inhabitants. In addition to the proposed renovation of cage facilities, this proposal is requesting funds to construct a new locker room facility for the animal caretakers who maintain baboons in these facilities. The current locker room was constructed in a former feed storage facility at a time when the animal caretaker staff was approximately 50% of its current size. The proposed new locker room facility will provide shower facilities and clothes changing space to accommodate the current animal care staff of 29 as well as provide for a modest expansion of the staff due to an increase in the size of the baboon colony and the development of the SNPRC. Furthermore, the proposed new locker room facility will provide separate locker room space for female staff which does not currently exist and is needed to accommodate an increase in the female proportion of this staff in recent years. Repairs on some heater lines has been completed and estimates on fees for the remaining work are expected soon.

CONSTRUCTION OF SPF RHESUS MACAQUE FACILITY (0276)

NPRC UNIT: ADMINISTRATIVE

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
VANDEBERG, JOHN D	PHD	C	DIRECTOR'S OFFICE	SNPRC, TX USA

AXIS I CODES: 1A, 11 **AXIS II CODES:** 31

ABSTRACT

The proposed construction will provide a complex of six buildings to be used for SPF Indian-origin rhesus monkeys and using them in AIDS-related research. The breeding facilities will consist of four buildings each with 14 indoor-outdoor cages. Total square footage of these buildings is [illegible]. The breeding cages are separated into four buildings to reduce disease transmission. A climate-controlled building ([illegible] sq. ft.) will be constructed in close association with the breeding cage buildings to be used for treating ill animals. It will have a treatment room, an isolation room and support rooms. The remaining building in the complex will be a personnel support facility. It will include two locker rooms, an office and a break room (624 sq. ft.). The SPF breeding colony to be housed in this complex is funded by a National Institutes of Health (NIH) Cooperative Agreement (U42-RR16024). Under this cooperative agreement, the SNPRC will produce SPF rhesus monkeys for use primarily by NIH-grantees conducting AIDS-related research. The SWRPRC breeding colony, currently consisting of about 290 animals, is housed in a 40-year-old complex approximately 20 miles from the SNPRC and on a military base that is scheduled to be turned over to the City of San Antonio in 2002. In addition to the operational difficulties of maintaining such a facility from a distance, the present facility can not accommodate the approximate doubling in colony size that is expected within the next four years. The SNPRC combines experienced professional staff, proven methods, and excellent facilities for the virological and immunological evaluation of SPF rhesus macaques used in simian immunodeficiency virus (SIV)/AIDS research. These resources, combined with the recently acquired SPF rhesus colony and staff skilled in state-of-the-art genetic and demographic management, position the SWRPRC to play a pivotal role in meeting the national need for SPF rhesus in AIDS-related research. The proposed construction will provide the animal housing facilities necessary for the SNPRC to fully realize its potential to meet this national research need.

IMPROVEMENT OF ANIMAL FACILITY (0277)

NPRC UNIT: ADMINISTRATIVE

%NPRC S: 0.100% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
VANDEBERG, JOHN D	PHD	C	DIRECTOR'S OFFICE	SNPRC, TX USA

AXIS I CODES: 1A, 11 **AXIS II CODES:** 31

ABSTRACT

The objective of this application is to provide emergency electrical power capability for buildings used to house NHPs and to perform experimental and clinical procedures with these animals. The primate housing areas include both conventional and Animal Biosafety Level 2 (ABSL2) conditions. The procedures areas include treatment rooms, surgical suites, x-ray rooms, ultrasound room, densitometry room, neonatal intensive care unit, necropsy, pathology laboratories and tissue samples storage. The primary use of these areas is for research purposes (approximately 80 percent) with the remaining use being the clinical care of primates. Four emergency power generators, each driven by a diesel engine, will be installed and electrically connected to four power circuits. These circuits provide electricity to approximately [illegible] sq. ft. spread over nine buildings. Obtaining emergency power capability will respond to and AAALAC, Int. finding; but, more importantly, will protect against a potential catastrophic loss of animals and research results consequent to power outages. Additionally, the emergency power capability will prevent a potential compromise in biocontainment conditions due to loss of power for heating, ventilation, and air-conditioning (HVAC) units. There will be no architectural or engineering renovation of the nine buildings. No movable equipment is requested.

IMPROVEMENT OF PRIMATE CLINICAL CARE FACILITY (0278)

NPRC UNIT: ADMINISTRATIVE

%NPRC $: 0.100% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
VANDEBERG, JOHN D	PHD	C	DIRECTOR'S OFFICE	SNPRC, TX USA

AXIS I CODES: 1A, 11 **AXIS II CODES:** 31

ABSTRACT

Research on chronic diseases has been and will continue to be an important and well-funded component of the National Institutes of Health (NIH)-supported research program at the SNPRC. The ongoing success of chronic disease research is dependent upon the continued provision of high-quality clinical care; however, growth in investigator research support and animal utilization has taxed ability to provide necessary clinical care and support for NHPs. This application requests funding to improve existing animal care facilities to fulfill the following long-term objectives: 1) to modernize and expand the Institution's capacity for providing clinical care for treating NHPs, especially baboons, that are active participants in or are being held for future research protocols; 2) to equip the renovated treatment rooms with additional examination tables, gurneys, carts, and procedure lights which are needed to provide high-quality animal care; 3) to upgrade the Institution's radiographic capabilities by acquisition of digital x-ray equipment; and 4) to bring the facilities into compliance with current National Research Council (NRC) ventilation recommendations for animal care areas. The proposed alteration and renovation will remediate current inefficiencies of space utilization and traffic movement and will utilize the space gained to create a larger treatment area. Clinical procedure capabilities will be expanded and modernized with needed equipment, and a critical care area will be established adjacent to the clinic area. An office space currently adjacent to the clinic will be relocated away from animal care areas. Finally, the heating, ventilation, and air-conditioning (HVAC) system will be replaced with a system that supplies 100 percent fresh air. The net result of the proposed renovations is to modernize aged facilities and to increase institutional capacity for provision of high-quality animal care.

RESEARCH SUBPROJECTS

IMMUNOGENECITY OF NP-ISS COMBINED WITH INFLUENZA VIRUS VACCINE (0319)

NPRC UNIT: COMPARATIVE MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BRASKY, KATHLEEN M	MS, VMD	A		

AXIS I CODES: 1 **AXIS II CODES:**66

ABSTRACT

The aim of this study is to test a novel influenza virus vaccine consisting of recombinant Nuclear Protein(NP) conjugated to 1018 ISS (immunostimulatory phosphorothioate oligonucleotide). The NP-ISS formulation will be injected in combination with a standard commercially available influenza virus vaccine consisting of hemagglutinin antigen (HA). The ability of the NP-ISS conjugate formulation to generate a strong antigen-specific (NP and HA) humoral and cellular immune response, and to enhance the response to a commercial influenza vaccine will be assessed. The outcome of these experiments are to show that in baboons NP-155 formulation combined with standard commercial influenza vaccine induces higher immune responses (antibody and cytokines) over the standard influenza vaccine alone. These experiments will help decide if the new NP-155 conjugate vaccine can significantly increase the immune responses of baboons to inlfuenza vaccine, which will assist in the development of novel influenza vaccine for humans.

DIETARY DOCOSAHEXAENOIC ACID/ARACHIDONIC ACID INFLUENCE ON MOTOR FUNCTION (0314)

NPRC UNIT: COMPARATIVE MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BRENNA, JAMES THOMAS	PHD	A		CORNELL UNIVERSITY, NY USA

AXIS I CODES: 1 AXIS II CODES:71

ABSTRACT

In 2002, the USA and Canada introduced docosahexaenoic acid (DHA) and arachidonic acid (ARA) into infant formulas. The justification was a result of human and animal studies, including studies in baboons, showing improved brain and retina development when DHA/ARA are provided in the diet. However, there is very little clear evidence to guide the amount of DHA/ARA that should be added to formulas. More recently, maps of the central nervous system (CNS) of the developing baboon show that DHA and ARA are at high concentration in the basal gaglia, limbic system, and other deep brain structures, and are particularly concentrated in regions associated with motor function. We will investigate the role of DHA/ARA supplementation on biochemical parameters and development of motor function in three dietary groups of term baboons maintained from birth to 12 weeks. The groups will be (U) unsupplemented, (1X) supplemented with the concentration of DHA/ARA in commercial formula (about 0.32%DHA/0.64%ARA), (3X) supplemented with 3-times the concentration of DHA (0.96%) and a constant amount of ARA (0.64%).. These diets are normal balanced diets that should promote normal development; formulas U and 1X are commercial human infant formulas, and 3X has a higher amount of DHA that is hypothesized to promote improved development. The behavioral outcomes, to be measured every two weeks after birth, are neuromotor assessments via subjective testing, and startle reflexes. This work is of immediate importance to human health as it will help guide the formulation of human formulas. Similar formulas are being fed by other researchers (in Dallas) to human infants, and the results found in baboons will provide important mechanistic information to guide interpretation of those studies. Further, we expect these studies to help explain recent results showing that human babies of pregnant and lactating mothers consuming DHA are born more mature and have higher IQs than babies of mothers not consuming DHA.

GENE THERAPY IN BABOONS (0313)

NPRC UNIT: COMPARATIVE MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
CAREY, K DEE	DVM, PHD	C	COMPARATIVE MEDICINE	SFBR, TX USA

AXIS I CODES: 1 **AXIS II CODES:** 58

ABSTRACT

Systemic delivery of HDAd by injection into a peripheral vein has been widely employed for liver-directed gene transfer for the purpose of a gene therapy due to the method's simplicity and noninvasiveness. However, in order to achieve efficient hepatocyte transduction, high doses of vector are required which unfortunately result in severe acute toxicity. Attempts to circumvent this obstacle have been made by direct vector injection into the portal vein of the liver. However, the results, in terms of toxicity and hepatocyte transduction efficiency, wer no different than following peripheral vein injection. The objective of this project is to determine the feasilbity of delivering helper-depender adenoviral vectors exclusively to the liver for hepatocyte gene transfer by first isolating the liver circulation prior to delivery of the vector via the portal vein. We hypothesize that this strategy will result in high efficiency hepatocyte transduction using significantly lower vector doses and thus reduce, if not eliminate, acute toxicity. Furthermore, the ability to control the liver circulation may permit efficient transduction in the presence of preexisting neutralizing anti-Ad antibodies, important for later vector readministration, as well as prevent systemic dissemination of the vector which would further improve safety.

We have successfully isolated the liver of 7 animals and administered the vector by portal vein delivery. While the first 6 animals were sacrificed shortly after receiving the vector, we are currently following the progress of one animal to determine the long-term effects of the procedure. We plan to optimize the isolation process by implementing the use of balloon catheters in an effort to improve hepatocyct transduction efficiency.

DELIVERY OF HD-AD VECTORS TO PRIMATE LUNG (0315)

NPRC UNIT: COMPARATIVE MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
CAREY, K DEE	DVM, PHD	C	COMPARATIVE MEDICINE	SFBR, TX USA

AXIS I CODES: 1 **AXIS II CODES:**55

ABSTRACT

In this study, baboons will be treated with a new form of gene delivery system in an attempt to produce new gene products in the cells of the airways. The gene delivery vehicle is a modified virus vector expressing common protein marker genes (beta-galactosidase (Bgal) or the baboon alpha fetoprotein (AFB) gene). Adenovirus vectors are modified versions of a common virus usually responsible for upper respiratory infections in humans. The new vector to be used in these trials has been delivered to the livers and lungs of mice, and to the livers of some primates, with very promising results. Expression of the newly introduced genes has lasted for much longer periods of time in studies with the previous vectors, and the inflammatory response has been greatly reduced.

We will begin to study the use of these new vectors in the lungs, which are very complex and immunologically active organs. Animals will first be treated with a chemical agent called EGTA (n-tetra acetic acid), which relaxes in the cells of the airway surface to help them take up the virus, and then with a viral vector, which will be delivered directly to the airways using a flexible fiberoptic bronchoscope. After recovery, the animals will undergo serial chest radiographs and several blood tests, but there will be no further invasive procedures until sacrifice. The animals will be necropsied so that the location and degree of transgene expression in the lungs can be evaluated. We will also examine the animals carefully for evidence of inflammation in the lungs and regional lymph nodes, and for expression of the transgene in locations other than the lung.

The use of the Bgal vector will allow us to examine the distribution of transgene expression with the greatest accuracy. AFB expressing vector will be a better indicator of vector-associated inflammation or duration of expression, and will allow us to track the true extent of vector-associated inflammation. These experiments will help determine the appropriate doses, timing and delivery methods for further preclinical and human trials of pulmonary gene delivery using these agents.

MENB ANTIBODIES IN INFANT BABOONS (0316)

NPRC UNIT: COMPARATIVE MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
CAREY, K DEE	DVM, PHD	C	COMPARATIVE MEDICINE	SFBR, TX USA

AXIS I CODES: 1 **AXIS II CODES:** 71

ABSTRACT

A vaccine is being developed to prevent meningitis and sepsis (blood infection) caused by the bacterium Neisseria meningitidis group B (MenB). Infants and children aged 6 months to 2 years are at greatest risk of this highly lethal disease and currently there is no vaccine approved in the US or Europe. Previous experience with preclinical development of vaccines against the bacterium Haemophilus influenzae type b showed that infant baboons are a good predictor of whether a vaccine will be effective in human infants. Therefore our long term goals is to test experimental vaccines in the infant baboons model to select candidates for study in human infants and children. Human clinical studies have shown that the presence of a particular type of antibodies in blood, termed serum bactericidal antibodies (SBB), correlates with protection from bacterial meningitis. In our studies of baboon infants we will use SBA as a marker to predict the efficacy of the vaccine. Some individuals have SBA even before they are immunized, because Neisseria meningitidis can colonize the respiratory tract of normal humans and nonhuman primates. The probability of colonization increases with age. Before we conduct a vaccine trial we need to determine the age range during which baboons normally acquire SBA. This will help us to determine the appropriateness of the species for these studies and choose the appropriate age range for future studies of the vaccine. To this end, we have collected peripheral blood from 24 infant baboons aged 9 to 18 months. We have isolated serum from the blood, and will assay the serum for the presence of SBA. On the basis of this data we will define the prevalence of MenB SBA in normal infant baboons and select an appropriate age range for future vaccine studies.

PARENTERAL ADMINISTRATION OF REDUCED GESTRINONE TO A BABOON (0317)

NPRC UNIT: COMPARATIVE MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
CAREY, K DEE	DVM, PHD	C	COMPARATIVE MEDICINE	SFBR, TX USA

AXIS I CODES: 1 **AXIS II CODES:** 50

ABSTRACT

The purpose of the study was to administer the reduced gestrinone to an animal and then find the metabolites (the product produced from the reduced gastrinone by the animal) following the dose. The reduced gestrinone may be an anabolic steroid that can be used by weight lifters and other athletes to improve performance. The metabolites will be used to help develop means to detect improper use of the substance in sport. To this end, an adult male baboon was dosed with the reduced gestrinone and urine was collected for period of one week following drug administration. The urine was then analyzed for any detectable metabolites.

A COMPOUND TO PREVENT PREECLAMPSIA (0310)

NPRC UNIT: COMPARATIVE MEDICINE

%NPRC S: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LELAND, M MICHELLE	DVM	A		

AXIS I CODES: 1 **AXIS II CODES:** 71

ABSTRACT

Preeclampsia is a disorder that occurs only during pregnancy and affects both the mother and the unborn baby. It affects at least 5 percent of all pregnancies and is a rapidly progressive condition characterized by high blood pressure, swelling and protein in the urine. Typically, preeclampsia occurs in the late 2nd or 3rd trimesters. Preeclampsia and other hypertensive disorders of pregnancy are a leading global cause of maternal and infant illness and death. By conservative estimates, these disorders are responsible for 76,000 deaths each year. This project will assess the safety of an antibody to digoxin in pregnant baboons by administering it four times daily over a period of 8 weeks during the third trimester of pregnancy. 10 pregnant baboons have successfully completed the two months of antibody dosing, and have been monitored for physical, clinical, and behavioral changes during pregnancy. Following delivery, the infants and mothers are also being monitored for an additional six months postpartum.

IMMUNOLOGICAL RESPONSE TO HEALOSMP52 UPON RE-EXPOSURE (0318)

NPRC UNIT: COMPARATIVE MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LELAND, M MICHELLE	DVM	A		

AXIS I CODES: 1 **AXIS II CODES:** 48

ABSTRACT

HealosMP52 is a unique and new device and the purpose of this study is to demonstrate immunogenic safety to the device prior to clinical human use. HealosMp52 is a sponge-like bone graft substitute composed of mineralized bovine type I collagen and a bone forming protein MP52. Implants of HealosMP52 stimulate the formulation of new bone and could potentially replace autogenous bone for grafting procedures, eliminating the pain risk of complications and expense associated with surgical procedures used to harvest autograft bone. We would like to determine the possible immunological effects associated with the implantation of HealosMP52 in three previously treated animals by re-exposing them a second time. Three naive animals will be added as a control group. The three-naive animals will undergo the exact same experimental procedures as the three previously exposed animals. The immune response to HealosMP52 requires in vivo assessment due to the inherent complexities of the immune system. In addition, this study will be ued to support the safety of the HealosMP52 device for use in humans and as such, use of an animal species that is phylogenetically close to the human is warranted.

APPLICATION OF TRANSGENIC TECHNOLOGIES TO BABOONS (0308)

NPRC UNIT: COMPARATIVE MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MCCARREY, JOHN R	PHD	A		UNIVERSITY OF TEXAS, SAN ANTONIO, TX USA
C Name 3	DVM, PHD	C	COMPARATIVE MEDICINE	SFBR, TX USA
	PHD	A		UNIV TX HEALTH SCIENCE CENTER, SAN ANTONIO, TX USA

AXIS I CODES: 1 **AXIS II CODES:** 95

ABSTRACT

Many of the human disorders studied in baboon models are based, at least in part, on a genetic etiology. Transgenesis has been an extremely valuable tool for whole animal, in vivo studies of gene function in the mouse, but it is often not possible to accurately mimic the relevant complex primate physiology in this or other non-primate species. Thus, the availability of transgenic technology for experimental research with baboons would create a powerful new genetic, developmental and physiological model system for biomedical research. The long-term goal of this project is to develop technology for producing transgenic baboons. The immediate goals are to demonstrate the feasibility and to optimize the efficiency of producing transgenic baboon embryos, and to improve the probability of yielding transgenic offspring. We have stimulated over 50 female baboons and have optimized recovery of mature (MII) oocytes that were then subjected to either in vivo fertilization (IVF) or intracytoplasmic sperm injection (ICSI). We have tested methods for culture of embryos up to the 12-cell stage, and for introducing and detecting a transgene encoding green fluorescent protein (GFP). We have detected the presence and expression of the GFP transgene in two baboon embryos. We plan to further optimize the endocrine stimulation protocol to yield oocytes that will undergo fertilization and subsequent development at maximum rates. We also plan to optimize methods of ICSI, embryo culture, embryo transfer, and introduction of transgene constructs.

GENETICS OF ANXIOUS/DEPRESSIVE BEHAVIORS IN MACAQUES (0341)

NPRC UNIT: GENETICS GROUP

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
CAMERON, JUDY L	PHD	A		UNIVERSITY OF PITTSBURGH, PA USA
	PHD	A		UNIVERSITY OF PITTSBURGH, PA USA
	PHD	A		OREGON REGIONAL PRIMATE RESEARCH CENTER, OR USA
	PHD	A		UNIVERSITY OF PITTSBURGH, PA USA
	PHD	A		UNIVERSITY OF PITTSBURGH, PA USA
	PHD	C	GENETICS	SFBR, TX USA
	PHD	A		UNIVERSITY OF PITTSBURGH, PA USA
	PHD	A		UNIVERSITY OF PITTSBURGH, PA USA

AXIS I CODES: 1A, 15, 21 **AXIS II CODES:** 36, 58, 60, 72

ABSTRACT

The overall goal of this study is to take a novel approach, using a nonhuman primate model, to identify genes that may underlie the development of two common psychiatric illnesses, anxiety and depression. These disorders are common psychiatric illnesses of both childhood and adulthood, that are highly comorbid and strongly aggregate within families, with the same genes affecting liability to both kinds of disorders. The commonness and complex nature of these disorders, however, argue it will be difficult to determine their genetic underpinnings. We plan to study the genetic underpinnings of behaviors in rhesus monkeys that parallel several interrelated behavioral and temperamental traits linked to anxiety disorders and depression in humans, including fearfulness, behavioral inhibition, propensity towards distress, and reactivity. In addition, we will evaluate the genetic basis of physiological attributes associated with anxiety and depression, specifically blunted growth hormone (GH) responsiveness to pharmacological stimulation, activity of the HPA axis, and CSF neurotransmitter levels. This proposal is particularly timely in that increased evidence supporting these behavioral and physiological measures as markers of an underlying predisposition to develop anxiety and depression in humans has recently been published, and we have recently found that in young infant rhesus monkeys there is a strong correlation between low GH responsiveness and behavioral inhibition, and that these measures how a high degree of heritability. The specific aims of the study include (1) phenotyping a large kindred of rhesus monkeys using four standardized human tests of anxious, fearful and inhibited behaviors, and a clinical protocol for testing GH and CRH responsiveness to stimulation, and measuring CSF monoamine metabolite levels, (2) a genome-wide scan using 300 QTLs, (3) identification of candidate linkage regions, and (4) screening candidate genes. This project has been developed as a collaborative effort between investigators at three institutions, in order to bring together a team with expertise in assessment of nonhuman primate behavior and physiological measurements, QTL analysis in nonhuman primates, and large scale genomics research. Dr. Rogers of the SNPRC is performing all genotyping and molecular analysis.

GENETIC MODIFIERS OF SEVERITY IN SICKLE CELL DISEASE (0340)

NPRC UNIT: GENETICS GROUP

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
PLATT, ORAH S.	MD	A		HARVARD CHILDREN'S HOSPITAL, MA USA
[illegible]	PHD	C	GENETICS GROUP	

AXIS I CODES: 1A, 13, 19 **AXIS II CODES:** 58, 75B

ABSTRACT

Despite the fact that all individuals with sickle cell anemia (SS) have the identical genetic defect (homozygous beta 67 glu to val), there is a wide variation in clinical severity. While clinicians have long been aware of this variability, it was the epidemiologic data amassed by the NHLBI's Cooperative Study of Sickle Cell Disease (CSSCD) that allowed objective measurement of this variability and identification of key risk factors for severity. In this study we focus on one of the key risk factors for severity identified by the CSSCD – baseline white blood cell count (baseline WBC). This initially unanticipated risk factor is becoming more obviously relevant as new investigations into the pathophysiology of the disease increasingly emphasize the importance of white cells and inflammation. At the same time, baseline WBC and other markers of inflammation are emerging as risk factors for mortality in the general population, making the exploration of genetic determinants of baseline WBC of interest not only to the SS population, but also to the population at large. Our strategy for locating the genes that are responsible for the variability in baseline WBC involves three unique populations: inbred strains of mice (Jackson labs, Bar Harbor), baboon pedigrees (Southwest Foundation for Biomedical Research, San Antonio), and nuclear and extended families of ~300 probands with SS (Boston, Creteil). The animals will be useful in determining quantitative trait loci (QTLs) and ultimately individual genes that influence baseline WBC.

The present study in baboons is a continuation of earlier NIH supported research (R01 HL054141) to detect, characterize, and localize the effects of genes on normal quantitative variation in platelet biology phenotypes related to the bioavailability and activity of PDGF in pedigreed baboons. In addition to WBC number, phenotypes for which data have been collected include: other standard indicators of hematologic status (e.g., erythrocyte counts, platelet number and mean platelet volume); concentrations of PDGF, platelet activating factor, thromboxane B2, insulin-like growth factor-1, total serum cholesterol and high-density lipoprotein cholesterol). Statistical genetic analyses are making use of the baboon genome map to perform whole genome linkage screens in search of genes that influence normal variation in these traits.

To date, significant genetic contributions to normal variation in all measured traits have been detected and quantified. Variance component linkage screens have detected suggestive evidence of quantitative trait loci (QTLs) for PDGF, thromboxane B2, and high-density lipoprotein cholesterol. Recent multivariate analyses have detected several pleiotropic networks -- i.e., sets of traits influenced to a significant extent by the same gene or suite of genes. A novel pleiotropic relationship between mean platelet volume and WBX number has recently been detected. A preliminary bivariate genome screen has tentatively localized minor QTLs influencing these two traits to several regions of the baboon genome corresponding to human chromosomes 15q, 19q, and 17q. Additionally, genotype-by-age effects have been detected for PDGF.

Bivariate linkage screens for all traits exhibiting significant pleiotropy are continuing to localize QTLs influencing pleiotropic networks. Also, linkage screens incorporating genotype-by-age effects are being conducted.

MOLECULAR GENETIC MARKERS IN PRIMATE DISEASE MODELS (0043)

NPRC UNIT: GENETICS GROUP

%NPRC $: 2.000% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
ROGERS, JEFFREY	PHD	C	GENETICS	SFBR, TX USA

AXIS I CODES: 1A **AXIS II CODES:** 31, 58, 59

ABSTRACT

Nonhuman primates are a critical component of biomedical research, as animal models for many human diseases. Increased genetic information about nonhuman primate animal models will expand opportunities for disease-related research. As the genetic characterization of primates progresses, future research projects using these species will be able to more fully investigate relationships between genetics and disease. The first objective is to add new genetic polymorphisms to the existing baboon genetic linkage map. The second objective is to identify additional genetic polymorphisms in rhesus monkeys and add them to the rhesus linkage map. We have identified new genetic markers to fill several existing gaps in the baboon linkage map. This project will improve the value of baboons and rhesus for a wide variety of disease studies related to heart disease, obesity, psychiatric disorders, osteoporosis and infectious disease, including AIDS.

GENETIC LINKAGE MAPPING IN RHESUS MACAQUES (0164)

NPRC UNIT: GENETICS GROUP

%NPRC $: 2.000% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
ROGERS, JEFFREY	PHD	C	GENETICS	SFBR, TX USA

AXIS I CODES: 1A **AXIS II CODES:** 31, 58, 59

ABSTRACT

Rhesus macaques are the most commonly used nonhuman primate in biomedical research. This species is used as a model organism for a wide range of human diseases, and it is widely acknowledged that genomic information, including gene maps, for rhesus monkeys would constitute an important resource for a large number of biomedical studies. This project will create a resource (a genetic linkage map) that will make rhesus monkeys more valuable for a wide variety of research projects, especially the analysis of the genetic basis of common human diseases. The objective is to produce a 10 centiMorgan genetic linkage map of the rhesus genome. The markers (polymorphisms) to be used to map the rhesus chromosomes will be microsatellite loci already mapped in the humane genome. Using human loci to map rhesus chromosomes will produce a rhesus genetic map that can be readily compared with the human genome map. We have identified several multi-generation families of rhesus monkeys that are suitable for linkage analysis. More than 800 blood samples have been received from rhesus maintained by the Oregon NPRC. To this set of 800 animals, we will add additional rhesus from ONPRC, and new families from the Southwest NPRC and other research centers. More than 200 microsatellite polymorphisms have been identified in rhesus, and we are screening additional loci to begin larger-scale genotyping. We will screen the 360 microsatellite polymorphisms previously identified in baboons to determine which of these loci are also polymorphic in rhesus. These loci will be used for the genetic mapping. Over the next three years, we will develop maps of each of the 21 rhesus chromosomes.

GENETICS OF MONOAMINE ENDOPHENOTYPES AND MENTAL HEALTH (0280)

NPRC UNIT: GENETICS GROUP

%NPRC $: 2.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
ROGERS, JEFFREY	PHD	C	GENETICS	SFBR, TX USA
[redacted]	PHD	A		
	PHD	A		
[redacted]	PHD	A		WAKE FOREST UNIVERSITY, NC USA
	PHD	A		UNIVERSITY OF TEXAS, SAN ANTONIO, TX USA

AXIS I CODES: 1A, 21 **AXIS II CODES:** 58, 72

ABSTRACT

The available data strongly suggest that the causes of psychiatric illnesses are complex, and that the risk of suffering from depression, schizophrenia, anxiety disorder and other psychiatric diseases is influenced by genetic inheritance, nongenetic biological factors and external environmental factors such as social stress. In addition, it is clear that monoamine neurotransmitters (serotonin, dopamine and norepinephrine) are related to the onset and treatment of depression, anxiety disorders and other psychopathologies. Despite the evidence for genetic influences on psychiatric disorders, on levels of monoamine neurotransmitters, and on normal variation in temperament related to disease, the specific genes that affect these traits are not well known. Whole genome scanning using linkage analysis in multi-generation pedigrees is a powerful method for locating functional genes that influence complex traits such as these. Unfortunately, for several reasons, this approach cannot be used with human families to locate genes that influence cerebrospinal fluid (CSF) levels of monoamines, or to investigate normal variation in behavior. In this project, we propose to conduct a whole genome linkage scan in a nonhuman primate model (baboons, Papio hamadryas). We will search for genes that influence CSF levels of monoamine metabolites (5-HIAA, HVA and MHPG) and also investigate individual variation in temperament by subjecting each baboon to a behavioral challenge involving response to novel objects. All 650 study animals have already been genotyped for a linkage map consisting of 350 human microsatellite loci, with 7 cM resolution. We will also use gene expression array methods to assess the molecular effects of identified QTL loci in prefrontal cortex. Preliminary results from about 300 baboons indicate that all three monoamine metabolites and several behavioral responses to challenge are strongly heritable. Most significantly, the available genotypes permit a preliminary genome scan, and four LOD scores greater than 1.9 have been obtained. Our preliminary data demonstrate the value of the baboon model and indicate that a larger sample from the same pedigrees would likely provide important new information about genes that influence both monoamine neurotransmitter levels and behavioral reactivity (i.e., temperament). Identification of these genes will be very significant for future studies of genetic risk factors for psychiatric illness in humans.

DIET AND GENOTYPE IN PRIMATE ATHEROSCLEROSIS (0044)

NPRC UNIT: GENETICS GROUP

%NPRC $: 17.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
VANDEBERG, JOHN D	PHD	C	DIRECTOR'S OFFICE	SNPRC, TX USA
	PHD	A		
	DVM, PHD	C	COMPARATIVE MEDICINE	SFBR, TX USA
	PHD	A		LAWRENCE BERKELEY NATIONAL LABORATORY, CA USA
	PHD	A		
	PHD	A		
	PHD	A		
	PHD	A	GENETICS	SFBR, TX USA
	DVM, MS	C		
	MD	A		LAWRENCE BERKELEY NATIONAL LABORATORY, CA USA
	DVM	A		
	PHD	C	GENETICS GROUP	
	PHD	A		
	PHD	C	GENETICS	SFBR, TX USA
	MD, PHD	A		LAWRENCE BERKELEY NATIONAL LABORATORY, CA USA
	MD, PHD	A		

AXIS I CODES: 1A, 1D, 13 **AXIS II CODES:** 58, 59, 74A, 78

ABSTRACT

The identification of specific genes that predispose to atherosclerosis will enable new strategies for preventing cardiovascular disease, which is the leading cause of death in the USA. The overall goal is to conduct a genome search to identify individual genes that contribute to variation in lipoprotein-and adiposity-related phenotypes. We are determining the chromosomal locations of genes that modulate the cholesterolemic responses to dietary cholesterol and/or to dietary saturated fatty acids and of genes that modulate adiposity-related phenotypes. Because most baboon and human genes are arranged in the same linear order, the localization of a gene in baboons may implicate one or more defined human genes as candidates. We have completed a basic baboon genetic linkage map consisting of 331 microsatellite markers distributed along the chromosomes at an average of internal of 7.2 centimorgans. Analysis of the results of plasma lipoproteins and other phenotypic characters in pedigreed families of baboons, together with genotype data, has provided evidence for the locations of nine major genes that may be pertinent to risk of atherosclerosis. Two of these genes, exert strong influences over levels of plasma HDL1 (a subfraction of high density lipoproteins, which are protective against atherosclerosis) and three of them exert strong influences over levels of plasma LDL cholesterol (directly correlated with risk of atherosclerosis). The other genes affect, respectively, sodium-lithium countertransport in red blood cells (associated with blood pressure levels), fat-free mass (which is related to obesity, a risk factor of atherosclerosis), and levels of Lipoprotein (a) (a positive risk factor) and angiotenson converting enzyme (associated with blood pressure). Inbred progeny are being produced and subjected to dietary challenge to measure genetic interactions with dietary fat and cholesterol in determining plasma lipoprotein characteristics. Measures of adiposity also are made on the progeny and their parents. The animals are being genotyped for microsatellite markers, and analyses will be conducted to localize pertinent genes. Efforts to identify these genes and their mechanisms of function will then be initiated.

ESTABLISHMENT OF A SPF RHESUS MACAQUE COLONY (0106)

NPRC UNIT: LABORATORY ANIMAL MED

%NPRC $: 3.000% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
FROST, PATRICE A III	DVM	A		
C name J	DVM	C		

AXIS I CODES: 1 **AXIS II CODES:** 31, 92(BREEDING)

ABSTRACT

The offspring of this colony will be SPF Indian-origin rhesus monkeys, which will be available for AIDS-related research. The goal is to establish and maintain a colony of SPF Indian-origin rhesus macaque monkeys to produce animals for AIDS-related research. The monkeys will be characterized both serologically (for herpes B virus, SIV, SRV and STLV-1) and genetically (for 15 microsatellite markers). The Mamu-A *01 status of each animal will be determined. The management and breeding strategies will be based on the serologic and genetic profiles as well as social and breeding histories. Demographic management strategies will be used to maximize production and harvest schedules. The SRPRC assumed management of the U.S. Air Force SPF rhesus colony effective June 1, 2001. Since that time we have tested all animals for serological status to the viruses of interest, archived DNA from essentially all animals and performed analyses for genetic markers. Work is underway to computerize all records of the colony by individual animal (history, clinical, breeding, pedigree, etc.). The first animals were assigned to an NIH-funded researcher, located at SRPRC. During the coming year the U.S. Air Force should give ownership of 250 animals to the SRPRC. Serological and genetic testing will continue. By establishing good breeding management the production is expected to increase. A sustained harvest of 70 animals per year is projected within the grant period.

ESTABLISHMENT OF AN OSTEOPENIC COLONY OF FEMALE BABOONS (0080)

NPRC UNIT: PHYSIOLOGY & MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
CAREY, K DEE	DVM, PHD	C	COMPARATIVE MEDICINE	SFBR, TX USA

AXIS I CODES: 1A, 23, 26 **AXIS II CODES:** 46, 74E, 77, 86, 93

ABSTRACT

There are two options for obtaining osteopenic animals: acquire very aged animals which have undergone a naturally occurring menopause and associated bone loss, or ovariectomize adult animals and wait for bone loss to occur. In a previous study we evaluated the bone density in the proximal femur, lumbar spine, distal radius, and proximal tibia in two healthy adults, two ovariectomized adults, and two aged female baboons. Results from that study indicated that both the ovariectomized and aged animals were osteopenic relative to the healthy adult animals. However, bone density in the aged animals was more variable than in the ovariectomized animals. Therefore, we decided that it would be preferable for future studies related to osteoporosis to ovariectomize animals, and wait for osteopenia to develop. Previous studies in baboons indicate that bone loss is detectable 6 months after ovariectomy, and osteopenia is established 12 to 18 months after ovariectomy. The primary objective of this study is to establish a group of osteopenic, female nonhuman primates for use in future studies examining the use of a bone growth stimulator for treatment of osteoporosis. Additional objectives of the study are to examine the relationships between ovariectomy-induced bone loss and biochemical markers of bone turnover, and to evaluate the number of marrow-derived osteoprogenitor cells and their responsiveness to bone growth stimulation before and after ovariectomy. The colony will be used to study bone loss related to osteoporosis.

LOCOMOTOR ONTOGENY OF PRIMATE QUADRAPEDALISM AND THE EVOLUTION OF PRIMATE GAIT (0177)

NPRC UNIT: PHYSIOLOGY & MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
CAREY, K DEE	DVM, PHD	C	COMPARATIVE MEDICINE	SFBR, TX USA

AXIS I CODES: 1A, 26 **AXIS II CODES:** 34, 52, 60

ABSTRACT

Changes in body weight and shape may influence the biomechanics of change in four leg walking behavior during the first six months of baboon life. Infants change from a "lateral sequence" (arm touches down after ipsilateral leg) gait to a "diagonal sequence" (arm touches down after contralateral leg) gait, in terms of body gait and motion. This is an important transition because the diagonal sequence gait in adult primates is unique among mammals, and there is no consensus on why it evolved. This project will address that question. Biomechanics of walking will be assessed in infant baboons between 4 and 26 weeks old age. Reflective markers will be placed on limbs and motion will be recorded with a 3D motion analysis system in conjunction with a video camera. Small weights will be placed on body segments to test for changes in gait with changes in body weight distribution. We supported initial work at the Foundation to demonstrate feasibility and gather pilot date. Funding was obtained from the [ ] and a laboratory was established in Austin to continue the work. We lease infant/juvenile baboons to the research program. This project is underway. The conclusion of this study will shed light on the evolution of walking motion in primates and will help identify the changes in body structure that might have led to the evolution of diagonal sequence gait in primates.

private funding

ENDOSCOPIC FUNDOPLICATION IN ADULT MALE BABOONS (0147)

NPRC UNIT: PHYSIOLOGY & MEDICINE

%NPRC S: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
RICE, KAREN S	PHD	C		

AXIS I CODES: 1A, 16A, 16F **AXIS II CODES:** 48, 70, 86

ABSTRACT

Gastroesophageal reflux disease (GERD) affects about 5% of the population in Western countries. Twenty-five to fifty percent of GERD patients develop progressive or recurrent disease which requires lifelong medical treatment. Surgical therapy is the treatment of choice but is under-utilized because of the invasiveness and morbidity of the procedure. A modified andoscopic; procedure to create a valve to prevent GERD has been developed. It is noninvasive in that the procedure is performed through the esophagus and in the stomach with a modified gastroscope and eliminates the need for major surgery. The intent is to perform the procedure in humans with local anesthetic and sedation and to avoid the risk of major anesthesia. The adult male baboon is an excellent model to develop this procedure because the anatomy and physiology are similar to those of the human, and the esophagus of large male baboons will accommodate instruments developed for use in humans. The objective is to evaluate creation of valvuloplasty with a modified gastroscope. The project is expected to provide data that justify taking the procedure to phase I clinical trials.

The results are proprietary.

KYPHOPLASTY AND VERTEBROPLASTY IN OSTEOPOROTIC BABOONS (0273)

NPRC UNIT: PHYSIOLOGY & MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
RICE, KAREN S	PHD	C		

AXIS I CODES: 1A, 26 **AXIS II CODES:** 30, 46, 48, 93

ABSTRACT

Pathologic vertebral compression fractures secondary to osteoporosis are a growing problem It is estimated that more than 700,000 fractures will occur this year, leading to over 250,000 physician visits Many of these will collapse into kyphosis (hunchback) and lead to prolonged pain and disability. There has been little satisfactory treatment to date and this has done little to limit the pain or deformity experienced by afflicted patients Narcotic analgesics carry some associated risks and complications Bracing provides minimal benefit and surgery is fraught with complications Recently, there have been some reports of success with placement of partially cured viscous cement into the fractured vertebral body, which provides immediate stability and pain relief The procedure has been termed "vertebroplasty". A related treatment, "Kyphoplasty" involves the use of an inflatable bone tamp to facilitate the reduction of fractured vertebrae and create a cavity. The resultant cavity is then filled with partially cured viscous cement in a low-pressure environment under direct control The Kyphoplasty technique minimizes the risk of cement leaks and works towards restoring the vertebral body and the spinal sagital alignment back to its pre-fracture state. This can be performed on one or two vertebrae at a time, though as many as 5 levels have been performed at a single setting. By performing this study we can gain a better understanding of the behavior of the cement and the bone, the interactions between the two, and whether or not the bone has the capacity to heal after such injury.

VAGINAL ABSORPTION OF NONSTEROIDAL CONTRACEPTIVE IN BABOONS (0275)

NPRC UNIT: PHYSIOLOGY & MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
RICE, KAREN S	PHD	C		

AXIS I CODES: 1A, 15, 23 **AXIS II CODES:** 50, 93

ABSTRACT

Oral contraceptives (OCs) first became available to American women in the early1960s. The convenience, effectiveness, and reversibility of action of birth control pills (popularly known as "the pill") have made them the most popular form of birth control in the United States. However, concerns have been raised about the role that steroid hormones play in a number of cancers, and how hormone-based OCs might contribute to their development. The advantages of nonsteroidal contraceptives that prevent implantation is that they avoid the risks of contraceptive steroid hormones and can be taken post-coitus. The compound being tested has previously been administered to monkeys through a small subcutaneous osmotic pump where it was effective as a contraceptive. Our objective is to administer the product via the vagina and measure blood levels within the first week of administration. We expect that using this route uterine levels will be increased and a greater local level achieved. If our hypothesis is true, we would be able to use the less intrusive vaginal route for this non-steroidal contraceptive agent.

NUCLEUS PULPOSUS REPLACEMENT THERAPY IN INTERVERTEBRAL DISC (0279)

NPRC UNIT: PHYSIOLOGY & MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
RICE, KAREN S	PHD	C		

AXIS I CODES: 1A, 9, 26 AXIS II CODES: 46

ABSTRACT

An estimated 5 million adults in the US alone suffer with chronic back or neck pain primarily due to disc degeneration. Surgical treatments for disc herniation and chronic pain of disc origin include removal of protruding tissue or complete disc removal and fusion of the bone. An estimated 250,000 spinal fusions are performed in the US each year to treat herniations and chronic disc degeneration. Spinal fusion is a traumatic procedure with lengthy recovery times and is a treatment of last resort.

Discs are cushions of cartilage between each bone of the spine that allow for movement. An outer ring of tough fibrous cartilage surrounds an inner water-filled center forming the discs. Discs are the largest structures in the body without a blood supply. Because of this, damaged or degenerated disc tissue is extremely limited in its ability to repair itself. An alternative to spine fusion would be of enormous clinical value. Patients who suffer chronic pain associated with degenerative disc disease (but who are not candidates for spinal fusion) would greatly benefit from disc replacement therapy. This therapy would be most useful in early and middle stages of disc disease and especially appropriate for younger (30-50 year old), active patients. Since the collapsed or bulging disc significantly contributes to chronic pain, disc implants would return the treated discs to their normal state.

To assure the safety and effectiveness of a disc replacement therapy for humans, it is first essential to perform the experiment using animals. In this study, six baboons will undergo disc surgery to create a disc defect and to implant replacement material. The implanted replacement will be monitored using X-ray imaging and magnetic resonance imaging. Baboons are necropsied at the end of the study so that spines can be processed for histology.

AUGMENTATION OF BONE MASS BY AN OSTEOCONDUCTIVE MATERIAL (0294)

NPRC UNIT: PHYSIOLOGY & MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
RICE, KAREN S	PHD	C		

AXIS I CODES: 1A, 9, 26 **AXIS II CODES:** 30, 33, 46, 50, 93

ABSTRACT

Osteoporosis affects over 25 million Americans, and the incidence of age-related hip fractures is approaching 300,000 cases annually. The goal of this program is to develop an osteoinductive protein/carrier combination that can be used to increase local bone mass in osteoporotic patients. These studies use ovariectomized nonhuman primates that mimic both the hormonal fluctuations and osteopenia that occur in postmenopausal women. The osteoinductive protein/carrier is delivered to metaphyseal sites such as the proximal and distal femur, proximal tibia, and distal radius, in a synthetic minipellet. Preliminary studies indicate that while this therapy results in up to 50% increase in local bone mass by 6 months. Animals will be necropsied to assess effect. In vivo outcome measurements will include radiographs and analysis of serum for biochemical markers of bone turnover; ex vivo outcome assessments will include peripheral QCT imaging, mechanical testing, and/or histology. These studies will be pivotal in determining efficacy of this therapy, and will be used to motivate clinical use for prevention of hip fracture by locally increasing bone mass in the proximal femur.

DETERMINANTS OF REPRODUCTIVE COMPETENCE IN CALLITRICHID PRIMATES (0221)

NPRC UNIT: PHYSIOLOGY & MEDICINE

%NPRC $: 2.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
TARDIF, SUZETTE D.	PHD	C	DIRECTOR'S OFFICE	SNPRC, TX USA
[illegible]	PHD	G		

AXIS I CODES: 1A, 23, 26

AXIS II CODES: 36, 60, 63H, 65, 71, 78, 93

ABSTRACT

This project is designed to both improve long-term captive propagation of the common marmoset and to define marmosets as models of life history effects on reproduction and maternal health. Specific Aim I will define the relation between maternal condition and reproductive investment through energy restrictions during gestation or lactation. Based on our preliminary findings, we expect to generate intrauterine growth retardation with minimal change in maternal condition – that is, mothers will sacrifice fetal growth to retain maternal state. We will also be testing the hypothesis that "poor" mothering in multiparous females is the result of "poor" infants (i.e. infants that are too small or have an atypical behavioral repertoire). Energy-restriction in the post-partum period is expected to result in more dilute milk and earlier weaning. Specific Aim 2 will define normal calcium metabolism during lactation and bone health in marmosets. This study will indicate whether marmosets might be a useful model for the study of maternal bone health in women, particularly relative to calcium restriction. Specific Aim 3 will define the relation between maternal age, fertility, and survival using a large demographic database.

CHEMOKINE RECEPTORS AND NATURAL HOST RESISTANCE TO SIV (0107)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC $: 0.200% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
ALLAN, JONATHAN S	DVM	C		

AXIS I CODES: 1A, 7B, 17, 19 **AXIS II CODES:** 31, 66, 83

ABSTRACT

Chemokine receptors constitute an important mechanism for immune modulation and are used by primate lentiviruses to gain entrance into CD4+ T cells. CCR5 is one such receptor that plays a prominent role in determining viral entry. Simian immunodeficiency viruses in the natural host do not cause disease, but in other species such as macaques they cause full blown AIDS. Differences in host genetic control over this species-related difference may result from profound differences in chemokine receptor expression and its regulation. The SIVagm model is a valuable tool for determining host genetic factors in natural host resistance to AIDS. The overall objective is to determine if CCR5 expression and regulation is responsible for this natural resistance to disease. In vitro infection of African green monkeys and pigtailed macaques with SIVagm will be examined and correlations made between in vitro susceptibility and CCR5 expression. CCR5 expression on CD4+ T cells in African green monkeys is much lower than expression in a susceptible primate species (pigtailed macaques). We have developed reagents to test our hypothesis and are examining directly the relationship between expression of CCR5 and in vitro susceptibility to infection with SIVagm. Chemokine receptor expression in natural and unnatural host species will be examined as a marker for disease in the animal model system. It is hoped that by studying the regulation of coreceptor expression in vivo models, a clearer understanding of viral and host determinants will be achieved. In particular, the evolution of coreceptor usage by SIVagm and its expression may be useful in predicting viremia and disease outcome.

DETERMINANTS OF NATURAL HOST RESISTANCE TO SIV AGM (0265)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC $: 5.000% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
ALLAN, JONATHAN S	DVM	C		
[redacted]	PHD	C	VIROLOGY AND IMMUNOLOGY	SFBR, TX USA

AXIS I CODES: 1A, 1D, 7B, 17, 19 **AXIS II CODES:** 31, 66, 83

ABSTRACT

Despite significant progress in identifying important mechanisms underlying HIV-1 pathogenesis, the role of host and viral factors contributing to progression to disease are still poorly understood. There is growing evidence supporting the hypothesis that differences in HIV/SIV coreceptor usage, and the host response to early infection are critical determinants of HIV-1 transmission and AIDS pathogenesis. The natural host species for SIV displays an unusual feature; lack of SIV-induced AIDS. A major focus of this proposal is to develop a differential model for pathogenesis. SIVagm infection in African green monkeys (Agms) does not result in clinical disease however, infection of pigtailed macaques(Ptm) results in classical T cell depletion and AIDS. Like HIV-1, most SIVagm and SIVsm strains utilize CD4 and CCR5 for viral entry, thus targeting these cells for infection and killing. Our studies have shown that there is a high level of viremia both in the plasma and cerebrospinal fluids of naturally infected monkeys however, the number of infected cells was generally lower than SIV infected macaques. Moreover, studies in the natural host have failed to correlate cellular immune responses with viral replication in the natural host. We have also shown that the CD4+CCR5+ T cell pool in PBMC of Agm is at least 5 fold lower than in Ptm suggesting fundamental differences in the size of the susceptible T cell pool may lead to profound differences in cell killing and by extension, cell-mediated killing. In this application, we propose to: 1. Determine if host-specific differences in receptor/coreceptor expression at anatomically relevant sites of viral replication are a factor in the differential pathogenesis of SIVagm. 2. Determine if SIVagm strains with broader cell tropism (R5X4) will alter pathogenesis in Agm and Ptm. We will also compare neurotropic SIVagm (R5) strains in terms of cell tropism, evolution in the central nervous system and define pathogenic outcomes. 3. Determine if host-specific differences in cellular immune responses at anatomic sites for viral replication are a factor in SIVagm pathogenesis. We will examine longitudinally, cell- mediated immunity in the natural and unnatural host. In summary, this proposal seeks to understand the role of coreceptor expression, viral replication and cellular immunity in the pathogenesis of SIV.

EFFECTS OF CD154 EXPRESSION DURING RETROVIRAL INFECTION (0018)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC $: 0.100% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
GIAVEDONI, LUIS D	PHD	C	VIROLOGY AND IMMUNOLOGY	SFBR, TX USA

AXIS I CODES: 1A, 7B, 17, 19 **AXIS II CODES:** 31, 39, 64, 66, 83, 91

ABSTRACT

CD154 (CD40 ligand) is a costimulatory molecule expressed by activated CD4+ T cells that binds to CD40 present on dendritic cells, B cells, and macrophages. The objective of this study was to investigate mechanisms that affect cellular and humoral immune responses to lentiviruses during the acute and chronic stages of infection. Specifically, we studied the role of the costimulatory molecule CD154 during infection of rhesus macaques with an attenuated virus control (SIVCNTL) or with a recombinant one that expressed CD154 (SIVCD154). These viruses lacked the regulatory gene nef. After inoculation with SIVCD154 or SIVCNTL, SIV Gag-specific CTL were identified for all animals. Virus isolated from the inoculated macaques was also studied for expression of CD154. Measurement of activation markers on the surface of PBMC and LNC from animals from both groups did not show any significant difference. Anti-SIV CTL and antibody levels were also similar for both groups. Virus isolated from animals inoculated with SIVCD154 expressed CD154 up to ten weeks after infection. These results indicate that signaling and expression of CD154 is not affected by infection of SIV viruses that lack the nef gene. CTL epitopes in other SIV proteins (Vpr, Vpx, Vpu, Vif, Tat, and Rev) were also identified for these macaques. There was a tendency to detect CTL directed against SIV regulatory proteins (Tat and Rev) during the acute phase of the infection, and Gag-specific CTL during the chronic stage. Four of these animals were challenged with SIVmac 251, and they resisted infection. We demonstrated that cellular components from the innate and adaptive immune system participated in the antiviral defense.

EVALUATION OF SIV EXPRESSING IGIF (0216)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
GIAVEDONI, LUIS D	PHD	C	VIROLOGY AND IMMUNOLOGY	SFBR, TX USA
name	DVM	C		

AXIS I CODES: 1A, 7B, 17, 19 **AXIS II CODES:** 31, 39, 64, 83, 91

ABSTRACT

Interleukin-18 (IL-18, interferon-gamma inducing factor [IGIF]) represents a functional link between effector cells of innate (phagocytic and NK cells) and adaptive (T-and B-lymphocytes) immune system. Expression of IL-18 by a live-attenuated SIV vaccine may reduce viral virulence and induce a Type-1 immune response that may prevent infection with pathogenic SIV. The objective of this study is to evaluate the in vivo effects of the infection of rhesus macaques with a recombinant SIV-nef that expresses the rhesus IL 18 gene and its potential use as a live-attenuated vaccine (SIVIL18). Rhesus macaques inoculated with SIVIL18 or SIVFIGI (a control virus), resisted an intravenous challenge with pathogenic SIVmac251. Eleven out of 12 macaques did not show the presence of pathogenic virus after the challenge and the single monkey from which challenge virus was isolated had very low viral loads and absence of systemic inflammation. Protected macaques have remained free from infection with pathogenic SIV for over 2 years. Animals without detectable viremia (for the attenuated virus) have shown declining levels of SIV-specific CTL and antibodies. CD8T cells will be depleted to evaluate the role of these cells in the containment of infection with attenuated virus.

MULTIPLEX NHC TYPING OF RHESUS MACAQUES (0300)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC $: 2.000% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
GIAVEDONI, LUIS D	PHD	C	VIROLOGY AND IMMUNOLOGY	SFBR, TX USA

AXIS I CODES: 1D, 2, 9, 17 **AXIS II CODES:** 31, 58, 64, 66, 88, 91

ABSTRACT

The main goal of this research is to develop a new technology that will allow the rapid identification of Major Histocompatibility Complex class I (MHC-I) alleles present in the genome of rhesus macaques (Macaca mulatta). MHC-I genes encode proteins central to the adaptive immune response, signaling infection by binding pathogenic peptides and presenting them on the cell surface to cytotoxic T cells. In addition, class I molecules are critical to the innate immune response, providing both inhibitory and stimulating signals to NK cells. Rhesus macaques are relevant preclinical models for human diseaes and transplantation, and experimentally infected rhesus monkeys serve as an indispensable animal model to assess the pathogenesis, to validate therapy approaches and to develop vaccination strategies against AIDS. As in humans, the disease course in macaques is variable, and certain MHC-I molecules appear to be associated with better control SIV replication. Current molecular methods for genotyping rhesus monkeys use PCR techniques with individual sets of sequence-specific primers for a handful of Mamu-A and -B alleles. We will combine the multiplexing capacity of the Luminex 100 platform with the high specificity of sequence-specific DNA probes (SSP) that contain minor groove binders (MGB). MGB allow the design of short probes with increase sensitivity to differentiate single nucleotide polymorphism (SNP), whereas the Luminex microspheres permit the simultaneous use of up to 100 different probes. We have designed primers that amplify the polymorphic exons 2 and 3 of all the known Mamu-A and -B alleles. We will probe these DNA fragments with Luminex microspheres coated with allele-specific probes. The rapid identification of these Mamu-A and -B alleles in Rhesus macaques will have significant consequences in understanding the role of MHC-I genes in transplantation, vaccine development, and infectious diseases studies that use this important animal model.

GBV-B: A SMALL PRIMATE MODEL FOR HEPATITIS C INFECTION (0108)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC $: 2.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LANFORD, ROBERT E	PHD	C	VIROLOGY AND IMMUNOLOGY	SFBR, TX USA

AXIS I CODES: 1A, 1D, 7B, 16D **AXIS II CODES:** 50, 66, 71, 91

ABSTRACT

Hepatitis C virus (HCV) is a major human pathogen, with an estimated 1-2% of the US population chronically infected. While many people with chronic infections will never have liver problems, a significant proportion will develop cirrhosis or liver cancer. The current model for study of HCV, the chimpanzee, has limited utility due to the high cost and short supply of animals. A possible surrogate model system is the study of hepatitis GB virus B (GBV-B) in tamarins. GBV-B is closely related to HCV and causes a reproducible, acute, self-limited hepatitis in tamarins. The objectives of this program are to establish the GBV-B virus/tamarin model as a surrogate for HCV infections, to develop a tissue culture system for GBV-B, to evaluate vaccine candidates for induction of neutralizing antibodies, and to evaluate HCV/GBV-B chimeric viruses for infectivity in tamarins. The infection profile of tamarins with GBV-B has been established using quantitative (TaqMan) RT-PCR for viral RNA and ELISA for antibodies to the viral NS3 protein. We have also used common marmosets in this model system. Attempts are in progress to induce chronic infection by immunosuppression with FK506. An infectious cDNA clone of GBV-B RNA was produced in collaboration with Stan Lemon at The University of Texas Medical Branch in Galveston, Texas. Several chimeric clones are currently being evaluated in tamarins. A tissue culture system for GBV-B has been established using primary cultures of tamarin hepatocytes, and the system has been validated for antiviral studies using interferon and ribavirin. The envelope proteins of GBV-B will be expressed in various insect and mammalian systems, the proteins will be purified and used to produce antibodies, and the antibodies will be tested for neutralization activity using newly developed tissue culture system. Efforts to produce infectious chimeric viruses between HCV and GBV-B will continue.

WMHBV: A SMALL PRIMATE MODEL FOR HEPATITIS B VIRUS (0109)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC $: 2.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LANFORD, ROBERT E	PHD	C	VIROLOGY AND IMMUNOLOGY	SFBR, TX USA

AXIS I CODES: 1A, 1D, 7B, 16D **AXIS II CODES:** 50, 66, 91

ABSTRACT

Chronic Hepatitis B virus (HBV) infections afflict approximately 350 million people worldwide. These infections can progress to liver cirrhosis and liver cancer, making HBV infections the fourth leading cause of death due to infectious disease. Until recently, HBV infection of chimpanzees was the only nonhuman primate model. Additional nonhuman primate models of this important infectious disease are needed, and this project proposes to develop one. We recently discovered the first HBV virus from a nonhuman primate in woolly monkeys (WMHBV). The goals of this project are to establish the spider monkey as a small primate model for WMHBV as a surrogate system for HBV, to develop a molecular infectious clone of WMHBV, and to define the host range determinants of primate hepadnaviruses using hepatitis D virus pseudotyped with the envelopes of WMHBV and HBV. The spider monkey is used for this project because woolly monkeys are in short supply. An infectious clone of WMHBV has been constructed and characterized for replication in tissue culture following transfection with the cloned DNA and in spider monkeys following infection In an attempt to establish chronic infections of WMHBV in spider monkeys, animals have been infected at birth or after immunosuppression with FK506. HDV particles pseudotyped with the envelope of HBV and WMHBV have been examined for the ability to infect primary hepatocytes from chimpanzees and spider monkeys. Synthetic peptides that mimic the HBV envelope block HDV infection suggesting that they will be useful probes for the HBV receptor. This strategy will provide a tool to explore the determinants of host range and to isolate the receptor for HBV.

EVALUATION OF ANTIVIRALS FOR HEPATITIS C VIRUS IN CHIMPANZEES (0210)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LANFORD, ROBERT E	PHD	C	VIROLOGY AND IMMUNOLOGY	SFBR, TX USA

AXIS I CODES: 1A, 7B, 16D AXIS II CODES: 50B, 66

ABSTRACT

Approximately 2% of the US population is chronically infected with hepatitis C virus (HCV). Chronic HCV infections result in significant liver disease, including cirrhosis and liver cancer in approximately 20% of infected individuals. The current therapy of interferon and ribavirin does not result in viral clearance in the majority of cases. The development of improved antiviral strategies to treat HCV chronic infection is essential for the control of this disease. The objective of this study is to test a series of small molecule antiviral inhibitors of HCV replication for efficacy in chimpanzees chronically infected with HCV. The level of viral RNA in the serum will be measured by TaqMan RT-PCR, and the animals will be monitored for safety and improved liver disease. Thus far, four antivirals have been tested and some have entered phase I human trials. Studies are in progress with new antivirals.

EVALUATION OF IMMUNE MODULATORS IN CHIMPANZEES (0211)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LANFORD, ROBERT E	PHD	C	VIROLOGY AND IMMUNOLOGY	SFBR, TX USA

AXIS I CODES: 1A, 7B, 16D AXIS II CODES: 50B, 66

ABSTRACT

Approximately 2% of the US population is chronically infected with hepatitis C virus (HCV). Chronic HCV infections result in significant liver disease, including cirrhosis and liver cancer in approximately 20% of infected individuals. The current therapy of interferon and ribavirin does not result in viral clearance in the majority of cases. The development of improved strategies to treat HCV chronic infection is essential for the control of this disease. The objective of this study is to evaluate a novel immune modulator compound in chimpanzees to determine the dose needed for appropriate biological response in chimpanzees. The level of specific cytokines in the blood will be measured by immunoassay, and alterations in gene regulation in the liver will be determined by microarray and TaqMan RT-PCR assays. The immune modulator was very effective at inducing cytokine expression, and has entered phase I human trials. This study is complete.

HCV ANTIVIRAL TESTING IN CHIMPANZEES (0301)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LANFORD, ROBERT E	PHD	C	VIROLOGY AND IMMUNOLOGY	SFBR, TX USA

AXIS I CODES: 1A, 7B, 16D AXIS II CODES:50B, 66

ABSTRACT

Approximately 2% of the US population is chronically infected with hepatitis c virus (HCV). Chronic HCV infections result in significant liver disease, including chrrhosis and liver cancer in approximately 20% of infected individuals. The current therapy of interferon and ribavirin does not result in viral clearance in the majority of cases. The development of improved antiviral strategies to treat HCV chronic infection is essential for the control of this disease. The objective of this study is to test a series of small molecule antiviral inhibitors of HCV replication for efficacy in chimpanzees chronically infected with HCV. The level of viral RNA in the serum will be measured by

TaqMan RT-PCR, and the animals will be monitored for safety and improved liver disease. This study is in progress and no data are yet available. If antiviral efficacy is demonstrated, the antiviral compounds will be tested in phase I human trials.

ANTIVIRAL EFFICACY OF INHIBITORS OF HCV REPLICATION IN CHRONICALLY (0302)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LANFORD, ROBERT E	PHD	C	VIROLOGY AND IMMUNOLOGY	SFBR, TX USA

AXIS I CODES: 1A, 7B, 16D **AXIS II CODES:** 50B, 66

ABSTRACT

Approximately 2% of the US population is chronically infected with hepatitis C virus (HCV). Chronic HCV infections result in significant liver disease, including cirrhosis and liver cancer in approximately 20% of infected individuals. The current therapy of inteferon and ribavirin does not result in viral clearance in the majority of cases. The development of improved antiviral strategies to treat HCV chronic infection is essential for the control of this disease. The objective of this study is to test a series of small molecule antiviral inhibitors of HCV replication for efficacy in chimpanzees chronically infected with HCV. The level of viral RNA in the serum will be measured by TaqMan RT-PCR, and the animals will be monitored for safety and improved liver disease. The study is complete. Antiviral efficacy was demonstrated.

IMMUNOGENICITY OF HSV AMPLICONS IN RHESUS MACAQUES (0307)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC $: 0.700% AIDS RELATED RESEARCH

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MARTIN, DAVID W	PHD	A		

AXIS I CODES: 1A, 1D, 7B, 9, 17 AXIS II CODES: 31, 64, 66, 77, 83, 91

ABSTRACT

The best strategy for preventing the continuing spread of infection with the human immunodeficiency virus (HIV) involves the development of an effective vaccine. Herpes simplex virus (HSV) amplicons represent a novel and promising strategy for vaccine development. HSV amplicons maintain several advantages as a vaccine strategy. First, HSV amplicons cannot cause any infectious disease. Second, HSV amplicons have a wide host cell tropism and are able to efficiently enter multiple cell types including mucosal cells. Third, HSV amplicons have a large coding capacity, which allows for the development of vectors that could encode mutliple antigens and/or immunostimulatory gene products. Finally, HSV amplicons do not contain the immunomodulatory genes that are a pat of replication-defective or attenuated HSV vectors. Previous studies with HSV amplicons have been performed in small animal model systems. However, the immunogenicity of these amplicons has never been tested in a nonhuman primate model system. The studies described in this proposal will determine if HSV amplicons can elicit a significant immune response in the rhesus macaque. Specifically, rhesus macaques will be inoculated via an intramuscular route with HSV amplicons that express the SIVmac39 gag gene product or by control amplicons that do not express any SIV gene product. The cellular immune response to Gag will be followed through analysis of CD4+ and CD8+ T cell responses, tetramer staining, and antigen-specific cytokine production. The humoral response will be determined by analysis of both serum and mucosal immunity. Finally, the innate immune response will be determined through analysis of both natural killer cells and by performing longitudinal studies of changes in lymphocyte proliferation and activation. Successful completion of these studies will allow for efficacy trials to be initiated in the SIV model system. Furture studies may be extended to utilize HSV as a vaccine delivery system to prevent against HIV infection of humans. In addition, the successful completion of these studies will have a significant impact on the continued development of HSV amplicons as gene and cancer therapy vectors.

THIS PAGE LEFT INTENTIONALLY BLANK

PILOT SUBPROJECTS

CONCORDANCE OF CIRCULATING AND ARTERIAL WALL RISK FACTORS (0297)

NPRC UNIT: GENETICS GROUP

%NPRC $: 0.240%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
WANG, JIAN	MD, PHD	A		

AXIS I CODES: 1D, 13 **AXIS II CODES:** 74B, 74H

ABSTRACT

Atherosclerosis is the most common reason for arterial luminal obstructions leading to ischemia or infarction of the supplying organs. Atherosclerotic changes appear frequently in medium-sized arteries among individuals with increased risk. It is the interaction between circulating and vascular wall factors determines whether, where and when the atherosclerosis occurs. Many circulating molecules produced by non-vascular tissues, such as LDL, have been associated with the increased risk of atherosclerosis. On the other hand, factors produced by arterial wall - the other side of the atherogenic equation, are the "endogenous" determinants for the local susceptibility to circulating "exogenous" risk factors. Some of these arterial wall factors can be released to and equilibrated with the circulating pool. They have been used as surrogate measures for arterial wall conditions. In the current study, we wish to examine the hypothesis that circulating plasma levels can be used as surrogates for corresponding arterial wall factors that are relevant to atherogenic changes in baboons. We will explore several important systems including oxidative stress, inflammation/infection, endothelial dysfunction and arterial hemodynamic regulators. These systems are actively involved in vascular physiological and pathological processes and have been assessed frequently in clinical studies relating to atherogenesis. We will measure these levels from simultaneously collected plasma and coronary, aortic, carotid and brachial arteries in 60 male and 60 female baboons undergoing necropsy and asses their quantitative relationships. Our study will have significant implications to both diagnostic applications and mechanistic understanding of arterial wall factors in atherogenesis.

GENETICALLY DETERMINED ENDOTHELIAL DYSFUNCTION IN BABOONS (0299)

NPRC UNIT: GENETICS GROUP

%NPRC $: 0.240%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
WANG, XING LI	MD, PHD	A		

AXIS I CODES: 1D, 13 **AXIS II CODES:** 58

ABSTRACT

Atherosclerosis, the most common cause of the coronary heart disease (CHD), which is the No. 1 killer in the USA, is the direct consequence of aberrant interactions between circulating blood and arterial wall. Numerous risk factors in circulating blood, either the direct result of environmental exposure such as cigarette smoking or the result of interactions of genes and environment such as hypercholesterolemia, have been identified and show significant efficacy in reducing the risk of CHD when modified. However, these risk factors only account for 50% of the variance among individuals in relation to CHD. Genetic differences in arterial wall susceptibility to atherosclerosis could account for the unexplained variance in CHD. Endothelial cells form the interior lining of arteries and play key roles in normal vessel function and atherogenesis. However, due to restricted access, the genetics of endothelial cell susceptibility to atherosclerosis has not been investigated in living human subjects. We propose to establish a baboon model, using the pedigreed and genetically characterized colony at the SFBR/SNPRC, for investigating the role of genetics in determining arterial wall susceptibility to atherosclerosis. As a pilot project, we seek to establish protocols for endothelial biopsy and functional profiling applicable to living baboons. We will further evaluate the feasibility of the techniques in a small number of baboons challenged by a high-fat, high-cholesterol diet. The proposed study has a high potential to evolve into a full-scale population genetic study including a full genome scan; through which identification of genes and their variants determining endothelial and arterial wall susceptibility to atherosclerosis will have novel implications to prevention of and intervention against CHD.

EARLY REARING INFLUENCES, STRESS AND SOCIAL FUNCTIONING IN JUVENILE BABOONS (0237)

NPRC UNIT: LABORATORY ANIMAL MED

%NPRC $: 0.240%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BRENT, LINDA Y	PHD	A		

AXIS I CODES: 1A, 15, 21 **AXIS II CODES:** 36, 60, 71, 72

ABSTRACT

The National Institute of Mental Health has a particular interest in research on the development of mental dysfunction during childhood, using both humans and animal models. The SNPRC pedigreed baboon colony provides the ideal opportunity to successfully move this research area into nonhuman primate models. This project will generate pilot data to support a proposal designed to assess the development of mental dysfunction and stress-related illness as a consequence of early environment in the baboon.

The project will take advantage of a uniquely well-characterized group of baboons that have been the subject of a study of determination of maternal behavior. This pilot study entails the collection of data on social functioning and response to stress in 120 juvenile baboons. The information will be used to measure the variability in behavior and stress reactivity among individuals and identify variables that warrant further study. The existence of detailed data on maternal behavior, maternal hormonal status, maternal response to stress and infant behavior for the subjects of this study while they are all kept in a nearly identical physical environment provides an exceptional opportunity to measure the relationship between early environment and outcome.

TELEMETRY OF BLOOD PRESSURE IN PREGNANT BABOONS (0296)

NPRC UNIT: LABORATORY ANIMAL MED

%NPRC $: 0.240%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
NATHANIELSZ, PETER W	MD, PHD	A		NEW YORK UNIVERSITY, NY USA
[name]	PHD	A		NEW YORK UNIVERSITY, NY USA

AXIS I CODES: 1A, 9, 13, 23 **AXIS II CODES:** 65, 71

ABSTRACT

A growing body of research supports the concept that the fetal environment contributes to health status in later life (also known as fetal programming). For example, there is compelling evidence that maternal under nutrition during pregnancy alters fetal and post-natal endocrine function, and in some species results in a hypertensive adult. Some investigators have suggested that prenatal exposure to glucocorticoids, given under threat of premature labor, increases mean arterial blood pressure in humans at 14 years of age. The present proposal utilizes the pregnant baboon to develop a set of normative maternal cardiovascular and uterine activity data throughout pregnancy, measured using telemetry. The purpose of the proposal is to obtain longitudinal data from unperturbed pregnancies that will form a core against which perturbed pregnancies can be compared.

The objective is to establish a telemetry system that will allow the monitoring of cardiovascular and myometrial function in the pregnant baboon. Blood pressure, ECG, uterine activity or body temperature and physical activity will be recorded.

Before pregnancy, we propose to surgically place telemetry implants that measure blood pressure from the femoral artery, ECG, uterine EMG or body temperature, and physical activity. Two 12 h periods of recording will be made twice per week before pregnancy, throughout pregnancy, labor and delivery, and into early lactation.

The pregnant baboon allows the controlled examination of primate pregnancy that studies of human pregnancy cannot provide. Ratio telemetry facilitates the collection of long term data in a manner that is unattainable via other techniques. Programming studies promise double benefit i.e., their results stand to improve both fetal and adult health. The establishment of this powerful combination of technology and a highly relevant human health question at the SFBR will form a platform on which to support currently funded projects and to build future funding applications. The data gathered allow specific determination of the maternal cardiovascular and myometrial responses that accompany pregnancy and labor and delivery, will contribute to studies investigating the mechanisms of programming of adult disease by a sub-optimal intrauterine environment.

PHYSIOLOGY OF THE PERIMENOPAUSE IN BABOONS (0238)

NPRC UNIT: PHYSIOLOGY & MEDICINE

%NPRC $: 0.240%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
HONORE, ERIKA K	PHD	A		
[illegible]	DVM, PHD	C	COMPARATIVE MEDICINE	SFBR, TX USA

AXIS I CODES: 1A, 15, 23 **AXIS II CODES:** 30, 77, 93

ABSTRACT

The proposed pilot study will provide hormonal and metabolic data on the physiological events occurring during the perimenopausal period in female baboons. This time period, the decade or so preceding menopause, is characterized by complex and dynamic changes in the neuroendocrine and reproductive systems. The sequence of events leading to menopause is controversial; it is unclear whether ovarian feedback or primary neuroendocrine alteration is the triggering mechanism. This study involves the collection of daily blood samples along with continuous monitoring of core temperature and physical activity for an entire menstrual cycle in 4 groups: young premenopausal females, old perimenopausal females, and old postmenopausal females. These preliminary data will provide novel information on endocrine and metabolic profiles of varying age and menstrual status, and will be the foundation for future mechanistic studies. The pathophysiology associated with menopause (heart disease, osteoporosis and others) has a major impact on public health in the U.S., affecting millions of women. It is now recognized that the perimenopause represents an important window for clinical intervention and implementation of preventive strategies. The NIH has called for proposals to study the biology of the menopause, with most of the focus on the perimenopausal years. Research into menopause has relied on ovariectomized primates as an animal model. This model does not adequately reflect the condition in women, nor does it permit mechanistic studies of the perimenopause. The baboon model of naturally-occurring menopause is currently being developed at the Southwest Regional Primate Research Center. Preliminary studies indicate that aging female baboons undergo a gradual transition into menopause with hormonal and physiological changes similar to those seen in women. The apparent existence of a perimnopausal period is a key advantage of this model, and enhances its potential utility for biomedical research. This study will utilize the tether system to collect daily blood samples from 16 female baboons. Samples will be assayed for selected steroids and gonadotropins, and novel assays will be developed to measure circulating concentrations of hypothalamic releasing factors that may be significant initiators of the menopausal process. Daily physical activity and core body temperature will be monitored in order to detect evidence of hot flashes, a common perimenopausal event.

REGULATORY RECEPTORS ON CD8+ CELLS DURING SHIV INFECTION (0298)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC $: 0.240% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
HODARA, VIDA	PHD	A		

AXIS I CODES: 1A, 7B **AXIS II CODES:** 31, 64, 66, 83

ABSTRACT

Four rhesus macaques, previously vaccinated with attenuated SIV, were challenged with SIVmac251. Immediate expansion of CTLs after infection was demonstrated by tetramer staining and IFN-γ ELISPOTs. Among the NK receptors, the presence of NKG2Cin NK cells was enhanced after one week of infection and again after three weeks, whereas no changes were seen for TRAIL or CD161.

NONHUMAN PRIMATE RESPONSE TO INTERFERON ALPHA (0304)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC $: 0.240%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LANFORD, ROBERT E	PHD	C	VIROLOGY AND IMMUNOLOGY	SFBR, TX USA

AXIS I CODES: 1A, 7B, 16D **AXIS II CODES:** 50B, 66

ABSTRACT

Worldwide, approximately 2% of the population is infected with HCV and 50-80% of those develop into persistent infections. Currently, the only approved therapy for treatment of chronic HCV infection is a 24-28 week course of the combination of pegylated IFNa2a or a2b and ribavirus with a response to treatment of 42% and 82% sustained viral clearance for genotypes 1 and 2/3, respectively. Even in persons not exhibiting sustained responses, IFNa treatment usually results in a rapid decline in HCV viral load; therefore, IFNa will, in all likelihood, continue to be used in treatment either in combination therapies or as an initial pretreatment to reduce viral load, despite the development of other antivirals. The mechanism of actions of IFN (or resistance to IFN) during antiviral therapy for HCV are not understood, yet an understanding of these mechanisms is critical for interpretation of future antiviral treatments for HCV, either in the context of IFNa therapy, or with second an third generation antivirals targeting specific aspects of the pathway. Furthermore, as chimpanzees are the only animal model for HCV studies at this time, pre-clinical trial treatments will be performed in HCV chronically infected chimps. An ability to reduce viral load in these animals is crucial to many aspects of these types of studies. As the animals do not respond to human IFN, these studies aim to clone and express the chimp (pt)IFNa2 gene to provide species-specific therapy in two chimpanzees (a naive animal to analyze the magnitude of the IFN response; and in an animal persistently infected with HCV to demonstrate a reduction in viral load). Liver gene expression studies will be performed using high density DNA microarrays with each treatment regime; and, real time RT-PCR analyses will be used to follow specific ISG expression and also viral load in the HCV infected animal.

MACAQUE IMMUNE RESPONSE TO HERPES B VIRUS (0218)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC $: 0.240%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MARTIN, DAVID W	PHD	A		

AXIS I CODES: 1A, 1D, 7B, 9 **AXIS II CODES:** 66, 77, 83, 91

ABSTRACT

Herpes B virus can cause life-threatening infections when the virus is passed from monkeys to humans. The majority of macaques in the United States are seropositive for herpes B virus. A macaque vaccine against herpes B virus would provide both virus-free animals for research and protect workers against potential fatal infection. An effective vaccine would both protect naive animals and be used as a therapy to reduce reactivation of latent infections in seropositive animals The objective of this product is to study the macaque immune response to herpes B virus. The results of these studies have many important applications. First, these studies will identify high priority targets for future vaccine development. Second, the macaque immune response to human herpes simplex viruses (HSV). Third, understanding the macaque immune response to herpesviruses will augment existing projects that examine HSV vectors as a vaccine delivery system in the simian immunodeficiency virus (SIV)/macaque model of disease. Fourth, the reagents developed in this study will further enhance herpes B virus neurovirulence in humans will help understand the biology of HSV infections in humans. In order to accomplish these important objectives, herpes B virus genes will be cloned and expressed. The ability of these proteins to elicit both humoral and cellular responses will be determined. The results of these studies will provide a clear picture of the macaque immune response to herpes B virus and will pave the way for the development of a macaque vaccine to eliminate the threat of human infection.

A GBV-B/HCV CHIMERA FOR THE EVALUATION OF HCV ANTIVIRAL COMPOUNDS (0306)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC S: 0.240%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
RINJBRAND, CORNELIUS	PHD	A		UNIVERSITY OF TEXAS MEDICAL BRANCH-GALVESTON, TX USA

AXIS I CODES: 1A, 7B, 16D **AXIS II CODES:** 50, 66

ABSTRACT

Approximately 1-2% of the world population is currently persistently infected with hepatitis C virus (HCV). In the USA alone there are more than 4 million infected people. HCV is spread primarily by exposure to contaminated blood or blood-derived products. A persistent infection with HCV will often result in significant liver injury, including cirrhosis, and can eventually lead to hepatocellular carcinoma. Currently only interferon and ribavirin are available to treat HCV infections. However, due to the severe side effects of interferon, many patients have to discontinue treatment. In addition, the efficacy of treatment is reduced by viral resistance associated with certain HCV genotypes. Although several new drugs are currently being developed against viral proteins and the internal ribosome entry site (IRES), there are no convenient small animal model systems availale in which it is possible to evaluate the efficacy of novel drugs. GB virus B (GBV-B) is the virus phylogenetically closest related to HCV. GBV-B replicates to high titers wihtin the liver of tamarins and marmoets and causes acute and on occasion chronic hepatitis. We have developed a GBV-B/HCV chimeric virus (GBV-V/111HC) in which the key domain III of the HCV 5'NTR has been substituted for the naive GBV-B sequence and provides the necessary translation and replication functions. This chimeric virus will be used to evaluate novel antivirals targeting this HCV domain III sequence. We will test the efficacy of selected phosphorodiamidate morpholino oligomers (PMOs) in a primary marmoset hepatocytes cultured and PMOs that show good efficacy in primary marmoset hepatocytes will be selected for further evaluation in GBV-B/111HC-infected marmosets. These studies will provide further support for the use of GBV-B infected marmosets as a model system for HCV infections.

GB VIRUS C INFECTION OF MACAQUES: AN HIV VACCINE MODEL (0305)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC $: 0.240% AIDS RELATED RESEARCH

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
THOMAS, DAVID L	MD	A		JOHNS HOPKINS UNIV, BALTIMORE, MD USA

AXIS I CODES: 17 AXIS II CODES:31; 91

ABSTRACT

The purpose of this study is to characterize GB virus C (GBV-C) infection in macaques toward the overriding goal of using GBV-C as a live viral vector for HIV vaccine development. Worldwide, an estimated 40 million people are infected with HIV, which has already killed more than 20 million persons, including 3 million in 2001 alone. Despite the enormous public health impact and investment of considerable biomedical resources, there is no vaccine available to prevent HIV infection. Most traditional vaccine strategies have failed and constructs based on live viral vectors (such as vacinia virus) or DNA vacines have not been fully developed because of concerns with safety or limited immunogenicity. We hypothesize that these impediments can be overcome by using GBV-C as a recombinant, live-virus vector. Initially, the study will confirm that macaques can be infected with GBV-C and characterize the natural history of infection. The tissue topism will be determined by examining the quantity of GBV-C RNA (plus strand) in bone marrow, lymph node, liver, plasma and PBMC, relative to input tissue, and be assessing the relative quantity of negative strand (replicantive) RNA. Animals with persistent GBV-C infection after one year will also undergo necropsy for additional investigation of topism and subclinical disease. It is anticipated that these data will form the basis for substantially expanded studies to investigate various GBV-C/HIV/SIV constructs in the macaque toward the goal of developing a vacccination that prevents AIDS.

DEVELOPMENT OF A XENOGRAFT MODEL TO TEST ANTI-SHIV ACTIVITY (0239)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC $: 0.240% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
ZHOU, PAUL	PHD	A		

AXIS I CODES: 1A, 1D, 7B **AXIS II CODES:** 31, 64, 66, 83

ABSTRACT

Previously, we demonstrated that a human CD4 T cell line transfected with a non-neutralizing human anti-HIV-1 gp41 single chain Fv antibody targeted into the endoplasmic reticulum (scFv-ER) or trans-Golgi network is resistant to HIV-1. More recently we developed a Moloney murine leukemia virus vector to transducer anti-HIV-1 gp41 scFv-ER and enhanced green fluorescent protein genes into rhesus macaque primary T cells. We demonstrated that a high efficiency gene transfer into rhesus macaque primary T cells could be achieved by using MuLV-10A1-pseudotyped recombinant viruses in combination with centrifugation at 320C and CH-296-coated plates. More importantly, we demonstrated that transducing anti-HIV-1 gp41 scFv-ER gene into rhesus macaque primary T cells markedly inhibits pathogenic simian/human immunodeficiency virus (SHIV) replication in vitro. In this proposal, we will develop a xenograft model to test in vivo efficacy of anti-SHIV activity of rhesus macaque hematopoietic progenitor cells (HPC) transduced with this anti-HIV-1 gp41 scFv-ER. First, we will determine and optimal ex vivo gene transfer protocol to transducer genes into rhesus macaque HPC. We will use a MMLV vector expressing EGFP to evaluate a number of ex vivo gene transfer protocols to transducer genes into rhesus HPC. Specifically, rhesus bone marrow aspirates will be CD34-enriched, prestimulated with a set of cytokines and transduced under three different conditions (320C centrifugation, CH-296-coated plates, or both). After the transduction, a small number of cells will be assayed by CFU-CEMM to determine regenerative capacity and gene marking of transduced rhesus HPC in vitro. The remaining cells will be transplanted into bnx mice (beige/nude/xid homozygous mice) to evaluate in vivo engraftment, gene marking and regenerative capacity of transduced rhesus HPC. Second, we will then test in vivo efficacy of anti-SHIV activity of rhesus HPC transduced with this anti-HIV-1 gp41 scFv-ER. After an optimal en vivo gene transfer protocol is defined, we will use this protocol to transducer EGFP and anti-HIV-1 gp41 scFv-ER into rhesus HPC. Transduced HPC will be transplanted into bnx mice. After the transplantation, mice will be challenged with pathogenic SHIV. At 2 weeks, 2, 4 and 6 months post challenge, 4 EGFP-reconstituted and another 4 anti-HIV-1 gp41 scFv-ER-reconstituted mice will be sacrificed. Blood, lymph node, spleen, thymus, intestine samples will be taken. SHIV replication and virus-induced pathology and the survival of rhesus CD4 and CD8 T cells will be monitored.

COLLABORATIVE SUBPROJECTS

FUNCTIONAL ANALYSIS OF GABAERGLC SEDATIVE/ANXIOLYTICS (0334)

NPRC UNIT: COMPARATIVE MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
ATOR, NANCY A.	PHD	A		JOHNS HOPKINS UNIVERSITY, MD USA

AXIS I CODES: 1A, 21 **AXIS II CODES:** 36, 87

ABSTRACT

Anxiolytics and sedative-hypnotics are among the most widely prescribed of all psychoactive medications. Misuse, abuse, and physiological dependence associated with their use are of continuing concern. Over the past 20 years, drug discrimination analysis has provided an animal model for classification of the subjective effects of psychoactive drugs relevant to preclinical drug abuse liability assessments. It also has proven uniquely sensitive and selective as a behavioral assay for examining functional in vivo relevance of novel chemical structures, novel receptor binding profiles, and novel cellular activity for centrally acting drugs. The aims of the present application are predicated on the evidence from our previous work that drug discrimination analysis is uniquely powerful for analyzing the relationship between the biochemical and behavioral effects of psychoactive drugs. Specific Aim 1 is to characterize the relation between in vitro profiles for GABAA modulators that bind the benzodiazepine (Bz) site and their in vivo profiles of discriminative stimulus effects. Advances in understanding the structure of the GABAA-receptor complex have led to development of novel compounds that preferentially bind GABAA receptor subtypes, have lower efficacy in modulating GABA, or both. The hope is that such compounds will be better treatments for anxiety and sleep disorders, produce less tolerance with chronic use, and have less abuse liability and dependence potential. The in vitro work on these compounds provides a platform for making predictions about specific behavioral effects, which we will test. Specific Aim 2 is to test predictions about the relation between chronic Bz administration and the effects of glutamatergic ligands administered during and after the chronic Bz. In vitro data and data from studies of convulsant thresholds in mice strongly suggest that the withdrawal syndrome that emerges after discontinuation of chronic Bz use may be due less to reduced GABAergic functioning as to overfunctioning of the ionotropic glutamatergic system. The proposed studies will exploit the sensitivity of drug discrimination training for neuronal substrates of drug action to explore the predictions of the glutamate hypothesis of the Bz withdrawal syndrome. These data will be critical to our understanding of mechanisms of Bz dependence and their relation to Bz tolerance. One of the studies under Specific Aim 2 will extend our work on physiological dependence on Bz ligands to provide a direct test of the use of non-competitive antagonists for the N-methyl-D-aspartate receptor to ameliorate Bz withdrawal.

The primate center provided baboons used in this project.

AMINE N-OXYGENATION BY FM03 AND FM04 (0332)

NPRC UNIT: COMPARATIVE MEDICINE

%NPRC S: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
CASHMAN, JOHN R.	PHD	A		HUMAN BIOMOLECULAR RESEARCH INSTITUTE, CA USA

AXIS I CODES: 1D, 21 AXIS II CODES:30, 46, 74C

ABSTRACT

Variation in neurotransmitter transporters, receptors and abnormal levels of neurotransmitters potentially are involved in neurological diseases including schizophrenia, bipolar affective disorder, autism, affective disorder, late onset Alzheimer's disease, Parkinson's disease and others. Fundamental information characterizing human neurotransmitter metabolism associated with neurodegenerative diseases could provide new approaches to understanding the pathology and developing new therapeutics. Our central hypothesis is that lack of detoxication of endogenous or xenobiotic amines underlies the pathological condition of some CNS diseases. The human flavin-containing monooxygenase (FMO) is one of the major human enzyme systems that contribute to the detoxication of endogenous, environmental and dietary nitrogen-containing substances. The overall goal of our work is to understand the details of FMO-mediated N-oxygenation of amines and hydroxylamines. Accumulation of hydroxylamines in the CNS may lead to cytotoxicity or apoptosis. To test this, fundamental information about human brain FMO N-oxygenation is required. The overall goal will be accomplished by addressing five Specific Aims including: Aim 1: cDNA-express the major forms of human brain FMO; Aim 2: Chemically synthesize amine metabolites of human brain FMO; Aim 3: Determine the kinetics and mechanism of human brain FMO amine N-oxygenation; Aim 4: Test the effects of human brain FMO amine metabolites on neuronal cell function including cytotoxicity and apoptosis, and Aim 5: Investigate the mechanism of amine metabolites on human neurotransmitter function. The significance is that fundamental biochemical information will result in new insight about the way endogenous and xenobiotic and dietary amines are metabolized in human brain. Such fundamental information will be useful in the development of safer drugs, the prevention of adverse drug reactions and the protection of humans from disease.

The primate center provided rhesus macaque tissues used in this project.

MECHANISMS OF NEOPLASTIC TRANSFORMATION IN HUMAN CELLS (0322)

NPRC UNIT: COMPARATIVE MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
COUNTER, CHRISTOPHER M.	PHD	A		DUKE UNIVERSITY, NC USA

AXIS I CODES: 1D **AXIS II CODES:** 76

ABSTRACT

Cancer is derived from the accumulation of mutations in genes that derail the normal growth regulatory mechanisms of cells. One of the most commonly mutated sets of genes are those belonging to ras family. These genes encode G-proteins that transfer growth-promoting signal from extracellular queues to the intracellular machinery. Mutations in these genes found in cancers leave the protein in a constitutively active state that results in the constant stimulation of three main classes of proteins, or effectors: Raf1, PI3-kinase and a group of proteins termed RalGEFs. Studies with murine cells categorically demonstrate that the most potent effector of ras in oncogenic transformation is Raf1. We recently developed the first system to test the effect of genetic changes in normal primary human cells on the processes of transformation in vitro and tumour growth in vivo. Using this novel system we tested whether mutations that leave ras capable of activating only one of the three effectors perturb the ability of oncogenic (12V) H-ras to transform human cells. We find that unlike the situation in murine cells, the mutation 37G, which leaves the RalGEFs pathway intact, was the only mutation that did not totally abolish the ability of H-ras12V to support the tumourigenic phenotype of anchorage-independent growth of human cells. RalGEFs had previously been envisioned to play only a small role in transformation. These results suggest that transformation as classically defined in NIH 3T3 murine cells is not representative of the transformation process in human cells. Dissecting the transformation process in human cells will be critical to the understanding of the process of oncogenesis. We propose to test whether the RalGEF pathway is essential while the Raf1 pathway is dispensable for transformation in vitro and tumourigenesis in vivo by: 1) Determine the role of RalGEFs in oncogenesis. 2) Determine what role the Raf1 pathway plays in oncogenesis. 3) Determine the role of effector proteins in tumourous growth of human cells in vivo. The accomplishment of the above aims will define a role for the RalGEF and Raf1 pathways in human cancer, which ultimately may help define proteins to targets for the treatment of human cancers.

The primate center provided baboons tissues used in this project.

FUNCITONAL GENOMICS AND TECHNOLOGY (0323)

NPRC UNIT: COMPARATIVE MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
DAVIS, RONALD W.	PHD	A		STANFORD UNIVERSITY, CA USA

AXIS I CODES: 1D, 9 **AXIS II CODES:** 59

ABSTRACT

The completion of the human genome project pushes us towards the next daunting task; namely that of translating sequence information into functional information. As in the case of the sequencing effort, this will necessitate innovative biological approaches combined with the development of new technologies. Approaches to functional genomics include whole genome deletion and mutation studies in model organisms as well as high-throughput mapping of complex traits in both human and model organisms through the use of polymorphism detection and resequencing. We propose to develop new functional genomics approaches to the study of Saccharomyces cerevisiae and human. Studies in S. cerevisiae employ a complete collection of bar coded yeast deletion strains for quantitative phenotypic analysis of fundamental cellular pathways as well for the identification of inhibitory compounds that act against every novel essential gene product. Other approaches to the elucidation of gene function and cellular pathways include mapping of complex traits using dense marker maps, the synthesis of every possible single base/amino acid mutation in any gene of choice, and the use of mass spectrometry to identify all small metabolites. We propose to extend these studies to human through genome-wide scanning for mutations and splicing defects. These ambitious goals will only be attainable through technological innovation in the areas of higher throughput sequence determination techniques (Pyrosequencing, HPLC, barcoded genotyping), low cost oligonucleotide and gene synthesis, and microarray automation and cost reduction. In addition, bioinfonnatics tools and databases that allow the integration of a large amounts of diverse data structures will need to be developed in order to maximize the deconvolution of vast amounts of biological data into biological function. All of these components will be tested in an implementation project to validate the technology and to enable its export from our laboratory.

The primate center provided rhesus macaque DNA used in this project.

TIGHT ADHERENCE GENES OF A PERIDONTAL PATHOGEN (0324)

NPRC UNIT: COMPARATIVE MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
FIGURSKI, DAVID H.	PHD	A		COLUMBIA UNIVERSITY, NY USA

AXIS I CODES: 1D, 7A, 22 **AXIS II CODES:** 58, 59, 66

ABSTRACT

The Gram-negative bacterium, Actinobacillus actinomycetemcomitans, is believed to be the etiologic agent for localized juvenile periodontitis (LJP), a particularly destructive disease in adolescents. The incidence of LJP varies among demographic groups and disproportionately burdens minorities and the poor. A. actinomycetemcomitans has been associated with a variety of other infections, notably brain abscesses, and it is a member of the clinically important HACEK group of bacteria implicated in infective endocarditis. A striking characteristic of fresh clinical isolates of A. actinomycetemcomitans is their ability to form extremely tenacious biofilms, a property thought to be critical for colonization of teeth and other surfaces. Molecular genetic studies in this laboratory have revealed that the genome of A. actinomycetemcomitans maintains a cluster of tad genes required for tight adherence to surfaces. The studies indicate that the tad genes are part of a locus of 14 genes encoding a novel secretion system for the assembly and release of long, bundled Flp fibrils and that the fibrils are required for tight nonspecific adherence to surfaces and bacterial autoaggregation. Remarkably similar tad-like loci were subsequently found in the genome sequences of a wide variety of Gram-negative and Gram-positive Bacteria, including many significant pathogens, and in Archaea. Given the clear requirement of the tad gene cluster for adherence of A. actinomycetemcomitans, the tad loci in other organisms are likely to be important for microbial colonization in a variety of environmental niches. Proposed here are molecular and genetic studies of the tad locus of A. actinomycetemcomitans. The objectives are the following: 1) to understand the mechanisms of expression and regulation of the genes of the tad locus; and 2) to determine the locations, interactions, and molecular functions of the gene products in secretion and fibril assembly. These studies are expected to lead to a basic understanding of a novel secretion system of bacteria and its role in the biogenesis of fibrils required for tight adherence and colonization by A. actinomycetemcomitans. Since of the widespread nature of the tad loci, these studies should also lead to new insights into colonization by other bacterial pathogens and may serve to identify new targets for development of antibiotics.

The primate center provided chimpanzee and baboon tissues used in this project.

PATHOPHYSIOLOGIC RESPONSE TO FETAL CARDIAC SURGERY (0335)

NPRC UNIT: COMPARATIVE MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
HANLEY, FRANK L.	MD	A		STANFORD UNIVERSITY, CA USA

AXIS I CODES: 1A, 13 AXIS II CODES:71, 86

ABSTRACT

The goal of this ongoing project is to continue the development of fetal cardiac surgery. Certain congenital defects are uncorrectable after birth and there is a clear advantage for intrauterine corrective surgery. This approach requires an understanding of the physiological effects of surgical intervention and extracorporeal circulation on the fetus. Our work in this area to date has allowed us to gain a substantial but incomplete understanding of these issues. The three major pathophysiological responses which limit fetal survival following intervention and extracorporeal circulation (which we identified in the original grant proposal) include: 1. The loss of fetal cardiovascular homeostasis in the pre-bypass phase of fetal intervention. 2. The "step function" rise in fetal vascular resistance at the institution of fetal bypass which is associated with acute decompensation. 3. The gradual rise in placental vascular resistance during and after fetal bypass which results in depressed placental blood flow. The specific focus of this project is to identify the mediators and detailed pathophysiologic mechanisms of these three responses with an eye towards clinical application of this information to advance the development of human fetal cardiac surgery. Each of the three responses will be systematically evaluated. Experiments examining the pre-bypass problem will focus on the role of the fetal stress response. Further understanding of this response is presently limited by our fetal animal model (sheep). We propose to study the efficacy of narcotic anesthesia in blunting the stress response in an instrumented primate model. Experiments addressing the 'step function' rise in fetal vascular resistances will examine the inhibition of this response using specifically designed bypass circuitry. Our methodology will include ultrasonic flow transducers to continuously measure instantaneous changes in organ flow in addition to our more specific microsphere techniques, which do not have this capability. In recognition of the multiple factors effecting the placental vasculature, experiments addressing the gradual rise in post bypass placental resistance will examine the role of placental vascular dysfunction in addition to the role of eicosanoids.

The primate center provided pregnant baboons of defined gestational age that were used in this project.

HERPES B VIRUS - A NATIONAL RESOURCE LABORATORY (0325)

NPRC UNIT: COMPARATIVE MEDICINE

%NPRC S: 0.100% AIDS RELATED RESEARCH

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
HILLIARD, JULIA K.	PHD	A		GEORGIA STATE UNIVERSITY, GA USA

AXIS I CODES: 1D; 7B AXIS II CODES:31, 66

ABSTRACT

The objective of this proposal is to continue to make available an established, continually growing resource for herpes B virus (Cercopithecine herpesvirus I), a national center for information access, rapid diagnostic assays, B virus-free colony monitoring, new isolate acquisition, drug efficacy testing, provision of standardized reagents and controls, and infection control monitoring in zoonotic outbreaks. The laboratory has over 10 years experience in assisting the Comparative Medicine community globally with respect to issues of identification and control of herpes B virus infections, having tested nearly 200,000 samples submitted to the resource and assisting clinicians and institutions in the management of five fatal zoonotic infections as well as 17 surviving cases. The specific aims essential to the continued operation of this national resource center include: 1) maintain a ready, trained diagnostic staff consisting of virologists and serologists that perform virological and serological testing for NIH AIDS animal model facilities as well as for occupational health services managing zoonotic exposures to herpes B virus on an emergency schedule; 2) isolate B virus from submitted materials collected from humans exposed as a result of injury or accidents while working with macaques or macaque cells or tissues; 3) identify B virus grown from submitted specimens using enhanced polymerase chain reaction (PCR) for multi-gene analysis along with restriction fragment polymorphisms for assessment of intra-strain variation, combined with phenotypic analysis by polypeptide analysis; 4) evaluate and standardize new, superior diagnostic technologies within the diagnostic arm of the laboratory as they are developed in the adjacent B virus research laboratory and other collaborating laboratories, e.g., enhanced antigen detection systems, rapid molecular analysis of novel strains, identification of drug resistant mutations, facilitation of easier testing for NIH's Regions Primate Research Centers and associated resources including Chinese and Indonesian macaques prior to and following importation; 5) disseminate updated information regarding B virus to veterinarians, investigators, and health care workers, including establishing network interactions that will educate as well as facilitate communication during emergency medical crises and meet the needs of colony managers of B virus negative animals. When emergencies strike, the resource will assist medical and scientific staffs together with the Centers for Disease Control and Prevention. The proposed diagnostic resource, as part of the ongoing B virus basic research laboratory, will facilitate prevention and control of future B virus outbreaks and fatalities in both human and non human primates.

The primate center provided cynomolgus macaque and baboon tissues for this project.

GLUCOCORTICOIDS AND CENTRAL FETAL VASOMOTOR CONTROL (0327)

NPRC UNIT: COMPARATIVE MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MCDONALD, THOMAS	PHD	A		NEW YORK UNIVERSITY, NY USA

AXIS I CODES: 1D, 15, 23 **AXIS II CODES:** 65, 71

ABSTRACT

Stereotaxic neurosurgical techniques and baroreflex challenges will be employed in the chronically-instrumented fetal sheep to surgically disconnect the PVN to evaluate the extent to which and the mechanisms by which the late gestation fetal sheep PVN: (1) modifies normal development of brainstem and sympathetic preganglionic neuron regulation of peripheral vascular tone; and (2) is a site for production of glucocorticoid-induced hypertension. The primate center provided baboons tissues that were used in this project.

MODULATION OF CHIMERISM FOR INTESTINAL TRANSPLANTATION (0338)

NPRC UNIT: COMPARATIVE MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MURASE, NORKO	MD	A		UNIVERSITY OF PITTSBURGH, PA USA

AXIS I CODES: 1A, 16 **AXIS II CODES:** 64, 88

ABSTRACT

Inbred rat and outbred canine models will be used to develop strategies that can elevate clinical intestinal and multivisceral transplant procedures from their present state of excessive morbidity and mortality to more safe and cost effective operations. The protocols are based on the discovery that passenger leukocytes of bone marrow in all organs migrate after transplantation and produce persistent chimerism, evidence suggests that this is essential for sustained survival of the grafts. However, intestinal passenger leukocytes have inferior tolerogenic qualities compared to bone marrow, and in addition have a lineage profile that predisposes to graft versus host disease (GVHD). This donor leukocyte population will be modified by irradiation of the intestinal and multivisceral organs at doses that are non-injurious to the epithelial/vascular components, with or without adjunct donor bone marrow. The end points will be quantity and quality of the post-transplant chimerism, weight, development, and survival of the recipients; clinical and histopathologic evidence of rejection and/or GVHD; and outcome after discontinuance of immunosuppression. Variables in the basic control and experimental groups will be: (a) the doses of irradiation and/or adjunct bone marrow, (b) recipient treatment with hematolymphopoietic growth factors, (c) alternative (to irradiation) methods of intestinal passenger leukocyte lineage depletion. The project calls for initial emphasis on inbred rat strain combinations in which rejection and GVHD can be delineated separately. These experiments are expected to elucidate more clearly the mechanisms of graft acceptance as these apply to all organs. Based on the results, work will proceed to the clinically more relevant outbred canine models.

The primate center provided baboons that were used in this project.

EFFECTS OF MODERATE MATERNAL UNDERNUTRITION ON FETAL DEVELOPMENT (0311)

NPRC UNIT: COMPARATIVE MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
NATHANIELSZ, PETER W	MD, PHD	A		NEW YORK UNIVERSITY, NY USA
name	MD	A		NEW YORK UNIVERSITY, NY USA

AXIS I CODES: 1 **AXIS II CODES:** 71

ABSTRACT

Several human epidemiological studies show that when pregnant women are under nourished at different periods of pregnancy, their offspring are susceptible to a higher incidence of major diseases such as diabetes, high blood pressure and obesity. This conditioning of lifetime health by the environment in the womb has been called fetal programming. Studies conducted in our laboratory and other laboratories throughout the world in non-primate species have shown that the maternal undernutrition alters the development of fetal organs such as the brain, lover, and pancreas. To date these studies have been carried out mostly in sheep and rats. The details of development of fetal sheep and fetal rats in the womb demonstrate both similarities and differences when compared to primates. It is necessary to carry out the experimental studies in a nonhuman primate species so that we can determine the extent to which nutrition compromises fetal development in primates.

We propose to study two groups of pregnant baboons. One group of animals will be allowed to eat the normal diet given to all members of our colony. This is the control group. A second group will be fed 70% of the food consumed by the first group for most of the first half of pregnancy. Food intake will be standardized by maternal body weight. It has been shown that the under nutrition has different effects on the fetus at different times of pregnancy. It is therefore logical that our first study will address effects of early under nutrition.

The objective of the study is to understand how the decreased availability of nutrients affects the development of key fetal organs such as the brain, heart and liver. Halfway through pregnancy, cesarean section will be performed on the mother. Tissues will be obtained from the fetus to study the changes produced by under nutrition at the molecular, cellular and mocroscopic levels.

COAGULATION PATHWAY IN ACUTE LUNG INJURY (0336)

NPRC UNIT: COMPARATIVE MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
PIANTODOSI, CLAUDE A.	MD	A		NATIONAL JEWISH MEDICAL AND RESEARCH CENTER, CO USA

AXIS I CODES: 1A, 24 **AXIS II CODES:**64

ABSTRACT

A critical pathophysiological feature of the acute respiratory distress syndrome (ARDS) is local activation of extrinsic coagulation and inhibition of fibrinolysis. These events promote deposition of fibrin in the lung as the injury evolves. Components of the extrinsic coagulation pathway, e.g. tissue factor, thrombin and fibrin, signal alterations in inflammatory cell traffic and increases in vascular permeability. Procoagulants and fibrin also promote other key events in the injury including complement activation, production of pro-inflammatory cytokines, inhibition of fibrinolysis and remodeling of the injured lung. To test the hypotheses that activation of extrinsic coagulation and disordered fibrin turnover in the lung are central to the pathogenesis of lung injury and impaired gas exchange in ARDS, it is proposed that specific blockade of the initiating steps of extrinsic coagulation with site-inactivated factor VIIa (FFR-FVIIa) or tissue factor pathway inhibitor (TFPI) will prevent acute lung injury and gas exchange impairment in experimental ARDS. It is also proposed that the two agents will have equivalent effects on blockade of extrinsic coagulation but FFR-FVIIa will have superior anti-inflammatory properties by inhibiting signaling by tissue factor-FVIIa complex. The hypotheses will be tested in non-human primates with acute lung injury from either sepsis or hyperoxia. The Specific Aims are: 1) To determine the key inflammatory mechanisms and the extent of protection from acute lung injury (ALI) effected by blockade of the extrinsic coagulation pathway in sepsis; 2) To determine the key inflammatory mechanisms and the extent of protection from ALI effected by blockade of the extrinsic coagulation pathway in hyperoxia; and 3) To determine the efficacy of inhibition of the extrinsic coagulation pathway when this treatment strategy is implemented after ARDS is established in baboons. The primate center provided baboons used in this project.

RECEPTORS FOR THE TRYPANOLYTIC FACTORS FROM HUMAN SERUM (0326)

NPRC UNIT: COMPARATIVE MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
RAPER, JAYNE	PHD	A		NEW YORK UNIVERSITY, NV USA

AXIS I CODES: 1D, 7C AXIS II CODES:64, 66

ABSTRACT

Our long-term objectives are to elucidate the difference between the host-parasite interactions of human infective and human non-infective trypanosomes of the T. brucei species, in order to understand the mechanism of resistance to lysis by human serum. T. b. brucei cannot infect humans because it is lysed by normal human serum, while T. b. rhodesiense is a human pathogen because it is resistant to lysis. We now know there are two discrete trypanosome lytic factors (TLFs) in human serum with distinct biochemical properties. We have directed our attention to the analysis of the putative receptors for the TLFs and the mechanism of lysis. Our specific aims are 1) elucidation of the mechanism of lysis by human serum in order to understand the mechanism by which T. b. rhodesiense is resistant to lysis, 2) to evaluate the fate of TLF1 and TLF2 following their interaction with serum-resistant and serum-sensitive trypanosomes, and 3) characterization and molecular cloning of the TLF1 and TLF2 receptors in trypanosomes. The hypotheses to be tested are as follows. 1) TLFs bind to a lipoprotein scavenger receptor that selectively acquires lipids to supply the trypanosome's needs. 2) Resistance to TLF is due to differential routing and processing of the internalized TLF particle within the resistant parasite. 3) TLF mediated lysis is initiated by membrane lesions that cause an osmotic imbalance and activation of a cytosolic protease. Since resistance to lysis by human serum appears to be the critical characteristic that allows trypanosomes to successfully infect humans, it follows that understanding the nature of TLF1 and TLF2 and the mechanism by which trypanosomes are either sensitive or resistant is central towards revealing possible avenues for therapeutic intervention. We have preliminary evidence that trypanosomes may use a lipoprotein scavenger receptor to fulfill their obligate need for lipid uptake. We have shown that this putative receptor, which can facilitate the uptake of HDL and LDL, appears to be responsible for uptake of TLFs. These findings provide the insight and reagents to purify and/or clone this scavenger receptor, which would be only the second receptor to be molecularly cloned from trypanosomes. In addition we have the first indication that TLF may be able to form an ion channel, or modify an existing channel, and thereby facilitate the flux of ions into trypanosomes to initiate lysis.

The primate center provided chimpanzee and baboon DNA and chimpanzee and baboon tissues for this project.

BIOLOGY OF PROTEOLYTIC DERIVATIVE OF LP(A) (0321)

NPRC UNIT: COMPARATIVE MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
SCANU, ANGELO M.	PHD	A		UNIVERSITY OF CHICAGO, IL USA

AXIS I CODES: 1D, 13 **AXIS II CODES:** 74F

ABSTRACT

The presence of immunoreactive fragments of apolipoprotein(a), apo(a), have been shown in the plasma, urine anc atheromas of human subjects. Moreover, derivatives of lipoprotein(a), Lp(a), and apo(a) can be generated in vitrc by the action of enzymes of the elastase and metalloproteinase (MMP) families. The goal of our proposed studies is to shed light on these products, in terms of their potential participation in the cardiovascular pathogenicity of Lp(a). In particular, we wish to test the hypothesis that enzymes of the MMP family shown in vitro to cleave Lp(a)in the hot spot of the linker region between kringle IV-4 and IV-5 of apo(a), generate at tissue sites, two main derivatives. One, miniLp(a), a particle that has as a protein moiety apoB 100 linked to P2, the C-terminal fragmen of apo(a) able to bind to members of the vascular matrix. The other, F1 representing the N- terminal domain of spo(a) containing the kringle IV-2 repeats and, lacking matrix binding function. A portion of F1 once releasec from apo(a) at tissue sites, would return to the plasma and then rapidly excreted into the urine. In turn, F2. either free or a member of a miniLp(a), would be preferentially retained at the sites of formation, preferentially in the sub endotheial intima where it undergoes atherogenic changes. This hypothesis will be tested by four related approaches: 1) structural, functional and immunological studies on the properties of apo(a) in order to define its various domains, and the basis for the cleavage specificities by MMPs; 2) on the premise that the linker 4 is the one most susceptible to MMP cleavage, express in vitro apo(a) species having linker 4 mutated to be resistant t MMP cleavage, and then compare the in vitro and in vivo properties of these mutants with those of their wild-type counterpart; 3) introduce via adenovirus technology in apoE mice and crosses between apoE-/- and human apoB100 transgenics in different stages of atherogenesis, either F1, P2, wild-type or linker 4-mutated apo(a) and assess the localization of these products in unaffected and lesion areas along with measurements of MMI activities; 4) study surgical segments of human carotid arteries with either stable or unstable plaques to determine using immunochemical and chemical methods, the comparative localization of apo(a) and fragments in these tw types of plaques and also determine whether the fragments resemble those generated in vitro from the digestion o Lp(a)/apo(a) with MMPs. The combined in vitro and in vivo studies are expected to improve our knowledge of the properties of the various domains of apo(a) and shed light on the potential role that MMP-mediated proteolysis may play in the atherogenicity of Lp(a)/apo(a) in the context of the general inflammatory theory of atherosclerosis. The primate center provided rhesus macaque tissues used in this project.

GENETIC AND EPIGENETIC STUDIES OF AGING (0328)

NPRC UNIT: COMPARATIVE MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
SMITH, JAMES R.	PHD	A		UNIVERSITY OF TEXAS HEALTH SCIENCES CENTER, SAN ANTONIO, TX USA

AXIS I CODES: 1D **AXIS II CODES:** 30, 58, 59

ABSTRACT

The long range goal of this program project is to understand the basic molecular mechanisms involved in human cellular senescence. The specific aims are to: 1) Bring together six individual laboratories using disparate model systems of cellular senescence: normal human fibroblasts, adrenocortical cells and melanocytes, various immortal human cell lines and animal models; to work together on similar goals, using common techniques and approaches to answer questions regarding the molecular and cellular mechanisms involved in senescence and immortalization. These studies will examine the changes in gene expression that occur in cells as they age in vitro and in vivo, and will establish the differences and similarities in the pathways that lead to inhibition of cell proliferation. Recognizing that aging is a multi-faceted process, the individual projects will explore various mechanisms of age related changes in gene expression, including DNA methylation, chromatic structure, senescence specific transactivating factors and RNA binding proteins and the relevance of in vitro to in vivo aging. 2) Provide core facilities that are requisite for all the projects and thereby consolidate resources that will benefit the research at a much lower cost. The aims of a program project will thereby be met, encouraging successful interactions and enhancing the utilization of common resources. 3) Provide a formal mechanism to promote research interactions via joint planning meetings.
The primate center provided rhesus macaque and baboon tissues used in this project.

GENE MODIFIED CLONED PIGS (0337)

NPRC UNIT: COMPARATIVE MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
STARZL, THOMAS	MD	A		UNIVERSITY OF PITTSBURGH, PA ,USA

AXIS I CODES: 1A **AXIS II CODES:** 59, 64, 88

ABSTRACT

The ultimate objective of this proposal is to relieve the organ shortage crisis by genetic alteration of pigs so porcine tissues and organs can be transplanted to humans (i.e. xenotransplantation) with results equivalent to those attainable with allografts under conventional immunosuppression. Progress toward this objective has been precluded by the innate immune reaction of higher primate recipients that targets the alphaGal epitopes that are expressed on the surface of pig but not human cells. Having characterized the full genomic organization and transcriptional regulation of the alphaGT gene in several lower mammals (including pigs) and in all of the higher mammals (including humans), we are collaborating with PPL Therapeutics in their efforts to generate for the first time recombinant pig cells that have double alpha1,3GT allele knockout (KO). These double KO cells can be used for somatic cell nuclear transfer (cloning) to produce cloned double KO fetuses and piglets. We intend to fully characterize the molecular alterations and phenotypic qualities of the recombinant fetal cells, as well as the cells, tissues, or organs of the anticipated full-term cloned piglets. In addition, the double KO fetal cells, and the cells, tissues, and organs of these piglets will be tested in transgenic mouse models that will allow prediction of the innate and adaptive immune responses generated by alphaGal-negative higher primate recipients (including humans) to the genetically altered porcine xenografts.

The primate center provided baboons used in this project.

MOLECULAR MECHANISMS OF CHROMOSOME CHOICE (0329)

NPRC UNIT: COMPARATIVE MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
STRAUSS, WILLIAM M.	PHD	A		UNIVERSITY OF COLORADO, CO USA

AXIS I CODES: 1D AXIS II CODES:39, 58

ABSTRACT

The goal of this project is to define the mechanism that determines Xist mRNA stability. Based on previous work by the investigator, the structure of the murine Xist gene has been revised to include new information on the 3' end of the gene. The investigator has shown that this area of the gene is significantly larger than previously reported. Sequence comparison between mouse and human revealed sequence similarity in the new 3' ends. Using both Northern analysis and RNAse protection experiments, the investigator has confirmed that both Xist mRNA isoforms are produced by a mechanism involving differential polyadenylation. These polyadenylation sites are located in the new 3' sequences identified. Additional expression studies have shown that Xist mRNA isoforms are developmentally regulated, and therefore show different stabilities. This pattern of expression suggests that regulatory elements may interact differentially with each mRNA isoform, which in turn may influences Xist expression early in development. The data suggest that Xist mRNA isoforms change independently of Tsix and that the developmental regulation of the Xist isoforms is influenced by mRNA stabilization during the period in which upregulation of the chosen X chromosome is observed. The specific mechanism responsible for Xist stability remains poorly characterized. Although early in development Xist is unstable, after development Xist is exceptionally stable (T1/2 = 5 hr). Recent data have placed in doubt the importance of the 5' end of Xist in this regulation. The investigator plans to explore the role of the new 3' end of Xist in gene stability. He also proposes to pursue the mechanism of developmental regulation of Xist stability from two directions. First, a complete a mutational analysis of Xist and the regions immediately adjacent to Xist will be done. Second, the investigator plans to evaluate genes in the methylation pathway and define their role in determining Xist mRNA stability.
The primate center provided baboon DNA used in this project.

REGION VI RCE - NONHUMAN PRIMATE CORE (0339)

NPRC UNIT: COMPARATIVE MEDICINE

%NPRC $: 0.960%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
WALKER, DAVID	MD	A		UNIVERSITY OF TEXAS MEDICAL BRANCH, GALVESTON, TX USA
[name]	PHD	C	DIRECTOR'S OFFICE	SNPRC, TX USA

AXIS I CODES: 1A, 7A, 7B **AXIS II CODES:** 50, 66

ABSTRACT

In response to NIAID's call for the creation of strong infrastructure and multifaceted research and development activities applying the best basic, translational, and clinical science to the generation of new diagnostic, therapeutic and vaccine countermeasures for Category A, B, and C pathogens posing threats as agents of bioterrorism, 22 institutions in Texas, New Mexico, Oklahoma, Arkansas, and Louisiana have combined their energy, creativity, and resources to propose creation of the Region VI Center of Excellence for Biodefense and Emerging Infectious Diseases (Region VI RCE). Nine scientific cores will provide access to state-of-the-art proteomics, genomics, standardized small animal and non-human primate models of infectious diseases, BSL-4 laboratory facilities, and GLP scale-up production, as well as crosscutting functions in computational biology and a streamlined process for translational development of vaccines and drugs leading to FDA approval. A consistently strong spirit of cooperation among traditionally competing institutions has established an interlocking network of projects, cores, and administration that will strengthen and flourish as the Center is implemented. The guidance of this network of interactive research projects and core resource facilities will be executed under a comprehensive administrative plan to contribute substantially to the nation's biodefense mission by fulfilling a carefully crafted scientific strategy on a common theme; Collaborations for host-pathogen biology based development of novel vaccines, diagnostics, and therapeutics against biothreat agents.

There is a clear consensus that nonhuman primates will be a necessary part of the development of therapeutics and vaccines for the NIAID Class A and Class B agents. For many of these agents, human trials will be very limited or impossible. In addition, appropriate animal BL3 facilities and personnel trained in the handling of primates under BL3 and perhaps BL4 conditions will be necessary in order to ensure efficient and timely transfer of advances in therapeutics and vaccines to the human population.

The NHP Core of the RCE will: 1. provide oversight and assistance in the acquisition of animals by investigators using nonhuman primates in this proposal and assure compliance with federal animal welfare and biosafety regulations; 2. provide for the routine veterinary care and husbandry for nonhuman primates assigned to projects contained within this program; 3. provide expertise and assistance in the design and implementation of experiments using nonhuman primates; 4. provide for clinical and pathology laboratory support for studies using nonhuman primates; 5. develop new and innovative nonhuman primate resources for use in testing therapeutics and vaccines.

IMAGING DOPAMINE/STEROTONIN MECHANISMS IN COCAINE CRAVING (0333)

NPRC UNIT: COMPARATIVE MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
WONG, DEAN F.	PHD	A		JOHNS HOPKINS UNIVERSITY, MD USA

AXIS I CODES: 1A, 21 **AXIS II CODES:** 36, 63E, 87

ABSTRACT

Craving has been implicated as a major contributor both to relapse and maintenance of addiction following abstinence in cocaine abusers. Although a mechanistic understanding of the biological basis of cocaine craving could identify therapeutic approaches to reduce cocaine dependence, information on the involvement of specific neurochemical systems in this phenomenon is scarce. Ongoing and previous studies in human volunteers have shown that environmental stimuli related to drug taking selectively increase cerebral glucose metabolism and perfusion in cortical and limbic areas of brain and that activation in the dorsolateral prefrontal cortex and amygdala is correlated with self-reports of craving. We propose to elucidate the role of dopaminergic and serotonergic systems in spontaneous and cue-elicited cocaine craving, in an integrated approach utilizing positron emission tomOgraphy (PET) scanning and selective radioligands for dopamine(DA) and serotonin (5-HT) receptors and transporters. Neurochemical markers, assayed by PET, will be related to self-reports of craving in cocaine abusers, and will be compared to measures in control subjects who have no significant history of illicit dmg abuse. Our premise is that, not only is there considerable evidence in the literature for the role of dopamine and serotonin in craving, but that the activated areas, previously seen in the amygdala and dorsal lateral prefrontal cortex can be examined further by examination of these neurotransmitter systems. We hypothesize that in our experimental paradigm following withdrawal, extracellular dopamine and to a lesser extent semtonin will be decreased. It is then predicted that both intrasynaptic DA (InsDA) and intrasynaptic 5HT (Ins5HT) will increase following the pharmacologic challenge and that cue-elicited craving will correlate significantly with this increase. It is predicted that spontaneous craving however, will correlate negatively with D1 D2 and 5HT 2a receptors. Finally, it is predicted that both when cue-elicited craving is induced during PET imaging, increased InsDA and 5HT will be measurable and will correlate significantly with the craving score. Testing of these hypotheses will provide novel and fundamental answers to craving mechanisms.

The primate center provided baboons used in this project.

CENTER FOR REPRODUCTIVE RESEARCH (0331)

NPRC UNIT: COMPARATIVE MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
WOODRUFF, TERESA K.	PHD	A		NORTHWESTERN UNIVERSITY, IL USA

AXIS I CODES: 1D, 15, 23 **AXIS II CODES:** 93

ABSTRACT

The Center for Reproductive Research at Northwestern University supports a multidisciplinary group of scientists who use innovative approaches toward an understanding of the mechanisms governing normal female fertility. The research focus of the Center will be to understand the structure-function relationships that exist between cells in the ovary and the hormones that regulate follicle maturation. The program is unique in its development of state-of-the-art biomaterials and advanced biophysical and structural approaches to achieve a more comprehensive understanding of ovarian function. The major hypothesis driving the proposed research is that normal follicle development depends upon the appropriate integration of signals derived from cell-cell contact and from the hormones and growth factors that are provided to the follicle structure in a cycle-dependent manner. Four projects will address this central hypothesis using innovative investigative strategies and a cohesive and highly effective partnership between basic biologists, structural biologists, chemical engineers, and clinical investigators. The projects that have been developed specifically for the Center include the derivation of an artificial three-dimensional environment in which individual oocyte-cumulus complexes can grow and to which endocrine factors can be applied; an investigation of the LH receptor and its role in follicular signal transduction pathways; an analysis of the interactions between ovarian co-activators, which are necessary for integrated gene activation and silencing; and the structural relationships between the follicle regulating hormones, inhibin and activin, and their signaling receptors. The rationale for creating such a Center is that elucidating the structure-function relationships between cells within the follicle and the hormones, receptors, and signaling molecules that control ovarian function will greatly advance our understanding of female reproductive physiology and thereby directly impact women's health.

The primate center provided baboon tissues used in this project.

THE USE OF PRIMATES FOR HUMAN XENOTRANSPLANTATION (0330)

NPRC UNIT: COMPARATIVE MEDICINE

%NPRC S: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
ZAHORSKY-REEVES, JOANNE L.	PHD	A		UNIVERSITY OF SOUTHERN CALIFORNIA, CA USA

AXIS I CODES: 1D **AXIS II CODES:** 64, 88

ABSTRACT

The long-term objective of this application is the prevention of the humoral rejection of porcine xenografts in patients. The objective of the current proposal is a detailed characterization of the xenoantibody response of an experimental model for human xenotransplantation, the cynomolgus monkey, and validation of this model as the basis for conducting clinically relevant experiments to prevent xenograft rejection in humans. In pursuit of this objective, our specific aims include determining the binding characteristics of IgM and IgG xenoantibodies in the cynomolgus monkey, and the sequences of the VH genes encoding them, both before and after transplantation of a vascularized porcine graft. Once this genetic information has been obtained, it will be used in the development and in vitro testing of an anti-idiotypic antibody against those xenoantibodies with the highest affinity to identified xenoantigens. This research should result in the full characterization of the xenoantibody response of an experimental model for human xenotransplantation and validation of this model as the basis for conducting clinically relevant experiments to prevent xenograft rejection in humans.

The primate center provided baboons tissues that were used in this project.

CHARACTERIZATION OF TYPE II DIABETES AND DIABETIC COMPLICATIONS IN BABOONS (0209)

NPRC UNIT: GENETICS GROUP

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
COMUZZIE, ANTHONY G	PHD	A		

AXIS I CODES: 1A, 13, 15, 16E AXIS II CODES: 49, 77

ABSTRACT

The goal of this study is to perform intensive observations of glucose metabolism and possible diabetic complications in a small number of female baboons. Seven study subjects were chosen. Three show normal fasting glucose and four animals show impaired glucose metabolism. All animals were placed on the tether system to allow serial blood draws and other measurements. The subjects show clear differences in their responses to intravenous glucose tolerance test (IVGTT), with some animals returning quickly to normal glucose levels after challenge, and other subjects exhibiting glucose intolerance and insulin resistance. Daily blood pressure and heart rate also show significant variation across the seven subjects. This research helps to establish that baboons exhibit variation in glucose metabolism similar to that seen in human populations, and that baboons can serve as a model organism for studies of diabetes, diabetic complications and related physiological phenomena.

PHYSICAL MAPPING OF A QTL REGULATING SODIUM-LITHIUM COUNTERTRANSPORT (0175)

NPRC UNIT: GENETICS GROUP

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
COX, LAURA A	PHD	A		

AXIS I CODES: 1A, 13 AXIS II CODES: 58, 74B, 77

ABSTRACT

We have identified a quantitative trait locus(QTL) on baboon chromosome5 regulating sodium-lithium countertransport activity, a hypertension-related trait. We have used microsatellite markers to fine map the region containing the QTL. To identify the gene encoding the QTL, we will use a chromosomal region expression array strategy which depends upon a physical map in the chromosomal region of interest. For this project we are constructing a physical map of the region of the baboon genome that contains the QTL regulating SLC. To construct the physical map, we have screened a baboon genome bacterial artificial chromosome (BAC) library to identify BAC clones in the region of interest. To date we have isolated 250 BAC clones and are aligning these BAC clones using DNA fingerprinting methods to construct a DNA contig of the chromosomal interval. We will use PCR with mapped microsatellite markers to anchor the contig with the baboon genome linkage map, ensuring that the contig maps to the QTL interval. The assembled DNA contig constructed in this study will be used as the foundation for assembly of a chromosomal region expression array to isolate the SLC-related gene.

MECHANISM AND INSTABILITY OF PERICENTROMERIC DUPLICATIONS (0282)

NPRC UNIT: GENETICS GROUP

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
EICHLER, EVAN	PHD	A		CASE WESTERN RESERVE UNIVERSITY, OH USA

AXIS I CODES: 1A **AXIS II CODES:** 39, 58, 59

ABSTRACT

Gene duplication followed by functional and structural specialization is one of the primary forces of evolutionary change. Despite its importance in genome expansion, speciation and the generation of evolutionary diversity, such processes have been implicated in predisposition to human genetic disease by creating regions of sequence similarity capable of undergoing illegitimate recombination. Interestingly, an unusual functional property of the human genome has emerged in which large genomic segments have been predisposed to duplicate to the pericentromeric regions of chromosomes. The available data indicate that this process has occurred relatively recently (1-15 mya); that it involves the inter/ intrachromosomal transposition of genomic segments ranging from approximately 5-50kb in length and that it has contributed to considerable variation in the genomic architecture of these regions among the higher primates. The investigators hypothesize that this mechanism is an ongoing evolutionary process which results in considerable genomic variability and provides the molecular context for instability associated with these regions. The aim of this proposal is to 1) investigate the molecular mechanism responsible for such pericentromeric duplications and 2) to assess the impact of this process in contributing to heteromorphism of normal human chromosomes and chromosomes associated with pericentromeric instability. To this end, the proposal will focus on the comparative analysis of 670 kb of pericentromeric sequence from human cytogenetic band interval 16p11.1 which appears to have been the target of multiple pericentromeric duplication events. Combining large-scale comparative sequencing and FISH (fluorescent in situ hybridization) methods with other molecular biology techniques, this proposal will specially define the "domains" of paralogy within this 670kb interval, identify the sequence junctions for both the "ancestral" and duplicated loci, reconstruct the phylogeny of each duplication and address the impact of these events on normal and disease variation. Due to the recent nature of this phenomenon and a reference human genomic sequence, the results of this analysis provide a unique opportunity to investigate the molecular mechanism underlying this form of human genome evolution. In addition, these results should provide the framework for understanding the peculiar genomic architecture of pericentromeric regions of chromosomes and the involvement of this structure in creating genetic diversity as well as a proclivity to genomic instability associated with genetic disease.

The primate center provided tissues used in this project.

COMPARATIVE GENOMIC ANALYSIS OF CARDIOVASCULAR GENE REGULATION (0285)

NPRC UNIT: GENETICS GROUP

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
KRAUSS, RONALD	MD	A		LAWRENCE BERKELEY NATIONAL LABORATORY, CA USA

AXIS I CODES: 1D, 13 **AXIS II CODES:** 58, 59

ABSTRACT

Disorders of the cardiovascular (CV) system are frequently due to temporal or quantitative changes in the expression of a large, but finite set of genes. Noncoding cis regulatory sequences play a central role in controlling gene expression and inter-species (i.e., human/mouse) genomic sequence comparisons serve as a rapid and accurate means for identifying such noncoding regulatory elements. The central goal of this PGA will be to use a comparative genomic approach first to identify, and them to determine the function of elements regulating the expression of genes affecting the CV system. The activities of this PGA are not centered on the discovery of new genes, but rather upon using comparative genomics to understand the role of cis regulating elements in the expression of genes already being studied by CV researchers. In this integrated program to "genomically" explore the regulation of CV genes, 200 human genomic intervals (=~200 BACs), each containing a CV gene(s), will be comparatively characterized. The components of this program will include: (1) The acquisition of orthologous human/mouse and other mammalian genomic sequence for a set of prioritized CV genes. Sequences will either be accessed from publicly funded databases or generated by the sequencing component of this PGA. (2) The creation of a cardiovascular comparative genomic database that will contain extensively annotated human and mouse sequences including the localization of conserved noncoding elements in proximity to well studied CV genes. (3) Genome-wide expression profiling to discover genes co-regulated with CV genes and identify shared noncoding regulatory elements, through intra-species analysis. (4) The identification of SNPs within conserved non- coding sequences, and analysis of their effect on CV gene expression in humans. (5) Analysis in genetically engineered mice of a prioritized set of the conserved noncoding elements for their role in CV gene expression. (6) The establishment of an educational program for cardiovascular researchers in the use of genomic databases and tools.
The primate center supplied tissues and DNA from the pedigreed baboon population for this project.

BABOON MODEL FOR THE GENETICS OF CHAGAS DISEASE (0176)

NPRC UNIT: GENETICS GROUP

%NPRC $: 2.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
WILLIAMS, JEFF T	PHD	A		

AXIS I CODES: 1A, 7C, 13 **AXIS II CODES:** 58, 66, 69, 77

ABSTRACT

Chagas disease is a zoonotic disease found throughout Central and South America The causative agent of Chagas disease is the protozoan parasite Trypanosoma cruzi, and is estimated to infect 16-18 million people. Chagas disease is the leading cause of heart disease in Latin America, with about 30-40% of those infected ultimately progressing to some degree of cardiac involvement. Currently there are no vaccines and no safe and effective drugs for prophylaxis or therapy. It is also estimated that at least 100,000 infected persons reside in the United States, raising public health concerns regarding the safety of blood and tissue banks. At SNPRC a large, pedigreed colony of baboons, many of which are naturally infected with T. cruzi, provides an ideal model system for investigating the genetics of susceptibility to infection with T. cruzi. The overall goal of this project is to develop the baboon as a primate model for studying the genetics of Chagas disease in humans. We will quantify the effect of environmental and genetic factors in determining seropositivity to T. cruzi in the pedigreed colony of baboons. We will also determine how genetic effects interact with aspects of the host environment such as shared sire environment, common cage environment and perhaps cage cohabitation history. We will perform a genome linkage scan to identify regions of the baboon genome that affect susceptibility to infection by T. cruzi as evidenced by seroconversion. Finally, we will use a novel method for joint linkage and linkage disequilibrium analysis to fine-map linkage regions and identify specific candidate genes that influence infection with T. cruzi. At this time, blood has been collected and processed from approximately 700 of the baboons maintained in large open corals. Serum from these samples is being typed for T. cruzi, using immunofluorescence and ELISA assays to determine the prevalence of Chagas disease in the corralled animals, and to determine if active transmission of the disease is occurring. DNA is being extracted from SNPRC pedigreed baboons for genotyping of additional markers in a region of human chromosomes 2 that may be involved in mounting a generalize response to infection. The development of this project was supported by the SNPRC pilot studies program.

REGULATION OF FETAL-PLACENTAL DEVELOPMENT IN THE PRIMATE (0295)

NPRC UNIT: LABORATORY ANIMAL MED

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
ALBRECHT, EUGENE D.	PHD	A		UNIVERSITY OF MARYLAND, MD USA
[name]	PHD	A		EASTER VIRGINIA MEDICAL SCHOOL, VA USA

AXIS I CODES: 1A, 23 AXIS II CODES: 60, 65, 71, 93

ABSTRACT

The high incidence of human neonatal morbidity and mortality associated with low birth weight and prematurity indicates need for more intensive study of the mechanisms underlying placental and fetal development. The long-term objective of this research proposal is to improve knowledge in this area by building on our previous in vivo studies in the pregnant baboon which demonstrate that estrogen plays an integrative role in placental-fetal communication by regulating maturation of the placenta and fetal adrenal gland. Study I will test the hypothesis that early in gestation estrogen-stimulates vascular endothelial growth/permeability factor and/or angiopoietin-1/-2 formation by villous trophoblasts and thus placental angiogenesis, and concurrently regulates expression of integrins-adhesion molecules by extravillous cytotrophoblasts to restrain their invasion of uterine spiral arteries, and that via these actions estrogen coordinates angiogenesis and placentation to ensure fetal-placental development. The goals of Studies I and II are interwoven to test the hypothesis that estrogen acts on the newly vascularized placenta to regulate expression of sodium-hydrogen exchangers (NHE-1 and -3) and their regulatory factors in the syncytiotrophoblast, directly (NHE-1), and indirectly by regulating the 11beta-hydroxysteroid dehydrogenase enzymes and thus local cortisol levels (NHE-3) to ensure placental-fetal homeostasis. Studies II and III are integrated to test the hypothesis that estrogen acts on the fetal adrenal to promote development of the transitional zone and restrain growth and development of the fetal zone, and that this in utero programming governs adrenal maturation and function in adulthood. Molecular, histological, biochemical, and in vivo physiological parameters of placental trophoblast and fetal adrenal development will be determined in baboons in which estrogen levels are prematurely elevated by estradiol administration or suppressed by a specific aromatase inhibitor. The estrogen-depleted/-repleted pregnant baboon provides a unique primate model to investigate the effects of altered trophoblast function on fetal-neonatal maturation, studies which cannot be performed in pregnant women or with in vitro approaches. Completion of the proposed study will provide new insight into communication between the fetus and placenta and improve our knowledge of the regulation of fetal development and neonatal self-sufficiency. The primate center provided baboons used in this project.

HEPATITIS C INFECTIVITY OF CHIMPANZEE PLASMA FROM PREVIOUS STUDY (0071)

NPRC UNIT: LABORATORY ANIMAL MED

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BRASKY, KATHLEEN M	MS, VMD	A		

AXIS I CODES: 1A, 7B **AXIS II CODES:** 64, 66, 77

ABSTRACT

The outcome of this study will have an important impact on the design of strategies to treat and/or prevent HCV-mediated disease since it will elucidate the relationship between HCV-specific T-cell responses (in the absence of HCV-specific antibodies) and the outcome of viral infection. One objective is to confirm that viral replication and proper packaging of virus occurred in an animal infected with a molecular clone of HCV-1. Another objective is to investigate cytotoxic T lymphocyte responses in the study animal and to investigate their role in viral clearance. Results will be proprietary. Future directions will depend on the commercial sponsor.

INDUCTION OF TOLERANCE IN BABOONS WITH AN ANTI-CD4 ANTIBODY I (0181)

NPRC UNIT: LABORATORY ANIMAL MED

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BRASKY, KATHLEEN M	MS, VMD	A		

AXIS I CODES: 1A **AXIS II CODES:** 64, 88

ABSTRACT

People and animals make immune responses to proteins that they recognize as foreign-a protein that is normally in their bodies. This is the reason that transplanted organs are rejected and why biologic therapies cannot be effective for a long period. Autoimmune diseases occur when a person makes an immune response to a protein that that is not foreign, but for some reason the immune system sees it as foreign. Tolerance induction would prevent an immune response to a specific targeted foreign protein while the immune system would still be able to respond to other foreign proteins. The goal of this study is to determine whether we can induce tolerance or acceptance to a foreign protein in baboons using a lower total dose of TRXI. In a previous study, we were able to induce tolerance to foreign horse proteins in baboons with 4 TRX1 treatments of 20 or 40 mg/kg doses given over 2 weeks. In this study, we would like to give 3 treatments of TRX1 at 20mg/kg within one week. Results will be proprietary. Future directions will be determined by the commercial sponsor.

INDUCTION OF TOLERANCE IN BABOONS WITH AN ANTI-CD4 ANTIBODY II (0182)

NPRC UNIT: LABORATORY ANIMAL MED

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BRASKY, KATHLEEN M	MS, VMD	A		

AXIS I CODES: 1A **AXIS II CODES:** 64, 88

ABSTRACT

The objective of the study is to determine if we can induce tolerance or acceptance to a foreign protein in baboons. People and animals make immune responses to proteins that they recognize as foreign –a protein that is not normally in their bodies. This is the reason that transplanted organs are rejected and why biologic therapies can not be effective for a long period. The ability to induce tolerance to foreign proteins would greatly benefit medicine because it could be an effective treatment for autoimmune diseases like rheumatoid arthritis and multiple sclerosis. It might also be an effective treatment for improving the survival of organ transplants. This study is in progress. Results will be proprietary. Future directions will be determined by the commercial sponsor.

EVALUATION OF EXPERIMENTAL HIV VACCINES IN RHESUS MACAQUES II (0186)

NPRC UNIT: LABORATORY ANIMAL MED

%NPRC $: 0.100% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BRASKY, KATHLEEN M	MS, VMD	A		

AXIS I CODES: 1A, 2 **AXIS II CODES:** 31, 64, 66, 91

ABSTRACT

To evaluate 4 different vaccines for HIV, that are expected to induce immune memory to the env antigen of HIV. Env is a prominent antigen and is the target of both neutralizing antibodies and cellular immunity. Their hope is to determine which of the vaccines induces the strongest immune responses. Immune responses will be measured using blood samples that will be taken periodically after each immunization. Over 20 million people have died from HIV/AIDS and another 36 million are infected. A vaccine that would prevent infection or at least help the body to fight off the virus and/or prevent the further spread of the virus is a major worldwide goal. Previous experimentation with these vaccine components have suggested that the vaccines in this protocol by themselves have good, but limited potency. The investigator has also shown that6 vaccine combinations similar to those that will be used here are significantly more potent that the individual components. From this study, the investigator expects to be able to find a potent combination of components that may be suitable for human testing. Results will be proprietary. Future directions will be determined by the commercial sponsor.

SAFETY OF HBV-ANTIBODY IN HEP B CARRIER CHIMPANZEES (0190)

NPRC UNIT: LABORATORY ANIMAL MED

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BRASKY, KATHLEEN M	MS, VMD	A		

AXIS I CODES: 1A, 7B, 16D **AXIS II CODES:** 50, 64, 66

ABSTRACT

The objective of the study is to determine the safety of multiple infusions of anti HbsAg human monoclonal antibodies in chronic HBV carrier chimpanzees. Parameters used to assess the health of the animals include clinical observations, physical examinations, body weights, serum chemistry, hematology, and urinalysis. Additional evaluations include Hepatitis B serum markers and measurement of viral (HBV) burden, anti-human Abs. The long-term goal of the program is to provide treatment for patients who are suffering from Hepatitis B. At this time, no adequate or curative treatment exists for Hepatitis B. It is the hope of the sponsor to develop a curative treatment for this disease. Results will be proprietary. Future directions will be determined by the commercial sponsor. The results from this study are expected to lead to human clinical trials.

DETERMINATION OF PROPHYLACTIC EFFICACY OF VARIOUS HEPATITS C VIRUS VACCINES (0199)

NPRC UNIT: LABORATORY ANIMAL MED

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BRASKY, KATHLEEN M	MS, VMD	A		

AXIS I CODES: 1A, 2, 7B, 16D **AXIS II CODES:** 64, 66, 91

ABSTRACT

There is an urgent medical need for a preventive HCV vaccine. HCV infection occurs commonly around the globe as a result of parenteral exposure to the virus. In developed countries, the most common risk factor is sharing of needles amongst iv drug users. Other "at-risk" groups include babies born to positive mothers, individuals with frequent and multiple heterosexual partners, health-care workers, individuals with an infected family member, and hemodialysis patients. In the USA, the CDC has estimated that there are roughly 30,000 new infections annually. In developing countries, the same risk factors are evident but in addition, non-sterile medical injection practices have contributed hugely and tragically to the current disease burden. Cultural practices involving parenteral exposure to the virus are also thought to play an important role in transmission in the developing world. Therefore, there is an urgent need for the development of a prophylactic vaccine. We intend to test efficacy against a delayed challenge with a heterologous HCV strain. Several candidate vaccines will be tested in groups of 5 chimpanzees for the elicitation of humoral and cellular immune responses to HCV. The demonstration of significant immunogenicity will then lead to challenge of vaccines with a heterologous 1a HCV strain. This study is in progress. Results will be proprietary. Future directions will be determined by the commercial sponsor.

DOSE ESCALATION STUDY FOR THE ANTIBODY MT102 (ANTI CPCAMXANTI-CD3) (0201)

NPRC UNIT: LABORATORY ANIMAL MED

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BRASKY, KATHLEEN M	MS, VMD	A		

AXIS I CODES: 1A, 2 **AXIS II CODES:** 50, 76

ABSTRACT

To determine the nature and severity the nature of possible side effects of MT 102 and the pharmacokinetics in the chimpanzee. MT102 is a compound especially created to treat patients with carcinomas. To make sure that the administration of this potential drug to humans does not have any unacceptable side effects and to minimize the risk for the patients, an animal study needs to be performed prior to the first treatment of patients. The chimpanzee is the only possible animal species for this kind of testing, since it is so closely related to humans. This study is in progress. Results will be proprietary. Future directions will be determined by the commercial sponsor.

IMMUNIZATION STUDY WITH MONOCLONAL ANTIBODY CNTO311 IN BABOONS (0204)

NPRC UNIT: LABORATORY ANIMAL MED

%NPRC S: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BRASKY, KATHLEEN M	MS, VMD	A		

AXIS I CODES: 1A, 2 AXIS II CODES:50, 64

ABSTRACT

The purpose of this study is to produce a sample of a primate antibodies specific to the experimental drug CNTO311. Humans are currently being treated with an experimental drug (CNTO311), but we need to better understand the interaction of the drug with the human immune system. One way in which we intend to do this is by testing for human antibodies against CNTO311. In order to develop such a test, we need a sample of primate antibodies. Exposure of any mammal to a foreign molecule can result in an antibody response, but every animals forms different sorts of antibodies. Human and non-human primates generally produce almost identical antibody specificities, so baboon antibodies make good models for the antibodies that might form in a human patient. Results will be proprietary. Future directions will be determined by the commercial sponsor.

STUDIES OF THE PHARMACOKINETICS OF A COMPOUND AFTER ORAL DOSING IN CHIMPANZEES (0252)

NPRC UNIT: LABORATORY ANIMAL MED

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BRASKY, KATHLEEN M	MS, VMD	A		

AXIS I CODES: 1A, 2, 16D **AXIS II CODES:** 50, 66

ABSTRACT

The study goals are to determine the pharmacokinetic parameters of compound #1(50mg/kg) after oral dosing in chimpanzees. The compound will be given via oral gavage as a suspension in 0.5% Tween. Blood (3ml) will be sampled from animals at 0.5., 1, 2, 4, 8, 12, 24 hours after dosing. Plasma is collected, frozen and shipped to Wyeth for analysis. The chimpanzees will be sedated for dosing up at the 1hr time point and given additional sedative doses for the subsequent sampling time points.

Data from the study will be used to estimate a target dose for a proposed efficacy study in HCV infected chimpanzees. From previous studies we expect Wyeth compound #1 to be highly bioavailable, but critical to further evaluation in chimpanzee will be its half-life and the time inhibitory levels of the compound are present. The study will provide the scientific basis to choose doses of compound # 1 for testing in the HCV chimpanzee model. Both the pharmacokinetics and the efficacy data from the chimpanzee model will assist in the design of the clinical testing of compound #1. Wyeth compound #1 is a small molecular inhibitor of Hepatitis C and has strong potential as a agent for the treatment of Hepatitis D disease .

EVALUATION OF EXPERIMENTAL HIV VACCINES IN RHESUS MACAQUES (0253)

NPRC UNIT: LABORATORY ANIMAL MED

%NPRC $: 0.100% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BRASKY, KATHLEEN M	MS, VMD	A		

AXIS I CODES: 1A, 7B **AXIS II CODES:** 31, 66, 91

ABSTRACT

We will evaluate 4 different vaccines for HIV that are expected to induce immune memory to the env antigen of HIV. Env is a prominent antigen and is the target of both neutralizing antibodies and cellular immunity. We hope to determine which of the vaccines induces the strongest immune responses. Immune responses will be measured using blood samples that will be taken periodically after each immunization.

Over 20 million people have died from HIV/AIDS and another 36 million are infected. A vaccine that would prevent infection or at least help the body to fight off the virus and/or prevent further spread of the virus is a major worldwide goal. Previous experimentation with these vaccine components have suggested that the vaccines in this protocol by themselves have good, but limited potency. We have also shown that vaccine combinations similar to those that will be used here are significantly more potent than the individual components. From this study we expect t be able to find a potent combination of components that may be suitable for human testing.

PHARMACOKINETICS AND IMMUNE RESPONSE STUDY WITH AN ANTI-CD3 MONOCLONAL ANTIBODY (0255)

NPRC UNIT: LABORATORY ANIMAL MED

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BRASKY, KATHLEEN M	MS, VMD	A		

AXIS I CODES: 1A **AXIS II CODES:** 50, 64

ABSTRACT

Monoclonal antibodies directed against the CD3 receptor of T lymphocytes (anti-CD3) have been shown to be effective immunosuppressive agents for use in clinical situations such as steroid-refractory allograft rejection following organ transplantation and diabetes. At the same time, administration of these monoclonal antibodies may be complicated by T-cell activation resulting in cytokine release syndrome (CRS). The purpose of this study is to investigate CNTO311, a genetically engineered anti-CD3 IgG monoclonal antibody, with regard to CRS. Favorable results will provide justification to develop CNTO311 for use in the clinical situations.

IMMUNOGENICITY OF HBSAG COMBINED WITH NEW POLYMIXIN FORMULATIONS (0256)

NPRC UNIT: LABORATORY ANIMAL MED

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BRASKY, KATHLEEN M	MS, VMD	A		

AXIS I CODES: 1A, 16D **AXIS II CODES:** 64, 66, 91

ABSTRACT

The objective of this experiment is to test the immunogenicity of new formulations consisting of yeast recombinant HBV antigen (HBsAg) combined to an immunostimulatory DNA sequence (1018 ISS, C295 or C296), and Polymixin B (PMX). HBsAg alone or HBsAg mixed with 1018 ISS (an immunostimulatory DNA sequence) will serve as controls. Injections are intramuscular (IM).

The experiment will help decide if mixing 1018 ISS, C295 or C296 with PMX formulation can further potentate the antibody response of baboons to HBsAg, and generate a T cell response in vitro to HBsAg compared to the formulations without PMX.

Historically, baboons have shown to be a good model for HBV vaccine. These studies will help decide of 1018 ISS, C295, or C296 formulated with Polymixin B can significantly increase the response of baboons to HBsAg, which will assist in the development of a new HBV vaccine for humans.

INDUCTION OF TOLERANCE IN BABOONS WITH HUMAN FACTOR VIII (0258)

NPRC UNIT: LABORATORY ANIMAL MED

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BRASKY, KATHLEEN M	MS, VMD	A		

AXIS I CODES: 1A, 17 **AXIS II CODES:** 50, 64

ABSTRACT

The goal of this study is to determine the pharmacokinetics and immunogenicity of human factor VIII in baboons so that we may do future studies with Factor VIII in baboons. We will determine the immunogenicity of Factor VIII by determining whether any of the animals that have been treated with Factor VIII have antibodies to human Factor VIII in their blood. The pharmacokinetics will be determined by measuring the blood levels of Factor VIII over time after a single dose is given to the animals.

Factor VIII is an approved drug used to treat hemophiliacs, people who lack or have defective Factor VIII (a protein) that impairs their ability to clot blood. These patients would have serious bleeding problems without treatment with Factor VIII. One of the major problems in the treatment of these patients is that they develop antibodies to the Factor VIII and this then makes treatment with Factor VIII ineffective. The latest estimate is that 30% of the patients treated with Factor VIII make inhibitors to Factor VIII.

The ability to prevent the immune response to Factor VIII in these patients would substantially improve the quality of their life. In other studies, we have been able to make baboons tolerant or non-responsive to foreign proteins by treating the animals with an antibody generated at TolerRx. It is our hope that we can use this antibody to induce tolerance to Factor VIII so that hemophiliacs will be able to continue their treatment with Factor VIII as needed.

EFFECTS OF IV ADMINISTERED AMG 108 IN CHIMPANZEES (0259)

NPRC UNIT: LABORATORY ANIMAL MED

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BRASKY, KATHLEEN M.	MS, VMD	A		

AXIS I CODES: 1A AXIS II CODES: 50, 64

ABSTRACT

This study will be testing a monoclonal antibody designed against the interleukin-1 receptor. Interleukin-1 is a key cytokine in inflammatory disorders and its inhibition has been demonstrated to provide therapeutic benefit for rheumatoid arthritis patients. As such KineretTM, a recombinant IL-1 receptor antagonist, it currently marketed for the treatment of rheumatoid arthritis. AMG 108 does not cross react with the IL-1 receptor of any rodent or lower primate species. In order for any meaningful safety studies to be carried out in animals, the animal species selected must retain biological activity against AMG 108. Only chimps and humans have demonstrated a biological response (binding to the IL-1 receptor) to AMG 108. The chimp, therefore, is the only primate species that may be used to evaluate the potential toxicity of AMG 108 prior to its introduction into humans. The effects of IL-1 inhibition through an antibody are largely unknown and data from this study will be useful in filling that knowledge gap as well as enabling the design of more appropriate clinical trials.

PHARMACOKINETIC PROFILE OF A SINGLE AMG 108 DOSE IN CHIMPANZEES (0260)

NPRC UNIT: LABORATORY ANIMAL MED

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BRASKY, KATHLEEN M	MS, VMD	A		

AXIS I CODES: 1A **AXIS II CODES:** 35, 50, 64

ABSTRACT

This study will be testing the pharmacokinetics of a monoclonal antibody designed against the interleukin-1 receptor. Interleukin-1 is a key cytokine in inflammatory disorders and its inhibition has been demonstrated to provide therapeutic benefit for rheumatoid arthritis patients. As such Kineret, an IL-1 receptor antagonist, is currently marketed for the treatment of rheumatoid arthritis. AMG 108 does not cross react with any rodent or lower primate species. In order for any meaningful safety studies to be carried out in animals, the animal species selected must retain biological activity against AMG 108. Only chimps and humans have demonstrated a biological response (binding to the IL-1 receptor) to AMG 108. The chimp as such, is the only primate species that may be sued to provide meaningful pharmacokinetic/pharmacodynamic (PK/PD) data for AMG 108 prior to its introduction into humans. Data from this study will enable a more appropriate clinical trial design.

IMMUNIZATION AND PRODUCTION OF PRIMATE ANTIBODIES IN CYNOMOLGUS MACAQUES (0261)

NPRC UNIT: LABORATORY ANIMAL MED

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BRASKY, KATHLEEN M	MS, VMD	A		

AXIS I CODES: 1A, 19 AXIS II CODES: 46, 50, 64

ABSTRACT

The purpose of this study is to generate primate monoclonal antibodies against human antigens that have been identified as potential therapeutic targets for treating cancer or autoimmune diseases. The animals will be injected with antigen at multiple sites near draining lymph nodes on a bi-weekly basis. Once adequate blood sera titers are established, a blood draw or lymph node removal will occur one week following the final immunization. Peripheral blood draw and a lymph node harvest will be performed in order to obtain B-lymphocytes that are secreting antibodies against our target antigen. From these B cells, monoclonal antibodies will be generated and genetically engineered to become drug candidates for the treatment of cancers and autoimmune diseases. The development of such antibodies has the potential to improve or extend the quality of life for patients suffering from these life threatening and debilitating diseases.

INFECTIVITY OF CULTURE FLUID FROM HCV RNA TRANSFECTED HUMAN LIVER CELLS (0262)

NPRC UNIT: LABORATORY ANIMAL MED

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BRASKY, KATHLEEN M	MS, VMD	A		

AXIS I CODES: 1A, 4, 16D **AXIS II CODES:**66

ABSTRACT

There is an urgent need for the prevention and treatment of HCV infection. HCV infection occurs commonly around the globe as a result of parenteral exposure to the virus. In developed countries, the most common risk factor is sharing of needles amongst iv drug users. Other "at-risk" groups include babies born to positive mothers, individuals with frequent and multiple heterosexual partners, health-care workers, individuals with an infected family member, and hemodialysis patients. In the USA, the CDC has estimated that there are roughly 30,000 new infections annually. In developing countries, the same risk factors are evident but in addition, non-sterile medical injection practices involving parenteral exposure to the virus are also thought to play an important role in transmission in the developing world. Therefore, there is an urgent need for the development of vaccines and therapies for this disease. The absence of an efficient culture system for hepatitis C virus has been an obstacle for HCV research. This study will help validate that a newly developed human liver cell culture is indeed producing infectious hepatitis C virus particles by determining if this material will infect a chimpanzee. Once validated by this chimp study, this cell culture system will accelerate research on the pathogenecity, prophylaxis and therapy of HCV infection.

PHARMACOKINETICS OF TRX1 MONOCLONAL ANTIBODY BY SINGLE IV INJECTION (0263)

NPRC UNIT: LABORATORY ANIMAL MED

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BRASKY, KATHLEEN M	MS, VMD	A		

AXIS I CODES: 1A AXIS II CODES: 35, 50, 64, 88

ABSTRACT

The purpose of this study is to evaluate how long TRX1 (a humanized monoclonal antibody) remains in the blood of a baboon after a single injection given by an intravenous infusion. TRX1 binds to the CD4 protein found on human white blood cells (lymphocytes) and is being evaluated as a potential treatment for autoimmune diseases (such as Multiple Sclerosis and Rheumatoid Arthritis), organ transplantation (kidney and skin), and also to prolong the effective use of currently available therapeutic agents (Factor VIII, enzyme replacement therapy). In these conditions, the human body is rejecting its own protein (causing tissue damage) or a given treatment (rendering it inactive). TRX1 is believed to prevent or delay this response and therefore may have an enormous benefit to patients with these diseases or medical needs.

In addition, to determine whether treatment with TRX causes a long term effect on the animals' immune system, the baboons will be treated with a rabies vaccine so that their immune response to the vaccine can be measured. The rabies antigen should be something that the animals have not been exposed to previously, so the immune system of all of the animals should make a strong response to the vaccine. Blood will be taken from the animals so that antibody titers to rabies can be measured.

BABOON LYMPH NODE CELL ACTIVATION BY OLIGONUCLEOTIDES IN VITRO (0264)

NPRC UNIT: LABORATORY ANIMAL MED

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BRASKY, KATHLEEN M	MS, VMD	A		

AXIS I CODES: 1A, 19 **AXIS II CODES:** 74G

ABSTRACT

This is a three-part study. The main objective of part one is to collect two lymph nodes and one skin biopsy from 6 baboons, and culture lymph node cells in vitro (for 6 hours) to test for background levels of gene products, using PCR analysis. The purpose of part two of this study is to determine if there is a correlate between the immune activity measured in vitro (Part 1) with in vivo activity in baboons following subcutaneous injection with 1018 ISS, 1018 ISS-PMXB, C274 and C792 formulations. For this part of the study 10 baboons will be added. The purpose of part three is to test the in vitro and in vivo responses of baboons to oligonucleotides. This experiment will determine if in vitro assays are possible for the detection of gene products of cellular activation after culture of cells with oligonucleotides/PMXB. The testing of these products has the potential to aid in the development of a treatment for asthma in humans.

BABOON MODEL FOR STUDY OF PRIMATE MATERNAL BEHAVIOR (0011)

NPRC UNIT: LABORATORY ANIMAL MED

%NPRC $: 1.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BRENT, LINDA Y	PHD	A		
[illegible]	PHD	A		UNIVERSITY OF NEBRASKA, NE USA
Nunez J	PHD	C	GENETICS	SFBR, TX USA

AXIS I CODES: 1A, 15, 23 **AXIS II CODES:** 36, 58, 60, 71, 77

ABSTRACT

Maternal behavior in primates is a complex process, involving a number of physiological and life history variables. This study is the first to include behavioral, life history, endocrine, and genetic data from a large number of nonhuman primate subjects in the determination of factors related to maternal behavior. The project will increase our knowledge of the heritable nature of variation in maternal behavior, will characterize mothers with poor maternal qualities, and will provide information useful for selecting females used in breeding programs. This project generates behavioral and hormonal profiles to be used in the development of the baboon as a model of maternal behavior by quantifying mother-infant interactions, determining infant outcome, and measuring hormone levels in a large sample of captive baboons. It will then examine the causes of variation in maternal behavior, including hormonal, experiential, and genetic factors. This project is ongoing and currently beginning Year 04 of the grant cycle. Data on maternal behavior have been collected on 145 subjects. Hormonal data, collected noninvasively through urine, have been obtained from 115 females. It is expected that the information resulting from this study will lead to new avenues of research on the mechanisms involved in the regulation of maternal behavior, as will as providing a model for related studies in reproductive endocrinology, colony management and behavioral research.

PERIODONTITIS AND PRETERM BIRTH: NONHUMAN PRIMATE MODEL (0288)

NPRC UNIT: LABORATORY ANIMAL MED

%NPRC $: 4.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
EBERSOLE, JEFFREY	DDS	A		UNIVERSITY OF KENTUCKY, KY USA
[name]	DMD, MPH	A		UNIVERSITY OF TEXAS HEALTH SCIENCES CENTER, SAN ANTONIO, TX USA

AXIS I CODES: 1A, 22, 23 **AXIS II CODES:**65, 66, 71

ABSTRACT

Current human epidemiologic reports indicate a positive association between preterm birth/low birth weight (PTB/LBW) neonates and periodontal disease prevalence in the mother. Sixty percent of infant mortality (not attributable to congenital/anatomical defects) is linked with PTB/LBW. It is the objective of this project to investigate potential mechanisms of the association between PTB/LBW and periodontitis in an in vivo model system. The baboon, Papio anubis, which has a 95 percent genetic homology to humans will be used to investigate. Aims testing hypotheses that: (1) the incidence and severity of periodontitis results in an increased incidence of PTB/LBW neonates; (2) the progression of periodontitis is characterized by an increase in pathogenic subgingival microbial species and systemic expression of plaque pathogenicity, which correlate with an increased incidence of PTB/LBW neonates; and (3) the progression of periodontitis is characterized by local and systemic inflammatory biomarkers, which correlate with an increased incidence of PTB/LBW neonates. 400 female baboons, housed at the Southwest Foundation for Biomedical Research (SFBR), a NIH Regional Primate Center, will be randomized into two groups. Following baseline sample collection (blood, crevicular fluid (GCF), subgingival plaque, clinical assessment) from all baboons, ligature will be placed (one maxillary/one mandibular quadrant; 6 molar teeth) in the experimental group (n=200). Both groups will then be introduced to males. Pregnancy will be confirmed and gestational age determined using ultrasound at approximately 3 months. Oral samples will be collected at this time point, followed by placement of ligatures on the contralateral maxillary and mandibular quadrants of the experimental group to extend the exposure variable (i.e., periodontitis). Animals will be sampled at approximately 30 days following the completion of the pregnancy and ligatures removed. In both experimental and control groups, dates of birth and post-natal weights will be obtained within 14 days of birth. Blood IGCF samples will be assayed for acute phase reactants and endotoxin activity. Sera will also be analyzed for IgG antibody to oral microorganisms. Differences in clinical and laboratory parameters will be assessed between outcome (PTB/LBW vs. normal neonates) and between groups (experimental vs. control). Results from this investigation will describe mechanisms of this linkage and contribute to the development of therapeutic and clinical intervention strategies.

PHARMACOKINETICS OF 114 ANTIBODY IN CHIMPANZEES AFTER RAPID IV ADMINISTRATION (0254)

NPRC UNIT: LABORATORY ANIMAL MED

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
FROST, PATRICE A III	DVM	A		

AXIS I CODES: 1A, 18 **AXIS II CODES:** 50, 64

ABSTRACT

114 antibody is being investigated for the treatment of patients with psoriasis. The proposed study is to investigate the safety, pharmacodynamics and pharmacokinetics of 114 antibody in chimpanzees following rapid intravenous administration (IV push). Three dose levels (0, 5, and 20 mg/kg) of 114 antibody per kilogram body weight will be investigated. Based on a previous chimpanzee IV infusion study with 114, the administration of 114 antibody via IV push is expected to be safe. The positive outcome of the study in chimpanzees will provide scientific evidence that 114 antibody can be safely administered to humans via IV push instead of the inconvenient IV infusion approach.

THERAPIES FOR PROGESTIN CONTRACEPTIVE INDUCED BLEEDING (0257)

NPRC UNIT: LABORATORY ANIMAL MED

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LOCKWOOD, CHARLES	MD	A		YALE UNIVERSITY, CT USA
[name]	MD	A		NEW YORK UNIVERSITY, NY USA

AXIS I CODES: 1A, 15, 23 AXIS II CODES:50

ABSTRACT

Long term, effective contraception can be achieved by the use of progestin (progesterone-type hormones) in either implantable or injectable form rather than oral. Many women prefer this method of contraception as it eliminates the daily need to think about birth control, it is a private method of contraception and is especially useful for nursing mothers as well as in areas where physician care is not immediately accessible (i.e., third world countries). Unfortunately, many women discontinue this otherwise efficient treatment due to its major side effect, unpredictable breakthrough bleeding from the lining of the uterus (called the endometrium). Although this endometrial bleeding is not dangerous, is not as heavy as a normal menstrual period, and generally stops occurring after a year of treatment, many women still opt to discontinue treatment. In order to study the mechanisms as well as potential therapies that would prevent this undesirable side effect of long term progestin-only contraceptives, a suitable animal model is essential. Ethical constraints preclude carrying out many of the necessary studies (such as repeated sampling) in women.

This study is intended to establish the baboon as a model to specifically study the bleeding that occurs following long term progestin-only contraception and develop therapies to prevent such bleeding. In addition, this animal model may prove to be a unique tool which can further our understanding of other causes of abnormal endometrial bleeding. In order to do this, we have developed techniques in the baboon similar to those performed to biopsy the human endometrium. These techniques are both cost effective and minimally invasive to the animal and will aid us in the study of the mechanisms and therapies which can ultimately limit the undesirable side effects of long term progestin only contraceptive in women.

FETAL NEUROENDOCRINOLOGY, PARTURITION AND THE MYOMETRIUM (0228)

NPRC UNIT: LABORATORY ANIMAL MED

%NPRC $: 1.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
NATHANIELSZ, PETER W	MD, PHD	A		NEW YORK UNIVERSITY, NY USA
C Name MD	MD	A		NEW YORK UNIVERSITY, NY USA
	PHD	A		NEW YORK UNIVERSITY, NY USA
Name J	MD	A		NEW YORK UNIVERSITY, NY USA

AXIS I CODES: 1A, 1D, 15, 23 AXIS II CODES:65, 71, 77

ABSTRACT

Prematurity and complications of late gestation and delivery are major obstetric problems with a profound effect on perinatal mortality and morbidity. Prematurity has a disproportionate effect on, and incidence in, minority women. Our proposed experiments will define similarities and differences between sheep and non-human primates.This program contains three integrated projects and three well established scientific cores that continue this laboratory's testing of hypotheses fundamental to understanding fetal neuroendocrine maturation and parturition. The hypotheses are related to fetal endocrinology, placental and fetal membranes and decidual and myometrial regulation. In parallel experiments the present proposal will continue to utilize chronically instrumented pregnant sheep and non-human primates and its unique in several aspects (particularly in focused efforts to correlate and compare work in ovine and non-human primate pregnancy). Project I continues work conducted in Years 1-10 with non-human primates to obtain a better understanding of the integrated function of fetal and maternal neuroendocrine systems and the myometrium. It tests the overall function of prostaglandin (PG) on fetal and maternal hypothalamo-pituitary-adrenal (HPA) placental feedback and feed-forward loops. We will also investigate the role of CRH on uterine blood flow, myometrial activity and neuroendocrine function.

The primate center has supplied timed-mated pregnant baboons for these studies. The baboons have been maintained at the primate center except when on study. It is anticipated that in the coming year that the in vivo, non-human primate aspects of this project will be conducted at the primate center.

GLUCOCORTICOID PROGRAMMING OF THE PITUITARY ADRENAL AXIS (0230)

NPRC UNIT: LABORATORY ANIMAL MED

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
NATHANIELSZ, PETER W	MD, PHD	A		NEW YORK UNIVERSITY, NY USA
C	MD	A		NEW YORK UNIVERSITY, NY USA
Name	PHD	A		NEW YORK UNIVERSITY, NY USA
3	MD	A		NEW YORK UNIVERSITY, NY USA

AXIS I CODES: 1A, 15, 23 **AXIS II CODES:** 65, 71, 77

ABSTRACT

It is customary in clinical practice to administer a course of glucocorticoids over 48 hours to pregnant women in premature labor to accelerate the lung maturation of the fetus so that if the baby is born early there will be less possibility of respiratory failure. However, there is now considerable concern that the current practice of giving multiple courses of glucocorticoids at weekly intervals has unwanted side effects on several systems other than the lungs.

We are particularly interested in the effects of fetal exposure to glucocorticoids on the developing fetal cardiovascular system and on hormone production. We have extensive information to show that the fetal exposure to glucocorticoids does predispose sheep to high blood pressure both as fetuses and adults. The time has come to use this background of knowledge to see if similar effects are observed in the baboon as much closer model to humans. If there are, then there will be more concern in relation to human fetuses. By studying the different endocrine glands involved in the secretion of adrenal hormones when the fetus is removed after euthanasia, we will be able to evaluate the mechanisms that underlie effects in the womb.

PATHOBIOLOGY & GENE TRANSFER IN CARDIOVASCULAR DISEASE (0082)

NPRC UNIT: PHYSIOLOGY & MEDICINE

%NPRC $: 1.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
CHAN, LAWRENCE	PHD	A		BAYLOR COL MED, TX USA
[redacted]	MD	A		BAYLOR COLLEGE OF MEDICINE, TX USA
[redacted]	PHD	A		

AXIS I CODES: 1A, 7B, 13, 17 **AXIS II CODES:** 55, 74F

ABSTRACT

Familial hypercholesterolemia is a heritable disease that is believed to be an excellent candidate for gene therapy. The genetic defect responsible for low density lipoprotein (LDL) receptor deficiency in our pedigreed familial hypercholesterolemic rhesus monkeys has been identified as a nonsense mutation in exon 6 of the LDL receptor gene. This defect in the LDL receptor gene results in the expression of a protein truncated at a position corresponding to amino acid 284 of the human LDL receptor. The defect has segregated with the phenotype of spontaneous hypercholesterolemia through three generations. This is the only primate model of familial hypercholesterolemia (FH), and proof of efficacy and safety of gene therapy in this model would be a major accomplishment toward human gene therapy for this disease.

The objective of the program project is to examine the effect of the hepatic transfer of rhesus LDL receptor and VLDL receptor genes to LDL receptor defective rhesus monkeys. The goal is to demonstrate that transgenes reduce plasma LDL levels, slow development of arterial lesions, and are safe during a 24-month period.

The helper-derived adenovirus/transgene complex (HD-Ad-LDL-R) provides good expression in mice for more than 6 months and we anticipated similar results in rhesus. HD-Ad holds great promise for gene therapy since the genes coding for viral proteins, the source of antigenicity, have been removed. Our first attempts to treat rhesus with HD-Ad-LDL-R resulted in good gene expression and reduction in cholesterol levels, but for only 2 weeks; less than 1% contamination of the preparation with helper virus induced an immune response that limited expression. Our current effort is focused on producing high grade vector with little or no helper virus contamination and establishing long term expression in the FH rhesus.

The results of this project will be sued to develop procedures for human clinical trials.

REGULATION OF THE DUCTUS ARTERIOSIS (0222)

NPRC UNIT: PHYSIOLOGY & MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
CLYMAN, RONALD I	MD	A		UNIV CA, SF, CA USA

AXIS I CODES: 1A, 13, 24 **AXIS II CODES:** 60, 65, 71

ABSTRACT

In the premature infant, the ductus arteriosus frequently remains open for many days or weeks after delivery. As many as 70% of newborns delivered prior to 28 weeks gestation will require some form of therapy to close their patient ductus. If left unclosed, a persistent patent ductus arteriosus is associated with significant morbidity: bronchopulmonary dysplasia (with its prolonged need for mechanical ventilation) and necrotizing enterocolitis. Numerous studies have shown that early closure of the ductus arteriosus decreases the severity of bronchopulmonary dysplasia and decreases the incidence of necrotizing enterocolitis. Although inhibitors of prostaglandin synthesis, like indomethacin, induce ductus closure in 85% of preterm infants in whom they are used, ductus reopening occurs in 20-30% of treated infants. Recent studies demonstrate that the postnatal development of ductus wall hypoxia is an essential step in the anatomic remodeling (luminal endothelial proliferation, migration, and smooth muscle cell death) that leads to permanent closure. The studies proposed in this application will examine the mechanisms involved in early, spontaneous ductus closure in the full-term newborn and those involved in the delayed closure of the premature baboon model of persistent patent ductus arteriosus, which is the only model that mimics the long-term events surrounding ductus patency in the preterm human. They will examine the hypothesis that vasoactive factors that alter ductus tone (e.g., prostaglandins, nitric oxide) also interact with an deregulate the growth factors and death factors involved in anatomic remodeling. They will examine mechanisms to increase ductus wall hypoxia in the preterm newborn. They will use immunohistochemical, Western, and Northern techniques to study changes in mRNA and protein expression; they will use assays of cell migration, proliferation, and cell death in isolated vessels, endothelial and smooth muscle cells in culture. They will characterize changes in receptor populations and test their findings in vivo. These studies should increase our understanding of what initiates and sustains the process of ductus closure after birth and why it does not occur in the preterm infant.

COLLABORATIVE PROGRAM IN BPD (0013)

NPRC UNIT: PHYSIOLOGY & MEDICINE

%NPRC S: 12.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
COALSON, JACQUELINE J	PHD	A		UNIV TX HEALTH SCIENCE CENTER SAN ANTONIO, TX USA
	DVM, PHD	C	COMPARATIVE MEDICINE	SFBR, TX USA
	MD	A		UNIV CA, SF, CA USA
	MD	A		NATIONAL JEWISH CENTER, CO USA
	MD	A		UNIV ROCHESTER, NY USA
	PHD	A		UNIV TX SW MED CENTER, DALLAS, TX USA
	PHD	A		BARNES-JEWISH HOSPITAL, MO USA
	MD	A		UNIV TX SW MED CENTER DALLAS, TX USA
	MD, PHD	A		BRIGHAM AND WOMEN'S HOSPITAL, MI USA
	MD	A		NATIONAL JEWISH MEDICAL AND RESEARCH CENTER, CO USA
	MD	A		UNIV TX HEALTH SCIENCE CENTER SAN ANTONIO, TX USA

AXIS I CODES: 1A, 24 **AXIS II CODES:** 60, 64, 65, 71

ABSTRACT

The baboon model of bronchopulmonary dysplasia (BPD) developed over the last 18 years at SFBR is unique. Baboons develop a disease that is very similar, if not identical, to the human disease of BPD, but in a controlled environment. In recent years, the widespread availability of surfactant-replacement therapy and increased clinical experience with very immature neonates have increased survival rates in newborns born prematurely at 28 weeks gestation with birth weights 1,000 grams. In those infants 1,000 grams, a high risk for chronic lung disease exist because 70-90% of these survivors develop chronic lung injury after receiving only minimal amounts of assisted ventilation. The syndrome that develops in these survivors is known as chronic lung disease of infancy.

The specific aims of the BPD Resource Core are 1) to produce and deliver cesarean section 100 timed baboon pregnancies per year of known gestational ages, 2) to maintain these premature baboons in a neonatal intensive care unit for up to 14 days, 3) to provide tissue specimens taken at the time of delivery, during the animal's clinical course, and tailored to each investigator's needs, 4) to provide a Data management Core for animal information retrieval. During this funding period, the BPD Resource has brought together 9 established investigators with various backgrounds and expertise who are examining the roles of several hormones, selected growth factors, and other modulators on lung maturation. Each is funded by a NIH R01 grant.

The results have been important contributions to understanding the effects of oxygen and hyperoxia on biological processes in premature lungs. The model for chronic lung disease of infancy has been well established.

The focus in the first 5 years of the project was to develop better understanding of BPD in the baboon model; the emphasis during the current 5 years is to focus on chronic lung disease of infancy, which involves lack of alveolar formation and fascularization of the premature lung.

TREATMENT OF BPD USING MIMETICS OF SUPEROXIDE DISMUTASE (0223)

NPRC UNIT: PHYSIOLOGY & MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
CRAPO, JAMES D	MD	A		NATIONAL JEWISH CENTER, CO USA

AXIS I CODES: 1A, 2, 24 **AXIS II CODES:** 50, 65, 71

ABSTRACT

High concentrations of oxygen and increased airway pressure are administered to most preterm neonates with respiratory distress syndrome. Among the survivors, 20 percent to 30 percent develop a form of chronic lung disease called bronchopulmonary dyplasia (BPD). Tissue damage caused by the superoxide anion (O2-) and other free oxygen radicals has been implicated in the pathogenesis of BPD. We have synthesized a class of novel, small Mn(III) porphyrin mimetics of superoxide dismutase (SOD) and catalase. These compounds have been shown to be effective in blocking injury in cell culture and whole animal models of oxidative stress. Preliminary results now suggest that these SOD mimetics will be efficacious in protecting against the oxidative stress component of BPD in premature infants. We propose designing, synthesizing, and characterizing Mn(III)-porphyrins with high SOD activity that can be delivered to critical targets located in the intracellular and extracellular spaces of the lung. The efficacy of the new SOD mimetics will be tested on BPD through use of the Bronchopulmonary Resource Center in San Antonio. Our specific goals in this proposal are to 1) determine the pharmacokinetic/toxicity profiles of our existing lead SOD mimetics; 2) design and develop new SOD mimetics; 3) screen new SOD mimetics in nonprimate models of oxidative injury; 4) test SOD mimetics in baboon BPD; and, 5) determine the mode of action of SOD mimetics in the BPD model. We expect these studies to provide new insights on the role of oxidative stress in BPD and to provide a novel new therapeutic approach to reduce the impact of this devastating disease in premature infants.

A NONHUMAN PRIMATE MODEL OF NATURAL MENOPAUSE (0240)

NPRC UNIT: PHYSIOLOGY & MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
HONORE, ERIKA K	PHD	A		

AXIS I CODES: 1A, 13, 23, 26 **AXIS II CODES:** 30, 63G, 63H, 77, 93

ABSTRACT

Studies will utilize a well characterized, pedigreed colony of more than 250 female baboons to establish a NHP model of naturally occurring perimenopause and menopause. Postmenopausal women are at increased risk for cardiovascular disease and osteoporosis, as well as other conditions. Hormone replacement therapy (HRT) effectively reduces the risk, but only a fraction of U.S. women receive HR Research into menopause and HRT has relied on surgically ovariectomized NHPs as models of menopause. This does not adequately reflect the condition in women, where ovarian function declines gradually over several years and the postmenopausal ovary continues to produce androgens. Pilot data from the SRPRC indicate that aging female baboons undergo a natural transition into menopause with hormonal and physiological changes similar to those seen in women. The specific aims of this proposal are 1) to characterize the perimenopausal period; 2) t determine the hormonal profiles of pre-, peri- and postmenopausal females; 3) to longtiudinally assess relevant physiological variables in these three cohorts. These aims will be achieved through menstrual cycle analysis, assays of annual blood sample of hormones and lipoproteins, ultrasound measurements of peripheral vascular reactivity, and radiographic measurements of bone density. Interventional studies of novel HRT regimens are proposed for years 4 and 5 with the goal of increasing national compliance with HRT by developing an acceptable alternative.

A COMPARISON OF OVARIAN HORMONE LEVELS IN BABOON URINE AND PLASMA (0271)

NPRC UNIT: PHYSIOLOGY & MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
KHAN, FIRYAL	MD	A		MOOREHOUSE SCHOOL OF MEDICINE, GA USA

AXIS I CODES: 1A, 15, 23 **AXIS II CODES:** 30, 74E, 93

ABSTRACT

Daily circulating serum reproductive hormones levels are useful for predicting the phase of the menstrual cycle in nonhuman primates and in older animals demonstrating cycle irregularities, such as persistent elevated Follicle Stimulating Hormone levels. Serum levels provide materials for assessment at a point in time while urine levels reflect average serum levels over the past few hours. For most primates, acquisition of daily blood samples requires either chemical immobilization or use of the tether system while urine samples can be collected with a metabolic pan and with minimal disturbance to the animal. The purpose of this project is to simultaneously collect urine and blood samples during the first 15 days of the menstrual cycle in normal cycling and pre and perimenopausal baboons and compare serum and urine values. This project will provide an opportunity to predict the value of using urine to assess reproductive hormone status.

VASCULAR ENDOTHELIAL GROWTH FACTOR IN EXPERIMENTAL BPD (0226)

NPRC UNIT: PHYSIOLOGY & MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MANISCALCO, WILLIAM M	MD	A		UNIV ROCHESTER, NY USA

AXIS I CODES: 1A, 1D, 13, 24 **AXIS II CODES:** 65, 71

ABSTRACT

Bronchopulmonary Dysplasia (BPD) is a common disease of premature infants who require oxygen and ventilator therapy. At times fatal BPD probably results from disordered healing if injury to developing lungs. Abnormal microvascular development is characteristic of BPD, leading to insufficient surface for gas exchange. The major goal of this proposal is to investigate expression of Vascular Endothelial Growth Factor (VEGF), a major angiogenic factor that is important for development of the microvasculature. The rationale for these studies, based on our preliminary data, are 1) that VEGF expression increases in lung development co-incident with expansion of the alveolar microvasculature, and 2) that hyperoxic injury to developing lung inhibits VEGF expression. Our overall hypothesis is that the development of experimental BPD in the baboon results in disruption of the normal gene program for VEGF expression. Abnormal VEGF expression may be central to the microvascular abnormalities found in BPD. The first Specific Aim investigates the cell-specific expression of VEGF in normal developing baboon lung, using Northern hybridization and in situ hybridization (ISH) combined with immunocytochemistry (ICC). These experiments will also examine the VEGF mRNA splice variants, protein isoforms and VEGF receptors. Using a model of BPD that develops in baboons delivered prematurely at 125 days gestation, the second Specific Aim investigates the hypothesis that VEGF/VEGF receptor expression is decreased when the animals develop BPD. These studies will also examine the VEGF splice variants and protein isoforms. Because extreme hyperoxia inhibits VEGF expression and alters the proportion of splice variants, the third Specific Aim will investigate these factors in a baboon model in which the animals are delivered at 140 days gestation and treated with 100 percent oxygen. VEGF is regulated by the HLF transcription factor, by cell differentiation and by cell proliferation. Using dual ISH and combined ISH/ICC, the fourth Specific Aim examines normal and BPD lungs for these characteristics in VEGF-expressing cells. Because VEGF is a survival factor for endothelial cells and protects them from oxidant injury, these data may lead to a novel therapy for the treatment of the microvascular abnormalities of BPD.

PEPTIDERGIC NEURONS OF THE PRIMATE RETINA (0173)

NPRC UNIT: PHYSIOLOGY & MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MARSHAK, DAVID	PHD	A		UNIVERSITY OF TEXAS MEDICAL SCHOOL, HOUSTON, TX USA

AXIS I CODES: 1A, 21, 25B **AXIS II CODES:** 42

ABSTRACT

One goal of this research is to describe the neural circuits that provide input to midget and parasol retinal ganglion cells, the neurons that give rise to two of the major parallel processing streams in the visual pathway of monkeys. Since the retinas of monkeys and humans are similar, the results would also be helpful for understanding human vision. We are studying the midget ganglion cells that project to the parvocellular layers and are thought to contribute to both spatial vision and red-green color vision. The working hypothesis is that interactions between two types of amacrine cells are essential to account for the surround responses of midget ganglion cells. We are also studying parasol ganglion cells that contribute to many aspects of perception, particularly to the perception of motion. The working hypothesis is that gap junctions are a common feature of this pathway. We are making realistic computer models of the neural circuits that provide input to the midget and parasol cells based on the anatomical results. The model of the circuit will be used to test a novel hypothesis to account for their cone-specific surrounds without any cone specific connections except those known to exist in the cells. The modeling studies will test the hypothesis that difference in the synaptic inputs to midget and parasol ganglion cells can account for physiological differences between these cells, specifically the higher sensitivity and more transient response to luminance contrast in parasol cells. The primate center provides tissues for this project.

REGULATORY MECHANISMS IN SURFACTANT SYNTHESIS (0227)

NPRC UNIT: PHYSIOLOGY & MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MENDELSON, CAROLE R	PHD	A		UNIV TX SW MED CENTER, DALLAS, TX USA

AXIS I CODES: 1A, 1D, 24 AXIS II CODES: 65, 71, 74E

ABSTRACT

To define mechanisms involved in type II cell-specific, developmental and hormonal regulation of surfactant synthesis in fetal lung we have focused on surfactant protein-A (SP-A), which is expressed in lung alveolar type II cells and is developmentally regulated in concert with surfactant phospholipid synthesis. We found that the fetal baboon serves as an excellent model for the human with regard to the surfactant protein-A (SP-A) genes and their regulation. Recently, we found that the transcription factor (TF) TTF-1 plays an essential role in camp induction of SP-A promoter activity . Camp treatment of type II cells increases TTF -1 phosphorylation, DNA -binding and transcriptional activity. Developmental and cAMP-induced changes in TTF-1 phosphorylation and DNA-binding may facilitate its interaction with others TFs and co-activators, resulting in an induction of SP-A promoter activity . To identify factors that interact with TTF-1, we will use a novel a yeast two-hybrid system. CDNAs of interest will be analyzed to study developmental regulation, cell-specific expression, as well as their ability to activate the SP-A promoter. We also have observed that the inductive effect of cAMP on SP-A gene expression is dependent upon a critical level of environmental O2. To define mechanisms for the permissive role of O2 on binding of fetal lung nuclear proteins to previously characterized response elements within the 5'-flanking region of the bSP-A gene. Changes in the levels of the O2-regulated TFs NF-kappaB, its inhibitory partner IkappaB, HIF-1 alpha and the related protein EPAS1/HLF in lung tissues of fetal baboons during development and after organ culture in 2 percents vs. 20 percent O2 will be analyzed. Previously, we found that lipogenic TFs C/EBPdelta, PPARgamma and SREBP-1 and -2 are expressed in type II cells and induced with type II cell differentiation. Expression, cellular/subcellular localization and DNA-binding activity of these TFs will be analyzed in baboon fetal lung during development and in association with changes in surfactant synthesis. We also have observed that postnatal ventilation of prematurely delivered baboons (125 days) resulted in a 4-fold increase in DSPC pool sizes to levels similar to those of term animals; postnatal Dex treatment stimulated increased mobilization of DSPC and SP-B into the airways without having an effect on total tissue pool sizes. The marked induction of surfactant phospholipid synthesis in the transition to air-breathing suggests that dramatic changes in O2 availability to the type II cell may play an important role in the induction of surfactant synthesis. Effects of ventilation and systemic treatment with Dex and Bt2cAMP on surfactant protein and phospholipid synthesis will be correlated with expression of the O2-regulated and lipogenic TFs. The studies outlined in this proposal should advance our understanding of basic mechanisms involved in developmental and hormonal regulation of type II cell differentiation and surfactant synthesis and facilitate development of therapies to accelerate lung development and surfactant production in prematurely born infants to avoid the deleterious effects of mechanical ventilation resulting in BPD.

LUNG ELASTIN IN BRONCHOPULMONARY DYSPLASIA (0231)

NPRC UNIT: PHYSIOLOGY & MEDICINE

%NPRC $: 1.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
PIERCE, RICHARD A	PHD	A		BARNES-JEWISH HOSPITAL, MO USA

AXIS I CODES: 1A, 1D, 24 **AXIS II CODES:** 65, 71

ABSTRACT

The focus of this proposal is to characterize mechanisms controlling elastin synthesis and turnover during the development of bronchopulmonary dysplasia (BPD) resulting from ventilation of the premature lung. Elastin confers the requisite property of elastic recoil to such lung structures as alveoli and alveolar ducts, bronchioles, and blood vessels, and thus is essential for lung function. We have previously demonstrated abnormal elastic fiber deposition in an experimental model of BPD, and others have demonstrated increased elastolytic activity in the BPD lung. Still, the root causes of elastic fiber abnormalities in BPD are not known. We hypothesize that mesenchymal cells of the premature lung respond to the strain of mechanical ventilation by increasing the expression and deposition of elastic extracellular matrix components out of proportion to what is required for alveolarization. Exposure to hyperoxia may result in the production and release of elastases such as neutrophil elastase or matrix metalloproteinases that damage elastic fibers, as well as cytokines or growth factors that alter extracellular matrix gene expression by lung fibroblasts. These events result in the excess deposition of disordered elastic fibers at sites of failed development of new alveolar walls. The accumulation of disorganized elastic fibers at these sites may limit the ability to recover from injury. To determine the causes of abnormal elastic fiber deposition during the development of BPD, we propose to study the expression of elastin, fibrillins1 and 2, and lysyl oxidase, all required for normal elastic fiber synthesis, and to characterize the elastases present in the injured lung. Our experimental approaches will include quantitative analysis of elastic fiber-related and elastase mRNA expression by RNAse protection assays, as well as localization of expression by in situ hybridization and immunohistochemical analyses. The molecular mechanisms regulating tropoelastin expression during normal baboon lung development and the development of BPD will be determined by assessing changes in tropoelastin gene transcription, steady-state mRNA levels, and protein synthesis, expression and activity of elastases in the BPD lung will be assessed by a combination of substrate zymography, immunohistochemistry, and in situ hybridization. Determining the effects of interventive treatments on the expression of elastic fiber-related genes and the elaboration of elastases will test the hypothesis that treatment which prevent BPD will also restore normal patterns of elastic fiber-related gene expression and elastic fiber deposition.

NEUROSCIENCE CENTER FOR INGESTIVE BEHAVIOR (0014)

NPRC UNIT: PHYSIOLOGY & MEDICINE

%NPRC $: 2.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
SHADE, ROBERT E	PHD	A	PHYSIOLOGY AND MEDICINE	SFBR, TX USA
	PHD	A		U MELBORNE, AUSTRALIA
	MD	A		HOWARD FLOREY INSTITUTE, AUSTRALIA
	MD	A		UNIV TX HEALTH SCIENCE CENTER SAN ANTONIO, TX USA
	PHD	A		HOWARD HUGHES MEDICAL INSTITUTE, NY USA
	MD, PHD	A		HOWARD FLOREY INSTITUTE, AUSTRALIA
	PHD	A		SALK INST, CA USA
	PHD	A		HOWARD FLOREY INSTITUTE, AUSTRALIA

names

AXIS I CODES: 1A, 21 **AXIS II CODES:** 36, 63E, 78

ABSTRACT

Ingestive behavior is a major factor in predisposing to a variety of diseases, but the neurohumoral mechanisms responsible for ingestive behavior are not well understood. An understanding of those mechanisms may lead to new strategies for controlling ingestive behaviors that are risk factors for specific diseases. This is a five component multi investigator program that involves several institutions. The objectives are to develop a better understanding of the following 1. Neurohumoral organization of ingestive behavior in a mouse model 2. Salt sensitivity of blood pressure in a chimpanzee model. 3. Appetite mechanisms in humans and in a baboon model. 4. Neurohumoral control of salt and water intake in a baboon model. 5. Brain receptor mechanisms in a baboon model. Projects 2 and 4 are conducted at the SNPRC. The preliminary results for Project 2 support the hypothesis that an increase in dietary salt causes a significant elevation of blood pressure within 9 months, and the effect is reversible when the animals are returned to a low salt diet. Preliminary results for Project 4 support the hypothesis that hormonal factors related to renal salt and water homeostasis are important in regulating salt intake behavior in primates. It is expected that the results will provide sufficient data to enable future research on the physiological mechanisms that control salt appetite and the underlying genetic factors that control these mechanisms.

BEHAVIOR AND BRAIN IMAGING IN BABOONS (0165)

NPRC UNIT: PHYSIOLOGY & MEDICINE

%NPRC $: 2.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
SHADE, ROBERT E	PHD	A	PHYSIOLOGY AND MEDICINE	SFBR, TX USA

AXIS I CODES: 1A **AXIS II CODES:** 63C, 74B, 74E

ABSTRACT

Very little is known in regard to the neurohumoral factors that regulate ingestive behaviors in primate species In earlier work, we showed that increased salt intake behavior produced by salt depletion in the baboon requires functional brain angiotensin mechanism. However, components of the hypothalamic pituitary adrenal axis that are potent stimuli for salt and water intake in mice, rats, rabbits and ungulates do not have any effect on ingestive bahaviors in baboons.

The objective of this study is to develop a baboon preparation that will permit administration of neurohumoral factors to brain structures so we can observe activation of brain centers using fMRI technology. The initial steps require development of a non-ferrous metal cannula, system for administration of hormonal and neurotransmitter agonists and antagonists into brain CSF while collecting fMRI images for brain activation observations. An intravenous anesthetic protocol has been developed that permits sedation of baboons for periods of up to 3 hours while collecting brain images. Using this procedure we have replicated in baboons a recent study we conducted in humans in which intravenous saline infusion was used to stimulate thirst while collecting PET images of brain activation. The areas of the baboon brain activated by hypertonic saline were identical to the brain centers activated in the human studies. We will explore several approaches for a non metallic cannula system for implanting in the baboon lateral brain ventricle. This system will enable the collection of PET images of brain activation responses to stimuli applied directly to the brain.

ANGIOTENSIN, SODIUM AND GENES IN PRIMATE HYPERTENSION (0289)

NPRC UNIT: PHYSIOLOGY & MEDICINE

%NPRC $: 4.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
SHADE, ROBERT E	PHD	A	PHYSIOLOGY AND MEDICINE	SFBR, TX USA

AXIS I CODES: 1A, 13, 27 **AXIS II CODES:** 58, 74B

ABSTRACT

Sodium-dependent hypertension has long been associated with a defect in renal function. Experimental models as well as human studies have also suggested that an alteration in genetic expression may contribute to the hypertensive process. Sodium-lithium countertransport (SLC) activity is one mechanism that helps maintain intracellular sodium concentrations, and in some hypertensive patients, SLC activity is increased. These individuals also experience an inappropriate response to sodium challenges that appears to result from a lack of suppression of the renin-angiotensin-aldosterone system (RAAS). The association between SLC activity and hypertension is genetically determined since it occurs in families. It is uncertain whether this reflects an alteration in the gene for SLC, one of the genes that may increase RAAS function, or an interaction between genes for the two systems. The goal of the proposed studies is to examine the relationship between SLC activity and the RAAS in a non-human primate model in which the SLC phenotype is high or low. The hypothesis to be tested is that a high SLC activity is associated with inappropriately high RAAS function and a greater arterial pressure sensitivity to dietary sodium. In three aims, the contributions of peripheral and central RAAS components to sodium-dependent hypertension will be studied in baboons with the high and low SLC phenotypes. In the first aim, regulation of the RAAS will be examined in high and low SLC animals during a step-wise increase in sodium intake. These experiments will determine whether animals with high SLC activity have a reduced ability to suppress the RAAS and develop salt-sensitive hypertension. The second aim will investigate the role of angiotensin and aldosterone in the stimulation of hypertension by sodium and their ability to cause blood pressure to rise in high and low SLC animals. This aim will determine whether by raising plasma angiotensin or aldosterone the high SLC animals are more likely to become hypertensive. The third aim will focus on central nervous system mechanisms associated with an inappropriately high RAAS in high and low SLC animals. These studies will determine whether the high SLC activity results in more sensitive central mechanisms driving the sympathetic nervous system to raise arterial pressure. These studies will help provide data to determine whether an inappropriately high RAAS activity can cause hypertension. Importantly, this work will also reveal whether the genetically determined phenotype of high SLC is important in predisposing an animal to sodium-dependent hypertension.

NITRIC OXIDE SYNTHASES IN LUNG DEVELOPMENT AND BRONCHOPULMONARY DYSPLASIA (0233)

NPRC UNIT: PHYSIOLOGY & MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
SHAUL, PHILIP W	MD	A		UNIV TX SW MED CENTER DALLAS, TX USA

AXIS I CODES: 1A, 1D, 24 **AXIS II CODES:**65, 71

ABSTRACT

The signaling molecule nitric oxide (NO) is critically involved in airway and vascular function in the developing lung. NO is produced by three isoforms of NO synthase (NOS), neuronal NOS (nNOS), endothelial NOS (eNOS), and inducible NOS (iNOS). Our preliminary work in normal baboon fetuses indicates that all three isoforms are expressed in airway epithelium, and that nNOS and eNOS are upregulated during late gestation to optimize No production in the perinatal period. Bronchopulmonary dysplasia (BPD) is an inflammatory condition which disrupts the development of the preterm human lung, and it is characterized by airway and pulmonary vascular dysfunction. Our initial studies in the baboon BPD model indicate that lung NO production and lung nNOS and eNOS expression are markedly attenuated during the genesis of BPD, and that NO replacement by inhalation (iNO) results in a sustained improvement in oxygenation index. The overall objective of this proposal is to investigate the role of alterations in NOS expression in the pathopysiology of BPD in the baboon model. The primary hypothesis is that pulmonary nNOS and eNOS expression are downregulated during the development of BPD, leading to diminished NO production and abnormal airway and vascular structure and function. The secondary hypothesis is that iNO reverses these abnormalities. Aim 1 is to define the normal ontogeny and changes in NOS protein and mRNA expression in early BPD, using approaches including laser capture microdissection to evaluate NOS mRNA levels in specific cell types harvested from frozen sections. Aim 2 is to determine the role of each NOS isoform in airway and vascular function in studies of NOS antagonism in intact animals. Aim 3 is to reveal the changes in exhaled NO levels with fetal development and BPD, as well as the contribution of each NOS isoform to exhaled NO. Aim 4 is to determine the effects of iNO on airway and vascular function, on the pulmonary course of early BPD, and on lung histology. Aim 5 is to determine the mechanisms underlying constitutive nNOS and eNOS gene expression in cultured in baboon airway epithelium, and the role of cytokines in their downregulation. The results obtained will increase our knowledge of the role of NO in normally successful postnatal pulmonary adaptation and in the pathophysiology of BPD, thereby possibly leading to novel therapies for this devastating disorder.

NEUROPEPTIDES IN LUNG DEVELOPMENT AND INJURY (0232)

NPRC UNIT: PHYSIOLOGY & MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
SUNDAY, MARY E	MD, PHD	A		BRIGHAM AND WOMEN'S HOSPITAL, MI USA

AXIS I CODES: 1A, 2, 24 **AXIS II CODES:** 50, 65, 71

ABSTRACT

Our overall hypothesis is that bombesin-like peptide (BLP) is an early mediator of lung injury in bronchopulmonary dysplasia (BPD). Increased numbers of pulmonary neuroendocrine cells (PNECs) containing BLP occur in human infants with BPD. Pulmonary BLP and BLP receptor mRNA levels normally peak during the canalicular period, declining to low levels during alveolarization. Excessive BLP in preterm infants could potentiate BPD, mediating peribrochiolar and interstitial fibrosis, reactive airways disease, and inhibiting alveolarization. We observe increased urine BLP levels approximately 48-72h after birth in 2 distinct baboon models of BPD, with BLP levels correlating with severity of subsequent chronic lung disease. Postnatal treatment with anti-BLP monoclonal antibody 2A11 protects against BPD in both models. We will address our overall hypothesis using three Aims. AIM 1: To determine the pharmacological mechanisms and clinical usefulness of 2A11 for preventing acute and chronic lung disease in preterm baboons in vivo. Hypothesis number 1: 2A11 functions by blocking pro-inflammatory effects of BLP during early BPD. We will also evaluate a BLP receptor antagonist. AIM 2: To analyze cellular and pharmacological mechanisms of BLP and 2A11 effects using simplified in vitro alveolarization systems. Hypotheses number 2: (a) Abnormally elevated BLP during the early saccular period inhibits alveolarization. (b) Key target cells for BLP during this process are mesenchymal cells, which alter production of mediators to become anti-angiogenic. We will characterize fibroblast-derived mRNAs included by BLP that are able to midulate alveolarization. AIM 3: To explore the role of BLP and/or PNECs as mediators of other BPD-associated changes, in collaboration with other U10 investigators. Hypothesis number 3: BLP is induced by oxidant injury and acts as proximal cytokine, promoting acute and chronic inflammation with interstitial fibrosis. Effective anti-oxidant therapy should decrease BLP secretion, leading to improved clinical outcomes. Combined modality treatment with anti-oxidants together with 2A11 will be considered as resources permit. These approaches will be instrumental in clarifying the underlying pathophysiology of BPD. The proposed investigations will facilitate rational improvement in therapeutics based on comprehensive understanding of disease mechanisms.

CHARACTERIZATION OF EPILEPSY IN THE PEDIGREED BABOONS (0268)

NPRC UNIT: PHYSIOLOGY & MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
SZABO, AKOS	MD	A		UNIVERSITY OF TEXAS HEALTH SCIENCES CENTER, SAN ANTONIO, TX USA

AXIS I CODES: 1A, 21 **AXIS II CODES:** 58, 77

ABSTRACT

In humans and animals, there are many different classifications of epilepsy. The classification of seizures and epilepsy requires a detailed clinical history and correlation with interictal (between seizure) electroencephalography (EEG). In animals, to further characterize the seizure types, a careful observation of the seizures and the frequency is required. Spontaneous seizures have been reported in the pedigreed baboons at SFBR for over 15 years. The seizures have occurred in the absence of any overt neuropathologic, toxic or metabolic abnormalities, but the seizure types and frequency have not been well characterized. The seizures occur too infrequently to warrant continuous observation or monitoring. Different types of epilepsy, however, have distinctive EEG patterns. The information from these EEGs can be obtained and studied in an awake epileptic individual that is not having clinical seizure activity during the exam. Also intermittent light stimulation (photostimulation) can, in predisposed animals, induce clinical manifestations of epilepsy, seizures. A preliminary survey of the epileptic baboons using a combination of photostimulation and EEG recordings to characterize the type of epilepsy has demonstrated 3 distinct epileptic types. We will characterize additional epileptic baboons and their relatives. These animals represent a unique animal model for inherited epilepsy. From a clinical and genetic standpoint they will be useful to study epilepsy in humans and to test new drugs used to treat epilepsy.

ACCOMODATION AND THE DEVELOPMENT OF REFRACTIVE STATE (0287)

NPRC UNIT: PHYSIOLOGY & MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
TROILO, DAVID	OD	A		NEW ENGLAND COLLEGE OF OPTOMETRY, MA USA

AXIS I CODES: 1D, 25B **AXIS II CODES:** 60

ABSTRACT

Myopia (nearsightedness) is on the rise around the world and in the United States. It affects tens of millions of Americans and, in progressive forms, is a leading cause of blindness. Earlier research with humans and experimental animal models has made it clear that the postnatal development of the eye and refractive state involves a combination of genetic and visual factors. The rise in incidence of human myopia has been associated with increases in literacy and levels of education, although the nature of the relationship is unclear. Research using animal models has established that visual stimuli related to retinal defocus regulate eye growth and refractive state. The studies described in this proposal use various visual manipulations to explore the temporal integration of visual stimuli that affect eye growth and the biochemical mechanisms that may underlie these changes. The following questions are asked: (1) How does the eye temporally integrate different visual stimuli for the regulation of eye growth? To answer this, the investigators will contrast the effects of different states of defocus or deprivation with corrected or clear vision and examine the stimulus durations necessary to elicit different ocular growth responses. (2) Do ocular circadian rhythms in IOP, axial length and choroid thickness play a role in the regulation of ocular growth? Specifically, the investigators will examine the phase relationships between these different rhythms during induced changes in ocular growth rate. (3) How do the temporal pattern and accuracy of accommodation affect the degree of blur experienced during near work tasks and when viewing through negative power spectacle lenses? These measures of accommodative behavior will then be correlated with the degree of experimental myopia induced. (4) What are the changes in scleral extracellular matrix during experimentally induced changes in ocular growth, and how are they controlled? Using ocular tissues from the other experiments, the investigators will quantify changes in scleral extracellular components and correlate them with visually induced increases and decreases in ocular growth rate. In addition, the possibility that retinoic acid synthesis by the choroids/RPE plays a role in the signal cascade from retina to sclera will be explored. This project will bring together several lines of investigation to help answer important questions relating to how myopia develops in response to altered visual experience. These studies will provide new information for understanding the association of near work, such as reading, and the development of myopia in humans.

The primate center supplied marmoset embryonic and fetal tissue for this project.

CRITICAL TARGETS IN HYPEROXIC MITOCHONDRIAL INJURY (0241)

NPRC UNIT: PHYSIOLOGY & MEDICINE

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
WHITE, CARL	MD	A		NATIONAL JEWISH MEDICAL AND RESEARCH CENTER, CO USA

AXIS I CODES: 1A, 1D, 24 **AXIS II CODES:** 65, 71, 74C

ABSTRACT

Bronchopulmonary dysplasia (BPD) is a common, disabling and sometimes fatal chronic lung disease. It frequently accompanies premature birth and treatment of respiratory distress with artificial ventilation and high concentrations of inspired oxygen (hyperoxia). The biochemical basis of BPD is not well understood. In the baboon, exposure to hyperoxia is required treatment in both the ultra-premature (125 d) and premature (140) model of BPD. Hyperoxia damages mitochondria results in loss of aconitase activity, decreased mitochondrial and cell respiration, and loss of ATP. On that basis, this proposal's principal hypothesis is that adaptation to hyperoxic stress requires up-regulation of glycolytic, and/or glutaminolytic, enzymes. Because hexokinase rate- limits glycolysis in lung, it is hypothesized that expression of lung hexokinase(s) is up-regulated. Replacement of deficient mitochondrial anti-oxidants may alleviate early respiratory distress and resulting BPD and decrease up regulation of glycolytic enzymes. These hypotheses will be tested in these AIMS; 1) Determine differential expression of mRNA's encoding components of the mitochondrial porin complex-hexokinases (HKs), porins, and adenine nucleotide translocators (ANT), these same proteins, and relevant glycolytic and glutaminolytic enzymes; 2) Define early status of critical anti-oxidants (glutathione [GSH], thioredoxin [TRX], superoxide dismutases]), their precursors (S-adenosylmethionine), and oxidant target (aconitase) markers, and (3) Define the efficacy of early, continuous infusion of S-adenosylmethionine (AdoMet), a precursor of cellular and mitochondrial glutathione (GSH), on these markers and pulmonary histopathology of BPD. Hexokinase binding to, or release from, mitochondria will be quantitied using immunogold electron microscopy. Activities of HK, phosphofructokinase, and additional critical glycolytic and glutaminolytic enzymes also will be assayed. Lung GSH, TRX, and AdoMet, as well as circulating GSH, AdoMet, and sulfur amino acids will be measured early in the 125 d model. Together, these approaches will help define whether changes in hexokinase activity expression, known to occur in lungs of adult rats made oxygen-tolerant, also occur in the premature newborn baboon. In addition, they will indicate whether or not increased expression of pulmonary glutamine- utilizing enzymes also occurs during pulmonary oxidative stress and whether anti-oxidant stress and whether anti-oxidant supplementation modifies these adaptations.

INTERFERON-RESPONSE GENE REGULATION IN HCV-INFECTED CHIMPANZEES (0212)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BIGGER, CATHERINE B	MD, PHD	A		

AXIS I CODES: 1D, 4, 7B, 16D AXIS II CODES:66

ABSTRACT

Hepatitis C virus (HCV) poses a worldwide health problem since the majority of individuals exposed to HCV become chronically infected and are predisposed for developing liver disease. Using DNA microarrays, we have previously described the changes in liver gene expression associated with acute or chronic HCV infection in chimpanzees. The most notable changes in gene expression, in both models, occurred in interferon (IFN)-response genes. Specifically, differences in the mRNA expression levels of a critical IFN-activated transcription factor (STAT1) were detected. Two splice variants of the STAT1 mRNA encode STAT1 and STAT1ß. Since, STAT1ß can function as dominant negative regulator of transcription of IFN-response genes, the possibility exists that differential expression of STAT1 mRNA splice variants may contribute to the establishment or maintenance of chronicity in chimpanzees. The objectives of these is to address the differential expression of STAT1 (mRNA and protein levels) in vivo from liver punch biopsies of HCV infected chimpanzees and in vitro using a tissue culture replicon system developed to study HCV replication. The data may provide insight into the interferon response to HCV. The specific goals include; analysis of the ratios of STAT /ß mRNA in HCV chronically infected chimpanzees by TaqMan real-time RT-PCR; analysis of the protein levels and activation status of STAT1 and STAT1ß in liver punch biopsies taken from chronically infected animals and animals that underwent acute-resolving infections; and examination of the role of STAT1 in regulation of HCV replication and IFNresponsiveness. This is a new study and no results are currently available from this study.

PATHOGENESIS OF A NOVEL LYMPH NODE-DERIVED SIV (0022)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC $: 1.800% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
KIMATA, JASON T	PHD	A		

AXIS I CODES: 1D, 7B, 17, 19 **AXIS II CODES:** 31, 64, 66

ABSTRACT

Simian immunodeficiency virus (SIV) becomes more virulent upon in vivo evolution. Also, tissue specific variants have been identified that may impact infection and disease. The mechanisms by which SIV acquires increased potential to replicate, and thereby drive disease progression, are not well understood. Identifying the molecular determinants of virulence will provide a basis for uncovering the host-virus interactions important for efficient virus replication. Our date demonstrate that the LN-derived SIVmne virus more efficiently utilizes antigen presenting cell-T-cell interactions for replication than do other variants of SIVmne. Pol and Nef mutations appear to be important for the phenotype of this virus. Additionally, adhesion molecules on dendritic cells and macrophages are critical for supporting replication of this virus. Further studies will focus on identifying how this virus is better able to utilize signaling between antigen presenting cells and T-cells for replication, and whether it alters the maturation state of dendritic cells and/or macrophages.

STRATEGIES TO PREVENT SIV BINDING TO MACAQUE DC-SIGN (0220)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC $: 2.000% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
KIMATA, JASON T	PHD	A		

AXIS I CODES: 1D, 7B, 17, 19 **AXIS II CODES:** 31, 64, 66

ABSTRACT

Sexual transmission is the primary route by which human immunodeficiency virus (HIV) is acquired. In the prevailing hypothesis about the initial events of infection, dendritic cells (DC) serve as major vehicle for trafficking HIV across the mucosa and to secondary lymphoid organs, such as lymph nodes (LN), where robust viral replication can be initiated. ADC-specific molecule, DC-SIGN, appears to be involved in binding and transfer of infectious HIV to CD4+ T-cells, although it does not function as an entry receptor. The SIV macaque model represents the best experimental system for examining the significance of DC-SIGN in transmission and pathogenesis. However, lack of suitable reagents for studying DC-SIGN's role in vivo has hampered efforts in this area. The goal of the study is to clone, express, and characterize macaque DC-SIGN for SIV transreceptor function. To generate monoclonal antibodies that prevent SIV-DC-SIGN interactions. Pig-tailed and rhesus macaque and African green monkey DC-SIGN were cloned from monocyte-derived DC grown in the presence of GM-CSF and IL4. DC-SIGN was amplified by PCR following cDNA synthesis of total mRNA harvested from DCs. Sequences were compared to human DC-SIGN. DC-SIGN from pig-tailed and rhesus macaques is nearly identical. African green monkey DC-SIGN has additional mutations. The macaque molecule is 92.1% identical with human DC-SIGN. were generated. These antibodies prevent some, but not all SIV variants from binding pig-tailed macaque DC-SIGN. Interestingly, expression of DC-SIGN is higher on pig-tailed macaque DCs than rhesus macaque DCs. Virus binding and transfer studies are ongoing. The binding site of the anti-DC-SIGN monoclonal antibodies is being mapped. The DC-SIGN binding site is being mapped for the SIV envelope proteins.

SOUTHEASTERN COOPERATIVE HEPATITIS C RESEARCH GROUP (0024)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC $: 1.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LEMON, STANLEY M	MD	A		UNIV TX MEDICAL BRANCH, GALVESTON, TX USA
[redacted]	PHD	C	VIROLOGY AND IMMUNOLOGY	SFBR, TX USA
[redacted]	MD	A		JOHNS HOPKINS UNIV, BALTIMORE, MD USA

AXIS I CODES: 1A, 1D, 7B, 16D **AXIS II CODES:**66

ABSTRACT

Approximately 2% of the US population is chronically infected with Hepatitis C virus (HCV). Chronic HCV infections result in significant liver disease including cirrhosis and liver cancer in approximately 20% of infected individuals. The current therapy of interferon and ribavirin does not result in viral clearance in the majority of cases. A better understanding of the replication of HCV at a molecular level as well as the factors that determine whether an infection will proceed to chronic infection or viral clearance is essential for the development of improved antiviral strategies. These studies are important for both vaccine and antiviral development. This Center grant is comprised of three research groups located at University of Texas Medical Branch in Galveston, John Hopkins University, and SFBR. The Principal Investigator for the SFBR component is Robert Lanford. The goals of his component are to develop HCV replicons and evaluate their replication in tissue cultures cells including primate hepatocytes, to characterize the changes in liver gene expression that occur during acute HCV infection in the chimpanzee model,l and to evaluate the immune correlates of viral clearance and persistent infections. An infectious cDNA clone of the HCV1 prototype strain was developed. Infectivity was confirmed by the direct intrahepatic inoculation of a chimpanzee with synthetic RNA produced from this clone. Several HCV clones have been used to construct HCV replicons and their replication in a variety of cells types is in progress. DNA microarray technology has been used to monitor changes in liver gene expression during HCV infection. The data imply that both innate immunity (interferon) and adaptive immunity are important in viral clearance. Rechallenge of chimpanzees that previously cleared HCV infection demonstrated that a strong CD4 T cell response is associated with protective immunity. Recently, the feasibility of producing a vaccine protective agains all strains of HCV was demonstrated by showing that chimpanzees that clear one genotype are protected agains all genotypes.

Direct comparison of immunological data with data obtained from DNA microarray technology in a series of HCV infected animals will provide insight to the parameters involved in viral clearance.

CHIMERIC VIRUS PRIMATE MODEL OF HEPATITIS C (0267)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LEMON, STANLEY M	MD	A		UNIV TX MEDICAL BRANCH, GALVESTON, TX USA
[name]	PHD	C	VIROLOGY AND IMMUNOLOGY	SFBR, TX USA

AXIS I CODES: 1A, 7B, 16D **AXIS II CODES:** 50, 66, 91

ABSTRACT

Chronic hepatitis C virus (HCV) infection is a major threat to the public health. Current therapies have limited efficacy, but the search for more effective treatments is hampered by the lack of available animal models of HCV infection. The chimpanzee (Pan troglodytes) is the only animal species permissive for infection with this virus. We will address this deficiency by developing a small nonhuman primate model of hepatitis C involving the closely related virus GBV-B. GBV-B replicates to high titers, is hepatotropic, and causes liver disease in susceptible tamarins (Saquinus sp.). Since tamarins are more readily available than chimpanzees for such studies, GBV-B infection of these animals represents a potentially useful surrogate for studies of hepatitis C. However, although GBV-B among all animal viruses has the closest phylogenetic relationship to HCV, its proteins still share only ~25% identity at the amino acid level. Moreover, unlike HCV, GBV-B does not appear capable of establishing persistent infection in these animals. These features of GBV-B limit its usefulness. To overcome these limitations, we will construct chimeric genome-length GBV-B cDNA clones in which specific functional domains of HCV are inserted in lieu of homologous GBV-B sequence. Our hypothesis is that the close phylogenetic relationship between GBV-B and HCV will allow the rescue of viable chimeric viruses from these clones, and that these viruses will represent uniquely valuable resources to the research community since they will allow the in vivo evaluation of HCV antivirals. Under Aim 1, we will construct a full-length, infectious cDNA copy of the GBV-B genome. In Aim 2, we will construct infectious chimeric cDNAs between HCV and GBV-B. In Aim 3, we will construct chimeras in which the structural proteins of GBV-B and HCV are placed within the genetic background of the alternate virus. An infectious clone of GBV-B has been produced and one viable chimeric virus has been constructed.

DEVELOPMENT OF HERPES SIMPLEX VACCINE PHASE I (0112)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MARTIN, DAVID W	PHD	A		

AXIS I CODES: 1A, 1D, 7B, 9, 23 **AXIS II CODES:** 66, 77, 83

ABSTRACT

Approximately 25% of the U.S. population is seropositive for herpes simplex virus type 2 (HSV-2). HSV-2 causes an important sexually transmitted disease and may enhance the chances of acquisition of HIV. Neonates can also acquire HSV-2 infections as they are born to infected mothers. Such infections result in a high rate of mortality. Current models to study the in vivo biology of HSV infections use small animals such as mice, rabbits, and guinea pigs. Although these models have made important contributions to the field of herpes biology, they cannot fully reproduce the full spectrum of natural virus/host interactions that occur during infection of a primate host HSV-2 infection of baboons may produce a model with more natural interactions between the virus and host than is possible with existing small animal models of disease. The objective iof this study s to develop the baboon as an experimental model for HSV-2 vaccine development. In a separate program, we are characterizing HPV-2 (herpes papio virus-2; the baboon homologue of human HSV-2) infection of baboons to more fully develop this natural primate host-virus interaction. In contrast, in this study, the human virus is being used to infect baboons in order to characterize the baboon as an experimental model for HSV-2 vaccine research. We will initially identify a group of female baboons that are seronegative for HPV-2. This background is necessary to perform HSV-2 infections, since it is likely that a pre-existing immune response to HVP-2 may block HSV-2 infections. The animals will then be infected with HSV-2 and the infection profile will be characterized.

Serological screening of female baboons has identified a group of seronegative animals that will be subjects for experimental infection. After a primary bleed, these animals have been kept separate from the rest of the colony and are being followed by successive bleeds to confirm that they remain seronegative for HVP-2. Experimental infection of naïve baboons with HSV-2 will establish the in vivo parameters for further development of this model system. These studies will be done in collaboration with a commercial sponsor.

HVP-2 MODEL OF HERPESVIRUS INFECTION (0117)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC S: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MARTIN, DAVID W	PHD	A		

AXIS I CODES: 1A, 1D, 7B, 9, 23 AXIS II CODES:66, 77, 83

ABSTRACT

Approximately 25% of the U.S. population is seropositive for herpes simplex virus type 2 (HSV-2). HSV-2 causes an important sexually transmitted disease and may enhance the chances of acquisition of HIV. Neonates can also acquire HSV-2 infections as they are born to infected mothers. Such infections result in a high rate of mortality. Greater than 80% of the U.S. population is seropositive for herpes simplex virus type 1 (HSV-1). This virus is typically associated with coldsores. HSV-1 infections of the eye are a leading cause of blindness due to infectious diseases in the U.S. in addition, the virus can cause severe infections in immunocompromised individuals. Current models to study the in vivo biology of HSV are not adequate because they cannot fully reproduce the full spectrum of natural virus/host interactions that occur during infections of a primate host. Herpesvirus papio 2 (HVP-2) naturally infects baboons and causes a similar disease to that caused by HSV infections of humans. Development of the HVP-2/baboon model system would allow for key aspects of herpes biology to be understood. The objective is to characterize experimental infections of naive baboons with HVP-2. The resulting pathology will be compared with the disease observed I naturally infected animals and in humans infected with HSV. Sensitive PCR assay and virus coculture systems have been established that will allow for detection of virus replication in inoculated animals. First round studies have shown the infection of animals with 108 106 plaque forming units/ml produces a disease that is similar to HSV infections in humans. Experimental infection of naive baboons with HVP-2 will establish the in vivo parameters for development of this model system. Lower doses of virus will be used to infect animals in order to define an end point. Future studies will focus on receptors/host tropism and viral immune evasion strategies.

THE HERPESVIRUS PAPIO 2 (HVP-2) GENOME (0156)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC $: 0:100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MARTIN, DAVID W	PHD	A		

AXIS I CODES: 1A, 1D, 7B, 9, 23 **AXIS II CODES:** 66, 77, 83

ABSTRACT

Approximately 25% of the U.S. population is seropositive for herpes simplex virus type 2 (HSV-2). HSV-2 causes a sexually transmitted disease and may enhance the chances of acquisition of HIV. Neonates can also acquire HSV-2 infections as they are born to infected mothers. Such infections result in a high rate of mortality. Greater than 80% of the U.S. population is seropositive for herpes simplex virus type 1 (HSV-1). This virus is typically associated with coldsores. HSV-1 infections of the eye are a leading cause of blindness due to infectious disease in the U.S. Current models to study the biology of HSV are not adequate because they cannot reproduce the full spectrum of natural virus/host interactions that occur during infection of a primate host. Herpesvirus papio 2 (HVP-2) naturally infects baboons and causes a similar disease to that caused by HSV infections of humans. Development of the HVP-2/baboon model system would allow for key aspects of the herpes biology to be understood. The first step in the development of the HVP-2 system is to characterize the molecular biology of this interesting virus. To accomplish this objective, this subproject has two specific aims. First, a complete physical map of the HVP-2 genome will be constructed. Second, HVP-2 genes will be identified based on cross-hybridization with known HSV-1 genes using Southern analysis. Early progress has been aimed at full characterization of HVP-2 at the molecular level. A number of viral genes have been cloned, and functional studies of these gene products are now in progress. The cloning, sequencing and mapping of the HVP-2 genome will be completed. Future studies will be aimed at understanding the contribution of specific viral genes to the virus life cycle.

BABOON IMMUNE RESPONSE TO HVP-2 (0217)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MARTIN, DAVID W	PHD	A		

AXIS I CODES: 1D, 7B, 9, 23 AXIS II CODES: 66, 77, 83, 91

ABSTRACT

The objective of these studies is to characterize the immune response to herpesvirus papio 2 (HVP-2) in naturally-infected colony animals. These studies are important in order to define viral targets that are consistently recognized by the baboon immune response and represent rational targets for development of a vaccine. To perform these studies, 40ml of whole blood will be collected from up to 70 mature male and female baboons. Serum collected from the whole blood will be assayed for antibodies to HVP-2 by ELISA and Western blot analysis in order to determine both titer and patterns of reactivity. Peripheral blood mononuclear cells will be isolated and to used to perform ELISPOT assays in order to identify targets of the cell-mediated immune system. The results of these studies will be compared to the immune response of humans against herpes simplex virus (HSV). Future studies will use this information to design vaccine strategies that will allow us to test proof-of-concept in the baboon system prior to initiation of human trials with HSV vaccine candidates.

CONSTRUCTION AND EVALUATION OF HERPES VIRUS VACCINE CANDIDATES IN A BABOON MODEL (0219)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MARTIN, DAVID W	PHD	A		

AXIS I CODES: 1A, 1D, 7B, 9, 23 **AXIS II CODES:** 66, 77, 83, 91

ABSTRACT

Herpes simplex viruses (HSV) are important human pathogens. Development of a vaccine against these viruses has been hampered due to the use of small animal models of infection which do not accurately reproduce the natural interaction between virus and host. Herpesvirus papio 2 (HVP-2) infection of baboons represents a powerful surrogate system to study the biology of herpesvirus infection in primates. In order to develop this system, key HVP-2 genes that are targets of the baboon immune response will be cloned and expressed. These genes will be transferred into a vaccine expression vector and used in future studies to test efficacy in a challenge model established using HVP-2 infection of baboons. The results of these studies will test proof-of-concept of herpesvirus vaccine strategies and will provide valuable data that will impact the development of human vaccines against HSV.

DEVELOPMENT OF HEPATITIS C VIRUS-LIKE PARTICLES AS CANDIDATE HCV VACCINE (0037)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC $: 3.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE; COUNTRY
MURTHY, KRISHNA K	DVM, PHD	A		
[name]	MD	A		NIDDK, NIH, MD USA

AXIS I CODES: 1A, 7B, 16D **AXIS II CODES:** 66, 91

ABSTRACT

At the present time, no vaccines to prevent infection with HCV are available and the epidemic continues unabated worldwide. The objectives of this study are to develop a candidate HCV vaccine consisting of HCV-like particles and to evaluate the immunogenicity of the vaccine in the chimpanzee model. HCV subtypes 1b and 1a are being titrated in four chimpanzees to provide a standardized inoculum for the vaccine challenge dose. Of the three animals inoculated with subtype 1b, one has resisted infection, and the remaining two have developed chronic infections. T cell responses in all three animals are being evaluated to understand the difference in the outcome of the infection and to delineate the role of T cells in protective immunity against HCV infection. The remaining animal has been inoculated with subtype 1a and is being monitored for evidence of infection. Two chronically infected animals are being utilized to determine whether a pool of human monoclonal anti-HCV antibodies is capable of clearing chronic infection. The animals were treated with 5 mg/kg dose of the antibody preparation and their virological and immunological status are being monitored. An additional four HCV naive chimpanzees were immunized with a HCV-VLP vaccine formulated with adjuvants and immunostimulatory complexes. The vaccinated animals have been challenged with infectious HCV to determine the efficacy of the vaccine in preventing infection.

CHIMPANZEES FOR HEPATITIS OR AIDS RESEARCH (0102)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC $: 4.000% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MURTHY, KRISHNA K	DVM, PHD	A		

AXIS I CODES: 1A, 7B, 16D, 17, 19 **AXIS II CODES:** 31, 66, 83, 91

ABSTRACT

Chimpanzees are being maintained under a NHLBI contract to perform hepatitis or AIDS research. These chimpanzees are available to all investigators interested in pursuing research projects that require the use of this nonhuman primate model. Interested investigators are required to discuss the project with the P.I. to ascertain that appropriate animals are available for the project, and must obtain permission from the Project Officer at NHLBI. Technical support for research projects is available at the SNPRC.

CATEGORY B MAO: IMMUNOGENICITY IF AD-HIVNEF RECOMBINANT VIRUSES (0103)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC $: 0.100% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MURTHY, KRISHNA K	DVM, PHD	A		

AXIS I CODES: 1A, 7B, 17, 19 **AXIS II CODES:** 31, 64, 66, 77

ABSTRACT

The chimpanzee is the only animal model available for the analysis of the pathogenesis of HIV and the efficacy of candidate vaccines for AIDS. This project will test a new strategy for an HIV-1 vaccine in the chimpanzee model. The objective is to determine the immune response of chimpanzees to the nef gene product of HIV. Chimpanzees will be immunized with adenovirus vectors expressing either wild type or mutant nef genes of HIV. The immune response to the nef protein will be analyzed prior to challenge with HIV-1. In vitro studies are in progress. The in vivo phase of the study has not been initiated. Immunization of chimpanzees with adenovirus vectors expressing "nef" gene of HIV induced both T cell and neutralizing antibody responses. Addition booster vaccinations with recombinant gp140 have been administered to enhance antibody titers and to broaden the neutralizing activity.

TITRATION OF HCV STRAIN STOCK IN VIVO IN CHIMPANZEES (0116)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MURTHY, KRISHNA K	DVM, PHD	A		

AXIS I CODES: 1A, 7B, 16D **AXIS II CODES:** 66, 91

ABSTRACT

Natural infection with HCV is associated with a population of viruses referred to as the quasispecies. These quasispecies affect the outcome of infection, make it difficult to determine the rate of mutation in the virus, and facilitate escape from immune responses. Therefore, molecular clones of HCV are being utilized to study pathogenesis, rate of mutation, and the role of the immune response in controlling HCV infection. The objective of this study is to determine the in vivo infectivity titer of a virus pool established from a molecular clone of HCV. After the titer is established, the standardized virus will be utilized as the challenge dose in vaccines studies for HCV. The in vivo titration revealed that the virus produces infections but has a relatively low titer. Infection was characterized by transient viremia and rapid viral clearance of the virus from circulation. Inoculation with three different molecular clones failed to infect the animal. Additional clones are being evaluated for infectivity.

DEFINING THE HCV INFECTIOUS WINDOW PERIOD IN THE CHIMPANZEE (0213)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MURTHY, KRISHNA K	DVM; PHD	A		
[name]	MD	A		NHLBI, MD USA

AXIS I CODES: 1A, 7B, 16D AXIS II CODES:66, 83

ABSTRACT

The infectious window period for hepatitis C virus (HCV), the time between exposure to the virus and the first detection of viral RNA, is not well defined. By establishing the window period, the risk of transmission of HCV by blood products can be further reduced and or prevented. The objective is to define and characterize the infectious window period for HCV in the chimpanzee model. Two chimpanzees have been selected and baseline liver enzyme levels have been determined. HCV borderline positive and negative plasma panels are being put together for the proposed studies. One chimpanzee was IV infused with 50 ml of plasma from each of five individual donors from a panel negative for HCV by nucleic acid testing (NAT). The animals become infected indicating that HCV was present below the level of detection by NAT. Additional virological and immunological assays are being performed at the present time. Virological assays indicated that the animal rapidly cleared the infection and did not seroconvert. The planned inoculation of the second animal is on hold until a final decision is made on using a different plasma panel.

IMMUNOTHERAPY OF CHRONIC HBV INFECTION IN CHIMPANZEES (0214)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC $: 0.100%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MURTHY, KRISHNA K	DVM, PHD	A		

AXIS I CODES: 1A, 7B, 16D **AXIS II CODES:** 64, 66, 83, 91

ABSTRACT

HBV is the cause of chronic infection in millions of people all over the world. As yet, there is no treatment or vaccine available to cure chronic infections. The objective is to evaluate a novel immunotherapy protocol to boost the cell-mediated immune response in order to clear the chronic infection. The high virus load present in this animal precluded proper evaluation of the role of immunotherapy in clearance of chronic infection. Therefore, the protocol has been amended to pre-treat the animal with Lamvudine to bring the viral load to a reasonable level and then reinitiate the immunotherapy protocol. More than four months of antiviral treatment was required to achieve 3 logs of decrease in viral load. Following drug treatment, the immunotherapy protocol was initiated. Presently, virological and immunological assays are being performed.

HIV-1 ADENOVIRUS-BASED VACCINE STUDY IN CHIMPANZEES (0266)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC $: 0.100% AIDS RELATED RESEARCH

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MURTHY, KRISHNA K	DVM, PHD	A		
[name]	PHD	A		NATIONAL INSTITUTES OF HEALTH, MD USA

AXIS I CODES: 1A, 7B, 17, 19 AXIS II CODES: 31, 66, 83, 91

ABSTRACT

Infection with HIV continues to spread worldwide and it is estimated that nearly 40 million people are infected with virus. Although combination therapy with several drugs controls virus replication, there is no cure for the infection and no effective vaccines to prevent infection are available at the present time. The objective of this study was to determine the immunogenicity of a adenovirus vector based vaccine for HIV in the chimpanzee model. Adenovirus with either E1 or E1 + E3 deletion, and expressing the env gene of HIV will be administered intranasally to chimpanzees and induction of virus neutralizing antibodies and secretion of IFN by antigen specific T cells will be determined. Different serotypes of adenovirus vectors will be utilized for priming and booster doses of the vaccine. Vaccination of chimpanzees with Adeno-HIV vaccine resulted in T cell activation and IFN secretion as assessed by ELISPOT assay. Serum samples are being analyzed for virus neutralizing antibody titers.

HCV REPLICATION AND IMMUNITY (0158)

NPRC UNIT: VIROLOGY & IMMUNOLOGY

%NPRC $: 1.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
WALKER, CHRISTOPHER M	PHD	A		OHIO STATE UNIV-CHILDREN'S RESEARCH INSTITUTE, OH USA
	MD, PHD	A		UNIV WA, WA USA
	MD	A		MASSACHUSETTS GENERAL HOSPITAL, MA USA
	DVM, PHD	A		

AXIS I CODES: 1A, 16D **AXIS II CODES:** 64, 66

ABSTRACT

Approximately 2% of the US population is chronically infected with Hepatitis C virus (HCV). Chronic HCV infections result in significant liver disease including cirrhosis and liver cancer in approximately 20% of infected individuals. The chimpanzee is the only animal model for HCV infection, thus a thorough characterization of the immune response to HCV infections and the mechanism of viral clearance will be critical for vaccine development. The role if host immune system in the control of HCV replication is poorly understood. Cellular immune responses mediated by T cells expressing the CD4 or CD8 surface antigens may play a role in spontaneous resolution of acute HCV infection and in control of ongoing replication. In contrast, a poor T cell response limits but does not terminate virus replication, resulting in chronic infection. The objective is to define the kinetics of acute phase virus replication and immune responses to determine if a temporal relationship exists between them. In addition, CD4+ and CD8+ T cells will be depleted in vivo by administration of subset specific monoclonal antibodies to assess their role in acute phase virus replication and possibly as mediators of hepatocellular injury. Chimpanzees have been genotyped and their HLA Class I alleles have sequenced for the production of recombinant Class I tetramers. This will permit the direct measurement of CTL frequencies. HCV infection has been characterized in untreated animal. During the next year, 3-6 chimpanzees will be infected. The analysis for each animal is expected to require 2 years from the time of initiation. Most of the results from these studies will not be available for 2-3 years.

RESEARCH SERVICES

NAME	NON-HOST INSTITUTION: STATE, COUNTRY	# SPECIES: SPECIMEN
	UNIVERSITY OF TEXAS, AUSTIN: TX	PAPIO: TISSUES
	UNIVERSITY OF TEXAS, AUSTIN: TX	MACACA MULATTA: TISSUES
	UNIVERSITY OF UTAH: UT	PAN TROGLODYTES: GENETIC MATERIAL
names	WILFORD HALL MEDICAL CTR, UNITED STATES AIR FORCE: TX	PAPIO: TISSUES
	UNIVERSITY OF ILLINOIS: IL	PAPIO: TISSUES
	NIA/NIH: MD	PAPIO: TISSUES
	UNIVERSITY OF MARYLAND	12 PAPIO: WHOLE
	W.K. WARREN MEDICAL RESEARCH INSTITUTE: OK	PAN TROGLODYTES: GENETIC MATERIAL
		PAPIO: TISSUES
		CALLITHRIX JACCHUS: TISSUES
	UNION MEMORIAL HOSPITAL: MD	PAPIO: TISSUES
names	KRONOS SCIENTIFIC LABORATORIES: AZ	PAN TROGLODYTES: TISSUES
	UNIVERSITY OF MARYLAND: MD	34 PAPIO: WHOLE
	DUKE UNIVERSITY: NC	5 PAPIO: WHOLE
	BROOKS AIR FORCE BASE: TX	PAPIO: TISSUES
	BOSTON SCIENTIFIC: MA	PAPIO: TISSUES
	JOHNS HOPKINS UNIVERSITY: MD	3 PAPIO: WHOLE
	HUMAN GENOME SCIENCES, INC.: MD	PAN TROGLODYTES: TISSUES
	OREGON NATIONAL PRIMATE RESEARCH CENTER: OR	6 PAPIO: WHOLE
	OREGON NATIONAL PRIMATE RESEARCH CENTER: OR	5 PAPIO: WHOLE
	UNIVERSITY OF TEXAS HEALTH SCIENCES CENTER, SAN ANTONIO: TX	PAPIO: TISSUES
names	TOLERX: MA	6 PAPIO: WHOLE
	MERCK RESEARCH LABORATORIES: NJ	PAN TROGLODYTES: TISSUES
	BAYLOR COLLEGE OF MEDICINE: TX	PAPIO: TISSUES
	COLUMBUS CHILDREN'S RESEARCH INSTITUTE: OH	PAPIO: TISSUES
	COLUMBUS CHILDREN'S RESEARCH INSTITUTE: OH	PAN TROGLODYTES: TISSUES
	COLUMBIA UNIVERSITY: NY	PAPIO: TISSUES
	MOREHOUSE SCHOOL OF MEDICINE: GA	PAPIO: TISSUES

WAYNE STATE UNIVERSITY MEDICAL SCHOOL: MI	PAPIO: TISSUES
NCI/NIH: MD	PAPIO: TISSUES
NCI/NIH: MD	MACACA MULATTA: TISSUES
SANTA ROSA HOSPITAL: TX	PAPIO: TISSUES
	PAPIO: TISSUES
	PAPIO: TISSUES
TOLERX: MA	CALLITHRIX JACCHUS: TISSUES
MONELL CHEMICAL SENSES CENTER: PA	CALLITHRIX JACCHUS: TISSUES
UNIVERSITY OF TEXAS HEALTH SCIENCES CENTER, SAN ANTONIO: TX	PAPIO: TISSUES
	PAPIO: TISSUES
UNIVERSITY OF TEXAS HEALTH SCIENCES CENTER, SAN ANTONIO: TX	PAPIO: TISSUES
	PAPIO: TISSUES
COMPARATIVE BIOSCIENCES, INC.: CA	MACACA MULATTA: TISSUES
UNIVERSITY OF TEXAS HEALTH SCIENCES CENTER, SAN ANTONIO: TX	PAPIO: TISSUES
UNIVERSITY OF BERGEN	PAN TROGLODYTES: GENETIC MATERIAL
UNIVERSITY OF TEXAS HEALTH SCIENCES CENTER, SAN ANTONIO: TX	PAPIO: TISSUES
	PAPIO: TISSUES
	MACACA FASCICULARIS: TISSUES
KENT STATE UNIVERSITY: OH	CALLITHRIX JACCHUS: TISSUES
UNIVERSITY OF TEXAS, AUSTIN: TX	CALLITHRIX JACCHUS: TISSUES
RES LAB OF BIOL PSYCHAITRY, SCT. HANS HOSPITAL	PAN TROGLODYTES: GENETIC MATERIAL
MAYO CLINIC: MN	12 PAPIO: WHOLE
USAMRID: MD	PAPIO: TISSUES
USAMRID: MD	CALLITHRIX JACCHUS: TISSUES
USAMRID: MD	PAN TROGLODYTES: TISSUES
NOVOCELL: CA	PAPIO: TISSUES
WYETH: MA	PAPIO: TISSUES
DEPUY ACROMED: MA	PAPIO: TISSUES
UNIVERSITY OF TEXAS, AUSTIN: TX	3 PAPIO: WHOLE
UNIVERSITY OF TEXAS, AUSTIN: TX	CALLITHRIX JACCHUS: TISSUES
	PAPIO: TISSUES
UNIVERSITY OF TEXAS HEALTH SCIENCES CENTER, SAN ANTONIO: TX	PAPIO: TISSUES
UNIVERSITATSCLINIKUM HAMBURG-EPPENDORF	CALLITHRIX JACCHUS: TISSUES
DUKE UNIVERSITY: NC	CALLITHRIX JACCHUS: TISSUES
BAYLOR COLLEGE OF MEDICINE: TX	PAPIO: TISSUES

	JOHNS HOPKINS UNIVERSITY: MD	4 PAPIO: WHOLE
	TOLERX, INC: MA	PAPIO: TISSUES
	TOLERX, INC.: MA	PAN TROGLODYTES: TISSUES
	UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER: TX	PAPIO: TISSUES
names	UNIVERSITY OF MARYLAND: MD	7 PAPIO: WHOLE
	UNIVERSITY OF LOUISVILLE: KY	PAPIO: TISSUES
	UNIVERSITY OF LOUISVILLE: KY	PAN TROGLODYTES: TISSUES
	ITBA-CNR	PAPIO: TISSUES
	BROOKS AIR FORCE BASE: TX	PAPIO: TISSUES
	BROOKS AIR FORCE BASE: TX	MACACA MULATTA: TISSUES

THIS PAGE LEFT INTENTIONALLY BLANK

PUBLISHED: ABSTRACTS, BOOKS & JOURNALS

‡ NPRC Cited *NPRC Personnel

SPIDs	Reference
Abstracts	
	Caperton, L;Brindle, E;Fujita, M;O'Connor, KA;Atencio, J; Jackson, E;Rice, K;Leland, M;Carey, KD;Eddy, C;McCarrey, JR TI Serum and urinary hormonal analytes for the prediction of ovulation in baboons. BIOLOGY OF REPRODUCTION 2003 V. 68 Suppl. 1 p. 281
	Havill, LM, Mahaney, MC, Almasy, L, Rogers, J . Genotype-by-age effects on bone mineral density in the spine and forelimb in baboons: Possible implications of mechanical usage. AMERICAN JOURNAL OF PHYSICAL ANTHROPOLOGY 2003 Suppl. 36 p. 112
	Kushwaha, R, McGill, HC TI Effect of cholesteryl ester transfer protein (CETP) inhibitor peptide on plasma lipoprotein cholesterol in nonhuman primates ATHEROSCLEROSIS SUPPLEMENTS V. 4 NO. 2 p. 220
0013	McAdams, RM, Yoder, BT, Coalson, J, McCurnin, DM. Age at ligation of patent ductus arteriosus does not impact pulmonary function in premature baboons. JOURNAL OF INVESTIGATIVE MEDICINE 2003 FEB V. 51 Suppl. 1 p. S291
0221	Power, M.L.; Tardif, S.D.; Power, R.A.; Layne, D.G. 2003. Energy metabolism in Callimico goeldii. Am. J. Primatol., 60(S1) :100.
0044	Shi, Q, Wang, J, Wang, XL, VandeBerg, JL, VandeBerg, JL Development of endothelial biopsy and culture method in baboons FASEB JOURNAL 2003 MAR 14 V. 17 NO. 4 Part 1 Suppl. S p. A125
0221	Tardif, S.D. 2003. What marmosets have taught me about life. Am. J. Primatol., 60(S1):143
0044	Tejero, ME, Cole, SA, Cai, G, Peebles, KW, Freeland-Graves, JH, Cox, L, Mahaney, MC, Rogers, JVandeberg, JLComuzzie, AG TI Genome wide scan of resistin mRNA expression in omental adipose tissue of baboons OBESITY RESEARCH 2004 JAN V. 12 NO. 1 p. 170
SPIDs	**Reference**
Journal Articles	
0233	Afshar S, Gibson LL, Yuhanna IS, Sherman TS, Kerecman JD, Grubb PH, Yoder BA, McCurnin DC, Shaul PW. Pulmonary NO synthase expression is attenuated in a fetal baboon model of chronic lung disease. Am J Physiol Lung Cell Mol Physiol. 2003 May;284(5):L749-58
0295	Albrecht ED, Aberdeen GW, Niklaus AL, Babischkin JS, Suresch DL, Pepe GJ. Acute temporal regulation of vascular endothelial growth/permeability factor expression and endothelial morphology in the baboon endometrium by ovarian steroids. J Clin Endocrinol Metab. 2003 Jun;88(6):2844-52.
0230	Antonow-Schlorke I, Schwab M, Li C, Nathanielsz PW. Glucocorticoid exposure at the dose used clinically alters cytoskeletal proteins and presynaptic terminals in the fetal baboon brain. J Physiol. 2003 Feb 15;547(Pt 1):117-23.
	Baerlocher GM, Mak J, Roth A, Rice KS, Lansdorp PM. Telomere shortening in leukocyte subpopulations from baboons. J Leukoc Biol. 2003 Feb;73(2):289-96.
0011	BARDI, MASSIMO;FRENCH, JEFFREY A;RAMIREZ, STEPHANIE M;BRENT, LINDA* The role of the endocrine system in baboon maternal behavior. Biol Psychiatry 55 724-32 2004
0108	BARRERA, AZENETH;LANFORD, ROBERT E* Infection of primary chimpanzee hepatocytes with recombinant hepatitis Dvirus particles: a surrogate model for hepatitis B virus. Methods Mol Med 96 131-42 2004
0218	BIGGER, JOHN E;MARTIN, DAVID W* Identification of an ICP47 homologue in simian agent 8 (SA8). Virus Genes 28 223-5 2004
0219	‡ BIGGER, JOHN E;MARTIN, DAVID W* The genome of herpesvirus papio 2 is closely related to the genomes ofhuman herpes simplex viruses. J Gen Virol 84 1411-4 2003
0295	Billiar RB, Zachos NC, Burch MG, Albrecht ED, Pepe GJ. Up-regulation of alpha-inhibin expression in the fetal ovary of estrogen-suppressed baboons is associated with impaired fetal ovarian folliculogenesis. Biol Reprod. 2003 Jun;68(6):1989-96.

Brent L. Solutions for research chimpanzees.
Lab Anim (NY). 2004 Jan;33(1):37-43.

Casimiro DR, Tang A, Chen L, Fu TM, Evans RK, Davies ME, Freed DC, Hurni W,Aste-Amezaga JM, Guan L, Long R, Huang L, Harris V, Nawrocki DK, Mach H, Troutman RD, Isopi LA, Murthy KK, Rice K, Wilson KA, Volkin DB, Emini EA, Shiver JW Vaccine-induced immunity in baboons by using DNA and replication-incompetent
adenovirus type 5 vectors expressing a human immunodeficiency virus type 1 gag gene. J Virol 2003 Jul;77(13):7663-8.

0044 ‡ COLE, S A;MARTIN, L J;PEEBLES, K W;LELAND, M M*;RICE, K;VANDEBERG, J L;BLANGERO, J;COMUZZIE, A G Genetics of leptin expression in baboons. Int J Obes Relat Metab Disord 27 778-83 2003

0314 Diau GY, Loew ER, Wijendran V, Sarkadi-Nagy E, Nathanielsz PW, Brenna JT. Docosahexaenoic and arachidonic acid influence on preterm baboon retinal composition and function.
Invest Ophthalmol Vis Sci. 2003 Oct;44(10):4559-66.

Dick EJ Jr, Hubbard GB, Martin LJ, Leland MM. Record review of baboons with histologically confirmed endometriosis in a large
established colony. J Med Primatol. 2003 Feb;32(1):39-47.

0321 Edelstein C, Pfaffinger D, Hinman J, Miller E, Lipkind G, Tsimikas S, Bergmark C, Getz GS, Witztum JL, Scanu AM. Lysine-phosphatidylcholine adducts in kringle V impart unique immunological and potential pro-inflammatory properties to human apolipoprotein(a). J Biol Chem. 2003 Dec 26;278(52):52841-7.

Fazleabas AT, Brudney A, Chai D, Langoi D, Bulun SE. Steroid receptor and aromatase expression in baboon endometriotic lesions. Fertil Steril. 2003 Sep;80 Suppl 2:820-7.

GROVE, KEVIN L;CHEN, PEILIN;KOEGLER, FRANK H;SCHIFFMAKER, ANDREW;SUSAN SMITH, M;CAMERON, JUDY L* Fasting activates neuropeptide Y neurons in the arcuate nucleus and theparaventricular nucleus in the rhesus macaque. Brain Res Mol Brain Res 113 133-8 2003

‡ HAVILL, L M;SNIDER, C L;LELAND, M M*;HUBBARD, G B;THERIOT, S R;MAHANEY, M C Hematology and blood biochemistry in infant baboons (Papio hamadryas). J Med Primatol 32 131-8 2003

Hlusko LJ, Mahaney MC. Genetic contributions to expression of the baboon cingular remnant. Arch Oral Biol. 2003 Sep;48(9):663-72.

‡ HLUSKO, LESLEA J;MAHANEY, MICHAEL C* Genetic contributions to expression of the baboon cingular remnant. Arch Oral Biol 48 663-72 2003

JAYASHANKAR, LAKSHMI;BRASKY, KATHLEEN M*;WARD, JOHN A;ATTANASIO, ROBERTA Lymphocyte modulation in a baboon model of immunosenescence. Clin Diagn Lab Immunol 10 870-5 2003

0044 Kammerer CM, Rainwater DL, Schneider JL, Cox LA, Mahaney MC, Rogers J, VandeBerg JF. Two loci affect angiotensin I-converting enzyme activity in baboons. Hypertension. 2003 Mar;41(3 Pt 2):854-9.

Kumar S, Brudney A, Cheon YP, Fazleabas AT, Bagchi IC. Progesterone induces calcitonin expression in the baboon endometrium within the window of uterine receptivity.
Biol Reprod. 2003 Apr;68(4):1318-23.

0024 Lanford, R.E., Guerra, B., Lee, H., Averett, D.R., Pfeiffer, B., Chavez, D., Notvall, L. and Bigger, C. Antiviral effect and virus-host interactions in response to alpha interferon, gamma interferon, poly(I)-poly(C), tumor necrosis factor alpha, and ribavirin in hepatitis C virus subgenomic replicons. J. Virol. 77: 1092-1104, 2003

0109 ‡ LANFORD, ROBERT E;CHAVEZ, DEBORAH;BARRERA, AZENETH;BRASKY, KATHLEEN M* An infectious clone of woolly monkey hepatitis B virus. J Virol 77 7814-9 2003

0108 ‡ LANFORD, ROBERT E;CHAVEZ, DEBORAH;NOTVALL, LENA;BRASKY, KATHLEEN M* Comparison of tamarins and marmosets as hosts for GBV-B infections and theeffect of immunosuppression on duration of viremia. Virology 311 72-80 2003

0024 LANFORD, ROBERT E;GUERRA, BERNADETTE;CHAVEZ, DEBORAH;BIGGER, CATHERINE;BRASKY, KATHLEEN M;WANG, XIAO-HONG;RAY, STUART C;THOMAS, DAVID L* Cross-genotype immunity to hepatitis C virus. J Virol 78 1575-81 2004

Langat DK, Morales PJ, Fazleabas AT, Mwenda JM, Hunt JS.
The olive baboon (Papio anubis): a potential animal model to study the function of human leukocyte antigen-G (HLA-G).
Gynecol Obstet Invest. 2004;57(1):33-6.

Leigh SR, Shah NF, Buchanan LS. Ontogeny and phylogeny in papionin primates. J Hum Evol. 2003 Oct;45(4):285-316.

0108 Lott L, Notvall L, Lanford RE. Expression and purification of functional hepatitis B virus polymerase in the baculovirus insect cell system. Methods Mol Med. 2004;95:271-9.

0109 Lott L, Notvall L, Lanford RE. Transcomplementation of core and polymerase functions of the woolly monkey and human hepatitis B viruses. Virology. 2003 Apr 10;308(2):330-9.

0108 Martin, A., Bodola, F., Sangar, D.V., Goettge, K.; Popov, V., Rijnbrand, R., Lanford, R.E. and Lemon, S.M. Chronic hepatitis associated with GB virus B persistence in a tamarin after intrahepatic inoculation of synthetic viral RNA. Proc. Natl. Acad. Sci. USA 100: 9962-9967, 2003.

0267, 0108 ‡ MARTIN, ANNETTE;BODOLA, FRANCIS;SANGAR, DAVID V;GOETTGE, KATHRYN;POPOV, VSEVOLOD;RIJNBRAND, RENE;LANFORD, ROBERT E;LEMON, STANLEY M* Chronic hepatitis associated with GB virus B persistence in a tamarinafter intrahepatic inoculation of synthetic viral RNA. Proc Natl Acad Sci U S A 100 9962-7 2003

‡ MARTIN, L J;CAREY, K D*;COMUZZIE, A G Variation in menstrual cycle length and cessation of menstruation incaptive raised baboons. Mech Ageing Dev 124 865-71 2003

0158 Meyer-Olson D, Brady KW, Blackard JT, Allen TM, Islam S, Shoukry NH, Hartman K, Walker CM, Kalams SA. Analysis of the TCR beta variable gene repertoire in chimpanzees: identification of functional homologs to human pseudogenes. J Immunol. 2003 Apr 15;170(8):4161-9.

Moore CM, Hubbard GB, Leland MM, Dunn BG, Best RG. Spontaneous ovarian tumors in twelve baboons: a review of ovarian neoplasms in non-human primates. J Med Primatol. 2003 Feb;32(1):48-56.

0295 Musicki B, Pepe GJ, Albrecht ED. Functional differentiation of the placental syncytiotrophoblast: Effect of estrogen on chorionic somatomammotropin expression during early primate pregnancy. J Clin Endocrinol Metab. 2003 Sep;88(9):4316-23.

0230 Nathanielsz PW, Berghorn KA, Derks JB, Giussani DA, Docherty C, Unno N, Davenport A, Kutzlers M, Koenen S, Visser GH, Nijland MJ. Life before birth: effects of cortisol on future cardiovascular and metabolic function. Acta Paediatr. 2003 Jul;92(7):766-72.

0295 Niklaus AL, Aberdeen GW, Babischkin JS, Pepe GJ, Albrecht ED. Effect of estrogen on vascular endothelial growth/permeability factor expression by glandular epithelial and stromal cells in the baboon endometrium. Biol Reprod. 2003 Jun;68(6):1997-2004.

0226 O'Reilly MA, Watkins RH, Staversky RJ, Maniscalco WM. Induced p21Cip1 in premature baboons with CLD: implications for alveolar hypoplasia. Am J Physiol Lung Cell Mol Physiol. 2003 Oct;285(4):L964-71.

0325 PERELYGINA, LUDMILA;PATRUSHEVA, IRINA;MANES, NINA;WILDES, MARTIN J;KRUG, PETER;HILLIARD, JULIA K* Quantitative real-time PCR for detection of monkey B virus (Cercopithecineherpesvirus 1) in clinical samples. J Virol Methods 109 245-51 2003

0325 PERELYGINA, LUDMILA;ZHU, LI;ZURKUHLEN, HOLLEY;MILLS, RYAN;BORODOVSKY, MARK;HILLIARD, JULIA K* Complete sequence and comparative analysis of the genome of herpes B virus(Cercopithecine herpesvirus 1) from a rhesus monkey. J Virol 77 6167-77 2003

Porter BF, Frost P, Hubbard GB. Polyarteritis nodosa in a cynomolgus macaque (Macaca fascicularis). Vet Pathol. 2003 Sep;40(5):570-3.

Porter BF, Frost P, Hubbard GB. Polyarteritis nodosa in a cynomolgus macaque (Macaca fascicularis). Vet Pathol. 2003 Sep;40(5):570-3.

PORTER, BRIAN F;GOENS, S DENISE;BRASKY, KATHLEEN M;HUBBARD, GENE B* A case report of hepatocellular carcinoma and focal nodular hyperplasiawith a myelolipoma in two chimpanzees and a review of spontaneoushepatobiliary tumors in non-human primates. J Med Primatol 33 38-47 2004

0221 POWER, MICHAEL L;TARDIF, SUZETTE D*;POWER, RACHEL A;LAYNE, DONNA G Resting energy metabolism of Goeldi's monkey (Callimico goeldii) issimilar to that of other callitrichids. Am J Primatol 60 57-67 2003

0044 ‡ RAINWATER, DAVID L;KAMMERER, CANDACE M;MAHANEY, MICHAEL C;ROGERS, JEFFREY;COX, LAURA A *;SCHNEIDER, JENNIFER L;VANDEBERG, JOHN L Localization of genes that control LDL size fractions in baboons. Atherosclerosis 168 15-22 2003

0280 ROGERS, JEFFREY*;MARTIN, LISA J;COMUZZIE, ANTHONY G;MANN, J JOHN;MANUCK, STEPHEN B;LELAND, MICHELLE;KAPLAN, JAY R Genetics of monoamine metabolites in baboons: overlapping sets of genesinfluence levels of 5-hydroxyindolacetic acid,3-hydroxy-4-methoxyphenylglycol, and homovanillic acid. Biol Psychiatry 55 739-44 2004

0314 Sarkadi-Nagy E, Wijendran V, Diau GY, Chao AC, Hsieh AT, Turpeinen A, Nathanielsz PW, Brenna JT. The influence of prematurity and long chain polyunsaturate supplementation in 4-week adjusted age baboon neonate brain and related tissues. Pediatr Res. 2003 Aug;54(2):244-52.

‡ Schalbritz-Loutsevich, NE; Howell, K, Rice, K, Glover, EJ, Nevill, CH, Jenkins, SL, Cummins, LB, Frost, PA, McDonald, TJ, Nathanielsz, PW. Development of a system for individual feeding of baboons maintained in an outdoor group social environment. J Med Primatol 33:1-10, 2004.

Schlabritz-Loutsevitch NE, Hubbard GB, Frost PA, Cummins LB, Dick EJ Jr, Nathanielsz PW, McDonald TJ. Abdominal pregnancy in a baboon: a first case report. J Med Primatol. 2004 Feb;33(1):55-9.

‡ Schlabritz-Loutsevitch, NE, Hubbard, GB, Dammann, MJ, Jenkins, SL, Frost, PA, MdDonald, TJ, Nathanielsz, PW. Normal concentrations of essential and toxic elements in pregnant baboons and fetuses (Papio species). J Med Primatol 33:1-10, 2004.

0158 Shoukry NH, Grakoui A, Houghton M, Chien DY, Ghrayeb J, Reimann KA, Walker CM. Memory CD8+ T cells are required for protection from persistent hepatitis C virus infection. J Exp Med. 2003 Jun 16;197(12):1645-55.

0158 Shoukry NH, Sidney J, Sette A, Walker CM. Conserved hierarchy of helper T cell responses in a chimpanzee during primary and secondary hepatitis C virus infections. J Immunol. 2004 Jan 1;172(1):483-92.

Siler-Khodr TM, Grayson M, Eddy CA. Action of gonadotropin-releasing hormone II on the baboon ovary. Biol Reprod. 2003 Apr;68(4):1150-6.

Srisuparp S, Strakova Z, Brudney A, Mukherjee S, Reierstad S, Hunzicker-Dunn M, Fazleabas AT. Signal transduction pathways activated by chorionic gonadotropin in the primate endometrial epithelial cells. Biol Reprod. 2003 Feb;68(2):457-64.

Strakova Z, Szmidt M, Srisuparp S, Fazleabas AT. Inhibition of matrix metalloproteinases prevents the synthesis of insulin-like growth factor binding protein-1 during decidualization in the baboon. Endocrinology. 2003 Dec;144(12):5339-46.

0232 Subramaniam M, Sugiyama K, Coy DH, Kong Y, Miller YE, Weller PF, Wada K, Wada E, Sunday ME. Bombesin-like peptides and mast cell responses: relevance to bronchopulmonary dysplasia? Am J Respir Crit Care Med. 2003 Sep 1;168(5):601-11.

Szabo CA, Leland M, Sztonak L, Restrepo S, Haines R, Mahaney MA, Williams JT. Scalp EEG for the diagnosis of epilepsy and photosensitivity in the baboon. Am J Primatol. 2004 Feb;62(2):95-106.

0221 TARDIF, SUZETTE D*;BALES, KAREN L Relations among birth condition, maternal condition, and postnatal growthin captive common marmoset monkeys (Callithrix jacchus). Am J Primatol 62 83-94 2004

0221 ‡ TARDIF, SUZETTE D*;SMUCNY, DARLENE A;ABBOTT, DAVID H;MANSFIELD, KEITH;SCHULTZ-DARKEN, NANCY;YAMAMOTO, MARIA EMILIA Reproduction in captive common marmosets (Callithrix jacchus). Comp Med 53 364-8 2003

0044 Tejero ME, Cole SA, Cai G, Peebles KW, Freeland-Graves JH, Cox L, Mahaney MC, Rogers J, Vandeberg JL, Comuzzie AG. Genome wide scan of resistin mRNA expression in omental adipose tissue of baboons. Obes Res. 2004 Jan;12(1):170.

VandeBerg JL. Need for primate models in biomedical research. Gynecol Obstet Invest. 2004;57(1):6-8.

0297, 0299 Wang J, Felux D, VandeBerg J, Wang XL. Discordance of endothelial nitric oxide synthase in the arterial wall and its
circulating products in baboons: interactions with redox metabolism. Eur J Clin Invest. 2003 Apr;33(4):288-95.

Woollard DJ, Grakoui A, Shoukry NH, Murthy KK, Campbell KJ, Walker CM . Characterization of HCV-specific Patr class II restricted CD4+ T cell responses in an acutely infected chimpanzee. Hepatology. 2003 Nov;38(5):1297-306.

0173 Yamada ES, Dmitrieva N, Keyser KT, Lindstrom JM, Hersh LB, Marshak DW. Synaptic connections of starburst amacrine cells and localization of acetylcholine receptors in primate retinas.
J Comp Neurol. 2003 Jun 16;461(1):76-90.

0176 Zabalgoitia M, Ventura J, Anderson L, Williams JT, Carey KD, Vandeberg JL. Electrocardiographic findings in naturally acquired chagasic heart disease in nonhuman primates. J Electrocardiol. 2003 Apr;36(2):155-60.

0295 Zachos NC, Billiar RB, Albrecht ED, Pepe GJ. Developmental regulation of follicle-stimulating hormone receptor messenger RNA expression in the baboon fetal ovary. Biol Reprod. 2003 May;68(5):1911-7.

0295 Zachos NC, Billiar RB, Albrecht ED, Pepe GJ. Regulation of oocyte microvilli development in the baboon fetal ovary by
estrogen. Endocrinology. 2004 Feb;145(2):959-66.

THIS PAGE LEFT INTENTIONALLY BLANK

IN PRESS: ABSTRACTS, BOOKS & JOURNALS

‡ NPRC Cited *NPRC Personnel

SPIDs	Reference
Journals	
0109	[In press publication]
	[In press publication]
	[In press publication]

THIS PAGE LEFT INTENTIONALLY BLANK

SOURCE OF INVESTIGATORS' SUPPORT

NON-FEDERAL

FOUNDATION

INVESTIGATOR ORGANIZATION	GRANT/CONTRACT		TOTAL FUNDING	SPID
COMUZZIE, ANTHONY G				
[ ]	1160	$	7,500	0209
MARTIN, DAVID W				
[ ]	1197	$	25,573	0218
SHADE, ROBERT E				
[ ]	1910	$	1,935,000	0014
[ ]				
[ ]	1822	$	250,000	0165
	FOUNDATION	$	2,218,073	

INDUSTRY

private funding

INVESTIGATOR ORGANIZATION	GRANT/CONTRACT		TOTAL FUNDING	SPID
BRASKY, KATHLEEN M				
COMMERCIAL	1297	$	48,871	0264
COMMERCIAL	1291	$	36,517	0258
COMMERCIAL	1303	$	74,223	0256
COMMERCIAL	1292	$	145,568	0263
COMMERCIAL	1272	$	114,327	0260
COMMERCIAL	1262	$	30,280	0262
COMMERCIAL	1276	$	715,886	0259
COMMERCIAL	1256	$	265,520	0255
COMMERCIAL	1233	$	0	0252
COMMERCIAL	1170	$	233,444	0190
COMMERCIAL	1131	$	1,397,900	0071
COMMERCIAL	1223	$	8,596	0204
COMMERCIAL	1217	$	195,554	0201
COMMERCIAL	0211	$	0	0199
COMMERCIAL	1982	$	344,064	0186
COMMERCIAL	1154	$	663,533	0181,0182
CAREY, K DEE				
COMMERCIAL	1955	$	688,460	0080
FROST, PATRICE A III				
COMMERCIAL	1253	$	308,169	0254
LANFORD, ROBERT E				
COMMERCIAL	1346	$	84,071	0302
COMMERCIAL	1343	$	91,181	0301
COMMERCIAL	1346			0302
COMMERCIAL	1174	$	80,646	0211
COMMERCIAL	1169	$	460,158	0210
LELAND, M MICHELLE				
COMMERCIAL	1286	$	70,985	0310
MARTIN, DAVID W				
COMMERCIAL	1063	$	14,934	0156

COMMERCIAL	1162	$	26,921	0217
COMMERCIAL	1144	$	116,245	0117
COMMERCIAL	1102	$	61,563	0112
MURTHY, KRISHNA K				
COMMERCIAL	1083	$	122,488	0116
COMMERCIAL	1242	$	0	0103
COMMERCIAL	1164	$	0	0214
RICE, KAREN S				
COMMERCIAL	1338	$	339,996	0294
COMMERCIAL	1275	$	81,803	0279
COMMERCIAL	1125	$	166,476	0147
	INDUSTRY	$	6,988,379	

OTHER NON FEDERAL

INVESTIGATOR ORGANIZATION	GRANT/CONTRACT		TOTAL FUNDING	SPID
MURTHY, KRISHNA K				
NIH	263-MM-115165	$	51,157	0213
NIH/NIDDK	263-MK-210133	$	485,664	0037
	OTHER NON FEDERAL	$	536,821	

FEDERAL

INVESTIGATOR ORGANIZATION	GRANT/CONTRACT		TOTAL FUNDING	SPID
FEDERAL - PHS				
ALBRECHT, EUGENE D.				
NIH	5R01HD013294-23	$	808,104	0295
ALLAN, JONATHAN S				
NIH	5R01AI051221-02	$	667,561	0265
ATOR, NANCY A.				
NIH	2R01DA004133-17A2	$	367,875	0334
BRENNA, JAMES THOMAS				
NIH	5R01GM049209-11	$	295,403	0314
BRENT, LINDA Y				
NIH	5R24RR013199-05	$	155,275	0011
CAMERON, JUDY L				
NIH	5R01MH062568-02	$	551,478	0341
CASHMAN, JOHN R.				
NIH	5R01DK059618-02	$	354,017	0332
CHAN, LAWRENCE				
NIH	5T32HL066991-02	$	236,002	
NIH	5R01HL056668-08	$	373,750	
NIH	5R01HL016512-29	$	433,317	
NIH	5R01HL051586-11	$	338,625	
NIH	2P01HL059314-06	$	1,486,224	0082
NIH	5U01HL066728-04	$	954,743	
CLYMAN, RONALD I				
NIH	2U01HL056061-09	$	354,576	0013,0222

NIH	5R01HL046691-11	$	464,108	
COALSON, JACQUELINE J				
NIH	5U01HL052636-10	$	2,098,296	0013
[illegible] name				
NIH	5R01HL070167-02	$	526,309	
COUNTER, CHRISTOPHER M.				
NIH	5R01CA094184-02	$	256,025	0322
NIH	5R21CA095155-02	$	25,641	
NIH	5R01CA082481-05	$	318,686	
CRAPO, JAMES D				
NIH	2S07RR018132-02	$	150,000	
NIH	2U01HL063397-05	$	384,641	0013,0223
NIH	5P01HL031992-20	$	1,577,182	
NIH	5K30HL004111-05	$	200,000	
[illegible] name				
NIH	5R24MH067346-02	$	372,500	
NIH	5R01MH061596-03	$	343,990	
NIH	5K02MH001362-08	$	117,225	
NIH	5R01AA012504-04	$	254,033	
NIH	1R13DA016688-01	$	25,000	
DAVIS, RONALD W.				
NIH	5P01HG000205-14	$	7,563,712	0323
NIH	1R01GM068717-01	$	544,281	
EBERSOLE, JEFFREY				
NIH	5R01DE013958-02	$	699,455	0288
EICHLER, EVAN				
NIH	5R01HD043569-02	$	420,827	
NIH	5R01HG002385-03	$	407,479	0282
NIH	2R01GM058815-05	$	315,491	
FIGURSKI, DAVID H.				
NIH	5R01DE014713-02	$	388,736	0324
[illegible] name				
NIH	5R21NS043738-02	$	174,290	
NIH	5R13MH062008-04	$	50,000	
[illegible] name				
NIH	5R01HD042882-02	$	156,570	
FROST, PATRICE A III				
NIH	5U42RR016024-04	$	554,737	0106
GIAVEDONI, LUIS D				
NIH	1R03AI055443-01	$	84,500	0300
[illegible] name				
NIH	5R01AI049168-03	$	418,421	0158
[illegible] name				
NIH	1F32AR049694-01A1	$	41,608	
HILLIARD, JULIA K.				
NIH	5P40RR005062-16	$	623,999	0325
HONORE, ERIKA K				
NIH	5K01RR000170-03	$	73,692	0240

[name]

NIH	5P01HL045666-12	$	2,248,531	
KIMATA, JASON T				
NIH	7R01AI047725-05	$	188,125	0022
KRAUSS, RONALD				
NIH	5U01HL069757-03	$	2,631,545	
NIH	5U01HL066691-04	$	140,358	

[name]

NIH	5R01RR015009-02	$	367,723	
LANFORD, ROBERT E				
NIH	5R01AI046609-05	$	456,474	0109
LEMON, STANLEY M				
NIH	1UC6AI058588-01	$	110,090,673	
NIH	5U19AI040035-08	$	1,021,880	0024
NIH	5R24RR015081-02	$	272,458	0267
NIH	5M01RR000073-41	$	2,390,953	
LOCKWOOD, CHARLES				
NIH	5R01HD033937-09	$	294,300	
NIH	1R01HL070004-01A1	$	619,899	0257
MANISCALCO, WILLIAM M				
NIH	2U01HL063400-05	$	195,358	0013,0226
MARSHAK, DAVID				
NIH	5R01EY006472-15	$	232,070	0173
MARTIN, DAVID W				
NIH	1R21AI055369-01	$	252,000	0307
MCDONALD, THOMAS				
NIH	1R01HL075615-01	$	417,500	
NIH	5R01HL065399-05	$	295,677	0327
MENDELSON, CAROLE R				
NIH	5R01DK031206-20	$	349,992	0013,0227
NIH	4R37HL050022-11	$	401,007	
MURTHY, KRISHNA K				
NIH	N01HB270910-10	$	0	0102
NATHANIELSZ, PETER W				
NIH	5R01AG020880-04	$	321,100	0230
NIH	7P01HD021350-15	$	1,605,754	0228
PIANTODOSI, CLAUDE A.				
NIH	5P01HL031992-21	$	1,098,724	0336
PIERCE, RICHARD A				
NIH	5R01HL054049-09	$	267,750	
NIH	2U01HL063387-04	$	268,636	0013,0231
PLATT, ORAH S.				
NIH	5R01HL068922-03	$	714,974	0340
RAPER, JAYNE				
NIH	2R01AI1041233-06	$	200,000	0326
ROGERS, JEFFREY				
NIH	5R24RR015383-04	$	317,120	0164

NIH	5R01RR008781-10	$	308,000	0043
NIH	5R01MH065462-02	$	396,000	0280
[name]				
NIH	5U01HL066735-04	$	367,128	
NIH	5U01HL066681-04	$	681,939	
NIH	5R01HL063897-04	$	469,597	
NIH	2T32HL007279-26	$	291,522	
NIH	1R01HL071954-01	$	556,170	
[name]				
NIH	5P01MH041712-17	$	1,352,800	
SCANU, ANGELO M.				
NIH	5R01HL063209-04	$	339,143	0321
SHADE, ROBERT E.				
NIH	5R01HL068180-02	$	483,444	0289
NIH	1C06RR017515-01A1	$	3,096,536	
SHAUL, PHILIP W.				
NIH	2U01HL063399-05	$	550,750	0013,0233
NIH	5R01HD030276-11	$	339,611	
NIH	5R01HL053546-09	$	303,701	
SMITH, JAMES R.				
NIH	5P01AG020752-03	$	1,657,486	0328
STARZL, THOMAS				
NIH	1R01DK064207-01	$	324,863	0337
STRAUSS, WILLIAM M.				
NIH	5R01GM061079-05	$	275,823	0329
TARDIF, SUZETTE D.				
NIH	5R01RR002022-20	$	257,359	0221
THOMAS, DAVID L.				
NIH	5R01DA016078-02	$	696,769	
NIH	5R01DA013806-04	$	458,130	
NIH	5R01DA013324-05	$	329,892	
TROILO, DAVID				
NIH	5R01EY011228-08	$	330,650	0287
NIH	1R24EY014817-01	$	274,500	
[name]				
NIH	2P01HD013527-24A1	$	1,400,377	
NIH	5P01DK026741-24	$	1,702,429	
VANDEBERG, JOHN D				
NIH	1G20RR018394-01	$	221,415	
NIH	1G20RR018362-01	$	462,272	
NIH	2P01HL028972-21	$	2,881,311	
WALKER, CHRISTOPHER M				
NIH	5U19AI1048231-04	$	1,047,020	0158
NIH	1R01AI060388-01	$	162,538	
NIH	5R01AI047367-05	$	521,002	
WALKER, DAVID				
NIH	1D43TW006590-01	$	150,000	
NIH	5R01AI031431-11	$	372,500	
NIH	5R01AI021242-19	$	372,500	

NIH	5U54AI057156-02	$	9,407,383	0339
WANG, XING LI				
NIH	5R01HL071608-03	$	376,250	
NIH	7R01HL066053-03	$	338,625	
WHITE, CARL				
NIH	2U01HL056263-09	$	224,109	0013,0241
WILLIAMS, JEFF T				
NIH	5R01RR016347-03	$	345,200	0176
NIH	5R01HL066480-03	$	638,490	
NIH	5R01AI044406-04	$	429,103	
NIH	5R01AI037091-06	$	693,115	
WONG, DEAN F.				
NIH	5R01NS038927-03	$	487,469	
NIH	5R01AA012839-04	$	756,964	
NIH	5K24DA000412-04	$	125,048	
NIH	5R01DA011080-05	$	297,485	0333
WOODRUFF, TERESA K.				
NIH	1R01HD044464-01A1	$	312,224	
NIH	5R01HD037096-05	$	229,727	
NIH	1U54HD041857-01A1	$	1,062,897	0331
ZAHORSKY-REEVES, JOANNE L.				
NIH	5K01RR016582-04	$	79,349	0330
ZHOU, PAUL				
NIH	5R01AI047682-04	$	287,000	
NIH	1R21AI054254-01A1	$	247,635	
	FEDERAL - PHS	$	194,442,215	
	FEDERAL	$	194,442,215	
TOTAL FUNDING:		**$**	**204,185,488**	

RESOURCE SUMMARY: SUBPROJECTS

The following only includes information associated with subprojects.

	Mgmt. A	Research B	Pilot C	Collab. D	Total (excludes
Number of Subprojects	7	36	11	87	141
Number of Investigators	1	39	13	78	111
Number of Published	0	21	2	25	47
Number In Press	0	1	0	0	1
%AIDS of NPRC Dollars	2.400%	16.000%	0.720%	8.300%	27.420%
%Non-AIDS of NPRC Dollars	1.000%	27.200%	1.920%	42.460%	72.580%
Total Percent of NPRC Funds Awarded	3.400%	43.200%	2.640%	50.760%	100.000%

THIS PAGE LEFT INTENTIONALLY BLANK

RESOURCE SUMMARY: ADMINISTRATIVE

PERSONNEL		On Subprojects	Not On Subprojects
Core Personnel			
DOCTORAL LEVEL SCIENTISTS (C)		11	1
	Core Personnel	11	1
Non-Core Personnel			
AFFILIATED (A)		99	7
GRADUATE STUDENT/POST DOCTORAL SCIENTIST (G)		1	7
	Non-Core Personnel	100	14
Personnel Total:		111	15

ACCESS BY NON-NPRC PERSONNEL

GEOGRAPHICAL USAGE BY INVESTIGATORS AT NON-HOST INSTITUTIONS

Foreign Investigators by Country	**4**
AUSTRALIA	4
USA Investigators by State	**91**
CA	9
CO	4
CT	1
FL	1
GA	2
IL	3
KY	1
MA	3
MD	7
MI	1
MN	1
MO	1
NC	2
NE	1
NV	1
NY	9
OH	2
OR	1
PA	9
TX	30
VA	1
WA	1
Total Investigators at Non Host Institutions:	**95**

RESEARCH SERVICES

Scientists Provided with Services	62
Services Provided	97

RESEARCH SERVICES BY COUNTRY

Research Services to Foreign Investigators by Country	**4**
DENMARK	1
GERMANY	1
ITALY	1
NORWAY	1
Research Services to USA Investigators by State	**50**
AZ	1
CA	2
GA	1
IL	1
KY	1
MA	6
MD	9
MI	1
MN	1
NC	2
NJ	1
NY	1
OH	2
OK	1
OR	2
PA	1
TX	16
UT	1
Research Services to Host Investigators	**7**
Research Services to Unknown Locations	**1**
Total Research Services :	**62**

INFRASTRUCTURE TABLE

GRANT REPORTED UNITS	**%NPRC USE**
ADMINISTRATIVE	0.000%
AIDS COMPONENT	0.000%
BLOOD TISSUE & DNA REPOS	2.750%
COMPARATIVE MEDICINE	0.000%
DIRECTORS OFFICE	20.760%
FACILITIES MAINT & IMPROV	14.240%
GENETICS GROUP	12.700%
LABORATORY ANIMAL MED	5.520%
PHYSIOLOGY & MEDICINE	7.570%
PILOT STUDIES	14.860%
PRIM RECORD & DB BIOSTAT	10.890%
PRIMATE RESOURCES	6.040%
TRAINING AND OUTREACH	1.310%
VIROLOGY & IMMUNOLOGY	3.360%
TOTAL NPRC:	**100.00%**

RESEARCH TABLE

UNITS GENERATED BY SUBPROJECTS	**%NPRC USE**
ADMINISTRATIVE	3.400%

COMPARATIVE MEDICINE		3.760%
GENETICS GROUP		26.080%
LABORATORY ANIMAL MED		11.780%
PHYSIOLOGY & MEDICINE		26.140%
VIROLOGY & IMMUNOLOGY		28.840%
	TOTAL NPRC:	**100.000%**

THIS PAGE LEFT INTENTIONALLY BLANK

RESOURCE SUMMARY: PUBLICATION/SUPPORT

PUBLICATIONS

	Cited	Not Cited	Total
Published			
Abstracts	0	8	8
Journals	12	57	69
In Press			
Journals	0	3	3
Total	12	68	80

INVESTIGATOR SUPPORT

NON-FEDERAL

FOUNDATION	$	536,821
INDUSTRY	$	2,218,073
	$	6,988,379
NON-FEDERAL	**$**	**9,743,273**

FEDERAL

PHS		
AA	$	1,010,997
AG	$	1,978,586
AI	$	126,919,430
AR	$	41,608
CA	$	600,352
DA	$	2,300,199
DE	$	1,088,191
DK	$	2,731,301
EY	$	837,220
GM	$	1,430,998
HB	$	0
HD	$	6,630,391
HG	$	7,971,191
HL	$	27,229,911
MH	$	3,183,993
NS	$	661,759
RR	$	9,676,088
TW	$	150,000
PHS	**$**	**194,442,215**
TOTAL SUPPORT	**$**	**204,185,488**

THIS PAGE LEFT INTENTIONALLY BLANK

COLONY STATISTICS

Non-Base Breeding Colony Only

Note: These animals are supported by NCRR Comparative Medicine.

1Genus Species	May-03	2Live Births	3Other Additions	Exper. Use	4Other Reduct.	5Sold or Trans.	6Trans. in Center	Apr-0
MACACA MULATTA (SPF)								
Adult Females(SPF)	171	0	0	0	11	0	0	160
Adult Males(SPF)	64	0	2	0	3	0	0	63
Infants/Juveniles(SPF)	106	49	0	0	10	0	0	145
PAPIO HAMADRYAS								
Adult Females	711	0	0	0	68	8	0	635
Adult Males	203	0	0	10	10	94	0	89
Infants/Juveniles	829	317	0	26	97	21	0	1,002
	2,084	**366**	**2**	**36**	**199**	**123**	**0**	**2,094**

Research Colony Only

Note: These animals are supported by NCRR Comparative Medicine.

1Genus Species	May-03	2Live Births	3Other Additions	Exper. Use	4Other Reduct.	5Sold or Trans.	6Trans. in Center	Apr-0
AETELES PANISCUS								
Adult Females	5	0	0	0	0	0	0	5
Adult Males	5	0	0	0	1	0	0	4
Infants/Juveniles	2	0	0	0	0	0	0	2
CALLITHRIX JACCHUS								
Adult Females	39	0	0	6	0	0	0	33
Adult Males	53	0	0	5	2	0	0	46
Infants/Juveniles	35	59	0	7	8	0	0	79
MACACA MULATTA								
Adult Females	55	0	0	0	4	0	0	51
Adult Males	50	0	0	0	5	2	0	43
Infants/Juveniles	33	12	1	0	2	1	0	43
MACACA NEMESTRINA LEONINA								
Adult Males	0	0	9	0	1	0	0	8
PAN TROGLODYTES								
Adult Females	130	0	0	0	1	0	0	129
Adult Males	89	0	0	0	2	0	0	87
Infants/Juveniles	2	1	0	0	0	0	0	3
PAPIO HAMADRYAS								
Adult Females	1,011	0	16	3	80	16	0	928
Adult Males	409	0	3	22	33	2	0	355
Infants/Juveniles	766	183	1	86	38	0	0	826
SAGUINUS								
Adult Females	14	0	0	1	3	0	0	10
Adult Males	13	0	0	1	1	0	0	11
Infants/Juveniles	7	0	0	0	0	0	0	7
	2,718	**255**	**30**	**131**	**181**	**21**	**0**	**2,670**

1 - Animals that are known free of SIV, STLV, SRV/D and Herpes B

2 - Live birth defined as inflated lungs

3 - Purchased from outside Center or transferred from another colony within the Center

4 - Includes deaths due to intercurrent diseases and other causes

5 - Permanent transfer or sale to outside the Center

6 - Transferred to another colony within the Center

RESEARCH HIGHLIGHTS

COMPARISON OF TAMARIN AND MARMOSETS AS HOSTS FOR GBV-B INFECTIONS AND THE DEVELOPMENT OF AN INFECTIOUS CLONE OF GBV-B

SPID(s): 0108

GBV-B virus is the virus that is phylogenetically most closely related to hepatitis C virus (HCV). GBV-B causes a hepatitis in tamarins that is very similar to HCV infections in human, and thus is an attractive surrogate model for HCV. There are a number of advantages to the use of GBV-B as a surrogate model for HCV. HCV studies are hampered by the low level of virus replication, the lack of a tissue culture system, and the lack of a small animal model The chimpanzee is the only animal other than man susceptible to HCV infection. For GBV-B, the level of viremia is 1000-fold higher than HCV, the tamarin is 100-times smaller than the chimpanzee, and we have developed a robust tissue culture system for GBV-B based on primary tamarin hepatocytes cultures. Nonetheless, the GBV-B model suffers from two short comings. Tamarins are not readily available, since they are not routinely bred at primate centers, except for Saguinus oedipus which is an endangered species. In addition, GBV-B normally does not induce chronic infections, and chronically infected animals are desirable for a number of types of studies. This year, we demonstrate that the host range of GBV-B extends to the common marmoset, Callithrix jaccus, with an infection profile very similar to that observed for tamarins. We also demonstrated that marmoset hepatocytes could be infected in vitro with GBV-B at a high efficiency. Virus was efficiently secreted into the medium, and approximately 25% of hepatocytes were positive for staining for viral antigens (Figure from the cover of the journal Virology). To further improve the system, we attempted to induce persistent infections by immunosuppression with FK506, the drug used in liver transplantation. Normally animals clear the virus after 12-16 weeks of acute infection. Although no chronic infections were induced in this study, the duration of viremia was increased in most animals. In one animal, the duration of viremia was extended to 46 weeks, but viral clearance occurred 18 weeks after stopping FK506 therapy. The greater availability of marmosets in comparison to tamarins will greatly facilitate future research efforts with this model. This year we also developed an infectious clone of the GBV-B RNA. Tamarins were infected with this clone by direct intrahepatic inoculation with synthetic RNA. One animal developed a spontaneous persistent infection. This is the first persistent infection ever observed for GBV-B. Although high levels of viremia persisted for 2 years, the animal eventual cleared the infection. This provides evidence that persistent infections should be possible under the correct conditions. Future studies will involve the inoculation of newborn marmosets and the use of immunomodulators to induce chronic infections.

Publications:

LANFORD, ROBERT E;CHAVEZ, DEBORAH;NOTVALL, LENA;BRASKY, KATHLEEN M* Comparison of tamarins and marmosets as hosts for GBV-B infections and theeffect of immunosuppression on duration of viremia. Virology 311 72-80 2003

MARTIN, ANNETTE;BODOLA, FRANCIS;SANGAR, DAVID V;GOETTGE, KATHRYN;POPOV, VSEVOLOD;RIJNBRAND, RENE;LANFORD, ROBERT E;LEMON, STANLEY M* Chronic hepatitis associated with GB virus B persistence in a tamarinafter intrahepatic inoculation of synthetic viral RNA. Proc Natl Acad Sci U S A 100 9962-7 2003

GENETICS OF MONOAMINE ENDOPHENOTYPES AND MENTAL HEALTH

SPID(s): 0280

The Genetics Group has made important research progress in a number of areas. New information about the genetics of heart disease, obesity, diabetes and other disorders has been generated through the use of nonhuman primate model species. Investigators within the SNPRC Genetics Group have also made substantial progress toward completion of a genetic linkage map of the rhesus genome, and development of new tools for functional genomic analysis of baboons.

One notable research accomplishment over the past year is the publication of a major study concerning the genetic basis of individual variation in monoamine neurotransmitter metabolism. Dr. Jeffrey Rogers, Dr. Anthony Comuzzie and their colleagues at SNPRC worked with [name] (Wake Forest University, [name] (Columbia University) and [name] University of Pittsburgh) on this novel analysis of serotonin, norepinephrine and dopamine function in the pedigreed baboons maintained by SNPRC. Cerebrospinal fluid was collected from 271 baboons by Dr. Michelle Leland, and the concentration of the metabolites of serotonin, norepinephrine and dopamine were measured. Quantitative genetic analyses showed that individual variation in neurotransmitter levels among baboons is strongly influenced by genetic differences, with heritability values ranging from 0.30 to 0.50).

Prior work in humans and in rhesus macaques had suggested that levels of these critical neurotransmitters are influenced by genetic differences. But previous research had not been able to determine the relationships among these three neurotransmitters, i.e. determine whether they are influenced by the same genes or by different genes. By performing genetic correlation analysis using the baboon data, we were able to show that dopamine and serotonin share some but not all of their genetic determinants in common, and that dopamine and norepinephrine also share some genetic factors. But serotonin and norepinephrine do not share any genetic factors in common. This information is valuable to neuroscientists and psychiatrists, since these neurotransmitters are known to be involved in depression, anxiety disorders, addiction, and other mental health problems that are influenced by genetics. A more thorough understanding of the genetic control of neurotransmitter levels will accelerate progress in understanding the genetics of these psychiatric illnesses. This work has been accepted for publication in the journal Biological Psychiatry.

This study is currently funded by an NIH R01 grant titled "Genetics of monoamine endophenotypes and mental health" (J. Rogers, PI). This project has benefited significantly from support by the SNPRC. All the animals used in the study are part of the SNPRC colony. More directly, a Pilot Study grant from SNPRC ("Heritability of monoamine metabolism and behavior, 1999-2001, J. Rogers, PI) was critical because it provided funding necessary to obtain essential preliminary data for the successful R01 application. In addition, work done prior to the SNPRC pilot study was funded by SFBR departmental funds and assisted by SNPRC staff.

Publications:

ROGERS, JEFFREY*;MARTIN, LISA J;COMUZZIE, ANTHONY G;MANN, J JOHN;MANUCK, STEPHEN B;LELAND, MICHELLE;KAPLAN, JAY R Genetics of monoamine metabolites in baboons: overlapping sets of genesinfluence levels of 5-hydroxyindolacetic acid,3-hydroxy-4-methoxyphenylglycol, and homovanillic acid. Biol Psychiatry 55 739-44 2004

REPORT BY THE NYU CENTER FOR WOMEN'S HEALTH RESEARCH GROUP

SPID(s): 0228, 0230, 0296, 0311

The research group from the Center for Women's Health Research at New York University Medical School (NYUSM) has been working with the Southwest Foundation for Biomedical Research since 1990 when they were located at the College of Veterinary Medicine at Cornell University. Since the group moved to NYUSM in March 2002 an even closer collaboration has developed with scientists at the Southwest National Primate Research Center in three major areas of investigation: the developmental origins of adult disease, an analysis of biological cost and benefit of antenatal glucocorticoid therapy given to pregnant women to accelerate fetal lung maturation, and the mechanisms of premature labor.

Compelling human epidemiologic and animal studies have indicated that adverse conditions during fetal development and in the immediate neonatal period can alter the trajectory of growth of major organ systems in ways that predispose an individual to important chronic diseases such as hypertension, obesity, diabetes and affective disorders. The majority of this work has been conducted on altered nutritional states during rodent or sheep development. Very little information is available from nonhuman primates.

Nonhuman primates offer a major advantage for study of the developmental origins of adult diseases since the environmental conditions affecting the mother can be carefully controlled before during and after pregnancy. We have developed an innovative system for recording and regulating maternal nutrition while still maintaining the female baboons in their normal group housing situation. We have published these methods together with data on maternal morphometry before pregnancy and normal food intake during the first half of pregnancy [1]. When maternal baboons are fed 70% of the global intake of control animals, placental growth is significantly decreased and both maternal and fetal insulin-like growth factor bioavailability are decreased [2].

Women threatening to deliver prematurely between 24 and 32 weeks of gestation are routinely given synthetic glucocorticoids to accelerate fetal lung development and prevent respiratory problems if their babies are born prematurely. We have demonstrated that while this therapy clearly saves lives there are unwanted side effects on the developing baby's cardiovascular system and brain in both sheep and baboons [3]. The current studies being undertaken at the Primate Center focus on determining the minimal dose of synthetic glucocorticoids the mother needs for the baby to benefit from the positive effects of the treatment while minimizing the negative aspects. We have developed methods to measure the function of nine key genes in the developing fetal lung to determine the optimum dosing regimen [4].

Premature birth occurs in only 10% of pregnancies and yet it leads to 50% of infant mortality and 75 % of long term morbidity. The mechanisms that regulate uterine contraction in both normal and premature labor are poorly understood. The NYU group has been actively studying the distribution of receptors to prostaglandins and other factors that cause the uterus to contract and the cervix to dilate. In the baboon we have shown that there are marked regional differences in the changes in late pregnancy in both the stimulatory and inhibitory prostaglandin receptors [5].

We are grateful for this opportunity to work with investigators at the Primate Center to combine our skills and past experience to study these critical questions. Only a truly multidisciplinary approach will yield the information required to improve both animal and human health.

Publications:

Schalbritz-Loutsevich, NE; Howell, K, Rice, K, Glover, EJ, Nevill, CH, Jenkins, SL, Cummins, LB, Frost, PA, McDonald, TJ, Nathanielsz, PW. Development of a system for individual feeding of baboons maintained in an outdoor group social environment. J Med Primatol 33:1-10, 2004.

THIS PAGE LEFT INTENTIONALLY BLANK

ADMINISTRATIVE INFORMATION

ALLOCATION OF RESOURCE ACCESS

Requests for resources may be directed to any doctoral level core staff member or to designated non-doctoral core staff. If the request is for specimens, the requestor is asked to complete a form on line at the SNPRC website (www.snprc.org). If the request is for animals or technical support, it is referred to an appropriate core staff member for evaluation and discussion with the requestor. Requests that can clearly be handled without a major commitment by the Center (e.g., a request for tissues collected during a necropsy scheduled for other purposes) are promptly filled. Requests that involve a major commitment of aniamls or of other Center resources are brought to the Research Advisory Committee, which meets monthly and is chaired by the Center Associate Director. After evaluation and discussion of the request, the Center Director decides whether or not the request will be fulfilled.

In instances where an expedited decision regarding a request that involves a major commitment is warranted, the Comparative Medicine Group Leader is authorized to make a preliminary commitment of resources, prior to evaluation by the Research Advisory Committee. If that leader has a concern in regard to the request, he consults with the Center Director, who makes a tentative decision prior to the next meeteing of the Research Advisory Committee.

The number of Center Access Requests during 2003 was 181. For the purpose of this report, we define Center Access Requests to be requests from individuals who are non-Core investigators at the time the request is made. Ninety-five requests were received for biological materials (including DNA) or animals, and were approved and fulfilled.

We were able to fulfill all reasonable requests for purchase of animals to be removed from the Center without jeopardizing the Center-based research programs or productivity of the breeding colonies. Requests for use of chimpanzees can generally be met but frequently require extensive waiting periods (months to years).

COMMITTEE REPORTS

There were no committee reports received.

EXTERNAL COMMITTEE MEMBERS

Names

STEERING COMMITTEE MEMBERS

*TARDIF, SUZETTE D:PHD
DIRECTOR'S OFFICE
SNPRC:TX, USA

CAREY, K DEE:DVM, PHD
COMPARATIVE MEDICINE
SFBR:TX, USA

GIAVEDONI, LUIS D:PHD
VIROLOGY AND IMMUNOLOGY
SFBR:TX, USA

LANFORD, ROBERT E:PHD
VIROLOGY AND IMMUNOLOGY
SFBR:TX, USA

MAHANEY, MICHAEL C:PHD
GENETICS GROUP

ROGERS, JEFFREY:PHD
GENETICS
SFBR:TX, USA

STEERING COMMITTEE MEMBERS

SHADE, ROBERT E:PHD
PHYSIOLOGY AND MEDICINE
SFBR:TX, USA

VANDEBERG, JOHN D:PHD
DIRECTOR'S OFFICE
SNPRC:TX, USA

DISSEMINATION

Technological development of the Center are disseminated by the doctoral level core staff who present invited papers, contributed papers, and posters at a wide array of national and international scientific and veterinary meetings. The scientific community is made aware of the availability of the resource via the same mechanism.

PATENTS, LICENSES, INVENTIONS AND COPYRIGHTS

There were no patents, licenses, inventions or copyrights issued.

AWARDS, HONORS, SPECIAL RECOGNITIONS

None of the key core staff received major honors, awards, or special recognition during 2003.

INFRASTRUCTURE

INFRASTRUCTURE

1. Physical Plant

Facilities Improvement

A number of major construction and renovation projects were initiated during 2003-2004. Money spent on these projects is reported below. These dollar amounts indicate spending during the reporting year and not spending to completion, as most of these projects are not yet completed.

Base grant funding:	
Construction and installation of modular ABL2 and ABL3 housing	104,590
Cage and animal enclosure maintenance	8,748
Subtotal	113,338
NIH/NCRR construction & renovation funding (C06- and G20 grants):	
Construction of long-term housing for chimpanzees	1,119,008
Addition of outdoor runs to chimpanzee housing	674,934
Construction of new outdoor gang housing	528,589
Renovation of outdoor baboon gang cages	311,581
Design and installation of emergency generators	298,961
Renovation of SPF rhesus macaque facility	20,000
Construction of laboratory and office space for Molecular & Biochemical Genetics	8,050
Subtotal	2,961,123
Host Institution funding:	
Construction of laboratory and office space for Molecular & Biochemical Genetics	3,997,507
Construction of a Genomics Computing Center	975,618
Renovation of quarantine housing into ABL3 housing	569,761
Construction of new outdoor gang housing	219,550
Construction of a shower/locker room facility	91,406
Addition of outdoor runs to chimpanzee housing	49,670
Renovation of small group housing	28,859
Construction of long-term housing for chimpanzees	7,786
Design and installation of emergency generators	2,972

Renovation of outdoor baboon gang cages		1,697
	Subtotal	5,944,826
Major equipment items purchased:		
Base Grant Funding		
Pressure, temperature & physical activity system		68,335
Anesthesia machine with cardiocap monitor		43,736
Oracle database		32,775
Anesthesia machine		10,000
DNA sequencer-Genescan		10,000
Sun Fire server		7,076
Stacker fork lift		6,317
Incubator/shaker		5,698
	Subtotal	183,937
Other NIH Grant Funding		
Neutilators		45,000
GE Logig portable ultrasound machine		40,850
Dual 384 well sample block PCR		17,927
Cell counter analyzer		13,743
Vetscan hematology analyzers		10,995
Kawasaki mule		7,565
Blood pressure system		6,390
Sample block module for PCR system		6,296
Chromatograph refrigerator		4,639
	Subtotal	153,405
Host Institution, Foundation or Commercial Funding		
GE Logig ultrasound system		79,839
Prism genetic analyzer system/Genemapper Workstation		27,500
Pick-up truck		22,084
Pick-up truck		18,000
Blood fluid warmer monitor system		13,000
Transfer cages with lifts		9,552
Hot water pressure washers		7,190
Chest freezer - 86°C		6,842
Anesthesia machines		6,388
Pharmacy refrigerator		6,176
Chest freezer - 86°C		5,751
Gas powered pressure washers		5,000
	Subtotal	207,322

2. Colony Management

Approximately 4,000 nonhuman primates at the SNPRC are divided into six colonies, each of which is a component under the Center. The overall management philosophy and execution for each colony are similar, with differences dependent on species and use of the respective colonies. All husbandry procedures are documented in SOPs, and no significant changes have been made during this reporting period. The feed type and source have not changed. The birth rate for the baboon breeding colonies remains relatively high at 0.8 births per breeder female per year. During the year some baboons have been sold to other biomedical research facilities. Due to a highly successful breeding program, we have surplus baboons which we are marketed for sale.

A major problem during 2003 was a severe shortage of cage space. This shortage was responsible for suboptimal maintenance conditions, delays in initiation of funded experiments, reduction in productivity in NIH-funding projects dependent on progeny for genetic studies, and inability to resurface floors and to repair cages as quickly as is desirable because of nonexistent swing space. The shortages are severe in relation to outdoor caging, indoor/outdoor caging, conventional indoor caging, and indoor ABSL-2/3 housing.

We are in varying phases of design and construction of 5 renovation projects (funded through G20 grants) and 4 construction projects (funded through C06 grants). However, in relation to all types of caging except ABSL-2/3, the benefits will be largely offset by projected growth of the primate resources by production of several species, and by acquisition of additional SPF rhesus macaques, and NCRR-owned chimpanzees.

The shortage of space and consequent inability to make necessary repairs, the delays in experiments, and the reduced rate of breeding are severe impediments to scientific progress, cause financial inefficiencies, and could jeopardize the welbeing of the animals if they are not rectified during the new few years.

3. Progress in Core Service Units

In addition to the component entitled 'Directors' Offices," the base grant supported 11 service components during 2003, as follows:

Center Operations
- Facilities Maintenance and Improvements
- Blood, Tissue, and DNA Repository
- Primate Records Database and Biostatistics

Training and Outreach
- Community Outreach
- Primate Center Web Site

Primate Resources
- Geriatric Baboon Colony

Laboratory Animal Medicine Group
- Clinical and Anatomical Pathology

Physiology and Medicine Group
- Tissue Collection and Distribution
- Veterinary Technical Services

Virology and Immunology Group
- Flow Cytometry

Genetics Group
- Molecular Genetic Services
- Genetic and Demographic Management

A summary of progress by the Director's Office and each of these service units is provided on the following pages.

DIRECTOR'S OFFICE

The Director's Office is responsible for the administration of the SNPRC, for oversight of all components of the Center, and for scientific leadership. The objectives are to strengthen and improve the Center each year, to increase the quality and quantity of research conducted at the Center, to minimize the administrative burden on the other core staff, and to provide research opportunities to core staff as well as outside investigators to the greatest extent possible within the constraints of the base grant budget. The activities of the Director's Office have proceeded smoothly and efficiently, and the Research Advisory Committee has met approximately monthly for discussion of Center activities and management. The administrative staff consists of the Director ( ] effort), the Associate Director ( ], and two secretaries ( ] each). The Director and Associate Director spent significant effort soliciting and developing new resource services and resource-related research initiatives as part of the competitive renewal of the base grant. This effort will result in the development of new resources for the research community in the coming years, including a new marmoset production colony, a new colony of Nepalese rhesus macaques, a genomics database, characterization of physiological variables related to metabolic syndrome in baboons, and broadening the genetic base of the baboons used in atherosclerosis research by characterization of the chacma subspecies.

Percentage of effort

The Director's Office continues efforts to organize and formalize the training and education activities of the primate center. A summer student internship program has been instituted and is advertised on our web site. The number of applicants to this program continues to grow (n=28 for 2004), but we have remained limited to funding of one student per year. This year's intern, from Grinnell University, will work in Dr. Jeffrey Rogers' laboratory.

We remain committed to offering training opportunities to veterinary students as a means to encourage their involvement in primate medicine. Contacts have been maintained with faculty and administrators at the Texas A&M College of Veterinary Medicine, with

TAMU staff being updated on the research and training opportunities for their students at the primate center. We developed a new two-summer veterinary externship program in collaboration with TAMU that was submitted for consideration in our competitive renewal and anticipate initiating this program in the coming year.

The Director's Office is also responsible for pursuit of construction and renovation funds. [illegible] pending support

[illegible]

Dr. Tardif continues to represent the primate center in major research resource initiatives, such as the recently finded Regional Center of Excellence in Biodefense and Emerging Infectious, based at the University of Texas Medical Branch, Galveston, for which she is the leader of the Nonhuman Primate Core.

FACILITIES MAINTENANCE AND IMPROVEMENTS

This unit is responsible for maintaining and improving facilities for the primate colony so that they comply with regulations and guidelines and provide adequate housing for the animals. The objectives are to provided maintenance and selected improvements of the facilities and equipment used in the care and use of approximately 4,500 nonhuman primates. There are 64 buildings that are either primary or secondary enclosures for the primates or are used to provide veterinary care and research support. These building contain more than [illegible] square feet of usable space. An additional [illegible] of semi- free ranging compounds are used. During this reporting period the Animal Facilities Maintenance Section responded to 632 work orders for repair of our aging primate facilities. These work orders ranged in type and scope from replacing a door cable to repair of unraveled woven-wire fencing to replacing deteriorated concrete block in primate housing. Repairs were also made to the built-in mechanical cage washers as well as several portable high pressure washing units, vehicles used to support the primates, and portable cages. The primate care and use areas, both indoor and outdoor, were serviced 3 times per week for vermin control. Twenty sets of double metal doors to animals' rooms were replaced including some door frames. Safety glass windows were placed in 12 doors. The support area for the two large six acre compounds was partially renovated. Inside work area was renovated. Other smaller items of equipment such as high pressure cleaning units, floor scrubbers, etc., also were purchased. The resources provided in this unit have permitted us not only to maintain facilities, but to enhance our capabilities of providing care for the primates and of facilitating their experimental use. We will continue maintaining and improving the facilities that support the animal care and use program.

BLOOD, TISSUE, AND DNA REPOSITORY

This unit is responsible for the processing and storage of serum, tissues, and DNA from nonhuman primates maintained at the SNPRC and, in conjunction with the Tissue Collection & Distribution Component, for the distribution of samples to investigators who request them. The repository increases the efficiency of use of these biological materials and enables samples to be used in research long after the animals are dead. It also provides resources for longitudinal studies of blood components. During 2003, the following samples had been collected by this unit:

Sample Type	Baboons	Chimpanzees	Macaques	Marmoset	Cynomolgus
Serum	918	97	46	0	3
White cells	986	97	62	0	7
Clots	918	97	47	0	3
Panel of five tissues	105	1	0	3	0
Extracted DNA	391	22	108	0	0
Total	3,318	314	263	3	13

During 2003, all requests for samples were fulfilled, and the unit provided the following samples for research purposes (these samples are reported in the Research Services Section)

Samples were provided to 15 investigators, 12 of which were NIH-funded projects.

We will continue to develop the blood repository from samples collected when animals are sedated for routine purposes. Tissues will be collected from animals being necropsied. DNA will be isolated to the extent that time permits.

PRIMATE RECORDS DATABASE AND BIOSTATISTIC

The Primate Records Database and Biostatistics unit serves all other components of the Southwest National Primate Research Center. Vital statistics and clinical records of Primate Center animals are captured, maintained, and disseminated as needed by the primate records database software developed and maintained by this component. This component designs and implements data quality assurance practices and testing methods.

The objectives are 1) to design, administer, manage, and program the Primate Records Database and the database applications for SNPRC staff and other Center investigators, 2) to provide administrative, management, and technical support for network based Web servers and collaboration tool servers, 3) to provide biostatistical support for Primate Center operations, 4) to provide biostatistical and database support for investigators conducting research at the Primate Center.

We have combined two desktop applications 'animal32' and 'clinic32' into a single application 'CAMP' (Computerized Animal Management Program). This combining of the many functions into a single application has simplified many management functions and reduced the number of database licenses required. We have developed two new Palm OS device applications 'ObsSingle' and 'ToyCount'. 'ObsSingle' is used to collect observation data on singly caged animals. 'ToyCount' is used to count manipulable enrichment devices (toys) in the nonhuman primate group-housing locations.

We have developed a large software module inside 'CAMP' that is used during the semiannual roundup of baboons in the two [redacted] corrals. This software has cut in half the time required to do the roundup and allows complete collection of all medical data including blood samples taken, physical examinations, weights, sonograms, and quick treatments for injuries. We have installed and configured an application server so that we now have the ability to provide 3-tier applications including Web based applications in a secure environment.

As a part of Dr. Sharp's participation as the SNPRC representative to the combined NPRC Data Sharing Committee, we have developed working prototypes of two data sharing models. One of these, the multi-tiered virtual repository, was presented at the 2003 American Society of Primatologists meetings.

We surveyed the Primate Records database for errors and then analyzed both electronic and paper records to correct the errors. While many records were corrected, this is an ongoing project.

We will continue our survey of the databases managed by this unit to identify anomalous data, to identify the causes of the anomalous data, and then to devise new software designs, new data collection methods, or new user training that will eliminate those sources of error. This component will provide both programming and statistical support for an application to identify perimenopausal baboons. We will begin using wireless networks for remote data collection where we can insure that someone from outside the center cannot connect.

COMMUNITY OUTREACH

Our staff continues to make valuable contributions to our community in terms of science education, and animal welfare. Examples of such contributions are as follows:

Education: Staff members continued their local service as judges for local middle- and high-school science fairs, and as mentors for local students. We have hosted numerous tours of the primate center for both local high school students and college students. These tours usually include presentations from both staff involved in animal management/welfare issues (e.g. veterinarian, environmental enrichment coordinator) as well as staff scientists.

Animal Welfare: Our veterinary staff and animal care staff act as "good-will ambassadors" within the local community through their participation in animal welfare activities, including volunteering with the 4H Club and animal shelters. One of our veterinarians has for many years served as a consultant at the San Antonio Zoo, providing them with technical expertise gleaned from the research environment. Two other veterinarians have provided veterinary care to local nonhuman primate sanctuaries.

Public Information: The Office of Communications at the SFBR serves as a centralized location for the dissemination of media information regarding both the SFBR and the SNPRC. Examples of stories that received local coverage in recent months include both newspaper and television stories about our largest program project, "Diet and Genotype in Primate Atherosclerosis." The coverage included information about the renewal of this grant and progress to date on this research program, which uses baboons to learn how diet and genes interact to determine an individual's risk of atherosclerosis. A related story ran a few months earlier in the San Antonio Express-News explaining how Drs. VandeBerg, Cox, and [redacted] have developed a powerful new method for identifying genes

that control susceptibility to common diseases. At times, the work of our scientists gains national media attention, either because our Communications Office has successfully "pitched" a story to a reporter with a national media outlet or because national media have called seeking our scientists' expertise on a particular topic. Carolyn Poirot won the 2002-2003 Michal E. DeBakey Journalism Award, an award designed to inspire exceptional and outstanding news coverage of biomedical research involving animals for her story in the Fort-Worth Star-Telegram describing our humane and successful research with nonhuman primates.

PRIMATE CENTER WEBSITE

The Internet, and specifically the World Wide Web, has become an indispensable source of information exchange for scientific research. The objective of the SNPRC Web site are 1) to make available basic information about the Southwest National Primate Research Center and its facilities 2) to disseminate scientific, management and clinical information about selected nonhuman primate species, 3) to provide a convenient ordering mechanism for blood and tissue samples, and 4) to serve as a distribution point for our analytic and management software. The SNPRC Web site is on line with information about the Center and about baboons, including tables of clinical parameters for both baboons and chimpanzees, Blood and tissue ordering forms and procedures are in public use, and colony management software downloads have been active. Additional information added to the website this year includes a table of cross-reactivity of commercially available human cytokine and chemokine kits with nonhuman primate molecules (see Flow Cytometry).

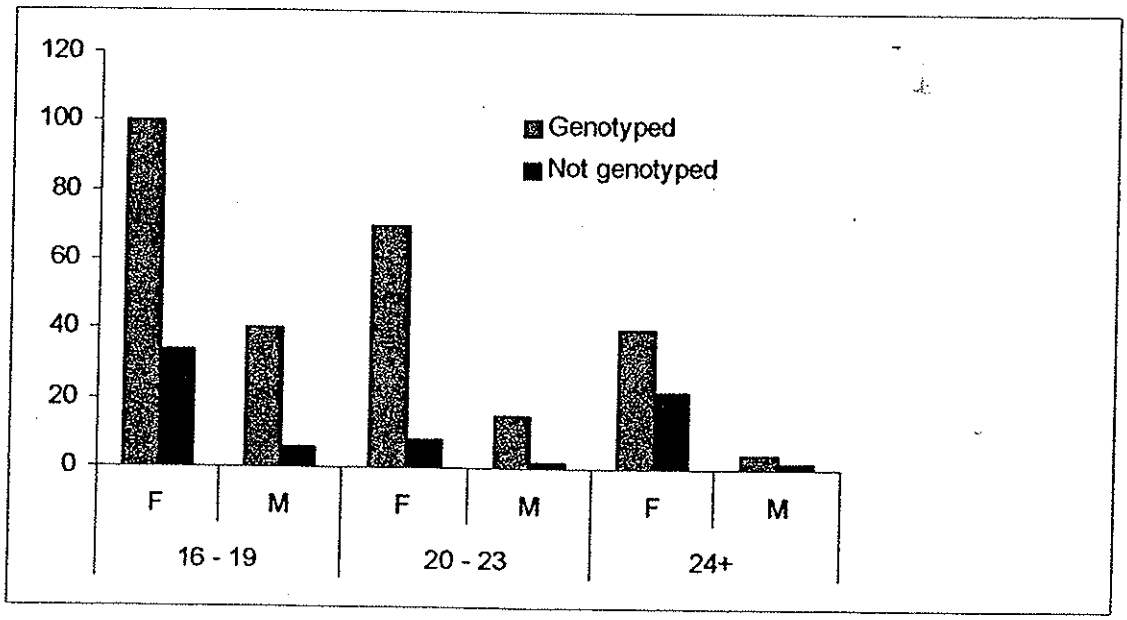
GERIATRIC BABOON COLONY

A colony of older pedigreed, mostly genotyped baboons have been developed from the pedigreed baboon breeding colony. This resource provides well-characterized, aged, nonhuman primates to examine somatic and reproductive age related changes, similar to those in humans; since the majority of animals are genotyped, there is an opportunity to examine genes associated with the age related changes. The facilities and personnel required to maintain and manipulate the colony are well established and stable. Many of the scientists who were responsible for developing the resource are using it today in independent studies relevant to aging research. One of the goals of the Geriatric Baboon colony is to measure selected reproductive, endocrine, cardiovascular, skeletal, immune, and central nervous system variables longitudinally to better characterize the aging baboon model. Using these data, we will identify somatic and reproductive phenotypes that predict age-related changes.

Current Status of the Geriatric Baboon Colony

The current census of the Geriatric Baboon Colony is 343 animals; 88% have been genotyped for the standard panel of microsatellite loci. Figure 1 displays the distribution of animals by age range, sex, and genotyped/non-genotyped ratio.

Figure 1. Demographics of the Pedigreed Geriatric Baboon Colony.



Geriatric Characterization

During the past year we performed the characterization protocol on 116 animals and we necropsied 60 geriatric baboons.

CLINICAL AND ANATAMOC PATHOLOGY

Pathology is the study of structural and functional changes in cells, tissues, and organs that underlie disease. Using morphologic, chemical, microbiologic, and immunologic techniques, pathology aids in the explanation of observed clinical changes and provides for rational clinical care, therapy, and scientific experimentation. The objectives are to support the clinical veterinary staff in maintaining the health of the animals in the colony and to assist investigators in evaluation tissue changes and clinical laboratory results from experimental animals. The pathology services improve the characterization of nonhuman primates through collaboration, publication, and tissue sharing. Methods used to achieve these aims include gross pathology, clinical chemistry, immunopathology, bacteriology, parasitology, urinalysis, coagulation, and analysis of blood gases. Clinical pathology performed 74,238 procedures during 2003 in hematology (8,348), chemistry (54,627), coagulation (2,220), parasitology (1,644), bacteriology (1,768), urinalysis (245), and send outs (5,386). Anatomic pathology had 1,361 accessions for 2003, of which 483 were surgicals, and 878 were necropsies. Slides produced numbered 10,500. This work supported essentially all projects using animals in biomedical research plus some off campus projects or approximately 230 research or research support accounts. The laboratory will continue to function and expand in its current manner but needs to hire an additional histotechnician, pathologist, and clerk. Equipment needs in order of priority include an updated coagulation unit, tissue processor, microscope, clinical pathology computer upgrade, dictating unit, computer for additional pathologist, and a walk-in refrigerator.

TISSUE COLLECTION AND DISTRIBUTION

Tissue sharing optimized the research uses of nonhuman primates by making tissues or body fluid samples available to investigators for exploratory, pilot, or feasibility studies. In addition, tissue sharing for major research projects enables efficient use of animals and reduces the total number of animals needed for research. The objective of this component is to promote the sharing of nonhuman primate tissues with intramural and extramural scientists. Whenever an animal is scheduled for necropsy, a concerted effort is made to alert investigators who may wish to preserve blood or tissue samples. During the reporting period, we provided 4,298 tissue and blood samples from animals that were necropsied or sedated for other purposes. We will continue tissue sharing and associated support activities.

VETERINARY TECHNICAL SERVICES

Veterinary Technical Services provides specialized techniques for a wide variety of investigators, thus greatly enhancing the nonhuman primate as a research resource. Projects that have benefited from Veterinary Technical Services within the past year are:

Environmental Stress and Changes Menstrual Cycle Regularity in Baboons. [name] Brown University, Providence, RI

Our goal is to examine the effect of increasing age on the daily sex hormone profile through one complete menstrual cycle in baboons. To minimize disturbance to the baboon, hormones are measured from urine collected from individually caged animals. Normally female baboons in breeding harems are maintained in social cages housing 15 to 20 animals. Moving nonhuman primates from social housing to individual caging is a stressful event that may induce an abnormal menstrual cycle. We hypothesized that moving animals during the luteal or follicular phase of the cycle would produce different results and that the quality of the cycle of the cycle would improve with increasing time in the individual cage. We identified 20 healthy female baboons of reproductive age and moved them from social housing to individual cages. Ten were moved in the early follicular phase and ten were moved in the early luteal phase of the cycle. We obtained blood and muscle samples and measured body weight and body composition by DEXA on the day of the move. We collected urine to measure cortisol for the first 10 days after the move to individual cages and urine to measure reproductive hormones for 3 cycles. Perineal turgescence was monitored daily to assess the status of the menstrual cycle. The animals were bled when they were returned to the social housing. Preliminary results demonstrate that moving the animals in the luteal disturbs the cycle least and the first menstrual cycle after the move is the most robust. Data have been compiled and are being prepared for publication and will be used to support a program project using aged baboons.

A Baboon Model of Celiac Disease. Michelle Leland, D.V.M, G. Hubbard, M.S., D.V.M., and [name] Southwest Foundation for Biomedical Research, San Antonio, TX

The predominant clinical sign of celaic disease is chronic diarrhea. A predominant morbidity of many nonhuman primate colonies is chronic diarrhea. Our objective is to identify baboons in the pedigreed colony with persistent, recurring diarrhea and test them for signs of celiac disease. When an animal is identified with chronic diarrhea, a baseline blood sample is taken to measure the antibody associated with celiac disease, a duodenal biopsy of the gut mucosa is taken and examined histologically for blunting of villae and lymphocyte infiltrate, and diet is changed to a gluten free chow. Additionally, gut samples for histological examination are being collected from animals with medically unmanageable diarrhea. We hypothetize that a percent of animals with chronic diarrhea may have celiac disease.

Characterization of epilepsy in the pedigreed baboons. Szabo, Akos, MD, University of Texas Health Sciences Center San Antonio, TX
We identify animals from the pedigreed baboon colony with naturally occuring seizures and transport them to the University of Texas Health Sciences Center where a neurologist has developed a laboratory specifically to perform electroencephalograms on these animals. The work has been continued and now includes MRI imaging in an attempt to locate the lesion in the CNS. This data has been used to develop a baboon model of epilepsy and is now being used to further characterize the model.

Normative Hematology and Blood Chemistry Values in Baboons Less Than One Year Old. [name] Department of Genetics, Southwest Foundation for Biomedical Research, San Antonio, TX
Normative values for hematological and clinical chemistry measures have been developed for adult baboons and provide the necessary baseline values for comparing values from diseased animals or animals being treated on research protocols. Our goal was to develop the same standards for baboons less than 12 months of age. We sampled and analyzed blood samples from 55 male and 55 female baboons ranging from 1 week to 12 months of age.

Effect and Feasibility of Administering Rosiglitazone to Insulin Resistant Baboons for Fourteen Days. [name], Department of Genetics, Southwest Foundation for Biomedical Research, San Antonio, TX
Thiazolidinediones are a class of antidiabetic agents that improves diabetic control by improving insulin sensitivity. They improve sensitivity to insulin in muscle and adipose tissues and inhibit hepatic gluconeogenesis. For this project we identified 2 obese female baboons with fasting blood glucose levels in excess of 130 mg/dl. We administered 4 mg of Rosiglitazone embedded in a half banana for 15 days. Blood samples for glucose and Hba1c were taken before and after drug administration.

SURVEILANCE OF HEPATITIS INFECTIONS IN THE CHIMPANZEE COLONY

This unit is responsible for screening the chimpanzee colony for all hepatitis markers and maintaining a database on the current status of each animal with respect to hepatitis B virus (HBV) and hepatitis C virus (HCV) exposure and serological status. Approximately 2% of the US population is chronically infected with hepatitis C virus (HCV). Chronic infections with HCV result in significant liver disease, including cirrhosis and liver cancer in approximately 20% of infected individuals. Hepatitis B virus infections are also a major cause of death due to infectious disease. The current therapies for these viruses do not result in viral clearance in the majority of cases. The chimpanzee is the only animal susceptible to infection with these viruses other than man. The development of improved strategies to treat HBV/HCV chronic infections is essential for the control of these diseases. The chimpanzee colony at the Southwest National Primate Research Center is a valuable resource for these studies. The animals have been used in a variety of transmission, drug and vaccine studies with various hepatitis viruses. A careful characterization of these animals is needed such that this information can be utilized when selecting animals for future studies and interpreting the results of studies. The objectives of this project are: 1) to conduct an evaluation of all chimpanzees at the Southwest National Primate Research Center with respect to HBV and HCV markers; 2) to perform an evaluation of all newly infected animals to determine whether chronic infection develops and to obtain a greater understanding of the disease outcome in HBV/HCV-infected chimpanzees; 3) to maintain a program on viral discovery to examine and archive samples potentially containing a novel hepatitis agents from nonhuman primates; and 4) to maintain a computerized database with current and historical infectious disease information on the chimpanzees. This year we have completed the review of all historical documents and entered the information into a computer database designed for this purpose. We have completed the initial screen and for most animals the second screen for all HBV and HCV assays. We have complied data on the status of each animal as well as the colony as a whole. This component will continue to monitor the colony and update the computer files.

DIAGNOSTICS OF RETROVIRUSES

The overall goal of this diagnostic component is to provide a resource to screen apes and monkeys for the known simian exogenous retroviruses. The aims are : 1. To further develop and improve retroviral screening technologies to assess infection by nonhuman primate retroviruses, 2. To provide support in testing for retroviruses found in nonhuman primates in the SNPRC colony, and 3. To provide support for outside investigators seeking to assess monkeys and humans for evidence of retroviral infections.

During the past year, this retroviral diagnostic component has developed the capacity to screen nonhuman primate species for evidence of exogenous retroviral infections known to persist in African and Asian nonhuman primates. Specifically we have developed serologic and nucleic acid based assays to screen Asian macaques for SRV, STLV, SIV and SFV. In addition, we have developed assays specific for African nonhuman primates including baboons, African green monkeys and chimpanzees that detects STLV, SFV, and SIV. Recently we have switched from using nested DNA PCR testing that can have false positives from PCR contamination to Real-Time Taqman PCR based assays which represent a rapid, high-throughput screening of SRV and STLV. We are now using these Taqman assays for routine screening which has substantially reduced both technician time and cost associated with retroviral screening. For the most part, we have concentrated on screening macaque colonies at the SNPRC. Two SPF rhesus colonies are being routinely screened. To briefly summarize, we have detected evidence of STLV (4/134) and SRV (4/126) in a small number of animals in our SPF Colony (2). Screening of the non-SPF colony has also been instituted and we have detected 6/95 STLV+ rhesus macaques.

These colonies are being retested on a quarterly basis until the colonies are retrovirus-free. In summary, our results have shown that STLV and SRV is present at low levels in our rhesus macaque colonies. Because commercially available diagnostic testing was initially used to screen these colonies, this component has been instrumental in detecting and removing true positives from the colonies. Our screening methods have greater specificity and sensitivity than assays previously used to screen these colonies.

FLOW CYTOMETRY

Flow cytometry is a widely used method for analyzing the expression of cell surface and intracellular molecules, characterizing and defining different cell types in heterogeneous populations, assessing the purity of isolated subpopulations, and analyzing cells size and volume. Flow cytometry analysis can provide critical information both in clinical evaluation as well as scientific research. The goal of this component is to provide assays based in flow cytometry that will allow for the characterization of blood cell subsets, activation markers, cytokine and chemokine quantification, and cell-mediated activity in cells of nonhuman primate species such as chimpanzees, baboons, African green monkeys, and several macaque species such as rhesus, pig-tailed, and cynomolgus macaques. Using a multicolor flow cytometer, we have determined that the combination of antibodies labeled with the fluorescent dyes FITC, PE, PerCP-Cy5.5, APC, and APC-Cy7 permits the identification of 5 different markers in a single cell with minimal spectral overlap and little compensation. This 5-marker capability allows the identification of several cell subsets that were not detected before with our old 3-color flow cytometer. The other main component of the Flow Cytometry core facility is the Luminex^{100} system, which is a bench-top flow cytometer with two low-power laser beams that allows the user to perform simultaneously up to 100 tests in a single tube (or well of a microtiter plate). Our laboratory has tested almost all the commercially available Luminex-based kits for human chemokines and cytokines for their crossreactivity with NHP molecules. We have identified 12 kits whose reagents recognize molecules from chimpanzees, baboons, rhesus macaques, pig-tailed macaques, cynomolgus macaques, and AGMs. We have also developed four sets of conjugated beads and detecting antibodies. All these reagents can be used simultaneously to detect 16 cytokines and chemokines in a single sample from a NHP species.

MOLECULAR GENETIC SERVICES

Nonhuman primates are a critical component of biomedical research as animal models for many human diseases. Development of pedigreed colonies of primates will expand opportunities for disease-related research by allowing primate species that are not now used for genetic studies to be used in that manner. The objective of this project is to use genetic polymorphisms (both currently known polymorphisms and new markers) to perform paternity testing, pedigree verification, and other colony management activities for funded colonies of nonhuman primates. We have established collaborative arrangements with the University of South Alabama to perform paternity testing in squirrel monkeys (*Saimiri boliviensis*), with the Oregon NPRC, Yerkes NPRC, NIAAA Animal Research Center (Poolesville, MD) for studies of rhesus monkeys (*Macaca mulatta*), and the Washington NPRC for pigtailed macaques. We continue to perform similar analyses for the baboons and other primates maintained at the SNPRC. We will continue to receive blood samples from various colonies, and use genetic markers developed at the SNPRC to complete the planned paternity testing. New collaborations to do pedigree testing for Yerkes NPRC mangabeys and M.D. Anderson Cancer Center chimpanzees are in the planning stages.

GENETIC AND DEMOGRAPHIC MANAGEMENT

Loss of genetic variability may reduce the likelihood that genes underlying biomedically relevant phenotypes can be detected, and may bias or reduce the generality of experimental outcome as animals become more genetically homogeneous. Knowledge of pedigree relationships is particularly crucial for genetic analyses, which depend on detecting Mendelian transmission patterns underlying the distribution of phenotypes in families.

The aims of this component are to monitor the genetic and demographic structures of Primate Center colonies, to provide information required for rational colony management, and to maintain and develop the software necessary to carry out these tasks.

We have continued to maintain PEDSYS, our database system and have developed and implemented new functions, updated user documentation, and uploaded these to the SNPRC web-site. Additionally, we have developed and are evaluating a prototype browser-based reporting system which is intended to serve as a tool for enhancement and expansion of our pedigree data management system.

We will continue our software maintenance operations, and will analyze genetic and demographic structures of SNPRC and other populations, as needed. Recent activities of this sort included (1) selection of unrelated progeny for assessment and validation of experimental dietary challenges and use of assay kits designed for use in human subjects in research using baboon model (e.g., NIH P01 HL028972 [PI: JL VandeBerg, SNPRC], NIH R01 HL068972 [PI: OS Platt, Harvard Children's Hospital]) and (2) identification/validation of pedigree relationships between living genotyped animals and archived skeletal samples from deceased animals for dental genetics studies (NSF [PI: Crawford, U of Illinois]).

In collaboration with the Genetics Group leader, Dr. Rogers, and the NCRR, we hosted a national meeting of the NCRR Primate Genomics Working Group at the SNPRC in December, 2003.

We have added a new objective to this component i.e. development and implementation of a Primate Genomics Database at SNPRC. We have proposed to expand this objective into a distinct component in the renewal of the SNPRC base grant. Meeting this objective will entail us doing the following: 1) design, implement, and maintain a Primate Genomics Database (PGD), including infrastructure and worldwide web (WWW) interface; 2) design, implement, and maintain informatics tools for the PGD; 3) curate the content of the PGD and provide documentation and user support; and 4) establish a mechanism for periodic evaluation of PGD research utility and determination of new goals and objectives in order to better serve those researchers most in need of nonhuman primate genetics and genomic data. In collaboration and consultation with investigators in Medical Informatics at the Oregon Health Sciences University and the Mouse Informatics group at the Jackson Laboratory, we will model the PGD after the established rat genome database (RGD; http://rgd.mcw.edu/) at the Medical College of Wisconsin and the mouse genome database (MGD; http://www.jax.org). Initial content for the PGD will include the baboon STR-based whole genome genetic linkage map and related information. Subsequently, data on QTLs, genes, phenotypes, etc. from analyses using this map; similar information for the rhesus macaque; and targeted sequence and expression data from these and other nonhuman primate species will be added.