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

2P51RR000167-45

NATIONAL PRIMATE RESEARCH CENTER SUPPORT

Final

UNIVERSITY OF WISCONSIN-MADISON

ANNUAL PROGRESS REPORT

Reporting From: 04/30/2005

Reporting To: 04/29/2006

66.500% AIDS Related

Patent or Copyright was not awarded this grant year.

PERSONNEL ROSTER

Core Doctoral Scientists

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

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
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withheld		Proprietary Info
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		U MASS. MEDICAL SCHOOL: MA, USA
		WAYNE STATE UNIVERSITY: MI, USA
		ONPRC: OR, USA
		UNIVERSITY OF TEXAS AT AUSTIN: TX, USA
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		UNIVERSITY OF MINNESOTA: MN, USA
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		UNIVERSITY OF OKLAHOMA: OK, USA
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Name, Degree	Department	Non-Host Institution: State, Country
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		ONPRC: OR, USA
		FELS INSTITUTE OF CANCER RESEARCH & TEMPLE U. SCH. OF MEDICINE, PHILADELPHIA: PA, USA
		UNIVERSITY OF NEW ORLEANS AND
		Proprietary Info LA, USA
		Proprietary Info
		CNPRC: CA, USA
		Proprietary Info
		OKLAHOMA HEALTH SCIENCES CENTER: OK, USA
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		ONPRC: OR, USA
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		UNIVERSITY OF MINNESOTA: MN, USA
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		CALIFORNIA NATIONAL PRIMATE RESEARCH CENTER: CA, USA
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		UNIVERSITY OF PITTSBURGH: PA, USA
		Proprietary Info
		Proprietary Info
		Proprietary Info

SUBPROJECT DESCRIPTIONS

NPRC MANAGEMENT SUBPROJECTS

WNPRC DIRECTOR'S OFFICE (0184)

NPRC UNIT: ADMINISTRATIVE

%NPRC $: 7.750% **AIDS RELATED RESEARCH**

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

SUBPROJECT DESCRIPTION

The Director's Office hosted two general staff meetings in FY2005-2006, five scientific seminars, three scientific retreats,
monthly internal advisory board meetings, an external advisory board meeting, and a chancellor's visit. The chancellor's
visit was also attended by the deans of the UW-Madison Graduate School and Medical Schools.

Highlights discussed at the retreats included a new Information Services initiative on bioinformatics and data sharing (see following section), meeting needs for specialized research resources, and updates in our current research program.
As part of the External Advisory Board meeting, five new scientific affiliates highlighted their work on movement disorders, aging and calorie restriction, kidney transplant survival, embryonic stem cell research, and genetics typing.

The director and colleagues visited China in August and September. Their visit began at the Proprietary Info
and ended at the Proprietary Info A private foundation hopes to establish a network of research expertise and
ability to include sufficient access to nonhuman primates, so that promising new therapies for Parkinson's disease can be
tested with minimal delay. The team worked with Chinese researchers and animal care staff to set up a new training and breeding site, an IACUC, CDC animal transfer protocols, data pools and other advancements.

The director was appointed to the Council of the Institute for Laboratory Animal Research (ILAR) of the National Academies. (See the awards section of this annual progress report.) He was also appointed to the long-range planning
committee for the General Clinical Research Center at UW-Madison and has been elected chair of the Biological Sciences
Section for GSA.

The director presided over a successful AAALAC site visit, the grand opening of the new UW-Madison and WNPRC AIDS
research lab, and the renaming of the Primate Center Library in honor of withheld The director attended the
following meetings off site in FY 2005-2006:
-- Rosalind Franklin Comprehensive Diabetes Center at the Chicago Medical School for scientific collaboration on diabetes, July.
-- NIDDK Special Emphasis Review Committee Panel, Washington, D.C., July.
-- Proprietary Info July and November.
--58th annual scientific meeting of the Gerontological Society of America (GSA), Orlando, November.

The Primate Center hired a new coordinator of Centralized Protocol Implementation. This position now reports to the
Director; it previously reported to the Associate Director of Animal Services.

Training in the Director's Office included three training courses for the public information officer and outreach specialist—
two embryonic stem cell culturing methods laboratory courses and an animal handling course. The executive

assistant
to the director attended a Spanish in the Workplace class. The PIO and the executive assistant attended a training meeting on research communications strategies in Chicago.

Most of the Center's general progress in FY2005-2006 is readily available via materials produced by the Public Information Office, with support from Information Services. These materials—press releases, publication lists, newsletter
articles and more appear at www.primate.wisc.edu. Local, national and international scientific media interest in WNPRC
activities remained high, while animal rights related press coverage about the Primate Center and UW-Madison was mostly limited to one downtown tabloid and two campus newspapers.

WNPRC ANIMAL SERVICES DIVISION (0214)

NPRC UNIT: ANIMAL SERVICES

%NPRC $: 22.000% **AIDS RELATED RESEARCH**

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

SUBPROJECT DESCRIPTION

The Division of Animal Services has undergone a major reorganization since a new Attending Veterinarian and Associate Director of Animal Services began on March 1, 2005. These changes include the creation of a new unit (Compliance and Training); the reorganization of the Colony Management unit; and the addition of several new key personnel. Currently, the division is responsible for the following duties:

1. Provision of veterinary care for the nonhuman primate colony.
2. Provision of animal husbandry for the nonhuman primate colony.
3. Provision of research support for the principal investigators performing animal research at the WNPRC.
4. Oversight of all regulatory compliance.
5. Training of all employees who may come in contact with live nonhuman primates or nonhuman primate tissues.

The Associate Director has formalized the regulatory component of Animal Services by hiring an experienced Compliance Coordinator and teaming her with the Animal Services Training Coordinator to ensure that the facilities, protocols, and personnel of the WNPRC are in compliance with all institutional, local, state, and federal laws, regulations, and guidelines.

Veterinary Services Unit

The Veterinary Services Unit is principally responsible for providing veterinary care to the nonhuman primate colonies of the WNPRC and for providing research support for the investigators who utilize the animals housed at the Center. Due to the continuing growth of the colony and the rapid growth in demand for research support, the unit hired two additional veterinary technicians and an additional surgery technician in 2005. Currently, four EFFORT veterinarians, four EFFOR veterinary technicians, one EFFO surgery technician, and one EFFORT surgery technician staff the unit. The unit's animal health program consists of a rigorous program of preventative medicine (e.g., quarantine, semi-annual tuberculin skin testing, routine physical exams, timely dental prophylaxis, periodic viral survey), extensive diagnostic capabilities, and excellent clinical care.

Colony Management Unit

This pivotal unit of Animal Services is responsible for an array of tasks including animal husbandry, the colony records system, and environmental enrichment. Under the leadership of the Associate Director of Animal Services, this unit has undergone extensive reorganization. To standardize the provision of animal care, the two-colony manager system was eliminated and one colony manager now oversees the entire unit. After an extensive national search, a candidate with extensive experience in nonhuman primate colony management was offered the Colony Manager position and is expected to begin employment at the WNPRC on April 15, 2006. Additionally, two new animal care supervisors with extensive nonhuman primate experience have been added to the unit to help oversee the 24 animal research technicians who provide daily husbandry for the nonhuman primate colony. In addition to performing all daily husbandry duties, the animal research technicians also check the health of each individual member of the nonhuman primate colony on a daily basis, report all evidence of morbidity to the veterinary staff, assist with the implementation of the environmental enrichment program, and provide research support (e.g., sample collection, data collection, medication administration, etc.) to the scientists performing research at the Center.

Colony Records

One EFFO DT and one EFFO assistant staff this subunit of Colony Management. The subunit is responsible for maintaining and updating all data on clinical procedures, animal location transfers, treatments, research procedures, surgical procedures, sample collections, and observations. The subunit is appropriately situated in the Colony Management unit to foster frequent communication among personnel performing the work being documented. The unit works closely with the Information Services Division of the WNPRC to continuously improve the
Internet-based version of the Colony Records Database to facilitate and simplify the data entry and retrieval process.

Environmental Enrichment

Under this Colony Management subunit's coordinator, the environmental enrichment program of the WNPRC is vibrant and growing. Currently the program utilizes social companionship, manipulanda, structural enrichment, edible enrichment, and positive human-nonhuman primate interaction to improve the psychological well being of the nonhuman primate colony. The enrichment program also focuses increased effort on improving the well being of those colony members that exhibit stereotypical or self-injurious behavior. Over the last year, the coordinator of the subunit has hired an assistant and a part-time student to facilitate implementation of the more rigorous components of the enrichment program.

Compliance and Training

This unit was established in 2005 to unify the compliance and training initiatives of the WNPRC. The compliance arm of this unit is led by the newly hired compliance coordinator and the training arm is led by the new training coordinator who work to ensure that the facilities, personnel, and IACUC protocols of the WNPRC comply with all
institutional, local, state, and federal laws, regulations, and guidelines pertaining to animal research. The Compliance and Training unit serves as a resource for any/all WNPRC personnel working with nonhuman primates to provide a safe work environment for the humans and animals through detailed education and intense hands-on experience.

DEVELOPMENT OF METHODS TO IMPROVE ISOLATED PANCREATIC ISLET FUNCTION (0396)

NPRC UNIT: IMMUNOLOGY

%NPRC $: 0.500%

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

SUBPROJECT DESCRIPTION

UNIT ALSO AGING AND METABOLIC DISEASE

To develop new methods for the isolation and evaluation of isolated pancreatic islets for the purpose of transplantation into patients with type I diabetes.

The results obtained using non-human primate tissue will aid in the development of methodologies for the isolation and assessment of human islets. Methods include; 1) characterization of the physiological response to glucose as a rapid potency indicator of the quality of the islet preparation prior to transplantation,. 2)- determination of the effects of hypoxia on islet viability and function after isolation, 3) determination of the sensitivity of islets to cytokine induced apoptosis. Determination of viability and apoptosis will be performed using a novel approach in which islets can be analyzed intact, preserving their complete architecture using Complex Object Parametric Analyzer and Sorter (COPAS) flow cytometry. We will also evaluate the ability of COPAS viability and apoptosis measurements to provide predictive data on islet function after transplantation using a marginal mass model of human islet transplant in streptozotocin-induced diabetic immunodeficient mice. In addition, the development of rapid, accurate, and predictive tests of islet viability and function post isolation will contribute to significant improvements in post transplant success. This research used WNPRC Research Services.

SUBPROJECT PROGRESS

Accurate quantification of total islet yield is an essential step prior to transplantation and for research. The standard method of manually determining an islets equivalent (IEQ) count is subjective and prone to error. We evaluated COPAS large particle flow cytometry for the determination of islet equivalent counts and purities of islet preparations. Initial validation of the sensitivity and accuracy of the COPAS flow cytometer was performed by analysis and sorting of uniform polystyrene microspheres with sizes similar to islets. Human and Rhesus monkey islets were stained with the zinc-specific fluorescent dye Newport Green to discriminate islet from non-islet tissue. Islet sizes were extrapolated from standard curves obtained using microspheres from which individual islet volumes were calculated. IEQ counts on six islet preparations were performed by the standard manual method and compared with results obtained by automated COPAS flow cytometry. The COPAS flow cytometer was highly accurate in the detection and measurement of both polystyrene microspheres and islets. IEQ counts determined by COPAS flow cytometry were consistent with manual counts although subject to error when assessing preparations with significant numbers of islets embedded within acinar tissue. Size specific islet sorting with retention of morphology and dithizone staining was also shown using the COPAS flow cytometer.

WNPRC INFORMATION SERVICES (0383)

NPRC UNIT: LIBRARY

%NPRC $: 0.500% **AIDS RELATED RESEARCH**

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

SUBPROJECT DESCRIPTION

The Information Services Division, established in January 2006, supports the research and outreach missions of the National Primate Research Center, University of Wisconsin Madison. The Division consists of two existing units, the
Jacobsen Library and the Data Management & Digital Imaging Unit (IT), and the newly established, yet-to-be populated,
Informatics Unit. All three Units will work closely together to provide a continuum of information services and resources
to the Wisconsin Center.

Beginning in January 2005, the Wisconsin National Primate Research Center embarked on an informatics strategic planning process. The Center hired on outside consultant to aid the staff in the process and to document the outcome. The Wisconsin Center, recognizing the importance of collaboration and data sharing, has invested both time and local funds to develop an understanding of what needs to be done to make this a reality. The Informatics Strategy takes the idea of sharing information and data to the next level, the creation of a systems environment to optimally support primate research activities collaboratively across the primate research community through the sharing of information, tools, and best practices. Each of the three units, under the auspices of the Information Services Division, while continuing to provide services and resources to the Wisconsin Center, will play a key role in
furthering the WNPRC's Informatics Strategy.

Staff Member Training/Conferences (all units):

• Medical Library Association Annual Meeting, May 15-19, 2006, San Antonio, TX.

• A Field Guide to GenBank and NCBI Molecular Biology Resources, NIH/NCBI/NLM, July 20, 2005, Sponsored by the
Jacobsen Library and the Ebling Health Sciences Library, University of Wisconsin-Madison.

• Annual Meeting of the American Society of Primatologists, Aug. 17-20, 2005, Portland, OR.

• WiLSWorld July 19-20, 2005, Madison, WI

• Apple World Wide Developers Conference, June 6-10, 2005, San Francisco, CA.

• Lockdown 2005 – Computer Security Conference, July 14-15, 2005, Madison, WI.

• Rapid Requirement Analysis: Capturing Your Customer's Real Needs, Jan. 31–Feb.1, 2006, Madison, WI.

• Using OSX (Mac), DoIT Professional Technical Education, Dec. 13, 2005, Madison, WI.

• 5th Annual Wisconsin State Training Conference, Wisconsin State Training Council, March 1, 2006, Madison, WI:

• Effective Technical Documentation, DoIT Professional Technical Education, March 21-22, 2006, Madison, WI.

OPERATIONAL SERVICES (0390)

NPRC UNIT: OPERATIONAL SERVICES

%NPRC $: 7.750% **AIDS RELATED RESEARCH**

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

SUBPROJECT DESCRIPTION

Operational Services is the WNPRC's business office and serves as the central point for the following administrative functions: Accounting, Human Resources, Payroll and Benefits, Purchasing, Grants Management, and Facilities and General Shop. The primary mission of Operational Services is to provide all necessary services and assistance to support the Center's infrastructure and independently funded research projects of WNPRC principal investigators. All personnel in Operational Services appreciate and promote a customer service approach in carrying out the day-to-day administrative functions. In addition, Operational Services staff work to assure compliance with all administrative and regulatory requirements of the university, State of Wisconsin and federal cognizant agencies.

Over the last 12 months Operational Services has accomplished the following:
1. Facility security upgrades.
2. Fully implemented a monthly financial reporting system to assist principal investigators in tracking and monitoring research project costs.
3. The Human Resources unit held training sessions for Animal Care Staff, as well as center-wide training for all staff. These sessions included: Safety and Occupational Health, Spanish in the Work Place, Sexual Harassment, and Improving Customer Service.

Operational Services continues to provide administrative support to the Center and its principal investigators while maintaining a high degree of customer support in light of flat Base Grant funding.

Capital Equipment List, May 2005 to April 2006
Equipment, Cost and Unit:

Vigie Primate Systems, $16,500, Parkinson's
Eppendorf Refrigerated Centrifuge, $10,689, AIDS Lab
MagnaPure LC Instrument, $84,500, AIDS Lab
Single Chamber Incubators, $15,080, AIDS Lab
C25 Incubator Shaker w/UNI Platform, $6,520, AIDS Lab
#ZFS - 4 Bowel Super -Q, $7,400, Stem Cell
REVCO -86 Deg. C Freezer, $6,484, Assay
Eppendorf Refrigerated Centrifuge, $5,344, AIDS Lab
Vertical Laminar Flow Bench, $8,729, Stem Cell
NAPCO 6000 CO2 Incubator, $6,196, Stem Cell
Melles Griot HENE Laser, $6,895, AIDS Lab

Total = $174,337

WNPRC RESEARCH SERVICES DIVISION (0340)

NPRC UNIT: RESEARCH SERVICES

%NPRC $: 10.000% **AIDS RELATED RESEARCH**

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

SUBPROJECT DESCRIPTION

The Associate Director for Research Services oversees activities in the Primate Center's five service units. As always, the organization and presence of different Units continues to be dynamic, and responsive to the needs of the investigators and cutting edge science. In 2005 the five Units consisted of Assay, Genetics, Pathology, Virology and Immunology, and Centralized Protocol Implementation (CPI) Services. Changes include moving the Genetics portion out of Immunogenetics and Virology and moving Library Services to the newly formed Information Services. Both moves indicate the success and increasing need for the services of each Unit. In the case of the Genetics Service, the technology and user base expanded rapidly when the activities in the Genetics Resource became part of the Service Unit of Immunogenetics and Virology. Given this increase in Unit activities, it became apparent that an independent Unit Head was needed, and one was appointed. In a similar manner, the expansion of information technology and use of the same in relation to the Center required formation of Information Services, the description of which is detailed elsewhere in this document. The CPI Service Unit continues to expand, and had a smooth transition when the administrative Unit Head retired in July and was replaced by a former colony manager with a doctorate degree in animal behavior. In 2005 both Assay and Pathology Services had major equipment purchases move from primarily developmental to full chargeback status. The high-pressure liquid chromatography system in Assay Services was used to measure multiple steroids in low concentrations for endocrinology studies and perform peptide identification for developmental studies. The Pathology Unit's confocal system with 4 visible light lasers and the pulsed near infrared laser for multiphoton excitation is being increasing utilized by stem cell investigators and developmental biologists as well as AIDS investigators.

RESEARCH SUBPROJECTS

AUDITORY THRESHOLDS AND AGING (0253)

NPRC UNIT: AGING & METABOLIC DISEASE

%NPRC $: 0.500%

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

SUBPROJECT DESCRIPTION

To determine noninvasively the effects of aging and reduced caloric intake on the physiological measures of sensitivity to sound stimuli.

Progressive sensorineural hearing loss (presbycusis) beginning in middle age is typical in humans. The change predominantly affects high- frequency tones. Reduced caloric intake (CR) has beneficial effects on aging in several models. This subproject assesses the effects of moderate CR on auditory evoked potentials in rhesus monkeys eating ad libitum compared to a reduced food allotment.

Thresholds were measured using auditory brainstem responses (ABR). Click thresholds increased with age, but indicated no difference with respect to diet group. For click thresholds, there was no progression of hearing loss over the past five years in either group as measured with click stimuli. These data may reflect the fact that some of the older monkeys whose thresholds would be expected to increase further with age had died in the intervening five years between assessments. ABR thresholds were also determined for 8, 16, and 32 kHz tone pips. Thresholds increased for each of these frequencies with aging. Threshold increases with age were minimal for 32 kHz, however, probably reflecting a ceiling effect as many thresholds reached equipment limits for older monkeys.

Distortion product otoacoustic emissions (DPOAE) are very low amplitude sounds emitted from the normal cochlea. In
both humans and rhesus monkeys, decreased amplitudes of DPOAEs have been documented in relation to aging. In this study, the effects of CR on hearing, as measured with DPOAEs, were not found to result in significant preservation
of auditory function. In fact, DPOAE amplitudes with aging were either statistically the same or significantly reduced in
the CR group compared to the controls.

We plan to continue these assessments on the effects of age, sex, and diet as the animals age. This research used WNPRC Animal Services and Aging Resources. No current reporting period funding.

MENOPAUSAL HOT FLASHES (0198)

NPRC UNIT: AGING & METABOLIC DISEASE

%NPRC $: 0.500%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
withheld				WAYNE STATE UNIVERSITY , MI USA

SUBPROJECT DESCRIPTION

To develop a primate model of menopausal hot flashes.

More than 30 million women in the U.S. suffer from menopausal hot flashes, which are associated with severe discomfort, sleep loss, fatigue and, possibly, depression. Although hormone replacement therapy is an effective treatment for hot flashes, most women do not receive it due to a fear of cancer. A better understanding of the causes of hot flashes will aid in the development of improved treatments. We have shown that hot flashes are triggered by small fluctuations in body temperature acting on a thermostat that is too tightly regulated. Since the thermostat (hypothalamus) is located in the middle of the brain, it is not easily studied in humans. We are studying whether we can replicate human indicators of hot flashes, such as increased skin temperature and sweating, in rhesus monkey models of menopause. This research used WNPRC Animal Services and Aging Resources.

WATER SOLUABLE NUTRIENT ABSORPTION (0318)

NPRC UNIT: AGING & METABOLIC DISEASE

%NPRC $: 0.500%

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

SUBPROJECT DESCRIPTION

To better understand the digestive physiology of non-human primates by measuring the extent of passive absorption of water-soluble nutrients.

This project has important implications for understanding the digestive physiology of humans and non-human primates, and also for understanding vertebrate nutritional ecology and toxicology. Many nutrients, natural toxins and synthetic toxins and drugs are hydrosoluble. Efficient transport of hydrosoluble chemicals across the vertebrate small intestine likely depends on membrane transport proteins (mediated transport); however, some animals can efficiently transport these chemicals through the gaps between cells (i.e., by a passive, paracellular pathway). We use physiological and pharmacokinetic techniques to test the extent of passive absorption in primates. This study began during the fall of 2003 and was completed by December of 2005. This research used WNPRC Animal Services. In Preparation

REGULATION OF FOOD INTAKE AND OBESITY (0255)

NPRC UNIT: AGING & METABOLIC DISEASE

%NPRC $: 0.500%

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

SUBPROJECT DESCRIPTION

To identify peptides that modulate ingestive behavior in primates.

Obesity has reached epidemic proportions in developed countries and this is having a profoundly negative impact on health and health care systems. Several peptides have recently been identified that may regulate appetite and feeding behaviors. We are evaluating the effects of central and peripheral administration of these substances and their antagonists in rhesus monkeys, with the long-term aim of reducing obesity and ameliorating its consequences. This research used WNPRC Animal Services and Aging Resources.

PRIMATE AGING DATABASE (0328)

NPRC UNIT: AGING & METABOLIC DISEASE

%NPRC $: 0.500%

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

SUBPROJECT DESCRIPTION

To develop and manage a database of primate biomarkers of aging to improve collaborative research and treatment efforts related to diseases and disorders of aging.

The Primate Aging Database (PAD) is a multi-center, relational database of biological variables in aging, captive nonhuman primates. The NIA, National Center for Research Resources (NCRR), and National Primate Research Center, University of Wisconsin-Madison, have already organized nearly 500,000 data points on 17 species at nine facilities. An invaluable research, veterinary and clinical resource, PAD now features biomarkers on body weight, blood chemistry and hematology. The PAD was made generally available during the current report period (http://ipad.primate.wisc.edu/index.jsp). This research used WNPRC Aging Resources and IT Services.

AGE-RELATED DECLINE IN TESTOSTERONE BIOACTIVITY (0341)

NPRC UNIT: AGING & METABOLIC DISEASE

%NPRC $: 0.500%

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

SUBPROJECT DESCRIPTION

To examine age-related changes in testosterone levels, control of testosterone secretion and testosterone metabolism in older rhesus monkeys.

Many middle-aged and elderly men are taking testosterone, believing it can restore the vitality of youth, improve mood and memory and increase sexual drive. Approximately 1.75 million prescriptions were written in 2002. Staff at the National Institute on Aging expressed concern that the testosterone boom was a public health issue and wanted a large clinical trial. Those at the National Cancer Institute were concerned about giving healthy men testosterone in large clinical studies when it might fuel the growth of prostate cancer. But all agreed that research needed to be done. Limited studies demonstrate that many symptoms of aging (weakness, diminished sex drive, osteoporosis and sense of malaise) occur in young men who do not make testosterone. These symptoms are reversible by testosterone therapy. Also, testosterone levels gradually decline as men grow older. However, there are limited published studies of this nature and they have been conducted with relatively small numbers of subjects. We are examining in more detail age-related changes in testosterone levels, control of testosterone secretion and testosterone metabolism, using older rhesus monkeys as an animal model. This project ended successfully this year. This research used WNPRC Animal Services and Aging Resources.

ASSESSING HIGH DIETARY VITAMIN A (0272)

NPRC UNIT: AGING & METABOLIC DISEASE

%NPRC $: 0.500%

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

SUBPROJECT DESCRIPTION

To further define the effects of chronically high dietary vitamin A.

Recent work examining the vitamin A (VA) status of rhesus monkeys (Macaca mulatta) used as models for human biomedical research revealed subtoxic hepatic VA concentrations. Marmoset monkeys (Callithrix jacchus), also showed high VA levels and high serum retinyl ester concentration. Both species consumed common research diets that provided up to four times the amount of VA recommended by the National Research Council. Further interpretation of these findings is limited to tissue retinol and retinyl ester profiles and extrapolation from other species rather than direct comparison to normal values. To further define VA status in rhesus monkeys, male rhesus monkeys were used for a study that involved stable isotopes and liver biopsies. While the VA analysis is still in process, we found "abnormal" values in the chemistry screening profiles in 10 of the 16 male rhesus monkeys (age range 8 to 15 years). Among the monkeys, these included elevated alkaline phosphatase, gamma-glutamyl transferase, lactate dehydrogenase, and aspartate aminotransferase. Elevations of these enzymes are cause for concern as they are all markers of liver disease or malfunction, which is a direct outcome of vitamin A toxicity. This research used WNPRC Research Services.

SUBPROJECT PROGRESS

In conjunction with the Oregon National Primate Research Center, we obtained liver and blood samples from 13 vervet female monkeys that were wild caught and held in captivity for 2.29 + 0.006 years. Monkeys were fed LabDiet #5047 (45 nmol VA and 3 nmol ?-carotene/g food). The liver VA reserve was 14.6 + 2.3 ?mol/g liver; hypertrophy and hyperplasia of liver stellate cells were observed. Subtoxicity is defined as 1 ?mol retinol/g liver. Based on consumption of 2 – 4% body weight as feed, these vervets consumed 78-156 g feed/d, leading to a VA intake of 3.5 to 7 ?mol/d. The excess liver concentration is 13.6 ?mol/g and 925 ?mol/liver. Dividing this by time in captivity shows 1.1 ?mol/d excess VA was consumed. An immediate reduction in the amount of VA is warranted.

DIETARY RESTRICTION AND AGING (0160)

NPRC UNIT: AGING & METABOLIC DISEASE

%NPRC $: 0.500%

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

SUBPROJECT DESCRIPTION

To explore the possibility that dietary restriction retards aging processes in a nonhuman primate species, this Program Project has provided a wealth of new information about the biology of aging and how the manipulation of diet can influence the process of growing old.

Rhesus monkeys eating 30 percent fewer calories of a nutritionally complete diet exhibit better health than study controls. Reduced caloric intake seems to slow basic aging processes and may extend the maximum life span in primates, as has been shown in rodents. Diabetes develops less frequently in monkeys on a restricted diet. Animals allowed to eat freely have a greater incidence of diabetic or pre-diabetic conditions. Fasting basal insulin and glucose concentrations are lower in monkeys on a restricted diet. Both fat mass and fat-free mass were lower in monkeys on a restricted diet. Monkeys on a reduced-calorie diet have fewer signs of spinal arthritis, a condition that manifests itself with age in both rhesus monkeys and humans. Fewer calories may reduce the risk of vascular disease. Caloric restriction altered circulating LDL in a manner that may inhibit atherogenesis. Caloric restriction retards several age-dependent physiological and biochemical changes in skeletal muscle, including oxidative damage. Controlled caloric restriction has not disrupted menstrual cycles of female monkeys. The next period of study should be even more insightful as the oldest monkeys in the study are now late middle age. During this phase, age-related diseases and disorders appear more frequently, including adult-onset diabetes, osteoporosis, cancers, obesity, hypertension and the loss of skeletal muscle mass. This research used Animal Services and Research Services.

GENE CONSTRUCT FOR DIABETES (0377)

NPRC UNIT: AGING & METABOLIC DISEASE

%NPRC $: 0.500%

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

SUBPROJECT DESCRIPTION

To test whether a newly developed gene therapy (using a recombinant adenoviral vector expressing a beta cell growth factor, betacellulin) can cure diabetes in rhesus macaques by the regeneration of insulin-producing beta-like cells.

Success with this gene therapy in the diabetic rhesus monkey may indicate a potential application of this gene therapy to human type 1 diabetes. The information obtained from this study will be invaluable for the development of methods to cure type 1 diabetes in humans. Project is just getting underway. This research used WNPRC Research Services.

SIV T CELLS IN VIVO (0292)

NPRC UNIT: AIDS COMPONENT

%NPRC $: 1.500% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
withheld				UNIVERSITY OF MINNESOTA, MN USA
				UNIVERSITY OF MINNESOTA, MN USA

SUBPROJECT DESCRIPTION

To study SIV specific CD8+ T cell function, localization, and association with SIV infected cells in vivo in vaccinated and non-vaccinated macaques in order to gain insights into SIV pathogenesis.

Studies of SIV infections in macaques serve as a corollary to HIV infections in humans. During the last year, we made progress in our efforts to gain insights into SIV specific CD8+ T cell responses in vivo. We stained SIV specific CD8+ T cells in specific tissue types and are determining the localization and abundance of SIV specific T cells in each tissue. In addition, we recently developed a method to visualize SIV infected cells and SIV specific CD8+ T cells simultaneously. We are using this novel methodology to characterize the SIV specific CD8+ T cell response and its relationship to SIV infected cells in vivo. This research used WNPRC Immunogenetics and Virology Services. No publications this reporting period.

PATHOGENESIS OF MUCOSAL TRANSMISSION/HIV ACUTE TRANSMISSION (0323)

NPRC UNIT: AIDS COMPONENT

%NPRC $: 1.500% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
withheld				UNIVERSITY OF MINNESOTA, MN USA

SUBPROJECT DESCRIPTION

To gain a deeper understanding of heterosexual transmission of HIV. Simian immunodeficiency virus (SIV) is an excellent animal model for HIV.

This project has been completed. These studies will establish mechanisms and dynamics of viral propagation and dissemination and the immune response to the viral challenge. This research used WNPRC Immunogenetics and Virology Services.

MAJOR HISTOCOMPATIBILITY CLASS I ALLELES (0344)

NPRC UNIT: AIDS COMPONENT

%NPRC $: 1.500% **AIDS RELATED RESEARCH**

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

SUBPROJECT DESCRIPTION

To provide genetics support to nonhuman primate researchers. This includes the establishment of a DNA sequencing service tailored to the needs of nonhuman primate researchers, identifying genetic markers important in immune responses to AIDS, and developing genetic tests for the presence or absence of these markers in individual animals.

In the past year, we have established a DNA sequencing service as a component of the WNPRC's genetics service. In its first month (January, 2006), the service processed more than 8400 sequencing samples. We have also continued to characterize genes associated with immune responses to AIDS in Cynomolgus macaques (Macaca fascicularis) from the island of Mauritius. 17 major histocompatibility complex class I (MHC-I) alleles were found in this population and we have now identified robust genotyping tests for all 17 alleles. Moreover, we discovered that the region containing these genes is much more conserved in Mauritian macaques than in Asian-origin macaques. The unusual MHC sharing in these animals may make them a uniquely valuable resource for AIDS, organ transplantation, and biodefense research. This research used WNPRC Immunogenetics & Virology Services and Animal Services.

SUBPROJECT PROGRESS

This item is included as a research subproject for the purposes of this report, but it is also a component of the Research Services Division SPID #0340. Funded by WNPRC Base Grant Genetics NL64.

IMMUNOGENETICS OF CYNOMOLGUS MACAQUES FROM DIFFERENT ORIGINS (0387)

NPRC UNIT: AIDS COMPONENT

%NPRC $: 1.500% **AIDS RELATED RESEARCH**

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

SUBPROJECT DESCRIPTION

We have recently discovered that cynomolgus macaques from different geographical locations have distinct major histocompatibility complex (MHC) genetics. Since cynomolgus macaques are increasingly used for biodefense and AIDS research, it is important to understand differences in MHC genetics. In this project, we are defining the MHC genetics of cynomolgus macaques from five geographic origins, developing genetic tests, and defining peptide-binding motifs from common MHC alleles.

This new subproject initiated in September 2005. Since the inception of this project, we have collected samples from Mauritian, Indonesian, Vietnamese, and Chinese cynomolgus macaques. Additionally, we are seeking regulatory approval to collect samples from a cohort of Filipino cynomolgus macaques. We are using a combination of approaches to identify the MHC genes present in each population of monkeys. High-throughput DNA sequencing of selected animals identified the first MHC class I alleles in Indonesian cynomolgus macaques, as well as extending the length of previously identified allele sequences from Mauritian cynomolgus macaques. Full-length MHC class II –DP, -DQ, and –DR sequencing is currently being performed on a select groups of animals from each geographic location. We have also recently developed a microsatellite map of the MHC in cynomolgus macaques and have used this map to identify common MHC haplotypes in Mauritian monkeys. This work has led to the identification of 'MHC' pseudo-twins – animals with identical MHC genetics on both chromosomes. We are currently evaluating the suitability of this technology to assay MHC genetics of other cynomolgus macaque populations. We have also modified a second MHC genetic assay, termed reference-strand mediated conformational analysis (RSCA), to study the MHC genetics of cynomolgus monkeys. RSCA successfully identified genetically matched animals for a WNPRC AIDS research study and intentionally genetically mismatched animals for a WNPRC solid organ transplant study.

CTL-BASED VACCINES FOR THE AIDS VIRUS (0147)

NPRC UNIT: AIDS COMPONENT

%NPRC $: 1.500% . **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
withheld				UNIVERSITY OF ALABAMA-BIRMINGHAM, AL USA

SUBPROJECT DESCRIPTION

To generate strong cytotoxic T lymphocytes (CTL) responses, in the absence of other immune responses, using several different vaccine approaches.

In this study, we vaccinated 8 Mamu A*01 rhesus macaques with DNA and Adenovirus vectors encoding Gag, Tat, Rev and Nef proteins from SIVmac239. The vaccinees, along with 8 control animals, were challenged multiple times with a low dose of SIVmac239 by the intrarectal route. Immune responses were determined after vaccination. Viral loads and immune responses were followed after infection. We saw robust immune responses after vaccination, which were recalled upon infection. Immune responses after infection were stronger and earlier in vaccinees than control animals. By 8 weeks post infection, we saw control of plasma viremia in vaccinees and this control is maintained even at one year post infection. We saw protection of critical CD4 memory subsets, protection of the CD4 compartment overall and protection of CD4 responses to SIV peptides in vaccinees. We showed that this protection was not due to neutralizing antibodies both because we did not vaccinate with Env, but also because only one of the vaccinees had any neutralizing antibody titer, and this was the animal which did not control its viral load. In contrast, all control animals had neutralizing antibody titers, but did not control viral loads. Strikingly, four of the control animals had viral loads at or below the level of protection for significant periods of time. This research uses WNPRC Immunogenetics and Virology Services.

MHC TYPING FOR AIDS RESEARCH (0368)

NPRC UNIT: AIDS COMPONENT

%NPRC $: 1.500% **AIDS RELATED RESEARCH**

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

SUBPROJECT DESCRIPTION

To offer MHC typing of the MHC class I and II loci for investigators working with macaques (Indian rhesus, Chinese rhesus,
and Cynomolgus). To adapt technologies for HLA typing to molecular typing of macaque (Indian rhesus, Chinese rhesus,
and Cynomolgus) MHC class I and II.

The increased utility of various species of macaques as animal models in both HIV vaccine development and pathogenesis
studies necessitates the continuation of reference MHC typing laboratories for these species. We plan to continue to offer
services to both the North American and European scientific communities for MHC typing of macaques. Initially, this will
include PCR-SSP tests for alleles encoding MHC class I and II molecules that bind peptides derived from SIV and SHIV. We
are developing additional molecular techniques for analysis of the Indian rhesus and Chinese rhesus and Cynomolgus
macaque MHC class I and class II alleles. Additionally, we offer training for individual laboratories that wish to set up MHC
typing in their own laboratories. Finally, we are developing a panel of well-characterized cell lines that will be invaluable for
the analysis of the MHC in the macaque. In 2004, we tested 1,684 macaque blood samples for 95 external investigators
and WNPRC scientists, performing 14,070 tests. To date, we have typed more than 6,807 macaques for over 100
investigators, performing 50,074 tests. These typings have supported the publication of over 50 manuscripts. In 2004 and
2005, we submitted a competitive renewal for this grant, which was awarded. This research used WNPRC Immunogenetics
& Virology Services.

A NOVEL, LOGICAL APPROACH TO HIV VACCINE DEVELOPMENT (0385)

NPRC UNIT: AIDS COMPONENT

%NPRC $: 1.500% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
withheld				UNIVERSITY OF ALABAMA-BIRMINGHAM, AL USA
				NENPRC & Proprietary Info
				Proprietary Info

SUBPROJECT DESCRIPTION

To generate strong cytotoxic T lymphocytes (CTL) responses, in the absence of other immune responses, using several different vaccine approaches.

In this study, we vaccinated 8 Mamu A*01 rhesus macaques with DNA and Adenovirus vectors encoding Gag, Tat, Rev and Nef proteins from SIVmac239. The vaccinees, along with 8 control animals, were challenged multiple times with a low dose of SIVmac239 by the intrarectal route. Immune responses were determined after vaccination. Viral loads and immune responses were followed after infection. We saw robust immune responses after vaccination, which were recalled upon infection. Immune responses after infection were stronger and earlier in vaccinees than control animals. By 8 weeks post infection, we saw control of plasma viremia in vaccinees and this control is maintained even at one year post infection. We saw protection of critical CD4 memory subsets, protection of the CD4 compartment overall and protection of CD4 responses to SIV peptides in vaccinees. We showed that this protection was not due to neutralizing antibodies both because we did not vaccinate with Env, but also because only one of the vaccinees had any neutralizing antibody titer, and this was the animal that did not control its viral load. In contrast, all control animals had neutralizing antibody titers, but did not control viral loads. Strikingly, four of the control animals had viral loads at or below the level of protection for significant periods of time. This research uses WNPRC Immunogenetics and Virology Services.