

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

5P51RR000167-46
NATIONAL PRIMATE RESEARCH CENTER SUPPORT

Final

UNIVERSITY OF WISCONSIN-MADISON

ANNUAL PROGRESS REPORT

Reporting From: 04/30/2006

Reporting To: 04/29/2007

43.000% AIDS Related

withheld



Patent or Copyright was awarded this grant year.

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PERSONNEL ROSTER

Core Doctoral Scientists

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

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
withheld		
		Proprietary Info
		UNIVERSITY OF ALABAMA-BIRMINGHAM: AL, USA Proprietary Info
		Proprietary Info
		Proprietary Info

Affiliated

Name, Degree

Department

Non-Host Institution: State, Country

withheld

UNIVERSITY OF ALABAMA: AL, USA

Proprietary Info

Proprietary Info

Proprietary Info

Proprietary Info

Proprietary Info

Proprietary Info

Proprietary Info

NENPRC & Proprietary Info

Proprietary Info

Proprietary Info

Proprietary Info

UNIVERSITY OF ILLINOIS, COLLEGE OF MEDICINE: IL, USA

Proprietary Info

U MASS. MEDICAL SCHOOL: MA, USA

Proprietary Info

WAYNE STATE UNIVERSITY: MI, USA

Proprietary Info

Affiliated

Name, Degree

Department

Non-Host Institution: State, Country

withheld

ONPRC: OR, USA

UNIVERSITY OF TEXAS AT AUSTIN:
TX, USA

Proprietary Info

UNIVERSITY OF MINNESOTA: MN,
USA

Proprietary Info

Proprietary Info

UNIVERSITY OF OKLAHOMA: OK,
USA

UNIVERSITY OF
WISCONSIN-MILWAUKEE: WI, USA

Proprietary Info

Proprietary Info

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

Proprietary Info

CNPRC: CA, USA

Proprietary Info

Proprietary Info

Affiliated

Name, Degree

Department

Non-Host Institution: State, Country

withheld

OKLAHOMA HEALTH SCIENCES
CENTER: OK, USA
UNIVERSITY OF PITTSBURGH: PA,
USA
ONPRC: OR, USA

Proprietary Info

Proprietary Info

OREGON HEALTH SCIENCES
UNIVERSITY: OR, USA

Proprietary Info

WANPRC: WA, USA

UNIVERSITY OF
CALIFORNIA-BERKELEY: CA, USA
UNIVERSITY OF
CALIFORNIA-DAVIS: CA, USA

UNIVERSITY OF
CALIFORNIA-RIVERSIDE: CA, USA

Proprietary Info

UNIVERSITY OF MINNESOTA: MN,
USA

VIRGINIA COMMONWEALTH
UNIVERSITY: VA, USA

Proprietary Info

Proprietary Info

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
withheld		UNIVERSITY OF CALIFORNIA-DAVIS: CA, USA SOUTHWEST NATIONAL PRIMATE RESEARCH CENTER: TX, USA Proprietary Info
		CALIFORNIA NATIONAL PRIMATE RESEARCH CENTER: CA, USA Proprietary Info
		Proprietary Info
		UNIVERSITY OF PITTSBURGH: PA, USA
		UNIVERSITY OF WISCONSIN-WHITEWATER: WI, USA UNIVERSITY OF NEBRASKA: NE, USA Proprietary Info
		Proprietary Info

SUBPROJECT DESCRIPTIONS

NPRC MANAGEMENT SUBPROJECTS

WNPRC ANIMAL SERVICES DIVISION (0214)

NPRC UNIT: ADMINISTRATIVE

%NPRC \$: 7.000% **AIDS RELATED RESEARCH**

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

SUBPROJECT DESCRIPTION

To oversee all animal care and other colony-related activities for the Wisconsin National Primate Research Center, toward the goal of studying nonhuman primates to improve human and nonhuman primate health:

- 1) To provide an excellent and consistent standard of animal husbandry for the nonhuman primate (nhp) colonies of the WNPRC.
- 2) To provide an excellent and consistent standard of veterinary care for the nhp colonies of the WNPRC.
- 3) To provide research support for researchers performing animal research at the WNPRC.
 - a. Through provision of healthy animals
 - b. Through provision of expert veterinary assistance
- 4) To ensure compliance of researchers, facilities with all institutional, local, state, federal laws, regulations, and guidelines pertaining to the performance of animal research.
- 5) To ensure proper and thorough training of all personnel employed by the WNPRC.

To fulfill the objectives outlined above, the Animal Services Division of the WNPRC is composed of four specialized individual units that maintain their own personnel and budgets. The individual units are: Colony Management, Veterinary Services, Behavioral Management, and Compliance and Training

Each of the four units performs their own individual duties but also act in synergy to fulfill the specific aims of the division. Furthermore, the individual units interact with the other divisions to fulfill the goals of the entire Center.

Veterinary Services Unit

The Veterinary Services Unit of the WNPRC is composed of five veterinarians and six veterinary technicians. The principal objective of the unit is to provide consistent and excellent care to the nhp colonies housed at the WNPRC. To achieve this objective, the unit has created and implemented a collection of policies that guide the provision of veterinary care at the WNPRC. These policies, which encompass pertinent topics such as nhp quarantine, preventative medicine, and clinical/surgical care, are based on the most contemporary techniques available to nhp veterinarians.

The second major objective of the unit is to provide support for the investigators performing research at the WNPRC.

The primary way in which the unit supports the investigators is by ensuring a consistent supply of healthy nhps is available for utilization in experimental studies. The veterinary staff also assists investigators by meeting with them prior to an experiment to discuss and plan for each proposed study, by helping compose IACUC protocols, by performing procedures beyond the skill level of the investigators, and by providing clinical care for the nhps assigned to research projects.

The final objective of the unit is to provide training for personnel working with nhps at the WNPRC and at other institutions. Through didactic and applied instruction, the unit provides training to veterinary and veterinary technical students, visiting veterinarians and veterinary technicians, WNPRC and visiting investigators, and scientific support staff.

The Veterinary Services Unit works closely with the other units of the Animal Services Division as well other divisions of the WNPRC. This collaboration ensures the most complete and effective care of our animals and benefits the Veterinary Services unit as well the other individual units and divisions of the WNPRC.

Colony Management Unit

The Colony Management Unit is one of the most crucial components of the WNPRC infrastructure as it supports the entire animal husbandry program of the Center. The Colony Management Unit consists of a colony manager, 3 supervisors, 22 full-time animal research technicians, and 2 colony records assistants. The daily tasks performed by the Colony Management Unit include:

- Provision of food to the nonhuman primate colonies
- Thorough cleansing of the enclosures and rooms that house the nonhuman primates
- Thorough cleansing of the remainder of the animal holding facilities
- Minor maintenance of the animal holding facilities

In addition to their husbandry duties, the personnel of the Colony Management Unit perform pivotal tasks for the Veterinary Services, Behavioral Management and Enrichment, and the Centralized Protocol Implementation Units of the

Center. These tasks include, but are not limited to the following:

- Documentation and communication of daily health reports on the nonhuman primate colonies
- Maintenance of colony records
- Collection of behavioral and scientific data
- Administration of medical and experimental treatments
- Delivery of environmental enrichment objects
- Collection of blood and other tissue samples for experimental and clinical purposes.

Finally, in cooperation with the Senior Management Team, the Colony Manager maintains the nhp breeding colonies of the Center and ensures that a sufficient supply of healthy, genetically characterized animals are available to core, collaborative, and outside investigators.

Colony Records Subunit

One **EFFO** and one **EFFOR** assistant staff this subunit of Colony Management. The subunit's staff is responsible for the daily entry of all data related to the nonhuman primate colony including clinical procedures, animal location transfers, treatments, research procedures, surgical procedures, sample collections, and health observations. Colony Records staff also assure the quality control of data entries, train new staff on how to use the Animal Records Database, and perform database queries. 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 and to facilitate and simplify the data entry and retrieval process.

Behavioral Management Unit

In 2006, the Environmental Enrichment Subunit of Colony Management was elevated to Unit status and was renamed Behavioral Management. The Behavioral Management Unit promotes and enhances psychological well being for the entire nhp colony while ensuring that the animals are free from unnecessary pain and distress. By utilizing a combination of environmental enrichment, behavior modification, and positive reinforcement, the program attempts to promote a diverse array of species typical behaviors in the captive nhps, increases each animal's control and utilization of their environment, and decreases the occurrence of stereotypical and self-injurious behavior

To help achieve the objectives of the Behavioral Management Program the personnel of the unit have fashioned a thorough and creative Environmental Enrichment Plan. This plan consists of the following components:

- Social companionship
- Foraging
- Food enrichment
- Human to non-human interaction
- Structural enrichment
- Manipulanda
- Additional sensory stimulation

Each component of the enrichment plan has been designed to work in unison with the other components to create a comfortable and psychologically challenging environment for the nhps. An active enrichment committee, which is composed of ARTs, members of the veterinary staff, and members of the Central Protocol Implementation group, along with all the Behavioral Management Unit's personnel, continually evaluates existing techniques and creates and implements new approaches.

Compliance and Training Unit

Compliance and Training is a multi-dimensional unit with a variety of responsibilities. The primary objectives of the unit are to train all personnel at the WNPRC who may come in contact with nhps or their tissue; to ensure that the WNPRC facilities and personnel remain compliant with all animal welfare regulations; to assist investigators in the development of IACUC protocols; and to guide the Occupational Health and Safety Program of the Center. Since its inception in 2005, the unit has worked in collaboration with the various divisions and investigators of the WNPRC to standardize training and promote a center-wide atmosphere of regulatory compliance.

Publications note: Animal Services support is involved in practically every journal article that depends in part or in full on WNPRC resources.

DIRECTOR'S OFFICE (0184)

NPRC UNIT: ADMINISTRATIVE

%NPRC S: 1.000% AIDS RELATED RESEARCH

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

withheld				
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SUBPROJECT DESCRIPTION

To oversee all research, services, infrastructure, planning and growth, facilities and communications for the Wisconsin National Primate Research Center, toward the goal of studying nonhuman primates to improve human and nonhuman primate health.

A notable accomplishment in the Director's Office has been the highly efficient teamwork and well honed institutional knowledge of its small but dedicated core staff **withheld** who has enjoyed a long and productive research career at the Wisconsin National Primate Research Center, has been its director **withheld**

withheld—who coordinates all conferences, retreats, seminars, numerous reports, scientific visits and other activities hosted by the Director's Office **withheld**

withheld The tenure of these three individuals together totals

withheld of dedication to the Primate Center.

The Director's Office hosted two general staff meetings in FY 2006-2007 (July and December), scientific research retreats (September, December and March), two strategic planning sessions (September and October), monthly internal advisory board meetings, and a chancellor's visit in December. The deans of the UW-Madison Graduate School and Medical Schools also attended the chancellor's visit. The Primate Center hosted a special seminar by **withheld** **withheld** Food Emergency Response Network in December.

Highlights discussed at the research retreats included progress in the new Information Services Division, progress in the Genetics Core, facilitation of project/grants management, updates in our current research program, and research presentations.

In other key updates:

- The director was awarded the Knox Courage Award from the Wisconsin Association for Biomedical Research in January 2007 (See the awards section of this annual progress report.)
- The director presided over a five-year NIH base grant renewal site visit in January 2007.
- The director hosted the first Pathology Image Database Steering Committee meeting at the Center in December.
- New hires included two **EFFOR** pathologists, who report to the director.
- Preparations began to host the Fall 2008 Nonhuman Primate Models for AIDS Conference in Madison, Wisconsin.

The director attended the following meetings off site in FY 2006-2007:

- Visit to BIRN and the California National Primate Research Center, July.
- Institute for Laboratory Animal Research Council meeting, Woods Hole, Massachusetts, July.
- Served as member of Special Emphasis Panel Review Committee (NIDDK), Washington, DC, July.
- 29th meeting of the American Society of Primatologists (ASP), San Antonio, TX, August.
- National Primate Research Centers Directors' meeting, Atlanta, GA, October.

- BIRN meeting, San Diego, CA, October.
- Institute for Laboratory Animal Research Council meetings, Washington, DC, November.
- The Gerontological Society of America 59th Annual Scientific meeting, Dallas, TX, November. (Program Chair for Biological Sciences)
- Kinetics Workshop, Dallas, TX, November.
- Institute for Laboratory Animal Research Council meeting, Irvine, CA, March, 2007.

The Primate Center's general progress is readily available to a variety of audiences via printed and electronic materials produced by the Public Information Office. Most of these materials—press releases, Centerline newsletter articles, a brochure and fact sheets—appear at www.primate.wisc.edu. In addition, the public information officer completed a major overhaul to the center's research portal on the website, based on input from the fall staff strategic planning sessions. The research link now includes more information useful to researchers, students, the media and the public. This includes links to 80 public lab pages of scientists who are using or have recently used the Primate Center. The PIO also edited a grants page for the website, and photographed all staff members for an internal Human Resources web page. Another major project completed was photographing the Center's entire aged rhesus colony. These images have been used already by at least three investigators for scientific talks.

Local, national and international scientific media interest in WNPRC activities remained high, with weekly scientific media queries and near monthly visits by science journalists and documentary crews. The P01 caloric restriction and aging study generated a record number of science news stories in this reporting period, being covered by more than 20 major news media outlets nationally and internationally, as well as numerous health sites and blogs. Other topics garnering science news media coverage and citing the Wisconsin National Primate Research Center included AIDS, Parkinson's disease and embryonic stem cell research. Animal rights related press coverage about the Primate Center was limited to sporadic local coverage and there were no organized protests.

The public information officer gave one invited out-of-state talk at the ST Dystonia Annual Symposium in Seattle in September, and numerous outreach talks for schools and community groups within Wisconsin on primate research and animal care. The PIO is active through the Chancellor's Speakers Bureau, UW-Madison Science Alliance and the Center's in-house outreach program in disseminating these presentations.

The biggest challenge to the PIO during this reporting period was trying to meet the demands of the job during a three-month period of 50% layoff due to funding cuts. Fortunately, the position returned to near **EFFORT** in November and the office continues to meet its deadlines and productivity standards in publishing, media relations, outreach, and in-house staff requests for information and photography.

WNPRC RESEARCH SERVICES DIVISION (0340)

NPRC UNIT: ADMINISTRATIVE

%NPRC S: 1.000% AIDS RELATED RESEARCH

INVESTIGATOR	DEGREES	STAFF	DEPARTMENT	NON-HOST INSTITUTION: STATE,
		CODE		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. The CPI Service Unit continues to expand and refine its operations. The Pathology Unit's confocal system with 4 visible light lasers and the pulsed near infrared laser for multiphoton excitation is being increasingly utilized by stem cell investigators and developmental biologists as well as AIDS investigators.

WNPRC INFORMATION SERVICES DIVISION (0383)

NPRC UNIT: ADMINISTRATIVE

%NPRC \$: 1.000% AIDS RELATED RESEARCH

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

SUBPROJECT DESCRIPTION

To support the research and outreach missions of the National Primate Research Center.

The Information Services Division, established in 2006, consists of two existing units, the Jacobsen Library and the Information Technology and Systems Services Unit (IT) Unit. In addition, we will continue to build upon the existing strengths within both Units in order to support the Centers informatics initiatives. Both Units will work closely together to provide a continuum of information services and resources to the Primate Center.

Beginning in January 2005, the Wisconsin National Primate Research Center embarked on an informatics strategic planning process. Recognizing the importance of collaboration and data sharing, the center 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, which is 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 units, under the auspices of the Information Services Division, while continuing to provide services and resources to the Primate Center, will play a key role in furthering the center's Informatics Strategy.

Staff Member Training/Conferences (all units):

- Sixth Comparative Medicine Resource Directors Meeting. Sponsored by the National Center for Research Resources (NCRR), California National Primate Research Center, Davis, CA, Nov. 15-16, 2006.
- Pathology Image Database: Steering Committee Meeting. Sponsored by the WNPRC, Madison WI, Dec. 14, 2006.
- BIRN (Biomedical Informatics Research Network) All Hands Meeting. NIH/NCRR/BIRN-CC, San Diego, CA, Oct. 23-25, 2006.
- Annual Meeting of the American Society of Primatologists, San Antonio, TX, Aug. 16-19, 2006.
- Promoting Effective Workplace Dynamics. 8th Annual Manager/Supervisor Conference, sponsored by the University of Wisconsin, Madison Office of Human Resource Development, Madison, WI, October 4, 2006.
- Moving at the Speed of Byte: Emerging Technologies for Information Management. 3.5 MLA contact hrs, MLA Webcast, Madison, WI, Nov. 8, 2006.
- NPRC Library Consortium Meeting. (Coordinated Information Services for Primate Research, P40

RR015311)

Madison, WI, April 3, 2006.

- Empowering Our Patrons. WiLSWorld Conference, Madison, WI, July 26-27, 2006.
- Academic Libraries: Pointing Toward New Directions. Wisconsin Association of Academic Librarians, Stevens Point, WI, March 28-31, 2006.
- OCLC Connexion Holdings Maintenance. Webinar, Feb. 23, 2006.
- Lockdown 2006. Sponsored by DoIT, University of Wisconsin-Madison, Madison, WI, July 28, 2006.
- Web Development Series. DoIT, University of Wisconsin-Madison, Madison, WI, June 5-9, 2006.

Publications note: Information Services support is involved in numerous journal articles that depend in part or in full on WNPRC resources.

WNPRC OPERATIONAL SERVICES DIVISION (0390)

NPRC UNIT: OPERATIONAL SERVICES

%NPRC \$: 1.000% AIDS RELATED RESEARCH

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

SUBPROJECT DESCRIPTION

To provide all necessary services and assistance to support the Center's infrastructure and independently funded research projects of WNPRC principal investigators.

Operational Services, directed by withheld is the WNPRC's business office and serves as the central point for the following administrative functions: Human Resources, Payroll and Benefits, Grants Management, Financial Services, Facilities, and General Shop.

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:

Human Resources withheld

The HR Office made a great deal of progress in FY2006-2007. In conjunction with an important initiative by our host institution, we engaged in a formal program to ensure equity and to increase our workforce diversity. Our program has six elements: establishment of an in-house committee to develop a mission statement and the guide the implementation of the program; seminars and training classes (e.g. a Spanish in the Workplace series); efforts to attract and retain employees from the growing Hispanic workforce locally; networking with other departments and programs on campus; advertising opportunities for employment in targeted media outlets; and analysis of applicant database and identification of successful strategies. The university and the community have praised our equity and diversity program.

We reorganized and enhanced our employee orientation program for new employees: The program is now a full-day event that incorporates more information, policies, meeting of key staff, tours, and time for questions than ever before.

We are enhancing our website to add an internal link for staff in addition to the public information we provide for prospective employees and students. Finally, travel coordination for Primate Center staff recently transferred from Purchasing to the HR Office.

Payroll and Benefits withheld

Payroll and Benefits worked hard over the past year to keep staff up to date on State of Wisconsin announcements, changes and resources regarding payroll, holidays, reimbursement plans for daycare and medical expenses, retirement benefits and planning, health, dental and life insurance, income continuation, long-term care, and myriad of other benefits.

Grants Management withheld

Grants Management continues to assist PIs with grants resources and assistance. A Grants Management link was just added to the Primate Center website.

Financial Services **withheld**

The Purchasing Unit further streamlined its cataloging, ordering and purchase tracking functions during this reporting period.

During the last period, the Accounting Unit worked with WNPRC IT Department to establish a web based chargeback system. This system improved efficiency by reducing staff processing time in down loading chargeback's from WNPRC Animal Services Area.

Facilities **withheld**

We are working within our Master Plan to redevelop our facilities on campus. Our target is to double our animal holding capacity to accommodate the increasing research demand for our resources. Construction is well underway on the Interdisciplinary Research Complex adjacent to UW Hospital and Clinics, in which we will have space for approximately 350 macaques. Our project there has been funded by a CO6 grant from NCR. Occupancy is expected to occur in 2008 or early 2009.

Pending Support

1) Due to budget constraints and to realize major costs savings, the facilities staff was instrumental in negotiating an early termination of our lease at UW Research Park. Through efficient coordination and the outstanding cooperation of those affected, we consolidated the administrative staff back into to the campus Primate Center location.

2) The Facilities Unit is responsible for Primate Center construction projects. The unit staff worked to gain NIH approved drawings and specifications for our CO6 construction grant. This CO6 construction grant will provide 350-primate space at the Integrated Research Center (IRC) on UW-Madison campus. In addition, construction has commenced on the IRC project and Facilities continues to work with the suppliers and contractors. Occupation is project to be in late 2008.

3) During the project period, this unit completed and finalized the Primate Center's Emergency Response Plan.

General Shop **withheld**

During the last project period the Shop has completed the following activities:

Parkinson's Research (Supporting **withheld**)

The Shop built three MRI Stereotaxic Instruments equipped with specialized hollow tipped ear bars, calibrated frame bars

and adjustable brass/delrin tooth and eye bars.

Animal Services - WNPRC

In terms of ongoing Primate Housing maintenance, the Shop completely disassembled and removed stationary non human primate housing in three rooms and six pens allowing Physical Plant trades people to perform required repairs to these areas. Made repairs and modifications to housing units and reinstalled.

Aging Research (Supporting withheld)

The Shop designed and built four testing cages and two isolation chambers used to study Cognitive Decline Behavioral Testing in Aging Monkeys. The chambers are equipped with a monitor screen, reward dispenser and white noise source.

Capital Equipment Purchases

The following capital equipment purchase was completed during the last project period:

- 1) Upgrade kit, 3730 50cm Array, \$125,000
- 2) BD LSRII #338301, \$39,600
- 3) Biosafe L-80XP Ultracentrifuge System, \$63,050
- 4) AS2800 TRI-CARB 2800TR Liquid Scintillation Analyzer, \$22,652
- 5) AutoMACS PRO Separator, \$37,400
- 6) Mirco Plate Washer, \$7,590
- 7) Computer Equipment, \$19,246

Publications note: Operational Services support is involved in numerous journal articles that depend in part or in full on WNPRC resources.

WNPRC AGING COLONY RESOURCE (0409)

NPRC UNIT: RESEARCH SERVICES

%NPRC S: 1.200%

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

SUBPROJECT DESCRIPTION

To maintain an aged rhesus macaque colony as a specialized resource for studies relating to normal aging.

Allocation of Resource Access

The WNPRC has approximately 90 rhesus monkeys over 20 years of age. Support is provided in part by the National Institute of Aging to maintain these animals for studies relating to normal aging. During FY2006-2007, approximately 20 investigators used these animals in studies related to neuroendocrinology, calorie restriction, glucose metabolism, ovarian dysfunction, bone mineral density, osteoarthritis, immunology, ophthalmology, oncology and reproduction. No request has been denied.

Dissemination

Knowledge is disseminated to the scientific community via publications in peer reviewed journals and scientific meeting attendance. The Wisconsin National Primate Research Center also holds quarterly research retreats to create increased communication between the various service and resource units.

Training

Training is available in established protocols food intake measurement, body composition assessment, physical activity monitoring, cognitive and motor skills assessment, and metabolic assessments. Training in all of these areas was carried out during the past year.

Progress

During the current reporting year, approximately 20 investigators have utilized animals from the aging colony. We continue to monitor the health and well-being of all animals in the colony and evaluate aging individuals from the general colony to evaluate their appropriateness for inclusion in the aging colony.

Publications note: Aging Resource support is involved in numerous journal articles that depend in part or in full on WNPRC resources.

WNPRC GENE TRANSFER RESOURCE (0411)

NPRC UNIT: RESEARCH SERVICES

%NPRC \$: 1.100%

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

SUBPROJECT DESCRIPTION

To develop a specialized resource for studies relating to gene transfer and primate transgenesis.

Allocation of Resource Access

The Gene Transfer resource unit at the Wisconsin National Primate Research Center provides expertise and reagents to interested investigators. Over the past year 2 investigators have received plasmids used for reporter gene expression. No request has been denied.

Dissemination

Knowledge is disseminated to the scientific community via publications in peer reviewed journals and scientific meeting attendance. The Wisconsin National Primate Research Center also holds quarterly research retreats to create increased communication between the various service and resource units.

Training

Training is available in established protocols for quantitative RT-PCR for transgene expression, and in developing individual investigator-specific target genes. Training in RT-PCR and gene expression analysis was carried out during the past year.

Progress

During the current year, we evaluated transgene expression in offspring from embryonic gene transfer experiments, and pilot studies in reproductive tract gene transfer. Transgene DNA and RNA was documented in individual tissue biopsies. Further evaluation is anticipated to define vector integration into individual tissues and gain insight into molecular events occurring during embryonic gene transfer.

Publications note: Gene Transfer Resource support is involved in several journal articles that depend in part or in full on WNPRC resources.

WNPRC GENETICS SERVICES UNIT (0405)

NPRC UNIT: RESEARCH SERVICES

%NPRC \$: 5.000% AIDS RELATED RESEARCH

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

To provide core, campus and non-host investigators with sophisticated and specialized genetics resources and expertise.

Progress and concerns

In 2006, the Genetics Service established a high-throughput DNA sequencing facility. From May 1, 2006 to December 31, 2006, the sequencing facility processed more than 30,000 DNA sequences for 22 users. Sequence quality was high, with an average read length of more than 670 bases in December, 2006. Responding to the popularity of the service in 2006, we recently upgraded the sequencing hardware to double throughput and capacity. The Genetics Service also provides increasingly sophisticated MHC genotyping of WNPRC macaques. The tools developed for these analyses are now being adapted by outside investigators with WNPRC assistance.

Allocation of resource access

The Genetics Service sequencing facility was designed as an economical and rapid alternative to existing DNA sequencing services for nonhuman primate researchers with medium-to-high throughput needs. Current clients are drawn largely from WNPRC AIDS laboratories that perform extensive SIV and immunogenetics research.

Dissemination

We request that projects utilizing Genetics Service acknowledge the service in manuscripts and presentations, the PI for Genetics Services, lectures regularly on NHP genetics.

Training

All 22 users of the sequencing service received training in the submission and retrieval of data during 2006. A subset of these users obtained advanced training in the analysis of sequence data from Genetics Services staff. Additionally, methods for MHC genotyping macaques using microsatellite markers were provided to laboratories in the USA, UK, and Australia.

WNPRC CENTRALIZED PROTOCOL IMPLEMENTATION UNIT (0404)

NPRC UNIT: RESEARCH SERVICES

%NPRC \$: 1.000% AIDS RELATED RESEARCH

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

To provide core, campus and non-host investigators with organized and efficient WNPRC and UW-Madison resources, protocol management and expertise.

Progress and Concerns

CPI had over 4000 procedures for more than 1400 experiments since May 1, 2006. These were for 56 different projects involving 30 investigators (13 WNPRC core scientists, 8 UW affiliates, 7 affiliates from other academic institutions, and 2 investigators from the industry/biotech sector). We have also developed 15 budget estimates for pending projects.

Allocation of Resource Access

So far there have been no denials on incoming project requests. Projects must fall within the mission of WNPRC, be approved by the director, and WNPRC have the resources to provide support. In addition, CPI will seek consultation with WNPRC core scientists.

Dissemination (All Divisions and Units)

In addition to the WNPRC web site, we rely on recommendations by core and affiliate scientists. We are also sending CPI staff to annual scientific meetings to present what resources and techniques are available to the scientific members in attendance.

Training (All Divisions and Units)

The veterinary head of CPI in coordination with other veterinary staff members, as needed, accomplishes training of CPI personnel for the multitude of procedures cited above. Verbal and written instruction as well as hands-on training and oversight of procedures to assure proficiency are utilized to provide a highly skilled technical staff to researchers. We are in the process of formalizing our training documentation, so that each technician will have a complete record of every procedure he/she is trained on and to what level of proficiency.

Publications

Virtually all publications relying on WNPRC resources in part or in full involved the use of the CPI Unit.

WNPRC PATHOLOGY SERVICES UNIT (0402)

NPRC UNIT: RESEARCH SERVICES

%NPRC \$: 1.000% AIDS RELATED RESEARCH

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

SUBPROJECT DESCRIPTION

To provide core, campus and non-host investigators with sophisticated and specialized pathology resources and expertise.

Progress and concerns

The WNPRC hired two **EFFOR** pathologists in 2006 to replace departed staff. These two individuals report to the Director. While there was some adjustment as with any major staff changes, the unit is functioning smoothly. In fact, Pathology Services was instrumental in organizing and participating in the first ever Pathology Image Database Steering Committee meeting at the Center in December.

Allocation of Resource Access

Pathology Services notifies investigators of the resource via the Primate Center website and scientific meetings. To date, no requests have been denied. Nearly all core WNPRC labs use Pathology Services at some point in their projects, and numerous campus affiliates avail of this service. In addition, since May 1, 2006, 11 investigators from non-host institutions received a total of 685 samples, representing tissues, organs and genetic material from macaca mulatta and callithrix jacchus. Please see the Research Services section of this progress report for a table of species, specimen types and numbers.

Dissemination

We request that projects utilizing Pathology Services acknowledge the WNPRC in manuscripts and presentations.

Training

In 2006 the Pathology Unit created a training manual for banking brain tissues. Two staff members participated in clinical pathology training to provide additional services for colony management. Unit members provided training for six pathology residents on campus.

Publications

Pathology Services has contributed to numerous publications that involved use in part or in full of the WNPRC.

WNPRC STEM CELL RESOURCE (0410)

NPRC UNIT: RESEARCH SERVICES

%NPRC S: 1.100%

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

SUBPROJECT DESCRIPTION

To maintain and further develop a specialized resource for studies relating to embryonic stem cell research.

Allocation of Resource Access

To date, the stem cell resource unit at the Wisconsin National Primate Research Center provides frozen rhesus and marmoset ES cells to interested investigators. Over the past year investigators have received three different strains of rhesus ES cells and one strain of marmoset ES cells. No request has been denied. Additionally, the stem cell resource unit provides zebrafish bFGF for culturing primate ES cells. To date five investigators have received the recombinant protein. The DNA plasmid used to purify the protein itself has been sent to over 10 investigators and is now available through Addgene (www.addgene.com)

Dissemination

Knowledge is disseminated to the scientific community via publications in peer reviewed journals and scientific meeting attendance. The Wisconsin National Primate Research Center also holds quarterly research retreats to create increased communication between the various service and resource units.

Training

Training in culture techniques of primate embryonic stem cells is available. Many new investigators have taken advantage of this resource in previous reporting periods however there have been no new investigators trained this year.

Progress

Cynomologous ES cell derivation: During 2006, 10 embryos were collected. Five were cultured to blastocyst and stem cell derivation was attempted using immunosurgery techniques. There has been one cell line in culture since March and this cell line is being characterized. The cell line is negative for Herpes B and mycoplasma and has been injected into Rag-1 mice to determine pluripotency.

Publications note: Stem Cell Resource support is involved in numerous journal articles that depend in part or in full on WNPRC resources.

WNPRC IMMUNOLOGY & VIROLOGY UNIT (0403)

NPRC UNIT: RESEARCH SERVICES

%NPRC \$: 5.000% AIDS RELATED RESEARCH

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

withheld

SUBPROJECT DESCRIPTION

To provide expert support to AIDS research conducted at the Primate Center.

PROGRESS AND CONCERNS

The Virology Services Unit (VS) continued to improve the sensitivity and throughput of our quantitative RT-PCR assay for SIV. Over 4,100 individual samples were assayed for SIV nucleic acids in 2006. Sensitivity improved from 50 SIV genome copy equivalents/ml plasma to 30 copy Eq/ml. We also produced over 2,500 vials of high-titer SIVmac239 stock and 16 custom SIV mutants for WNPRC investigators. Also in 2006, the Immunology Services Unit (IS) defined 9 new SIVmac239 epitopes restricted by the MHC class I allele Mamu-B*08. We developed Mamu-B*08 tetramers loaded with 8 of these epitopes. IS also provides expert support to Primate Center and extramural investigators wishing to use our flow cytometry and cell-sorting facilities. To enhance our range of services, we acquired a custom-made BD-LSR II cytometer capable of 14-color-16 parameter measurements. This enabled us to introduce multichromatic flow cytometric staining to quantify subsets of target and immune effector cell populations, and measure their function.

ALLOCATION OF RESOURCE ACCESS

The central mission of VS is to provide expert support to AIDS research conducted at the Primate Center. Our services are available to any investigators using Primate Center animals for their research. Currently our clients are mainly AIDS researchers based at UW. In fiscal 2006 IS served 9 on-campus and 6 off-campus laboratories in work supported by 20 federal and non-federally funded grants.

DISSEMINATION

We request that projects utilizing Virology and Immunology Services acknowledge the service in manuscripts and presentations. **withheld** the PIs of VS and IS units, consult closely with users of the service, helping to design experiments and interpret results.

TRAINING

withheld consults regularly with recognized leaders in SIV virology and molecular biology to develop and refine our techniques. For example, custom SIV mutagenesis methods were developed in collaboration with **withheld**

withheld

at the New England Primate Center. Quantitative RT-PCR techniques were developed in consultation with withheld

withheld

at the National Cancer Institute. Similarly withheld as developed IS protocols and technologies in collaboration with withheld at the Oregon Primate Center. IS staff have been trained in flow cytometry techniques at

Proprietary Info

WNPRC ASSAY SERVICES UNIT (0401)

NPRC UNIT: RESEARCH SERVICES

%NPRC \$: 1.100%

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

To provide core, campus and non-host investigators with sophisticated and specialized assay resources and expertise.

Progress and Concerns

Since May 1, 2006, Assay Services has received \$99,457.92 in charge backs for our service. We ran 17,646 determinations during this time. Assay Services has developed several new assays during this time including a kisspeptin RIA and an oxytocin EIA for use in blood, urine and cerebral spinal fluid.

Allocation of Resource Access

Assay Services has an international and national client base. During the past year we ran samples for investigators from many different states and several countries. We primarily provide services for NIH based grants using nonhuman primate samples for hormonal determinations.

Assay Services has a website that is easily assessable to the scientific community:
<http://ink.primate.wisc.edu/~assay/assay.php>

Disemmination

We have many clients who contact us via our website. Additionally, we attend meetings such as the American Society of Primatologists to make the primate community aware of our services. We also receive clients from recommendations by previous clients.

Training

Assay Services continues to train graduate students, technical support, post doc and scientists to run their own samples

as self service **withheld** visited the Assay Services Unit this last year to learn techniques in measuring

oxytocin. We trained two graduate students in hormonal validation methodology for the University of Wisconsin,

withheld

and the University of Texas at Austin

withheld

RESEARCH SUBPROJECTS

AUDITORY THRESHOLDS AND AGING (0253)

NPRC UNIT: AGING & METABOLIC DISEASE

%NPRC \$: 1.000%

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

In the current report period, we evaluated physiological function of the middle ear in these animals. Results parallel those in aging humans, i.e., we observed reduced peak compensated static acoustic admittance. Longitudinal studies are now underway.

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.

MENOPAUSAL HOT FLASHES (0198)

NPRC UNIT: AGING & METABOLIC DISEASE

%NPRC S: 1.000%

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

HYPOTHALAMIC MECHANISMS CONTROLLING FEEDING AND METABOLISM (0306)

NPRC UNIT: AGING & METABOLIC DISEASE

%NPRC S: 1.000%

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

SUBPROJECT DESCRIPTION

To evaluate feeding and metabolism in rhesus monkeys in response to chemical or electrical stimulation of the hypothalamus.

Morbid obesity is a major health problem that is suboptimally treated at present. Current procedures to control appetite and obesity suffer from either low efficacy or high morbidity and mortality. The hypothalamus plays a critical role in regulating appetite and energy balance. More specifically, the lateral hypothalamus appears to regulate hunger while the ventral medial hypothalamus (VMH) regulates satiety. The exact loci and pathways through which this is accomplished remain unclear. Our aim is to assemble pilot data for a physiologic model of hypothalamic function in feeding, metabolism and weight regulation. This will serve as an important foundation for future studies of feeding and metabolism. This research used WNPRC Animal Services and Centralized Protocol Implementation services.

WATER SOLUABLE NUTRIENT ABSORPTION (0318)

NPRC UNIT: AGING & METABOLIC DISEASE

%NPRC \$: 1.000%

INVESTIGATOR	DEGREES	STAFF	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 research used WNPRC Animal Services.

In Preparation

REGULATION OF FOOD INTAKE AND OBESITY (0255)

NPRC UNIT: AGING & METABOLIC DISEASE

%NPRC \$: 1.000%

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

Proprietary Info

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 S: 1.000%

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

withheld				
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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. During the current report period, there were 78 users, 6 contributions of new data, and

110 requests for information. This research used WNPRC Aging Resources and IT Services.

DIGESTIVE RETENTION TIMES IN CERCOPITHECUS AETHIOPS AND MACACA MULATTA (0399)

NPRC UNIT: AGING & METABOLIC DISEASE

%NPRC S: 1.000%

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

To evaluate subfamily (Cercopithecinae) patterns of primate digestion and to determine whether the trend of long mean retention times and slow passage rates in cercopithecines is exhibited by *Cercopithecus aethiops* and *Macaca mulatta*.

Feeding trials on a total of 24 animals (12 females, 12 males; 6 = *Cercopithecus aethiops*; 18 = *Macaca mulatta*, 3 treatments) were conducted to determine digestive passage rate and the effects of calorie restriction and fiber fraction differences. These patterns have important implications for understanding the evolution of feeding strategies. Longer digestive retention times mean better access to low-quality foods, so as habitat quality decreases as a consequence of human impact, the ability to consume a variety of foods becomes very important for the species. An additional goal of this study was to investigate the digestive retention times of calorie-restricted age study animals and normal age study animals. The results of this study could show a differential response of non-human primates to varying dietary regimes, while calorie restriction may mimic conditions of low resource availability in the wild. This research used Animal Services and the aging colony resource. UW start-up funds also contributed to this project.

ASSESSING HIGH DIETARY VITAMIN A (0272)

NPRC UNIT: AGING & METABOLIC DISEASE

%NPRC S: 1.000%

INVESTIGATOR	DEGREES	STAFF	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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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 15 of the 16 male rhesus monkeys (age range 8 to 15 years) in comparison to human values.

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

We have more evidence that the vitamin A toxicity that is present in rhesus macaques is causing adverse effects.

Pending Support

DIETARY RESTRICTION AND AGING (0160)

NPRC UNIT: AGING & METABOLIC DISEASE

%NPRC \$: 1.000%

INVESTIGATOR	DEGREES	STAFF	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
				CODE
withheld				UNIVERSITY OF ALABAMA-BIRMINGHAM, AL USA
				UNIVERSITY OF ALABAMA, AL USA
				UNIVERSITY OF CALIFORNIA-BERKELEY, CA USA
				UNIVERSITY OF CALIFORNIA-DAVIS, CA USA

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. The next phase should be even more insightful as the oldest study monkeys are now truly old. During this phase, age-related diseases and disorders appear more frequently, including adult-onset diabetes, osteoporosis, cancers, obesity, hypertension and loss of skeletal muscle mass. This research used Animal Services and Research Services.

SIV T CELLS IN VIVO (0292)

NPRC UNIT: AIDS COMPONENT

%NPRC \$: 2.000% AIDS RELATED RESEARCH

INVESTIGATOR	DEGREES STAFF CODE	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 two years, 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.

PATHOGENESIS OF MUCOSAL TRANSMISSION/HIV ACUTE TRANSMISSION (0323)

NPRC UNIT: AIDS COMPONENT

%NPRC S: 2.000% AIDS RELATED RESEARCH

INVESTIGATOR	DEGREES	STAFF	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.

The in vivo work has been completed and data analysis continues. 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.

IMMUNOGENETICS OF CYNOMOLGUS MACAQUES FROM DIFFERENT ORIGINS (0387)

NPRC UNIT: AIDS COMPONENT

%NPRC S: 2.000% AIDS RELATED RESEARCH

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

SUBPROJECT DESCRIPTION

To understand differences in MHC genetics, especially since cynomolgus macaques are increasingly used for biodefense and AIDS research.

We have recently discovered that cynomolgus macaques from different geographical locations have distinct major histocompatibility complex (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. 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. We now have a set of more than 60 MHC class I and class II alleles from Mauritian cynomolgus macaques. Preliminary peptide binding motifs have been determined for two of these alleles by Edman degradation. We have also recently developed a microsatellite map of the MHC that works in both cynomolgus and rhesus macaques. We have also adapted a second MHC genetic assay, reference strand mediated conformational analysis (RSCA), to a new high throughput hardware platform, the ABI 3130. This research used WNPRC Animal Services, Immunology & Virology Services, and Genetics Services.

MHC-BOUND, SIV-DERIVED, CTL AND HTL EPITOPES (0152)

NPRC UNIT: AIDS COMPONENT

%NPRC \$: 2.000% AIDS RELATED RESEARCH

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

UNIVERSITY OF OKLAHOMA, OK
USA

OREGON HEALTH SCIENCES
UNIVERSITY, OR USA

Proprietary Info

SUBPROJECT DESCRIPTION

To work on developing a vaccine for HIV, we will identify additional epitopes for cytotoxic and helper T cells and use this information to develop unique reagents for following immune responses.

The binding motif of Mamu-B*08 has been determined and shown to contain a dominant preference for arginine at the P2 anchor position along with a dominant preference for leucine at the P9 C-terminus. Nine novel SIV derived peptide epitopes restricted by Mamu-B*08 have been identified. These have been mapped by a combination of intracellular cytokine staining and ELISPOT in responder cell lines or PBMC's derived from animals that are elite controllers of a highly pathogenic SIVmac239 infection. Tetramers have been successfully produced and verified for 5 of the 9 epitopes thus far, with the other 4 under development. It is important to note that MHC typing data shows that Mamu-B*08 is over represented among a cohort of rhesus macaques that control SIV infection. While the overall frequency of this allele in a cohort of 120 WNPRC macaques infected with SIV is 5% (6 of 120), the frequency of this allele among elite controllers is 40% (4 of 10). Furthermore, the binding motif of this allele is similar to that of HLA-B*27, an allele in humans associated with control of HIV. Four CD4+ T cell epitopes and their restricting alleles have been defined for 4 SIV derived peptides using MHC class II transferents. These responses have been defined in rhesus macaques that control their SIV viral loads, but no causal relationship has been established. This research used WNPRC Immunogenetics & Virology Services and Animal Services.

MHC TYPING FOR AIDS RESEARCH (0368)

NPRC UNIT: AIDS COMPONENT

%NPRC S: 2.000% AIDS RELATED RESEARCH

INVESTIGATOR	DEGREES	STAFF	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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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. 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 successfully submitted a competitive renewal for this grant. In 2006, we have performed over 9,500 genotyping reactions, serving approximately 20 independent principal investigators from over 10 different institutions. In addition, we have developed and are preparing to offer expanded services, which include typing specificities for a total of 22 Class I and 17 Class II alleles of the Indian rhesus macaque. This research used WNPRC Immunogenetics & Virology Services.

IMMUNOGENICITY AND PROTECTION OF LIVE ATTENUATED SIV239 DELTA NEF IN RHESUS (0369)

NPRC UNIT: AIDS COMPONENT

%NPRC \$: 2.000% AIDS RELATED RESEARCH

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

withheld

SUBPROJECT DESCRIPTION

To use live-attenuated SIV vaccines as a unique opportunity to study effective anti-immunodeficiency virus immune responses.

These vaccines offer a unique opportunity to study effective anti-immunodeficiency virus immune responses.

These

vaccines are particularly effective at protecting against pathogenic strains of SIV that are genetically similar to the vaccine

strain. Nonetheless, live-attenuated SIV strains are considered less effective at protecting against pathogenic strains that

are considerably different from the vaccine strain. However, this assumption is primarily based on a single study using a

small cohort of animals. We, therefore, set out to reexamine and expand upon this earlier study to determine the extent

live-attenuated SIV provides protection against genetically different strains of pathogenic SIV.

We vaccinated 14 rhesus macaques with the live-attenuated SIV strain SIVmac239 Δ nef. We are monitoring the development of SIV-specific immune responses in this cohort using a variety of assays. The vaccinated animals, along with

naïve controls, will be challenged with either the parental strain, SIVmac239, or with the genetically distinct, uncloned

"swarm" virus SIVsmE660. We expect most of the vaccinated animals to control viral replication to low or undetectable

levels within two months post-challenge. To enhance detection of protective responses, we will administer anti-CD8

antibody to deplete CD8+ lymphocytes from the blood of protected animals. We expect a recrudescence in viral replication

during the depletion. As CD8+ lymphocytes begin to repopulate the blood we anticipate viral replication to be controlled

and provide an opportunity to further define responses associated with viral control. The research used and will continue to

use WNPRC Immunogenetics & Virology Services.

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

NPRC UNIT: AIDS COMPONENT
%NPRC \$: 2.000% AIDS RELATED RESEARCH

INVESTIGATOR	DEGREES	STAFF	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
withheld				UNIVERSITY OF ALABAMA-BIRMINGHAM, AL USA Proprietary Info
				NENPRC & Proprietary Info
				Proprietary Info
				Proprietary Info
				OREGON HEALTH SCIENCES UNIVERSITY, OR 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. After challenge, the vaccinees as a group were able to control viremia to nearly two logs lower than the control group at one year post-challenge. By two years post challenge, most of the control group has been euthanized. The remaining vaccinees have separated into animals that continue to control viremia well and those that have not. Those that control viremia have higher CD4+ T cells in both the PBMC and BAL. They have increased numbers of tetramer positive CD8+ T cells in the mucosa, even higher than in the PBMC. While we cannot tell if these results are cause or effect, the result is that you have CD4+ T cells and CTL that are specific for SIV epitopes in the mucosal areas, where they are most needed. In 2007, we are starting a new study in which we vaccinate with all SIV proteins except Env. This research uses WNPRC Immunology and Virology Services.

DEVELOPMENT OF IMMUNE MONITORING REAGENTS AND MHC TYPING TECHNOLOGIES (0388)

NPRC UNIT: AIDS COMPONENT

%NPRC \$: 2.000% AIDS RELATED RESEARCH

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

SUBPROJECT DESCRIPTION

To develop and implement MHC typing technologies for Cynomolgus macaques (*Macaca fascicularis*) and Indian Rhesus macaques (*Macaca mulatta*). We will adapt technologies from HLA typing in humans for MHC class I and class II typing in the macaque.

cDNA libraries were constructed from a total of 15 Indian Rhesus macaques. MHC class I and class II clones were captured from each library and more than 17,000 sequencing reactions were performed. A total of 42 novel class I and class II alleles were identified, 33 of which have been submitted to Genbank. Stable transfectants were produced from 6 MHC class I alleles and 3 MHC class II alleles.

83 MHC class I alleles in cynomolgus macaques of Vietnamese, Chinese and Mauritian origins have been defined. Additionally, 29 MHC class II alleles from Mauritian cynomolgus macaques have been defined. A microsatellite map containing more than 15 loci distributed throughout the MHC was developed and used to define Mauritian cynomolgus macaque haplotypes. Six haplotypes account for all of the MHC diversity in this population. The MHC class I and II alleles on each of the six haplotypes is now known. This research used WNPRC Animal Services and Immunology & Virology Services.

RENAL TRANSPLANTATION GRAFT SURVIVAL (0378)

NPRC UNIT: IMMUNOLOGY

%NPRC S: 0.500%

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

withheld

SUBPROJECT DESCRIPTION

To improve long-term survival in kidney transplant patients by discovering better ways to prevent organ rejection.

We are evaluating whether donor-derived monocytes (M_d cells) cultured in the presence of cytokines are capable of inducing donor-specific tolerance to renal allografts in rhesus macaques. The cells are infused approximately one week pre-

or post-transplant. We are also assessing the effects of a new Fc-based immunosuppressive regimen in a life-supporting

model of kidney transplantation in non-human primates. We are also researching the role of chemokines and their receptors in transplant rejection and acceptance. This research used WNPRC Animal Services.

SUBPROJECT PROGRESS

Our general protocol now is to dose our recipient monkey with FK506 i.m. at a dose of 0.02 to 0.1 mg/kg. We adjust dosing based on trough levels aiming for a range of 4 to 8 ng/ml. Dosing was done on postoperative days 0 to 6, 8, 10, 12, and 14. Graft survival of the first two control animals was 20 and 21 days. Tacrolimus (TAC) trough levels tended to be on the low end of our target range. We have also completed six transplants that received both FK506 and donor M_d cells. Prolonged graft survival has been seen only in one of the six monkeys. We are now looking at the immune response to M_d cells in vivo in one animal in the absence immunosuppression or transplant. This study is ongoing. Eleven animals were treated with mut-IL-15-Fc in different treatment groups. In this small study of cynomolgus renal transplantation, we observed no benefit in graft survival in mut-IL-15-Fc treated animals. The experimental drug is a MUT IL-15/FC supplied by the study funder. We are preparing to use chemokine receptor blockade in combination with an anti-T cell immunotoxin. Experiments are pending.

COORDINATED INFORMATION SERVICES FOR PRIMATE RESEARCH (CIS) (0211)

NPRC UNIT: LIBRARY

%NPRC \$: 1.000%

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

SUBPROJECT DESCRIPTION

To support the coordination of information services among the NPRCs as well as outreach to the national and international primatological and biomedical communities.

1) The Jacobsen Library has been moved to the Information Services Division as the result of the reorganization of the Centers' administrative infrastructure. 2) The Jacobsen Library continues to provide document delivery services to scientists and researchers at the various NPRC's and the **Proprietary Info** PrimateLit (1940-present) is freely available as an NCRR resource via the Web. The library, in collaboration with the General Library System, enabled the open URL protocol (ANSI/NISO Z39.88-2004) supporting the use of link resolver software in conjunction with the PrimateLit database. This was implemented in the summer of 2006. This functionality allows users to link directly to a citation in the database using software such as SFX or LinkFinderPlus. 4) The Library staff is currently reviewing and updating content across the Primate Info Net (PIN) website. This insures content is both up-to-date and relevant. In addition staff developed a "New Books" page with an RSS feed and links to OCLC Worldcat. 5) There are currently 24 in-depth Primate Factsheets available through the PIN website. These Factsheets provide access to information by species name and geographical location. Factsheets are organized by Taxonomy, Morphology, & Ecology, Behavior, Conservation, References, and Links. 6) Both Primate-Jobs and Primate-News are now available via RSS feed. 7) The Jacobsen Library continues development of the PrimateImages database. PrimateImages will make available over 11,600 natural history and art & illustration images via PIN and the UW-Madison Digital Collections site. This web-based resource will be publicly available fall of 2007. 7) The library hosted the 3rd NPRC Library Consortium Meeting in Madison April 3, 2006. Attendees included representatives from the Washington, Southwest and Wisconsin NPRC's. Subcontractors on the grant are the Primate Information Center, WaNPRC, Seattle, providing indexing for PrimateLit, and the UW Madison Libraries providing technical support for the PrimateLit database. te Jobs also underwent a redesign in 2005. Both Primate-Jobs and Primate-News are now available via RSS feed. 7) New initiatives include a review and update of the PrimateLit interface and the development of the PrimateImages database. PrimateImages will make available over 11,600 natural history and art & illustration images via PIN and the UW-Madison Digital Collections site. Subcontractors on the grant are the Primate Information Center, WaNPRC, Seattle, providing indexing for PrimateLit, and the UW Madison Libraries providing technical support for the PrimateLit database.

SUBPROJECT PROGRESS

Resources and services developed through the support provided by the CIS grant have played a significant role in disseminating information about nonhuman primates across all eight National Primate Research Centers and to the biomedical and primatological communities at large. The Wisconsin NPRC's document delivery service continues to be a popular program, in calendar year 2006 we handled 6616 requests. The PrimateLit database is now available free via the web to the U.S. and international research communities. During 2005 (Jan, through Dec.) there were 59,021 discrete PrimateLit sessions, each session consisting of an average of 2.92 searches per session. This translates into approximately 172,557 searches done in PrimateLit during this time period. Primate Info Net has emerged as a major resource in primatology. During the calendar year 2006 Primate Info Net received a total of 15.4 million hits and the AskPrimate reference service received 454 questions. The 24 Primate Factsheets received an average of 420,000 hits per month. We currently have 75 listings in PrimateJobs, the PrimateScience e-mail list has 699 members, Primate-News has 1088 members and the Primate Enrichment Forum has 258 members. These numbers are not insignificant. There is undoubtedly both a demand and a need for the information and services provided by the National Primate Center Libraries. Publications link note: This grant provides related support to too many publications for practical listing in this report.

MOVEMENT DISORDERS AND EYE MOVEMENTS (0395)

NPRC UNIT: NEUROBIOLOGY

%NPRC S: 0.500%

INVESTIGATOR

DEGREES STAFF DEPARTMENT
CODENON-HOST INSTITUTION: STATE,
COUNTRY

withheld

SUBPROJECT DESCRIPTION

To understand how higher order processes or cognition contribute to the control of voluntary movement.

Because the execution of voluntary actions usually involves processes such as target selection, learning, memory, planning and expectation, motor systems are well suited for study of these processes. We investigate neuronal processes leading up to the execution of movements of the eyes, in particular, those eye movements that lead to rapid changes in the line of sight - saccades.

We have a multi-technique approach to the study of these processes. First, we record electrical activity of single neurons while the subjects perform eye movement tasks designed to tap into cognitive processes. Second, we activate or inactivate particular regions of the brain to produce behaviors or interfere with ongoing behaviors and neural processing. Finally, because damage to certain brain regions produces profound clinical disorders such as Parkinson's disease and Huntington's disease, we study eye movements of both healthy and diseased human subjects to further our understanding of the role these structures play in both cognition and in producing the debilitating effects of these disorders. This research used WNPRC Animal Services.

MATERNAL-FETAL TRANSPORT OF NEUROTOXINS USING PET IMAGING (0414)

NPRC UNIT: NEUROBIOLOGY

%NPRC \$: 0.500%

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

SUBPROJECT DESCRIPTION

To assess in vivo maternal-fetal transport of putative neurotoxins using PET imaging.

We used PET-CT imaging to study maternal-fetal transport of materials in one preliminary study involving a pregnant rhesus macaque of the WNPRC breeding colony. The goal of this study was to assess the in vivo transport from the mother to the fetus of a dopamine receptor tracer. Rapid transport was observed and specific uptake and retention of the tracer in the fetal striatum, which is rich with dopamine receptors, was seen. This study demonstrates the feasibility of this non-invasive technique. Pending Support will assess fetal uptake of environmental neurotoxins in order to make science-based risk assessment of neurotoxin exposure in utero. This research used Animal Services. Pending Support

REMYELINATION AND NEUROPROTECTIVE STRATEGIES IN MULTIPLE SCLEROSIS (0384)

NPRC UNIT: NEUROBIOLOGY

%NPRC \$: 0.500%

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

To build on work previously done on marmosets, namely the induction of an experimental allergic with support from the **Private Source**

We are moving on from these pilot studies and initiating new work. No publications yet. This work used WNPRC Animal Services.

LENTIVIRAL DELIVERY OF GDNF AND BCL-2 FOR PARKINSON'S DISEASE (0375)

NPRC UNIT: NEUROBIOLOGY

%NPRC \$: 0.500%

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

SUBPROJECT DESCRIPTION

To assess neuroprotective strategies for Parkinson's disease using gene therapy to deliver the trophic factor GDNF or the antiapoptotic molecule Bcl-2.

Aging and environmental toxins have been identified as risk factors for Parkinson's disease. In order to assess the potential for functional recovery induced by GDNF of a diseased aged primate brain, old male rhesus monkeys presenting a parkinsonian syndrome received intracerebral injections of lentiviral vectors encoding for GDNF or a control treatment. Our results using behavioral tests, imaging and postmortem brain analysis indicate that the aged primate brain exposed to a neurotoxic insult is responsive to GDNF trophic stimulation locally delivered by lentiviral vectors. The value of this research is directly applied to clinical trials to prevent progression of Parkinsonism in patients and this work also provides data on the safety of the method of delivery using lentiviral vectors.

This research used WNPRC Animal Services and Aging Resources.

Funding note: NIH R01NS040578-01 funding ended during this reporting period, and publications are linked here based on project results.

SUBPROJECT PROGRESS

Aging and environmental toxins have been identified as risk factors for sporadic Parkinson's disease (PD). In order to assess the potential for functional recovery induced by GDNF of a diseased aged primate brain, male rhesus monkeys, 24-30 yrs old, received a single intracarotid infusion of MPTP, followed one week later by MRI-guided stereotaxic intrastriatal and intranigral injections of lentiviral vectors encoding for GDNF (lenti-GDNF; n=5) or lac-Z (lenti-lac-Z; n=4). Behavioral analysis revealed that the lenti-GDNF treated monkeys had a significant improvement in the clinical rating compared to lenti-lac-Z starting at 5 weeks post surgery that persisted until necropsy. The fine motor skills slowly improved in the lenti- GDNF treated monkeys while lenti-lac-Z animals had extremely difficulties or were unable to complete the task. Three months after surgery (before necropsy) PET scans revealed increased fluoro-dopa uptake in the caudate and putamen ipsilateral to lenti-GDNF treatment compared to lenti-lac-Z that correlated with the clinical rating score. GDNF ELISA of striatal brain samples confirmed high GDNF expression in lenti-GDNF treated monkeys, that it was higher in animals with increased FD uptake and behavioral improvement. Immunohistochemistry revealed: 1) GDNF and Lac-Z gene expression 3 months postsurgery in the target areas; 2) increased dopaminergic markers immunoreactivity (TH and VMAT2) associated to areas of GDNF expression; 3) minimal micro and astrogliosis as observed with CD68 and GFAP specific antibodies. Our results indicate that the aged primate brain exposed to a neurotoxic insult is responsive to GDNF trophic stimulation locally delivered by lentiviral vectors. We are currently in quantifying dopaminergic striatal terminals and performing stereological cell counts of dopaminergic nigral neurons to complete the assessment.

TRANSPLANTATION OF ES CELLS-DERIVED DOPAMINERGIC NEURONS (0391)

NPRC UNIT: NEUROBIOLOGY

%NPRC \$: 0.500%

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

withheld				
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SUBPROJECT DESCRIPTION

To explore the use of human and monkey embryonic stem (ES) cells derived dopamine neurons for cell replacement therapy in Parkinson's disease.

Cell replacement strategies have been proposed as a treatment for advanced Parkinson's disease. Two years ago, we began

a pilot study using dopaminergic-human ES cells to assess viability and safety in the monkey brain. Last year, we analyzed

the data. Our results suggest that differentiated hES cells in the monkey brain are able to elicit an immune response that

affects their dopaminergic characteristics and survival. This research used WNPRC Animal Services and Stem Cell Resources.

SUBPROJECT PROGRESS

Cell replacement strategies have been proposed as a treatment for advanced Parkinson's disease. In the past year we have performed a pilot study using dopaminergic-human ES cells to assess viability and safety in the monkey brain. Three animals received intracarotid MPTP. Five months later, the animals received MRI-guided stereotaxic injections of differentiated embryonic hSCs labeled with GFP into the striatum and substantia nigra. Forty-eight hours before surgery immunosuppression of cyclosporine was started (20-40 mg/kg p.o.). The animals were sacrificed 3 months later, their brains harvested and processed. Our morphological results confirmed a unilateral dopaminergic lesion induced by MPTP intracarotid administration, observed as a unilateral loss of striatal and nigral TH staining. GFP positive cells were found in the implant areas. GFP positive cells did not colocalize with TH dopamine marker. There was a strong CD68 positive reaction in the implant area, indicating recruitment of macrophages. These results suggest that differentiated hSCs in a non human primate brain maybe able to induce immune rejection. We have plans to perform new studies increasing cyclosporine levels and comparing xeno vs. allografts, in order to improve the fate of the grafts.

TRANSPLANTING NEURAL PROGENITOR STEM CELLS EXPRESSING GDNF IN PARKINSON'S (0392)

NPRC UNIT: NEUROBIOLOGY

%NPRC S: 0.500%

INVESTIGATOR

DEGREES STAFF DEPARTMENT
CODENON-HOST INSTITUTION: STATE,
COUNTRY

withheld

SUBPROJECT DESCRIPTION

To explore the use of human neural progenitor stem cells (HNPCs) genetically modified to deliver the trophic factor GDNF as a therapy for Parkinson's disease and compare its effects to in vivo delivery and unmodified HNPCs.

HNPCs have been proposed as a source of cells for ex vivo gene therapy. We performed a pilot study using HNPCs genetically modified to deliver the trophic factor GDNF to assess viability and safety in the monkey brain. Our results showed HNPCs survival and production of GDNF in the monkey brain via genetically modified HNPCs and restoration/ protection of dopaminergic fibers in target areas. Based on this data, we started a second project with extensive behavioral testing comparing the effects of 1) lentiviral vectors delivering GDNF vs. 2) HNPCs delivering GDNF vs. 3) HNPCs alone vs. 4) control media. The impact of this study is that it assesses, side-by-side, in vivo vs. ex vivo, gene therapy for the delivery of trophic factors. It also assesses whether HNPCs by themselves can affect neurodegeneration. These are key questions for the application of these new biological therapies for the treatment of Parkinson's disease and other neurodegenerative disorders. This Research used WNPRC Animal Services and Stem Cell Resources.

SUBPROJECT PROGRESS

HNPCs are a potential source of cells for ex vivo gene therapy. In a pilot study, three 5-year-old female cynomolgous monkeys received a single intracarotid infusion of MPTP, followed one week later by MRI-guided stereotaxic intrastratial and intranigral injections of male hNPCs transgenic for GDNF. Immunosuppression with oral cyclosporine (20-40 mg/kg) was started 48 hrs before hNPC transplants and continued until the end of the study. The animals were monitored using a clinical rating scale (CRS). Three months post surgery the animals were euthanized by transcardiac perfusion and their brains retrieved and processed for morphological analysis. Our findings include: 1) hNPCs survived and produced GDNF in all animals three months post surgery, 2) hNPCs remained in the areas of injection as observed by GDNF immunostaining and in situ hybridization for the human Y chromosome. 3) A "halo" of GDNF expression was observed diffusing from the center of the graft out into the surrounding area. 4) Increased TH and VMAT2 positive fibers were observed in areas of GDNF delivery in two of the three animals. The two animals with TH and VMAT2 positive fibers also showed reductions in their CRS scores. 5) Some GFAP positive perivascular cuffing was found in transplanted areas. 6) General blood chemistry and necropsies did not reveal any abnormalities. Therefore, we conclude that hNPCs releasing GDNF may be a possible alternative for intracerebral trophic factor delivery in Parkinson's disease. Based on this data a second phase was started. Thirty female cynomolgous monkeys were assigned to this project. The animals are trained to perform a fine motor skills task, an object retrieval detour task (to assess motor planning) and delayed responses test (working memory) and baseline data was collected. Baseline general activity data and clinical rating score are also obtained. MRI brain scans are performed for screening purposes (in case of brain abnormalities) and surgical targeting. After baseline data is completed, animals receive a single intracarotid injection of MPTP followed one week later by 5 intrastratial and 1 intranigral injections ipsilateral to the side of MPTP administration of one of the following treatments: lentiviral vectors encoding for GDNF, HNPCs genetically modified to deliver GDNF, HNPCs wild type or culture media. Immunosuppression with oral cyclosporine (20-40 mg/kg) is started 48 hrs before brain surgery and continued until the end of the study. Up to now, 20 animals have completed the in vivo part of the study. We are evaluating behavioral data and histological measures. Three monkeys had to be excluded from the study as they did not meet the criteria defined by the protocol (score over 9 points in the clinical rating scale after MPTP administration and before intracerebral treatment). We expect to use at least another five monkeys to finish with the appropriate number of animals in each group. The impact of this study is that it assesses, side-by-side,

in vivo vs. ex vivo gene therapy for delivery of trophic factors. It will also show whether HNPSCs by themselves can affect neurodegeneration. These are key questions for the application of these new biological therapies for treatment of Parkinson's disease and other neurodegenerative disorders.

