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

5P51RR000165-43

YERKES NATIONAL PRIMATE RESEARCH CENTER

Final

EMORY UNIVERSITY

EMORY UNIVERSITY WOODRUFF HEALTH SCIENCES CENTER

ANNUAL PROGRESS REPORT

Reporting From: 05/01/2003
Reporting To: 04/30/2004

43.213% AIDS Related

Signature Date

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Patent or Copyright was not awarded this grant year.

PERSONNEL ROSTER

Core Doctoral Scientists

Name, Degree	Department	Non-Host Institution : State, Country
ANDERSON, DANIEL C, DVM	RESEARCH RESOURCES	
DE WAAL, FRANS B M, PHD	PSYCHOBIOLOGY	
GORDON, THOMAS P, MS	PSYCHOBIOLOGY	
HERNDON, JAMES G, MPH, PHD	NEUROSCIENCE	
HOWELL, LEONARD L, PHD	NEUROSCIENCE	
KUHAR, MICHAEL J, PHD	NEUROSCIENCE	
LEVESQUE, DENYSE, DVM	ANIMAL RESOURCES	
MCCLURE, HAROLD M, DVM	RESEARCH RESOURCES	
MUSTARI, MICHAEL J, PHD	VISUAL SCIENCE	
NOVEMBRE, FRANCIS J, PHD	MICROBIOLOGY & IMMUNOOGY	
ORKIN, JACK L, DVM	ANIMAL RESOURCES	
PAUL, KATHERINE S, DVM	ANIMAL RESOURCES	
ROBINSON, HARRIET, PHD	MICROBIOLOGY & IMMUNOLOGY	
SANCHEZ, MAR	PSYCHOCIOLOGY	
SMITH, YOLAND, PHD	NEUROSCIENCE	
SPECK, SAMUEL H, PHD	MICROBIOLOGY & IMMUNOLOGY	
STROBERT, ELIZABETH A, DVM	ANIMAL RESOURCES	
TUSA, RONALD J, MD, PHD	VISUAL SCIENCE	
WALLEN, KIM, PHD	PSYCHOBIOLOGY	
WILSON, MARK E, PHD	PSYCHOBIOLOGY	
WINSLOW, JAMES T, PHD	PSYCHOBIOLOGY	
ZOLA, STUART M, PHD	NEUROSCIENCE	

Affiliated

Name, Degree	Department	Non-Host Institution : State, Country
AHMED, RAFI	VACCINE RESEARCH CENTER	
name	BIOLOGY & PSYCHOLOGY	GA STATE UNIVERSITY: GA, USA
ALTMAN, JOHN, PHD	VACCINE RESEARCH CENTER	
ANSARI, AFTAB A, PHD	PATHOLOGY	
name		
name	GENETICS	SALK INSTITUTE: CA, USA
name		
name		GA STATE UNIVERSITY: GA, USA
name		CORIELL INSTITUTE: NJ, USA
name	PSYCHIATRY	
BICKFORD, MARTHA E, PHD	ANATOMY & NEUROBIOLOGY	UNIVERSITY OF LOUISVILLE : KY, USA
name	NEUROSCIENCE	
BLOOMSMITH, MOLLIE A, PHD	RESEACH RESOURCES	GA INSTITUTE OF TECHNOLOGY : GA, USA
BODEN, SCOTT D, MD	RESEARCH RESOURCES	

Affiliated

Name, Degree	Department	Non-Host Institution : State, Country
name	LAB OF VIRAL DISEASES	NIAID/ NIH: WA, USA
name	MICROBIOLOGY & IMMUNOLOGY	
BRADLEY, DOLORES V, PHD	VISUAL SCIENCE	SPELLMAN COLLEGE: GA, USA
name	DEPT OF ANATOMY & NEUROBIOLOGY	WASHINGTON UNIVERSITY SCHOOLOF MEDICINE : MO, USA
name	ORGANIZ MEDICINAL CHEMISTRY	RESEARCH TRIANGLE INSTITUTE: NC, USA
name	NEUROSCIENCE	RESEARCH TRIANGLE INSTITUTE: NC, USA
name	NEUROSCIENCE	
name	SURGERY	
name	RESEARCH RESOURCES	VA MEDICAL CENTER / COLLEGE OF PHARMACY : GA, USA
COLLINS, WILLIAM E, PHD	INFECTIOUS DISEASES	CENTERS FOR DISEASE CONTROL : GA, USA
COMPANS, RICHARD W, PHD	MICROBIOLOGY & IMMUNOLOGY	
name		USCH RES. & DEV. CENTER: SC, USA
name	PHARMACOLOGY	
name		
name	SCHOOL OF PUBLIC HEALTH	
name		GA STATE UNIVERSITY: GA, USA
DAS, VALLABH E	VISUAL SCIENCE	
name	PSYCHIATRY	
name	CENTER BEHAVIORAL NEUROSCIENCE	UNIVERSITY OF MA: MA, USA
name	NEUROLOGY	
name	NIAID	NIH: MD, USA
name	PHARMACOLOGY	
name	ANIMAL RESOURCES	
name	NEUROSCIENCE	
DONAHOE, ROBERT, PHD	PSYCHIATRY	
name		: VA, USA
name	CENTER BEHAVIORAL NEUROSCIENCE	
name		JEFFERSON MED COLLEGE : PA, USA
name	ANIMAL RESOURCES	
name	VIRAL & RICKETTSIAL DISEASES	CDC: GA, USA
FEINBERG, MARK B, MD, PHD	VACCINE RESEARCH CENTER	
name	PSYCHIATRY	UNIVERSITY OF MA MEDICAL SCHOOL : MA, USA
name	VISUAL SCIENCE	WASHINGTON UNIVERSITY : WA, USA

Affiliated

Name, Degree	Department	Non-Host Institution : State, Country
name	INFECTIOUS DISEASES	CENTERS FOR DISEASE CONTROL : GA, USA
FREEDMAN, LORIN J, MD, PHD	NEUROSCIENCE	
name		WAKE FOREST UNIVERSITY : NC, USA
name	PHYSIOLOGY	HOKKAIDO UNIVERSITY, JAPAN
GALINSKI, MARY R, PHD	VACCINE RESEARCH CENTER	
name		JEFFERSON MED COLLEGE : PA, USA
name	RESEARCH RESOURCES	
name		WAKE FOREST UNIVERSITY : NC, USA
name	NEUROLOGY	UCLA SCHOOL OF MEDICINE : CA, USA
GINSBURG, BRETT C	CNTR BEHAVIORAL NEUROSCIENCE	
name	VIRAL & RICKETTSIAL DISEASES	CENTERS FOR DISEASE CONTROL : GA, USA
name	SOUTHERN RESEARCH INSTITUTE	UNIVERSITY OF ALABAMA : AL, USA
GOULD, KENNETH G, DVM, PHD	RESEARCH RESOURCES	
name		WAKE FOREST UNIVERSITY : NC, USA
GRANT, ROBERT M, MD, MPH, MS	MICROBIOLOGY & IMMUNOBIOLOGY	GLADSTONE INSTITUTE OF VIROLOGY & IMMUNOLOGY : CA, USA
GREENAMYRE, J T, MD, PHD	NEUROSCIENCE	
name	MOLECULAR & CELLULAR BIOLOGY	ROCKEFELLER UNIVERSITY : NY, USA
GRIFFIN, DIANE, PHD	MICROBIOLOGY & IMMUNOLOGY	JOHN HOPKINS UNIVERSITY : MD, USA
name	BIOMEDICAL ENGINEERING MED	
name	CENTER BEHAVIORAL NEUROSCIENCE	
HAMMOCK, ELIZABETH, BS	NEUROSCIENCE	
HANSON, STEPHEN R, PHD	BIOMEDICAL ENGINEERING	
name		MEDICAL COLLEGE OF GA : GA, USA
HEMBY, SCOTT E, PHD	NEUROSCIENCE	
name		MAYO CLINIA: MN, USA
name	PHARAMACOLOGY	
HOPKINS, WILLIAM D, PHD	PSYCHOBIOLOGY	BERRY COLLEGE: GA, USA
name		GA STATE UNIVERSITY: GA, USA
HUNTER, RICHARD, PHD	NEUROSCIENCE	
name	VACCINE RESEARCH CENTER	
JABBAR, M A, PHD	VACCINE RESEARCH CENTER	
JACOB, JOSHY, PHD	VACCINE RESEARCH CENTER	

Affiliated

Name, Degree	Department	Non-Host Institution : State, Country
[name]	NEUROSCIENCE	
JAWORSKI, JASON, PHD	NEUROSCIENCE	
JIANG, BAOMING, DVM, PHD	INFECTIOUS DISEASE	CENTERS FOR DISEASE CONTROL : GA, USA
JOHNS, MICHAEL M E, MD	HEALTH SCIENCES CENTER	
[name]	MICROBIOLOGY & IMMUNOLOGY	NE REGIONAL PRIMATE RESEARCH CENTER : MA, USA
[name]	CENTER COGNITIVE NEUROSCIENCE	DARTMOUTH UNIVERSITY : NH, USA
[name]	CHEMISTRY	
[name]		WAKE FOREST UNIVERSITY : NC, USA
[name]		MCP HANNEMANN: PA, USA
KAUR, AMITINDER, MD	IMMUNOLOGY	NE REGIONAL PRIMATE RESEARCH CENTER : MA, USA
	PEDIATRICS	
[name]	NEUROSCIENCE	BOSTON UNIVERSITY: MA, USA
[name]	PSYCHIATRY	
	BIOMEDICAL ENGINEERING MEDICIN	
[name]	NEUROSCIENCE	
	NEUROLOGY	
		MAX PLANK INSTITUTE, GERMANY
LARSEN, CHRISTIAN, MD	SURGERY	
[name]		GA STATE UNIVERSITY: GA, USA
		UNIVERSITY OF FLORIDA : FL, USA
LENNOX, JEFFREY L, MD	DIVISION OF INFECTIOUS DISEASE	
[name]	NEUROLOGY	
		U MARYLAND MEDICAL SCHOOL : MD, USA
MAESTRIPIERI, DARIO, PHD	PSYCHOLOGY	UNIVERSITY OF CHICAGO : IL, USA
[name]	RADIOLOGY	
	ANATOMY	MISSISSIPPI MEDICAL CENTER : MS, USA
[name]	PSYCHOBIOLOGY	
[name]		UNIVERSITY OF SOUTH CAROLINA : SC, USA
MCDONALD, KELLY, MD	MICROBIOLOGY & IMMUNOLOGY	MT. SINAI MEDICAL CENTER : NY, USA
[name]	IMMUNOGENTICS	CENTERS FOR DISEASE CONTROL : GA, USA
MITTLER, ROBERT, PHD	VACCINE RESEARCH CENTER	
[name]		UNIVERSITY OF PITTSBURGH MEDICAL CENTER : PA, USA

Affiliated

Name, Degree	Department	Non-Host Institution : State, Country
[name]	VIRAL & RICKETTSIAL DISEASES	CDC: GA, USA
[name]		DUKE UNIVERSITY MEDICAL CENTER: NC, USA
[name]	ANATOMY & NEUROBIOLOGY	BOSTON UNIVERSITY: MA, USA
[name]	NEUROSCIENCE	
MORENO, ALBERTO, MD	VACCINE RESEARCH CENTER	
[Names]	VIRAL DISEASES	NIAID/NIH: WA, USA
MULY, E CHRISTOPHER, MD, PHD	CNTR BEHAVIORAL NEUROSCIENCE	UAB: AL, USA
NAIR, HEMANTH, PHD	CENTER BEHAVIORAL NEUROSCIENCE	
[Names]		VA MED CENTER: GA, USA
NARAYAN, OPENDRA, DVM, PHD	MICROBIOLOGY	UNIVERSITY OF KANSAS: KS, USA
[	RESEARCH RESOURCES	
	PSYCHIATRY	
Names		UNIVERSITY OF REGENSBURG, GERMANY
]	MICROBIOLOGY & IMMUNOLOGY	
[Names]	PSYCHIATRY	
		NATIONAL JEWISH CENTER : CO, USA
[	NEUROLOGY	
	PSYCHOBIOLOGY	
Names	SURGERY	
]		LOS ALAMOS NATIONAL LAB : NM, USA
[	NEUROSCIENCE	UNIVERSITE' LOUIS PASTEUR, UK
Names	PSYSIOLOGY	
	PSYCHOBIOLOGY	
]	OPHTHALMOLOGY	CASE WESTERN RESERVE UNIVERSITY: OH, USA
[name]	COGNITIVE EVOLUTION GROUP	U LOUISIANA LAFAYETTE : LA, USA
PRUESS, TODD M, PHD	NEUROSCIENCE	
PULENDRAN, BALI, PHD	VACCINE RESEARCH CENTER	
[name]	PATHOLOGY	
RAINNIE, DONALD G, PHD	NEUROSCIENCE	
[name]	VACCINE CENTER	
	NEUROSCIENCE	

Affiliated

Name, Degree	Department	Non-Host Institution : State, Country
RESSLER, KERRY J, PHD	CENTER BEHAVIORAL SCIENCES	
		UNIVERISTY OF OXFORD, UK
	ANTHROPOLOGY	
	ANATOMY AND NEUROBIOLOGY	BOSTON UNIVERSITY: MA, USA
		CENTER FOR DISEASE CONTROL : GA, USA
ROTHBAUM, BARBARA	CENTER BEHAVIORAL NEUROSCIENCE	
RUPRECHT, RUTH M, MD, PHD	RESEARCH RESOURCES	DANA FARBER CANCER INSTITUTE: MA, USA
		HARVARD MEDICAL SCHOOL : MA, USA
SCHINAZI, RAYMOND F, PHD	PEDIATRICS	VA MEDICAL CENTER: GA, USA
	SCHOOL OF PUBLIC HEALTH	
	ANIMAL RESOURCES	
SILVESTRI, GUIDO, MD	VACCINE RESEARCH CENTER	
	OPTOMETRY	
	MICROBIOLOGY & IMMUNOLOGY	
SMITH, MARY ALICE, PHD	BIOLOGY	UNIVERSITY OF GEORGIA : GA, USA
SODORA, DONALD L, PHD	INTERNAL MEDICINE	UNIVERSITY OF TEXAS: TX, USA
		UNIVERSITY OF CA, SAN DIEGO : CA, USA
STAPRANS, SILVIJA, PHD	VACCINE RESEARCH CENTER	
	ANIMAL RESOURCES	
		HARVARD MEDICAL SCHOOL : MA, USA
	DENTAL SCHOOL	UNIVERSITY OF MD: MD, USA
	PHARMACOLOGY	
TUNG, FRANK, PHD	RESEARCH RESOURCES	GENECURE: GA, USA
	VISUAL SCIENCE	WASHINGTON UNIVERSITY OF MEDICINE : MO, USA
VILLINGER, FRANCOIS, DVM, PHD	PATHOLOGY	
VINCENTIC, ALEKSANDRA, PHD	NEUROSCIENCE	
	NEUROSCIENCE	
	VACCINE RESEARCH CENTER	
WALKER, LARY, PHD	NEUROSCIENCE	
	IMMUNOLOGY, NEPRC	
		FLORIDA STATE UNIVERSITY : FL, USA
	GENETICS	

Affiliated

Name, Degree	Department	Non-Host Institution : State, Country
[illegible]	WISCONSIN PRIMATE RESEARCH CNT	UNIVERSITY OF WISCONSIN : WI, USA
Name		SIMON FRASER UNIVERSITY, BC, CANADA
[illegible]	VACCINE RESEARCH CENTER	UNIVERSITY OF WISCONSIN : WI, USA
[illegible]		DUKE UNIVERSITY MEDICAL CENTER : NC, USA
	GENETICS	
Name	VIRAL & RICKETTSIAL DISEASES	CENTERS FOR DISEASE CONTROL : GA, USA
		ST. ANDREWS, UK
[illegible]	VIRAL & RICKETTSIAL DISEASES	CDC: GA, USA
YOUNG, LARRY J, PHD	CNTR BEHAVIORAL NEUROSCIENCE	
[illegible]		CLAREMONT GRADUATE UNIVERSITY : CA, USA
Name	MEDICINE	
[illegible]		BOSTON UNIVERSITY SCHOOL OF MEDICINE : MA, USA

Graduate Student/Postdoctoral Scientists

Name, Degree	Department	Non-Host Institution : State, Country
[illegible]	MICROBIOLOGY & IMMUNOLOGY	
AMARA, RAMA R, PHD	MICROBIOLOGY & IMMUNOLOGY	
Name	CENTER BEHAVIORAL NEUROSCIENCE	
GARBER, DAVID A, PHD	VACCINE RESEARCH CENTER	
[illegible]	PSYCHOBIOLOGY	
KIMMEL, HEATHER, PHD	NEUROSCIENCE	
LIM, MIRANDA M, BS	NEUROSCIENCE	
LINDSEY, KIMBERLY P	CNTR BEHAVAIORAL NEUROSCIENCE	
MOSER, JANICE	MICROBIOLOGY & IMMUNOLOGY	
[illegible]	VISUAL SCIENCE	
PARR, LISA, PHD	CNTR BEHAVIORAL NEUROSCIENCE	
[illegible]		

SUBPROJECT DESCRIPTIONS

NPRC MANAGEMENT SUBPROJECTS

SPF COLONY (0309)

NPRC UNIT : ADMINISTRATIVE

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
GORDON, THOMAS P	MS	C	PSYCHOBIOLOGY	
	DVM, MS	A	ANIMAL RESOURCES	
	DVM	C	RESEARCH RESOURCES	

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

ABSTRACT

The central objective of the present project is to breed SPF macaque monkeys (chiefly rhesus monkeys of Indian ancestry) that are specific pathogen free (SPF) and genetically characterized - as defined by the National Center for Research Resources in RFA RR -02-005 – specifically to provide subjects to NIH supported investigators for AIDS related research and thus to contribute to national health priorities . This objective will be achieved at the YNPRC initially utilizing the existing colony of SPF macaque monkeys . Specifically, an existing SPF rhesus of Indian ancestry will be increased via breeding, recruitment of young animals from YNPRC non -SPF breeding colonies and via appropriate testing and separation . The overall aim of the project is to provide all the trained personnel and resources that are necessary to maintain and enlarge SPF breeding groups and to manage them in order to optimize health and reproductive performance in support of national health related priorities established by NIH and NCRR . The YNPRC will work closely with NCRR and the Coordinating Committee they have established in implementing recommendations regarding uniform husbandry procedures, standarization of screening tests and such other matters as the committee may decide . The YNPRC also will work in coordination with other facilities maintaining NCRR supported SPF colonies and with any investigators identified by NCRR to maximize the potential that national priorities for SPF production will be attained .

OPERATION OF THE YERKES PRIMATE RESEARCH CENTER (0191)

NPRC UNIT : ADMINISTRATIVE

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
JOHNS, MICHAEL M E	MD	A	HEALTH SCIENCES CENTER	
	DVM, MS	A	ANIMAL RESOURCES	
Names	MS	C	PSYCHOBIOLOGY	
	DVM	C	RESEARCH RESOURCES	
	PHD	C	NEUROSCIENCE	

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

ABSTRACT

This goal of this administrative project is the operation of the Yerkes National Primate Research Center of Emory University . This core provides overall direction of the following components to support the Center's scientific mission : administration, scientific leadership, management, comprehensive business services, information technology, human resources, and a public information office . In addition, the administrative core oversees facilities management; animal resources (veterinary medicine, animal care, animal records, and environmental enrichment); research resources (service pathology, environmental health and safety and comprehensive support to outside investigators); and four Service Cores : Endocrinology, Molecular Pathology, DNA Microchip Array and Virology General direction also is provided for four scientific divisions : Microbiology and Immunology, Neuroscience, Psychobiology and Visual Science The Center's goals are to conduct a research program focused on scientific problems relevant to human health and the NIH mission, to provide the resource infrastructure and expertise in appropriate scientific and veterinary specialties to support such a program and to enhance the Center's ability to serve as a resource to core investigators as well as to scientists regionally, nationally and internationally

MAINTENANCE OF YPC ANIMAL COLONY (0292)

NPRC UNIT : ANIMAL RESOURCES

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
ZOLA, STUART M	PHD	C	NEUROSCIENCE	
[	PHD	A	RESEACH RESOURCES	GA INSTITUTE OF TECHNOLOGY, GA USA
		A	ANIMAL RESOURCES	
	DVM, MS	A	ANIMAL RESOURCES	
	MS	C	PSYCHOBIOLOGY	
Names	DVM	C	ANIMAL RESOURCES	
	DVM	C	ANIMAL RESOURCES	
	DVM	C	ANIMAL RESOURCES	
	BS	A	ANIMAL RESOURCES	
	DVM	C	ANIMAL RESOURCES	
]	DVM	A	ANIMAL RESOURCES	

AXIS I CODES: 1A, 28(BREEDING) **AXIS II CODES** 31, 36, 54B, 60, 92(COLONY MANAGEMENT)

ABSTRACT

The Yerkes animal colony is maintained by the Division of Animal Resources, which is responsible for veterinary and animal care, environmental enrichment, and animal records . Maintenance of such a resource requires certain animal care and use procedures that are an integral part of the support of such a colony . These include : holding the animals in captivity; maintaining breeding colonies (including SPF macaque and mangabey colonies); movement and handling of the animals as required for management purposes; periodic health surveillance, which may include physical examination, tuberculin testing, radiographs, blood collections; treatment of intercurrent diseases and injuries; and occasional euthanasia of animals unresponsive to treatment or animals with untreatable clinical problems or injuries .

CENTER FOR BEHAVIORAL NEUROSCIENCE (0359)

NPRC UNIT : CNTR BEHAV NEUROSCIENCE

%NPRC $: 0.500%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
ZOLA, STUART M	PHD	C	NEUROSCIENCE	
L name J	PHD	A	BIOLOGY & PSYCHOLOGY	GA STATE UNIVERSITY , GA USA

AXIS I CODES: 21 **AXIS II CODES** 36, 63, 71, 72

ABSTRACT

This project is an interdisciplinary, inter -institute researchand education program in behavioral neuroscience . The project includes over 80 faculty from 8 Atlanta colleges and universities including 5 schools that primarily serve African-American students . The sclentific program focuses on the neural basis of social behaviors using molecular, cellular, and sytematic approaches . The administrative home and several research labs for the Center are based at Yerkes . The Center is currently in its sixth year of funding from the NSF and the State of Georgia .

DNA MICROARRAY CORE (0255)

NPRC UNIT : NEUROSCIENCE

%NPRC $: 0.300% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
HEMBY, SCOTT E	PHD	A	NEUROSCIENCE	

AXIS I CODES: 1B, 1D, 28(TISSUE) **AXIS II CODES** 31, 58, 92(GENE ARRAY)

ABSTRACT

The DNA Microarray Facility at the Yerkes Primate Center has been established to provide an academic base for continuing research and education in the nascent field of funtional genomics and bioinformatics . The facility will promote ease of access to state of the art functional genomics technology including the production, use and analysis of cDNA microarrays and will provide services for (1) probe preparation (2) microarray production and hybridization, (3) image and bioinformatics analysis (4) cDNA library construction and (5) DNS sequencing . The facility produces high density human, mounse and rat cDNA microarrays for quantitative measurement of mRNAs from experimental, disease and control samples .

THE DEVELOPMENT OF A CENTER FOR THE SCIENTIFIC STUDY OF CHIMPANZEES (0253)

NPRC UNIT : NEUROSCIENCE

% NPRC $: 0.520%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
ZOLA, STUART M	PHD	C	NEUROSCIENCE	

AXIS I CODES: 11 **AXIS II CODES:** 41

ABSTRACT

Two key aspects of the Yerkes National Primate Research Center, i .e. the diversity of research activities and the availability of a large number of chimpanzees, positioned us to become world leaders in chimpanzee -related research. This proposal funded the development of a new testing facility for assessing cognitive function in chimpanzees. The testing facility has been completed and chimpanzees are currently being habituated to the facility This proposal is also funding an international conference at the Yerkes Research Center . Approximately a 60 world -renowned experts in nonhuman primate research from across the U .S., Europe and Japan will attend, together with about 25 researchers from institutions throughout Georgia . The conference will include platform presentations focused on chimpanzee research as well as advisory discussions with respect to future ideas and proposals for chimpanzee research.

LIVING LINKS CENTER FOR STUDY OF APE & HUMAN EVOLUTION (0062)

NPRC UNIT : PSYCHOBIOLOGY

%NPRC $: 0.460 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
DE WAAL, FRANS B M	PHD	C	PSYCHOBIOLOGY	
		A		CORIELL INSTITUTE, NJ USA
names)	PHD	A	PSYCHOBIOLOGY	BERRY COLLEGE, GA USA

AXIS I CODES: 1A **AXIS II CODES** 30, 36, 41, 59, 63C

ABSTRACT

The Living Links Center is a research and educational center for the study of ape and human evolution, using behavioral, cognitive, anatomic, and molecular approaches . The LLC was formed in 1997 in response to developments . The first was the intellectual convergence of the fields of evolutionary psychology, comparative cognition, and field primatology around the importance of using extant species to understand extinct hominid ancestors . Second, technical developments in brain imaging and genomic sequencing provided new non -invasive approaches to study similarities and differences between great apes and humans . The LLC was formed to utilize this colony in non -invasive comparative research and to provide a base for philanthropic fund raising for both scientific and colony support . The LLC was launched in September, 1997 with joint support from the Office of the Provost and the Executive Vice President for Health Affairs . A more detailed mission statement can be found at our website (see below). Major activities over the past years have been 1) organization of a hugely successful symposium on human origins that drew nearly 2,000 people from Emory and beyond, and 2) an international conference with the Chicago Academy of Sciences, in Chicago that has just been turned into a book .

MOLECULAR PATHOLOGY CORE (0357)

NPRC UNIT : RESEARCH RESOURCES

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
ANDERSON, DANIEL C	DVM	C	RESEARCH RESOURCES	
names		A	RESEARCH RESOURCES	
	DVM	C	RESEARCH RESOURCES	

AXIS I CODES: 1A, 1D, 7, 16, 19, 21 **AXIS II CODES** 31, 64, 66, 76

ABSTRACT

The Molecular Pathology Core is a service laboratory established to provide both diagnostic and investigative molecular pathology support to investigators at the Yerkes National Primate Research Center, investigators at Emory University, and investigators outside of the Emory University community . Working in concert with Yerkes' Diagnostic Pathology Laboratory (which provides conventional histotechnical services), this laboratory applies immunohistochemistry, in situ hybridization, and immunoenzymatic technologies toward the investigation of physiologic and pathologic processes in tissues of nonhuman primates .

During the past year, the Molecular Pathology Core has provided investigators with several areas of expertise, including : (1) in situ hybridization to localize and quantitate target nucleic acids (e.g. to localize SIV or HIV RNA), 2) morphometric analysis of tissue sections, (3) immunohistochemistry to localize target proteins (e.g. to identify cell phenotype and markers of cellular activation, or to localize expression of extracellular matrix proteins), and (4) immunoenzymatic assays (e.g. localization of cells undergoing programmed cell death). In addition to these services, the Molecular Pathology Core serves as an information resource for the Yerkes Center staff and outside investigators, providing information concerning nonhuman primate histopathology, histologic techniques, specimen collection and processing, and the safe operation of the cryostat in the BSL -3 space.

SPECIMEN COLLECTION AND DISTRIBUTION PROGRAM (0291)

NPRC UNIT : RESEARCH RESOURCES

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
MCCLURE, HAROLD M	DVM	C	RESEARCH RESOURCES	
	DVM	C	RESEARCH RESOURCES	
		A	RESEARCH RESOURCES	
		A	RESEARCH RESOURCES	
	DVM	C	ANIMAL RESOURCES	
	DVM	C	ANIMAL RESOURCES	
	DVM	C	ANIMAL RESOURCES	

Names

AXIS I CODES: 1D **AXIS II CODES** 31, 64, 66

ABSTRACT

During the past year, 8,405 specimens were collected and provided to 81 investigators . A partial listing of specimens provided to these investigators included blood, serum, a variety of tissue specimens, eyes, brain, bone marrow, fecal samples, urine samples and CSF samples . Specimens provided included 58,188 ml of whole blood, 559 ml of plasma and 4,428 ml of serum from six nonhuman primate species. These specimens were provided to 9 investigators in 6 different departments at the host institution, 69 investigators at U .S. institutions other than Emory University, and three foreign institutions .

The provision of various biological specimens to non -Yerkes investigators is an important contribution to biomedical research at the host institution as well as other regional, national, and international institutions . Specimens provided to outside investigators result in a number of publications each year (see publications list). These specimens also often prove to be extremely valuable for educational purposes when used in undergraduate or graduate courses in anatomy, anthropology, etc .

CHIMPANZEE MANAGEMENT RESEARCH PROGRAM (0037)

NPRC UNIT : RESEARCH RESOURCES

%NPRC $: 0.520%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
ZOLA, STUART M	PHD	C	NEUROSCIENCE	
[	PHD	A	RESEACH RESOURCES	GA INSTITUTE OF TECHNOLOGY, GA USA
Names	DVM, MS	A	ANIMAL RESOURCES	
	DVM, PHD	A	RESEARCH RESOURCES	
]	DVM	C	ANIMAL RESOURCES	

AXIS I CODES: 1A, 11, 23 **AXIS II CODES** 36

ABSTRACT

With the characterization of the chimpanzee genome, there has been an increased interest in this species as a research model. This, along with continued Yerkes support of research for which the species is uniquely suitable, has lead to the need for more careful monitoring and management of animal assignments, a process that is now underway . Given that most of our animals are housed socially, considerable effort continues to be invested in contraception to prevent pregnancies . To permit continued observation of menstrual cyclicity, IUDs are the primary method of choice, with females unsuitable for IUD insertion receiving hormonal interventions for contraception . Continued improvements to chimpanzee living arrangements have included resurfacing living environs and providing additional interconnecting doors to facilitate not only social housing but husbandry and management. Positive reinforcement training continues to be a high priority, including providing support to and working with Yerkes Neuroscience personnel .

VACCINE RESEARCH CENTER (0177)

NPRC UNIT : VACCINE RESEARCH CENTER

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
AHMED, RAFI		A	VACCINE RESEARCH CENTER	

AXIS I CODES: 28(MANAGEMENT) **AXIS II CODES** 31, 92(MANAGEMENT)

ABSTRACT

Vaccines are among the greatest advances in modern medicine . Thanks to their development and cost -effectiveness, crippling diseases like smallpox and polio have been eliminated . However, millions of people worldwide are still plagued by today's infectious diseases, which have proven more difficult to restrain .

The goal of the Emory Vaccine Research Center is to create new techniques to prevent AIDS, tuberculosis, malaria, influenza, and respiratory illnesses . Scientists at the Center are pioneering scientific initiatives and are poised to move promising pre -clinical discoveries to the next level, with the aim of making a positive impact on world health .

The Vaccing Research Center's proximity to local institutions such as the CDC and Ponce Center, a leaving HIV clinical facility, and to the unique animal resources and technical support at Yerkes Primate Center, provide a comprehensive research megaplex unlike any other in the world .

CENTER FOR AIDS RESEARCH (0181)

NPRC UNIT : VACCINE RESEARCH CENTER

% NPRC $: 0.600 % **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
FEINBERG, MARK B	MD, PHD	A	VACCINE RESEARCH CENTER	
C	PHD	A	VACCINE RESEARCH CENTER	
	MD, PHD	A	SCHOOL OF PUBLIC HEALTH	
NAMES	PHD	A	VACCINE RESEARCH CENTER	
	PHD	A	VACCINE RESEARCH CENTER	
	EDD	A	SCHOOL OF PUBLIC HEALTH	
J	PHD	A	VACCINE RESEARCH CENTER	

AXIS I CODES: 1D, 7B **AXIS II CODES** 31, 64, 66, 91

ABSTRACT

The Emory Center for AIDS Research (CFAR) provides administrative and shared facilities support for HIV /AIDS research at Emory . There are 16 other NIH -funded CFARs around the country . Components of the Emory CFAR include the Rollins School of Public Health, Emory University School of Medicine, the Yerkes National Primate Research Center, the Emory Emory Vaccine Center, and Emory College . The Emory CFAR currently provides services for over 120 faculty who engage in more than $ 44 million dollars of funded HIV /AIDS research annually in the areas of prevention science, vaccine development, AIDS pathogenesis, and clinical science . CFAR services are provided through six CFAR Cores : Administrative, Developmental, Behavioral & Social Sciences, Clinical Research, Immunology, and Virology /Pharmacology .

RESEARCH SUBPROJECTS

TAILORING ENRICHMENT TO REARING AND RESEARCH (0206)

NPRC UNIT : ANIMAL RESOURCES

% NPRC $: 0.520 % **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
BLOOMSMITH, MOLLIE A	PHD	A	RESEACH RESOURCES	GA INSTITUTE OF TECHNOLOGY, GA USA

AXIS I CODES: 1A **AXIS II CODES** 31, 36

ABSTRACT

In order to continue progress in improving the care of primates in research facilities, it will also be necessary to better determine how enrichment techniques should be tailored to the management of primates used in biomedical research. Biomedical studies may require restrictions on the type of enrichment techniques that can be implemented for study animals, and may at the same time alter the psychological needs of the animals . The project provides direct benefit to the well -being and management of Rhesus macaques (Macaca mulatta). Focus is placed on three aspects of management that may vary considerably with rearing and research use : 1) Compare the behavioral, physiological, and clinical effects of protected contact versus full contact for pair -housed Rhesus macaques in order to determine the optimal means for providing social contact to singly -housed individuals; 2) Determine the quantity and form of human/primate interaction that best compensates for single caging for Rhesus macaques; and 3) Assess the benefits of interventions for Rhesus macaques exhibiting self -injurious behavior, compare the efficacy of enrichment interventions, pharmacological treatment, and positive reinforcement training for eliminating this behavior .

CRF-R1 MEDIATION OF FEAR: A VIRAL VECTOR APPROACH (0316)

NPRC UNIT : CNTR BEHAV NEUROSCIENCE

% NPRC $: 0.500 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
NAIR, HEMANTH	PHD	A	CENTER BEHAVIORAL NEUROSCIENCE	

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

ABSTRACT

The aim of the proposal is to assess the effects of a lentiviral -mediated over -expression of the CRF -R1 receptor in the bed nucleus of the stria terminalis (BNST) or central nucleus of the amygdala (CEA) on different forms of facilitation of the acoustic startle reflex . The reflex is a simple, unconditioned startle reaction to a loud sound, which can be potentiated by fear - or anxiety -like states . Facilitation of the reflex by discrete, aversively conditioned cues (e.g. a light previously paired with shock), known as fear-potentiated startle, depends on the CEA but not the BNST whereas facilitation by less defined, unpredictable, or unconditioned stimuli may depend on the BNST . It is hypothesized that over -expression of the CRF -R1 receptor in the BNST will potentiate baseline levels of acoustic startle as well as exposure to bright lights (an unconditioned, anxiogenic stimulus), but not have much of an impact on conditioning to discrete cues . Alternatively, over -expression in the CEA should enhance fear -potentiated startle, but have little effect on baseline or light -enhanced startle .

BIOPHYSICAL PROPERTIES OF NEURONES OF THE BNST (0312)

NPRC UNIT : CNTR BEHAV NEUROSCIENCE

% NPRC $: 0.500 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
RAINNIE, DONALD G	PHD	A	NEUROSCIENCE	

AXIS I CODES: 1D, 21 **AXIS II CODES** 89

ABSTRACT

Experiments are conducted using whole -cell patch -clamp recordings from neurons of the lateral BNST in a coronal brain slice, in vitro . During recording, brain slices will be maintained submerged in a recording chamber at 32 C, and continuously perfused with pre -oxygenated artificial cerebrospinal fluid (ACSF). Under these conditions we will employ current - and voltage -clamp recording modes to examine the biophysical properties of BNST neurons and their response to drug application . In addition, we will record from visually identified projection neurons using concurrent infra -red differential interference microscopy (IR-DIC) and epifluorescence, in association with retrograde labeling of neurons with fluorescent latex beads . This technique enables us to record from specific subpopulations of BNST neurons . Three specific aims are addressed in this proposal : i) characterization of the biophysical properties of projection neurons of the lateral BNST, ii) identification of the postsynaptic response of lateral BNST projection neurons to CRF receptor activation, and iii) identification of the postsynaptic response of lateral BNST projection neurons to 5-HT receptor activation .

ROLE OF NPY AND NPY EXPRESSING INTERNEURONS IN BASOLATERAL AMYGADALA (0313)

NPRC UNIT : CNTR BEHAV NEUROSCIENCE

%NPRC $: 0.500 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
RAINNIE, DONALD G	PHD	A	NEUROSCIENCE	

AXIS I CODES: 1D, 21 **AXIS II CODES** 36, 89

ABSTRACT

This project will involve a collaboration between the CBN laboratories and use electrophysiological and behavioral paradigms to study the functional role of neuropeptide Y (NPY) and NPY -expressing interneurons in the basolateral amygdala (BLA). At least four distinct subpopulations of interneurons exist in BLA . At the cellular level, little is known about how these interneuron subgroups contribute to signal processing in the BLA . One subpopulation of BLA interneurons exclusively express NPY, and recent evidence suggests that NPY receptor activation in the amygdala plays a critical role in the central response to stress and anxiety . Hence, NPY is thought to inhibit much of the anxiety -like behavioral response induced by stress . However, the functional role of these BLA NPY interneurons, and the consequences of NPY release on neuronal activity in the BLA are at present unknown . Here, we investigate the mechanisms by which NPY, and NPY -expressing interneurons contribute to network activity in the BLA using two different experimental approaches . In the first approach, we examine the response of BLA neurons to exogenous NPY application, using whole -cell patch -clamp recordings . In the second approach, we will use a cell -specific neurotoxin to ablate NPY -containing interneurons in the BLA and examine the functional consequences of this ablation using several acoustic startle paradigms .

DOPAMINERGIC MODULATION OF NETWORK ACTIVITY IN BASOLATERAL AMYGDALA (0314)

NPRC UNIT : CNTR BEHAV NEUROSCIENCE

%NPRC $: 0.500%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
RAINNIE, DONALD G	PHD	A	NEUROSCIENCE	

AXIS I CODES: 1D, 2, 21 **AXIS II CODES:** 72

ABSTRACT

The primary goals of this study are to : 1) determine the effects of dopamine receptor activation on the membrane properties of neurons of the basolateral amygdala (BLA), and 2) determine the effects of acute and chronic clozapine treatment on the response of BLA neurons to dopamine . The rationale for this study is that there is a growing body of evidence to suggest that some of the clinical efficacy of antipsychotic agents in treating the emotive components of schizophrenia may lie in their ability to modulate the response of BLA neurons to dopamine receptor activation . However, before we can make predictive statements about any possible clinical correlations with drug action, it is imperative that we first determine the normal response of BLA neurons to dopamine receptor activation and then determine how this may effected by antipsychotic agents, such as clozapine . Having done so, we may then extrapolate these findings to the pathological state . Using patch -clamp recording techniques we will test the hypothesis that chronic clozapine treatment differentially regulates the postsynaptic response of projection neurons and interneurons of the BLA to exogenous dopamine application . We predict that chronic clozapine treatment will attenuate the response of BLA interneurons to exogenous dopamine application without effecting the response of BLA projection neurons to exogenous dopamine .

SNAPTIC ORGANIZATION OF THE BASOLATERAL AMYGDALA (0315)

NPRC UNIT : CNTR BEHAV NEUROSCIENCE

% NPRC $: 0.500 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
RAINNIE, DONALD G	PHD	A	NEUROSCIENCE	
E name	J	A		UNIVERSITY OF SOUTH CAROLINA, SC USA

AXIS I CODES: 1D, 2, 21 **AXIS II CODES** 72, 89

ABSTRACT

The project is the continuation of a long -term investigation of the neuronal and synaptic organization of the basolateral amygdala (ABL) with a focus on the regulation of ABL interneurons by transmitter -specific neuromodulator systems . Every brain region consists of a unique array of cell types, each with its own distinctive morphological, cytochemical, connectional, electrophysiological, and pharmacological features . One of the basic premises of the research is that a thorough understanding of the anatomy, pharmacology, physiology and pathophysiology of any brain region requires a detailed knowledge of the neurobiological characteristics of specific neuronal populations . The study will investigate several important aspects of distinct interneuronal subpopulations in rodents and primates, including their electrophysiological characteristics and their innervation and modulation by monoaminergic systems and the basal forebrain . The studies include the first comprehensive analysis of the electrophysiological properties of immunohistochemically -identified ABL interneuronal subpopulations in both rodent and primate brain slices . In addition, the modulation of key electrophysiological properties in these neurons by serotonin and serotonergic drugs will be investigated . These studies will contribute to an understanding of inhibitory mechanisms in the ABL and should be critical for the development of novel ways to modulate the activity of the ABL in epilepsy and psychiatric disorders .

VISUAL IDENTIFICATION OF PROJECTION NEURONS IN THE AMYGDALA (0356)

NPRC UNIT : CNTR BEHAV NEUROSCIENCE

% NPRC $: 0.500 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
RAINNIE, DONALD G	PHD	A	NEUROSCIENCE	

AXIS I CODES: 1F **AXIS II CODES** 64, 68

ABSTRACT

The amygdala and prefrontal cortex are thought to be essential compontents of the neural circuit mediating emotional responses to sensory cues . Most of our understanding of this neural circuit of emotion is based on preclinical work performed in rodents . Evidence now points to critical species differences in the neurochemical and neuroanatomy understanding of limbic mediation of emotion is possible . This project aims to utilize the expertise of three CBN laboratories and combine whole -cell patch clamp eletrophysiology, tract tracing and molecular biology to provide functional description of a critical cortical -amygdala pathway, its functional architecture and its modulation by neurotransmitters . Elucidation of this circuit in primates should further the understanding of mood and anxiety disorders well as inform future approaches for these devastating illnesses .

RODENT MODEL OF PTSD: FEAR CONDITIONING (0317)

NPRC UNIT : CNTR BEHAV NEUROSCIENCE

% NPRC $: 0.500 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
RESSLER, KERRY J	PHD	A	CENTER BEHAVIORAL SCIENCES	

AXIS I CODES: 1A, 2, 21 **AXIS II CODES** 36, 72

ABSTRACT

This project aims to replicate preliminary data that mice have enhanced fear conditioning and diminished extinction during a low corticosterone state, leading to a rodent model for Posttraumatic Stress Disorder, one in which animals over-consolidate a trauma memory and fail to extinguish it over time .

NOVEL MODEL OF SCHIZOPHRENIA: HEABNULA LESIONS FOLLOWED BY STRESS (0319)

NPRC UNIT : CNTR BEHAV NEUROSCIENCE

%NPRC $: 0.500 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
RESSLER, KERRY J	PHD	A	CENTER BEHAVIORAL SCIENCES	

AXIS I CODES: 1A, 2, 21 **AXIS II CODES** 36, 72

ABSTRACT

This proposal aims to create a novel model for schizophrenia symptomatology in rodents . We have found that the habenula, an understudied midbrain region that is a primary regulator of serotonergic and dopaminergic tone, is very plastic with emotional learning . Lesions of this region when combined with stress lead to reversible deficits in pre-pulse inhibition as well as alterations in GAD 67 and EAAC 1 gene expression as have been shown in schizophrenics .

DEVELOPMENT OF VIRAL VECTOR FOR GENE DELIVERY & NEURAL TRACT TRACING (0320)

NPRC UNIT : CNTR BEHAV NEUROSCIENCE

%NPRC $: 0.500 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
RESSLER, KERRY J	PHD	A	CENTER BEHAVIORAL SCIENCES	

AXIS I CODES: 1A, 1D, 21 **AXIS II CODES** 59

ABSTRACT

This proposal aims to complete design and production of a lentivirus vector that co -expresses a gene of interest, such as the TrkB receptor gene, in combination with a trans -synaptic tracer such as Wheat Germ Agglutinin fused to a fluorescent protein, for the study of synaptic connectivity and dependence of that connectivity on specific gene products .

TRANSLATIONAL RESEARCH ON EXTINCTION AND PTSD (0318)

NPRC UNIT : CNTR BEHAV NEUROSCIENCE

% NPRC $: 0.500 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
ROTHBAUM, BARBARA		A	CENTER BEHAVIORAL NEUROSCIENCE	
	PHD	A	PSYCHIATRY	
	PHD	A	CENTER BEHAVIORAL NEUROSCIENCE	
	PHD	A	CENTER BEHAVIORAL NEUROSCIENCE	
	PHD	A		GA STATE UNIVERSITY, GA USA
	PHD	A	CENTER BEHAVIORAL SCIENCES	

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

ABSTRACT

This is an interdisciplinary pilot project to bridge animal studies and well -controlled human studies examining the mechanisms of fear learning in animals and people and its relationship to PTSD as well the mechanisms of extinction learning in animals and people, with hopes of translating this knowledge to treatment and prevention of PTSD. This study is currently in its beginning phases of basic animal and human research on pre -clinical mechanisms of fear and extinction learning .

CENTRAL VASOPRESSIN RECEPTORS AND AFFILIATION (0118)

NPRC UNIT : CNTR BEHAV NEUROSCIENCE

%NPRC $: 0.520%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
YOUNG, LARRY J	PHD	A	CNTR BEHAVIORAL NEUROSCIENCE	
	BS	A	NEUROSCIENCE	
	BS	A	NEUROSCIENCE	
	BS	G	NEUROSCIENCE	
	PHD	A	NEUROSCIENCE	
	PHD	A		
	PHD	A		HARVARD MEDICAL SCHOOL, MA USA
	PHD	A		FLORIDA STATE UNIVERSITY, FL USA

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

ABSTRACT

Voles provide an excellent animal model for investigating the molecular, cellular and neural mechanisms underlying affiliative behavior and social attachment . Pharmacological studies have demonstrated that vasopressin plays an important role in pair bond formation in the monogamous prairie vole . Comparisons of the vasopressin system between prairie voles and non -monogamous vole species demonstrate that species differences in the promoter of the V1a receptor (V1aR) gene and the neuroanatomical pattern of expression of the gene may be responsible for species differences in social behavior . Prairie voles express high levels of V 1aR gene expression in the ventral pallidum, laterodorsal thalamus and medial amygdala, compared to non -monogamous montane and meadow voles . Using transgenic mice, we have demonstrated that neuroanatomical distribution of V 1aR does influence the behavioral response to vasopressin . In addition, using an adeno -associated viral vector, we have demonstrated that over-expressing the V 1a receptor in the ventral pallidum of male prairie voles leads to increased affiliative behavior and facilitates the formation of a pairbond . The ventral pallidum is a major component of the mesolimbic reward pathway, and has been identified as a site of action for drugs of abuse such as cocaine and amphetamine . Other non-related monogamous species, including Peromyscous californicus and the common marmoset, also have high levels of V1aR in the ventral pallidum compared to non -monogamous species such as P . leucopus and rhesus macaques. The results from experiments described in this project may provide information useful in understanding the biological basis of psychiatric diseases characterized by deficits in social behavior .

OXYTOCIN AND SOCIAL ATTACHMENT (0175)

NPRC UNIT : CNTR BEHAV NEUROSCIENCE

% NPRC $: 0.520 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
YOUNG, LARRY J	PHD	A	CNTR BEHAVIORAL NEUROSCIENCE	
F	PHD	A		
names	BS	G		
	PHD	A		
3	BS	G		

AXIS I CODES: 1A **AXIS II CODES** 36

ABSTRACT

Although a considerable body of research has focused on the neural substrates of social separation, relatively little is known about the neurobiology of social attachment . This proposal focuses on a monogamous rodent, the prairie vole, which forms selective, enduring social attachments or pair bonds . Several lines of evidence implicate central oxytocin (OT) pathways in prairie vole pair bond formation . OT increases and a selective OT antagonist decreases mating induced pair bonding in female prairie voles . This project investigates the molecular, cellular and neural mechanisms by which oxytocin facilitates social attachments in the vole brain .

NEURAL BASIS OF SEXUALLY DIMORPHIC BRAIN FUNCTION (0321)

NPRC UNIT : CNTR BEHAV NEUROSCIENCE

%NPRC $: 0.500%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
YOUNG, LARRY J	PHD	A	CNTR BEHAVIORAL NEUROSCIENCE	
[illegible]	PHD	A	CENTER BEHAVIORAL NEUROSCIENCE	UNIVERSITY OF MA, MA USA

AXIS I CODES: 1A, 21 **AXIS II CODES** 36, 39, 72

ABSTRACT

This subcontract is designed to use a vasopressin receptor viral vector to determine when in the brain vasopressin is acting to facilitate paternal care in prairie voles .

PROJECT 2 AND CORE A: PRECLINICAL TRIALS (0224)

NPRC UNIT : MICROBIOLOGY & IMMUNOLOGY

%NPRC $: 0.920% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
AHMED, RAFI		A	VACCINE RESEARCH CENTER	
	PHD	G	MICROBIOLOGY & IMMUNOLOGY	
	DVM	C	RESEARCH RESOURCES	

F Names 3

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

ABSTRACT

Prime/boost immunizations using DNA priming and recombinant MVA boosters have proved to raise much higher levels of T cells than either DNA or MVA immunizations alone . The goals of this Program Project are to evaluate the cross clade activity of DNA /MVA protocols for immunodeficiency virus vaccines . Can worldwide vaccination be accomplished with a single DNA /MVA immunogen, or will a mixture of DNA /MVA immunogens, or geographically targeted clade -specific immunogens, be necessary? The charges for Project 2 are to perform the preclinical testing that will determine which DNAs or formulated DNAs will be used for priming MVA boosters in human trials, and to provide preclinical data to support IND applications for human trials . One major goal for Project 2 is to determine in preclinical models how DNA /MVA immunogens from two different clades affect the height and breadth of T cell responses compared to those raised by single clade immunogens . A second major goal is to identify conditions that will allow the amount of DNA needed for priming MVA boosters to be reduced by ten-fold. Project 2 will be accomplished by a team of Emory investigators . Dr. Ahmed will be responsible for screening novel DNAs and formulated DNAs in mouse models for effects on the height and breadth of the memory T cell response . Dr. Robinson will be responsible for GLP studies in macaques testing the ability of selected immunogens, both singly and in combination, to raise memory T cell responses . Studies will be done with clade B immunogens that represent the HIV -1 epidemic in North America and with clade AG immunogens that match the predominant infection at the CDC test site in Abidjan, C ôte d'Ivoire .

MVA/HIV-48 DUAL VACCINE FOR HIV & SMALLPOX (0256)

NPRC UNIT : MICROBIOLOGY & IMMUNOLOGY

%NPRC $: 0.490% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
AMARA, RAMA R	PHD	G	MICROBIOLOGY & IMMUNOLOGY	

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

ABSTRACT

The overall goal of this project is to determine whether a recombinant modified vaccinia Ankara (rMVA) that is being developed for use as an HIV -1 vaccine (MVA/HIV-48) has potential for the use as a vaccine for both AIDS and smallpox. MVA was developed for use in immunocompromised individuals towards the end of smallpox eradication. During attenuation in chicken embryo fibroblasts, MVA lost the ability to replicate in primate cells. Despite this, it has shown good promise as a vaccine vector, a promise that likely reflects both its good expression of foreign genes and its loss of many of the immune evasion genes expressed by conventional vaccinia viruses. Because smallpox had been controlled in first world countries by the time that MVA was developed, individuals who were vaccinated with MVA were not exposed to variola, and the efficacy of MVA as a smallpox vaccine was not determined. With the recent bioterrorism, the development of a vaccine with fewer side effects than the conventional smallpox vaccine has become of high importance. In this proposal, we seek to compare the anti-vaccinia immune responses raised by the conventional smallpox vaccine Dryvax and MVA /HIV-48 to assess whether MVA/HIV-48 might be able to provide comparable protection to Dryvax. These studies will be done using human samples from employees at the CDC who are receiving the standard human dose of Dryvax and human samples from a phase I trial in which a dose escalation will test for the safety of MVA /HIV-48. The project will be a collaborative undertaking between researchers at the CDC, the NIAID, and the NIAID HIV Vaccine Trial Network (HVTN). The focus of this proposal is the quantification and phenotyping of responding T cells using intracellular cytokine staining (ICS). These ICS assays will be standardized using blood obtained from DNA /MVA vaccinated macaques.

POXVIRUS IMMUNITY AND DNA/MVA HIV VACCINES (0332)

NPRC UNIT : MICROBIOLOGY & IMMUNOLOGY

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

INVESTIGATOR		DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
AMARA, RAMA R		PHD	G	MICROBIOLOGY & IMMUNOLOGY	
F	J	PHD	C	MICROBIOLOGY & IMMUNOLOGY	

AXIS I CODES: 1A, 4, 7B **AXIS II CODES** 31, 64, 66, 83, 91, 94

ABSTRACT

We recently demonstrated the ability of an AIDS vaccine, consisting of DNA priming and recombinant modified vaccinia Ankara (MVA) booster immunizations (DNA/MVA SHIV vaccine) to control a pathogenic SHIV 89.6P challenge that was administered seven months after the final immunization in macaques (Amara, Science 292, 69-74, 2001). The prototype HIV -1 clade B version of our DNA /MVA vaccine (DNA/MVA HIV vaccine) entered phase I safety trials in humans in January of 2003. Due to the recent bioterrorism threat the US government is prepared to vaccinate a subset of people with the current smallpox vaccine (Dryvax/ New York Board of Health strain of vaccinia). The anti-vaccinia virus immunity generated by Dryvax may limit the boosting ability of MVA, hence the efficacy of DNA/MVA HIV vaccines. This is a very important question that needs to be addressed as DNA /MVA vaccines go forward in human trials .

There is a serious need for a smallpox vaccine alternative because of the high incidence of adverse events to the current vaccine. Also, many people are not qualified to receive the current smallpox vaccine due to immunodeficiency, skin disorders, old age, young age (1 yr), or pregnancy. These groups are major populations and must be accounted for in any reasonable national smallpox vaccination strategy . MVA was developed towards the end of smallpox eradication for use in immunocompromised individuals and was used to vaccinate about 120,000 individuals . However, because smallpox had been controlled in first world countries by the time that MVA was developed, individuals who were vaccinated with MVA were not exposed to variola, and the efficacy of MVA as a smallpox vaccine was not determined .

In this project we wish to address 1) the effect of preexisting immunity to smallpox on the ability of DNA /MVA vaccine to control pathogenic SHIV challenge, 2) the ability of vaccinia -specific immune responses raised by DNA/MVA vaccine to protect from a lethal monkeypox challenge and 3) the ability of a candidate DNA /MVA vaccine to control both SHIV and monkeypox challenges that are administered sequentially in the presence and absence of preexisting immunity to smallpox .

THERAPEUTIC VACCINES FOR HIV (0333)

NPRC UNIT : MICROBIOLOGY & IMMUNOLOGY

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
AMARA, RAMA R	PHD	G	MICROBIOLOGY & IMMUNOLOGY	

AXIS I CODES: 1A, 4, 7B **AXIS II CODES** 31, 64, 66, 83, 91, 94

ABSTRACT

The overall aim of this study is to determine the potential of post infection vaccinations to help with the control of immunodeficiency virus infections . These vaccinations will be tested in infected animals in which triple drug treatments (HAART) have been used to reduce viral loads and allow partial recovery of immune system cells . The ability to use therapeutic vaccines in HIV -infected humans would offer a much needed low cost, low toxicity approach for long term control of viral replication .

Our approach to a therapeutic vaccine will test our DNA /MVA vaccine that has shown high promise when administered before infection, for its ability to help control an established infection 1,2. We will also conduct pilot studies to determine whether a dendritic cell vaccine would be more effective than our DNA /MVA vaccine against an established infection . Pilot studies on this latter approach are warranted in view of a recent promising report on the use of dendritic cell vaccines to control established immunodeficiency virus infections in macaques 3. Both of these vaccine approaches will be conducted in infected animals that have been drug treated to reduce viral loads and allow at least partial immune system recovery . In this pilot study we aim to obtain preliminary data addressing the following questions :

a. Characterization of the control of SHIV replication by triple drug therapy and the extent of immune system reconstitution that takes place in animals with controlled infections

b. Temporal analysis of SHIV -specific immunity raised by DNA /MVA and dendritic -cell vaccines in animals with controlled infections (HAART will be continued during the immunizations).

c. Temporal control of re-emergent virus in drug treated and vaccinated macaques following the termination of drug treatment.

ROLE OF VIRUS SPECIFIC IMMUNITY IN PRIMATE MODELS (0324)

NPRC UNIT : MICROBIOLOGY & IMMUNOLOGY

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
ANSARI, AFTAB A	PHD	A	PATHOLOGY	
+ Name I	DVM, PHD	A	PATHOLOGY	

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

ABSTRACT

This project investigates the potential for cytokines promoting cell mediated immune responses for restoring /augmenting antiviral immune responses following SIV infection by administration of IL -12 alone or in combination with IL -2 or Il-15 using a PMPA structured antiviral chemotherapy interruption protocol . The goal of these studies is to devise and test strategies aimed at weaning HIV infected patients off the otherwise lifelong antiviral chemotherapy .

CD4T CELL ACTIVATION IN SIV INFECTED DISEASE RESISTANT SOOTY MANGABEYS (0326)

NPRC UNIT : MICROBIOLOGY & IMMUNOLOGY

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
ANSARI, AFTAB A	PHD	A	PATHOLOGY	
E YAMEJ	PHD	A	MICROBIOLOGY & IMMUNOLOGY	

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

ABSTRACT

This project is aimed at delineating potential mechanistic differences of co -stimulatory pathways between CD 4+ T cells from SIV disease susceptible rhesus macaques and SIV disease resistant sooty mangabeys, based on the initial observation that adult sooty mangabey CD 4+ T cells are resistant to in vitro anergy induction in contrast to rhesus macaques and human CD 4+ T cells. Hence, peripheral blood na ïve and memory CD4+ T cells are obtained and stimulated in vitro to comparatively evaluate pathways including IL -2 synthesis regulation, CREB /CREM and p300 complex assembly, mTOR and cyclin dependent kinase regulation . It is hypothesized that identification of such differences may provide novel investigation and potential therapeutic avenues to counter lentiviral mediated immune defects in macaques and humans infected with SIV and HIV respectively .

AIDS & OPIATES: A MONKEY STUDY (0005)

NPRC UNIT : MICROBIOLOGY & IMMUNOLOGY

% NPRC $: 0.510 % **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
DONAHOE, ROBERT	PHD	A	PSYCHIATRY	
R	DVM	C	RESEARCH RESOURCES	
Names	PHD	C	MICROBIOLOGY & IMMUNOOGY	
J	DVM, PHD	A	MICROBIOLOGY & IMMUNOLOGY	

AXIS I CODES: 1A, 7B, 15, 17, 19, 21 **AXIS II CODES** 31, 50B, 64, 66, 72, 87

ABSTRACT

There is continued controversy about whether opiates modulate expression of AIDS . This is an important issue since AIDS and drug abuse are inseparable . Various data have been presented that opiates have exacerbatory and inhibitory effects on AIDS progression, and a large amount of data show no effects . We conducted a small pilot study that showed that morphine -dependent macaques have slower progression to AIDS induced by SIVsmm 9. Another contemporaneous small pilot study showed opiates to exacerbate AIDS in monkeys infected with SIVmac-239. To clarify these conflicting findings, we initiated a large well -controlled study to ascertain whether morphine-dependency affects AIDS progression in macaques infected with SIVsmm 9. This study has been ongoing for over three years. It is clear at this point that AIDS progression is, indeed, slowed by opiates and the early viral set-points are lower in opiate exposed animals . A number of immune parameters are also affected, some of which interact with the virus to change responses of individual monkeys to virus . These viral /immune interactions have been linked with induction of delayed hypersensitivity responses to morphine in selected monkeys . Whether these interactions also affect AIDS progression remains to be seen but the possibility is high that they will . It will take more time for the data to become unambiguous . Until then, we maintain that opiates slow AIDS progression with this viral model .

MEASLES VACCINE DEVELOPMENT (0023)

NPRC UNIT : MICROBIOLOGY & IMMUNOLOGY

% NPRC $: 0.520 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
GRIFFIN, DIANE	PHD	A	MICROBIOLOGY & IMMUNOLOGY	JOHN HOPKINS UNIVERSITY, MD USA
[illegible]		A		U MARYLAND MEDICAL SCHOOL , MD USA
Names	PHD	C	MICROBIOLOGY & IMMUNOLOGY	
]		A		CENTER FOR DISEASE CONTROL, GA USA

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

ABSTRACT

A measles vaccine trial was undertaken to compare the ability of DNA priming and boosting (DNA/DNA), DNA priming and recombinant MVA boosting (DNA/MVA), and the live attenuated Moraten vaccine to raise protective immunity in the presence and absence of maternal antibody . The DNA and MVA immunogens expressed both measles H and F. Studies were done in 3 month-old macaques born to na ïve and Moraten -immunized mothers. The immunogenicity phase of the trial was initiated in July 2000. Infants were primed intradermally at week 0 with either H+F DNA (groups 1 and 2) or control Moraten vaccine (group 3). Animals were boosted intradermally at week 8 with either H +F DNA (group 1), H+F MVA (group 2) or no boost (group 3). The vaccinated infants have undergone challenge with wild -type measles (15-18 months after immunization) at Johns Hopkins University to determine protection .

TOLERANCE INDUCTION TO PRIMATE ISLET ALLOGRAFTS (0259)

NPRC UNIT : MICROBIOLOGY & IMMUNOLOGY

% NPRC $: 0.490 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
LARSEN, CHRISTIAN	MD	A	SURGERY	
E name J	MD	A	SURGERY	

AXIS I CODES: 1A, 2, 16 **AXIS II CODES** 49, 75, 75A, 88

ABSTRACT

The recent reports from Edmonton have ushered in renewed optimism for islet transplantation . While this series represents a major step forward in the effort to treat type I diabetes, the reliance on long -term immunosuppressive agents with significant toxicities will undoubtedly limit wide scale application of this approach . The central goal of this project is to develop novel strategies which permit islet allograft acceptance utilizing agents with reduced toxicities, and ultimately to promote durable allograft acceptance without the need for long -term immunosuppression (transplantation tolerance). Over the past decade our knowledge of the biology of allograft rejection and transplantation tolerance has advanced dramatically . Among the most promising emerging strategies to promote islet allograft acceptance are those that take advantage of a new class of agents that inhibit T cell costimulation . Our group has shown that LEA 29Y, a second generation inhibitor of CD 28 dependent costimulation potently inhibits the rejection of kidney allografts with minimal toxicity in nonhuman primates . Our preliminary experiments suggest that these agents may be an exciting alternative to the toxic calcineurin inhibitors, used in the Edmonton protocol . In this project we determine whether an LEA 29Y-based, calcineurin inhibitor -free regimen can prevent rejection in an immediately preclinical model of islet transplantation in non -human primates. The ultimate goal of this project is develop strategies that promote transplantation tolerance . Several strategies have been devised to induce tolerance in adult animal models . The most robust of these protocols have in common the incorporation of methods to induce hematopoietic chimerism . We have recently developed strategies using costimulation blockade that induce titratable levels of chimerism and durable unperterbable tolerance in rigorous mouse skin graft models . Aims #2 and 3 will test the ability of these approaches in the non -human primate islet transplant model .

ENGINEERING IMMUNE ACCEPTANCE OF ALLOGENEIC ISLETS IN MACAQUES (0260)

NPRC UNIT : MICROBIOLOGY & IMMUNOLOGY

% NPRC $: 0.490 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
LARSEN, CHRISTIAN	MD	A	SURGERY	
[name]	MD	A	SURGERY	

AXIS I CODES: 1A, 2, 16E, 17 **AXIS II CODES :** 41, 49, 86, 88

ABSTRACT

Based on our murine experiments, we hypothesize the combination of donor bone marrow, busulfan, and costimulation blockade will lead to stable hematopoietic chimerism, indefinite allograft survival, and robust donor-specific tolerance . Therefore, we seek to determine whether a protocol consisting of administration of donor bone marrow, busulfan, and costimulation blockade (anti-CD40L and CTLA 4-Ig) can induce indefinite survival of, and donor specific tolerance to, allogeneic islets in Rhesus macaques .

Blockade of the CD 40 and CD 28 pathways has been shown to be remarkably effective at inhibiting rejection responses in rigorous rodent and non -human primate allograft models . However, with long -term follow-up most of these grafts fail . Similarly, administration of a single donor specific transfusion with costimulation blockade can lead to greatly prolonged survival, but not imperturbable tolerance . More recently, we and others have defined systems in which administration of donor bone marrow cells and costimulation blockade results in stable hematopoietic chimerism, long-term graft survival, and robust deletional tolerance . We will plan to use combined CD 40/CD28 blockade rather than anti -CD40L alone because of the ability of CTLA 4-Ig to inhibit anti -donor antibody responses .

COSTIMULATION, CHIMERISM AND TOLERANCE (0261)

NPRC UNIT : MICROBIOLOGY & IMMUNOLOGY

% NPRC $: 0.250%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
LARSEN, CHRISTIAN	MD	A	SURGERY	
[illegible] name_I	MD	A	SURGERY	

AXIS I CODES: 1A, 2, 17 **AXIS II CODES** 86, 88

ABSTRACT

Transplantation has emerged as the preferred method of treatment for many forms of end -state organ failure . While short -term results have improved, long -term outcomes remain inadequate . To maintain their allografts, patients must rigidly adhere to life -long treatment regimens using costly immunosuppressive agents that dramatically increase the risks of cardiovascular disease, infections and malignancies . The development of strategies to promote the acceptance of allogeneic tissues without the need for chronic immunosuppression could not only reduce the risk of these life-threatening complications, but also greatly expand the application of organ, tissue and cellular transplantation for diseases such as the hemoglobinopathies and genetic immunodeficiencies, Type I diabetes, and possibly other autoimmune diseases . We have developed novel non -myelosuppressive protocols using anti -CD40L and CTLA 4-Ig to permit the induction of titratable levels of hematopoietic chimerism and robust deletional donor -specific tolerance in rodents . The goal of this project is to develop and optimize protocols to induce stable macrochimerism and transplantation tolerance to renal allografts in non -human primates. Specifically, we will 1) test the effects of recipient conditioning with non or minimally myelosuppressive doses of busulfan or total body irradiation on the level and durability of hematopoietic chimerism when used in conjunction with a regimen consisting of anti -CD40L, CTLA-Ig, sirolimus and donor bone marrow, 2) determine whether escalating doses of G-CSF mobilized CD 34+ cells will a) increase the level of hematopoietic chimerism, b) decrease the requirement for recipient conditioning, and c) induce transplantation tolerance to renal allografts in MHC -disparate rhesus macaques and 3) determine the effects of an optimized tolerance induction protocol on the survival of concurrently placed renal allografts, anti -donor immune responses and protective memory T cell responses in MHC -disparate Rhesus macaques.

ACTIVATION. APATHY, ANERGY & APOPTOSIS (0361)

NPRC UNIT : MICROBIOLOGY & IMMUNOLOGY

%NPRC $: 0.500%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
LARSEN, CHRISTIAN	MD	A	SURGERY	
E name 1	MD	A	SURGERY	

AXIS I CODES: 1A, 2 **AXIS II CODES** 86, 88

ABSTRACT

One proven method to induce tolerance is the establishment of hematopoietic chimerism . Concerns regarding toxicities associated with recipient pre -conditioning have precluded clinical application . Recently we and others have developed non -myelosuppresive protocols to induce stable mixed chimerism in the murine model . Utilizing donor BM, blockade of the CD 40 CD28 pathways, rapamycin, and busulfan we have established high -level mixed chimerism in Rhesus macaques for 100 d. Rhesus macaques were used as both donors and recipients . The % donor chimerism was determined using real -time PCR to detect donor MHC allele specific DNA in recipient blood samples. Chimerism became readily detectable by day 28 and increased to 50% by day 42. Donor -derived granulocytes, monocytes, and B cells emerged prior to and in higher levels than T cells . Following discontinuation of treatment at 4 months chimerism levels progressively decreased to 200,000. CD8 T cells have been shown to play an important role in CD 28/CD154 independent rejection, however, the addition of a depleting anti -human CD8 mAb for the first 3 weeks of therapy did not significantly alter either the amount or duration of donor chimerism . To evaluate the role of central vs peripheral mechanisms of failure we also performed experimental thymectomies prior to initiation of the therapy . Removal of the thymus did not significantly alter the course of marrow rejection suggesting that the current therapy primarily failed to adequately tolerize T cells already present in the periphery . T cells in the periphery can be broadly categorized into either naive or antigen -experienced T cells . While costimulation blockade strategies are effective in promoting tolerance in the naive component, memory and effector T cells are less dependent on traditional costimulatory signals and often resistant to the effects of costimulation blockade . The proportion of memory T cells in non -human primates differs greatly from experimental rodents primarily due to their exposure to environmental pathogens . We and others have shown that a proportion of the memory response to various pathogens can also be alloreactive possibly explaining the lack of long -term tolerance. Future approaches to tolerance induction should incorporate strategies to target both naive and memory T cell responses .

PROJECT 3: CLINICAL TRIALS (0225)

NPRC UNIT : MICROBIOLOGY & IMMUNOLOGY

%NPRC $: 0.520% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
LENNOX, JEFFREY L	MD	A	DIVISION OF INFECTIOUS DISEASE	
	PHD	G	MICROBIOLOGY & IMMUNOLOGY	
	MD, PHD	A	VACCINE RESEARCH CENTER	
	PHD	A	VACCINE RESEARCH CENTER	
	MD	A	IMMUNOGENTICS	CENTERS FOR DISEASE CONTROL, GA USA
	PHD	A		DUKE UNIVERSITY MEDICAL CENTER, NC USA
	MD	A		DUKE UNIVERSITY MEDICAL CENTER, NC USA

AXIS I CODES: 7B, 12A **AXIS II CODES** 31, 64, 66, 83, 91

ABSTRACT

Immunization strategies using DNA priming and recombinant modified vaccinia Ankara (rMVA) boosters have proved to raise broad and high titer T cell responses in preclinical models . Here we evaluate the ability of selected DNA/rMVA vaccines for safety and ability to raise cross -clade immune responses in phase 1 trials in humans and will provide data on whether worldwide vaccination can be accomplished with a single DNA /MVA immunogen, or whether a mixture of DNA /MVA immunogens or regional DNA /MVA immunogens will be required . Included are assay development, diagnostic and immune assay standardization, and vaccine trials . Specifically, (i) To develop and optimize T cell assays to measure HIV specific immune responses in humans receiving HIV -1 DNA/MVA vaccines . The goals are for assays to be quantitative, sensitive, high throughput, field adaptable and capable of measuring the breadth of responses to HIV clades A and B . (ii) To test the validity of molecular diagnostic techniques for differentiating vaccination from infection and to optimize detection of HIV infection in vaccinees who may have low level viral replication due to strong cytotoxic T -cell responses (iii) To test clade B and IbNG-like AG DNA /MVA vaccines, singly and in combination, for safety and their ability to generate intra -clade and cross -clade T-cell and antibody responses . Specific aims 1 and 2 will involve participants in both the United States and the Ivory Coast (through our CDC collaboration). Specific aim 3 will be accomplished in the United States. For specific aim 3, three phase I vaccine protocols will test the safety and immunogenicity of single clade, mixed clade and formulated DNA /MVA vaccines . Each of these will be preceded by protocols establishing the safety of the proposed MVA boosters, and formulations . The goals of these trials are to provide data regarding the need for clade specific vaccines, and to establish the foundations for phase II /III testing of DNA /MVA vaccines .

METHYLATION IN ESTABLISHMENT & MAINTENANCE OF LATENCY IN GAMMAHERPESVIRUSES (0364)

NPRC UNIT : MICROBIOLOGY & IMMUNOLOGY

% NPRC $: 0.500 %

INVESTIGATOR	DEGREES STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
MOSER, JANICE	G	MICROBIOLOGY & IMMUNOLOGY	

AXIS I CODES: 1A, 7B **AXIS II CODES** 64, 66, 76B, 95

ABSTRACT

Human -herpesviruses, such as Epstein Barr virus and Kaposi's sarcoma -associated herpesvirus, have been associated with the development of lymphomas, as well as other tumors . Since -herpesviruses have an extremely limited host range, study of these viruses in vivo has been difficult . Recently, the murine gamma-herspesvirus 68 (HV68) has been used for studying the pathogenesis of -herpesviruses in vivo . This model system is providing valuable insights into the understanding of the factors involved with the establishment and maintenance of latency by -herpesviruses . One of the main factors critical in the establishment of latency is the ability of the virus to silence the promoters of genes necessary for the lytic cycle of the virus . The key mechanism in silencing both cellular and viral promoters is increased methylation of CpG motifs by cellular methyltransferases . For this reason, we propose to investigate the role of methylation in the establishment and maintenance of latency of HV 68 in vivo . These studies will advance our knowledge of the pathogenesis of -herpesviruses and will provide a basis for understanding the establishment of latency, reactivation from the latent state and hence the development of tumors .

COMBINATION DNA & ATTENUATE VIRUS VACCINE FOR SIV (0241)

NPRC UNIT : MICROBIOLOGY & IMMUNOLOGY

% NPRC $: 0.920 % **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
NOVEMBRE, FRANCIS J	PHD	C	MICROBIOLOGY & IMMUNOOGY	

AXIS I CODES: 1A, 1D, 7B **AXIS II CODES** 31, 39, 66, 77

ABSTRACT

The live attenuated virus approach for AIDS vaccines has been one of the most successful methods tested . However, incidents of AIDS disease in neonatal macaques receiving this vaccine have slowed further development . We hypothesize that a DNA prime will not only boost the immune responses observed in live attenuated virus infection, but will also prevent the incidence of vaccine -induced AIDS . Our strategy first is to test the immunogenicity and protection of this strategy . Seven rhesus macaques have been immunized with the pGA 2/M2Gag-Pol construct DNA plasmid . This DNA expresses the Gag and Pol proteins of SIVmac 239. Another seven macaques have received an empty DNA plasmid . These animals were immunized twice by intradermal inoculation . Significant immune responses in the animals receiving the SIV DNA construct have been detected, further demonstrating the DNA vaccine method does induce immune responses . Subsequently, the animals have been immunized with the live attenuated SIVmac 239 deltanef virus . Viral loads in animals receiving the pGA 2 DNA were significantly lower than those of animals receiving empty vector DNA . Immune responses were significantly boosted in all animals . Viral loads in animals receiving the DNA prime were significantly greater than those in animals not receiving the DNA prime at the first time point 2 weeks post infection . Thereafter, the animals that received the DNA prime showed lower viral loads . At 65 weeks post the first DNA inoculation, all animals were challenged with an intravenous injection of SHIV 89.6p. All animals were infected . However, DNA -primed animals showed consistently lower viral loads and maintained normal CD 4+ T cell counts . Three of the seven animals that did not receive the DNA prime suffered pathogenic effects of SHIV 89.6p infection, including CD 4+ T cell loss . The results suggest that the DNA prime was able to induce a better protective effect from a highly rigorous challenge .

GENETICS OFNEUROPATHOGENIC SIV INFECTION (0327)

NPRC UNIT : MICROBIOLOGY & IMMUNOLOGY

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
NOVEMBRE, FRANCIS J	PHD	C	MICROBIOLOGY & IMMUNOOGY	
	MPH, PHD	C	NEUROSCIENCE	
Names 3	DVM	C	RESEARCH RESOURCES	

AXIS I CODES: 1A, 1D, 7B, 21 **AXIS II CODES** 31, 36, 39, 41, 66, 77

ABSTRACT

AIDS dementia is a progressive neurological disease that affects a significant portion of HIV . -infected persons . However, the pathogenesis of neurological disease development in HIV -infected persons is not well understood . While human studies have improved our understanding of the interaction of HIV with the central nervous system (CNS), an appropriate animal model system would enable a detailed examination of the mechanisms of induction of AIDS dementia . A major gap in knowledge concerns the evolution of virus in the CNS and the role of genotype in the induction of neurologic disease . We have identified a simian immunodeficiency virus (SIV) isolate, derived from a sooty mangabey, that is highly neuropathogenic in infected pigtailed macaques . This virus, termed SIVsmmFGb, also induces clear neurologic dysfunction in these animals . We believe that this virus provides an excellent system for investigating the basis of HIV -1 induced neurologic disease . The central hypothesis to be evaluated is that there is genetic selection and evolution of SIV that occurs in the CNS, separate from that in the periphery, which is directly related to the development of neurologic disease . Specific hypotheses to be investigated are : 1) genotypic selection occurs after virus enters the CNS; 2) viral evolution is the CNS is distinct from the lymphoid tissue; 3) genotypic compartmentalization occurs in the CNS and is related to the development of neurologic disease; and 4) along with genotypic evolution of SIV in the CNS, phenotypic evolution also occurs, which facilitates growth in the CNS and also facilitates development of neurologic disease . To address these aims, we compare the selection and evolution of SIV genotypes in the CNS and the lymphoid system . Investigations both early and late during infection in SIVsmmFGb -infected macaques will enable a determination of what virus enters the CNS, how it is related to the virus in the periphery and what virus persists after the primary immune response . In an effort to determine if genotypic compartmentalization occurs, macaques infected with SIVsmmFGb will undergo behavioral /cognitive testing and magnetic resonance spectroscopy scanning to localize effects of virus on the CNS These areas will then be examined for SIV genotype . Finally, along with genotypic change comes phenotypic change . We will investigate the ability of viruses isolated at various times after infection to replicate in macrophages and microglia . This will enable us to determine if viral evolution in the CNS is accompanied by viral fitness to grow in the CNS . Finally, we will investigate the evolution of the ability of these viruses to induce the production of neurotoxins in CNS derived cells .

EVALUATION OF A CANDIDATE MICROBICIDE ON HIV-1 (0331)

NPRC UNIT : MICROBIOLOGY & IMMUNOLOGY

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
NOVEMBRE, FRANCIS J	PHD	C	MICROBIOLOGY & IMMUNOOGY	
[illegible]	DVM	C	RESEARCH RESOURCES	

AXIS I CODES: 1A, 1D, 7B, 23 **AXIS II CODES** 31, 50, 66, 77

ABSTRACT

The availability of a safe and effective topical vaginal microbicide would provide women with a product that they control and use to protect themselves and their sexual partners from HIV . Unfortunately, there are now more microbicides ready for human trials than can be evaluated in the next five years by existing clinical research cohorts .

The ability to evaluate highly promising candidate microbicides for their safety and efficacy against HIV -1 shedding in a chronically -infected chimpanzee model would be a scientifically important, and time and cost -effective effort The first product proposed for testing is UC 781 , a non-nucleoside reverse transcriptase inhibitor that is specific in its activity against HIV -1 but not for HIV -2 or SIV. This product has demonstrated efficacy in -vitro, and the proposed data collection could be produced in a relatively short period of time . Data obtained from testing microbicides in infected chimpanzees would be highly valuable in determining whether human clinical trials of such products are warranted . It is now understood that female -to-male sexual transmission of HIV -1 is a major route of infection in developing countries and that many HIV -1-infected women who would use a vaginal microbicide would likely not know their infection status . Therefore, the use of HIV-1-infected chimpanzees, including females, in topical microbicide testing would provide vital information on product safety and effectiveness .

DNA AND PROTEIN IMMUNOGENS FOR SIV/HIV VACCINES (0024)

NPRC UNIT : MICROBIOLOGY & IMMUNOLOGY

%NPRC $: 0.920% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
ROBINSON, HARRIET	PHD	C	MICROBIOLOGY & IMMUNOLOGY	
	DVM	C	RESEARCH RESOURCES	
	MD	A	IMMUNOGENTICS	CENTERS FOR DISEASE CONTROL, GA USA
	PHD	A		DUKE UNIVERSITY MEDICAL CENTER, NC USA
	PHD	A	VIRAL DISEASES	NIAID/NIH, WA USA
	DVM, PHD	A	PATHOLOGY	

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

ABSTRACT

This Integrated Preclinical /Clinical AIDS Vaccine Development program project has excelled in both its preclinical and clinical development of a multiprotein DNA /MVA vaccine for AIDS. The program has been a collaborative effort between researchers at Emory University who have developed vaccine DNAs and conducted preclinical studies in macaques, and researchers in [name] laboratory at the NIAID who have developed the MVA portion of the vaccine. The preclinical studies have demonstrated the ability of a multiprotein DNA /MVA SHIV-89.6 vaccine to control a mucosal SHIV -89.6P challenge administered in the memory phase of the vaccine response. This trial is approaching three years post challenge, and only one macaque, immunized with a partial dose of the vaccine, has failed to control the challenge. In the remaining 23 macaques, 12 vaccinated with a full dose of the vaccine and 11 with a partial, the protection has held. In the last two months of 2002, the Science publication reporting this study was the most frequently cited paper in the field of immunology.

The clinical studies of the program have led to the development of a multiprotein DNA and MVA clade B HIV vaccine. The DNA component of this vaccine expresses Gag, PR, RT, Env, Vpu, Tat and Rev. The MVA component expresses Gag, PR, RT, and Env. The IPCAVD program conducted GLP potency and stability tests on the DNA component of the vaccine and GLP immunogenicity tests in macaques for the DNA and DNA /MVA components. The DNA product entered phase I trials on Jan. 21, 2003 under the sponsorship of the HVTN (HVTN-045).

Names

BASIC PRINCIPALS OF DNA-BASED IMMUNIZATIONS (0115)

NPRC UNIT : MICROBIOLOGY & IMMUNOLOGY

% NPRC $: 0.520 % **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
ROBINSON, HARRIET	PHD	C	MICROBIOLOGY & IMMUNOLOGY	

AXIS I CODES: 1A, 7B **AXIS II CODES** 31, 64, 66, 91

ABSTRACT

Studies have been conducted to determine the ability of various genetic adjuvants to increase the efficiency of DNA -based immunizations . In particular, mutant caspase genes were found to have a strong ability to enhance DNA -raised CD 8 responses . Co-transfected interferon response factor genes were found to have relatively minor effects on DNA -raised immune responses . Co-transfection of IFN -gamma had stronger effects on immune responses in the neonate than in the adult . Studies also have been conducted on the effect of DNA -raised Th 1 and Th2-biased immune responses on the expression of cytokines by CD 8 T cells. These studies have suggested that secreted antigens expressed by gene gun delivered DNA raise Th 2 biased responses that are associated with IL -4 producing CD 8 cells.

DNA/MVA IMMUNOGENS, CROSS-CLADE RESPONSES (0222)

NPRC UNIT : MICROBIOLOGY & IMMUNOLOGY

% NPRC $: 0.920 % **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
ROBINSON, HARRIET	PHD	C	MICROBIOLOGY & IMMUNOLOGY	
[		A	VACCINE RESEARCH CENTER	
	PHD	G	MICROBIOLOGY & IMMUNOLOGY	
	MD, PHD	A	VACCINE RESEARCH CENTER	
	PHD	A	VACCINE RESEARCH CENTER	
	MD	A	DIVISION OF INFECTIOUS DISEASE	
	DVM	C	RESEARCH RESOURCES	
	PHD	A		DUKE UNIVERSITY MEDICAL CENTER, NC USA
	PHD	A	VIRAL DISEASES	NIAID/NIH, WA USA
	MD	A		UAB, AL USA
	PHD	A	MICROBIOLOGY & IMMUNOLOGY	
]	MD	A		DUKE UNIVERSITY MEDICAL CENTER, NC USA

Y ames

AXIS I CODES: 1A, 7B, 12A **AXIS II CODES** 31, 64, 66, 83, 91

ABSTRACT

This multidisciplinary program project addresses the development and evaluation of a cross -clade AIDS vaccine using a rhesus macaque model . Immunogens focus on the use of DNA priming followed by recombinant modified vaccinia Ankara (rMVA) boosters to raise T as well as B cell responses . The program is a collaborative effort of scientists at Emory University, NIAID, and the CDC . This program builds on the preclinical trials of the Program Director in which DNA priming followed by recombinant poxvirus boosters raised neutralizing antibody -independent containment of serial SHIV challenges . The program will develop and test in phase I trials two sets of HIV -1 immunogens : clade B immunogens representing viruses endemic in the United States, and clade AG immunogens representing the IbNG -like infections at the CDC test site in Abidjan, C ôte d'Ivoire . Hypotheses address the impact of clade -specific as opposed to non -clade specific or mixed clade immunogens on cross -clade T cell responses . Critical milestones include the evaluation of clade -specific sequences on cross -clade responses and the development of DNA immunogens or formulations that allow DNA to be used at micrograms rather than mg levels for priming . Project 1, "DNA and MVA Immunogens " will develop immunogens to allow the evaluation of cross -clade T cell responses and increase the efficiency of DNA priming . Project 2, "Preclinical Trials " will evaluate DNAs or formulated DNAs in mouse and macaque models and provide safety and immunogenicity data to support INDs for phase I clinical trials . Project 3, "Clinical Trials " will develop T cell assays to measure vaccine responses in human trials, establish criteria for distinguishing vaccinated and infected humans, and conduct phase I trails testing clade B and clade AG DNA /MVA vaccines singly and in combination .

PROJECT 1: DNA AND MVA IMMUNOGENS (0223)

NPRC UNIT : MICROBIOLOGY & IMMUNOLOGY

% NPRC $: 0.920 % **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
ROBINSON, HARRIET	PHD	C	MICROBIOLOGY & IMMUNOLOGY	
[	PHD	A	LAB OF VIRAL DISEASES	NIAID/ NIH , WA USA
names	PHD	A	INFECTIOUS DISEASES	CENTERS FOR DISEASE CONTROL, GA USA
	PHD	A	VIRAL DISEASES	NIAID/NIH, WA USA
]	PHD	A	MICROBIOLOGY & IMMUNOLOGY	

AXIS I CODES: 7B, 12A, 28(7B, 12A) **AXIS II CODES** 31, 64, 66, 83

ABSTRACT

Heterologous prime /boost immunization using DNA priming and recombinant MVA boosters have proved to raise much higher levels of T -cell responses than either of these modalities of immunization alone . The goals of this Program Project are to develop and evaluate the cross clade activity of DNA /MVA protocols for immunodeficiency virus vaccines . The charges for Project 1 are to provide DNA and MVA immunogens for the preclinical and clinical trials supported by projects 2 and 3. Two major goals for Project 1 are to develop immunogens that increase the efficiency of DNA priming and MVA boosters and to construct immunogens that allow evaluation of cross -clade responses . To increase the immunogenicity of vaccine DNAs, plasmids will be optimized for expression in the presence of interferons (IFN), and vaccine inserts will be codon optimized . Both clade A and clade B immunogens will be built to facilitate the analysis of cross -clade responses . A team of Emory, CDC and NIAID investigators will accomplish project 1. [names] will be responsible for the construction of the DNA immunogens; [name] will be responsible for the construction of MVA immunogens, and [name] will provide clade A sequences and conduct safety tests .

PROJECT 1: DNA IMMUNOGENS AND PRECLINICAL TRIALS (0226)

NPRC UNIT : MICROBIOLOGY & IMMUNOLOGY

% NPRC $: 0.920 % **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
ROBINSON, HARRIET	PHD	C	MICROBIOLOGY & IMMUNOLOGY	
E	MD	A	IMMUNOGENTICS	CENTERS FOR DISEASE CONTROL, GA USA
Names	PHD	A		DUKE UNIVERSITY MEDICAL CENTER, NC USA
J	PHD	A	VIRAL DISEASES	NIAID/NIH, WA USA

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

ABSTRACT

In this project we continue studies using DNA and MVA Immunogens in a macaque model to test the ability to elicit protective immunity . Both the DNA and MVA Immunogens express the three major proteins of immunodeficiency viruses : Gag, Pol, and Env . In the past year we have continued the long term monitoring of our initial DNA /MVA vaccine study, which demonstrated successful control of the challenge infection . These studies have demonstrated continuing control of the challenge infection at levels below 300 copies of viral RNA per ml of plasma. They also have demonstrated IL -2 as well as IFN production by responding T cells, a lymphokine pattern that is characteristic of T cells with a normal memory phenotype .

Studies using GM -CSF DNA as a genetic adjuvant at the time of DNA immunizations have demonstrated that GM-CSF can serve as an adjuvant for the elicitation of neutralizing antibody . This neutralizing antibody required time to develop and appeared to be the result of improved affinity maturation of the anti -Env antibody response in the presence of the GM -CSF adjuvant . The breadth of this neutralizing activity for primary isolates is currently under investigation .

The ability of GM -CSF to serve as an adjuvant for the elicitation of neutralizing Ab is being further explored in a new macaque trial in which higher levels of GM -CSF and vaccine DNAs as well as two MVA boosters are being examined for the ability to elicit cross -reactive neutralizing antibody for HIV -1.

CHARACTERIZATION OF THE GAMMA HERPES VIRUS HV68 V CYCLIN (0198)

NPRC UNIT : MICROBIOLOGY & IMMUNOLOGY

%NPRC $: 0.520%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
SPECK, SAMUEL H	PHD	C	MICROBIOLOGY & IMMUNOLOGY	

AXIS I CODES: 1A, 7B **AXIS II CODES** 64, 66, 76B

ABSTRACT

This research investigates the mechanisms by which cyclin homologs encoded by g -herpesviruses (v-cyclin) contribute to gammaherpesvirus pathogenesis and latency . The human gammaherpesviruses, KSHV and EBV, are important causes of cancer, especially in immunocompromised individuals . Because of the specificity of these viruses, in vivo studies of their pathogenesis have been limited . We and others have been developing a small animal model system, infection of inbred mice with gHV 68, for analysis of the pathogenesis of gammaherpesvirus infection and the role of individual gammaherpesvirus genes in latency and tumor induction . gHV68 infection is associated with the development of lymphoma and lymphoproliferative disease, severe vasculitis of the great elastic vessels and splenic fibrosis . Studies to date indicate that gHV 68 shares pathogenetic mechanisms with EBV, KSHV and HVS, validating it as a model for analysis of important questions in gammaherpesvirus pathogenesis . This work is focused on the role of the gHV 68 v-cyclin in disease pathogensis . Notably, the g 2-herpesvirus (HVS, KSHV and gHV68) all encode homologs of D -type cyclins, while EBV infection upregulates expression of host d -type cyclins . We have shown that the gHV 68 v-cyclin is an oncogene that promotes cell cycle progression in primary lymphocytes and that a gHV 68 v-cyclin mutant reacts inefficiently from latently infected MM and or B cells .

CONTROL OF EBV LYTIC GENE EXPRESSION DURING LATENCY (0199)

NPRC UNIT : MICROBIOLOGY & IMMUNOLOGY

% NPRC $: 0.520 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
SPECK, SAMUEL H	PHD	C	MICROBIOLOGY & IMMUNOLOGY	

AXIS I CODES: 1A, 7B **AXIS II CODES** 64, 66, 76B

ABSTRACT

The major goal of this research is the elucidation of the mechanisms controlling the switch from latency to viral replication in Epstein -Barr Virus (EBV) infected B lymphocytes . More specifically, this research focuses on the regulation of two linked EBV genes, BSLF 1 and BRLF 1, that are integrally involved in this switch . A detailed understanding of how viral reactivation is controlled is essential for understanding maintenance of latency, and may reveal strategies for interfering with viral persistence in the host . During the previous reporting period, significant progress has been made in identifying the critical cis -elements involved in regulating the BZLF 1 gene promoter (Zp), and the cellular factors that bind to these sites . In addition, two calcium response pathways have been identified that can trigger viral reactivation . However, we only have a partial picture of how transcription of the BZLF1 gene is regulated . Furthermore, regulation of the BRLF 1 gene has not been carefully analyzed . Thus, this project seeks to identify and further define the cis -elements, cellular transcription factors and signaling pathways involved regulating the BRLF 1/BZLF1 gene locus .

REGULATION OF EBV TRANSCRIPTION IN BURKITT'S LYMPHOMA (0200)

NPRC UNIT : MICROBIOLOGY & IMMUNOLOGY

%NPRC $: 0.520 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
SPECK, SAMUEL H	PHD	C	MICROBIOLOGY & IMMUNOLOGY	

AXIS I CODES: 1A, 7B **AXIS II CODES** 64, 66, 76B

ABSTRACT

Epstein -Barr virus infection is closely associated with the development of several human malignancies, including the endemic form of Burkitt's lymphoma and nasopharyngeal carcinoma . The major goal of this research is to understand the regulation of EBF gene expression during restricted viral latency (group 1 or group 2 latency), observed in the EBV -associated tumors that arise in immunocompetent individuals . Specifically, of the six Epstein -Barr nuclear antigens (EBNAs) expressed during the growth transforming form of EBV latency (group 3 latency), only EBNA 1 is expressed during restricted viral latency . EBNA 1 is essential for maintenance of the viral episome, and has recently been shown to be refractile to presentation by MHC class I . Thus, expression of EBNA 1 does not lead to recognition of tumor cells by the host immune response . Recent characterization of the long term reservoir in healthy seropositive individuals indicates that EBV is present in a population of memory B cells in which there is minimal viral gene expression, suggesting that a restricted form of viral latency may also be involved in persistence in vivo . We have identified a distinct viral promoter, Qp, involved in driving exclusing expression of the EBNA 1 gene during restricted viral latency; characterixed methylation of the viral genome and observed a tight correlation between methylation of the EBNA gene promoters Cp and Wp (active during group 3 latency) and establishment of restricted viral latency; determined that the region aroung Qp remains hypomethylaed during either restricted viral latency or group 3 latency; and mapped critical cis -elements involved in regulating Qp activity, including identification and characterization of an IRF 1/IRF2 site adjacent to the site of transcription iniation .

VIRAL TRANSCRIPTION IN EBV TRANSFORMED B CELLS (0262)

NPRC UNIT : MICROBIOLOGY & IMMUNOLOGY

% NPRC $: 0.250 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
SPECK, SAMUEL H	PHD	C	MICROBIOLOGY & IMMUNOLOGY	
L name J		G	MICROBIOLOGY & IMMUNOLOGY	

AXIS I CODES: 1A, 7B **AXIS II CODES** 64, 66, 76B

ABSTRACT

The long term goal is to understand how Epstein -Barr virus (EBV) gene expression is regulated during immortalizing latency. EBV establishes a life -long infection within the infected host, and is closely associated with the development of endemic Burkitt's lymphoma, nasopharyngeal carcinoma, 30-50% of Hodgkin's disease, and nearly half of the lymphomas that arise in immunosuppressed patients . Notably, EBV infection of peripheral resting B cells results in growth transformation resulting, ex vivo, in the generation of immortalized lymphoblastoid cell lines Based on recent analyses of EBV infection in seropositive individuals, it seems likely that the ability of EBV to drive B cell proliferation, and subsequent differentiation, plays an important role in the dissemination of virus infected B cells and the establishment of a long -lived latency reservoir in memory B cells (in which there is very limited viral gene expression). Understanding how EBV regulates viral gene expression during immortalizing latency may ultimately provide strategies for interfering with this phase of the virus life cycle, which could interfere with the establishment of latency in the memory B cell compartment . We continue to focus analyses on identifying and characterizing cis -elements involved in regulated EBNA gene expression during the immortalizing latency program of EBV.

ROLE OF B CELLS IN MURINE GAMMAHERPES -68 LATENCY (0328)

NPRC UNIT : MICROBIOLOGY & IMMUNOLOGY

% NPRC $: 0.500 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
SPECK, SAMUEL H	PHD	C	MICROBIOLOGY & IMMUNOLOGY	

AXIS I CODES: 1A, 7B **AXIS II CODES** 64, 66, 76B, 95

ABSTRACT

Gammaherpesviruses are closely associated with the development of lymphoproliferative disease and lymphomas, as well as other cancers . The long -term goal of this research is to understand how gammaherpesviruses manipulate normal B or T cell development to persist within the lymphoid compartment of the infected host . Understanding the mechanisms used by gamma -herpesviruses to persist in the infected host may lead to the development of strategies for interfering with chronic infection . The focus of the proposed studies on murine gamma -herpesvirus 68 represents an ongoing effort to develop a tractable small animal model for characterizing establishment and maintenance of gammaherpesvirus infection .

FUNCTION OF THE GAMMAHV68 M2 ANTIGEN (0329)

NPRC UNIT : MICROBIOLOGY & IMMUNOLOGY

%NPRC $: 0.500 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
SPECK, SAMUEL H	PHD	C	MICROBIOLOGY & IMMUNOLOGY	

AXIS I CODES: 1A, 7A **AXIS II CODES** 64, 66, 76B, 95

ABSTRACT

Gammaherpesviruses are closely associated with the development of lymphoproliferative disease and lymphomas, as well as other cancers . The long -term goal of this research is to understand how gammaherpesviruses manipulate normal B or T cell development to persist within the lymphoid compartment of the infected host . Understanding the mechanisms used by gammaherpesviruses to persist in the infected host may lead to the development of strategies for interfering with chronic infection . The focus of the proposed studies on murine gammaherpesvirus 68 (gHV68; also referred to as MHV -68) represents an ongoing effort to develop a tractable small animal model for characterizing establishment and maintenance of gammaherpesvirus infection . The proposed studies focus on determining the function of one of the critical latency -associated antigens of gHV 68, the M2 antigen .

DEVELOPMENT OF A NON HUMAN PRIMATE MODEL FOR CHRONIX EBV INFECTION (0330)

NPRC UNIT : MICROBIOLOGY & IMMUNOLOGY

%NPRC $: 0.500%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
SPECK, SAMUEL H	PHD	C	MICROBIOLOGY & IMMUNOLOGY	

AXIS I CODES: 1D, 7B **AXIS II CODES** 64, 66, 76B

ABSTRACT

Epstein -Barr virus (EBV) is a ubiquitous human pathogen that is the etiologic agent of infectious mononucleosis, a self limiting lymphoproliferative syndrome . EBV is also closely associated with the development of several cancers in humans, including the endemic form of Burkitt's lymphoma, Hodgkin's lymphoma, AIDS -related lymphomas and nasopharyngeal carcinoma . EBV is a member of the gammaherspesvirus family, all of which establish chronic infections within the lymphoid compartment of their natural host - latently infecting either B cells or T cells . In the case of EBV and murine gammaherpesvirus 68 it has been shown that these viruses persist within memory B cells . It appears for EBV that it is capable of driving na ïve B cells to differentiate into memory B cells, thus providing the virus a long lived lymphocyte population in which to persist undetected within the host . As described below, a great deal is known about the strategies utilized by EBV to gain access to the B memory compartment . The major goal of this proposal is to establish a non -human primate model for chronic EBV infection that will allow us to verify the current model of how EBV maintains a chronic infection, and ultimately to develop an effective strategy to vaccinate against EBV infection .

RESOURCE FOR NONHUMAN PRIMATE IMMUNE REAGENTS (0140)

NPRC UNIT : MICROBIOLOGY & IMMUNOLOGY

% NPRC $: 0.520 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
VILLINGER, FRANCOIS	DVM, PHD	A	PATHOLOGY	
F NAME 3	PHD	A	PATHOLOGY	

AXIS I CODES: 1D, 7B, 17, 19 **AXIS II CODES** 64, 66, 91

ABSTRACT

Recent therapeutic attempts include a variety of cytokines, hematopoietic growth factors, or specific ligands for the modulation of immune responses and hematopoiesis for the treatment of various clinical conditions or as an adjuvant to immunization protocols . A significant number of such applications are studied using various nonhuman primate models, yet while most human factors appear biologically active in nonhuman primates, data shows that injection of human recombinant cytokines most often does not allow repeated or long -term treatment due to rapid development of an immune response towards these "foreign" molecules, resulting in inactivation and rapid clearance of these cytokines . Furthermore the immune response of primate cells to the stimulation by certain human cytokines has been found to be markedly lower than the response of equivalent cells from human origins . Therefore, cDNA coding for various nonhuman priamte cytokines were cloned and sequenced . Such recombinant macaque cytokines have been and are currently used in vivo in a veriety of protocols using nonhuman primate models of human disease . These studies bear the potential to rapidly translate into therapeutic applications for the treatment of human diseases .

CD4 IMMUNE RECONSTITUTION IN SIV INFECTION (0325)

NPRC UNIT : MICROBIOLOGY & IMMUNOLOGY

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
VILLINGER, FRANCOIS	DVM, PHD	A	PATHOLOGY	
names ?	PHD	A	PATHOLOGY	
	PHD	A		

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

ABSTRACT

This project was aimed at immune reconstitution of SIV infected macaques using autologous CD 4+ T cells collected prior to SIV infection and expanded in vitro using anti -CD3/anti-CD28 coated immunobeads .

This is a new project to expand our original observations that purified CD 4+ T cells collected prior to infection were highly functional and capable of restoring /enhancing antiviral immune responses leading to low or undetectable viral loads for extended periods of time without continuous antiviral chemotherapy . This proposal is aimed at testing whether such functional CD 4+ T cells can be obtained also after SIV infection, either under the umbrella of antiviral chemotherapy or not, and what are the correlates of such function . Thus, from groups of rhesus macaques will be collected large numbers of "pre-infection " CD4+ T cells for purposes of control . The animals will then be infected with SIVmac239 and allowed to reach viral load set points, at which time CD 4+ T cells will be collected from one viremic group while another group will be treated with PMPA prior to cell collection . Following intro expansion via incubation in the presence of anti -CD3/CD28 coated magnetic beads, the cells will be readministered to the monkeys . Viral and immune parameters will then be followed and the protocol repeated if warranted .

SYNAPTIC ORGANIZATION OF THE PRIMATE PULVINAR NUCLEUS (0276)

NPRC UNIT : NEUROSCIENCE

%NPRC $: 0.340%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
BICKFORD, MARTHA E	PHD	A	ANATOMY & NEUROBIOLOGY	UNIVERSITY OF LOUISVILLE, KY USA
[illegible] Names	PHD	A	ANATOMY	MISSISSIPPI MEDICAL CENTER, MS USA
[illegible] :	MD, PHD	A	CNTR BEHAVIORAL NEUROSCIENCE	

AXIS I CODES: 1A, 21 **AXIS II CODES:** 41, 89

ABSTRACT

The pulvinar nucleus appears to play a key role in directing visual attention, in the process of selecting salient visual targets, and directing eye movements toward these targets . However, theories of pulvinar function remain quite speculative . The goal of this project is to understand how cortical and subcortical inputs structurally interact within the synaptic circuitry of the primate pulvinar nucleus . This work focuses on the dorsal /medial regions of the monkey pulvinar nucleus because in this region physiological studies have demonstrated a clear relation to visual attention, but little is known regarding its synaptic circuitry . We also examine the ultrastructure and synaptic targets of terminals that originate from the pretectum, the penduculopontine tegmentum, and cortical areas 7a and 23. These four areas display activity related to eye movements, attentional state, visual spatial location, and memory. All of these areas are themselves extensively interconnected and have been predicted to contribute to networks underlying visual attention . The results of these studies will provide the first comprehensive ultrastructural description of the primate pulvinar nucleus, providing an anatomical basis for further investigation of this region's role in visual attention .

PREFRONTAL CONTROL OF SOCIAL BEHAVIOR IN NON HUMAN PRIMATES (0044)

NPRC UNIT : NEUROSCIENCE

%NPRC $: 0.270%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
FREEDMAN, LORIN J	MD, PHD	A	NEUROSCIENCE	

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

ABSTRACT

In a variety of neurological and psychiatric diseases, impairments in social judgment are one of the most disabling, yet poorly studied aspects . The difficulty in understanding this problem arises partly from the possibility that poor judgment can be thought of as a consequence of other difficulties, such as memory loss in Alzheimer's disease, elevated mood in mania, and delusional thinking in schizophrenia . However, isolated poor social judgment with preservation of cognitive function has been described in a relatively small group of patients with lesions in ventromedial and orbital prefrontal cortex, which raises the possibility that there are distinct neurobiological mechanisms underlying this phenomenon . These patients also fail to demonstrate the usual autonomic responses to important social stimuli, such as mutilation, while being able to describe these verbally without difficulty .

The goal of this project is to create a model of this phenomenon in non -human primates and to analyze it from a behavioral and anatomical standpoint . Previously we had implanted cannulae in the amygdala and orbitofrontal cortex of several animals . This year, we did begin to use the animals remaining with intact cannulae to develop a new technique for tract tracing, involving injection of Mn and subsequent MRI scanning to determine neuronal connections . This will result in improved understanding of the functional connectivity of these areas . Preliminary investigations show the feasibility of this technique .

MONOAMINE FUNCTION IN SQUIRREL MONKEYS DURING COCAINE USE (0124)

NPRC UNIT : NEUROSCIENCE

%NPRC $: 0.270%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
GINSBURG, BRETT C		A	CNTR BEHAVIORAL NEUROSCIENCE	
name	PHD	C	NEUROSCIENCE	

AXIS I CODES: 1A, 2, 21 **AXIS II CODES** 36, 50B, 87

ABSTRACT

No pharmacological therapy exists for cocaine addiction . Further understanding of the mechanism of cocaine -reinforced behavior could aid in the development of medications to treat cocaine abuse . Cocaine acts pharmacologically to inhibit presynaptic uptake of monoamines including dopamine . Specific dopamine reuptake inhibitors can attenuate cocaine self -administration behavior in a nonhuman primate model of cocaine use . This project explored the behavioral and neurochemical effects of dopamine uptake inhibition on cocaine -reinforced behavior . Several phenyltropane analogs of cocaine were synthesized to vary in their relative potency at monoamine transporters . The compounds were administered as pretreatments to characterize their effectiveness in reducing cocaine self -administration . Drug doses that had desirable behavioral effects were also characterized for their neurochemical effects on extracellular dopamine . Selective inhibitors of the dopamine transporter that reduced cocaine use also attenuated cocaine -induced increase in dopamine . However, the drug pretreatments induced significant increases in dopamine prior to cocaine challenge . Hence, it appears that the dopamine transporter inhibitors reduce cocaine use by elevating basal dopamine levels and attenuating subsequent increases in dopamine by cocaine . Collectively, these experiments have yielded valuable insights into the mechanisms of dopamine uptake inhibitors in modulating cocaine use and neuropharmacology .

A NOVEL MODEL OF PARKINSON'S DISEASE (0362)

NPRC UNIT : NEUROSCIENCE

% NPRC $: 0.500 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
GREENAMYRE, J T	MD, PHD	A	NEUROSCIENCE	

AXIS I CODES: 1A, 21 **AXIS II CODES** 46, 50

ABSTRACT

Parkinson's disease (PD) is a chronic and continuously progressive neurodegenerative disorder . In contrast, current animal models of PD rely on acute administration of toxins to produce acute or subacute neurodegeneration . Even in "chronic " models of the neurotoxin MPTP, intoxication involves repeated acute doses, with each dose causing incremental, but acute, neurotoxicity . Although these models have been and are still extremely for defining anatomical and physiological correlates of the disease and for screening new symptomatic therapies, there is a clear need for a new animal model that mimics the slowly and continuously progressive nature of the neurodegeneration of PD. In the current proposal we propose to develop and characterize such a model . Successful development of this model will allow us to define the relevant mechanisms of the neurodegeneration in an in vivo system that more accurately models the human disease and test potential neuroprotective strategies in an in vivo model of chronic neurodegeneration that is highly relevant to PD .

A NOVEL MODEL OF PARKINSON'S DISEASE (0362)

NPRC UNIT : NEUROSCIENCE

% NPRC $: 0.500 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
GREENAMYRE, J T	MD, PHD	A	NEUROSCIENCE	

AXIS I CODES: 1A, 21 **AXIS II CODES** 46, 50

ABSTRACT

Parkinson's disease (PD) is a chronic and continuously progressive neurodegenerative disorder . In contrast, current animal models of PD rely on acute administration of toxins to produce acute or subacute neurodegeneration . Even in "chronic " models of the neurotoxin MPTP, intoxication involves repeated acute doses, with each dose causing incremental, but acute, neurotoxicity . Although these models have been and are still extremely for defining anatomical and physiological correlates of the disease and for screening new symptomatic therapies, there is a clear need for a new animal model that mimics the slowly and continuously progressive nature of the neurodegeneration of PD. In the current proposal we propose to develop and characterize such a model . Successful development of this model will allow us to define the relevant mechanisms of the neurodegeneration in an in vivo system that more accurately models the human disease and test potential neuroprotective strategies in an in vivo model of chronic neurodegeneration that is highly relevant to PD .

GLUTAMATE IN PARKINSON'S DISEASE (0363)

NPRC UNIT : NEUROSCIENCE

% NPRC $: 0.500 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
GREENAMYRE, J T	MD, PHD	A	NEUROSCIENCE	
[illegible]	MD	A	NEUROLOGY	

AXIS I CODES: 1A, 21 **AXIS II CODES:** 46, 50

ABSTRACT

Loss of striatal dopaminergic innervation in Parkinson's disease (PD) is associated with complex changes in the functional and neurochemical anatomy of the basal ganglia . Prominent amongst the neurotransmitters altered in PD is the glutamatergic system . For example, the glutamatergic pathways from subthalamic nucleus the to internal segment of the globus pallidus and the substantia nigra pars reticulata become overactive after nigrostriatal dopamine depletion . Moreover, there is increasing evidence that corticostriatal projections also become overactive in models of PD . Our laboratory and others have shown that this glutamatergic overactivity has clinically relevant functional consequences and contributes importantly to the pathophysiology of parkinsonian signs and symptoms Stereotactic or systemic blockade of glutamate receptors has remarkable antiparkinsonian and antidyskinetic effects in experimental animals and in patients with PD . We propose to continue to study in a systematic fashion the effects of various classes of glutamate antagonists in MPTP -treated parkinsonian monkeys, and to examine functional changes in the glutamatergic system in this model of PD . In so doing, we expect to identify viable pharmacological targets for therapeutic intervention in PD .

V1AR GENE STRUCTURE, EXPRESSION & SOCIAL BEHAVIOR (0277)

NPRC UNIT : NEUROSCIENCE

% NPRC $: 0.300 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
HAMMOCK, ELIZABETH	BS	A	NEUROSCIENCE	

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

ABSTRACT

This proposal aims to characterize the effects of a variable genetic element in regulation of expression of the vole vasopressin 1a receptor (V1aR) gene. Vasopressin and the V 1aR are involved in the regulation of species -specific social behaviors . Receptor distribution patterns are species -specific and correlate with social structure . Monogamous and non -monogamous voles differ in their behavioral response to vasopressin and expression pattern of V1aR in the brain . In addition, there is a tremendous amount of intra -specific variability in the V 1aR expression in the monogamous prairie voles . A large, highly repetitive microsatellite region is found in the flanking region of the V1aR gene of monogamous voles but not in non -monogamous vole species . Within the prairie vole, the length of this microsatellite correlates with the level of V 1aR binding in the brain . This research tests the hypothesis that I) this polymorphic promoter sequence plays a role in the expression of the V 1aR gene, and that ii) the individual variability in the V 1aR expression resulting from this variable promoter structure translates into individual variability in social behavior . Luciferase reporter assays in cell culture and a selective prairie vole breeding strategy with extensive behavioral characterization and subsequent molecular analysis will be used to test these hypotheses This research will provide a possible mechanism producing intra -specific variability in gene expression and behavior that may be relevant to psychopathologies .

ACCUMBENS-PALLIDAL GABA AND MORPHINE REINFORCEMENT (0278)

NPRC UNIT : NEUROSCIENCE

% NPRC $: 0.300 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
HEMBY, SCOTT E	PHD	A	NEUROSCIENCE	

AXIS I CODES: 1A, 9, 21 **AXIS II CODES** 39, 50B, 87

ABSTRACT

Opiate abuse continues to be a major public health concern in the United States, especially in light of dramatic increase in the number of first - time users. Development of more effective pharmacotherapies requires more detailed understanding of the neurochemical, molecular and behavioral variables that mediate opiate reinforcement . To date, a vast majority of animal studies assess biological underpinnings of opiate reinforcement in the absence of physical dependence, even though physical dependence is a characteristic of human opiate abuse . GABAergic medium spiny neurons projecting from the NAc to the ventral pallidum (VP) are likely neuronal loci for reinforcing effects of opiates and are necessary for expression of opiate self -administration . Our long -term objective is to further understanding the involvement of accumbens -pallidal pathway in morphine self -administration in physically -dependent rats . Specifically, these xperiments determine extracellular GABA concentrations ([GABA]) in the ventromedial VP and dorsolateral VP, projection terminal regions of shell and core accumbal -pallidal MSNs, respectively . These effects are compared with subjects receiving yoked morphine and saline to assess the contribution of VP GABA in reinforcing and direct pharmacological effects of morphine, respectively .

The effects of systemic and intra -VP administration of selective antagonists will be compared with food -maintained responding . Also, regional and single cell gene expression techniques will be employed to assess morphine -induced regulation of cAMP pathway transcripts in accumbens -pallidal MSN projections from the NAc shell to ventromedial VP and NAc core to dorsolateral VP . Changes in expression levels of multiple genes will be assessed in terms of morphine reinforcement and direct pharmacological effects of the drug .

MOLECULAR FINGERPRINT OF COCAINE ABUSE : SINGLE CELL & REGIONAL ANALYSIS (0279)

NPRC UNIT : NEUROSCIENCE

%NPRC $: 0.300%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
HEMBY, SCOTT E	PHD	A	NEUROSCIENCE	

AXIS I CODES: 1D, 6, 9, 21 **AXIS II CODES** 36, 39, 50B, 59, 87

ABSTRACT

Cocaine use leads to activation of specific circuits in the brain, notably mesolimbic dopamine neurons . With continued use, neuroadaptive changes occur in these neurons resulting in protracted use of cocaine . Significant progress has been made in elucidating biochemical mechanisms underlying the neuroadaptive changes; however, regulation of gene transcription by cocaine in human post -mortem tissue has received less attention . First, we will compare regional gene expression between the ventral tegmental area (VTA) versus lateral substantia nigra (l-SN) and nucleus accumbens (NAc) versus putamen in post -mortem tissue from cocaine overdose victims and age-matched, non-drug controls . We predict that chronic cocaine use is preferentially associated with altered expression of genes encoding dopamine - and signal transduction -related proteins in the VTA and NAc compared with the SN and putamen, respectively . Secondly, gene expression in a discrete neuronal population is examined by comparing profiles of tyrosine hydroxylase immuno -positive neurons in the VTA and l -SN between cocaine overdose victims and controls . Studies are also underway to assess differential expression of genes encoding dopamine - and signal transduction -related proteins in dopamine neurons in the VTA compared with the l -SN in cocaine overdose victims . The results will provide correlative evidence of the involvement of multiple transcripts and a detailed expression profile of human cocaine abuse . In the past year, we have established 2 dimensional differential gel electrophoresis coupled with MALDI -ToF/ToF analysis and identified 70 differentially expressed proteins from the NAc of COD and controls . Characterization of altered expression patterns of genes and proteins will provide a panoramic view of potential molecular underpinnings of cocaine reinforcement and neuroadaptive changes in these neurons associated with long -term use. Moreover, identification of differentially expressed genes should provide novel targets for pharmacotherapeutic development and /or refinement of existent pharmacotherapies .

MOLECULAR FINGERPRINT OF DOPAMINE NEURONS : RELATION TO AXONAL TARGET (0280)

NPRC UNIT : NEUROSCIENCE

%NPRC $: 0.300 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
HEMBY, SCOTT E	PHD	A	NEUROSCIENCE	
[illegible]	MD, PHD	A	CNTR BEHAVIORAL NEUROSCIENCE	

AXIS I CODES: 1A, 6, 9, 16D, 21, 28(ADRENALS) **AXIS II CODES** 39, 50B, 63B, 72

ABSTRACT

Considerable research effort has been directed to understanding alterations in brain function of schizophrenic patients; however, distinct neurobiological substrates specific for schizophrenia have remained elusive . In terms of pathophysiology, axonal targets of the mesolimbic and mesocortical dopamine pathways, including the nucleus accumbens/amygdala and dorsolateral prefrontal cortex, are dysregulated . Studies in post -mortem human tissue have identified alterations in gene expression in brain regions associated with these pathways . However, two problems exist: 1) the identified molecular profile is a function of both schizophrenia and the neuroleptic drug history; and 2) the studies have not discerned changes occurring at the affected neurons from those occurring in other neuronal and non-neuronal populations . The present study combines retrograde tracing and single cell gene expression profiling in rhesus monkeys allowing the study of gene expression in neuronal populations defined by their projection targets (mesolimbic-nucleus accumbens /amygdala; mesocortical -dorsolateral prefrontal cortex; nigrostriatal -dorsal caudate). The effects of neuroleptic medication on gene expression in these different cell populations will be studied by comparing rhesus monkeys treated with haloperidol for six months with non -treated controls, providing a detailed gene expression profile of neuroleptic effects in defined mesencephalic dopamine systems . Secondly, this utilizes the detailed knowledge of the projection patterns obtained in the rhesus as guide for single cell gene expression studies in these midbrain dopamine populations using human post -mortem tissue provided by the Stanley Foundation Brain Bank . Gene expression will be assessed using high density human cDNA microarrays generated at Emory University and secondary screening using candidate gene arrays and quantitative real -time PCR. From previous experiments, genes of interest include second messenger signaling, synaptic and cytoskeletal proteins; however, the identification of novel pathways and genes are of interest as well . The precision of these techniques will provide heretofore -unattainable information of how the complex neural circuitry of this region is altered in schizophrenia .

STUDIES OF AGING AND COGNITION IN NONHUMAN PRIMATES (0047)

NPRC UNIT : NEUROSCIENCE

% NPRC $: 0.270 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
HERNDON, JAMES G	MPH, PHD	C	NEUROSCIENCE	
E	PHD	A	NEUROSCIENCE	BOSTON UNIVERSITY, MA USA
	PHD	A	NEUROSCIENCE	
	PHD	A	RADIOLOGY	
names	PHD	A	ANATOMY & NEUROBIOLOGY	BOSTON UNIVERSITY, MA USA
	PHD	A	VIRAL DISEASES	NIAID/NIH, WA USA
	PHD	A	ANATOMY AND NEUROBIOLOGY	BOSTON UNIVERSITY, MA USA
3	DVM	C	ANIMAL RESOURCES	

AXIS I CODES: 1A, 21 **AXIS II CODES** 30, 36, 41

ABSTRACT

Our work prior to this project period has centered on characterizing the cognitive and brain changes that occur with aging in the rhesus monkey . We have thus identified changes in recognition memory and in executive function which parallel closely the changes that occur in aging humans . We have also characterized morphological changes during aging of the eye, an organ system that obviously has important implications for studies of cognition . In the present project period, we continued our studies of cognitive function . Salient among recent findings was our confirmation that spatial recognition memory declines more rapidly in males than in females . This finding was based on several years of study in which 90 rhesus monkeys were tested on the Delayed Recognition Span Test (spatial condition). Although we had previously reported a similar finding on a small group or same -sex, age-matched individuals, the confirmation of this finding in a group covering the entire adult lifespan increases the generality of this conclusion In related studies on motor function, we also found that males appear to lose functionality more rapidly than females. These two sets of findings have important implications for human behavioral aging, since they suggest that interventions aimed at ameliorating decline need to be adapted to the sex as well as the age of the individual .

EFFECTS OF ESTROGENS AND RALOXIFENE ON COGNITION IN AGED FEMALE RHESUS MONKEYS (0131)

NPRC UNIT : NEUROSCIENCE

% NPRC $: 0.270 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
HERNDON, JAMES G	MPH, PHD	C	NEUROSCIENCE	
	PHD	A	NEUROSCIENCE	
		A	ANTHROPOLOGY	
	PHD	A	NEUROSCIENCE	
	PHD	C	PSYCHOBIOLOGY	

names

AXIS I CODES: 1A, 15, 21 **AXIS II CODES** 30, 36, 41

ABSTRACT

Estradiol replacement therapy (ERT) is regularly prescribed to hypoestrogenic women to protect against osteoporosis, cardiovascular disease, sexual dysfunction, mood disorders and cognitive impairments associated with ovariectomy or menopause . However, ERT increases a woman's risk of developing breast or uterine cancer . Selective estrogen receptor modulators (SERMs) have been developed to address these problems . SERMs mimic the positive effects of estrogens on specific tissues, yet have minimal proliferative effects on breast and endometrium. The effects of SERMS on cognitive functions, however, are not known . We use the rhesus monkey model to determine if the SERMs tamoxifen and raloxifene act as E 2 agonists or antagonists in female cognitive functions . Animals are tested on a battery of computerized memory and attentional tests that are sensitive to sex hormones or ovarian status, including Delayed Non -Matching to Sample, Delayed Recognition Span, Delayed Response and Visual Search tests . Progress on the cognitive testing continues, and all behavioral testing stations are now in use on a daily basis . We have recently added automated database capability to the test battery . With this new feature, each response, tagged with identifying information showing the monkey's ID, test type, date, and latency and performance information, is automatically transferred to a central server for later analysis . We have also collected motor data on all monkeys in the study and compared the females of this project with males of similar ages, as well as with older animals . Among our findings were that older females were indeed motorically slower, but that estradiol had no influence on speed or accuracy . These findings will enable us to eliminate changes in motor ability as a confounding factor in the cognitive effects we are measuring in this study . Work continues on the influences of the treatments on more complex cognitive tasks .

COCAINE USE & MONOAMINE FUNCTION IN NON HUMAN PRIMATES (0049)

NPRC UNIT : NEUROSCIENCE

% NPRC $: 0.250%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
HOWELL, LEONARD L	PHD	C	NEUROSCIENCE	
F Yamres J	PHD	A	CHEMISTRY	
	PHD	C	NEUROSCIENCE	

AXIS I CODES: 1A, 21 **AXIS II CODES** 36, 50B, 87

ABSTRACT

There is a critical need to develop effective medications to treat cocaine addiction . The current project investigated monoamine transporters as potential targets for cocaine medication development . Medication effectiveness in reducing cocaine use was determined in a nonhuman primate model of intravenous drug self -administration . In addition, the neurochemical mechanisms underlying drug interactions on drug -taking behavior were characterized with in vivo microdialysis . Phenyltropane analogs of cocaine were synthesized to vary in their relative potency at different monoamine transporters . Selective dopamine transporter inhibitors were effective in reducing cocaine self-administration, but they also exhibited cocaine -like behavioral effects and were readily self -administered . Mixed-action inhibitors of the dopamine and serotonin transporters also reduced cocaine self -administration, but they were weaker behavioral stimulants and did not reliably maintain self -administration . Hence, their abuse liability may be less than the selective dopamine transporter inhibitors . Additional efforts have been focused on compounds that differ in their pharmacokinetic profile . Slow onset, long duration drugs have limited cocaine -like properties while maintaining effectiveness in reducing cocaine use . In contrast, rapid onset, short duration drugs exhibit behavioral effects more typical of cocaine . Accordingly, the abuse liability of the medications under development may be limited by pharmacokinetic considerations . The project will contribute to the development of effective treatment strategies for stimulant abuse by identifying neurochemical substrates that reduce cocaine self-administration in nonhuman primates .

PET IMAGING & COCAINE NEUROPHARMACOLOGY IN MONKEYS (0050)

NPRC UNIT : NEUROSCIENCE

% NPRC $: 0.520 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
HOWELL, LEONARD L	PHD	C	NEUROSCIENCE	
Cname 2	PHD	A	NEUROSCIENCE	

AXIS I CODES: 1A, 21 **AXIS II CODES** 50B, 63C, 63E, 87

ABSTRACT

The development of effective medications to treat cocaine addiction will depend on a better understanding of cocaine neuropharmacology . The current project utilized positron emission tomography (PET) neuroimaging techniques in nonhuman primates as a noninvasive approach to investigate cocaine -induced functional changes in central nervous system activity . A PET tracer, FECNT, was developed to label the dopamine transporter . Displacement studies allowed quantification of dopamine transporter occupancy by cocaine and several phenyltropane analogs of cocaine under development as potential medications . It was determined that approximately 70% occupancy was required for selective dopamine transporter inhibitors to reduce cocaine use effectively in drug self -administration protocols . However, drugs with mixed action at dopamine and serotonin transporters required lower occupancy to reduce cocaine self -administration . Since the dopamine transporter is considered to be a critical recognition site for the addictive properties of cocaine, lower transporter occupancy by medications may limit their abuse potential . Parallel studies labeled several of the phenyltropane analogs in order to characterize their pharmacokinetic profile . All of the drugs tested entered the brain more slowly and lasted longer than cocaine . When the same drugs were substituted for cocaine in self -administration protocols, they were less effective in maintaining drug self -administration . Hence, the reinforcing properties and abuse liability of the medications under development may be limited by pharmacokinetic considerations . The identification of neurochemical mechanisms that mediate the CNS effects of cocaine will support medication development efforts for the treatment of cocaine addiction .

COCAINE USE AND PHARMACOTHERAPY EFFECTIVENESS IN MONKEYS (0128)

NPRC UNIT : NEUROSCIENCE

% NPRC $: 0.520 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
HOWELL, LEONARD L	PHD	C	NEUROSCIENCE	
name 2	PHD	A	ORGANIZ MEDICINAL CHEMISTRY	RESEARCH TRIANGLE INSTITUTE, NC USA

AXIS I CODES: 1A, 21 **AXIS II CODES** 36, 50B, 63E, 87

ABSTRACT

The current project is the nonhuman primate component of a multi -site program project grant to develop substitute -agonist medications for the treatment of cocaine addiction . Efforts have focused on the characterization of phenyltropane analogs of cocaine in drug self -administration protocols . Compounds that selectively inhibit the dopamine transporter were effective in reducing cocaine self -administration . However, high levels of dopamine transporter occupancy were required to suppress cocaine self -administration . In fact, PET imaging studies with a highly selective dopamine transporter inhibitor indicated that 90% occupancy of the transporter was required to reduce cocaine self-administration . When the compounds were substituted for cocaine, they reliably maintained drug self-administration but at lower rates compared to cocaine . The latter results indicate that the phenyltropanes are reinforcing, but they have a lower abuse liability than cocaine . Several compounds were labeled, and their rate of entry into brain was determined with PET neuroimaging . Drugs with slow entry into and clearance from brain were less reinforcing compared to cocaine . Lastly, studies co -administered a selective dopamine transporter inhibitor during chronic administration of the selective serotonin reuptake inhibitor (SSRI), fluoxetine. Chronic SSRI treatment actually enhanced the effectiveness of the dopamine transporter inhibitor and lower the level of occupancy required to reduce cocaine self -administration . Hence, dual actions at dopamine and serotonin transporters appear to enhance medication effectiveness . Compounds with documented therapeutic efficacy will be tested in clinical components of the program project for safety and initial clinical trials in cocaine abusers .

DEVELOPMENT OF FMRI FOR BEHAVIORAL STUDIES IN NONHUMAN PRIMATES (0233)

NPRC UNIT : NEUROSCIENCE

% NPRC $: 0.520 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
HOWELL, LEONARD L	PHD	C	NEUROSCIENCE	
L Howell	PHD	A	PSYCHIATRY	UNIVERSITY OF MA MEDICAL SCHOOL, MA USA

AXIS I CODES: 1A, 21 **AXIS II CODES** 50B, 63C, 63E, 87

ABSTRACT

The primary objective of the project is to develop appropriate methodology to extend functional magnetic resonance imaging (fMRI) into conscious nonhuman primates trained to engage in behavioral activities . The protocols will be used to study cocaine -induced changes in brain function and the neural basis of cognition . Efforts have focused on the development of an effective restraint apparatus and on behavioral training and habituation in young rhesus monkeys . A prototype has been completed, and a second unit is under construction . Four juvenile rhesus monkeys have been trained to sit quietly in the apparatus for several hours at a time . In addition, radiofrequency electronics have been engineered and adapted for neuroimaging awake rhesus monkeys on the 3.0T magnet. Acquisition of fMRI data in conscious rhesus monkeys was obtained through a collaborative effort established with Insight Neuroimaging Systems, Inc . A dual transmitter /receiver coil was tested in an awake rhesus monkey, and quality blood oxygen level dependent (BOLD) signals were obtained . In addition, MR spectroscopy data were acquired with exceptional resolution . Plasma cortisol assays will document physiological changes associated with stress due to the restraint system . Animals are currently being trained to engage in operant behavior during image acquisition .

CART & THE DOPAMINE SYSTEM IN THE NUCLEUS ACCUMBENS (0281)

NPRC UNIT : NEUROSCIENCE

% NPRC $: 0.300 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
HUNTER, RICHARD	PHD	A	NEUROSCIENCE	
[name]	PHD	C	NEUROSCIENCE	

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

ABSTRACT

CART mRNA and peptides were discovered most recently by injecting psychostimulants and identifying mRNAs that increased in the (ventral) striatum . While a variety of findings support the involvement of CART in the action of psychostimulants, the originally observed increase in CART mRNA after cocaine and amphetamine has been difficult to reproduce . Accordingly, we are examining the detailed interactions of dopamine and CART in the nucleus accumbens . This effort will likely clarify how dopamine regulates CART peptide and the role of CART in the action of psychostimulant drugs .

PSYCHOSTIMULANT-LIKE EFFECTS OF CART NEUROPEPTIDES (0282)

NPRC UNIT : NEUROSCIENCE

%NPRC $: 0.300%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
JAWORSKI, JASON	PHD	A	NEUROSCIENCE	
[name]	PHD	C	NEUROSCIENCE	

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

ABSTRACT

CART peptides are found in several regions in the central nervous system . While some functional roles for CART are known, the effects of CART in most specific brain regions are not known . Because CART peptides appear to be mediators /modulators of psychostimulant drugs, we examined the behavioral effects of peptide injection into the nucleus accumbens, an area mediating effects of those drugs . Injection of CART peptide alone into the accumbens had no effect on spontaneous locomotor activity . However, intra -accumbal CART inhibited increases in locomotor activity produced by either systemic cocaine or intra -accumbal dopamine . In addition, while direct infusion of CART into the VTA alone produces mild increases in locomotion, this same treatment actually inhibits locomotion produced by systemic cocaine . These results support the notions that CART peptide may be an endogenous modulator of cocaine's effects, and that CART may be an interesting target for medications development .

REGULATION OF DOPAMINE TRANSPORTER IN THE RAT (0129)

NPRC UNIT : NEUROSCIENCE

%NPRC $: 0.520 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
KIMMEL, HEATHER	PHD	G	NEUROSCIENCE	
[illegible]	PHD	C	NEUROSCIENCE	

AXIS I CODES: 1A, 1D, 21 **AXIS II CODES** 36, 77, 87

ABSTRACT

Cocaine is a potent inhibitor of monoamine uptake in the central nervous system, thereby potentiating the neurochemical actions of dopamine, serotonin and norepinephrine . It is important to understand the physiological changes that occur to the dopamine transporter protein (DAT) during repeated use of cocaine . These changes may be involved in maintaining cocaine use and in cocaine withdrawal . This study examined how DAT is regulated in the rat using biochemical methods . Using the irreversible ligand, RTI -76, DAT half-life was determined to be about 2 days in both the striatum and the nucleus accumbens of the rat . In animals that received repeated cocaine injections, the half-life of DAT was reduced to 0.94 days in striatum, but unchanged in nucleus accumbens . Therefore, it appears that repeated cocaine treatment and withdrawal results in a faster cycling of the dopamine transporter in the rat striatum but not in the nucleus accumbens . Since cocaine elevates dopamine levels, thus increasing stimulation of pre - and post -synaptic dopamine receptors, the changes in DAT turnover are likely due to direct activation of dopamine receptors . To test this hypothesis, we administered various dopamine receptor agonists and antagonists systemically to rats and measured DAT turnover . In the striatum, the D 1 agonist and antagonist had no effect on DAT half-life. However, the half -life after treatment with the D 2 agonist was shortened to 1.1 days, while the D 2 antagonist extended the half -life to 2.6 days. In the nucleus accumbens, the D 1 agonist increased the DAT half-life to 2.8 days, while the D 1 antagonist decreased the half -life to 1.3 days. In contrast to the striatum, the D2 agonist increased DAT half -life to 2.8 days, while the D 2 antagonist did not alter DAT kinetics . Thus, direct (by receptor agonists or antagonists) or indirect (by cocaine) stimulation and /or inhibition of dopamine receptors can influence DAT kinetics .

MONOAMINE TRANSPORTERS & NONHUMAN PRIMATE COCAINE (0335)

NPRC UNIT : NEUROSCIENCE

% NPRC $: 0.500 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
KIMMEL, HEATHER	PHD	G	NEUROSCIENCE	
C name . AJ	PHD	C	NEUROSCIENCE	

AXIS I CODES: 1A, 1D, 2, 21

AXIS II CODES 36, 50B, 63C, 63E, 87

ABSTRACT

Currently, there is no effective medication for treating cocaine addiction . A better understanding of how cocaine exerts its effects on the brain will focus on medication development . Although cocaine blocks the reuptake of the monoamine neurotransmitters dopamine, serotonin and norepinephrine, the reinforcing effects of cocaine have been attributed primarily to its effects at the dopamine transporter (DAT). However, not all DAT inhibitors are equally reinforcing . It is important to examine the properties involved in the reinforcing effects of these compounds . In the present research, the reinforcing effectiveness of several monoamine transporter inhibitors (DAT-selective and mixed-action) is assessed in nonhuman primates . The stimulant effects of these compounds are assessed by administering them systemically to squirrel monkeys trained on a stimulus -termination task . The reinforcing effects are assessed in separate groups of squirrel monkeys and rhesus monkeys trained to self -administer cocaine . These data will enable us to determine the relative stimulant and reinforcing efficacy and potency of each combination . To determine drug effects on brain dopamine function, squirrel monkeys undergo in vivo microdialysis procedures following drug administration to establish how dopamine levels are altered by the administration of these drug combinations . PET imaging of DAT occupancy is conducted in rhesus monkeys to correlate DAT occupancy with observed behavior and neurochemistry . Additionally, ex vivo binding assays are conducted in rodents to determine the rate that these compounds bind to DAT . These data will further characterize the role of pharmacokinetics in the addictive properties of cocaine and provide critical information for the development of effective pharmacotherapies that are not, themselves, addictive . This research will extend the Principal Investigator's research training in rodent behavioral pharmacology and neurochemistry to nonhuman primate behavioral pharmacology and neurochemistry Moreover, the training experiences described will provide for the candidate's transition from a mentored scientist to an independent investigator .

CART: A NOVEL COCAINE REGULATED NEUROCHEMICAL (0054)

NPRC UNIT : NEUROSCIENCE

% NPRC $: 0.360 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
KUHAR, MICHAEL J	PHD	C	NEUROSCIENCE	
	PHD	A	NEUROSCIENCE	RESEARCH TRIANGLE INSTITUTE, NC USA
	PHD	A	NEUROSCIENCE	
		G	CENTER BEHAVIORAL NEUROSCIENCE	
	PHD	C	NEUROSCIENCE	

AXIS I CODES: 1A, 1B, 2, 21 **AXIS II CODES** 50B, 72, 87

ABSTRACT

CART peptides are involved in drug addiction, feeding, and other physiologic processes . In the past year, we have continued our clarification of both the localization and functional significance of CART peptides . We have made several new findings : 1. We have found that CART is involved in stress, since it is under glucocorticoid control . This may be a major role for the peptide . 2. Also, we showed, for the first time, that CART has supraspinal antinociceptive effects in the rat . 3. An important finding from the perspective of drug abuse was that CART seems to antagonize or oppose the effects of cocaine in limbic neural circuitry; thus CART may be homeostatic in these circuits . 4. We have described the detailed localization of CART peptide in the stomach, gut and pancreas . This description will be a basis for functional studies in the gut . Taken together these findings demonstrate again that CART peptide is physiologically important, and this could be exploited in a medications development program.

MEDICATION DEVELOPMENT FOR COCAINE ABUSERS (0056)

NPRC UNIT : NEUROSCIENCE

% NPRC $: 0.520 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
KUHAR, MICHAEL J	PHD	C	NEUROSCIENCE	
E narne J	PHD	A	ORGANIZ MEDICINAL CHEMISTRY	RESEARCH TRIANGLE INSTITUTE, NC USA

AXIS I CODES: 1A, 1B, 2, 21 **AXIS II CODES** 50B, 72, 87

ABSTRACT

The goal of this project is to examine phenyltropane analogs of cocaine as potential medications for cocaine addicts . The effect of placing substituted isoxazols in the 2 beta position was examined in the past year . In addition to characterizing these novel compounds and chemical syntheses, we have shown that many of these compounds have psychostimulant -like properties, which is important given our goal . Results from these studies also clarified how various compounds interact with the dopamine transporter . The data indicate that this subgroup of compounds have properties desirable in potential medications .

PROMOTES CHARACTERIZATION OF THE CART GENE (0283)

NPRC UNIT : NEUROSCIENCE

%NPRC $: 0.340%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
KUHAR, MICHAEL J	PHD	C	NEUROSCIENCE	
F name J	PHD	A	NEUROSCIENCE	

AXIS I CODES: 1C, 2, 20, 21 **AXIS II CODES** 72

ABSTRACT

Changes in CART mRNA levels have been observed in brain as a result of various physiologic stimuli including feeding, drugs of abuse, stress and glucocorticoids, and activators of the cyclic AMP (cAMP) and protein kinase A (PKA) pathway . Previously we had shown that the CART promoter contains a canonical CRE site that is partially regulated by a cAMP -dependent pathway in GH 3 cells (pituitary cell line). CATH.a cells were used next as a neuronal -like in vitro model; these cells express a 213 bp CART mRNA species that is translated and processed . Promoter constructs containing the conserved CRE site were responsive to changes in cAMP levels resulting from forskolin and corticotropin -releasing factor stimulation and mutation of the CRE site significantly reduced promoter activity . Additionally, forskolin -induced transcription was inhibited by a dominant negative mutant of CREB in CATH.a cells . This study establishes that in a neuronal cell line the CART proximal promoter can also be regulated via the cAMP /PKA /CREB pathway .

TRAINING PROGRAM IN THE NEUROBIOLOGY OF DRUG ABUSE (0336)

NPRC UNIT : NEUROSCIENCE

%NPRC $: 0.200%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
KUHAR, MICHAEL J	PHD	C	NEUROSCIENCE	
		A	PSYCHIATRY	
	PHD	A	PSYCHIATRY	
	PHD	A	PHARMACOLOGY	
	MD	A		, VA USA
	PHD	A	NEUROSCIENCE	
		A	PHARAMACOLOGY	
	PHD	C	NEUROSCIENCE	
	PHD	A	CHEMISTRY	
	PHD	A	PSYCHIATRY	
	MD, PHD	A	CNTR BEHAVIORAL NEUROSCIENCE	
	MD	A	PSYCHIATRY	
	PHD	A	PSYCHIATRY	
		A	PSYCHOBIOLOGY	
	PHD	C	NEUROSCIENCE	
	PHD	A	PHARMACOLOGY	
	PHD	A	GENETICS	
	PHD	A	GENETICS	

AXIS I CODES: 1A, 1B, 1C, 1D, 1E, 6, 21 **AXIS II CODES** 36, 63C, 63E, 87

ABSTRACT

This is a training grant in the neurobiology of drug abuse . It supports 2 predoctoral students after their second year when they make a commitment to work in a laboratory on a drug abuse problem . It also supports 3 postdoctoral fellows. The training may be with any of the approved faculty listed above using a variety of molecular, neurochemical, anatomical, behavioral or genetic approaches . This is the first year of this training program which has been approved for 5 years.

NEURAL MECHANISMS OF PAIR BONDING (0284)

NPRC UNIT : NEUROSCIENCE

%NPRC $: 0.340%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
LIM, MIRANDA M	BS	G	NEUROSCIENCE	

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

ABSTRACT

This research focuses on a fundamental question in behavioral neuroscience : What is the neural basis of social attachment? In our model of social attachment using the monogamous prairie vole, we have identified a brain region, the ventral pallidum, and a neuropeptide receptor, the vasopressin receptor (V1aR), that appear to be critical for the formation of the pair bind between monogamous mates . The three specific aims outlined in the proposal will further elucidate the role of the V 1aR in the ventral pallidum during pair bind formation . First, we examine the neuronal activation, assessed by induction of c -Fos expression, in the ventral pallidum and other candidate brain regions during mating . Next, we will determine the necessity of V 1aR in the ventral pallidum or other candidate regions in pair bond formation using pharmacological manipulation . Finally, we identify the other neurotransmitter and neuropeptide systems that colocalize with the V 1aR in these critical regions, and which of these may be involved during pair bond formation . The results from these aims will help us understand how the V 1aR may be acting to mediate pair bonding and ultimately, generate novel and viable hypotheses regarding the neurobiology of social attachment .

COMBINATION PHARMACOTHERAPIES FOR COCAINE ADDICTION (0138)

NPRC UNIT : NEUROSCIENCE

% NPRC $: 0.520 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
LINDSEY, KIMBERLY P		G	CNTR BEHAVAIORAL NEUROSCIENCE	
E NAME 3	PHD	C	NEUROSCIENCE	

AXIS I CODES: 1A, 2, 21 **AXIS II CODES** 36, 50, 63E, 72, 87

ABSTRACT

The focus of this research is the development of potential pharmacotherapeutic strategies for cocaine addiction . The project characterized the effects of several phenyltropane analogs of cocaine on the reinforcing properties of cocaine using a nonhuman primate model of drug self -administration . Neuroimaging using positron emission tomography (PET) imaging was used to determine the level of dopamine transporter (DAT) occupancy required to reduce cocaine use . Drugs that selectively inhibit the dopamine transporter effectively reduced cocaine self-administration in a dose -dependent manner . Moreover, the greater the selectivity, the higher the level of dopamine transporter occupancy required . One compound with equal potency at dopamine and serotonin transporters significantly reduced cocaine use at levels of dopamine transporter occupancy that were below the limit of detection . Moreover, the latter compound failed to maintain drug self -administration when substituted for cocaine . The latter results are in direct contrast to those obtained with selective dopamine transporter inhibitors which reliably maintain drug self -administration . Hence, medication effectiveness may be enhanced while abuse liability may be reduced by simultaneously inhibiting the reuptake of dopamine and serotonin . These results have important implications for the development of pharmacotherapies to treat stimulant abuse .

CORTICAL CIRCUITRY RELATED TO NEUROTRANMISSION PROTEINS (0122)

NPRC UNIT : NEUROSCIENCE

% NPRC $: 0.520 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
MULY, E CHRISTOPHER	MD, PHD	A	CNTR BEHAVIORAL NEUROSCIENCE	
	PHD	A	MOLECULAR & CELLULAR BIOLOGY	ROCKEFELLER UNIVERSITY, NY USA
	PHD	A	NEUROSCIENCE	
	PHD	A	NEUROSCIENCE	UNIVERSITE' LOUIS PASTEUR, UK

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

ABSTRACT

This work examines prefrontal cortical circuitry as it relates to the molecular components of dopamine neurotransmission, which subserves the circuitry of working memory, which is dysfunctional in schizophrenia . Working memory function depends on an optimal level of D 1 receptor activation and is impaired by both over and under stimulation of D 1 receptor. It is expected that our results will lead to a better understanding of the mechanism of the D1 receptor's complex modulation of working memory, and ultimately to a better understanding of antipsychotic drug action . To identify the source of afferents that terminate onto spines that contain D 1 and protein phosphatase -1 (PP 1) isoforms PP 1(alpha) and PP 1(gamma)1. We have injected neuroanatomical tract tracers into the brains of young adult macaque monkeys to label parietal, thalamic and posterior cingulate afferents to prefrontal cortex, and within prefrontal cortex to label local horizontal axons . We are using double -labeling techniques appropriate for electron microscopy to stain the labeled axons and either D 1, PP 1(alpha) or PP 1(gamma)1. We are using serial section electron microscopy to determine if the postsynaptic targets of labeled axons contain these proteins . The distribution of these proteins subdivides cortical spines, and the results will suggest aspects of cortical circuitry that are critical for working memory function and extend our understanding of the mechanisms by which cortical circuitry may be specialized . We have used post -embedding immunogold labeling to examine the distribution of PP 1 targeting proteins (spinophilin and neurabin) in spines and are now extending this to PP 1(alpha) and PP 1(gamma1). Finally we have used single and pre -embedding double label methods to examine the subcellular localization of group I mGluRs (mGluR 1a and mGluR 5) and determined a number of differences in their distribution, both between each other, between monkey cortex and rat cortex and between cortex and basal ganglia .

INTERACTION BETWEEN DOPAMINE & GLUTAMATE NEUROTRANSMISSION IN PREFRONTAL CORTEX (0123)

NPRC UNIT : NEUROSCIENCE

%NPRC $: 0.520%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
MULY, E CHRISTOPHER	MD, PHD	A	CNTR BEHAVIORAL NEUROSCIENCE	
	PHD	C	NEUROSCIENCE	
[names]	PHD	C	NEUROSCIENCE	

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

ABSTRACT

Drugs that affect either the glutamate or the dopamine neurotransmitter systems have been shown to cause or exacerbate psychosis . In particular, dopamine -releasing drugs and NMDA glutamate receptor antagonists cause psychosis, while antipsychotic drugs are all dopamine antagonists . Study of the interaction between these neurotransmitter systems is necessary to understand the mechanisms by which these systems cause and might treat the symptoms of schizophrenia . NMDA antagonists increase dopamine turnover, while agonists at the more recently described group I metabotropic glutamate receptors (mGluRs) have the same effect. We are studying the structural basis for this interaction between glutamate receptors and the dopaminergic system . We have studied the distribution of the group I mGluRs (mGluR1a and mGluR5) in the primate prefrontal cortex and have determined quantitative differences in their subcellular localization . The pattern of localization we observed in monkey prefrontal cortex contrasts with that reported for rodent cortex and provides further evidence for differences in the organization of key neurotransmission proteins in rodents and primates . We have used double -label techniques to determine that the group I mGluRs are present in cortical pyramidal cells and interneurons containing parvalbumine, but are not present in the dopamine -containing axons of the primate prefrontal cortex . The results of these experiments are establishing the circuit basis for the action of group I mGluRs in prefrontal cortex and suggest there is no direct interaction between these receptors and dopaminergic neurotransmission within the prefrontal cortex .

EVOLUTION OF APE & HUMAN FRONTAL LOBES (0304)

NPRC UNIT : NEUROSCIENCE

% NPRC $: 0.340 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
PRUESS, TODD M	PHD	A	NEUROSCIENCE	
[names]	PHD	A	NEUROSCIENCE	

AXIS I CODES: 1A, 21 **AXIS II CODES** 34, 36, 59, 89

ABSTRACT

The emergence of human cognitive specializations, such as aspects of language and theory of mind (i.e., the propensity to reason about mental states), must be related, at least in part, to modifications of frontal lobe anatomy. The nature of these modifications is unkown, however . Although the cortex expanded greatly during human evolution, it is not known what internal structural changes accompanied this expansion . Were new areas added or were existing areas enlarged? Were certain regions differentially enlarged, or was the expansion more global . By producing accurate and methodologically consistent cortical maps of frontal lobes from humans, apes, and monkeys, this research will produce the data needed to understand the microstructural changes that occurred in human brain evolution . Precise cortical maps will make it possible to accurately assess the relative and absolute expansion of the prefrontal and premotor regions during primate evolution and provide a more detailed picture of when modern regional organization emerged in human evolution . Additionally, they will provide a way of evaluating the functions of human frontal areas based on experimental studies of the homologous areas of nonhuman primates.

INTERROGATING THE GENOME TO UNCOVER HUMAN SPECIALIZATIONS OF BRAIN & COGNITION (0305)

NPRC UNIT : NEUROSCIENCE

% NPRC $: 0.340 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
PRUESS, TODD M	PHD	A	NEUROSCIENCE	
	MD, PHD	A	GENETICS	SALK INSTITUTE, CA USA
	MD, PHD	A	NEUROLOGY	UCLA SCHOOL OF MEDICINE, CA USA
	PHD	A	CENTER COGNITIVE NEUROSCIENCE	DARTMOUTH UNIVERSITY, NH USA
J	PHD	A	COGNITIVE EVOLUTION GROUP	U LOUISIANA LAFAYETTE, LA USA

AXIS I CODES: 1A, 6, 21 **AXIS II CODES** 34, 36, 46, 59, 89

ABSTRACT

Human brains have unique functional capacities, but how the human brain differs structurally and biochemically from that of other primates is poorly understood . We are pursuing these questions by identifying differences in gene and protein expression between species (humans, chimpanzees, and macaque monkeys), between brain regions (multiple cortical and subcortical sites), and between hemispheres . Gene-expression differences are determined using unfixed tissue samples from short post -mortem time(8 hours or less) cases. Samples are flash-frozen and stored at -70-80°C. Messenger RNA is later extracted and hybridized to oligonucleotide microarrays to determining gene-expression levels for each sample . Possible species differences and regional differences are flagged by comparing microarray results across samples, and then are corroborated using quantitative real -time RT-PCR. Differences in levels are protein expression are determined by Western blotting . Finally, mRNA and protein are localized in cortical tissue using in situ hybridization and immunocytochemistry .

MOLECULAR NEUROBIOLOGY OF FEAR IN MAMMALS (0286)

NPRC UNIT : NEUROSCIENCE

% NPRC $: 0.340 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
RESSLER, KERRY J	PHD	A	CENTER BEHAVIORAL SCIENCES	

AXIS I CODES: 1A, 2, 6, 21 **AXIS II CODES** 59, 72

ABSTRACT

The primary goal of this project is to further characterize synaptic plasticity genes during fear learning, specifically using olfactory fear learning in an "olfactory split -brain" preparation allowing different hemispheres to be differentially trained and to be used as the experimental and control sides within the same animal .

GLUTAMATE AND GABA-A RECEPTORS IN THE BASAL GANGLIA (0133)

NPRC UNIT : NEUROSCIENCE

%NPRC $: 0.520%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
SMITH, YOLAND	PHD	C	NEUROSCIENCE	

AXIS I CODES: 1A **AXIS II CODES** 92(92)

ABSTRACT

The long-term goal of this project is to better characterize the subcellular and subsynaptic localization of metabotropic glutamate receptors (mGluRs) and GABA receptors in the monkey basal ganglia. To reach this goal, we use different immunocytochemical approaches at the electron microscopic level to visualize and determine the localization, density and relative abundance of various subtypes of receptors in relation to specific synaptic inputs that impinge upon neuronal populations in the basal ganglia. The main findings obtained in this project over the past year are: (1) The two group I mGluRs display a differential pattern of subcellular and subsynaptic localization in the monkey striatum. Although both receptor subtypes are associated post-synaptically with glutamatergic inputs from the cerebral cortex and thalamus,mGluR 1a is also found pre-synaptically in a substantial subset of thalamic terminals from the centre median intralaminar nucleus. (2) MGluR 1a, but not mGluR 5, is found pre-synaptically in a subset of midbrain dopaminergic terminals. (3) MGluR 5, but not mGluR 1a, is expressed post-synaptically at the edges of dopaminergic synapses. (4) Both mGluR 1a and mGluR 5 are occasionally found in the main body of putative GABAergic synapses on striatal neurons. These data open up the possibility for differential roles of the two group I mGluRs in the primate striatum and provide an important substrate for the interpretation of functional studies of these receptors in the basal ganglia circuitry. A differential distribution of mGluR 1a and mGluR 5 was also found in the monkey prefrontal cortex.

SYNAPATIC INPUTS TO THALAMOSTRIATAL NEURONS (0134)

NPRC UNIT : NEUROSCIENCE

% NPRC $: 0.520 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
SMITH, YOLAND	PHD	C	NEUROSCIENCE	

AXIS I CODES: 1A, 21 **AXIS II CODES** 46

ABSTRACT

This project aims at elucidating the synaptic organization and localization of GABA and glutamate receptors in motor and caudal intralaminar thalamic nuclei in monkeys . To do so, we use a large variety of pre - and post -embedding immunocytochemical approaches combined with tract -tracing methods at the electron microscopic level . The main findings of this project obtained over the past year are the evidence for a highly complex and specific neurochemistry of ascending cholinergic inputs to the monkey thalamus . We have shown that the ascending brainstem cholinergic inputs to the thalamus are chemically heterogeneous depending on their target sites in the thalamus . More than 70% of cholinergic terminals to the caudal intralaminar nuclei co -express GABA or glutamate whereas cholinergic inputs to thalamic sensory relay nuclei are devoid of glutamate or GABA immunoreactivity . We have also demonstrated that almost 30% of cholinergic terminals to the intralaminar nuclei express both GABA and glutamate suggesting that they could potentially release three different neurotransmitters at their synaptic junctions . These findings open up exciting and challenging research avenues for comparing the functional role of brainstem cholinergic ascending inputs to intralaminar versus thalamic relay nuclei in primates .

KAINATE RECEPTORS IN STRIATUM: IMPLICATION WITH EXCITOTOXICITY (0135)

NPRC UNIT : NEUROSCIENCE

%NPRC $: 0.520%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
SMITH, YOLAND	PHD	C	NEUROSCIENCE	

AXIS I CODES: 1A, 21 **AXIS II CODES** #6

ABSTRACT

The main goal of this project is to characterize the localization and functions of kainate receptors (KARs) in the primate basal ganglia . To do so, we combine high -resolution electron microscopic procedures to visualize and analyze the subsynaptic and subcellular localization of KARs with in vitro patch clamp recording procedures in brain slices to study the functional effects KARs activation on basal ganglia neuronal activity . Studies performed last year have focused on the role of KARs in the globus pallidus (GP). Data obtained so far are : (1) KARs are expressed pre - and post -synaptically in the rat and monkey GP . At the pre -synaptic level, KARs are found in both excitatory and inhibitory terminals suggesting that they may act as auto - or hetero -receptors to modulate glutamate and GABA release, respectively . (2) KARs activation induces dose -dependent inward currents that are not affected by specific AMPA and NMDA receptor antagonists in GP neurons .(3) KARs activation depolarizes the membrane of GP neurons . Together, these findings demonstrate the existence of functional KARs in the GP . Studies are in progress to determine the role of these receptors in regulating excitatory and inhibitory synaptic transmission at pallidal synapses .

GABA-B RECEPTORS AND PARKINSON'S DISEASE (0136)

NPRC UNIT : NEUROSCIENCE

%NPRC $: 0.520%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
SMITH, YOLAND	PHD	C	NEUROSCIENCE	

AXIS I CODES: 1A, 21 **AXIS II CODES:** 16

ABSTRACT

This project aims at studying the localization, functions and potential antiparkinsonian benefits of GABAB receptors modulation in monkeys . To achieve these goals we use various immunocytochemical and functional approaches that include high resolution immunogold procedures at the electron microscopic level, microdialysis technique to measure glutamate and GABA release following intracerebral drug injections and in vivo single unit recording in rhesus monkey basal ganglia . Over the past year, we developed a novel technique for continuous on -line detection of glutamate using brain microdialysis in awake primate basal ganglia . This method offers significantly improved time resolution compared to detection methods based on high -pressure liquid chromatography . This approach will allow us to better assess the role of GABA -B receptors on glutamate release in basal ganglia of awake monkeys. We also demonstrated that local injection of GABA -A and GABA -B receptor agonists reduce neuronal activity in the monkey globus pallidus . The long lasting responses induced by GABA -B receptors activation suggest that complex pre - and post -synaptic mechanisms are involved in mediating these effects . Finally, we also demonstrated that GABA -A and GABA -B receptors display strikingly different patterns of subcellular and subsynaptic localization in the monkey subthalamic nucleus which is consistent with a differential role and mechanisms of activation of these two receptor subtypes in the CNS .

METABOTROPIC GLUMATE RECEPTORS IN BASAL GANGLIA (0337)

NPRC UNIT : NEUROSCIENCE

%NPRC $: 0.500%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
SMITH, YOLAND	PHD	C	NEUROSCIENCE	

AXIS I CODES: 1A, 21 **AXIS II CODES** 46

ABSTRACT

This is a new project that aims at better understand the localization and functional roles of Homer proteins in regulating trafficking and synaptic targeting of group I mGluRs in the CNS . This project involves electron microscopic immunogold approaches combined with biochemical immunoblotting techniques in rats and mice . Two series of experiments are currently in progress . The goal of the first set of studies is to elucidate the subcellular and subsynaptic localization of group I mGluRs in the subthalamic nucleus of normal versus Homer -2 knock out mice . Data obtained far indicate a substantial increase in the proportion of plasma membrane -bound mGlur 5 in Homer-2 knock out mice compared to controls, which suggest that Homer 2 might be involved in intracellular retention of mGlur5. In a second series of experiments, we showed that systemic injection of cocaine up -regulates Homer 1a protein by approximately 2 fold 3-6 hours after injection . However, cocaine does not have any effects on the expression of the constitutive forms of Homer proteins (Homer 1b/c, 2 and 3). These findings demonstrate that the expression level of Homer 1a protein is up -regulated by acute cocaine stimulation, suggesting that the trafficking and synaptic targeting of group I mGluRs might be changed during that time period . Further studies are on their way to address this issue .

IDENTIFICATION OF COCAINE-REGULATED GENES (0288)

NPRC UNIT : NEUROSCIENCE

%NPRC $: 0.340%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
VINCENTIC, ALEKSANDRA	PHD	A	NEUROSCIENCE	
[name]	PHD	C	NEUROSCIENCE	

AXIS I CODES: 1A, 1D, 5 **AXIS II CODES** 87

ABSTRACT

A goal of this project is to elucidate the role of genes that are regulated by psychostimulant drugs, and CART is one of these genes . The product of the CART gene is a peptide neurohormone, with likely peripheral actions . Because CART is found in endocrine tissues such as the pituitary, it is not surprising that CART peptides are found in blood . The goals of this study were to examine the levels and species of CART peptides in blood, to determine if they undergo diurnal rhythms and to elucidate their sources and regulatory factors . Data indicate that a diurnal rhythm for CART peptide does exist in blood of rat and monkeys . The data also show that the partial source of CART peptide is adrenal glands and that its levels are controlled by corticosterone and fasting . These data suggest the possibility that CART peptides in blood may be influenced by hypothalamic -pituitary -adrenal interactions . Our additional data demonstrate for the first time that CART peptide levels undergo a diurnal variation in many brain regions that is disrupted by fasting . These findings suggest a variety of regulatory mechanisms for CART and additional considerations for CART's role in brain .

A NEW MODEL OF ALZHEIMER'S DISEASE PATHOGENESIS (0338)

NPRC UNIT : NEUROSCIENCE

% NPRC $: 0.500 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
WALKER, LARY	PHD	A	NEUROSCIENCE	
	DVM, PHD	A	NEUROSCIENCE	
	MD	A		JEFFERSON MED COLLEGE, PA USA
	MD, PHD	A		JEFFERSON MED COLLEGE, PA USA
	MPH, PHD	C	NEUROSCIENCE	
	PHD	A	NEUROLOGY	
	MD, PHD	A	NEUROLOGY	

AXIS I CODES: 1A, 2, 21 **AXIS II CODES** 30, 41, 46, 77, 95

ABSTRACT

This project was initiated to demonstrate the feasibility of creating a transgenic nonhuman primate model of Alzheimer 's disease (AD) pathology using a novel lentiviral strategy . AD is a significant and growing dementing disorder of old age that presently afflicts four million Americans . While progress in modeling has been made with transgenic rodents, a clinically and behaviorally valid animal model is not yet available . Nonhuman primates are well suited for modeling AD, and the most promising model entails using transgenic technology to drive the pathology . The project began September 1, 2003 , and will model AD -associated pathogenesis in nonhuman primates by delivery of a mutant -amyloid precursor protein (APP) + presenilin /lentiviral vector to specific regions of the brain . To date we have injected two lentiviral /green fluorescent protein vectors into rats, preliminary to injecting the AD transgene into both rats and monkeys .

EXCHANGE OF VIRAL VECTOR & MICRODIALYSIS TECHNIQUES STUDYING (0289)

NPRC UNIT: NEUROSCIENCE

%NPRC $: 0.340%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
YOUNG, LARRY J	PHD	A	CNTR BEHAVIORAL NEUROSCIENCE	
[illegible]	PHD	A		MAX PLANK INSTITUTE, GERMANY
Named	PHD	A	NEUROSCIENCE	
	PHD	A		
	PHD	A		UNIVERSITY OF REGENSBURG, GERMANY

AXIS I CODES: 1, 2 **AXIS II CODES** 36, 39, 55, 72, 95

ABSTRACT

This project is designed to support collaborative research activities between the laboratories of the Principle Investigators; Larry J . Young (NSF STC-Center for Behavioral Neuroscience, Emory University, Atlanta GA) and NAME . They share a common interest in the role of the neuropeptides oxytocin (OXT) and vasopressin (VP) in the regulation of social behaviour and stress coping . Despite the common research interest, the technical expertise of each group is quite different, with each group being an internationally recognized expert in the technology to be transferred through this collaboration . The research conducted during this collaboration addresses two distinct questions that are central to the research programs of each lab, yet because of technical limitations of each lab, these questions cannot be addressed without collaboration .

VASOPRESSIN RECEPTORS AND SOCIAL ATTACHMENT (0290)

NPRC UNIT : NEUROSCIENCE

% NPRC $: 0.340 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
YOUNG, LARRY J	PHD	A	CNTR BEHAVIORAL NEUROSCIENCE	

AXIS I CODES: 1, 21 **AXIS II CODES** 36, 39, 55, 72, 95

ABSTRACT

Larry J. Young is an Assistant Professor in the Department of Psychiatry and Behavioral Sciences at Emory University . Throughout his career, Dr . Young has had a strong interest in the molecular and neural mechanisms underlying behavior . Dr. Young uses a wide range of experimental techniques, from behavioral and pharmacological to molecular and transgenic techniques, to address important behavioral neuroscience questions . Dr. Young is also committed to the comparative approach, learning from the natural differences in behavior of closely related species . Currently, Dr . Young's research focuses on the role of neuropeptides in the modulation of social behaviors and attachment. Vasopressin (AVP) facilitates affiliation and pair bond formation in monogamous species . Compared to non-monogamous species, monogamous species have high levels of AVP receptors in the ventral pallidum, a brain region associated with reinforcement and reward . Enhancing AVP receptor gene expression in the ventral pallidum using viral vector gene transfer facilitates pair bonding in the male prairie vole . This has led to the hypothesis that vasopressin stimulates social attachment by activating reward circuits via activation of AVP receptors in the ventral pallidum . The specific aims of this proposal will investigate the role of the ventral pallidum in social attachment and characterize the activity, phenotype, and connectivity of vasopressin receptor containing cells in this region . Further studies will investigate the molecular mechanisms controlling AVP receptor expression in the ventral pallidum . Understanding the link between social interactions, reward circuitry and social attachment may provide useful insights into potential mechanisms underlying psychiatric diseases characterized by social deficits, such as autism. This project will provide opportunity to significantly develop the technical skills in Dr . Young's laboratory, including antibody development, retrograde tract tracing, and analysis of DNA -protein interactions . Emory University and the Center for Behavioral Neuroscience provide an excellent environment for career development in the field of behavioral neuroscience .

NEUROLOGIC STUDIES OF MEDIAL TEMPORAL LOBE FUNCTION (0252)

NPRC UNIT : NEUROSCIENCE

%NPRC $: 0.520%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
ZOLA, STUART M	PHD	C	NEUROSCIENCE	
[name]		A		UNIVERSITY OF CA, SAN DIEGO, CA USA

AXIS I CODES: 1A, 21 **AXIS II CODES** 30, 36, 41, 72

ABSTRACT

This work builds on our previous success in identifying specific structures and connections within the medial temporal lobe that are important for memory . Specifically, this work seeks to clarify the role in memory of the hippocampal region and the adjacent and interconnected perirhinal cortex . Using a series of behavioral tasks we are determining whether and to what extent monkeys with lesions of these two brain regions are impaired on recognition memory, spatial memory, the memory for motor skills, and perception . This work is relevant to our understanding of how memory is organized in the brain and to understanding the memory impairment associated with a wide range of human conditions, e .g. aging, Alzheimer's disease, and stroke .

THE NEUROLOGY OF MEMORY (0275)

NPRC UNIT : NEUROSCIENCE

% NPRC $: 0.450 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
ZOLA, STUART M	PHD	C	NEUROSCIENCE	
F name 3		A		UNIVERSITY OF CA, SAN DIEGO, CA USA

AXIS I CODES: 1A, 21 **AXIS II CODES** 30, 36, 41, 72

ABSTRACT

The major goals are to distinguish between the functions of perirhinal cortex and inferotemporal area TE in the visual modality, determine the effects on memory of ibotenate lesions limited to the hippocampal region, and to contrast the effects of spatial and nonspatial visual memory of damage to the hippocampal region, perirhinal cortex, and parahippocampal cortex .

REACTIONS TO (IN) EQUALITY IN CAPUCHIN MONKEYS (0061)

NPRC UNIT : PSYCHOBIOLOGY

%NPRC $: 0.520%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
DE WAAL, FRANS B M	PHD	C	PSYCHOBIOLOGY	

AXIS I CODES: 1A **AXIS II CODES** 34, 36, 40, 41, 72

ABSTRACT

Social emotions, known by economists as passions, guide human reactions to the efforts, gains, and losses of others . Reactions such as envy, retaliation, and punishment, are sometimes seen as irrational, but may have evolved to promote cooperation . The present study seeks to determine the same reactions in a large -brained, highly cooperative primate, the capuchin monkey (Cebus apella). In previous research these monkeys reacted negatively if a partner received a better reward for equal or less effort . The project experimentally addresses the degree to which monkeys monitor the efforts and pay -offs of others, and how they react to (un)equal reward division . Available is a colony of capuchins in an indoor /outdoor enclosure, trained for temporary separation for testing . Monkeys will pull in a tray that rewards their partner at the same time that it rewards themselves . An individual's pulling activity is expected to decline if the partner's rewards substantially exceed those for itself . Females are expected to be more sensitive to reward division than males . This sex difference will be tested in two further paradigms, one that measures the feeding speed of two monkeys eating side by side from different foods . Second, in a task of imitation, in which food rewards play a role .

EVOLUTIONARY PERSPECTIVE ON EMPATHY (0063)

NPRC UNIT : PSYCHOBIOLOGY

%NPRC $: 0.520%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
DE WAAL, FRANS B M	PHD	C	PSYCHOBIOLOGY	

AXIS I CODES: 1A **AXIS II CODES** 34, 36, 41, 72

ABSTRACT

Chimpanzees console victims of attack . They also show targeted help in which they provide others with assistance they need, such as saving them from drowning or supporting an injured companion . Several investigators have considered it unlikely that empathy arose in recent evolutionary history . Indeed, there is experimental evidence for emotional contagion in other animals, such as rats and monkeys . Studies on our closest relatives, the anthropoid apes, are particularly rich, suggesting more intelligent forms of empathy than in monkeys . The present study is behavioral, with both an observational and experimental component . Observations of spontaneous behavior among chimpanzees in two social groups at the Yerkes Primate Center to measure social responses to hurt or distressed individuals, such as individuals who have lost a fight . The experimental component of the project seeks to test responses to social sequences on video, particularly the preferred outcome of sequences, which outcomes may range from escalation of aggression to reassurance provided by others to a victim of attack . This work takes advantage of six trained chimpanzees who have been used in the past in computerized (joystick mediated) tasks . They select images on a computer screen, and we will measure what kind of emotional contents or outcomes they prefer .

SOCIAL LEARNING AND CULTURE IN CHIMPANZEES (0064)

NPRC UNIT : PSYCHOBIOLOGY

% NPRC $: 0.520 % **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
DE WAAL, FRANS B M	PHD	C	PSYCHOBIOLOGY	
[NO-NIH]		G	PSYCHOBIOLOGY	
		A		ST. ANDREWS, UK

AXIS I CODES: 1A, 9 **AXIS II CODES** 31, 34, 36, 72, 74E

ABSTRACT

This porject studies the process of social learning in outdoor housed groups of chimpanzees :

What is the mechanism of social transmission : are apes capable of true imitation? This has been questioned by several investigators . We have been at the forefront designing tests of imitation, using "artificial fruits " (a sort of puzzle box), and finding positive results that have been widely accepted .

How does behavior spread in a group? Thus far, most studies have subjected chimpanzees to human behavior to see how it spreads, but we want to know about chimp -to-chimp transmission, which is the only kind of transmission that matters in the natural habitat .

The unique feature of these studies, compared to all studies done before, is that the models from which the chimpanzees will learn will be conspecifics . So, instead of a human demonstrator, they will learn from another chimpanzee. This series of experiments will match more closely the processes of social transmission in the field .

HEMISPHERIC SPECIALIZATION AND COMMUNICATION (0263)

NPRC UNIT : PSYCHOBIOLOGY

%NPRC $: 0.460%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
HOPKINS, WILLIAM D	PHD	A	PSYCHOBIOLOGY	BERRY COLLEGE, GA USA

AXIS I CODES: 1A, 19, 23 **AXIS II CODES** 36, 50, 54

ABSTRACT

This year, studies in our laboratory focused on the link between asymmetries in manual and vocal signals and neuroanatomical asymmetries in language homologs in the chimpanzee brain . Preliminary analyses revealed a positive association between lateralized hand use in gestural communication and inferior frontal regions of the brain In addition, manual gestures correlated with asymmetries in the cingulated gyrus .

DEVELOPMENT CONSEQUENCES OF INFANT ABUSE IN PRIMATES (0101)

NPRC UNIT : PSYCHOBIOLOGY

%NPRC $: 0.520%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
MAESTRIPIERI, DARIO	PHD	A	PSYCHOLOGY	UNIVERSITY OF CHICAGO, IL USA
Cname 3		A	PSYCHOBIOLOGY	

AXIS I CODES: 1A **AXIS II CODES** 36, 60, 71, 74E

ABSTRACT

This project investigates the behavioral and neuroendocrine development of rhesus macaque infants who are abused by their mothers and their nonabused controls . In this year of the project, we continued to collect behavioral and neuroendocrine data on two cohorts of abused and nonabused infants . Neuroendocrine measures included plasma cortisol levels under baseline conditions, following a novelty test, and in response to dexamethasone, CRH challenge, and ACTH stimulation test . CSF levels of corticotropin -releasing -hormone (CRH) and other neurochemicals were also monitored . Preliminary data analyses indicate some main effects of abuse on behavioral and neuroendocrine reactivity to stress as well as on other physiological variables .

A PILOT STUDY OF FACE PROCESSING IN CHIMPANZEES (0265)

NPRC UNIT : PSYCHOBIOLOGY

% NPRC $: 0.430 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
PARR, LISA	PHD	G	CNTR BEHAVIORAL NEUROSCIENCE	

AXIS I CODES: 1A, 2, 15, 23, 26 **AXIS II CODES** 36, 41, 63G, 72

ABSTRACT

Individual recognition is critical for the maintenance of social groups . We must be able to recognize and remember our family and friends and discriminate these individuals from our rivals . One way in which individuals are recognized is through the face . In humans, faces are a unique category of visual signal and appear to be recognized in ways that are distinct from general object recognition . Recent evidence suggests the involvement of specific brain regions in face recognition that are not active during general complex visual object recognition . Recent studies also suggest that chimpanzees, unlike monkeys, process faces in ways that are similar to humans . This suggests that the specificity of face recognition may be a modern specialization that we share with apes, our closest living relatives . This project investigates the specificity of face recognition by using brain imaging techniques (Positron Emission Tomography, PET) to examine whether chimpanzees also show a similar pattern of brain activation during face processing .

OXYTOCIN, VASOPRESSIN & SOCIAL BEHAVIOR IN NON HUMAN PRIMATES (0074)

NPRC UNIT : PSYCHOBIOLOGY

% NPRC $: 0.520 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
SANCHEZ, MAR		C	PSYCHOCIOLOGY	
][Names]?	PHD	G	CNTR BEHAVIORAL NEUROSCIENCE	
	PHD	C	PSYCHOBIOLOGY	

AXIS I CODES: 1A, 21 **AXIS II CODES** 36, 41, 50

ABSTRACT

Several recent studies have demonstrated that central oxytocin and vasopressin pathways are important for species typical social behaviors in rodents . This project extends this work to non -human primates by investigating oxytocin and vasopressin in both normal and socially abnormal rhesus monkeys . Twenty -four monkeys were recruited and housed in differential rearing environments . We have completed the initial phase of neuroanatomical studies in one cohort of 12 monkeys and have progressed to analysis of several neuropeptide receptor patterns . In the remaining cohort, we continue studies of social and emotional behavior and social cognition . In addition, we have begun studies of physiological measures of emotionality including endocrine levels and heart rate profiles during challenge situations . These studies have provided evidence that macaques with deprived social rearing experiences exhibit deficits in oxyocin, corticotropin -releasing factor and dopaminergic systems . Pharmacological studies have also been performed to examine the influence of systemically administered oxytocin and vasopressin antagonists on neural substrates activated during social interactions among our experimental and control animals .

EMORY CONTE CENTER FOR THE NEUROSCIENCE OF MENTAL DISORDERS (0077)

NPRC UNIT : PSYCHOBIOLOGY

% NPRC $: 0.520%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
SANCHEZ, MAR		C	PSYCHOCIOLOGY	
		A	PSYCHOBIOLOGY	
E Nowlin		A	PSYCHOBIOLOGY	
J	PHD	C	PSYCHOBIOLOGY	

AXIS I CODES: 1A, 21 **AXIS II CODES** 36, 41, 50

ABSTRACT

The major goal of this work is to produce and characterize a non -human primate epigenetic early life stress model in rhesus monkeys . A number of procedures have been offered as potential primate models of early stress experience associated with subsequent risk for anxiety and affective disorders in adulthood . These range from the chronic infant isolation paradigms to short -term (1-24 hr) mother-infant separations followed by reunion . The former produce near-permanent disruptions in social competence and sensitivity to stress . The latter produce acute changes in social behavior and transient changes in sensitivity to stress, but apparently no long -term behavioral deficits . We have imposed a schedule of repeated mother -infant separations during a critical period of development (3-6 months of age). The purpose of this project is to provide monkeys with an early developmental stress to the Emory Center for the Neuroscience of Mental Disorders . We have detected short -term alterations in mother -infant relation and stress reactivity in the infant . Some long-term alterations include alterations in diurnal activity of the hypothalamic -pituitary -adrenal axis and increased levels of fear /anxiety as juveniles . We are following the animals longitudinally, including current studies of other circadian rhythms, as well as brain metabolism measured by positron emission tomography (PET) neuroimaging .

EARLY EXPERIENCE, STRESS NEUROBIOLOGY AND PREVENTION SCI (0311)

NPRC UNIT : PSYCHOBIOLOGY

% NPRC $: 0.000 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
SANCHEZ, MAR		C	PSYCHOCIOLOGY	
		A	PSYCHOBIOLOGY	
C NAMUS]		A	PSYCHOBIOLOGY	

AXIS I CODES: 1A, 15, 21 **AXIS II CODES** 36, 63, 71

ABSTRACT

The focus of this grant is to study the impact of early experiences (such as abuse or neglect) on the development of behavior and the Limbic -Hypothalamic -Pituitary -Adrenocortical (LHPA) system in rhesus monkeys . Altered regulation of this system (both hyper - and hypo -functioning) is associated with affective and physiological disorders in animals and human adults . Neglect in human and non -human primates may also result in a blunting of the daytime rhythm in cortisol production, although it is not clear whether this is accompanied by cortisol hypo - or hyperresponsiveness to stressors . We are studying : 1) the HPA axis circadian pattern of activity, 2) the LHPA responsiveness to psychological stress and how well social or maternal cues "buffer" it, 3) levels of fearfulness/anxiety, 4) the neural substrates underlying the behavioral and neuroendocrine alterations detected (e.g. analysis of CRF -related systems).

BEHAVIORAL DEVELOPMENT PRENATAL HORMONAL INFLUENCES (0071)

NPRC UNIT : PSYCHOBIOLOGY

% NPRC $: 0.520 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
WALLEN, KIM	PHD	C	PSYCHOBIOLOGY	

AXIS I CODES: 1A, 15, 23, 25A, 26 **AXIS II CODES** 36, 41, 45, 60, 71, 74E

ABSTRACT

The early hormone environment has been thought to influence the development of male /female behavioral and neuroendocrine differences through the life span . This study exposed developing male and female rhesus monkeys to atypical prenatal hormonal environments and has been investigating their behavioral and neuroendocrine development . Treatments were designed to mimic accidental exposure to or suppression of androgens prenatally . This study investigated whether prenatal androgen exposure, social rank, and body weight are factors regulating pubertal development in female rhesus monkeys . Subjects' mothers received injections of testosterone enanthate (20 mg/week), flutamide (an androgen receptor blocker, 30 mg/kg twice daily), or vehicle during gestational days 35/40-70 (early) or days 105/110-140 (late). To monitor pubertal development, frequent assessment of menstruation, circulating steroids, and weight began around 2.5 years of age during the fall breeding season . Menarche was delayed by one and a half months in females treated late in gestation with either androgen or flutamide, and no effect of prenatal manipulations on first ovulation were found . Social rank did not affect menarche, but low ranked females were less likely than high and middle ranked females to ovulate at an early age . Females ovulating early, around 2.5 years, had higher body weights than did females ovulating later, suggesting that better nutritional reserves or positive energy balance affect pubertal development . This study suggests that perturbation of the late gestation hormonal environment, social rank, and nutritional status interact to influence pubertal development .

FEMALE SEXUALITY: MODULATION BY ESTROGEN AND ANDROGEN (0310)

NPRC UNIT : PSYCHOBIOLOGY

%NPRC $: 0.500%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
WALLEN, KIM	PHD	C	PSYCHOBIOLOGY	
Name 2	PHD	C	PSYCHOBIOLOGY	

AXIS I CODES: 1A, 15, 23 **AXIS II CODES** 36

ABSTRACT

The hypothesis is investigated that female sexual interest is stimulated by the neural actions of ovarian estrogens and that androgens regulate the bioavailability of these estrogens through interactions with sex hormone binding globulin (SHBG). Three projects, using a rhesus monkey model of endocrine function and behavior, investigate the hormonal basis of female sexual initiation . Project I investigates sexual initiation in females across the menstrual cycle, comparing the occurrence of female sexual initiation in a social group context during normal to cycles treated with an androgen receptor blocker (flutamide) or an estrogen receptor blocker (tamoxifen). This will clarify whether androgens or estrogens act neurally to modulate female sexual motivation . Project II tests the novel hypothesis that SHBG regulates bioavailable estrogens and androgens through these steroids' different affinities for SHBG . This project uses a monkey model of hormonal replacement therapy for reproductively prime females after surgical removal of the ovaries and tests the hypothesis that chronic estradiol (E2) ceases to effectively stimulate female sexual interest as estrogen is sequestered by SHBG . It further investigates whether an androgen, 5a-dihydrotestosterone (DHT), with a markedly higher affinity for SHBG than estradiol, can acutely and rapidly reinstate female sexual interest by increasing free estradiol by displacing SHBG -bound estradiol . Ovariectomized females receiving chronic estradiol treatment mimicking mid follicular estradiol levels will be observed for sexual initiation during chronic E 2 treatment alone and following chronic E 2 and an injection of DHT or E 2. Concurrent administration of flutamide or tamoxifen with the estrogen or DHT, will discriminate between behavioral changes resulting from the activation of neural androgen or estrogen receptors . The effects of these treatments on neuroendocrine function will also be investigated . Project III investigates whether common human hormonal replacement therapies of chronic estrogen, or chronic estrogen plus testosterone with or without concurrent progestin can reinstate female sexual interested in reproductively prime ovariectomized female monkeys . The hypothesis will be tested that chronic progestin therapy reduces or eliminates the effectiveness therapies that reinstate female sexual interest without progestin . These therapies will also be compared on their effects on neuroendocrine function Theses studies will markedly increase our understanding of the role that ovarian steroids play in modulating female sexuality .

GROWTH REGULATION OF THE NEUROBIOLOGY OF PUBERTY (0072)

NPRC UNIT : PSYCHOBIOLOGY

% NPRC $: 0.520 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
WILSON, MARK E	PHD	C	PSYCHOBIOLOGY	
	DVM, PHD	A	RESEARCH RESOURCES	
[Nonmb]	DVM	C	ANIMAL RESOURCES	

AXIS I CODES: 1A, 2, 15, 23, 26 **AXIS II CODES** 36, 60, 63G, 71, 74E

ABSTRACT

This project exames the hypothesis that a developmental increase in the anabolic protein insulin -like growth factor (IGF)-I is the signal for the initiation of puberty . Ongoing studies in the current year involved five subprojects . Infants, living in social groups, who had received monthly saline treatments from birth through 8 months and were compared to infants who had received either monthly Sandostain LAR or Lupron injections . Subjects will be studied for a year to determine how pertubations of the GH or reproductive axis during the neonatal period affect growth and maturation . In a second project, ovariectomized juveniles received either monthly treatments of saline or Sandastain LAR beginning at 12 months of age to test the hypothesis that a dimunition of GH secretion would delay the onset of puberty as assessed from diurnal changes in gonadotropins . Analayses reveal that, in the absence of estradiol replacement, developmental increases in nocturnal luteining hormone (LH) secretion are not affected by GH deficiency . However, GH deficient animals are more sensitive to the negative feedback actions of estradiol than control females. In the third project, juvenile females received mothly treatments with saline, Lupron, or Lupron plus Sandostatin LAR . Lupron treatment, which experimentally suspends reproductive maturation, continued until 28 months of age. The study tested the hypothesis that puberty, assessed from diurnal changes in gonadotropins, will be dalayed by a dimunition of GH secretion . Analyses showed that GH deficiency further delays the onset of puberty . The fourth project tested the hypothesis that gonadal negative feedback is important for timing developmental increases in nocturnal LH secretion . Prior to ovariectomy, nocturnal LH in prepubertal females is at the sensitivity of the assy . However, within 14 days of ovariectomy, nocturnal LH values rise significantly . Immediate replacement with estradiol returns LH to pre -ovariectomy levels . These data wil provide new information on how how growth and sexual maturation are casuallly linked .

PSYCHOBIOLOGY OF ESTROGEN RECEPTOR MODULATORS (0098)

NPRC UNIT : PSYCHOBIOLOGY

%NPRC $: 0.520%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
WILSON, MARK E	PHD	C	PSYCHOBIOLOGY	
[NoMod	MS	C	PSYCHOBIOLOGY	
	PHD	C	PSYCHOBIOLOGY	
]	PHD	A	CNTR BEHAVIORAL NEUROSCIENCE	

AXIS I CODES: 1A, 1D, 2, 15, 21, 23 **AXIS II CODES** 30, 36, 50B, 74E, 93

ABSTRACT

Studies were continued during the current year to examine the hypothesis that the selective estrogen receptor modulators (SERMs), tamoxifen and raloxifene act as estrogen (E) agonists on the induction of affliative and sexual behavior in hypoestrogenic females and as an estrogen antagonist on these behaviors in the presence of E . These SERMs are used to treat specific peripheral target tissues but their effects on briain function regulating social behavior are not fully understood . During the current year, studies were continued in rats to determine the effects of tamoxifen and E given alone or in combination on female behavior and specific gene expression in the rat brain . Focus is on changes in serontiergic system and CRH expression, and glucocorticoid receptor expression . In addition to these studies in rodents, projects were continued with ovariectomized female rhesus monkeys housed in small social groups with a single adult male . The first project comapred the affects of E to tamoxifen or tamoxifen plus E on the induction of female sexual behavior . Analyses indicate that tamoxifen blocks the induction of female sexual initiation and reduces social affiliation by E . Tamoxifen alone does not act as an E agonist on female sexual motivation, tamoxifen blocks the negative feedback inhibition of LH by E, thus is neither an agonist nor antagonist on the GH or prolactin secretion . Tamoxifen increases concentrations of CRH in CSF but not to the same degree as E, tamoxifen exacerbates glucocorticoid negative feedback of ACTH and blunts the pituitary response to CRH . Additional studies showed that raloxifene also increases glucocorticoid negative feedback and diminishes the response to exogenous CRH . However, raloxifene has no effect on female sexual behavior or LH secretion in monkeys .

MELANOCORTIN STIMULATING HORMONE & SEXUAL BEHAVIOR (0266)

NPRC UNIT : PSYCHOBIOLOGY

%NPRC $: 0.470%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
WILSON, MARK E	PHD	C	PSYCHOBIOLOGY	

AXIS I CODES: 1A, 2, 15, 21, 23 **AXIS II CODES** 36, 50B, 72, 74E, 93

ABSTRACT

Studies were completed this year to test the hypothesis that an analogue of alpha melanocortin stimulating hormone, which binds preferentailly to the MC 4 receptor increases sexual initaion in males and females . Studies of 6 males living in separate runs with 3 to 5 females each reveal that the drug did not increase male behavior at any dose above that seen in placebo treatments . In contrast, high doses of the drug did increase female sexual initiation above placebo, but given the individual variability in the response, the increase was only significant at p = 0.09. Additional studies showed that the analog given to adult male rhesus monkeys (n = 7) increased the incidence of masturbation . These data could provide new insights into treatments of sexual dysfunction for men and women .

BEHAVIOR EFFECTS OF GNRH IN PRIMATES (0267)

NPRC UNIT : PSYCHOBIOLOGY

%NPRC $: 0.470%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
WILSON, MARK E	PHD	C	PSYCHOBIOLOGY	
[name]	PHD	C	PSYCHOBIOLOGY	

AXIS I CODES: 1A, 2, 15, 21, 23 **AXIS II CODES** 36, 50B, 72, 74E, 93

ABSTRACT

Studies were continued this year to test the hypothesis that, in addition to its regulation of the reproductive axis, GnRH acts as a neurotransmitter mediating the effects of estradiol on the induction of female sexual behavior . Preliminary studies determined that the peripheral administration of a GnRH analog would cross the blood rain barrier as the analysis of CSF from GnRH analog -treated females showed the presence of the drug . The verified the approach to be used in the study . Adult, ovariectomized pigtail macaques, living in a heterosexual social group were administered a dose of estradiol that is just below the threshold for inducing female sexual behavior . The experimental plan treated the females, in a counterbalanced design with saline, both forms of the GnRH peptide (GnRH I and II) and antagonist of GnRH I and II . The hypothesis is that GnRH I is the ligand responsible for the neuroendocrine regulation of the reproductive axis whicle GnRH II will facilitate estradiol's effects on behavior . The results showed that neither form of GnRH caused an increase in female sexually motivated behavior .

ENHANCEMENT OF LUMBAR FUSION W/ RHBMP 2/ COLLAGEN OR LMP (0034)

NPRC UNIT : RESEARCH RESOURCES

% NPRC $: 0.520 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
BODEN, SCOTT D	MD	A	RESEARCH RESOURCES	

AXIS I CODES: 1A, 1D, 2, 26 **AXIS II CODES** 46, 48, 88, 89

ABSTRACT

Lumbar spinal fusion is commonly performed in humans but the failure of bone union is a frequent complication . Osteoinductive growth factors synthesized by recombinant DNA technology have been shown to induce bone formation in heterotopic sites . Recombinant human BMP -2 (rhBMP -2) has been effective in generating spine fusions in a rabbit model . To determine the dose of the growth factor in humans and to determine the speed of healing, a non -human primate model is used . Higher doses than expected were required to make bone in the primate . The growth factor was delivered inside a hollow titanium threaded fusion cage through a minimally invasive approach . This work resulted in the initiation of a human pilot clinical trial with excellent results at one year followup . Studies have focussed on fine tuning the dose and studying alternative carrier materials including different combinations of ceramic materials for use in the posterolateral spine . Studies in 2002 have demonstrated that optimization of the carrier matrix could allow lower doses of rhBMP -2 to be successful . These studies are critical to providing the information needed for human clinical trials for the posterior spine fusion application . Recent studies showed it was possible to induce bone with the gene therapy approach, but not consistently when scaled up to a large enough number of cells . Studies in 2003 investigated the ability of concentrated bone marrow cells to augment healing . In 2004 we will investigate new carriers for BMP -2 and continue studies with LMP -1.

PORPHYRINS AS MICROBICIDES FOR STDS (0202)

NPRC UNIT : RESEARCH RESOURCES

% NPRC $: 0.520 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
GOULD, KENNETH G	DVM, PHD	A	RESEARCH RESOURCES	

AXIS I CODES: 1A, 2, 23, 27 **AXIS II CODES** 50, 52, 83

ABSTRACT

This is one project within a program project (Dr. R. Compans P .I.) designed to evaluate newly synthesized porphyrins for antimicrobial activity against STDs . This project tests candidate compounds for safety (gross toxicity) using the mouse as a model . Compounds are administered by vaginal or IP routes for 21 days and tissues collected for subsequent analysis for compound deposition in various organs . Clinical effects are noted by direct observation at least twice daily . Agents shown to be without demonstrated adverse clinical or histological effects in the mouse are being evaluated for protection in vivo using the monkey model . At this time nine compounds have been tested in mice (two more are currently being evaluated). Five have been tested in the monkey . In addition, the compounds are tested in vitro for spermicidal activity against chimpanzee sperm . Among the compounds tested so far, three have shown spermicidal activity and two have been without effect . Indirect analyses of fertilizing capacity, using the sperm penetration assay (SPA) are underway, but at this time have shown no results that could not be correlated with the observed effects on sperm viability .

ACUTE ANTITHROMBOTIC SAFETY AND EFFICACY OF DIRECT ANTICOAGULANTS (0339)

NPRC UNIT : RESEARCH RESOURCES

%NPRC $: 0.500%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
HANSON, STEPHEN R	PHD	A	BIOMEDICAL ENGINEERING	
E Name 7	MD	A	BIOMEDICAL ENGINEERING MED	
	PHD	A	BIOMEDICAL ENGINEERING MEDICIN	

AXIS I CODES: 1A, 2, 3, 13, 17 **AXIS II CODES:** 48, 50B, 50C, 52, 63F, 77

ABSTRACT

We investigated whether direct inhibitors of specific coagulation factors, including thrombin, factor V, or factor XI (FXI) could be safe and efficacious antithrombotic agents when compared to standard anticoagulants that inhibit several coagulation factors . We deployed thrombogenic synthetic vascular graft segments (Dacron or Teflon) into implanted chronic femoro -femoral arteriovenous shunts in juvenile baboons, and treated the animals with antithrombotic doses of experimental anticoagulants . In these non -terminal experiments, thrombus formation was monitored using radioimaging techniques . Safety was assessed with template bleeding and blood clotting time measurements. The novel direct thrombin inhibitor compound, melagatran, showed dose response . Hemostatic safety was compromised at high doses, as evidenced by prolonged bleeding and clotting times . However, high -dose recombinant human activated factor VII successfully reversed the antihemostatic effect of high -dose melagatran . We also initiated research on testing the maximum antithrombotic and anticoagulant effects of a new recombinant thrombin analog (WE) that activates endogenous protein C, which is a potent inhibitor of coagulation factor Va . The data to date suggest that the anticoagulant effect of WE is self limiting and produces no significant hemostatic safety concern. High -dose aFXI Pab produced systemic anticoagulation, and inhibited thrombus formation in the grafts without prolongation of the template bleeding time . The aFXI-Pab treatment was safer than standard heparin, which prolonged both the bleeding and the prothrombin times . Our research suggests that direct coagulation factor inhibitors are as efficacious and potentially safer than standard anticoagulants, thus pointing towards the future of antithrombotic therapy .

EVALUATION OF SMALL VESSEL PROSTHESESS (0358)

NPRC UNIT : RESEARCH RESOURCES

% NPRC $: 0.500 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
HANSON, STEPHEN R	PHD	A	BIOMEDICAL ENGINEERING	

AXIS I CODES: 1A, 3, 13, 17 **AXIS II CODES** 50B, 52, 63F, 77

ABSTRACT

Hemodynamics and material properties may impact vascular graft thrombosis and healing . We postulated that changes in local hemodynamics exert little change on short -term graft healing. To test this hypothesis, we implanted either a control or a stenotic ePTFE graft with a 60 m internodal porosity into the abdominal aorta of 15-20 kg male baboons using end -to-end anastomoses. Six control studies utilized grafts 4 cm in length with a 6 mm inner diameter (i.d.). The four stenotic grafts demonstrated a 75 % reduction in cross -luminal area. At the stenotic throat shear stress values were increased locally by 8-fold, which was expected to decrease neointima formation. The stenotic segments consisted of a center portion with a 1.5 cm length and a 3 mm id. melded to two grafts with a 1.25 cm length and a 6mm id. We harvested all grafts at one month using in situ pressure perfusion. The tissues were then embedded, sectioned, and stained. At the mid-point of the six stenotic grafts, the throat region demonstrated an average intimal thickness that was 180 % greater than observed in the control grafts (142 2.0 m vs. 78.7 2.0 m, respectively; p 0.05). Interestingly, this intimal thickening occurred at the stenotic throat (3 mm id.) where the wall shear stress was highest. At the anastomoses of stenotic grafts, we also saw pannus formation. However, at proximal and distal anastomoses, the intimal thickness decreased up to the graft midpoint, i .e., the stenotic throat, at which point the intimal thickness exceeded the values seen either just proximally or distally. The results demonstrate that changes in local hemodynamics fail to inhibit intimal thickening during short -term graft healing, as opposed to conditions of chronic healing where higher shear stresses have been shown to reduce intimal lesion formation.

PASSIVE IMMUNIZATION OF PIGTAILED MACAQUES PREVENTS ROTAVIRUS INFECTION (0340)

NPRC UNIT : RESEARCH RESOURCES

% NPRC $: 0.500 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
JIANG, BAOMING	DVM, PHD	A	INFECTIOUS DISEASE	CENTERS FOR DISEASE CONTROL, GA USA-
	MD, PHD	A	VIRAL & RICKETTSIAL DISEASES	CENTERS FOR DISEASE CONTROL, GA USA
	DVM	C	RESEARCH RESOURCES	
	PHD	A	VIRAL & RICKETTSIAL DISEASES	CENTERS FOR DISEASE CONTROL, GA USA

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

ABSTRACT

Experimental infection of macaques with the simian rotavirus YK -1 is a useful model for studies of infectivity, immunity and vaccine effectiveness . The design of a rotavirus vaccine would be helped if the basis of the protective immunity could be elucidated . Passive immunization offers a means to determine the relative role of antibodies in protection against infection . We have evaluated the protective role of circulating antibodies in a nonhuman primate model of rotavirus infection by passive transfer of immune sera . Pooled serum with rotavirus -specific IgG titers that were either high (1:10,000) or intermediate (1:300) were infused intravenously into na ïve pigtailed macaques (ages 4-6 months). Control animals were infused with pooled serum with rotavirus -specific IgG, IgA, and IgM titers 1:25. Rotavirus -specific IgG could be detected in the serum at 18 hours in all animals infused with antibody -containing serum and fecal IgG titers could be detected only in animals given high -titer pooled sera . When orally challenged with 106 ffu of YK-1 at 18 hours after serum transfer, control animals shed virus 1-3 days after challenge and continued to shed virus at high titers for 6-8 days, whereas passively immunized macaques did not shed virus or shed virus for 1-3 days at low titer days after challenge . Thus passively transferred antibodies can suppress or delay viral infection in rotavirus challenged pigtailed macaques . These findings will have important implications for the design and testing of rotavirus vaccines .

PREVALENCE OF ROTAVIRUS AND NOROVIRUS ANTIBODIES IN NHP (0341)

NPRC UNIT : RESEARCH RESOURCES

%NPRC $: 0.500%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
JIANG, BAOMING	DVM, PHD	A	INFECTIOUS DISEASE	CENTERS FOR DISEASE CONTROL, GA USA
	BS	A	VIRAL & RICKETTSIAL DISEASES	CDC, GA USA
	MD, PHD	A	VIRAL & RICKETTSIAL DISEASES	CENTERS FOR DISEASE CONTROL, GA USA
	DVM	C	RESEARCH RESOURCES	
	PHD	A	VIRAL & RICKETTSIAL DISEASES	CDC, GA USA

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

ABSTRACT

Rotavirus and norovirus are associated with a substantial burden of diarrheal disease in humans and some animals, but their role in acute viral gastroenteritis in nonhuman primates has not been established . We examined sera from 5 species of Old and New World monkeys and chimpanzees for antibodies to rotavirus and norovirus by enzyme immunoassays using RRV and 3 recombinant human norovirus capsid proteins, respectively . Most (88%) of the 3 Old World monkey species (mangabey, pigtail, and rhesus) and apes were seropositive for rotavirus . Norovirus antibody was prevalent in the 3 monkey species, with 53% (44/83) and 58% (48/83) seropositive for GI and GII strains, respectively . Eleven (92%) of the 12 chimpanzees tested were seropositive for GI norovirus . Given the high rate of infection with both viruses, the role of these agents in causing acute gastroenteritis in nonhuman primates and the value of these animals as models of infection and disease need to be assessed .

ROTAVIRUS-SPECIFIC ANTIBODY RESPONSES IN INFECTED PIGTAILED MACAQUES (0342)

NPRC UNIT : RESEARCH RESOURCES

% NPRC $: 0.500 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
JIANG, BAOMING	DVM, PHD	A	INFECTIOUS DISEASE	CENTERS FOR DISEASE CONTROL, GA USA
	MD, PHD	A	VIRAL & RICKETTSIAL DISEASES	CENTERS FOR DISEASE CONTROL, GA USA
	DVM	C	RESEARCH RESOURCES	
	PHD	A	VIRAL & RICKETTSIAL DISEASES	CENTERS FOR DISEASE CONTROL, GA USA
	DVM	A	VIRAL & RICKETTSIAL DISEASES	CDC, GA USA

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

ABSTRACT

To further understand the immunity of rotavirus disease and improve testing of candidate rotavirus vaccines, we have developed a nonhuman primate model of rotavirus infection . Oral inoculation of sero -negative pigtailed macaques with the simian rotavirus YK -1 resulted in fecal shedding of rotavirus antigen up to 10 days, while sero-positive pigtailed macaques showed a marked reduction in fecal antigen shedding after challenge . Rotavirus -specific antibody responses to YK -1 were evaluated in both sero -negative and sero -positive macaques . Serum and fecal antibodies were detected by an immunoassay and an ELISPOT assay was used to enumerate isotype -specific antibody -secreting cells (ASC) from PBMC. Similar to that seen in primary rotavirus infections, sero-negative macaques developed an early YK -1-specific serum IgM and IgM -ASC response, immediately followed by YK -1-specific IgA -ASC and a fecal and serum IgA response . Rotavirus -specific serum-IgG and IgG-ASC responses in sero -negative macaques appeared by 2-3 weeks and peaked 4 weeks after challenge . Similar to that seen in a secondary rotavirus exposure, an immediate rise in YK -1-specific fecal IgA, serum-IgG and IgA and IgG-ASC could be detected in the sero -positive challenged macaques, with little or no fecal IgG, IgA -ASC, or IgM responses . These results indicate that the viral shedding patterns and rotavirus -specific antibody responses of YK-1 inoculated pigtailed macaques are dependent on the immune status of the monkey prior to challenge .

EFFECT OF HIS PROTEASE INHIBITORS ON ENDOTHELIAL DYSFUNCTION NHP CORE (0294)

NPRC UNIT : RESEARCH RESOURCES

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
MCCLURE, HAROLD M	DVM	C	RESEARCH RESOURCES	
C Names	MD, PHD	A	SURGERY	
	PHD	A	PEDIATRICS	VA MEDICAL CENTER, GA USA
	PHD	A	VACCINE RESEARCH CENTER	
3	PHD	A		

AXIS I CODES: 1A, 7B, 13 **AXIS II CODES** 31, 50B, 66, 74F, 77

ABSTRACT

These studies are designed to improve our understanding of and eventual prevention of vascular complications and abnormalities of lipid metabolism in HIV -1 infected individuals associated with treatment with protease inhibitors . Studies will seek to define the role of HIV protease inhibitors in endothelium -dependent vasorelaxation and endothelial morphology; to determine the effect of protease inhibitors on NO production, eNOS activity and expression; to determine the effect of protease inhibitors on superoxide anion (O2-) production, NADH oxidase activity, and peroxynitrite formation; and to develop strategies to prevent protease inhibitor -associated endothelial dysfunction . These studies will be done in the rhesus macaque model, either infected or not infected with SIV or SHIV and treated or untreated with a protease inhibitor . Baseline lipid profiles, hemograms and lymphocyte subset values have been established for an initial group of animals . Six rhesus macaques were subsequently placed on treatment with Kaletra (1 capsule twice daily given orally in food or juice). Drug levels in the blood of these animals are not yet available . Monthly blood chemistry determinations in these animals have shown no significant changes in cholesterol or triglyceride values during six months of treatment . In preparation for in vitro studies of vascular tissue from animals treated with protease inhibitors, aortas and coronary vessels from non -treated animals (either SIV infected or uninfected) were provided for evaluation .

SHIV MACAQUE MODEL OF ORAL IMMUNIZATION AGAINST SEXUALLY TRANSMITTED HIV (0293)

NPRC UNIT : RESEARCH RESOURCES

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
NARAYAN, OPENDRA	DVM, PHD	A	MICROBIOLOGY	UNIVERSITY OF KANSAS, KS USA
[name]	DVM	C	RESEARCH RESOURCES	

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

ABSTRACT

Eighteen macaques that were immunized with a live SHIV vaccine were challenged at various periods after immunization . Six were challenged 6 months after immunization and were observed for 5 years. Six were challenged 1-* years after immunization and were observed for 3 years, and the remaining 6, challenged at 3 years after immunization and were observed for 1 year. The first group was protected for 4 years but at year 5 one succumbed to the challenge virus which had remained dormant in lymph nodes for the previous 5 years. In the remainder of this first group, continuous protection correlated with persistence of the vaccine DNA in lymph nodes . Animals in group 2 also controlled challenge virus replication for more than 2 years, but 2 of the 6 succumbed to AIDS in year 3. Of the 6 animals challenged 3 years after immunization, all developed high virus burdens typical of infection in animals without immunity . These studies thus showed that although a live vaccine can confer protection for several years, challenge virus always persists and could become activated after prolonged periods of dormancy . The longer the period between immunization and challenge, the greater the chances that vaccine induced protection would wane.

SAFETY AND EFFICACY OF SHIV VACCINE IN MACAQUES (0343)

NPRC UNIT : RESEARCH RESOURCES

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
NARAYAN, OPENDRA	DVM, PHD	A	MICROBIOLOGY	UNIVERSITY OF KANSAS, KS USA

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

ABSTRACT

Two types of studies were conducted . First, studies were directed to mechanisms regulating neuropathogenesis of SHIVKU infection in macaques . This is a virus that invades the brain during the viremic phase of infection and remains dormant until the animal becomes immunosuppressed as a result of the highly productive replication of the virus in CD 4 T lymphocytes . Productive virus replication in the brain was confined to macrophages and neuropathological changes correlated with expression of the chemokine CXCL 10 that was toxic to neurons (Sui et al) and IL-4 that promoted virus replication in the macrophages (Buch et al). Second, continuation of studies on efficacy of a live vaccine showed that immunity induced by the live vaccine depended on persistence of the vaccine virus, and that following elimination of the virus, the animal became susceptible to fatal disease by pathogenic challenge viruses . The live virus apparently failed to induce memory immune responses . The duration of protection by the live vaccine could be extended by re -immunization with the live vaccine . This re-established the persistent infection and the concomitant protective immunity . The persistent infection was characterized by dormant infection and virus replication could only be reactivated by immunosuppression of the immunized animals with antibodies against CD 8 lymphocytes . Following recovery of the CD 8 cell count, replication of the vaccine virus was again suppressed .

INFANT IMMUNOPROPHYLAXIS AGAINST A PRIMATE LENTIVIRUS (0296)

NPRC UNIT : RESEARCH RESOURCES

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
RUPRECHT, RUTH M	MD, PHD	A	RESEARCH RESOURCES	DANA FARBER CANCER INSTITUTE, MA USA
[name 2	DVM	C	RESEARCH RESOURCES	

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

ABSTRACT

The overall goal of this project is to develop passive immunization with human neutralizing monoclonal antibodies (nmAbs) against oral HIV transmission through breast feeding in a primate model .

We have demonstrated safety and efficacy of intramuscular (i.m.) nmAb treatment and showed potent cross -clade neutralization in cultured peripheral blood mononuclear cells (PBMC); primary African HIV clade A and D isolates were effectively neutralized by a quadruple combination of anti -HIV clade B nmAbs (Kitabwalla et al ., 2003). Aim #1 has been successfully completed, using SHIV 89.6P as challenge virus .

Eight neonatal rhesus macaques were orally challenged with 15 50% animal infectious doses (AID 50) of pathogenic SHIV89.6P. Twenty -four hours post -inoculation (p.i.), four animals were given mAbs 2F5, 4E10, and 2G12 (i.m at 40 mg/kg). Treatment was repeated 8 days later . All four control infants, which were left untreated, were heavily infected by week 1 p.i. and lost their CD 4+ T cells by week 2. All 4 controls were sacrificed by 14 weeks of age because of AIDS. In contrast, mAb -treated monkeys had delayed peaks of viremia and lower plasma virus levels than the controls . None of the treated infants had CD 4+ T-cell depletion, these animals remained healthy during 6-months of follow -up. These results show that protection from virus -induced disease was still provided even when mAb treatment was given 24 h p.i.

MOLECULAR EVOLUTION OF MULTIPLY DELETED SIV IN VIVO (0297)

NPRC UNIT : RESEARCH RESOURCES

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
RUPRECHT, RUTH M	MD, PHD	A	RESEARCH RESOURCES	DANA FARBER CANCER INSTITUTE, MA USA
E name JI	DVM	C	RESEARCH RESOURCES	

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

ABSTRACT

We continue to focus on SIV 3, a live attenuated SIV mutant with deletions in nef, vpr and in the negative regulatory element (NRE) of the long terminal repeat (LTR). SIV 3 was previously shown to cause AIDS in monkeys vaccinated as infants . Here, we demonstrated that SIV 3 is pathogenic in most adults, given enough time . Eleven macaques vaccinated as adults with this virus were followed for up to 6.8 years; signs of immune dysregulation were present in all, such as persistently inverted CD 4+/CD8+ T-cell ratios (100%), recurrent viremia (64%), and CD4+ T-cell depletion (53%). Two adult vaccinees (18%) subsequently developed AIDS . Given our long -term observation with this live attenuated virus, mass vaccination of humans with similarly constructed live attenuated HIV vaccines, recently suggested for countries with high HIV -1 transmission rates, seems contraindicated .

We have also studied SHIV -vpu+, which encodes HIV -IIIB env and which was thought originally to be non-pathogenic in rhesus monkeys . Nevertheless, lethal AIDS developed in a neonatally infected monkey; during its disease progression, we isolated virus, which evolved despite high neutralizing antibody titers . Late viruses still used CXCR4, but in contrast to parental virus, replicated in macrophages . DNA sequence analysis revealed three new potential glycosylation sites in gp 120; another two were lost . Strikingly similar mutations had been detected in a laboratory worker who progressed to AIDS after accidental HIV -IIIB infection and in pig -tailed macaques after rapid passage of chimeric viruses encoding IIIB env . Thus, HIV-IIIB env evolved similarly in three different species, and we postulate that common evolutionary pressures led to the outgrowth of more aggressive viral variants .

The last project we have performed under this grant involves the generation of novel assays for rhesus monkey cytokines and -chemokines . These molecules are important mediators of the immune system and are expressed in many infectious diseases .

VACCINATION AGAINST INTRAPARTUM HIV-1 CLADE C TRANSMISSION (0298)

NPRC UNIT : RESEARCH RESOURCES

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
RUPRECHT, RUTH M	MD, PHD	A	RESEARCH RESOURCES	DANA FARBER CANCER INSTITUTE, MA USA
[name]	DVM	C	RESEARCH RESOURCES	

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

ABSTRACT

This Program Project seeks to develop combination immunoprophylaxis against maternal HIV clade C transmission, using a cocktail of human nmAbs and DNA prime /protein boost vaccination . Project 1 will isolate potent human nmAbs from HIV clade C-infected individuals . Project 2 will define combinations of human nmAbs that synergistically neutralize primary HIV clade C isolates in vitro and protect infant macaques against oral challenge with a SHIV that encodes env of an HIV clade C isolate . Lastly, Project 3 will develop DNA prime /protein boost vaccination against the same SHIV . In years 04 and 05, Projects 2 and 3 will test a combined approach involving passive immunoprophylaxis with human nmAbs and active vaccination with DNA priming /protein boosts in infant macaques.

The Projects and Cores continue to work closely together . Significant progress has been made . Primary HIV clade C strains have been isolated from Zambian infants with documented recent infection . Several env genes have been cloned, sequenced, assigned to clade C, and used to construct different SHIV strains . Two such strains, SHIV -1084 i and SHIV-1157 i, replicated in rhesus monkey PBMC and were rapidly passaged in vivo . Large stocks of both passaged viruses have been generated . SHIV-1157 ip has been titrated orally in neonatal rhesus monkeys . The first passive immunization study has been conducted with a quadruple combination of anti -HIV clade B nmAbs; the data showed potent cross -clade protection in neonates .

DNA vectors encoding codon -optimized gag -protease, env, and tat have been generated and tested for expression in vitro . All three vectors were immunogenic in mice .

This Program Project has also supported follow -up studies in rhesus macaques previously vaccinated with a DNA prime/protein boost approach . These animals were used to study the role of CD 8+ T cells in controlling viremia and disease during chronic, low -level SHIV infection . The results suggest that in the absence of CD 8+ T cells, nAb act as an effective second line of defense by limiting the spread of infectious virus to new target cells and the loss of CD4+ T cells.

MECHANISMS OF ORAL SIV TRANSMISSION (0299)

NPRC UNIT : RESEARCH RESOURCES

% NPRC $: 0.880 % **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
RUPRECHT, RUTH M	MD, PHD	A	RESEARCH RESOURCES	DANA FARBER CANCER INSTITUTE, MA USA
C name J	DVM	C	RESEARCH RESOURCES	

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

ABSTRACT

In the past year, we reported the unexpected finding that older rhesus monkey infants were more susceptible to oral challenge with the dual -tropic SHIV 89.6P than newborn monkeys . We are now testing whether the same finding holds true for oral challenge with a SHIV strain that encodes the envelope gene of a primary HIV that uses CCR 5 as the sole chemokine co -receptor. A titration in newborn rhesus monkeys will be run in parallel with one in older animals; we are now seeking to determine whether older animals differ in their susceptibility to oral transmission of this virus . We plan to study the mucosal tissues of the gastrointestinal tract for age -related differences in chemokine co -receptor expression .

We seek to examine host factors that lead to age -specific differences in susceptibility to oral immunodeficiency virus transmission . A better understanding of such factors may have the potential to give important new information for minimizing oral virus transmission .

ATTENUATED RECOMBINANT LISTERIA AS ORAL AIDS VACCINE (0344)

NPRC UNIT : RESEARCH RESOURCES

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
RUPRECHT, RUTH M	MD, PHD	A	RESEARCH RESOURCES	DANA FARBER CANCER INSTITUTE, MA USA
[illegible]	DVM	C	RESEARCH RESOURCES	

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

ABSTRACT

We seek to develop recombinant Lmdd, a vector generated from Listeria monocytogenes (Lm) by deleting two genes essential for the biosynthesis of the unnatural D -alanine (D-ala), as an oral AIDS vaccine . Without exogenous D-ala, the resulting vector, termed Lmdd, is unable to form cell walls or replicate . The first vaccine candidate, Lmdd-gag, was generated by stably inserting HIV gag into the Lmdd chromosome . In mice, Lmdd-gag, co-administered with D -ala, elicited long -lived CD 8+ T-cell responses . In rhesus monkeys, wild -type Lm closely mimics infection and pathogenesis in humans (stillbirths, sepsis), who get infected mostly via contaminated food . Because of this natural oral route of Lm infection, Lmdd vectors hold promise as oral AIDS vaccines . In a pilot study, we administered Lmdd -gag orally to two monkeys with short D -ala courses; one monkey was boosted orally and developed cytotoxic T -lymphocyte (CTL) responses against HIV Gag, indicating that this candidate vaccine is immunogenic after oral administration . The other monkey developed strong antibody responses after i .m boosting . These primate studies represent crucial steps towards developing recombinant Lmdd vectors for clinical trials as oral AIDS vaccine candidates that could be administered easily, even in the developing world .

DETERMINATION OF BIOMARKERS OF INCREASED SUSCEPTIBILITY TO FOODBORNE LISTERIOSIS (0301)

NPRC UNIT : RESEARCH RESOURCES

% NPRC $: 0.885 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
SMITH, MARY ALICE	PHD	A	BIOLOGY	UNIVERSITY OF GEORGIA, GA USA
[illegible]	DVM	C	RESEARCH RESOURCES	-

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

ABSTRACT

Perinatal listeriosis and pregnancy loss due to listeriosis is thought to be partially due to increased susceptibility to infection as a result of immunosuppression in the mother . The objective of this project is to identify and quantify markers of exposure and resistance to Listeria monocytogenes in non -pregnant animals and compare those endpoints to pregnant animals exposed to the same strain and concentration . This study will extend the on -going effort to determine a dose response model for exposure to Listeria monocytogenes using the pregnant rhesus monkey as an animal model for humans . Quantitative information is obtained to determine the effect of pregnancy on markers of resistance and exposure to Listeria monocytogenes .by comparing the non -pregnant with the pregnant animals. Listeria monocytogenes is administered to non -pregnant female rhesus monkeys at a concentration of 109 cfu in sterile whipping cream . Fecal and blood samples are collected . Fecal samples are analyzed for shedding of Listeria monocytogenes and blood samples are analyzed for immune parameters including antibody to Listeria monocytogenes, peripheral blood lymphocyte surface markers, and proliferative responses of peripheral blood lymphocytes to antigens and mitogens . Results indicate that 4 of 10 animals responded immunologically to L . monocytogenes antigens, as measured by antibody response and T cell proliferation . T cells from responding animals were used to produce IL -2 dependant cell lines . One of these lines has been found to be CD 8 positive and exhibits antigen -dependant lysis of autologous target cells .

ANALYSIS OF THYMIC FUNCTION DURING SIV INFECTION (0086)

NPRC UNIT : RESEARCH RESOURCES

%NPRC $: 0.800% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
SODORA, DONALD L	PHD	A	INTERNAL MEDICINE	UNIVERSITY OF TEXAS, TX USA
[illegible]	DVM	C	RESEARCH RESOURCES	

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

ABSTRACT

Elevated levels of interleukin (IL)-7 have been correlated with various T -cell depletion conditions including HIV infection and suggested as an indicator of HIV disease progression (AIDS and death). Our studies undertaking an assessment of the pathogenic simian immunodeficiency virus (SIVmac239) infection in rhesus macaques (Macaca mulatta) demonstrated a clear association between a significant elevation in IL -7 levels and disease progression . In five macaques that progressed to simian AIDS and death, elevated IL -7 levels were unable to restore T -cell homeostasis . In-contrast, increased IL -7 levels were followed by relatively high and stable T -cell numbers in the SIV-infected macaques with a slow progressing phenotype . Further, studies in sooty mangabeys that do not progress to simian AIDS and maintain stable T -cell numbers despite high levels of viral replication support the importance of IL-7 and T-cell homeostasis in disease progression . These data suggest that during pathogenic SIV infection with high viral replication, elevated IL -7 levels are unable to recover T -cell homeostasis thereby leading to disease progression . The utility of IL -7 as a potential immunotherapeutic to improve HIV /SIV related T-cell depletion may therefore depend on controlling the pathogenic effects of viral replication prior to the IL -7 administration .

Recent studies have focused on the role of the T -cell homeostasis and IL -7 on the absence of disease progression in the sooty mangabeys (Cercocebus atys).

REPLICATION DEFECTIVE HIV VACCINE (0079)

NPRC UNIT : RESEARCH RESOURCES

%NPRC $: 0.921 % **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
TUNG, FRANK	PHD	A	RESEARCH RESOURCES	GENECURE, GA USA
C name 2	DVM	C	RESEARCH RESOURCES	

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

ABSTRACT

Live attenuated simian immunodeficiency virus (SIV) has elicited protective immunity in rhesus monkeys . This animal model provides evidence that protective immunity can be elicited by vaccination . In the vaccinated animals, immune responses may be elicited due to endogenous expression of native SIV proteins and /or prolonged antigen presentation in vivo . However, this vaccine approach is hindered by safety concerns that a live attenuated HIV -1 may cause disease in humans .

To increase safety and maintain immunogenicity of HIV -1 vaccines, we developed a single -cycle HIV-1 as a vaccine candidate to test if protective immunity can be elicited in vaccinated animals . First, we investigated whether the single -cycle HIV can elicit immune responses (cellular and /or humoral) in rhesus monkeys . Second, we studied whether co -expression of a cytokine gene can enhance cell -mediated immune response . The immune responses are monitored and compared between these two vaccine candidates . Third, we studied the anti -envelope immunity in vaccinated animals after challenge with SHIV . These studies provide important information for AIDS vaccine development .

ENDOCRINE CORE LAB (0360)

NPRC UNIT : RESEARCH RESOURCES

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
WILSON, MARK E	PHD	C	PSYCHOBIOLOGY	
		A		GA STATE UNIVERSITY, GA USA
	PHD	A	RESEACH RESOURCES	GA INSTITUTE OF TECHNOLOGY, GA USA
	DVM, PHD	A	NEUROSCIENCE	
		A		USCH RES. & DEV. CENTER, SC USA
		A		GA STATE UNIVERSITY, GA USA
	PHD	A	PSYCHIATRY	
		A		WAKE FOREST UNIVERSITY, NC USA
		A		WAKE FOREST UNIVERSITY, NC USA
		A	SOUTHERN RESEARCH INSTITUTE	UNIVERSITY OF ALABAMA, AL USA
	PHD	A		WAKE FOREST UNIVERSITY, NC USA
		A		MEDICAL COLLEGE OF GA, GA USA
		A		MAYO CLINIA, MN USA
	PHD	A		GA STATE UNIVERSITY, GA USA
	PHD	A		WAKE FOREST UNIVERSITY, NC USA
	PHD	C	NEUROSCIENCE	
		A		GA STATE UNIVERSITY, GA USA
		A		UNIVERSITY OF FLORIDA, FL USA
	PHD	A	PSYCHOLOGY	UNIVERSITY OF CHICAGO, IL USA
		A		UNIVERSITY OF PITTSBURGH MEDICAL CENTER , PA USA
	MD	A		VA MED CENTER, GA USA
		A		NATIONAL JEWISH CENTER, CO USA
	PHD	G	CNTR BEHAVIORAL NEUROSCIENCE	
	PHD	A	PSYCHOBIOLOGY	
	PHD	A	PSYSIOLOGY	
		A	PATHOLOGY	
	PHD	A	CENTER BEHAVIORAL SCIENCES	
		A		HARVARD MEDICAL SCHOOL, MA USA
		A	DENTAL SCHOOL	UNIVERSITY OF MD, MD USA
	PHD	C	PSYCHOBIOLOGY	
		A		SIMON FRASER UNIVERSITY, BC, CANADA
	PHD	A	GENETICS	
	PHD	C	PSYCHOBIOLOGY	

C	J	A	CLAREMONT GRADUATE UNIVERSITY, CA USA
C	J	A	MEDICINE

AXIS I CODES: 15, 17 **AXIS II CODES** 31

ABSTRACT

The Endocrine Core Lab continues to provide steroid and protein hormone assay services for investigators . Investigators who use lab services are located throughout the country, including Emory (46%), other academic institutions (46%), governmental labs (6%) and private industry (2%). During the last year the lab processed 27,354 samples in support of research protocols . Costs incurred in the performance of these assays are recovered using a charge back to all users .

VACCINE INDUCED IMMUNITY IN THE YOUNG AND AGED (0349)

NPRC UNIT : VACCINE RESEARCH CENTER

% NPRC $: 0.500 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
AHMED, RAFI		A	VACCINE RESEARCH CENTER	
[illegible]	PHD	A	VACCINE RESEARCH CENTER	
	MD, PHD	A	VACCINE RESEARCH CENTER	
[illegible]	PHD	A	VACCINE RESEARCH CENTER	
	PHD	A	VACCINE RESEARCH CENTER	
	PHD	A	VACCINE RESEARCH CENTER	
	MD	A	VACCINE RESEARCH CENTER	
[illegible]	PHD	A	VACCINE RESEARCH CENTER	

AXIS I CODES: 1D **AXIS II CODES** 30, 64, 66, 91

ABSTRACT

The long-term goals of this U 19 Application are three fold : One, to study the human immune response to a vaccine in it's entirety; starting from the innate responses, to the peak effector T and B cell responses, to the development and maintenance of immunological memory . Two, to understand how a successful vaccine works and to use this knowledge for designing strategies for enhancing vaccine efficacy . Three, to understand the cellular basis of immune senescence and develop strategies for improving responses of the elderly to vaccination . Also, a major emphasis of this proposal is on using genomics and proteomics to define the molecular signatures of innate and adaptive responses after vaccination . In fact, our overarching hypothesis is that there will clearly be molecular and cellular signatures of "good" and "bad" vaccines and that identifying these signatures will allow us to manipulate the immune response to either enhance immunity in the case of vaccines and immune therapy, or to decrease it for autoimmunity, transplantation and gene therapy . To achieve our goals we have put together a highly interactive and integrated Application consisting of three research projects : 1. Immunological memory to vaccination; 2. Modulating vaccine responses with dendritic cells and TLRs; and 3. Immune senescence. These research projects are closely tied to the Technical Development Components that consist of : 1. Molecular signatures of immune responses to vaccination ; 2. Human monoclonal antibodies to category A pathogens ; and 3. Development of novel T cell assays . This overall research effort will be supported by an Administrative /Statistical Core and a Clinical Research Core. In addition, there is a program for the education and training of scientists who wish to do research in human immunology and a Review Committee for evaluating and funding high risk /high impact projects in human immunology .

SE REGIONAL CENTER FOR EXCELLENCE FOR EMERGING INFECTIONS & BIODEFENSE (0351)

NPRC UNIT : VACCINE RESEARCH CENTER

%NPRC $: 0.500 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
AHMED, RAFI		A	VACCINE RESEARCH CENTER	
	PHD	A	VACCINE RESEARCH CENTER	
	MD, PHD	A	VACCINE RESEARCH CENTER	
	PHD	G	VACCINE RESEARCH CENTER	
	PHD	A	VACCINE RESEARCH CENTER	
	PHD	A	VACCINE RESEARCH CENTER	
		A		BOSTON UNIVERSITY SCHOOL OF MEDICINE, MA USA
	PHD	C	NEUROSCIENCE	

AXIS I CODES: 1A **AXIS II CODES** 30, 64, 66, 91

ABSTRACT

Concerns about the potential use of variola as an agent of bioterrorism have recently resulted in decisions to re-initiate smallpox vaccination programs . However, the currently available vaccinia virus (VV)-based smallpox vaccines (eg, Dryvax) are associated with high rates of adverse reactions and are not safe for use in immunodeficient individuals or those with a variety of common medical conditions . As such, development of new smallpox vaccines that are substantially safer, but of equivalent or better immunogenic potency than the current VV vaccine preparations is imperative . While certain attenuated strains of VV, especially modified vaccinia Ankara (MVA), have highly desirable safety features and impressive immunogenicity when used to express heterologous antigens, a variety of data suggest that MVA may be an insufficiently immunogenic vaccine to reliably engender protective responses against variola or other highly pathogenic orthopoxviruses . However, we have recently discovered important aspects of the nature of how both replication -competent VV and replication -restricted MVA interact with host dendritic cells (DCs) that suggest promising approaches to increase the protective potential of MVA as a smallpox vaccine . The overall goal of the proposal is to modify the currently available strain of MVA, so that novel vaccine variants are derived with preserved safety profiles, but with substantially enhanced abilities to raise durable, high level cellular and humoral immune responses that are cross -reactive with major virulent orthopoxviruses . To accomplish this goal, we propose to (1) delete from the MVA genome, residual viral immune evasion genes; (2) express within recombinant MVAs specific cytokines and chemokines that promote DC recruitment and activation; and (3) express specific late viral structural gene products from early vaccinia promoters in recombinant MVAs to facilitate induction of increased host protective immune responses against key orthopoxvirus antigens

PORPHYRINS AS MICROBICIDES FOR PREVENTION OF STDS/HIV (0271)

NPRC UNIT : VACCINE RESEARCH CENTER

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
COMPANS, RICHARD W	PHD	A	MICROBIOLOGY & IMMUNOLOGY	
Cname_1	PHD	A	VACCINE RESEARCH CENTER	

AXIS I CODES: 7D **AXIS II CODES** 31, 64, 66, 91

ABSTRACT

We have evaluated the anti -HIV activity of a series of natural and synthetic porphyrins and phthalocyanines to identify compounds that could potentially be used as microbicides to provide a defense against infection by sexually transmittted virus . For assays we used an epithelial HeLa -CD4 cell line with an integrated LTR - -galactosidase gene . For structure -activity analysis, we divided the porphyrins tested into three classes : I) natural porphyrins, II) metallo-TPPS 4 derivatives, and III) sulfonated tetraarylporphyrin derivatives . None of the natural porphyrins studied reduced infection by more than 80% at a concentration of 5 g/ml in these assays . Some metal chelates of tetraphenylporphyrin tetrasulfonate (TPPS 4) were more active and a number of sulfonated tetraaryl derivatives showed significantly higher activity . Some of the most active compounds were the sulfonated tetranaphthyl porphyrin (TNapPS), sulfonated tetraanthracenyl porphyrin (TanthPS), sulfonated 2,6-difluoroTPP [TPP (2,6-F2)S] and its copper chelate [TPP (2,6-F2)S,Cu], reducing infection by 99, 96, 94, and 96%, respectively . Sulfonated phthalocyanine itself (PcS), as well as its copper, nickel and vanadyl chelates, were the most effective in blocking viral infection . Sulfonated phthalocyanines bearing metals (aluminum, cobalt, chromium, iron, silicon and zinc) were less effective in blocking HIV infection and also less effective at inhibiting fusion . Active compounds also tended to block binding of gp 120 to CD4. Our observations indicate that at least some of these compounds are virucidal; i .e., that they render the virus noninfectious . The active compounds were found to inhibit binding of the HIV-1 gp 120 to CD4, and also completely inhibited the ability of Env proteins expressed from recombinant vectors to induce cell fusion with receptor -bearing target cells . These results support the conclusion that modified porphyrins and phthalocyanines exhibit substantial activity against HIV .

NEW LIVE VIRAL VECTORS AS CANDIDATE AIDS VACCINES (0007)

NPRC UNIT : VACCINE RESEARCH CENTER

%NPRC $: 0.600% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
FEINBERG, MARK B	MD, PHD	A	VACCINE RESEARCH CENTER	
[Manager	MD	A	VACCINE RESEARCH CENTER	
]	PHD	A	VACCINE RESEARCH CENTER	

AXIS I CODES: 1D, 7B, 19 **AXIS II CODES** 31, 64, 66, 91

ABSTRACT

This multi -disciplinary, multi -national HIVRAD proposal uses the favorable attributes of currently available vaccines to explore immunization strategies against HIV . The measles virus (MV), yellow virus (YFV), modified vaccinia virus Ankara (MVA) and varicella zooster virus (VZV) vaccines will be adapted as vectors for the expression of SIV and HIV, antigens, and characterized for their ability to elicit durable and protective immune responses in experimental animals . Project 1 (Enhancing the Magnitude and Longevity of Vaccine -Induced Immune Responses) at Emory University utilizes recent insights into antigen processing and presentation and the processes of initiation and maintenance of immune responses to design more effective HIV immunogens . Recombinant MVA-HIV vectors will be used to probe the determinants of immunologic memory . Project 2 (Recombinant YFV as a Candidate AIDS Vaccine), at the University of California, adapts and optimizes the YFV vaccine for the expression of HIV and SIV antigens . Project 3 (Recombinant Measles Virus as a Candidate AIDS Vaccine), at the University of Zurich and the Institute Pasteur adapts attenuated MV vaccines as vectors to express HIV and SIV antigens . An AffiliatedProject will explore the ability of recombinant VZVs that express HIV antigens to elicit favorable, long -lasting immune responses in non -human primates. An immunology Core at Emory University will analyze the immunogenicity of recombinant HIV /SIV vaccines in non -human primates, using quantitative, state -of-the-art assays of cellular immune responses . An Animal Trials Core at the Yerkes Region Primate Research Center and Emory Vaccine Center will oversee the care of non -human primates participating in vaccine studies and conduct virologic analyses of vaccine vector replication, and SHIV virus infection and levels of replication in experimentally challenged animals . An Administrative and Data Management Core coordinates the HIVRAD projects and facilitate communication of ideas and experimental results between investigators .

T LYMPHOCYTE POPULATION DYNAMICS AND AIDS PATHOGENESIS (0008)

NPRC UNIT : VACCINE RESEARCH CENTER

% NPRC $: 0.600 % **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
FEINBERG, MARK B	MD, PHD	A	VACCINE RESEARCH CENTER	

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

ABSTRACT

The project studies T cell population dynamics in a series of SIV non -infected and SIV infected primates to include both AIDS sensitive rhesus macaques and AIDS resistant sooty mangabeys (SMMs). A primary goal will be to assess the validity of current methodologies used to study T cell turnover by direct comparison of T cell turnover rates generated using stable isotope /mass spectrometric analysis (SI/MS) of deuterated [6,6-2H2] glucose incorporation, BrdU labeling and Ki 67 expression . Furthermore, comparison of T cell turnover rates in peripheral blood vs . secondary lymphoid tissues will be measured in the presence and absence of retroviral infection .

NOVEL METHOD TO EVALUATE HIV-SPECIFIC CTL RESPONSES (0194)

NPRC UNIT : VACCINE RESEARCH CENTER

% NPRC $: 0.600 % **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
FEINBERG, MARK B	MD, PHD	A	VACCINE RESEARCH CENTER	
E name 3	MD	A	VACCINE RESEARCH CENTER	

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

ABSTRACT

Development of a safe and effective HIV vaccine remains a critically important, but elusive goal . Progress towards an effective HIV vaccine will likely require a better understanding of immune effector mechanisms that can control or prevent HIV infection, as well as the derivation of immunization strategies that are significantly more potent than those currently available . The cytotoxic T cell (TCL) response is believed to play an essential role in eliminating HIV-infected cells and controlling the levels of virus replication in infected persons, and strategies for the development of HIV vaccines are increasingly focused on elicitation of strong and durable anti -HIV CTL responses . Unfortunately, newer methods to quantify CD 8 T cell responses in HIV -infected persons (e.g., MHC tetramers or cytokine detection methods) do not measure lytic function, and thus may not reveal key functional differences that may exist within the population of HIV -specific CD 8 T cells. We have developed a new non -radioactive flow cytometry -based CTL assay based on caspase -mediated activation of fluorogenic substrates that is more sensitive, more convenient, and faster than available CTL assays . To refine this assay and evaluate its utility in HIV vaccine studies, particularly as conducted in developing countries, we are working to (1) to optimize and validate simple and rapid flow cytometric CTL assays, (2) to evaluate methods to optimize the detection of memory CTL responses through short term ex vivo treatment with costimulatory activators or cytokines, (3) investigate the ability of anti -HIV CTLs to kill relevant primary target cells of different hematopoetic lineages and (4) to transfer the technology of flow -cytometry based CTL assays to laboratories in developing countries where the AIDS epidemic is most acute and where major efficacy trials of candidate HIV vaccines will be conducted .

CELLULAR IMMUNE RESPONSES IN AIDS PATHOGENESIS (0217)

NPRC UNIT : VACCINE RESEARCH CENTER

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
FEINBERG, MARK B	MD, PHD	A	VACCINE RESEARCH CENTER	
[illegible]	PHD	A	VACCINE RESEARCH CENTER	

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

ABSTRACT

Sooty mangabey monkeys (SMs) naturally infected with SIV maintain normal levels of CD 4 T lymphocytes and do not develop AIDS despite chronic high level virus replication, short longevity of infected CD 4+ T cells and increased rates of CD 4+ T cell turnover . Interestingly, despite otherwise intact immune function, SIV -infected SMMs manifest limited or absent anti -SIV specific cytotoxic T cell (CTL) responses . We have further shown that SIV-infected SMMs possess preserved bone marrow, thymic and peripheral lymphoid sources for T lymphocyte production, and manifest levels of immune activation and apoptosis far lower than those seen in pathogenic infections with SIV in rhesus macaques (RMs) and with HIV in humans . These data suggest that the direct consequences of high level virus replication alone cannot account for the progressive CD 4+ T cell depletion leading to AIDS . Rather, SIV-infected SMs may be spared, by their failure to mount significant antiviral immune responses, much of the bystander damage seen in pathogenic primate lentivirus infections that contributes to both accelerated CD4 depletion and compromised host immune regenerative capacity . We are testing the hypothesis that the type and magnitude of the host immune responses to virus infection determines whether or not disease occurs by (1) detailed characterization of primary SIV infection in RMs and SMs by virologic, immunologic and genetic methods, (2) induction of active cellular anti -SIV responses in acutely -infected SMs and evaluation of whether disease develops in an otherwise refractory host and (3) blockade or alteration of host cellular immune responses to SIV in acutely -infected RMs, and evaluation of whether protection from disease progression is achieved in an otherwise susceptible host .

MOLECULAR BASIS OF ANTIGENIC VARIATION ON MALARIA (0236)

NPRC UNIT : VACCINE RESEARCH CENTER

% NPRC $: 0.420 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
GALINSKI, MARY R	PHD	A	VACCINE RESEARCH CENTER	
C name ⊥	MPH, PHD	A		
	PHD	A		

AXIS I CODES: 1A, 1D, 7C, 17 **AXIS II CODES** 58, 64, 66

ABSTRACT

The basic objective of this research is to understand the molecular mechanisms that govern variant antigen gene expression in Plasmodium . Antigenic variation is a fundamental adaptation to evade a host protective immune response and is one of the major factors contributing to the establishment of chronic blood infections . The classic P . knowlesi -rhesus monkey model of malaria is the primary focus of investigations . This simian malaria model is amenable to both in vitro and in vivo studies and unique stable clones of the P . knowlesi H strain expressing distinct SICA (Schizont Infected Cell Agglutination) variant antigen phenotypes after induced sequential switchings can be maintained after numerous in vivo passages (60 generations) in naive rhesus monkeys . These isogenic clonal lines provide a special tool for studies of the cellular and genetic mechanisms underlying clonal antigenic variation . Recently, we have also initiated complementary investigations on malaria variant antigens using the simian malaria, P . coatneyi, since this species has a similar periodicity, and morphological and immunopathophysiological characteristics that are comparable to the most severe human malaria, P . falciparum. Studies this past year have focused on continued genome wide analyses of the SICAvar gene family and studies developing molecular data relating to our hypothesis of post transcriptional gene silencing as a mechanism to control variant antigen gene expression .

MALARIA VACCINE INITIATIVE TRIAL #2 (0238)

NPRC UNIT : VACCINE RESEARCH CENTER

% NPRC $: 0.520 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
GALINSKI, MARY R	PHD	A	VACCINE RESEARCH CENTER	
[illegible]	MD	A	VACCINE RESEARCH CENTER	

AXIS I CODES: 1A, 1D, 7C, 17 **AXIS II CODES** 58, 64, 66, 91

ABSTRACT

The purpose of this project is to evaluate the general safety and the magnitude and duration of the immune response to the P . vivax bacterial expressed Duffy Binding Protein -Region II (PvDBP -RII) malaria vaccine candidate with different adjuvants in the Macaca mulatta model . PvDBP -RII of P.vivax represents the erythrocyte binding portion of the malaria parasite's Duffy Binding Protein . This is considered a prime vaccine candidate, which confers protection in non -human primates (Aotus monkeys) when Freund's adjuvant is used . The aim is to determine what other adjuvants, which are acceptable for human use, will provide a strong immune response and have the potential to provide protection with this promising vaccine candidate . The candidate vaccine was prepared by the Malaria Vaccine Development Unit (MVDU) of the U.S. National Institutes of Health (NIH) and was provided by the Malaria Vaccine Initiative (MVI) for testing with the adjuvants alum, QS 21, and Montanide 51 and Montanide 720. This past year the immunizations were completed and the humoral immune responses were evaluated . This past year ELISPOT assays have been performed to assess the cellular responses to this vaccine . The data from this project has been under analysis and a manuscript reporting this trial has been initiated .

MOLECULAR ANALYSIS OF PLASMODIUM VIVAX SURFACE ANTIGENS (0270)

NPRC UNIT : VACCINE RESEARCH CENTER

% NPRC $: 0.500 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
GALINSKI, MARY R	PHD	A	VACCINE RESEARCH CENTER	
L names	MPH, PHD	A		
	MD	A	VACCINE RESEARCH CENTER	

AXIS I CODES: 1A, 1D, 7C, 17 **AXIS II CODES** 56, 58, 64, 66, 89, 91

ABSTRACT

The long -term objective of this research is to provide basic fundamental molecular biological and immunobiological information that will aid in the development of a blood stage merozoite vaccine against Plasmodium vivax, one of the two most prevalent species of human malaria . This research is also relevant for increasing the understanding of the biology of P . falciparum merozoites, the other major species of human malaria . The related non -human primate malarias P . cynomolgi, P . coatneyi and P . knowlesi, which infected rhesus monkeys, are excellent models for these investigations . This project entails the characterization of several Plasmodium merozoite proteins and the genes encoding them, with emphasis on molecules that 1) have an apparent direct or indirect function in the receptor mediated processes of merozoite invasion of erythrocytes, and 2) are likely to have a role in affecting the immunobiological relationship between P . vivax and humans by stimulating anti -P. vivax immune responses . Three of these form a family that may also have a paradoxical role of promoting chronicity . The research is aimed at investigating aspects of the genetics and diversity of the family members and how this may affect the immune response mechanisms induced by these proteins . The coordinated use of in -vitro merozoite invasion and attachment assays, immunoelectron microscopy, gene knockout technologies, defined antibody and recombinant DNA reagents, and the use of the simian malaria models, aid in the precise determination and clarification of the location (s), function, structure and possible interactive relationships of the merozoite proteins under investigation . Understanding these properties is important for the rational development of potential malaria vaccine candidates . This past year special emphasis has been on interspecies comparative analyses, the evaluation of putative erythrocyte adhesion domains, development and expression of vaccine constructs, and ongoing studies evaluating the naturally acquire immune responses produced against these proteins .

EMORY NAVY MALARIA VACCINE TRIAL #2 (0307)

NPRC UNIT : VACCINE RESEARCH CENTER

%NPRC $: 0.500 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
GALINSKI, MARY R	PHD	A	VACCINE RESEARCH CENTER	
[redacted]	MD	A	VACCINE RESEARCH CENTER	

AXIS I CODES: 1, 1D, 7C, 17 **AXIS II CODES** 58, 64, 66, 91

ABSTRACT

Malaria is an infectious parasitic disease that affects 300-500 million people each year worldwide in over 90 countries and kills several million . In the last five years, major advances have been made by the US Navy's Malaria Program in producing a malaria vaccine based on immunization with DNA . Plasmids that code for parasite antigens have been injected into muscle where they are taken up by cells and small amounts of the parasite proteins are expressed. The animal mounts an immune response against the plasmid antigen, and this immune response has been shown to be able to kill malaria parasites . For several antigens, protection of mice has been achieved using this methodology . More recent studies have shown that DNA plasmids encoding malaria can induce an immune response in rhesus monkeys, and that boosting DNA immunized monkeys with recombinant attenuated vaccinia vaccines can give partial protection against malaria challenge . The current study aims to evaluate whether use of the CRL-1005 adjuvant enhances the immunogenicity of five promising malaria vaccine DNA constructs representing P falciparum antigens PfCSP, PfSSP 2, PfLSA1, PfMSP1-42, and PfAMA 1.

VALIDATION OF UNIVERSAL T CELL EPITOPE APPROACH AS PREDICTOR FOR VACCINES (0354)

NPRC UNIT : VACCINE RESEARCH CENTER

%NPRC $: 0.500%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
GALINSKI, MARY R	PHD	A	VACCINE RESEARCH CENTER	
E name J	MD	A	VACCINE RESEARCH CENTER	

AXIS I CODES: 1A, 1D, 7C, 17 **AXIS II CODES** 56, 58, 64, 66, 89, 91

ABSTRACT

This is a Venture sub -Project of the Base Grant of the Yerkes National Primate Research Center to obtain data for the testing of selected universal T cell epitopes as vaccine components in Macaca mulatta monkeys

MOLECULAR BASIS OF ANTIVENIC VARIATION ON MALARIA (0347)

NPRC UNIT : VACCINE RESEARCH CENTER

% NPRC $: 0.500 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
GARBER, DAVID A	PHD	G	VACCINE RESEARCH CENTER	
t name 3	MD, PHD	A	VACCINE RESEARCH CENTER	

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

ABSTRACT

This proposal is aimed at creating an effective, practical, economical and safe AIDS vaccine through the development of novel Modified Vaccinia Ankara (MVA)-based vaccine vectors that possess a substantially enhanced ability to generate immune responses against HIV antigens . Recent studies of candidate AIDS vaccines that employ recombinant MVA -based HIV vaccines as components of "prime-boost " immunization regimens have generated very encouraging results in preclinical studies in non -human primate models, and MVA -based HIV vaccines are now being studied in Phase I clinical trials in humans . Immune responses generated against the vector -encoded vaccinia proteins will both dilute the extent to which the host immune response is specifically targeted to the antigens of interest (eg, HIV), and dramatically impair the efficacy of booster immunizations . Furthermore, we have found that although MVA has the unexpected and favorable property of targeting dendritic cells (DCs: the most important host antigen presenting cells) for infection in vivo, the infected DCs rapidly die as a result of virus -induced apoptosis . The timing of DC apoptosis coincides with the transition for the "early" to "late" stage of the vaccinia life cycle . Based on these observations, we propose to develop two new classes of MVA-based vaccine vectors that are designed to elicit augmented immune responses towards immunodeficiency virus antigens by increasing the magnitude and duration of presentation of HIV antigens by DCs, while at the same time minimizing undesirable responses against the vaccine vector . These new vector systems will be analyzed in rhesus macaques to determine the relative magnitude and durability of vaccine -elicited antiviral immune responses as compared to the AIDS vaccines based on parental MVA vectors . While our primary interest is to develop an effective vaccine against HIV /AIDS, the proposed MVA -based vaccine vectors are expected to be widely adaptable for creation of vaccines against other infectious diseases .

TARGETED DELIVERY OF ANITGENS TO INDUCE HIV IMMUNITY (0189)

NPRC UNIT : VACCINE RESEARCH CENTER

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
JABBAR, M A	PHD	A	VACCINE RESEARCH CENTER	

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

ABSTRACT

Dendritic cells (DCs) are endowed with the remarkable ability to capture, process and present antigens to T cells to elicit immune responses . Each of the steps leading to T cell activation is finely orchestrated in the immune systems of the vertebrates and the quality of immunity generated by vaccines or infections depends largely on how DC function is modulated in vivo . We focused on DNA vaccine strategies capable of inducing enhanced levels of immune responses against HIV antigens . Like viral (live or attenuated) infections, DNA vaccines exploit the inherent abilities of DCs to elicit immunity against diverse pathogens . However, the process of immune activation by DNA vaccines alone is rather ineffective to provide protective immunity . This limitation appears to be due to their inability to induce innate mediators (through Toll -like receptors, TLRs, and others) of the immune response. We have devised experimental strategies to optimize the efficiency of genetic vaccination and these involve the augmentation of both the numbers (Flt-3 ligand) and activation (CpG DNA) of DCs in vivo . Flt-3 L is a haematopoetic growth factor, which dramatically increases the numbers of DCs by engaging its receptor (Flt-3) on CD34+ haematopoetic stem cells (HSC). Recently, we have had success in the expansion of DCs in vivo by plasmid -encoded Flt -3 L and such expanded DCs have been shown to enhance DNA vaccine -induced immune responses in mice (1, 2). In addition, we have also focused on T cell proteins (CTLA4 and CD40L) having the ability to target antigens directly to DCs or other antigen -presenting cells (3). Based on our mouse studies, we have moved to experiments to test this vaccine concept in rhesus macaques with the hope of eliciting protective immunity against HIV /AIDS in this animal model system .

T CELL MEMORY (0193)

NPRC UNIT : VACCINE RESEARCH CENTER

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
JACOB, JOSHY	PHD	A	VACCINE RESEARCH CENTER	

AXIS I CODES: 1A, 1D **AXIS II CODES** 31, 64, 66, 91, 95

ABSTRACT

The immune system is remarkable in its ability to mount responses against a wide array of antigens and to respond with enhanced vigor to antigens encountered in the past . This exaggerated recall immune response or immune memory is a central concept in immunology and it forms the basis of vaccination against infectious diseases . . Immune memory is mediated by memory lymphocytes that persist in the host long after resolution of the infection or antigenic insult . To study immune memory, we have developed a novel and powerful transgenic mouse model system. In this system, both effector and memory pools of T lymphocytes are indelibly tagged with the marker, human placental alkaline phosphatase (PLAP) by an irreversible genetic recombination event . Our long -range goal is to understand how immune memory is generated, regulated and maintained . The objective of this application, which is the first step in pursuit of this goal, is to further validate the transgenic mouse model system and to ask fundamental questions about how CD 8 T cell memory is generated . The central hypothesis of this application is that antigen -specific effector and memory CD8 T cells can be unambiguously identified . We will use this model system to probe lymphocytic choriomeningitis (LCMV) virus -induced immune responses and the differentiation pathway of immune memory generation . It is our expectation that the resultant approaches will identify key events involved in the generation of CD 8 T cell memory. The research will be of significance because what is learned from these studies will contribute to broader understanding of how vaccines that provide long -term protective immunity can be rationally designed .

ANTHRAX VACCINE RESEARCH PROGRAM (0180)

NPRC UNIT : VACCINE RESEARCH CENTER

% NPRC $: 0.520%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
MITTLER, ROBERT	PHD	A	VACCINE RESEARCH CENTER	
		A	VACCINE RESEARCH CENTER	
	PHD	A	VACCINE RESEARCH CENTER	
	MD	A	PEDIATRICS	
	DVM	C	ANIMAL RESOURCES	
	DVM	C	ANIMAL RESOURCES	

F Named 2

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

ABSTRACT

Bacillus anthracis, an encapsulated spore -forming bacterium is the causative agent of anthrax . Depending upon the route of infection and the time of diagnosis and proper antibiotic treatment, anthrax may be fatal in greater than 90% of the infected population . Disease and fatality occur as a result of the bacterium's ability to secrete two exotoxins . These binary toxins are composed of Protective Antigen and Lethal Factor, or Protective Antigen and Edema Factor. The spore-forming capacity of this organism assures its long -tem survival under inhospitable conditions . Anthrax, in causing lethal infection following the inhalation of its spores makes it an ideal weapon for bioterrorism . An approved protective vaccine against anthrax has been developed using cell -free culture supernatants from bacterial cultures absorbed onto aluminum hydroxide and termed Anthrax Vaccine Adsorbed, or AVA . This vaccine is currently being given to members of the armed forces as a series of six injections . Immunized individuals produce high titers of IgG subclass antibodies, in particular, IgG 1 that have neutralizing activity against the three toxin components . However, it has been found that a significant number of vaccinees experience adverse side effects including localized edema and induration that may be classified as severe, moderate or mild in nature . In some cases systemic reactions have been reported . Despite the fact that the vaccine has been licensed for use for some time and over 1.5 million doses have been given since 1990 very little is known about the human immune response to the vaccine beyond the fact that a protective humoral immune response develops to the exotoxins in vaccinees . A component of this protocol has been developed to include three groups of eleven rhesus monkeys . Each group will be vaccinated with different concentrations of the approved anthrax vaccine (anthrax vaccine adsorbed AVA) at several time points (0, 4 weeks and 6 months). This administration route and frequency of vaccination differs from the current human AVA series recommendations . No anthrax challenge will be performed for this study . The intent of this proposal is to analyze in detail the cellular components of the immune system that participate in the development of protective immunity to anthrax in humans and non -human primates.

ANALYSIS OF ANIT 4-1BB MEDIATED TUMOR IMMUNITY (0214)

NPRC UNIT : VACCINE RESEARCH CENTER

%NPRC $: 0.270 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
MITTLER, ROBERT	PHD	A	VACCINE RESEARCH CENTER	

AXIS I CODES: 1A, 1D **AXIS II CODES** 32, 50B, 64, 66, 91

ABSTRACT

TCR recognition of antigen + MHC (signal 1) and T cell costimulation (signal 2) are essential for full T cell activation, differentiation, and survival . The prototypical T cell costimulatory receptor, CD 28, is a constitutively expressed type I integral transmembrane protein displayed on naive CD 4+ and CD 8+ T cells. Following the identification of CD 28 as a costimulatory receptor, a number of inducible receptors having similar function have been identified . Several of these receptor molecules, including 4-1BB receptors, are members of the tumor necrosis factor receptor (TNFR) superfamily. Our laboratory has been studying the costimulatory activity of 4-1BB receptors in T cell activation and we have characterized 4-1BB mediated signaling in T cell proliferation, inhibition of T-dependent humoral immunity, enhancement of CTL -mediated anti -tumor immunity, anti -viral immunity; and T cell survival against apoptosis (AICD). Our current application seeks to extend these earlier studies in defining potential clinical applications of anti -4-1BB mAbs for treating autoimmune diseases such as SLE and RA, post -surgical metastatic cancer, and to define structure /function relationships that enable 4-1BB receptors to mediate T cell immune responses . This study ended in April 2003 .

EFFECT OF ANTI-4 1BB ON SIV SPECIFIC CELLULAR IMMUNITY (0215)

NPRC UNIT : VACCINE RESEARCH CENTER

%NPRC $: 0.270 % **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
MITTLER, ROBERT	PHD	A	VACCINE RESEARCH CENTER	

AXIS I CODES: 1A, 1D, 7B, 28(28) **AXIS II CODES** 31, 50B, 64, 66, 91

ABSTRACT

The goal of this project is to ascertain the effect of in vivo anti -4-1BB treatment on rhesus macaque cellular immune responses to SIV vaccination and /or infection . In so doing, we will explore new ways to stimulate SIV -specific cellular immunity and at the same time, determine the effect of this treatment on the course of disease in SIV-infected animals . Monoclonal antibodies to the 4-1BB receptor (CDw137), a member of the TNF receptor superfamily expressed on activated T cells and NK cells, preferentially stimulate CD 8+ T cells in vitro and in vivo . Recent data suggests that ligation of the 4-1BB receptor on CD 8+ T cells not only provides necessary co-stimulation and thus activation but may also prolong their survival . The latter effect is intriguing given the importance of CD 8+ T cells in controlling viremia in both HIV and SIV infections . This proposal therefore addresses the areas of emphasis of the program announcement in that we are potentially identifying a co -stimulator that may optimize the CD 8+ T cell response and ultimately be used as part of a vaccine against HIV . The specific aims are: 1) To test the in vitro effect of anti -4-1BB monoclonals on macaque lymphocytes in terms of activation, proliferation and cytokine secretion . 2) To determine the effect of anti-4-1BB monoclonals on CD 8+ T cell responses induced by vaccination of Rhesus macaques with a DNA prime followed by a modified vaccinia Ankara (MVA) boost, both encoding SIVmac 239 genes . 3) To administer anti -4-1BB during the course of an acute SIVmac239 infection and thus determine the effect of the treatment on viral loads, CD 4 counts, anti -SIV CD8 activity and ultimately disease course .

ANTI-CD137 BLOCKS PROGRESSION SYSTEMIC LUPUS ERYTHEMATOSUS IN PROTEINURIC MICE (0245)

NPRC UNIT : VACCINE RESEARCH CENTER

%NPRC $: 0.270%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
MITTLER, ROBERT	PHD	A	VACCINE RESEARCH CENTER	

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

ABSTRACT

CD137 (4-1BB), an inducible, type I transmembrane cell surface receptor expressed on activated T cells and NK cells. CD137L, a counter-receptor for CD137 is expressed on activated APCs and B cells . For the past 6 years our laboratory has been studying the regulatory activities of CD 137 in the context of T cell activation and effector function. Our studies have helped to further characterize CD 137 mediated signaling in T cell activation and proliferation . From these studies we have learned that CD 137 signaling suppresses T cell -dependent humoral immunity but amplifies CD 8+ T cell responses . CD137 signaling also induce anti -tumor immunity and enhance anti-viral CTL immunity following vaccination; and these signals protect CD 8+ T cells against activation induced cell death (AICD). In our current studies we demonstrate for the first time, the powerful effect of anti -CD137 mAbs in blocking the development of SLE, or its progression in proteinuric NZB /W F1 mice. We found that a single 200 µg injection of anti -CD137 mAbs into proteinuric mice virtually blocked all IgG anti -dsDNA autoantibody production, and that this occurred through a CD 4+ T helper cell dependent process . Extending our studies further, we demonstrate the lifelong need for CD 4+ T cell help in driving disease progression in these mice . Our current studies are focused on three specific objectives that we believe will further define how the CD 137-CD137 ligand -signaling pathway regulates the development or progression of SLE -like disease : (1) Identify the cellular basis of anti-CD137 mAb induced protection against SLE . (2) Determine whether CD 137 ligand signaling can regulate autoantibody production and the generation and survival of memory B cells . (3) Compare and contrast signaling properties that are shared between the CD 137 costimulatory receptor and the TCR in the NZB /W F1 and BALB/c mouse.

NOVEL LINEAR PEPTIDE UNIVERSALE MALARIA VACCINES (0302)

NPRC UNIT : VACCINE RESEARCH CENTER

% NPRC $: 0.400 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
MORENO, ALBERTO	MD	A	VACCINE RESEARCH CENTER	

AXIS I CODES: 1A, 1D, 7C, 17 **AXIS II CODES** 56, 58, 64, 66, 91

ABSTRACT

Clinical trials of synthetic peptide vaccines have indicated that biological adjuvants are required to induce a sustained immunity . Although several strategies have been used to optimize the delivery of peptide antigens, the data available show that an optimal formulation is not yet available . We recently reported a novel system to deliver subunit vaccines based in peptide constructs . The strategy includes the association of malaria universal T cell epitopes described by us and synthesized in tandem with B cell epitopes . Amino and carboxyl terminal cysteine residues were included in the linear sequences to increase subunit valence . We have confirmed that this topology favors the spontaneous polymerization of such linear peptide chimeras (LPCs) using SELDI mass spectroscopy, and that the immunogenicity of the peptide constructs depend on the presence of universal T cell epitopes and homo polymerization . These LPCs induced high antibody titers, cytokine production and long -lasting immune responses . This technological approach for antigen delivery has been advanced further, with the design and testing of an additional set of LPC immunogens, which elicited high affinity antibodies as well as Th 1 and Th2 immune responses in different strains of mice . Complex LPCs containing up to three epitopes, which include a CTL -class I restricted nonamer, induce immune response against individual components . The successful delivery of CTL epitopes to the MHC class I compartment opens the possibility of using LPCs containing universal T cell epitopes for developing vaccines against intracellular pathogens as well as for induction of anti -tumoral immunity .

MODULATING IMMUNITY IN AGED MICE WITH DENDRITIC CELLS (0272)

NPRC UNIT : VACCINE RESEARCH CENTER

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
PULENDRAN, BALI	PHD	A	VACCINE RESEARCH CENTER	

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

ABSTRACT

The immune system is severely compromised in aged individuals . This is characterized by decreased antibody titers, failure to produce germinal centers and high affinity antibodies and decreased CD 4+ and CD 8+ T cell function . Such decline in immune function is frequently associated with illness arising from influenza infections, hospitalization and mortality in aged individuals . However, the mechanism (s) of this immune dysfunction is largely unknown . Here we postulate that a critical factor in this immune dysfunction lies at the antigen presentation level . More specifically, we hypothesize that dendritic cells (DCs), which are the most efficient antigen -presenting cells in the body are impaired . In this context, the Specific Aims of the current projest are : 1) To determine the numbers, phenotype, function and microenvironmental localization of DC subsets in aged versus young mice : 2) To determine whether Flt 3-Ligand and GM -CSF, cytokines which enhance DC numbers in vivo, stimulate enhanced antigen -specific B and T-cell responses in aged mice; 3) To determine whether Flt 3-ligand and GM -CSF confer enhanced protection against influenza in aged mice . This research will provide us with a deeper understanding of DCs in the control immune responses against influenza in the elderly . it should ultimately permit more effective use of DCs and their growth factors for vaccination of the elderly against influenza and other infections .

MICROBES, DENDRITIC CELL SUBSETS AND T-CELL IMMUNITY (0273)

NPRC UNIT : VACCINE RESEARCH CENTER

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
PULENDRAN, BALI	PHD	A	VACCINE RESEARCH CENTER	

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

ABSTRACT

The adaptive immune system has evolved several different lines of attack, each one optimally effective against a given pathogen . For example, in response to intracellular microbes, CD 4+ T-helper cells (Th) differentiate into Th 1 cells; in contrast helminths induce Th 2 cells, whose cytokines (IL-4, IL-5 & IL-10) induce IgE and eosinophil -mediated destruction of the pathogens . Although these diverse responses have been characterized in detail, the mechanism by which a particular type of immune response is initiated is poorly understood . Analogous to the situation in Drosophila, signaling through distinct TLRs can yield qualitatively different immune responses . Furthermore, we suggest that different DC subsets are endowed with a distinct, repertoires of pattern recognition receptors, which enable them to recognize distinct classes of pathogens, and initiate different types of immune responses . In this project, we will co -inject a soluble protein (ovalbumin) with either of two different LPs molecules that signal through distinct pattern recognition receptors : (i) E. coli LPS, which signals through TLR 4, and induces Th 1 cytokines, and (ii) P. gingivalis LPS, which signals independently of TLR 4. P. gingivalis infections are often characterized by Th 2 cytokines . This research will provide us with a novel mechanism by which distinct pathogens can elicit distinct adaptive immunity, by targeting different cells of the innate immune system . It should also offer novel strategies for manipulating immune responses in clinical settings .

POLARIZING T CELL RESPONSES IN VIVO WITH DENDRITIC CELLS (0274)

NPRC UNIT : VACCINE RESEARCH CENTER

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
PULENDRAN, BALI	PHD	A	VACCINE RESEARCH CENTER	

AXIS I CODES: 1D **AXIS II CODES** 31, 64, 66

ABSTRACT

T-cell dependent immunity against antigens is heterogeneous with respect to the cytokines made by the CD 4+ T helper cells (Th cells), and the isotypes of antibodies secreted by the B cells . The type of Th response is critical in determining the clinical outcome of various disease processes . Thus a number of diseases result from a skewing of Th1 to Th2 responses (HIV, allergy), or Th2 to Th1 responses (organ-specific autoimmunity). A deep understanding of Th responses, and the ability to redirect such responses in vivo, may provide attractive strategies for immunotherapy against such diseases . While it is known that the cytokines produced early in a response are crucial in determining the Th polarization of the response, the cell types that initiate the Th polarization in vivo are unknown . The present project seeks to understand the roles played by dendritic cells (DCs) in this process . In mice DCs can be classified into the lymphoid and myeloid families . This research will provide us with a deeper understanding of DCs in the control of Th responses in vivo . It should also ultimately permit more effective use of DCs for the immunotherapy of autoimmunity and infectious diseases .

ANTHRAX TOXIN, DENDRITIC CELLS AND ADAPTIVE IMMUNITY (0355)

NPRC UNIT : VACCINE RESEARCH CENTER

%NPRC $: 0.500%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
PULENDRAN, BALI	PHD	A	VACCINE RESEARCH CENTER	

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

ABSTRACT

Anthrax poses a clear and present danger as an agent of biological terrorism . The major virulence factor of Bacillus anthracis is the anthrax toxin, which comprises 3 subunits : protective antigen (PA), edema factor(EF) and lethal factor (LF). LF and PA together form a toxin known as lethal toxin (LT), which appears to play exquisitely different immunomodulatory roles, depending on the dose of toxin used . The effects of LT on dendritic cells (DCs), the most efficient antigen -presenting cells in the body, are not known . These mechanisms and their pathophysiological relevance are being investigated in the following aims : Aim 1: To determine the effect of LT on routine DC,function and adaptive immunity . Aim 2: To determine the effect of LT on murine DC function and adaptive immunity . Aim 3: To determine the effect of LT on distinct human DC subsets and adaptive immunity . Aim 4: To determine the pathophysiological relevance of LT -induced suppression during B .anthracis infection . Thus, the overall goal of this project is to acquire a deeper, mechanistic understanding of anthrax pathogenesis, and to use this knowledge to devise novel therapeutic modalities, which may be optimally effective at different stages of the infection .

STUDIES OF HOMEOSTATIC PROLIFERATION OF T-CELLS IN PRIMATES (0268)

NPRC UNIT : VACCINE RESEARCH CENTER

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
SILVESTRI, GUIDO	MD	A	VACCINE RESEARCH CENTER	

AXIS I CODES: 1D **AXIS II CODES** 31, 64, 66

ABSTRACT

The goal of this project is to study the effect of homeostatic proliferation of T cells on the TCR repetoire and the apoptotic cell death in vivo .

STUDIES OF THE HIV ASSOCIATED CELL CYCLE DISEASE (0348)

NPRC UNIT : VACCINE RESEARCH CENTER

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
SILVESTRI, GUIDO	MD	A	VACCINE RESEARCH CENTER	

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

ABSTRACT

The generation of an effective AIDS vaccine is complicated by our limited knowledge of the correlates of immune protection during HIV and SIV infection . We propose to study the cellular immune responses generated by different immunization strategies that include MVA - and Adenovirus /MVA-based HIV and SIV vaccines, and to compare them with those generated during natural HIV and experimental SIV infection . An improved understanding of the determinants and generation of protective cellular immune responses against a model virus infection have emerged from studies of LCMV infection in mice . These studies elucidated the crucial distinction between central memory T cells (Tcm) and effector memory T cells (Tem), and described the predominant role of Tcm cells in protecting from re-challenge . We seek to determine if responses elicited by vaccination result in a better ability to develop and maintain functional, durable Tcm -mediated responses to HIV and SIV antigens . The phenotypes and functions of the HIV-specific Tem and Tcm cell populations induced by different vaccination regimens will be defined, and compared to the memory T cell responses that arise following HIV and SIV infections as well as those that will be observed after SIV-challenge of previously vaccinated macaques . In this way, we will explore potential mechanisms by which vaccine -induced HIV - and SIV-specific memory T cell responses may be more effective in controlling virus replication than those following infection, and less likely to precipitate immunopathologic consequences . In all, these studies are aimed at defining markers that will predict vaccine effectiveness in inducing host responses that can contain virus replication, prolong disease -free survival, and decrease secondary transmission . Definition of the characteristics of such effective immune responses will ideally advance our understanding of the correlates of protection to be pursued in future efforts of AIDS vaccine development .

HOMEOSTASIS OF T CELLS IN PRIMATES (0350)

NPRC UNIT : VACCINE RESEARCH CENTER

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
SILVESTRI, GUIDO	MD	A	VACCINE RESEARCH CENTER	

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

ABSTRACT

Little is known about the mechanisms regulating T cell homeostasis in primates . The overall aim of this project is to study the homeostatic regulation of T cells in healthy rhesus macaques (RM) and sooty mangabeys (SM) via antibody -induced depletion of specific T cell subsets . We believe that this proposal is relevant to AIDS research due to the specific features of SIV -infection in the two species, i .e. pathogenic in RM and non -pathogenic in SM . If our study identifies differences in T cell homeostasis between RM and SM, we may then hypothesize that these differences play a role in determining the clinical outcome after SIV -infection . The performed analyses will include : (1) immunophenotypic studies, (2) determination of levels of recent thymic emigrants, and (3) examination of levels of cytokines, i .e. IL-7, IL-15 and IL-2, that may play a role in T cell homeostasis . In this application we also propose to evaluate the role of the thymus in T cell homeostasis by performing CD 4+ and CD 8+ T cell depletions in both normal and thymectomized animals . We believe that this comparative study may provide information on (1) the differential role of BM, LN and thymus in T cell homeostasis; (2) the specific features of the homeostasis ofCD4+ and CD 8+ T cells; (3) the immunophenotype of T cells that are proliferating via homeostatic mechanisms; and (4) the role of cytokines in reconstituting acutely depleted T cell populations . Importantly, this approach may allow us to define differences in the way T cell homeostasis is maintained in RM vs SM, which could provide clue regarding the markedly different impact of SIV -infection in the two species . In all, we believe that this project may provide useful information on the homeostasis of T cells in primates, and how the failure of this homeostasis may play a role in the pathogenesis of AIDS .

DETERMINANTS OF NON PATHOGENIC SIV INFECTION (0345)

NPRC UNIT : VACCINE RESEARCH CENTER

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
STAPRANS, SILVIJA	PHD	A	VACCINE RESEARCH CENTER	

AXIS I CODES: 1A, 1D, 6, 7B, 9, 19 **AXIS II CODES** 31, 39, 64, 66, 77, 83

ABSTRACT

In order to gain insight into the determinants of non pathogenic SIV infection in the naturally infected sooty mangabey host, SIV replication in mangabeys is assessed and compared to SIV replication observed in pathogenically infected rhesus macaques . Significant methodologic progress has been made in two areas : 1) implementation of a kinetic PCR method for the high throughput quantification of SIV nucleic acid in infected monkeys. Real-time PCR-based assays for SIV RNA were implemented . The assays have the capability to detect a variety of SIV isolates, including SIVmac -related and SIVsmn viruses . Two different primer/probe sets have been implemented and evaluated with respect to assay sensitivity, linearity, reproducibililty, and ability to detect divergent viral variants . Well-characterized and independently quantified SIV virion standards for an external standard curve have also been implemented . The standards were used to identify optimal RT -PCR conditions . Our ability to rapidly develop quantitative, real -time PCR assays for both viral DNA and RNA demonstrates that this methodology can be readily applied to the analysis of virtually any RNA or DNA virus . Application of radiolabelled SIV in situ hybridization probes demonstrated the increased sensitivity of this method compared to non-isotopic methods previously used . The enhanced sensitivity has demonstrated similar or slightly lower frequency of SIV-infected T cells in mangabey lymphoid tissues as compared to macaques .

HOST SPECIFIC RESPONSES IN SIV-INDUCED HEMATOSUPPRESSION (0352)

NPRC UNIT : VACCINE RESEARCH CENTER

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
STAPRANS, SILVIJA	PHD	A	VACCINE RESEARCH CENTER	

AXIS I CODES: 1D **AXIS II CODES** 31, 50, 64, 66, 91

ABSTRACT

HIV disease is characterized by impairment of two key bone marrow (BM) functions : multilineage hemapoiesis and T cell homeostasis . Abnormal hemapoiesis leads to failure of diverse lineages (WBCs, RBCs, platelets, thymic progenitors), while compromised T cell homeostasis contributes to progressive CD 4+ T cell loss . It is difficult to study HIV -induced BM suppression in humans, and there are no systematic analyses of the precise stages of hemapoiesis and T cell homeostasis that are altered . Direct HIV infection of BM cells does not appear to play a major role in suppression, pointing to indirect mechanisms of damage . These pathogenic mechanisms can be studied in SIV-infected non -human primates, in particular by comparing the divergent responses of natural and non -natural hosts to SIV infection, and by experimental manipulation to test hypotheses about disease mechanisms . Our studies of SIV-infected sooty mangabeys (SMs), the natural reservoir host from which HIV -2 arose, demonstrate that SMs avoid CD 4+ T cell loss and BM suppression despite high viremia . In contrast, SIV infection of the non -natural rhesus macaque (RM) host, recapitulates the BM suppression and lymphopenia seen in human AIDS . In RMs, the chronic immune activation that accompanies an active, yet ineffective immune response correlates with lymphopenia and immune dysfunction . We believe that these inflammatory processes lead to both increased bystander death of uninfected lymphocytes, as well as active suppression of BM regenerative capabilities . In contrast, SMs mount limited cellular immune responses to SIV infection, sparing them of the chronic immune activation and its associated pathogenic bystander effects . In our studies, we also observed that the BM is a site of significant T cell proliferation in healthy, uninfected animals, suggesting a previously unappreciated role for the BM in the homeostasis of T cells .

DEVELOPMENT OF A LOW INOCULUM SHIV CHALLENGE MODEL (0353)

NPRC UNIT : VACCINE RESEARCH CENTER

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
STAPRANS, SILVIJA	PHD	A	VACCINE RESEARCH CENTER	

AXIS I CODES: 1D **AXIS II CODES** 31, 50, 64, 66, 91

ABSTRACT

Development of an HIV -inhibiting microbicide is a priority . Consensus exists that an effective microbicide may be feasible. Simian AIDS models can help guide the development and prioritization of HIV prevention strategies . However, current models may not provide realistic pre -clinical tests of HIV prevention efficacy . The viral inoculum sizes used to infect macaques exceed those that humans are exposed to, and may underestimate the efficacy of HIV preventions . The small inocula associated with most human HIV exposures, combined with the likely stochastic nature of early infection events, may even make HIV transmission particularly susceptible to intervention . This proposal brings together investigators with expertise in AIDS virology and immunology, simian AIDS model development, and the mathematical analysis of HIV transmission events, to develop a challenge model that better recapitulates HIV transmission . The model uses vaginal inoculation with low doses of a CCR 5-utilizing SHIV . Overall hypotheses : 1) Low -dose inocula, applied repeatedly, will achieve experimental SHIV infection with enough reproducibility so that prevention efficacy studies could be performed; power analyses predict that the animal numbers required to demonstrate efficacy are similar to those used in current high -dose challenge models, and 2) A low -dose challenge model will provide a more sensitive, physiologically relevant measure of the efficacy of microbicides, vaccines or other preventions . Efficacy would be demonstrated by showing that an intervention increases the number of challenges required to achieve infection, compared to controls .

EFFECTS OF VIEWING DISTANCE ON EYE GROWTH & REFRACTIVE DEVELOPMENT (0322)

NPRC UNIT : VISUAL SCIENCE

% NPRC $: 0.500 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
BRADLEY, DOLORES V	PHD	A	VISUAL SCIENCE	SPELLMAN COLLEGE, GA USA

AXIS I CODES: 1A, 21, 25B **AXIS II CODES** 60, 71

ABSTRACT

While there is a significant positive correlation between the amounts of time a person engages in nearwork tasks (e.g. reading) and the incidence of myopia, there is no direct evidence of a causal association, and the nature of this relationship has remained a mystery for over a century (ethical considerations preclude the use of human subjects to address this question directly through empirical research). The present project was undertaken to determine whether prolonged performance of nearwork tasks could lead to the development of myopia . The objectives were to identify an appropriate task and behavioral setup and to ensure that optical performance was appropriate . Prior to the onset of training on the behavioral task, adolescent rhesus monkeys exhibited a stable refractive error of a few degrees of hyperopia, which is the norm for this species . In daily sessions monkeys worked for food reinforcement on a visual discrimination task displayed on a computer located within arm's reach (at near). Over time, all 3 subjects have undergone a myopic shift in refractive error, exhibiting zero or nearly zero refractive error . These data may provide the first direct evidence that prolonged performance of a nearwork task is associated with the development of myopia . Recently, we have verified that during the performance of the task, the monkeys are focused on the computer screen, which confirms that the optical /visual demands of the task are similar to those of reading (i.e. focused at near). This monkey model will allow us to determine what aspects of the visual task contribute to the effects of refractive development and the development of myopia and will prove useful in clinical efforts to prevent myopia or reduce its progression .

BINOCULAR COORDINATION OF EYE MOVEMENT IN MONKEYS WITH STRABISMUS (0244)

NPRC UNIT : VISUAL SCIENCE

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
DAS, VALLABH E		A	VISUAL SCIENCE	
E nagnes J	PHD	C	VISUAL SCIENCE	
	MD, PHD	C	VISUAL SCIENCE	

AXIS I CODES: 1A, 21, 25B **AXIS II CODES** 92(92)

ABSTRACT

Binocular alignment must be maintained in the horizontal, vertical and torsional planes to ensure binocular sensory fusion. Unfortunately, abnormal visual experience during development usually leads to ocular misalignment (strabismus). In fact, various studies have reported the incidence of strabismus to be about 2-5% of the infant population . We have developed an animal model for strabismus by rearing monkeys that only view the world through one eye at a time . This is accomplished by placing an opaque contact lens on one eye and alternating to the other eye on a daily basis . Our data from strabismic monkeys have confirmed human data that ocular misalignment is accompanied by a lack of binocular coordination . However we found that conjugate adaptation of saccadic gain is normal. Though strabismus is most often associated with a horizontal misalignment, often a combined horizontal, vertical and torsional misalignment is observed . There also appears to be substantial dynamic cross -talk between the principal eye movement planes . In the clinical literature these apparent cross -axis interactions are usually described as 'A/V' patterns of strabismus . There is a lack of understanding of the neural or mechanical bases for these cross-axis movements, the putative relationship or lack thereof to the neural control of horizontal, vertical or torsional eye movements and the relationship to the etiology of the strabismus . Competing hypothesis include static malpositioning of extraocular muscle pulleys, sideslip of extraocular muscles and muscle pulleys, torsional control of eye movements gone awry leading to apparent muscle dysfunction and finally simply unexplained overaction /underaction of individual extraocular muscles . Our results suggest that in monkeys with strabismus due to visual sensory deprivation, errant signals emanating from central structures are responsible for cross -axis movements and A/V patterns of strabismus . Completion of our studies will be of benefit to the understanding and treatment of certain types of strabismus .

EARLY FUNCTIONAL & STRUCTURAL REPAIR IN MACAQUE STABISMUS (0323)

NPRC UNIT : VISUAL SCIENCE

% NPRC $: 0.500 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
DAS, VALLABH E		A	VISUAL SCIENCE	

AXIS I CODES: 1A, 21, 25 **AXIS II CODES** 44, 60, 71

ABSTRACT

The oculomotor system is immature at birth . For example, it is known that the two eyes are misaligned upon birth . Other instances of immature behavior include reports of a nasalward bias in optokinetic eye movements and slow saccadic eye movements . Normal visual experience is necessary to promote the alignment of the two eyes within the first year of life. Thus, interfering with normal visual experience during infancy leads to permanent problems such as strabismus (ocular misalignment) or amblyopia . However, there are still many questions regarding developmental mechanisms that result in the normal adult pattern of eye movements . In this project we propose to precisely measure eye movements in infant monkeys over the first year of life to examine certain aspects of development in the oculomotor system . Specifically, we will examine the critical period of development for binocular coordination and its relationship to development of binocular alignment . We also examine the maturation of saccadic eye movements and the neural integrator circuit that allows us to hold gaze on an eccentrically located object . Finally, we determine and compare critical periods of development for optokinetic and ocular following eye movements as they might be indicators of visual system development in the brain . This project has significant relevance in understanding visual system development in normals and setting the stage for understanding various developmental problems including strabismus, amblyopia and nystagmus .

STUDIES OF VISUAL PROCESSING & SMOOTH EYE MOVEMENTS (0093)

NPRC UNIT : VISUAL SCIENCE

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
MUSTARI, MICHAEL J	PHD	C	VISUAL SCIENCE	
[illegible]		A	VISUAL SCIENCE	
[illegible]	PHD	A	OPHTHALMOLOGY	CASE WESTERN RESERVE UNIVERSITY, OH USA
[illegible]	MD, PHD	C	VISUAL SCIENCE	

AXIS I CODES: 1A, 21, 25B **AXIS II CODES** 92(NONE)

ABSTRACT

Our studies are directed at defining the neural substrate for normal visual -smooth pursuit eye movements and gaze holding . We are particularly interested in defining the relationship between early visual experience and development of eye movement systems, eye alignment and gaze holding . The visual and oculomotor systems are not mature at birth . If early visual experience is compromised by injury or congenital defect, eye movement disorders can follow that can compromise clear vision . In humans these disorders often comprise well defined clustered deficits such as infantile esotropia syndrome . In this syndrome, smooth pursuit eye movements are defective, showing a bias for nasalward directions of movement . In addition, a pattern of latent nystagmus (LN) is evident during monocular viewing . We have hypothesized that LN is associated with a disruption of binocularity in the pretectal nucleus of the optic tract (NOT). During the last year we have provided further support for this hypothesis and demonstrated the neurons in the MT /MST cortex of monkeys with LN retain binocular sensitivity . This finding supports the suggestion that the focus of the defect producing LN is in the brainstem and not in the motion processing regions of the extrastriate cortex . We have also demonstrated that gaze holding disorders can be separated from strabismus suggesting that different forms of impoverished early experience are likely to produce different sensory -motor deficits .

NEURAL CONTROL OF VISUAL VESTIBULAR BEHAVIOR (0246)

NPRC UNIT : VISUAL SCIENCE

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
MUSTARI, MICHAEL J	PHD	C	VISUAL SCIENCE	
		A	VISUAL SCIENCE	
Names	MD, PHD	A	PHYSIOLOGY	HOKKAIDO UNIVERSITY, JAPAN
	MD, PHD	C	VISUAL SCIENCE	

AXIS I CODES: 1A, 21, 25B **AXIS II CODES** 92(92)

ABSTRACT

Normal posture, balance and stable vision are dependent on interactions between the visual and vestibular systems . Our studies are directed at defining the neural substrate for normal visual -vestibular -oculomotor behavior . There is a continuous need to calibrate the motor output of the vestibular ocular reflex due to normal development or injury to the vestibular system . Without this calibration, difficulties in maintaining balance and clear vision during locomotion would occur . In addition to long -term calibration, vision is supported by moment -by-moment or dynamic visual -vestibular interactions . The neural structures involved in processing visual motion information for vestibular function are incompletely understood . Our earlier studies have shown that the pretectal nucleus of the optic tract (NOT) and the dorsolateral pontine nucleus (DLPN) receive visual information from different central structures and play a critical role in visual -oculomotor behavior . Furthermore, the NOT and DLPN have efferent connections with the vestibulo -cerebellum and vestibular nuclei; structures known to play a role in visual -vestibular function per se . Progress has been made in the last year regarding the potential role of the DLPN in short -term plasticity in the VOR . We found that visual modification of the VOR during lens viewing (x0.5x or x2.0) occurred in the presence of unilateral DLPN inactivation that produced profound smooth pursuit deficits . We conclude that visual signals supporting modification of the VOR may travel in other pathways .

PILOT SUBPROJECTS

TRANSITIONAL STATES IN DRUG ADDICTION (0334)

NPRC UNIT : NEUROSCIENCE

% NPRC $: 0.500 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
HOWELL, LEONARD L	PHD	C	NEUROSCIENCE	
[illegible]	PHD	A	NEUROSCIENCE	
[illegible]	PHD	A	NEUROSCIENCE	

AXIS I CODES: 1A, 21 **AXIS II CODES** 50, 63C, 63E, 87

ABSTRACT

The progression of drug addiction in humans typically involves a transition from casual, recreational drug use to compulsive drug use that leads to serious adverse consequences . Hence, the frequency and pattern of drug use changes as a function of drug history . This is a new project in its first year to utilize i .v. drug self-administration protocols in rhesus monkeys to identify critical behavioral endpoints indicative of transitional states in drug addiction . Efforts will focus on the importance of response -contingent drug history and drug -related environmental stimuli . Subjects will be exposed to a limited -access condition designed to incorporate features of recreational drug use in humans, followed by a binge period with increased duration of access and marked elevations in drug intake . Changes in the pattern and frequency of drug intake during the limited -access and binge conditions will be a major focus. Reinstatement of drug -seeking behavior by cocaine priming injections and drug -paired stimuli will provide another objective behavioral measure indicative of transitional states in drug use . Parallel studies will utilize in vivo microdialysis in awake subjects to characterize functional changes in monoamine neurochemistry associated with the behavioral changes observed . In addition, positron emission tomography will document the pattern of drug-induced brain activation at different transitional states observed in behavioral and neurochemical studies . Brain tissue obtained at different transitional states will be assayed for gene expression profiles and protein products, providing relevant molecular markers to complement in vivo functional measures in a nonhuman primate model of drug use . These integrated efforts, including behavioral and mechanistic approaches, will provide a comprehensive analysis to identify transitional states in cocaine addiction .

ROLE OF MIDDLE TEMPORAL VISUAL CORTICAL AREA VISUALLY GUIDED MOTOR PERFORMANCE (0234)

NPRC UNIT : VISUAL SCIENCE

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
MUSTARI, MICHAEL J	PHD	C	VISUAL SCIENCE	
		A	VISUAL SCIENCE	
		G	VISUAL SCIENCE	

AXIS I CODES: 1A, 21, 25B **AXIS II CODES** 92(92)

ABSTRACT

The major focus of this pilot project is to examine the role of MT cortex in visual -vestibular -oculomotor behavior . MT cortex is a pivotal cortical center in the analysis of visual motion that could be essential for supporting visual -vestibular behavior . Our hypothesis is that area MT may be essential for producing initial commands for smooth eye movements that could play a role in some types of behavior such as suppression of the VOR . We have made considerable progress in our single unit studies of area MT and MST . We find that at least some neurons in MT/MST cortex appear to respond relative to gaze (eye and head). However, we have not found any examples of units with vestibular sensitivity per se . Recently, we have found that neurons in the frontal eye fields carry signals related to gaze including vestibular sensitivity .

COLLABORATIVE SUBPROJECTS

PROMOTING CHIMPANZEE WELL-BEING THROUGH APPLIED RESEARCH (0102)

NPRC UNIT : ANIMAL RESOURCES

% NPRC $: 0.520 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
BLOOMSMITH, MOLLIE A	PHD	A	RESEACH RESOURCES	GA INSTITUTE OF TECHNOLOGY, GA USA

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

ABSTRACT

A variety of studies were completed around the theme of improving the behavioral management of captive chimpanzees. Many of these projects were collaborative with other institutions, so only some of the data were collected at Yerkes . Findings included : (1) an analysis of early mother -infant interactions among primiparous chimpanzees which identified differences between mothers that ultimately cared for their infants and those who did not; (2) an archival analysis of records indicated that one year or more of mother rearing increased the likelihood that a primiparous female cared for her own first infant; (3) maternal response to the permanent separation of their offspring (over 2 years old) was evaluated and there were few consistent behavioral responses during the first three weeks following the separation; (4) various abnormal behaviors were catalogued across different groups of chimpanzees and analyses indicated the possibility of cultural transmission of these behaviors; (5) positive reinforcement training was evaluated with durations of training required as well as social and other behavioral consequences recorded, indicating benefits of this animal management technique; (6) few behavioral differences were documented between elderly and prime adult aged chimpanzees when observed in their normal living conditions indicating that changes in social or physical housing may not be in order for aged chimpanzees; (7) a variety of behaviors including abnormal behavior, sexual behavior, agonism and the diversity of social partners were influenced by early social rearing conditions of young chimpanzees . The findings of each of these studies are applied to improving our care and management of the captive chimpanzee population .

PROJECT 3: SUBCONTRACT MACAQUES MHC & MOTIF ANALYSIS (0231)

NPRC UNIT : MICROBIOLOGY & IMMUNOLOGY

%NPRC $: 0.920 % **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
MCDONALD, KELLY	MD	A	MICROBIOLOGY & IMMUNOLOGY	MT. SINAI MEDICAL CENTER, NY USA

AXIS I CODES: 7B **AXIS II CODES** 31, 64, 66, 83, 91

ABSTRACT

Project 3 subcontract has addressed the longitudinal dynamics of the CD 8+ T cell response to SIV Gag antigenic peptides in previously SIV -immunized, infected macaques from Project 1. Mapping and MHC restriction of Gag epitopes have been completed and PBMC samples from three time points (week 20, 62 and 82 post challenge) have been tested . We have identified five SIV CTL epitopes in Gag, restricted by the common MHC class I allele Mamu-B*01, an allele for which no epitopes were previously known . Epitope specific CTL tetramers can now be designed for Mamu -B*01 and will allow a more extensive and accurate measurement of cellular immune responses in SIV vaccine studies in macaques . Analyses of new candidate epitopes for other alleles are ongoing . Comparison of the pattern of CTL epitope reactivity at multiple time points post challenge has been performed to monitor epitope stability, diversification and drift . The gain and loss of epitopes, as well as neutral antigenic drift with time have been documented in each of the vaccinated /infected macaques. Sequencing of plasma viral RNA has been performed at the time points week 62 and 82 post challenge, using RT -PCR and TA cloning . Analysis of the sequencing data is ongoing . The data will be subject to statistical analysis to correlate CTL epitope reactivity with viral escape as well as with clinical and lab parameters of SHIV disease progression . Positive results in this work will contribute to an understanding of the immune mechanisms involved in long -term viral containment in the context of CTL -based non-sterilizing vaccine strategies .

SYNTHESIS AND BIOTRANSFORMATION OF ANTI-VIRAL PRODRUGS (0032)

NPRC UNIT : MICROBIOLOGY & IMMUNOLOGY

% NPRC $: 0.900 % **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
SCHINAZI, RAYMOND F	PHD	A	PEDIATRICS	VA MEDICAL CENTER, GA USA
[illegible] names [illegible]	PHD	A	RESEARCH RESOURCES	VA MEDICAL CENTER / COLLEGE OF PHARMACY, GA USA
[illegible]	DVM	C	RESEARCH RESOURCES	

AXIS I CODES: 1A, 2, 7B **AXIS II CODES** 31, 50B

ABSTRACT

Beta-L-3'-fluoro-2',3'-didehydro -2',3'-dideoxycytidine (L-3'-FD4C) is an antiretroviral nucleoside with activity against 3TC resistant human immunodeficiency virus type 1 (HIV-1) and hepatitis B virus (HBV). Therefore, L-3'-FD4C warrants further development as an antiviral agent . The pharmacokinetics of L -3'-FD4C were characterized in three rhesus monkeys given single intravenous and oral doses (25 mg/kg in solution). The plasma and urine data were fitted to a 2-compartment open model, and descriptive non -compartmental analysis . Plasma concentrations declined in a bi -exponential fashion resulting in an average beta half -life of2.45 h, central and steady -state volumes of distribution of 0.25 and 0.62 l/kg, respectively . The average systemic and renal clearance values were 0.29 and 0.14 l/kg, respectively (averages). The apparent mean terminal half-life of the oral dose was 12.5 h. The serum concentrations exceeded the EC 90 value for 3TC resistant and wild type HIV -1. A large variation in the oral bioavailability was observed ranging from 17 - 48 %. To determine whether the bioavailability may be improved using a buffered solution, an additional 25 mg/kg oral dose was administered in a sodium bicarbonate solution, to the same animals, and the data were analyzed . The bioavailability of L -3'-FD4C administered with sodium bicarbonate was not significantly different when compared to the oral dose in the absence of buffer, ($p = 0.49$), suggesting that a stronger buffer may be necessary to inhibit gastric breakdown, and /or that a prodrug approach should be considered to improve the oral absorption of L -3'-FD4C.

METABOTROPIC GLUTAMATE RECEPTORS AND PARKINSON'S DISEASE (0137)

NPRC UNIT : NEUROSCIENCE

% NPRC $: 0.520 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
SMITH, YOLAND	PHD	C	NEUROSCIENCE	
	PHD	A	PHARMACOLOGY	
	MD	A	NEUROLOGY	
	MD, PHD	A	NEUROLOGY	

AXIS I CODES: 1A, 21 **AXIS II CODES** 46

ABSTRACT

The goal of this project is to elucidate the localization and functions of pre and post -synaptic metabotropic glutamate receptors in the rat basal ganglia . The main approaches used to address these issues are whole cell patch clamp recording techniques and high -resolution immunocytochemistry at electron microscopic level . Over the past year, we focused our interest on two major topics; the functional interactions between mGluR 1 and mGluR 5 in modulating activity of neurons in the globus pallidus (GP) and the pre -synaptic effects of group II mGluRs activation on glutamatergic transmission in the rat GP . Our first set of studies demonstrated interesting and novel mechanisms of interactions between mGluR 1 and mGluR 5 in GP . The main conclusion of this study is that mGluR5 activation desensitizes mGluR 1 response to glutamate through a protein kinase C -dependent pathway . This is the first report of such an interaction between these two receptor subtypes in the CNS . In a second set of experiments, we demonstrated that group II mGluRs activation has powerful pre -synaptic inhibitory effects on glutamatergic transmission in the rat GP . These data provide an important substrate for novel therapies aimed at reducing the hyperactive glutamatergic subthalamofugal projection in Parkinson's disease .

NEUROBIOLOGY OF HEMISPHERIC SPECIALIZATION IN PRIMATES (0068)

NPRC UNIT : PSYCHOBIOLOGY

% NPRC $: 0.520 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
HOPKINS, WILLIAM D	PHD	A	PSYCHOBIOLOGY	BERRY COLLEGE, GA USA

AXIS I CODES: 1A, 19, 23 **AXIS II CODES** 36, 50, 54

ABSTRACT

Studies were conducted examining the presence of neuroanatomical asymmetries in the limbic system, posterior temporal lobe and frontal operculum . Apes showed left hemisphere asymmetries in the frontal operculum and posterior temporal lobe . No population -level asymmetries were found for the amygdale, cerebellum and cingulate gyrus . Right hemisphere asymmetries were found for the hippocampus . Additional studies conducted this year revealed population -level asymmetries in motor skill of chimpanzees .

PSYCHOBIOLOGY OF INFANT ABUSE IN PRIMATES (0100)

NPRC UNIT : PSYCHOBIOLOGY

% NPRC $: 0.520 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
MAESTRIPIERI, DARIO	PHD	A	PSYCHOLOGY	UNIVERSITY OF CHICAGO, IL USA
E marre J	PHD	C	PSYCHOBIOLOGY	

AXIS I CODES: 1A **AXIS II CODES** 36, 65, 71

ABSTRACT

This project investigates the mechanisms underlying the cross -generational transmission of infant abuse in rhesus macaques and the possible biological correlates of abusive maternal behavior . In this year of the project, we continued our observations of social development of the female juveniles that were cross -fostered after birth . Almost all of our subjects have now given birth and their maternal behavior is currently being studied in relation to rearing experience . Preliminary analyses have provided evidence for genetic heritability of selected measures of female affiliation, aggression, and parent -offspring conflict .

INDUCTION OF PLASMODIUM INFECTIONS TO SUPPORT MALARIA VACCINE STUDIES (0078)

NPRC UNIT : RESEARCH RESOURCES

% NPRC $: 0.520 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
COLLINS, WILLIAM E	PHD	A	INFECTIOUS DISEASES	CENTERS FOR DISEASE CONTROL, GA-USA

AXIS I CODES: 1A, 3, 4, 7C, 17 **AXIS II CODES** 64, 66

ABSTRACT

Short-term infections with P . vivax, P . ovale and P . malariae were induced in chimpanzees to obtain blood -stage parasites for (1) preparation of genomic libraries, (2) extraction of m-RNA for genetic engineering studies, (3) antigen for serologic testing, (4) infection of mosquitoes through membrane feeding to produce sporozoites for (a) genetic engineering studies, (b) production of monoclonal antibodies, (c) sporozoite antigens for serologic testing, (d) to infect Aotus and Saimiri monkeys, and (e) to test the efficacy of experimental transmission -blocking and anti-sporozoite vaccines, and (5) production of immune sera . Emphasis continues on the evaluation of transmission -blocking vaccines by mixing gametocytes from the blood of chimpanzees infected with P . vivax and P . ovale with sera from immunized animals and feeding the mosquitoes through membranes on various dilutions of sera plus gametocytes . These studies will continue for the assessment of sera from humans being immunized with candidate transmission -blocking vaccines .

CHARACTERIZATION OF CO-RECEPTOR DEPENDENCE OF PRIMATE ISOLATES OF SIVSMM (0203)

NPRC UNIT : RESEARCH RESOURCES

% NPRC $: 0.300 % **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
GRANT, ROBERT M	MD, MPH, MS	A	MICROBIOLOGY & IMMUNOBIOLOGY	GLADSTONE INSTITUTE OF VIROLOGY & IMMUNOLOGY, CA USA
[illegible]	DVM	C	RESEARCH RESOURCES	

AXIS I CODES: 7B **AXIS II CODES** 31, 66

ABSTRACT

We hypothesized that a restricted pattern of cell receptor utilization, combined with host polymorphisms in the receptors, may account for the lack of progressive SIV pathogenesis in sooty mangabeys . This hypothesis is suggested by the finding that both of the SIV receptors are polymorphic in sooty mangabeys : ie: both CD 4 and CCR5. Over the last year we have used sooty mangabey blood shipped from Yerkes to develop methods for the isolation and culture of mangabey monocyte -derived macrophages . Extensive experimentation was required to identify conditions required for mangabey macrophage culture, including variation in specimen collection, cell separation, dilution, temperature, cell density, serum source (mangabey vs bovine vs human) and soluble cofactors . At this time, we have established conditions that reliably isolate and culture mangabey macrophages . Using these cultures, we have found that CCR 5 expression on mangabey macrophages is high, but expression of other SIVsmm coreceptors was not detected . This likely explains the CCR 5 dependence of SIVsmm replication on macrophages, which was not evident on mangabey lymphocytes that express substantial amounts of alternative coreceptors . We are currently evaluating whether SIVsmm replication in mangabey macrophages is cytopathic and whether viral tropism and cytopathicity is affected by CCR 5 and CD4 haplotype . In the course of this work, we have developed a novel method for antigen quantitation based on flow cytometry, which we have named "flourescence -linked antigen quantification or FLAQ ." Because of their rapid format, precise quantitation, and wide dynamic range, the FLAQ assays have proven to be useful for rapid quantification of SIV Gag p 27 and HIV Gag p 24 in cell cultures . This research, based on tissues uniquely available from Yerkes, are designed to evaluate the role of viral infection of macrophages in lentiviral pathogenesis that occurs in HIV -1 infected humans .

T LYMPHOCYTE TURNOVER IN NATURALLY SIV-INFECTED SOOTY MANGABEYS (0110)

NPRC UNIT : RESEARCH RESOURCES

%NPRC $: 0.921 % **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
KAUR, AMITINDER	MD	A	IMMUNOLOGY	NE REGIONAL PRIMATE RESEARCH CENTER, MA USA
	PHD	A	NIAID	NIH, MD USA
	MD	A	MICROBIOLOGY & IMMUNOLOGY	NE REGIONAL PRIMATE RESEARCH CENTER, MA USA
	DVM	C	RESEARCH RESOURCES	
	PHD	A		LOS ALAMOS NATIONAL LAB, NM USA
	PHD	A		UNIVERISTY OF OXFORD, UK

AXIS I CODES: 1A, 19 **AXIS II CODES** 31, 64, 66

ABSTRACT

Sooty mangabeys are natural hosts of the simian immunodeficiency virus (SIV) that do not progress to AIDS despite sustained high viral loads . Understanding the dynamics of T -lymphocyte turnover in these animals may shed light on the mechanisms of CD 4+ T cell depletion in HIV -infected humans and SIV -infected rhesus macaques . Six SIV-infected and 5 uninfected sooty mangabeys were given daily BrdU i .p. for 2 weeks . BrdU incorporation in T-cells was measured frequently during the labeling (first 2 weeks) and the follow -up de-labeling phase (median 10 weeks). The percentage of BrdU labeled T -cells vs time was fitted using a model of T -cell dynamics, from which we estimated the average death rate of the T -cell population . The mean death rate for both uninfected and infected CD4+ T-cells was 0.01 day-1, and for CD8+ T-cells it was 0.008 day-1 and 0.009 day-1, respectively . Using the Mann-Whitney U -test, there was no statistically significant difference in the average death rates of uninfected and infected monkeys, either in the CD 4+ (p=0.53) or the CD 8+ (p=0.41) T cell subsets . In contrast to hosts with pathogenic sequelae of lentiviral infection, CD 4+ and CD 8+ T-cell turnover as measured by BrdU incorporation is not increased in SIV -infected sooty mangabeys . This suggests that the natural host and virus have co -evolved so that viral infection does not increase average CD 4+ T cell death rates despite ongoing viral replication . Understanding how this equilibrium is achieved may be relevant for treating or preventing HIV infection .

CELLULAR IMMUNE RESPONSES IN SIV INFECTED SOOTY MANGABEYS (0209)

NPRC UNIT : RESEARCH RESOURCES

% NPRC $: 0.921 % **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
KAUR, AMITINDER	MD	A	IMMUNOLOGY	NE REGIONAL PRIMATE RESEARCH CENTER, MA USA
	DVM	C	RESEARCH RESOURCES	
	PHD	A	VACCINE RESEARCH CENTER	
	PHD	A	IMMUNOLOGY, NEPRC	

AXIS I CODES: 1A, 19 **AXIS II CODES** 31, 64, 66

ABSTRACT

The role of SIV-specific cellular immune responses in maintaining nonpathogenic SIV infection in sooty mangabeys is being investigated using Elispot and intracellular cytokine staining assays as well as by in vivo CD 8+ T lymphocyte depletion studies . In vivo CD 8 depletion using the mouse -human chimeric anti -CD8 mAB cM-T807 resulted in a two -log or greater increase in SIV viremia in 5/6 mangabeys . Return of SIV viremia levels to baseline values was coincident with recovery of peripheral CD 8+ T lymphocytes . These data suggest that CD 8+ T lymphocytes do inhibit SIV replication in vivo in SIV -infected sooty mangabeys . In a cross-sectional analysis, positive SIV -specific interferon -gamma Elispot responses ranging between 510-5244 spot forming cells per million PBMC were observed in 25/25 SIV-infected mangabeys and were comparable to that observed in four rhesus macaques infected for more than one year with SIVmac 251 . In the majority of sooty mangabeys, the interferon -gamma responses to SIV Gag and /or Env proteins accounted for at least two -thirds of the total SIV-specific response . In 9 mangabeys examined, the interferon -gamma responses to Gag and Env were predominantly mediated by high avidity CD 8+ T lymphocytes . In conclusion, naturally SIV -infected sooty mangabeys mount a substantial SIV -specific cellular immune response, suggesting that immune tolerance is neither a feature nor a requirement for maintenance of nonpathogenic infection in this natural host of SIV infection .

RISK ASSESSMENT DOSE RESPONSE MDL FOOD BORNE LISTERIA MONOCYTOGENES (0085)

NPRC UNIT : RESEARCH RESOURCES

% NPRC $: 0.522 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
SMITH, MARY ALICE	PHD	A	BIOLOGY	UNIVERSITY OF GEORGIA, GA USA
[illegible]	DVM	C	RESEARCH RESOURCES	

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

ABSTRACT

The objective of this study is to obtain dose response data for Listeria monocytogenes (Lm) for use in quantitative risk assessment using the pregnant rhesus monkey as a surrogate for humans . During the first phase of the study, we identified that the monkey clinical isolate 12443 was consistantly present in tissue samples of abortuses belonging to mothers fed a five strain mixture of Lm in whipping cream . The monkey clinical isolate 12443 was independently fed to five more monkeys at dosages ranging from 1.2 x 103 - 3.5 x 106 CFU. Three of these five pregnancies resulted in stillbirth . Twenty -four pregnant monkeys were given ca . 3.00 x 102 to 1.16 x 107 CFU Lm monkey clinical strain 12443 in whipping cream . Of these 24, four delivered stillbirths that were confirmed positive for Lm, three delivered stillbirths from which Lm could not be isolated, 17 others had normal births . No outward sign of illness was observed during the pregnancy for any of the adult monkeys .

Preinfection Lm antibody titres ranged from 800 - 1600 . At delivery, animals with normal infants had antibody titres no more than four -fold greater than pre -infection . Animals with stillbirths had antibody titres between 8 to 32-fold greater than preinfection . Antibody titers in the serum at 14-days post infection remained the same as preinfection in all monkeys regardless of the outcome of pregnancy . The antibody titers remained high during the recovery from the pregnancy . There was a difference in fecal shedding of Lm between animals that delivered stillbirths and animals that delivered normal infants . The former shed more often and for longer periods of time and shed higher numbers of organisms .

MACAQUES MHC AND MOTIF ANALYSES (0184)

NPRC UNIT : VACCINE RESEARCH CENTER

% NPRC $: 0.250 % **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
ALTMAN, JOHN	PHD	A	VACCINE RESEARCH CENTER	
[illegible] J	PHD	A	WISCONSIN PRIMATE RESEARCH CNT	UNIVERSITY OF WISCONSIN, WI USA

AXIS I CODES: 1D **AXIS II CODES** 31, 64, 91

ABSTRACT

Studies of the course of HIV -1 infection in humans point to an important role of major histocompatibility complex (MHC)-resstricted, HIV -specific, cytotoxic T lymphocytes (CTL) in the control of viral burden . At the same time, rhesus macaques challenged SIV or chimeric HIV /SIV viruses (SHIV) have emerged as the best animal model for pathogenesis and vaccine studies a major deficiency of this model is that characterization of SIV /SHIV CTL epitopes and their class I MHC restriction elements in macaques lags significantly behind CTL studies in humans The goal of the project is to intensively study the MHC allele found in the macaques used for the DNA vaccination studies (described by Dr Harriet Robinson in Project 1 of this program), providing data essential for an adequate interpretation of the results of those vaccine trials . The three specific aims of this project are : 1) genotypic analysis of the macaque class I MHC alleles (Mamu) using locus -specific PCR primers to clone the macaque cDNAs, followed by development of allele -specific primers for more rapid genotypic analyses; 2) characterization of the peptide binding motifs of the Mamu Class I proteins found at high frequency in our colony at the Yerkes Regional Primate Center, leading to testable predictions of CTL epitopes; and 3) production of novel MHC tetramers based on the alleles studied in Aim 2, leading to studies of the frequency and phenotype of the SIV /SHIV-specific CD 8+ T cells induced by the vaccination protocol or by challenge infection . Together with the data from the cellular immune response project of this program (Project 4, led by Dr. Villinger and [illegible]) and from the clinical course of the SHIV-challenged animals, these data will allow us to determine the epitope -specificity of CTL responses which correlate with protection from viral challenge .

T CELL REPERTOIRES SPECIFIC FOR DEFINED VIRAL EIPTOPES (0187)

NPRC UNIT : VACCINE RESEARCH CENTER

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
ALTMAN, JOHN	PHD	A	VACCINE RESEARCH CENTER	

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

ABSTRACT

We prepared and verified expression constructs for nine Mamu class I MHC alleles . We have obtained from the Watkins laboratory at the University of Wisconsin a list of approximately 30 peptide epitopes that they have mapped that are restricted by various MHC alleles, and have had those peptides synthesized . We have prepared about a third of the MHC tetramers for these MHC /peptide combinations, and are continuing to prepare the remainder of the tetramer reagents . The reagents we have prepared will be used for studies of the kinetics of CD 8+ T cell responses in rhesus macaques that are infected with various immunodeficiency viruses, and will be used to study the effects of escape mutations characterized by the Watkins laboratory on existing CD 8+ T cell responses .

DIETARY RESTRICTION AND AGING IN RHESUS MACAQUES (0210)

NPRC UNIT : VACCINE RESEARCH CENTER

% NPRC $: 0.520 %

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
ALTMAN, JOHN	PHD	A	VACCINE RESEARCH CENTER	
[name] J	PHD	A	VACCINE RESEARCH CENTER	UNIVERSITY OF WISCONSIN, WI USA

AXIS I CODES: 1A, 1D, 12 **AXIS II CODES** 30, 64, 78

ABSTRACT

Our hypothesis is that dietary restriction (DR) will similarly retard aging in a primate species, as reflected by attenuated rates of change of most biological indicators of aging, delayed diseases and increased longevity . Two Specific Aims will continue to be addressed . Aim 1 is to contribute to the development of the rhesus monkey (Macaca mulatta) as a model for the study of aging . An improved understanding of biological aging and its longitudinal measurement is needed in this species . Aim 2: to determine the influence of DR on the rate of aging in a primate species . Our structurally uncomplicated project has interdependent components . Dr. Altman will lead in the preparation of biotinylated rhesus macaque class I MHC monomers and fluorescently -labeled tetramers, a new class of extremely powerful reagents for the study of antigen -specific T cell immune responses . Production of these reagents requires considerable skill in protein chemistry and a laboratory that is well equipped for sophisticated protein purification . The experiments performed in Dr. Altman's laboratory will be directly related to testing the hypothesis on the effects of aging and dietary restriction . The lab will prepare new tetramers for quantitative analyses of the immunodominant CD 8+ T cell responses .

EVALUATION OF CELLULAR IMMUNITY INDUCED BY HIV VACCINES (0218)

NPRC UNIT : VACCINE RESEARCH CENTER

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
ALTMAN, JOHN	PHD	A	VACCINE RESEARCH CENTER	
[illegible]		A	VACCINE RESEARCH CENTER	
Names [illegible]	MD	A		DUKE UNIVERSITY MEDICAL CENTER, NC USA

AXIS I CODES: 12A **AXIS II CODES** 31, 64, 66, 91

ABSTRACT

The mission of the HIV Vaccine Trials Network is to develop and test the efficacy of candidate HIV Vaccines . The Central Immunology Laboratory (CIL) of the HVTN is responsible for assessment of immune responses induced by those vaccines in human subjects . The CIL has established a number of satellite laboratories called "Special Emphasis Groups " for the purposes of developing and validating novel assays of T cell function . The role of our laboratory in this project is to develop novel MHC tetramer reagents based upon a large panel of HLA alleles and the epitopes presented by those alleles in candidate vaccines, and to validate the use of these reagents in the evaluation of human clinical trials .effective communication within the laboratory network as well as between the CL and various functional units of the HVTN .

NIAID TETRAMER FACILITY (0243)

NPRC UNIT : VACCINE RESEARCH CENTER

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
ALTMAN, JOHN	PHD	A	VACCINE RESEARCH CENTER	
[illegible]	PHD	A	VACCINE CENTER	

AXIS I CODES: 9 **AXIS II CODES** 31, 64, 66, 91

ABSTRACT

The National Institute of Allergy and Infectious Diseases (NIAID) supports reagent programs and repositories that provide centralized resources for the research community. These facilities support research by providing reliable sources of quality assured materials, specimens, or experimental animals at reasonable cost to qualified investigators. The NIAID Tetramer Facility, established at Emory University in 1998 under the direction of John Altman, Ph.D., serves the scientific community as a centralized source of quality-controlled tetramer reagents for basic, preclinical, and clinical research. The NIAID Division of AIDS oversees the Facility, which is contracted by the AIDS Research and Reference Reagent Program with subcontracts to McKesson BioServices and Virginia Mason.

The Facility has provided tetramer reagents, comprising human, murine, and non-human primate MHC alleles to researchers at non-profit organizations both in the U.S. and abroad, including investigators supported by ten NIH Institutes, the Food and Drug Administration, the Department of Defense, the Centers for Disease Control and Prevention, and private non-profit U.S. foundations, as well as to researchers in Europe, Australia, Israel, and Canada; has produced tetramers applicable to a wide range of T cell studies, including research on AIDS and other infectious diseases, cancer, organ transplantation, autoimmunity, clinical vaccine evaluation, and basic studies on T cells and immune responses; and has developed standardized methodology for tetramer usage and evaluated new advances in tetramer design and production to assure that the Facility's reagents reflect state-of-the-art capabilities.

IN VITRO STIMULATION OF HIV SPECIFICS CD8+ T CELLS VACCINES (0247)

NPRC UNIT : VACCINE RESEARCH CENTER

%NPRC $: 0.520% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
ALTMAN, JOHN	PHD	A	VACCINE RESEARCH CENTER	
[name]	PHD	A		MCP HANNEMANN, PA USA

AXIS I CODES: 12 **AXIS II CODES** 31, 64, 91

ABSTRACT

We will provide MHC Tetramer reagents to, [name] the principal investigator of the grant, for use in cell free antigen -specific stimulation experiments . We will also consult with him about the design of his experiments and the use of tetramers . There is no scientific overlap with any of our studies .

EARLY FUNCTIONAL & STRUCTURAL REPAIR IN MACAQUE STRABISMUS (0089)

NPRC UNIT : VISUAL SCIENCE

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
BRADLEY, DOLORES V	PHD	A	VISUAL SCIENCE	SPELLMAN COLLEGE, GA USA
	PHD	A	DEPT OF ANATOMY & NEUROBIOLOGY	WASHINGTON UNIVERSITY SCHOOL OF MEDICINE, MO USA
Name	MS	A	VISUAL SCIENCE	WASHINGTON UNIVERSITY, WA USA
		A	OPTOMETRY	
	MD	A	VISUAL SCIENCE	WASHINGTON UNIVERSITY OF MEDICINE, MO USA

AXIS I CODES: 1A, 21, 25B **AXIS II CODES** 60, 71

ABSTRACT

The long term goal of this research is to reveal the neural mechanisms that explain each of the behavioral deficits of infantile strabismus (eye misalignment), and the time in development at which they occur. The specific goal of the project is to determine if eye realignment early in the critical period can repair the behavioral and structural deficits of the visual cortex that result from infantile strabismus. The present project is a subcontract to an R 01 from Washington University C Name I. Newborn macaques are reared wearing Dr. Bradley's goggles that were designed for young monkeys, and which are fitted with prism lenses to induce optical strabismus. The strabismus is "repaired" at one of three postnatal ages: 3 weeks, 3 months, 6 months; corresponding to "very early" (humans: 3 months of age), "average" (humans: 12 months of age), and "late" (humans: 2 years of age) strabismus surgery in children. In this preparation, repair of strabismus consists of the simple act of the removal of the prism goggles. The specific hypotheses generated for this project have in common the prediction that the earlier the realignment of the eyes, the greater the recovery of visual function.

RESEARCH SERVICES

NAME	NON-HOST INSTITUTION : STATE, COUNTRY	# SPECIES: SPECIMEN
L. Nemes	CHILDREN'S HOSPITAL: MA	2 PAN TROGLODYTES: WHOLE
	UNIVERSITY OF ALABAMA -BIRMINGHAM : AL	2 MACACA MULATTA: ORGANS
	EMORY UNIVERSITY-SCHOOL OF MEDICINE : GA	530 MACACA MULATTA: WHOLE
	EMORY UNIVERSITY-SCHOOL OF MEDICINE : GA	57 MACACA MULATTA: WHOLE
	EMORY UNIVERSITY-SCHOOL OF MEDICINE : GA	1 MACACA MULATTA: WHOLE
	EMORY UNIVERSITY-SCHOOL OF MEDICINE : GA	51 CERCOCEBUS ATYS: WHOLE
	EMORY UNIVERSITY-SCHOOL OF MEDICINE : GA	1 MACACA MULATTA: WHOLE
	EMORY UNIVERSITY-SCHOOL OF MEDICINE : GA	1 MACACA MULATTA: ORGANS
	EMORY UNIVERSITY-SCHOOL OF MEDICINE : GA	18 MACACA MULATTA: WHOLE
	EMORY UNIVERSITY-SCHOOL OF MEDICINE : GA	36 MACACA MULATTA: WHOLE
	EMORY UNIVERSITY-SCHOOL OF MEDICINE : GA	6 CERCOCEBUS ATYS: OTHERS
	EMORY UNIVERSITY-SCHOOL OF MEDICINE : GA	274 CERCOCEBUS ATYS: OTHERS
	MILLENIUM PHARMACEUTICALS, INC : CA	10 PAPIO: OTHERS
	ECCLES INST. OF HUMAN GENETICS, UNIVERSITY OF UTAH : UT	13 PAN TROGLODYTES: CELLS
	CORIELL INSTITUTE-CAMDEN : NJ	2 PAN TROGLODYTES: WHOLE
	CORIELL INSTITUTE-CAMDEN : NJ	4 PAN TROGLODYTES: TISSUES
	UNIVERSITY OF ILLINOIS -URBANA : IL	14 MACACA MULATTA: OTHERS
	UNIVERSITY OF ILLINOIS -URBANA : IL	12 MACACA MULATTA: OTHERS
	UNIVERSITY OF ILLINOIS -URBANA : IL	20 CERCOCEBUS ATYS: OTHERS
	EMORY UNIVERSITY, DEPT OF SURGERY : GA	8 MACACA MULATTA: TISSUES

EMORY UNIVERSITY, DEPT . OF SURGERY : GA	4 MACACA MULATTA: OTHERS
REPLIGEN CORPORATION -WALTHAM : MA	6 MACACA MULATTA: OTHERS
CELERA SSF, SOUTH SAN FRANCISCO : CA	7 PAPIO: OTHERS
INTERNATIONAL CENTER FOR GENETIC ENGINEERING AND BIOTECHNOLOGY, NEW DELHI	36 MACACA MULATTA: OTHERS
NATIONAL CANCER INSTITUTE, BETHESDA : MD	1 PAN TROGLODYTES: WHOLE
NATIONAL CANCER INSTITUTE, BETHESDA : MD	1 MACACA MULATTA: WHOLE
NATIONAL CANCER INSTITUTE, BETHESDA : MD	1 PAPIO: WHOLE
DEPT OF MICROBIOLOGY AND IMMUNOLOGY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	5 MACACA MULATTA: WHOLE
KRONOS SCIENCE LABORATORIES, PHOENIX : AZ	1 PAN TROGLODYTES: WHOLE
DEPT OF PSYCHIATRY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	126 MACACA MULATTA: WHOLE
DEPT OF PSYCHIATRY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	109 MACACA MULATTA: WHOLE
DEPT OF PSYCHIATRY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	47 MACACA MULATTA: OTHERS
DEPT OF PSYCHIATRY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	20 MACACA MULATTA: TISSUES
DEPT OF PSYCHIATRY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	46 MACACA MULATTA: OTHERS
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO : CA	1 MACACA MULATTA: ORGANS
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO : CA	1 MACACA MULATTA: ORGANS
CASE UNIVERSITY, CLEVELAND : OH	2 MACACA MULATTA: WHOLE
BIOQUAL INC ., ROCKVILLE : MD	3 PAN TROGLODYTES: WHOLE

BIOQUAL INC ., ROCKVILLE : MD	1 PAN TROGLODYTES: ORGANS
NATIONAL CANCER INSTITUTE, FREDERICK : MD	33 MACACA MULATTA: WHOLE
THE SCRIPPS RESEARCH INSTITUTE, LAJOLLA : CA	3 PAPIO: OTHERS
UNIVERSITY OF PENNSYLVANIA, SCHOOL OF MEDICINE : PA	15 MACACA MULATTA: OTHERS
BIORECLAMATION, INC ., HICKSVILLE : NY	30 PAN TROGLODYTES: OTHERS
UNIVERSITY OF CALIFORNIA AT LOS ANGELES : CA	2 PAPIO: ORGANS
UNIVERSITY OF TENNESSEE, MEMPHIS : TN	1 PAN TROGLODYTES: ORGANS
SAN FRANCISCO GENERAL HOSPITAL : CA	86 CERCOCEBUS ATYS: WHOLE
UNIVERSITY OF ALABAMA AT BIRMINGHAM : AL	6 PAN TROGLODYTES: OTHERS
UNIVERSITY OF ALABAMA AT BIRMINGHAM : AL	16 CERCOCEBUS ATYS: WHOLE
UNIVERSITY OF ALABAMA AT BIRMINGHAM : AL	4 PAN TROGLODYTES: WHOLE
NIH, BETHESDA: MD	4 CERCOCEBUS ATYS: WHOLE
VIRXSYS, GAITHERSBURG : MD	10 MACACA MULATTA: OTHERS
VIRXSYS, GAITHERSBURG : MD	9 MACACA MULATTA: OTHERS
CENTERS FOR DISEASE CONTROL AND PREVENTION, ATLANTA : GA	39 CERCOCEBUS ATYS: WHOLE
CENTERS FOR DISEASE CONTROL AND PREVENTION, ATLANTA : GA	17 MACACA NEMESTRINA: WHOLE
CENTERS FOR DISEASE CONTROL AND PREVENTION, ATLANTA : GA	40 MACACA MULATTA: OTHERS
CENTERS FOR DISEASE CONTROL AND PREVENTION, ATLANTA : GA	31 MACACA NEMESTRINA: OTHERS
CENTERS FOR DISEASE CONTROL AND PREVENTION, ATLANTA : GA	190 MACACA MULATTA: OTHERS
CENTERS FOR DISEASE CONTROL AND PREVENTION, ATLANTA : GA	6 MACACA NEMESTRINA: WHOLE

CENTERS FOR DISEASE CONTROL AND PREVENTION, ATLANTA : GA	52 MACACA NEMESTRINA: OTHERS
AUBURN UNIVERSITY: AL	18 MACACA MULATTA: OTHERS
DEPT OF OPTHALMOLOGY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	1 MACACA MULATTA: ORGANS
NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	122 CERCOCEBUS ATYS: WHOLE
NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	104 CERCOCEBUS ATYS: WHOLE
NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	3 MACACA MULATTA: WHOLE
NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	4 CERCOCEBUS ATYS: WHOLE
NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	6 CERCOCEBUS ATYS: ORGANS
NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	5 CERCOCEBUS ATYS: ORGANS
NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	6 CERCOCEBUS ATYS: ORGANS
NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	3 CERCOCEBUS ATYS: ORGANS
NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	4 CERCOCEBUS ATYS: OTHERS
NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	6 CERCOCEBUS ATYS: ORGANS
NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	3 CERCOCEBUS ATYS: TISSUES
NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	2 CERCOCEBUS ATYS: TISSUES

L	NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	2 CERCOCEBUS ATYS: TISSUES
	NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	4 CERCOCEBUS ATYS: ORGANS
	HARVARD UNIVERSITY, BOSTON: MA	3 PAN TROGLODYTES: WHOLE
names	NATIONAL INSTITUTE ON AIDS RESEARCH, BETHESDA : MD	3 CERCOCEBUS ATYS: WHOLE
	CENTERS FOR DISEASE CONTROL AND PREVENTION, ATLANTA : GA	6 CERCOCEBUS ATYS: WHOLE
	CENTERS FOR DISEASE CONTROL AND PREVENTION, ATLANTA : GA	7 MACACA MULATTA: WHOLE
	DEPT SRUGERY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	1 MACACA MULATTA: ORGANS
	DEPT SURGERY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	5 MACACA MULATTA: WHOLE
	DEPT SURGERY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	1 MACACA MULATTA: OTHERS
	DEPT SURGERY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	4 MACACA MULATTA: ORGANS
	DEPT SURGERY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	1 MACACA MULATTA: ORGANS
	DEPT SURGERY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	4 MACACA MULATTA: ORGANS
	DEPT SURGERY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	4 MACACA MULATTA: ORGANS
	DEPT SURGERY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	3 MACACA MULATTA: ORGANS
	DEPT SURGERY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	2 MACACA MULATTA: ORGANS
	DEPT SURGERY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	3 MACACA MULATTA: OTHERS
	DEPT SURGERY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	4 MACACA MULATTA: ORGANS
L	DEPT SURGERY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	4 MACACA MULATTA: ORGANS

names

DEPT SURGERY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	1 PAPIO: ORGANS
DEPT SURGERY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	9 PAPIO: TISSUES
DEPT SURGERY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	4 PAPIO: ORGANS
DEPT SURGERY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	2 PAPIO: WHOLE
DEPT SURGERY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	4 MACACA MULATTA: CELLS
DEPT SURGERY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	1 MACACA MULATTA: CELLS
DEPT SURGERY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	1 MACACA MULATTA: TISSUES
DEPT SURGERY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	2 MACACA MULATTA: ORGANS
DEPT SURGERY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	2 MACACA MULATTA: ORGANS
DEPT SURGERY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	1 MACACA MULATTA: ORGANS
DEPT SURGERY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	1 MACACA MULATTA: ORGANS
DEPT SURGERY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	2 MACACA MULATTA: CELLS
DEPT SURGERY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	4 MACACA MULATTA: ORGANS
DEPT SURGERY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	155 MACACA MULATTA: TISSUES
DEPT SURGERY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	6 MACACA MULATTA: WHOLE
DEPT SURGERY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	84 MACACA MULATTA: WHOLE
DEPT SURGERY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	7 MACACA MULATTA: WHOLE
DEPT SURGERY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	195 MACACA MULATTA: OTHERS
DEPT. SURGERY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	22 MACACA MULATTA: WHOLE

DEPT. SURGERY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	28 MACACA MULATTA: WHOLE
DEPT ANTHROPOLOGY, UNIVERSITY OF ILLINOIS, URBANA : IL	88 CERCOCEBUS ATYS: OTHERS
NATIONAL CANCER INSTITUTE, FREDERICK : MD	1 MACACA MULATTA: OTHERS
NATIONAL CANCER INSTITUTE, FREDERICK : MD	11 MACACA MULATTA: WHOLE
NATIONAL CANCER INSTITUTE, FREDERICK : MD	3 CERCOCEBUS ATYS: WHOLE
NATIONAL CANCER INSTITUTE, FREDERICK : MD	2 MACACA MULATTA: TISSUES
TULANE NATIONAL PRIMATE RESEARCH CENTER, COVINGTON, : LA	1 CERCOCEBUS ATYS: WHOLE
NATIONAL INSTITUTES OF HEALTH, ROCKVILLE : MD	12 MACACA MULATTA: OTHERS
TULANE NATIONAL PRIMATE RESEARCH CENTER : LA	2 CERCOCEBUS ATYS: WHOLE
NATIONAL INSTITUTE OF HEALTH, BETHESDA : MD	3 MACACA MULATTA: CELLS
NATIONAL INSTITUTES OF HEALTH, BETHESDA : MD	3 CERCOCEBUS ATYS: CELLS
UNIVERSITY OF WISCONSIN, MADISON : WI	10 MACACA MULATTA: WHOLE
UNIVERSITY OF WISCONSIN, MADISON : WI	10 MACACA MULATTA: OTHERS
DUKE UNIVERSITY MEDICAL CENTER, DURHAM : NC	302 MACACA MULATTA: OTHERS
DUKE UNIVERSITY MEDICAL CENTER, DURHAM : NC	13 MACACA MULATTA: OTHERS
UNIVERSITY OF KANSAS SCHOOL OF MEDICINE, KANSAS CITY : KS	26 MACACA NEMESTRINA: WHOLE
UNIVERSITY OF KANSAS SCHOOL OF MEDICINE, KANSAS CITY : KS	110 MACACA MULATTA: WHOLE
UNIVERSITY OF KANSAS SCHOOL OF MEDICINE, KANSAS CITY : KS	2 MACACA NEMESTRINA: WHOLE
NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM, ROCKVILLE : MD	55 MACACA MULATTA: WHOLE
NEW ENGLAND NATIONAL PRIAMTE RESEARCH CENTER, SOUTHBOROUGH : MA	3 CERCOCEBUS ATYS: ORGANS

L	NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	11 MACACA MULATTA: TISSUES
	NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	1 MACACA NEMESTRINA: ORGANS
	NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	1 MACACA NEMESTRINA: CELLS
	NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	1 MACACA NEMESTRINA: ORGANS
	NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	2 MACACA NEMESTRINA: ORGANS
names	NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	1 MACACA NEMESTRINA: TISSUES
	NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	1 MACACA NEMESTRINA: TISSUES
	NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	1 MACACA NEMESTRINA: TISSUES
	NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	2 MACACA NEMESTRINA: TISSUES
	NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	1 MACACA NEMESTRINA: TISSUES
	NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	1 MACACA NEMESTRINA: ORGANS
	NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	2 MACACA NEMESTRINA: TISSUES
	NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	1 MACACA NEMESTRINA: ORGANS
J	NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	2 MACACA NEMESTRINA: ORGANS

L	NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	1 MACACA NEMESTRINA: TISSUES
	NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	2 MACACA NEMESTRINA: TISSUES
	NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	2 MACACA NEMESTRINA: TISSUES
	NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	2 MACACA NEMESTRINA: TISSUES
	NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	2 MACACA NEMESTRINA: TISSUES
names	NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	2 MACACA NEMESTRINA: TISSUES
	NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	2 MACACA NEMESTRINA: TISSUES
	NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	1 MACACA NEMESTRINA: CELLS
	NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	2 MACACA NEMESTRINA: CELLS
	NEW ENGLAND NATIONAL PRIMATE RESEARCH CNETER, SOUTHBOROUGH : MA	2 MACACA NEMESTRINA: CELLS
	NEW ENGLAND NATIONAL PRIMATE RESEARCH CNETER, SOUTHBOROUGH : MA	17 MACACA MULATTA: TISSUES
	NEW ENGLAND NATIONAL PRIMATE RESEARCH CNETER, SOUTHBOROUGH : MA	17 MACACA MULATTA: TISSUES
	NEW ENGLAND RESEARCH CENTER, SOUTHBOROUGH : MA	4 CERCOCEBUS ATYS: TISSUES
	NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, SOUTHBOROUGH : MA	1 MACACA NEMESTRINA: TISSUES
⌟	MAX PLANCK INSTITUTE, LEIPZIG	4 PAN TROGLODYTES: ORGANS

MAX PLANCK INSTITUTE, LEIPZIG	2 PAN TROGLODYTES: TISSUES
MAX PLANCK INSTITUTE, LEIPZIG	3 PAN TROGLODYTES: ORGANS
MAX PLANCK INSTITUTE, LEIPZIG	3 PAN TROGLODYTES: ORGANS
MAX PLANCK INSTITUTE, LEIPZIG	1 PAN TROGLODYTES: ORGANS
MAX PLANCK INSTITUTE, LEIPZIG	1 PAN TROGLODYTES: ORGANS
MAX PLANCK INSTITUTE, LEIPZIG	1 PAN TROGLODYTES: TISSUES
MAX PLANCK INSTITUTE, LEIPZIG	1 PAN TROGLODYTES: TISSUES
MAX PLANCK INSTITUTE, LEIPZIG	1 PAN TROGLODYTES: ORGANS
BAYER DIAGNOSTICS, BERKELEY : CA	20 MACACA MULATTA: OTHERS
SCHOOL OF MEDICINE, STANFORD UNIVERSITY : CA	35 PAN TROGLODYTES: WHOLE
NATIONAL MALARIA RESEARCH CENTER, SILVER SPRINGS : MD	20 MACACA MULATTA: OTHERS
NATIONAL MALARIA RESEARCH CENTER, SILVER SPRINGS : MD	20 MACACA MULATTA: CELLS
UNIVERSITY OF WISCONSIN, MADISON : WI	37 MACACA MULATTA: WHOLE
POLO UNIVERSITARIO ANNUNZIATA, MESSINA	17 MACACA MULATTA: CELLS
POLO UNIVERSITARIO ANNUNZIATA, MESSINA	8 MACACA MULATTA: TISSUES
NEW YORK UNIVERSITY SCHOOL OF MEDICINE, NEW YORK : NY	14 CERCOCEBUS ATYS: OTHERS
NEW YORK UNIVERSITY SCHOOL OF MEDICINE, NEW YORK : NY	1 MACACA MULATTA: OTHERS
NEW YORK UNIVERSITY SCHOOL OF MEDICINE, NEW YORK : NY	2 CERCOCEBUS ATYS: WHOLE
TULANE UNIVERSITY, NEW ORLEANS : LA	2 MACACA MULATTA: CELLS
TULANE UNIVERSITY, NEW ORLEANS : LA	6 MACACA MULATTA: OTHERS
SUN LEALTH RESEARCH INSTITUTE, SUN CITY: AZ	3 MACACA MULATTA: ORGANS
NATIONAL CANCER INSTITUTE, FREDERICK : MD	1 MACACA MULATTA: WHOLE
NATIONAL CANCER INSTITUTE, FREDERICK : MD	2 MACACA MULATTA: CELLS
NATIONAL CANCER INSTITUTE, FREDERICK : MD	1 MACACA MULATTA: OTHERS

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DADA -FARBER CANCER INSTITUTE, BOSTON: MA	4 MACACA NEMESTRINA: WHOLE
DANA -FARBER CANCER INSTITUTE: MA	1 MACACA MULATTA: TISSUES
DANA -FARBER CANCER INSTITUTE, BOSTON: MA	3 MACACA MULATTA: WHOLE
DANA -FARBER CANCER INSTITUTE, BOSTON: MA	526 MACACA MULATTA: OTHERS
DANA -FARBER CANCER INSTITUTE, BOSTON: MA	5 MACACA MULATTA: OTHERS
DANA -FARBER CANCER INSTITUTE, BOSTON: MA	21 MACACA MULATTA: OTHERS
DANA -FARBER CANCER INSTITUTE, BOSTON: MA	1 MACACA MULATTA: OTHERS
DANA -FARBER CANCER INSTITUTE, BOSTON: MA	1 MACACA MULATTA: TISSUES
DANA -FARBER CANCER INSTITUTE, BOSTON: MA	1 MACACA MULATTA: TISSUES
DANA -FARBER CANCER INSTITUTE, BOSTON: MA	1 MACACA MULATTA: TISSUES
DANA -FARBER CANCER INSTITUTE, BOSTON: MA	1 MACACA MULATTA: TISSUES
DANA -FARBER CANCER INSTITUTE, BOSTON: MA	1 MACACA MULATTA: TISSUES
DANA -FARBER CANCER INSTITUTE, BOSTON: MA	4 MACACA MULATTA: TISSUES
DANA -FARBER CANCER INSTITUTE, BOSTON: MA	4 MACACA MULATTA: TISSUES
DANA -FARBER CANCER INSTITUTE, BOSTON: MA	4 MACACA MULATTA: TISSUES
DANA -FARBER CANCER INSTITUTE, BOSTON: MA	4 MACACA MULATTA: TISSUES
DANA -FARBER CANCER INSTITUTE, BOSTON: MA	4 MACACA MULATTA: TISSUES
DANA -FARBER CANCER INSTITUTE, BOSTON: MA	4 MACACA MULATTA: ORGANS
DANA -FARBER CANCER INSTITUTE, BOSTON: MA	4 MACACA MULATTA: ORGANS
DANA -FARBER CANCER INSTITUTE, BOSTON: MA	4 MACACA MULATTA: ORGANS
DANA -FARBER CANCER INSTITUTE, BOSTON: MA	16 MACACA MULATTA: OTHERS
DANA -FARBER CANCER INSTITUTE, BOSTON: MA	1 MACACA MULATTA: ORGANS
DANA -FARBER CANCER INSTITUTE, BOSTON: MA	5 MACACA MULATTA: TISSUES
DANA -FARBER CANCER INSTITUTE, BOSTON: MA	5 MACACA MULATTA: ORGANS
DANA -FARBER CANCER INSTITUTE, BOSTON: MA	9 MACACA MULATTA: ORGANS
DANA -FARBER CANCER INSTITUTE, BOSTON: MD	9 MACACA MULATTA: ORGANS
DANA -FARBER CANCER INSTITUTE, BOSTON: MA	1 MACACA MULATTA: TISSUES
DANA -FARBER CANCER INSTITUTE, BOSTON: MA	8 MACACA MULATTA: TISSUES

names

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DANA -FARBER CANCER INSTITUTE, BOSTON: MA	4 MACACA MULATTA: TISSUES
DANA -FARBER CANCER INSTITUTE, BOSTON: MA	16 MACACA MULATTA: TISSUES
DANA -FARBER CANCER INSTITUTE, BOSTON: MA	21 MACACA MULATTA: OTHERS
DANA -FARBER CANCER INSTITUTE, BOSTON: MA	22 MACACA MULATTA: TISSUES
DANA -FARBER CANCER INSTITUTE, BOSTON: MA	1 MACACA MULATTA: WHOLE
DANA -FARBER CANCER INSTITUTE, BOSTON: MA	32 MACACA MULATTA: WHOLE
DANA -FARBER CANCER INSTITUTE, BOSTON: MA	36 MACACA NEMESTRINA: WHOLE
DANA -FARBER CANCER INSTITUTE, BOSTON: MA	1,043 MACACA MULATTA: WHOLE
DANA -FARBER CANCER INSTITUTE, BOSTON: MA	112 MACACA MULATTA: WHOLE
HARVARD UNIVERSITY, CAMBRIDGE : MA	1 PAN TROGLODYTES: TISSUES
HARVARD UNIVERSITY, CAMBRIDGE : MA	1 PAN TROGLODYTES: ORGANS
HARVARD UNIVERSITY, CAMBRIDGE : MA	4 PAN TROGLODYTES: ORGANS
DEPT OF PEDIATRICS EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	12 MACACA MULATTA: CELLS
DEPT OF PEDIATRICS, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	185 MACACA MULATTA: OTHERS
DEPT OF PEDIATRICS, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	120 MACACA MULATTA: OTHERS
BIOANALYTICAL SYSTEMS, INC., WEST LAFAYETTE : IA	6 PAPIO: OTHERS
CHILDREN'S HOSPITAL, OAKLAND : CA	1 PAN TROGLODYTES: WHOLE
UNIVERSITY OF NORTH CAROLINA, CHAPEL HILL : NC	3 MACACA MULATTA: OTHERS
UNIVERSITY OF TEXAS, DALLAS : TX	12 CERCOCEBUS ATYS: WHOLE
UNIVERSITY OF TEXAS, DALLAS : TX	51 CERCOCEBUS ATYS: WHOLE
UNIVERSITY OF TEXAS, DALLAS : TX	6 CERCOCEBUS ATYS: TISSUES
UNIVERSITY OF TEXAS, DALLAS : TX	6 CERCOCEBUS ATYS: TISSUES
MOREHOUSE SCHOOL OF MEDICINE, ATLANTA : GA	12 MACACA MULATTA: ORGANS
MOREHOUSE SCHOOL OF MEDICINE, ATLANTA : GA	2 MACACA NEMESTRINA: ORGANS
ARIZONA STATE UNIVERSITY, TEMPE : AZ	2 PAN TROGLODYTES: WHOLE

UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA : PA	3 MACACA MULATTA: ORGANS
UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA : PA	3 MACACA MULATTA: ORGANS
DEPT OF PATHOLOGY EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	1 MACACA MULATTA: CELLS
GEORGIA STATE UNIVERSITY, ATLANTA : GA	43 MACACA MULATTA: WHOLE
GEORGIA STATE UNIVERSITY, ATLANTA : GA	2 MACACA MULATTA: WHOLE
UNIVERSITY OF CALIFORNIA AT SAN DIEGO : CA	10 PAN TROGLODYTES: WHOLE
DEPT OF PATHOLOGY EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	3 MACACA MULATTA: OTHERS
DEPT OF PATHOLOGY EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	1 MACACA MULATTA: ORGANS
DEPT OF PATHOLOGY EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	2 MACACA MULATTA: ORGANS
DEPT OF PATHOLOGY EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	1 MACACA MULATTA: TISSUES
DEPT OF PATHOLOGY EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	3 MACACA MULATTA: ORGANS
DEPT OF PATHOLOGY EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	3 MACACA MULATTA: ORGANS
DEPT OF PATHOLOGY EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	3 MACACA MULATTA: CELLS
DEPT OF PATHOLOGY EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	3 MACACA MULATTA: ORGANS
DEPT OF PATHOLOGY EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	3 MACACA MULATTA: ORGANS
DEPT OF PATHOLOGY EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	6 MACACA MULATTA: ORGANS

names

DEPT OF PATHOLOGY EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	4 MACACA MULATTA: ORGANS
DEPT OF PATHOLOGY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	29 MACACA MULATTA: WHOLE
DEPT OF PATHOLOGY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	29 MACACA MULATTA: WHOLE
DEPT OF PATHOLOGY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	1 MACACA MULATTA: TISSUES
DEPT OF PATHOLOGY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	1 MACACA MULATTA: TISSUES
DEPT OF PATHOLOGY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	14 MACACA MULATTA: WHOLE
DEPT OF PATHOLOGY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA : GA	3 MACACA MULATTA: ORGANS
DEPT OF PATHOLOGY EMORY UNIVERSITY SHCOOL OF MEDICINE, ATLANTA : GA	2 MACACA MULATTA: ORGANS
FOOD AND DRUG ADMINISTRATION, LAUREL : MD	3 MACACA MULATTA: WHOLE
FOOD AND DRUG ADMINISTRATION, LAUREL : MD	72 MACACA MULATTA: WHOLE
FOOD AND DRUG ADMINISTRATION, LAUREL : MD	12 MACACA MULATTA: OTHERS
FOOD AND DRUG ADMINISTRATION, LAUREL : MD	2 MACACA MULATTA: OTHERS
FOOD AND DRUG ADMINISTRATION, LAUREL : MD	2 MACACA MULATTA: OTHERS
FOOD AND DRUG ADMINISTRATION, LAUREL : MD	3 MACACA MULATTA: OTHERS
WASHINGTON UNIVERSITY SCHOOL OF MEDICINE, ST LOUIS : MO	2 PAN TROGLODYTES: WHOLE
WASHINGTON UNIVERSITY SCHOOL OF MEDICINE, ST LOUIS : MO	2 PAN TROGLODYTES: WHOLE

names

	BAYER DIAGNOSTICS, EMERYVILLE : CA	20 MACACA MULATTA: OTHERS
	VIRXSYS, GAITHERSBURG : MD	19 MACACA MULATTA: OTHERS
	VIROLOGIC COMPANY, SOUTH SAN FRANCISCO : CA	32 MACACA MULATTA: OTHERS
	SANTEEN SERUM PHARMACEUTICAL, CHANTILLY : VA	40 PAN TROGLODYTES: OTHERS
	ADMINISTRATION PUGET SOUND HEALTHCARE SYSTEM, SEATTLE : WA	1 SAIMIRI SCIUREUS: OTHERS
	SOUTHWEST FOUNDATION FOR BIOMEDICAL RESEARCH, SAN ANTONIO : TX	2 CERCOCEBUS ATYS: WHOLE

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In press publication

SOURCE OF INVESTIGATORS' SUPPORT

NON-FEDERAL

FOUNDATION

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KUHAR, MICHAEL J			
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PRUESS, TODD M			
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WILSON, MARK E			
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WINSLOW, JAMES T			
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private funding

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DHHS	0000264878	$	60,204	
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DHHS	200-2000-10064	$	1,000,000	0180
MULY, E CHRISTOPHER				
NSF	01-1068	$	34,152	0276
PULENDRAN, BALI				
DHHS		$	105,960	0272
SMITH, YOLAND				
DOD	DAMD17-99-1-9546	$	142,404	0136
YOUNG, LARRY J				
NSF	INT-0233145	$	12,312	0118
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NIH	5R01DA010344-07	$	400,000	
NIH	5K02DA000517-03	$	95,879	
NIH	1R01DA016589-01	$	413,181	
L Name J				
NIH	5R01MH062044-03	$	214,500	
NIH	5R01MH062044-02	$	250,250	
HUNTER, RICHARD				
NIH	5F31DA015277-02	$	24,418	
JABBAR, M A				
NIH	5R21AI44334-02	$	246,750	0189
JACOB, JOSHY				
NIH	5R01AI047253-03	$	280,000	
L Name J				
NIH	5R01NS039852-04	$	220,200	
NIH	1R01MH065634-01A2	$	248,936	
JAWORSKI, JASON				
NIH	5F32DA015279-02	$	46,420	
JOHNS, MICHAEL M E				
NIH	RR00165	$	8,789,700	0191
L Name J				
NIH	1K05DA015805-01A1	$	119,556	
L Name J				
NIH	5P01HL045666-12	$	2,248,531	
L Name J				
NIH	5R01AI052005-02	$	339,750	
NIH	5R01AI046719-06	$	275,137	
KAUR, AMITINDER				
NIH	5R01AI043890-06	$	422,500	
NIH	5R01AI049809-03	$	294,690	
KIMMEL, HEATHER				
NIH	1K01DA015092-01A1	$	117,867	
KUHAR, MICHAEL J				
NIH	5R01DA010732-06	$	414,702	
NIH	5R01DA015162-02	$	240,000	
NIH	5K05DA000418-05	$	120,463	
NIH	1T32DA015040-01A1	$	222,221	
LARSEN, CHRISTIAN				

NIH	5R01AI040519-08	$	342,000	
NIH	5U19AI051731-02	$	1,014,106	
NIH	5P01AI044644-06	$	1,428,478	
L Name J				
NIH	5R01AG017994-04	$	284,879	
NIH	1R01AG021042-01A1	$	347,173	
L Name J				
NIH	5R01NS030454-14	$	312,665	
NIH	5T32GM008169-17	$	802,606	
L Name J				
NIH	1U54AI057168-01	$	3,986,438	
NIH	5R01AI040297-07	$	371,250	
NIH	5T32AI007524-07	$	235,234	
LIM, MIRANDA M				
NIH	5F30MH065050-03	$	24,096	
MAESTRIPIERI, DARIO				
NIH	5K02MH063097-03	$	98,608	
NIH	5R01MH062577-04	$	210,994	
L Name J				
NIH	1R01EY014263-01A1	$	285,920	
MCCLURE, HAROLD M				
NIH	5R01HL065937-04	$	240,000	
L Name J				
NIH	2R01NS038998-05	$	328,175	
MITTLER, ROBERT				
NIH	5R01CA085860-02	$	284,800	
L Name J				
NIH	5R01AG013396-08	$	243,311	
NIH	5R01AG013396-07	$	243,311	
NIH	1P01AG020677-01A1	$	1,570,710	
MORENO, ALBERTO				
NIH	5R01AI052371-03	$	400,000	0302
MOSER, JANICE				
NIH	1F32CA103388-01	$	17,795	
L Name J				
NIH	5U01AI047996-04	$	1,261,890	
MULY, E CHRISTOPHER				
NIH	5K08MH001994-03	$	154,614	
MUSTARI, MICHAEL J				
NIH	5R01EY013308-02	$	390,400	
NIH	2R01EY006069-18A1	$	392,500	
NAIR, HEMANTH				
NIH	1F32MH066551-01A1	$	46,420	
L Name J				
NIH	5R01AR046452-04	$	186,240	
NARAYAN, OPENDRA				
NIH	5P20RR016443-03	$	2,123,599	
NIH	5R01AI051220-02	$	712,734	

NIH	5R01RR006753-13	$	690,390
NIH	5R01NS040238-05	$	600,247
L Name J			
NIH	5R01MH042088-17	$	380,000
NIH	5R01MH039415-20	$	342,000
NIH	5P50MH058922-05	$	2,881,761
NIH	1U19MH069056-01	$	748,728
NOVEMBRE, FRANCIS J			
NIH	1R01MH067769-01	$	511,887
L Name J			
NIH	3R01RR006555-12S1	$	33,150
NIH	5R01RR006555-12	$	232,050
NIH	5R37AI028433-12	$	217,086
L Name J			
NIH	5R01NS031621-10	$	288,800
L Name J			
NIH	5R01EY012779-04	$	249,315
NIH	5R01EY009834-11	$	226,500
NIH	5T32EY007157-04	$	226,507
PULENDRAN, BALI			
NIH	5R01DK057665-05	$	257,662
NIH	5R01AI048638-04	$	240,000
NIH	1R01AI056499-01	$	190,125
I Name J			
NIH	1R24HD047142-01A1	$	382,500
RESSLER, KERRY J			
NIH	1K01MH069884-01	$	172,556
ROBINSON, HARRIET			
NIH	3P01AI043045-05S1	$	1,119,409
NIH	5P01AI049364-03	$	3,892,120
L Name J			
NIH	5P01AG000001-28	$	2,032,301
ROTHBAUM, BARBARA			
NIH	1R24MH067314-01A1	$	356,752
NIH	1R41DA016462-01	$	171,186
RUPRECHT, RUTH M			
NIH	5R37AI034266-09	$	689,455
NIH	5P01AI048240-04	$	1,966,903
NIH	5R01RR014180-05	$	739,280
NIH	5R01DE012937-05	$	386,329
NIH	1R21AI054183-01	$	497,060
SCHINAZI, RAYMOND F			
NIH	5R37AI041980-07	$	195,507
SILVESTRI, GUIDO			
NIH	1R21AI054234-01A1	$	331,100
NIH	1R01AI052755-01A1	$	400,000
SMITH, YOLAND			
NIH	2R01NS037423-06A1	$	312,650
NIH	5R01NS042937-02	$	342,000

NIH	5R01NS037948-06	$	190,000
SODORA, DONALD L			
NIH	2R01AI035522-11A1	$	194,802
SPECK, SAMUEL H			
NIH	1R01AI058057-01	$	338,000
NIH	1R01CA095318-01A2	$	320,400
NIH	2R01CA052004-15	$	338,400
NIH	5R01CA087650-04	$	324,000
NIH	5R01CA058524-10	$	265,501
NIH	5R01CA043143-17	$	284,800
L Name J			
NIH	5R01MH024600-31	$	485,071
STAPRANS, SILVIJA			
NIH	1R01HL075766-01	$	759,317
NIH	1R21AI054260-01	$	400,000
L Name J			
NIH	1F32CA101509-01	$	49,864
L Name J			
NIH	2R01NS037424-04A1	$	342,551
L Name J			
NIH	5R01NS039419-04	$	342,000
NIH	5R01NS036654-06	$	324,900
VILLINGER, FRANCOIS			
NIH	1R01HL075833-01	$	649,987
NIH	5R24RR016988-02	$	304,000
L Name J			
NIH	5R01GM063824-02	$	202,117
WALLEN, KIM			
NIH	5R01MH050268-09	$	320,000
NIH	1R01HD044161-01	$	360,000
L Name J			
NIH	5R01MH058616-05	$	146,527
NIH	5R21MH066734-02	$	182,500
NIH	5R01MH058616-04	$	142,260
L Name J			
NIH	5R37HD020521-19	$	293,866
NIH	5P01HD035576-06	$	1,012,391
NIH	5R37HD020521-18	$	285,307
L Name J			
NIH	5R24RR016038-03	$	490,135
NIH	5R24RR015371-04	$	551,851
NIH	5R01AI049120-03	$	931,391
NIH	5R01AI046366-05	$	440,507
NIH	1R01AI052056-01A1	$	661,445
L Name J			
NIH	1P20CA103697-01	$	586,000
NIH	5R01AG018922-03	$	372,081
NIH	5P01AG011915-10	$	1,416,472
NIH	5T32AG000213-13	$	385,144

L Name J			
NIH	5U01AI046725-04	$	8,314,361
WILSON, MARK E			
NIH	5R01HD038917-03	$	360,000
NIH	5R01HD037583-04	$	324,000
YOUNG, LARRY J			
NIH	5R01MH056538-08	$	360,000
NIH	5K02MH064692-02	$	106,730
NIH	5R01MH056897-07	$	288,429
L Name J			
NIH	5R01DK055850-04	$	296,909
ZOLA, STUART M			
NIH	1G20RR018323-01	$	695,449
	FEDERAL - PHS	$	122,802,184
	FEDERAL	$	126,141,364
TOTAL FUNDING:		**$**	**129,807,933**

RESOURCE SUMMARY SUBPROJECTS

The following only includes information associated with subprojects

	Mgmt. A	Research B	Pilot C	Collab . D	Total (excludes
Number of Subprojects	12	155	2	18	187
Number of Investigators	30	193	6	34	227
Number of Published	26	219	2	12	258
Number In Press	0	61	0	6	67
%AIDS of NPRC Dollars	7.785%	29.196%	0.000%	6.232%	43.213 %
%Non-AIDS of NPRC Dollars	2.000%	49.345%	1.150%	4.292%	56.787 %
Total Percent of NPRC Funds Awarded	9.785%	78.541%	1.150%	10.524%	100.000 %

RESOURCE SUMMARY ADMINISTRATIVE

PERSONNEL		On Subprojects	Not On Subprojects
Core Personnel			
DOCTORAL LEVEL SCIENTISTS (C)		22	0
	Core Personnel	22	0
Non-Core Personnel			
AFFILIATED (A)		192	0
GRADUATE STUDENT /POST DOCTORAL SCIENTIST (G)		13	0
	Non-Core Personnel	205	0
Personnel Total :		227	0

ACCESS BY NON -NPRC PERSONNEL

GEOGRAPHICAL USAGE BY INVESTIGATORS AT NON -HOST INSTITUTIONS

Foreign Investigators by Country	7
BC, CANADA	1
GERMANY	2
JAPAN	1
UK	3
USA Investigators by State	84
AL	2
CA	5
CO	1
FL	2
GA	24
IL	1
KS	1
KY	1
LA	1
MA	11
MD	4
MN	1
MO	2
MS	1
NC	8
NH	1
NJ	1
NM	1
NY	2
OH	1
PA	4
SC	2
TX	1
VA	1
WA	3
WI	2
Total Investigators at Non Host Institutions :	91

RESEARCH SERVICES

Scientists Provided with Services	81
Services Provided	8,405

RESEARCH SERVICES BY COUNTRY

Research Services to Foreign Investigators by Country	**3**
GERMANY	9
INDIA	1
ITALY	2
Research Services to USA Investigators by State	**78**
AL	3
AZ	3
CA	12
GA	14
IA	1
IL	2
KS	1
LA	3
MA	8
MD	15
MO	1
NC	2
NJ	1
NY	2
OH	1
PA	2
TN	1
TX	2
UT	1
VA	1
WA	1
WI	2
Total Research Services :	**81**

INFRASTRUCTURE TABLE

GRANT REPORTED UNITS	**% NPRC USE**
ADMINISTRATIVE	2.000 %
ANIMAL RESOURCES	3.570 %
CNTR BEHAV NEUROSCIENCE	2.380 %
MICROBIOLOGY & IMMUNOLOGY	23.460 %
NEUROSCIENCE	17.240 %
PSYCHOBIOLOGY	10.090 %
RESEARCH RESOURCES	20.380 %
VACCINE RESEARCH CENTER	15.680 %
VISUAL SCIENCE	5.200 %
TOTAL NPRC:	**100.00 %**

RESEARCH TABLE

UNITS GENERATED BY SUBPROJECTS	**% NPRC USE**
ADMINISTRATIVE	3.000 %
ANIMAL RESOURCES	3.040 %
CNTR BEHAV NEUROSCIENCE	7.040 %
MICROBIOLOGY & IMMUNOLOGY	19.460 %
NEUROSCIENCE	18.300 %

PSYCHOBIOLOGY		8.510 %
RESEARCH RESOURCES		18.040 %
VACCINE RESEARCH CENTER		18.360 %
VISUAL SCIENCE		4.250 %
	TOTAL NPRC:	**100.000 %**

RESOURCE SUMMARY PUBLICATIONSUPPORT

PUBLICATIONS

	Cited	Not Cited	Total
Published			
Abstracts	43	74	117
Books	12	28	40
Journals	66	141	207
In Press			
Abstracts	1	14	15
Books	9	27	36
Journals	31	51	82
Total	162	335	497

INVESTIGATOR SUPPORT

NON-FEDERAL		
FOUNDATION	$	3,313,779
INDUSTRY	$	352,790
NON-FEDERAL	**$**	**3,666,569**
FEDERAL		
NON-PHS		
DHHS	$	1,211,778
DOD	$	313,222
NSF	$	1,677,480
VA	$	136,700
NON-PHS	**$**	**3,339,180**
PHS		
AA	$	3,383,130
AG	$	8,405,190
AI	$	47,473,153
AR	$	186,240
CA	$	2,471,560
DA	$	7,455,072
DE	$	386,329
DK	$	554,571
ES	$	1,307,200
EY	$	2,004,142
GM	$	1,196,540
HD	$	3,109,864
HL	$	5,059,339
MH	$	16,319,382
NS	$	7,277,238
RR	$	16,213,234

	PHS	**$ 122,802,184**
	TOTAL SUPPORT	**$ 129,807,933**

COLONY STATISTICS

Base Breeding Colony Only

Note: These animals are supported by NCRR Comparative Medicine

[1]Genus Species	May-03	[2]Live Births	[3]Other Additions	Exper. Use	[4]Other Reduct.	[5]Sold or Trans.	[6]Trans. in Center	Apr-04
CERCOCEBUS ATYS (SPF)								
Adult Females(SPF)	33	0	1	0	3	0	0	31
Adult Males(SPF)	26	0	10	0	2	0	0	34
Infants/Juveniles(SPF)	24	0	0	0	1	0	0	23
MACACA MULATTA								
Adult Females	291	0	70	0	11	0	19	331
Adult Males	13	0	2	0	1	0	3	11
Infants/Juveniles	438	249	114	0	76	0	82	643
MACACA MULATTA (SPF)								
Adult Females(SPF)	177	0	0	0	4	0	9	164
Adult Males(SPF)	27	0	0	0	1	0	0	26
Infants/Juveniles(SPF)	154	84	1	0	9	0	24	206
MACACA NEMESTRINA								
Adult Females	37	0	0	0	3	0	2	32
Adult Males	17	0	0	0	0	0	3	14
Infants/Juveniles	39	14	2	0	1	0	3	51
MACACA NEMESTRINA (SPF)								
Adult Females(SPF)	45	0	0	0	5	0	4	36
Adult Males(SPF)	7	0	0	0	3	0	0	4
Infants/Juveniles(SPF)	66	21	11	0	34	0	0	64
	1,394	**368**	**211**	**0**	**154**	**0**	**149**	**1,670**

1 - Animals that are known free of SIV, STLV, SRV/D and Herpes B
2 - Live birth defined as inflated lungs
3 - Purchased from outside Center or transferred from another colony within the Center
4 - Includes deaths due to intercurrent diseases and other causes
5 - Permanent transfer or sale to outside the Center
6 - Transferred to another colony within the Center

Non-Primate Colony Only

Note: These animals are not supported by NCRR Comparative Medicine

[1]Genus Species	May-03	[2]Live Births	[3]Other Additions	Exper. Use	[4]Other Reduct.	[5]Sold or Trans.	[6]Trans. in Center	Apr-04
MICROTUS OCHROGASTER/MONTANUS								
Gender Undetermined	720	1,054	0	1,099	0	0	0	675
MUS MUSCULUS								
Gender Undetermined	4,184	2,978	6,893	10,578	0	0	0	3,477
RATTUS RATTUS								
Gender Undetermined	128	0	1,161	841	0	0	0	448
	5,032	**4,032**	**8,054**	**12,518**	**0**	**0**	**0**	**4,600**

Non-Base Breeding Colony Only

Note: These animals are supported by NCRR Comparative Medicine

[1]Genus Species	May-03	[2]Live Births	[3]Other Additions	Exper. Use	[4]Other Reduct.	[5]Sold or Trans.	[6]Trans. in Center	Apr-04
PAN TROGLODYTES								
Adult Females	11	0	0	0	0	0	0	11
Adult Males	4	0	0	0	0	0	0	4
Infants/Juveniles	7	0	0	0	0	0	0	7
	22	**0**	**0**	**0**	**0**	**0**	**0**	**22**

Research Colony Only

Note: These animals are supported by NCRR Comparative Medicine

[1]Genus Species	May-03	[2]Live Births	[3]Other Additions	Exper. Use	[4]Other Reduct.	[5]Sold or Trans.	[6]Trans. in Center	Apr-04
CEBUS APELLA								
Adult Females	13	0	0	0	0	0	0	13
Adult Males	7	0	0	0	0	0	0	7
Infants/Juveniles	8	4	1	0	1	0	0	12
CERCOCEBUS ATYS								
Adult Females	87	0	0	0	11	1	0	75
Adult Males	88	0	0	0	4	0	10	74
MACACA ARCTOIDES								
Adult Females	1	0	0	0	0	0	0	1
MACACA FASCICULARIS								
Adult Females	1	0	0	0	0	0	0	1
Adult Males	17	0	0	0	1	0	0	16
MACACA MULATTA								
Adult Females	552	0	22	14	19	9	61	471
Adult Males	426	0	4	49	10	18	2	351
Infants/Juveniles	420	129	103	41	31	15	70	495
MACACA NEMESTRINA								
Adult Females	56	0	6	4	5	0	0	53
Adult Males	30	0	17	2	0	0	0	45
Infants/Juveniles	23	18	3	0	4	0	2	38
PAN TROGLODYTES								
Adult Females	83	0	0	1	3	0	0	79
Adult Males	61	0	0	0	3	0	0	58
Infants/Juveniles	5	0	0	0	0	0	0	5
PAPIO								
Adult Males	23	0	0	5	2	0	0	16
SAIMIRI SCIUREUS								
Adult Males	48	0	0	0	0	0	0	48
Infants/Juveniles	14	0	6	3	0	0	0	17
	1,963	**151**	**162**	**119**	**94**	**43**	**145**	**1,875**

1 - Animals that are known free of SIV, STLV, SRV/D and Herpes B
2 - Live birth defined as inflated lungs
3 - Purchased from outside Center or transferred from another colony within the Center
4 - Includes deaths due to intercurrent diseases and other causes
5 - Permanent transfer or sale to outside the Center
6 - Transferred to another colony within the Center

RESEARCH HIGHLIGHTS

PSYCHOSTIMULANT-LIKE EFFECTS OF CART NEUROPEPTIDES

SPID(s): 0282

CART peptide, a chemical that occurs naturally in both the rodent and human brain, reduces some effects of cocaine when additional amounts are administered to the region of the brain that is associated with reward and addiction . The investigators infused CART peptide into the nucleus accumbens (NA) of rodents to determine how it affects the increase of body movement, or locomotor activity, that is widely seen as one effect of psychostimulant drugs . The researchers observed that the cocaine -induced movement was reduced after the rodents received CART peptide . This is the first study to demonstrate CART peptides in the nucleus accumbens hinder the effects of cocaine and opens a door to develop potential treatment options for cocaine addiction .

When infused into other areas of the "pleasure pathway, " the part of the brain in both rodents and humans that is activated when cocaine is administered, CART peptide has been shown to produce minimal psychostimulant -like effects. Past studies have shown CART peptide is slightly cocaine-like in other areas of the brain, but nevertheless inhibits further stimulation from the drug . Additional research will be necessary to demonstrate the importance of CART peptide in combating or slowing down some of the effects of cocaine .

Publications :

JAWORSKI, JN, KOZEL, MA AND KUHAR, MJ : Intra-accumbal injection of CART peptide reduces cocaine -induced locomotor activity . Journal of Pharmacology & Experimental Therapeutics 307:1038-1044, 2003

INTERROGATING THE GENOME TO UNCOVER HUMAN SPECIALIZATION OF BRAIN & COGNITION

SPID(s): 0305

Because the DNA sequences of humans are so similar to those of chimpanzees, scientists have long speculated that differences in the activity level of particular genes, otherwise known as gene expression, and, as a result, the amounts of particular proteins cells produced are what distinguish humans from chimpanzees. The recent sequencing of the human genome has led to the development of "gene chips " that enable researches to examine the expression levels of thousands of genes at a time as well as compare expression levels in different species .

Using gene chips to compare samples of the cerebral cortex of humans, chimpanzees and rhesus monkeys, investigators identified 91 genes that are expressed in different amounts in humans compared to the other primate species . Upon further study, the team observed 83 of these genes showed higher levels of activity in humans, and as a result, regulated neural activity . When compared with other tissues, such as heart and liver, investigators found nearly equal numbers of genes showing higher or lower levels of expression in humans as compared to chimpanzees and rhesus . The observed changes in gene activity in the cortex suggest increases in the rate of brain activity, providing a basis for the evolution of the enhanced cognitive abilities in humans .

In addition to finding changes in activity -related genes, the researchers found the human brain shows increased expression of genes that protect against activity -related damage . This finding may help explain why humans have the potential to live decades longer than other primates, but also why humans are especially vulnerable to age -related, neurodegenerative diseases, such as Alzheimer's disease . It is probable that the combination of long lifespan and high neural activity makes humans particularly vulnerable to neurodegenerative disease, and that activity -related damage accumulates with age and has the potential to cause catastrophic breakdown late in life .

Publications :

CACERES, M. LACHUER, J . ZAPALA, MA, REDMOND, JC, KUDO, L, GESCHWIND, DH, LOCKHART, DJ, PREUSS, TM AND BARLOW, C : Elevated transcript levels distinguish the human from non -human primate brains . Proceedings of the National Academy of Sciences, USA 100 :1330 -1335 , 2003

ANTHRAX TOXIN, DENDRITIC CELLS AND ADAPTIVE IMMUNITY

SPID(s): 0355

In the first study of its kind, researchers have shown anthrax lethal factor . (LF) impairs the function of dendritic cells and thereby compromises the immune system 's ability to fight the microbe. The findings have implications for developing more effective anthrax therapies and guiding researchers in better controlling detrimental immune responses, such as in autoimmune diseases and organ rejection following transplant surgeries . Dendritic cells are widely recognized as the most efficient antigen -presenting cells, making them pivotal in initiating and modulating any immune response against microbes . This is the first study that demonstrates any interaction between Bacillus anthracis and dendritic cells and reveals a novel mechanism of action by which the microbe targets the host -immune reaction.

In the study, the research team demonstrated LF impairs dendritic cell function by disrupting the mitogen-
activated protein (MAP) kinase enzymes within dendritic cells . Consequently, the dendritic cells become lethargic and unable to act normally, thereby preventing the activation of the immune system to attack microbes such as anthrax .

When a person is infected with a microbe, the immune system is needed to begin fighting the foreign substance immediately . When the dendritic cells are compromised, such as in this study with the anthrax lethal factor, the innate immune system is unable to stimulate the immune response, thus permitting the microbe to spread unchecked . The ultimate goal is to apply this novel finding to develop better anthrax treatments and to shape future research into controlling immune responses more appropriately .

Publications :

AGRAWAL, A, LINGAPPA, J, LEPPA, S, AGRAWAL, S, JABBAR, A, QUINN, C AND PULENDRAN, B : Impairment of dendritic cells and adaptive immunity by anthrax lethal factor. Nature 424:329-334, 2003

REACTIONS TO (IN)EQUALITY IN CAPUCHIN MONKEYS

SPID(s): 0061

Nonhuman primates respond negatively to unequal reward distribution, a reaction often seen in humans based on their universal sense of fairness . While researchers have long recognized the sense of fairness within the human species, these findings are the first to confirm this trait in nonhuman primates.

In this study, researchers made food -related exchanges with brown capuchin monkeys . The subjects refused previously acceptable rewards (cucumbers) if they witnessed their partners receiving higher -value rewards (grapes) for equal or less work . This is similar to the negative response humans display when they see other individuals receiving a better deal . The results showed the subjects compared their rewards with those of their partners and refused to accept a lower-value reward if their partners received a higher -value reward .

Publications :

BROSNAN, SF AND DEWAAL, FBM : Monkeys reject unequal pay . Nature 425:297 -299, 2003

CELLULAR IMMUNE RESPONSES IN AIDS PATHOGENESIS

SPID(s): 0217

HIV-infected humans and SIV -infected rhesus macaques who remain healthy despite long -term infection exhibit exceptionally low levels of virus replication and active antiviral cellular immune responses . In contrast, sooty mangabey monkeys that represent natural hosts for SIV infection do not develop AIDS despite high levels of virus replication and limited antiviral CD 8(+) T cell responses . We report here that SIV -infected mangabeys maintain preserved T lymphocyte populations and regenerative capacity and manifest far lower levels of aberrant immune activation and apoptosis than are seen in pathogenic SIV and HIV infections . These data suggest that direct consequences of virus replication alone cannot account for progressive CD 4(+) T cell depletion leading to AIDS . Rather, attenuated immune activation enables SIV -infected mangabeys to avoid the bystander damage seen in pathogenic infections and protects them from developing AIDS .

Publications :

SILVESTRI, G, SODORA, DL, KOUP, RA, PAIARDINI, M, O'NEIL, SP, MCCLURE, HM, STAPRANS, S AND FEINBERG, MB : Nonpathogenic SIV infection of sooty mangabeys is characterized by limited bystander immunopathology despite chronic high -level viremia . Immunity 18:441-452, 2003

EARLY FUNCTIONAL & STRUCTURAL REPAIR IN MACAQUE STRABISMUS

SPID(s): 0323

Studies examine the effect of strabismus on binocular coordination of eye movements . Using the double -step paradigm, we were able to elicit conjugate saccade gain adaptation in both the viewing eye and the non -viewing eye in the normal and strabismic monkeys . This suggested that the lack of binocular coordination observed in strabismic humans and animals is unlikely to be due to a generalized degeneration of the adaptive process . We have also shown that in animals with large angles of strabismus due to visual sensory deprivation rearing, the lack of binocular deprivation leads to characteristic 'A/V' patterns of ocular misalignment that resemble A /V patterns observed in certain humans with strabismus .

Neurophysiological studies showed that motoneuron firing is correlated with the cross -axis movements that result in A /V patterns suggesting that in animals with sensory induced strabismus, cross -axis movements and A /V patterns are due to a innervational signal from central structures rather than to a mechanical alteration of the oculomotor plant via extraocular muscle pulleys . These studies have implication in understanding and treating the various types of strabismus observed in young children and also in elucidating the development and calibration of neural circuits that are important for the ocular alignment and binocular coordination of eye movements .

Publications :

DAS, VE, ONO, S, TUSA, RJ, MUSTARI, MJ. Conjugate adaptation of saccadic gain in non -human primates with strabismus . J. Neurophysiology 91:1078 -1084, 2004

FEMALE SEXUALITY: MODULATION BY ESTROGEN AND ANDROGEN

SPID(s): 0310

This study used a rhesus monkey model of endocrine function and behavior; investigate the hormonal basis of female sexual initiation . Project I investigates sexual initiation in females across the menstrual cycle, comparing the occurrence of female sexual initiation in a social group context during normal cycles treated with an androgen receptor blocker (flutamide) or an estrogen receptor blocker (tamoxifen) to clarify whether androgens or estrogens act neurally to modulate female sexual motivation . Ovariectomized females receiving chronic estradiol treatment mimicking mid follicular estradiol levels were observed for sexual initiation during chronic E 2 treatment alone and following chronic E 2 and an injection of DHT or E 2. Concurrent administration of flutamide or tamoxifen with the estrogen or DHT, allowed for discrimination between behavioral changes resulting from the activation of neural androgen or estrogen receptors . Additional work will investigate whether common human hormonal replacement therapies of chronic estrogen, or chronic estrogen plus testosterone with or without concurrent progestin can reinstate female sexual interested in reproductively prime ovariectomized female monkeys . Theses studies will markedly increase our understanding of the role that ovarian steroids play in modulating female sexuality .

Publications :

BIELSKY, I, FELGER, J, GRAVES, F, MOOK, D, WALLEN, K AND WILSON, ME : Tamoxifen is an estrogen antagonist in the regulation of gonadotropin secretion and the responsiveness of the hypothalamic "pituitary " adrenal axis in female monkeys. Endocrine 22:305-315, 2003

DNA AND PROTEIN IMMUNOGENS FOR SIV/SHIV VACCINES

SPID(s): 0024

This Integrated Preclinical /Clinical AIDS Vaccine Development program project has excelled in both its preclinical and clinical development of a multi -protein DNA /MVA vaccine for AIDS. The program has been a collaborative effort between researchers at Emory University who have developed vaccine DNAs and conducted preclinical studies in macaques, and researchers in [illegible] laboratory at the NIAID who have developed the MVA portion of the vaccine. The preclinical studies have demonstrated the ability of a multi -protein DNA /MVA SHIV-89.6 vaccine to control a mucosal SHIV -89.6P challenge administered in the memory phase of the vaccine response. This trial is approaching three years post challenge, and only one macaque, immunized with a partial dose of the vaccine, has failed to control the challenge. In the remaining 23 macaques, 12 vaccinated with a full dose of the vaccine and 11 with a partial, the protection has held. In the last two months of 2002, the Science publication reporting this study was the most frequently cited paper in the field of immunology.

The clinical studies of the program have led to the development of a multi -protein DNA and MVA clade B HIV vaccine. The DNA component of this vaccine expresses Gag, PR, RT, Env, Vpu, Tat and Rev. The MVA component expresses Gag, PR, RT, and Env. The IPCAVD program conducted GLP potency and stability tests on the DNA component of the vaccine and GLP immunogenicity tests in macaques for the DNA and DNA /MVA components. The DNA product entered phase I trials on Jan. 21, 2003 under the sponsorship of the [illegible]

Publications :

In press publication

ADMINISTRATIVE INFORMATION

ALLOCATION OF RESOURCE ACCESS

• Center Access Requests

Initial contact to the Center from potential users may be via the Directors office, to one of the Associate Directors or Division Chiefs, or to any core scientist . Additionally, some initial queries come via NCRR, campus departments at Emory University or other sources . All inquiries are evaluated by the Associate Director for Scientific Programs and /or the Associate Director for Resource Resources, typically both . After appropriate consultation with other offices (Associate Director for Animal Resources, Chief Fiscal Officer) a response is prepared . If the proposed activity is particularly large in scope or has other unusual features, the request is presented for review at the weekly meeting of the Directors Advisory Committee . In the rare instances when the response is not positive, generally because the required resources are not available, assistance is offered in locating another suitable resource location When the response is positive, a Division Chief guides the investigator through the access process, with the assistance of Animal Resources personnel, the CFO and others as appropriate . Before initiation, the Research Advisory Committee reviews the project .

• Research Advisory Committee

The Research Advisory Committee, prior to initiation of any project, must review all projects, both internal and external, proposing to utilize Center resources . This committee meets monthly to review and make recommendations regarding research applications requiring animal and other Center resources . This committee also tracks resource commitments and makes periodic recommendations regarding the changes needed to meet these requirements . In instances where resources limitations (e.g. animals or space) preclude immediately availability, the Executive Committee meets to recommend priorities taking into account factors including scientific merit, urgency, recent allocation and the need to balance internal and external access to resources .

• Regulatory Compliance

The Emory University Institutional Animal Care and Use Committee (IACUC) must approve all research involving animals at Yerkes The Committee is charged with ensuring proper care, use, and humane treatment of animals used in research, testing and education . Animals are not assigned to any research project until IACUC approval is received . The Emory IACUC is composed of 26 member This Committee meets monthly and evaluates all University research proposals that involve the use of laboratory animals . All research protocols that involve the use of laboratory animals are submitted to the IACUC office by the first Wednesday of the month in which they are to be considered by the committee . These are provided to all IACUC members prior to the scheduled committee meeting (third Wednesday of each month). Each proposal is discussed by a primary and secondary reviewer and then discussed by committee members and voted on at the meeting . The proposal may be approved, approved with stipulations, disapproved, or deferred for clarification or modifications . All research protocols receive a thorough review, regardless of whether they are being submitted to an outside funding agency or are being internally funded . The latter type of proposals is also reviewed for scientific merit. Committee members are not present for review of proposals with which they are involved . In addition to the approval of research applications involving animals, the Committee also inspects all research and animal facilities semi -annually and compiles reports and recommendations from these inspections .

• Accreditation

The Yerkes NPRC is fully accredited by AAAALAC, with the most recent site visit having been in November, 2002 .

COMMITTEE REPORTS

This information can be found in the Infrastructure Section.

MEMBERS

(Non-Voting)

DISSEMINATION

1. Publications in peer reviewed scientific journals, as well as presentations at national and international scientific meetings .

2. Brochures and other literature distributed to Yerkes staff, officers and departments of Emory University, various other universities, legislators, professional societies and interested lay public .

3. Articles by and /or about Yerkes staff and scientists are published in Emory University publications and in local, regional and national newspapers and magazines .

4. Lectures and videotape and slide presentations are presented to local community groups and at other public forums .

5. A monthly speaker series features Yerkes investigators describing their latest projects to faculty and staff . Outside scientists also present lectures and seminars throughout the year .

The Center also has a web site (http :www .emory.edu.WHSC/YERKES) that presents information about its various divisions, centers and cores facilities, as well as the resources and expertise available .

Also included on the web site is information on the humane use of animals, the many benefits of animal research to human health, and a children 's corner to help young students understand the importance of such research .

Promoting Availability of the Resource

The web site also has information and an application for investigators interested in initiating research projects at the Center . The application includes information on research opportunities at the Center, criteria for the use of primates in research, Center access policy, standards and procedures for working with nonhuman primates, guidelines for experimental surgery and guidelines for the preparation and submission of research proposals . This information may also be requested by mail .

Additional information promoting resource availability and providing information on accessing the RPCs is provided on the NCRR web site .

PATENTS, LICENSES, INVENTIONS AND COPYRIGHTS

N/A

AWARDS, HONORS, SPECIAL RECOGNITIONS

Frans deWaal, PhD, a core scientist at the Yerkes National Primate Research Center and C .H. Candler Professor of Primate Behavior in the Department of Psychology, Emory University, was elected as a foreign associate to the National Academy of Sciences .

INFRASTRUCTURE

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