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

5P51RR000164-42
TULANE NATIONAL PRIMATE RESEARCH CENTER

Final

TULANE NATIONAL PRIMATE RESEARCH CENTER

TULANE SCHOOL OF MEDICINE AND TULANE SCHOOL OF PUBLIC HEALTH AND TROPICAL MEDICINE

ANNUAL PROGRESS REPORT

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

57.792% AIDS Related

Signature Date 4/15/04

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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
AERTKER, MIKE W, MENG	DIRECTORS OFFICE	
ALVAREZ, XAVIER A, PHD	COMPARATIVE PATHOLOGY	
APETREI, CRISTIAN, MD, PHD	MICROBIOLOGY & IMMUNOLOGY	
AYE, PYONE P, DVM, PHD	COMPARATIVE PATHOLOGY	
BAKER, KATE C, PHD	VETERINARY MEDICINE	
BLANCHARD, JAMES L, DVM, PHD	COLLABORATIVE RESEARCH	
BOHM, RUDOLF P, DVM	VETERINARY MEDICINE	
BORDA, JUAN, PHD, DVM	COMPARATIVE PATHOLOGY	
BUNNELL, BRUCE A, PHD	GENE THERAPY	
COGSWELL, FRANK B, PHD	BACTERIOLOGY AND PARASITOLOGY	
DAVISON, BILLIE B, DVM	COMPARATIVE PATHOLOGY	
DENNIS, VIDA A, PHD	BACTERIOLOGY AND PARASITOLOGY	
DIDIER, ELIZABETH S, PHD	MICROBIOLOGY AND IMMUNOLOGY	
DIDIER, PETER J, DVM, PHD	COMPARATIVE PATHOLOGY	
DUFOUR, JASON, DVM	VETERINARY MEDICINE	
[name]	DIRECTORS OFFICE	
GORMUS, BOBBY J, PHD	MICROBIOLOGY AND IMMUNOLOGY	
HARRISON, RICHARD M, PHD	VETERINARY MEDICINE	
KAACK, M BERNICE, PHD	COMPARATIVE PATHOLOGY	
KANG, SOO KYUNG, PHD	GENE THERAPY	
KUBISCH, H. MICHAEL, PHD	VETERINARY MEDICINE	
LACKNER, ANDREW A, DVM, PHD	DIRECTOR	
LING, BINHUA, PHD	MICROBIOLOGY AND IMMUNOLOGY	
MACLEAN, ANDREW, PHD	COMPARATIVE PATHOLOGY	
MARTIN, LOUIS N, PHD	MICROBIOLOGY AND IMMUNOLOGY	
MARX, PRESTON A, PHD	MICROBIOLOGY AND IMMUNOLOGY	
[name]	VETERINARY MEDICINE	
ORANDLE, MARLENE S, DVM, PHD	COMPARATIVE PATHOLOGY	
PANDREA-VASILE, IVONA, MD, PHD	COMPARATIVE PATHOLOGY	
PHILIPP, MARIO T, PHD	BACTERIOLOGY AND PARASITOLOGY	
[name]	VETERINARY MEDICINE	
PURCELL, JEANETTE, DVM	VETERINARY MEDICINE	
RAMAMOORTHY, RAMESH, PHD	BACTERIOLOGY AND PARASITOLOGY	
RATTERREE, MARION S, DVM	VETERINARY MEDICINE	
RIBKA, ERIN, DVM	VETERINARY MEDICINE	

Core Doctoral Scientists

Name, Degree	Department	Non-Host Institution: State, Country
SESTAK, KAROL, DVM, PHD	MICROBIOLOGY AND IMMUNOLOGY	
TELFER, PAUL T, PHD	MICROBIOLOGY/IMMUNOLOGY	
TRAINA-DORGE, VICKI L, PHD	MICROBIOLOGY AND IMMUNOLOGY	
VEAZEY, RONALD S., DVM, PHD	COMPARATIVE PATHOLOGY	
YANG, GUI-BO, PHD	COMPARATIVE PATHOLOGY	

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
		CIRMF, GABON
		TEXAS A&M: TX, USA
		WNPRC: WA, USA
	NEUROLOGY	UNIVERSITY OF PENNSYLVANIA: PA, USA
	BACTERIOLOGY	VETERINARY RESEARCH INSTITUTE, CZECH
	MICROBIOLOGY	YALE UNIVERSITY: CT, USA
		ORGANON, INC: NJ, USA
AMEDEE, ANGELA M, PHD	MICRO/IMMUNO/PARASIT	LSU HEALTH SCIENCES CENTER: LA, USA
		WNPRC: WA, USA
		FRED HUTCHISON CANCER RESEARCH CENTER: WA, USA
		CENTRE PASTEUR, CAMEROON
BAGBY, GREGORY, PHD	PHYSIOLOGY	LSU MEDICAL CENTER: LA, USA
		UNIVERSITY OF NOTTINGHAM, UK
	MICRO & IMMUNO	UPSTATE MEDICAL SCHOOL: NY, USA
		BAYLOR U: TX, USA
		INSTITUTE DE PASTEUR, FRANCE
		UNIV OF CALIFORNIA/DAVIS: CA, USA
	PATHOLOGY	CHARLES RIVER/SIERRA BIOMEDICAL: NV, USA
		UNIVERSITY OF NEW ORLEANS: LA, USA
		UNIVERSITY OF CA/SF: CA, USA
BEILKE, MARK A, MD	MEDICINE	TULANE UNIVERSITY HEALTH SCIENCES CENTER: LA, USA
	CENTER FOR INFECTIOUS DISEASES	SUNY: NY, USA
		DUKE UNIVERSITY: NC, USA
		AARON DIAMOND AIDS RESEARCH CENTER: NY, USA
		GILEAD SCIENCES: CA, USA

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
	DEPARTMENT OF BIOLOGY	UNIV. OF NORTH CAROLINA/CHARLOTTE: NC, USA
		CIRMF, GABON
		UNIVERSITY OF NEW ORLEANS: LA, USA
		TULANE UNIVERSITY SPHTM: LA, USA
	TROPICAL MEDICINE	MAHIDOL UNIVERSITY, THAILAND
BUCHANAN, K, PHD		TULANE UNIVERSITY: LA, USA
		SCRIPPS RES INST: CA, USA
		BAYLOR COLLEGE OF MEDICINE: TX, USA
	ANTHROPOLOGY	BOSTON UNIVERSITY: MA, USA
	VIRAL PATHOGENESIS	BETH ISRAEL DEACONNESS: MA, USA
		PASTEUR INSTITUTE, FRANCE
	NEURORADIOLOGY	MASSACHUSETTS GENERAL HOSPITAL: MA, USA
	SCHOOL OF MEDICINE	WASHINGTON UNIV.: MO, USA
		ABGENIX, INC.: CA, USA
		BETH ISRAEL DEACONNESS HOSPITAL: MA, USA
CHEN, ZHIWEI, PHD		AARON DIAMOND AIDS RES: NY, USA
CHENG-MAYER, CECILIA, PHD		AARON DIAMOND AIDS RESEARCH CENTER: NY, USA
		CHILDREN'S HOSPITAL: OH, USA
	MICROBIOLOGY/IMUNOLOGY	TUHSC: LA, USA
		CIRMF, GABON
	MOLECULAR MICROBIOLOGY & IMMUN	JOHNS HOPKINS UNIVERSITY SCHOOL OF PUBLIC HEALTH: MD, USA
	OPHTHALMOLOGY	TULANE SCHOOL OF MEDICINE: LA, USA
COOK, STEPHEN D, PHD	ORTHOPAEDICS	TULANE UNIVERSITY MEDICAL CENTER: LA, USA
		UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL: MA, USA
	GENE THERAPY CENTER	UNIVERSITY OF ALABAMA: AL, USA
CURIEL, TYLER J, MD	MEDICINE	TULANE HSC: LA, USA
		ST. JUDE CHILDEN'S RESEARCH HOSPITAL: TN, USA
	INFECTIOUS DISEASE/CLINICAL BI	ABBOT LABORATORIES: IL, USA
	TULANE CANCER CENTER	TULANE UNIVERSITY: LA, USA

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
		HARVARD UNIVERSITY: MA, USA
	MICROBIOLOGY	THOMAS JEFFERSON UNIVERSITY: PA, USA
		EUROPEAN VETERINARY LAB, THE NETHERLANDS
		CENTRE PASTEUR, SENEGAL
		NEW YORK UNIVERSITY: NY, USA
	MICROBIOLOGY	UNIVERSITY OF PA: PA, USA
		LOYOLA UNIVERSITY: LA, USA
		ACRES: LA, USA
		MONTEFIORI MEDICAL SCHOOL: NY, USA
		UNIVERSITY OF NEBRASKA VET SCHOOL: NE, USA
		NIAID/NIH: MD, USA
		MED RES STATION, CAMEROON
		WISTAR INSTITUTE: PA, USA
		ALFRED I. DUPONT HOSPITAL FOR CHILDREN: DE, USA
		YALE: CT, USA
		CHILDRENS HOSPITAL OF PHILADELPHIA: PA, USA
		WA NATIONAL PRIMATE RES. CENTER: WA, USA
	PHARMACOLOGY	JOHNS HOPKINS UNIVERSITY: MD, USA
	ANIMAL RESOURCES	SCRIPPS RESEARCH INSTITUTE: CA, USA
		LSU: LA, USA
FRANCHINI, GENOVEFFA, MD	BASIC RESEARCH LAB	NCI, NIH: MD, USA
		UNIVERSITY OF ALABAMA: AL, USA
	NEURORADIOLOGY	MA GEN HOSPITAL/HARVARD MED SCHOOL: MA, USA
		DUKE UNIVERSITY: NC, USA
GARRY, ROBERT, PHD	MICROBIOLOGY/IMMUNOLOGY	TULANE UNIVERSITY MEDICAL CENTER: LA, USA
	PHARMACOLOGY AND EXP. THERAPY	LSU HEALTH SCIENCES CENTER: LA, USA
		ADARC: NY, USA
		, ARGENTINA
		UNIVERSITY OF COLORADO HSC: CO, USA
		UNIVERSITY OF MISSISSIPPI MEDICAL CENTER: MS, USA
		UNIVERSITY OF MISSISSIPPI MEDICAL CENTER: MS, USA

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
GONZALEZ, R. GILBERTO, PHD	NEURORADIOLOGY	MASSACHUSETTS GENERAL HOSPITAL: MA, USA
	NEUROLOGY	UNIV. OF PENNSYLVANIA: PA, USA
	MICROBIOLOGY	UNIVERSITY OF ARKANSAS: AR, USA
GRECO, J.B.	NEURORADIOLOGY	MASSACHUSETTS GENERAL HOSPITAL: MA, USA
	MICROBIOLOGY AND IMMUNOLOGY	XAVIER UNIVERSITY: LA, USA
GURNER, DEBORAH, MD, PHD		ADARC: NY, USA
		U ALABAMA: AL, USA
	BIOLOGICAL SCIENCES	LOUISIANA STATE UNIVERSITY: LA, USA
		NATIONAL CANCER INSTITUTE: MD, USA
		ADARC: NY, USA
	DE BIOCHIMIE MEDICALE	CENTRE MEDICALE UNIVERSITAIRE, SWITZERLAND
HAYNES, BARTON, MD		DUKE UNIVERSITY: NC, USA
	NEURORADIOLOGY	MASSACHUSETTS GENERAL HOSPITAL: MA, USA
	VIROLOGT	BIOMEDICAL PRIMATE RES. CTR., THE NETHERLANDS
HENSON, MICHAEL C, PHD	OB/GYN	TULANE UNIVERSITY HEALTH SCIENCES CENTER: LA, USA
		ONPRC: OR, USA
HO, DAVID D, MD	DIRECTOR	AARON DIAMOND AIDS RES: NY, USA
	COMPARATIVE MEDICINE	UNIVERSITY OF CALIFORNIA: CA, USA
		COLLEGE OF VETERINARY MEDICINE: CO, USA
		UNIVERSITY OF PENNSYLVANIA: PA, USA
		AARON DIAMOND AIDS RESEARCH CTR: NY, USA
		ADARC: NY, USA
		WASHINGTON U: MO, USA
	SCHOOL OF MEDICINE	WASHINGTON UNIV: MO, USA
HURWITZ, JULIA L		ST. JUDES CHILDREN'S RESEARCH HOSPITAL: TN, USA
		ALBERT EINSTEIN SCHOOL OF MEDICINE: PA, USA
	TROPICAL MEDICINE	TULANE UNIVERSITY HEALTH SCIENCES CENTER: LA, USA
		MEDIMMUNE VACCINES INC.: CA, USA

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
	VECTOR-BORNE INFECTIOUS DIS.	CDC: CO, USA
		UNIVERSITY OF WASHINGTON: WA, USA
	BIOLOGICAL SCIENCES	UNIVERSITY OF CINCINNATI: OH, USA
	IMMUNOLOGY	NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER: MA, USA
		WEILL MEDICAL COLLEGE: NY, USA
	MICROBIOLOGY, IMMUNOLOGY, PARA	LSUHSC: LA, USA
	NEURORADIOLOGY	MA GEN HOSPITAL/HARVARD MED SCH: MA, USA
	PARASITOLOGY/VETERINARY SCIENC	LSU SCHOOL OF VETERINARY MEDICINE: LA, USA
		NEPRC: MA, USA
		NEPRC: MA, USA
	VIROLOGY	BIOMEDICAL PRIMATE RES. CTR., THE NETHERLANDS
		LOS ALAMOS NATIONAL LABS: NM, USA
		PATEUR INSTITUTE, FRANCE
		NIAID/NIH: MD, USA
KOUSOULAS, KONSTANTIN G, DVM, PHD		LSU SCHOOL OF VETERINARY MEDICINE: LA, USA
		MEDIMMUNE, INC.: MD, USA
	TROPICAL MEDICINE	TULANE UNIVERSITY HEALTH SCIENCES CENTER: LA, USA
	PEDIATRICS INFECTIOUS DISEASES	UCLA SCHOOL OF MEDICINE: CA, USA
		JOHNS HOPKINS U: MD, USA
		NORTHWESTERN UNIVERSITY SCHOOL OF MEDICINE: IL, USA
KURODA, MARCELO, PHD		BETH ISRAEL DEACONESS MEDICAL CENTER: MA, USA
		SOUTHERN RESEARCH INSTITUTE: AL, USA
	COLLEGE OF MEDICINE	UNIVERSITY OF PENNSYLVANIA: PA, USA
LARUSSA, VINCENT, PHD	PHARMACOLOGY	TULANE UNIVERSITY: LA, USA
		OHIO STATE UNIVERSITY: OH, USA
		CASE WESTERN RESERVE UNIVERSITY: OH, USA
		HARVARD UNIV. SCHOOL OF PUBLIC HEALTH: MA, USA
		AUDUBON CENTER: LA, USA

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
	NEURORADIOLOGY	MA GEN HOSPITAL/HARVARD MED SCH: MA, USA
		WANPRC: WA, USA
		BETH ISRAEL DEACONESS MEDICAL CENTER: MA, USA
LEVY, LAURA S., PHD	MICROBIOLOGY/IMMUNOLOGY	TULANE MEDICAL SCHOOL: LA, USA
	BIOCHEMISTRY	TULANE SCHOOL OF MEDICINE: LA, USA
LIFSON, JEFFREY, MD	RETROVIRAL PATHOGENESIS	NCI FREDERICK: MD, USA
		SCIENTIFIC DEVICE: IL, USA
	CLINICAL TROP MED	MAHIDOL UNIVERSITY, THAILAND
	CHEMICAL ENGINEERING	FLORIDA STATE UNIVERSITY: FL, USA
		SOUTHERN RES INSTITUTE: AL, USA
	DEPT. NEUROLOGY	UNIVERSITY OF COLORADO HSC: CO, USA
		NIAID: MD, USA
	NEUROSCIENCES	UC-SAN DIEGO: CA, USA
	VACCINE RESEARCH CENTER	NIH: MD, USA
		YERKES NPRC: GA, USA
		SEQUELLA, INC.: MD, USA
	BIOCHEMISTRY	THOMAS JEFFERSON UNIVERSITY: PA, USA
		UNIVERSITY OF ALABAMA: AL, USA
	NUFFIELD DEPT OF CLIN. MED	CENTRE FOR TROP MED, UK
	MICROBIOLOGY	THOMAS JEFFERSON UNIVERSITY: PA, USA
		CHILDREN'S HOSPITAL: OH, USA
	EPIDEMIOLOGY AND MICROBIOLOGY	UNIVERSITY OF NC/CHAPEL HILL: NC, USA
	PHARM/EXPERIMENTAL THERAPEUTIC	LSUHSC: LA, USA
MOHAMADZADEH, MANSOUR, PHD	MICROBIOLOGY AND IMMUNOLOGY	TULANE UNIVERSITY HEALTH SCIENCE CENTER: LA, USA
MOHRI, HIROSHI, PHD		AARON DIAMOND AIDS RES: NY, USA
MOLINA, PATRICIA E, MD, PHD		LSUHSC: LA, USA
	BASIC RESEARCH LAB	NCI: MD, USA
		DUKE UNIVERSITY MEDICAL CENTER: NC, USA
		OCHSNER MED FDN: LA, USA
		CORNELL UNIVERSITY: NY, USA

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
		UPPSALA INNOVATION CENTER, SWEDEN
	MICROBIOLOGY AND IMMUNOLOGY	TULANE UNIVERSITY HEALTH SCIENCES CENTER: LA, USA
		WANPRC: WA, USA
		NIAID/NIH: MD, USA
	ANTHROPOLOGY	YALE UNIVERSITY: CT, USA
		THOMAS JEFFERSON UNIVERSITY: PA, USA
		CENTRE INTERNATIONAL DE RECHERCHES MEDICALES, GABON
	MOLEC GENET&BIOCHEM	U PGH SCH MED: PA, USA
	BIOSTATISTICS	TULANE UNIVERSITY SPHTM: LA, USA
	IMMUNOLOGY	SEQUELLA, INC.: MD, USA
	MICRO, MOLEC. GENETICS & IMM.	UNIVERSITY OF KANSAS MED CTR.: KS, USA
		NIH: MD, USA
	DEAN, DENTAL SCHOOL	UNIVERSITY OF WA: WA, USA
NELSON, STEVE, MD		LSU HEALTH SCIENCES CENTER: LA, USA
		PASTEUR DU CAMEROON CTR, AFRICA
		NEW YORK BLOOD CENTER: NY, USA
	DEPT OF RESEARCH	BETH ISRAEL DEACONNESS MED CTR: MA, USA
	MICROBIOLOGY AND IMMUNOLOGY	TULANE UNIV. HSC: LA, USA
		GLADSTONE INSTITUTE, UCSF: CA, USA
	SHOKLO MALARIA RES. UNIT	MAHIDOL UNIVERSITY, THAILAND
	RESEARCH AND DEVELOPMENT	IDEXX LABS, INC.: ME, USA
		CIRMF, GABON
		GWU: DC, USA
	EAST/WYLE LAB/LIFE SCI RES. LA	NASA: TX, USA
	MAGEE-WOMENS RES. INST	PITTSBURGH DEVE CENTER LAB: PA, USA
		UNIVERSITY OF MONTPELLIER, FRANCE
		UNIVERSITY OF TX MEDICAL BRANCH: TX, USA
		ADARC: NY, USA
PHINNEY, DONALD G, PHD, DVM	MICROBIOLOGY AND IMMUNOLOGY	TULANE UNIVERSITY HEALTH SCIENCES CENTER: LA, USA

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
PINCUS, SETH, MD		CHILDREN'S HOSPITAL: LA, USA
		WASHINGTON U: MO, USA
POLES, MICHAEL, MD, PHD		AARON DIAMOND AIDS RESEARCH CENTER: NY, USA
	DIVISION OF INFECTIOUS DISEASE	THOMAS JEFFERSON UNIVERSITY: PA, USA
POPE, MELISSA, PHD		POPULATION COUNCIL: NY, USA
PROCKOP, DARWIN, MD	GENE THERAPY	TULANE UNIVERSITY HSC: LA, USA
		LOS ALAMOS NATIONAL LABS: NM, USA
		YALE UNIVERSITY: CT, USA
		NORTHWEST ZOOPATH: WA, USA
	MICROBIOLOGY	UNIVERSITY OF PENNSYLVANIA: PA, USA
		UNIVERSITY OF WISCONSIN HOSPITAL: WI, USA
		BETH ISRAEL DEACONNESS MED CTR: MA, USA
	MEDICINE	LSU HEALTH SCIENCES CENTER: LA, USA
		UNIVERSITY OF MANCHESTER, UK
		WNPRC: WA, USA
ROBINSON, PREMA, PHD		BAYLOR UNIVERSITY: TX, USA
		CENTRE INTERNATIONAL DE RECHERCHES MEDICALES, GABON
		YALE U SCH MED: CT, USA
		YALE UNIVERSITY: CT, USA
	PATHOBIOLOGY	UNIVERSITY OF WA: WA, USA
		LA STATE POLICE CRIME LAB: LA, USA
		CIRMF, GABON
	NEURORADIOLOGY	MASSACHUSETTS GENERAL HOSPITAL: MA, USA
	MEDICINE	CASE WESTERN RESEARCH UNIVERSITY: OH, USA
		UNIVERSITY OF PENNSYLVANIA: PA, USA
		BETH ISRAEL DEACONNESS MEDICAL CENTER: MA, USA
SCHNELL, MATTHIAS J., PHD, MS	CENTER FOR HUMAN VIROLOGY	THOMAS JEFFERSON UNIVERSITY: PA, USA
	HUMAN VACCINE INSTITUTE	DUKE UNIVERSITY: NC, USA
		UNIVERSITY OF NOTTINGHAM, UK

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
	INFECTIOUS DIS. & MEDICINE	ST. GEORGE HOSPITAL MED SCHOOL, UK
	TROP. MED/CLINICAL MEDICINE	JOHN RADCLIFFE HOSPITAL, UK
		NIAID/NIH: MD, USA
		CENTRE INTERL DE RECHERCHES MED, GABON
		NERPRC: MA, USA
	FACILITIES AND WATER	EPA: OH, USA
	INFECTIOUS DISEASE	ST MICHAELS MED CTR: NJ, USA
	FORENSIC LAB	LAS VEGAS METRO POLICE: NV, USA
	SW MEDICAL CENTER	UNIVERSITY OF TEXAS: TX, USA
	INSECT PATHOLOGY	LSU: LA, USA
		CIRMF, GABON
		MERCK & CO: NJ, USA
		DUKE UNIVERSITY: NC, USA
STAMATATOS, LEONIDAS, PHD	SEATTLE BIOMED RES. INST	ADARC: WA, USA
		YERKES NAT. PRIMATE RES. CTR.: GA, USA
	BASIC RESEARCH LAB	NCI: MD, USA
		UNIVERSITY OF NC: NC, USA
SVEC, FRANK	MEDICINE	LSU HEALTH SCIENCES CENTER: LA, USA
		TRIANGLE PHARMACEUTICALS, INC.: NC, USA
		CNPRC: CA, USA
	VIROLOGY	BIOMEDICAL PRIMATE RES. CTR., THE NETHERLANDS
	DEPARTMENT OF PATHOLOGY	UNIVERSITY OF TX MEDICAL BRANCH: TX, USA
	DEPARTMENT OF PATHOLOGY	UNIVERSITY OF TX MEDICAL BRANCH: TX, USA
		AARON DIAMOND AIDS RESEARCH CENTER: NY, USA
	BIOMED. SCIENCE/VET DIAGNOSTI	TUFTS UNIV. SCHOOL OF VET MED: MA, USA
	PATHOBIOLOGY/TROPICAL MEDICINE	TULANE SCHOOL OF PUBLIC HEALTH: LA, USA
	DE ANATOMIA APATOLGIA	INSITUTO DE MEDICINA TROPICAL, CUBA
	SECT. PARASITOLOGY	ACADEMIC MEDICAL CENTER, THE NETHERLANDS
		AGRICULT EXPMTL STATION: CT, USA
		UNIVERSITY OF TEXAS MEDICAL BRANCH: TX, USA

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
	LAB ANIMAL DIAGNOSTIC CTR	BIORELIANCE CORP: MD, USA
		CHANNING LABS: MA, USA
		CHILDREN'S HOSPITAL: OH, USA
	VET. GENETICS LAB	UNIV. OF CA/DAVIS: CA, USA
	PATHOLOGY	UNIVERSITY OF UT: UT, USA
WEISS, DANIEL, MD, PHD		UNIVERSITY OF VT/BURLINGTON: VT, USA
		EINSTEIN UNIVERSITY SCHOOL OF MEDICINE: NY, USA
	TROPICAL MEDICINE	TULANE UNIV. SCH OF PUB HEALTH: LA, USA
		NERPRC: MA, USA
		TULANE UNIVERSITY HEALTH SCIENCES CENTER: LA, USA
	MOLECULAR VIROL & IMMUNO	OHIO STATE UNIVERSITY: OH, USA
	INFECTIOUS DISEASES/TROP MED	ACADEMIC MEDICAL CENTRE, THE NETHERLANDS
		INTL RECHERCHES CTR, FRANCE
		HARVARD, BETH ISRAEL DEACONESS MED. CTR.: MA, USA
	VIRAL PATHOGENESIS	BETH ISRAEL DEACONESS MED. CTR.: MA, USA
		UNIV. OF PENNSYLVANIA: PA, USA
		STANFORD UNIVERSITY: CA, USA
WINSAUER, PETER J, PHD	PHARM/EXPERIMENTAL THERAPEUTIC	LSUHSC: LA, USA
	SCHOOL OF VET MED/PEDIATRICS	UNIV PA CHILDREN HOSP OF PHIL: PA, USA
	MICROBIOLOGY	NORTHWESTERN UNIVERSITY: IL, USA
		NEW YORK MEDICAL COLLEGE: NY, USA
	DEPARTMENT OF PATHOLOGY	UNIVERSITY OF TX MEDICAL BRANCHG: TX, USA
	GENE THERAPY	TULANE UNIVERSITY SCHOOL OF MEDICINE: LA, USA
		AARON DIAMOND AIDS RES: NY, USA
	FCRDCM	NATIONAL CANCER INSTITUTE: MD, USA
	MEDICINE	CASE WESTERN RESEARCH UNIVERSITY: OH, USA
	PATHOLOGY	TULANE UNIVERSITY SCHOOL OF MEDICINE: LA, USA

Graduate Student/Postdoctoral Scientists

Graduate Student/Postdoctoral Scientists

Name, Degree	Department	Non-Host Institution: State, Country
	BACTERIOLOGY AND PARASITOLOGY	
	BACTERIOLOGY AND PARASITOLOGY	
	BACTERIOLOGY AND PARASITOLOGY	
	GENE THERAPY	
names	VETERINARY MEDICINE	
	MICROBIOLOGY AND IMMUNOLOGY	
		TUHSC: LA, USA
	COMPARATIVE PATHOLOGY	
	MICROBIOLOGY AND IMMUNOLOGY	

SUBPROJECT DESCRIPTIONS

NPRC MANAGEMENT SUBPROJECTS

INFORMATION TECHNOLOGY SERVICES (0542)

NPRC UNIT: ADMINISTRATIVE

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
AERTKER, MIKE W	MENG	C	DIRECTORS OFFICE	

AXIS I CODES: 9 **AXIS II CODES:** 42, 68

ABSTRACT

The mission of the Information Technology Unit is to provide technology support for the faculty and staff of the Tulane National Primate Research Center, including maintaining an animal records system database, assisting with desktop and network computing, and assisting with multimedia presentation development and production. IT provides support for a complete clinical animal records system, which provides clinical veterinarians, clinical lab technicians, pathologists and research scientists the ability to enter and retrieve data on the research animals. Besides the necessary maintenance and reporting, the primary issue facing the IT unit database staff was a migration from the PI/open DBMS to Oracle. This project was begun in late December of 2002, but was put on hold because of increased demands on the database staff. We expect its completion by mid-2004. Desktop Support staff provides support for Windows-based and Macintosh computers, laser printers and other devices comprising a nearly 300 node 100BaseT Ethernet network. The campus has six main network servers. Solaris-based server provide e-mail access and access to the animal records system, while Windows 2000 servers act as file servers for both Macintosh and Windows-based desktop clients. Internet access is provided through two T1 lines interconnecting the TNPRC to the Tulane University uptown campus. Desktop support personnel custom-build and repair Windows-based PCs. They advise staff on the purchase of computer hardware and software. They also install site licensed and public domain software for all computers and assist users in maintenance and system upgrades. Desktop support calls numbered over 2200 currently. The Media Lab staff provides multimedia production support by assisting with the following: slide presentation production, 35mm slide creation, 35mm slide scanning, document and image scanning, color document and image creation, video production (including filming and editing), and research poster creation. This lab receives dozens of requests each week for service. The Media Lab continues to grow, with new digitizing equipment, improved 35mm slide production, better color print processing and better video presentation equipment. During the year video conferenced presentations became an important function. IT coordinated video conferenced presentations are now regularly scheduled

ADMINISTRATIVE SERVICES/BUSINESS OFFICE (0583)

NPRC UNIT: ADMINISTRATIVE

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
AERTKER, MIKE W	MENG	C	DIRECTORS OFFICE	

AXIS I CODES: 28(ADMINISTRATIVE) **AXIS II CODES:**92(ADMINISTRATION)

ABSTRACT

Because the Center is located 40 miles from the University, the Center Division of Administrative Services is the central point of contact for Center faculty and staff for virtually all financial and administrative functions. All transactions submitted by the Primate Center are reviewed and approved by the Business Office to assure compliance with both Federal and University regulations and policies. Pre and post grant and contract award functions processed by Grants Administration include budget preparation and application submission, award administration, account reconciliation and all required financial reporting. Both annual and five-year base grant budgets are prepared as well. Cost recovery rates are set and administered for all research studies, both internal and outside collaborative. Billable outside collaborative projects are invoiced and their payments processed by the Business Office. Administrative Services staff work closely with IT staff in developing and maintaining databases and applications for the tracking of animal assignments and acquisitions, project cost recovery and various administrative records. All aspects of Human Resources are handled by the Division of Administrative Services, including hiring and termination of employees, initiation and distribution of payroll, on the job injury reporting, employee counseling, etc. General support services are provided, including reception, switchboard, maintenance of telephone and radio systems, postage and shipping and Center wide central filing.

FACILITIES AND OPERATIONS (0584)

NPRC UNIT: ADMINISTRATIVE

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
AERTKER, MIKE W	MENG	C	DIRECTORS OFFICE	

AXIS I CODES: 11 **AXIS II CODES:**92(ADMINISTRATION/OPERATIONS)

ABSTRACT

Facilities and operations services are managed by Facilities Services which is responsible for maintenance, building construction and renovations, HVAC systems and controls, groundskeeping, incinerator operation, sewerage treatment plant operation, security and day-to-day operations in the power plant and boiler room. The unit is also responsible for compliance with relevant local, state and federal regulations that govern the Center's facilities operations.

Facilities Services maintains eight main buildings [sq. ftg.] and 69 primate corrals located on the Center's 500 acres. In addition to the eight main buildings, the Center has numerous other buildings such as generator sheds and storage buildings that support the Center's operations.

OFFICE OF OCCUPATIONAL HEALTH AND SAFETY (0684)

NPRC UNIT: ADMINISTRATIVE

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
AERTKER, MIKE W	MENG	C	DIRECTORS OFFICE	
L name J	CRNP	C	DIRECTORS OFFICE	

AXIS I CODES: 28(ADMINISTRATIVE) **AXIS II CODES:**92(ADMINISTRATIVE)

ABSTRACT

The Occupational Health and Safety Officer (Nurse Specialist) has implemented an active risk assessment database, an occupational health and safety educational program and active Tetanus/Diphtheria and Hepatitis B vaccination programs. New databases have been established to track TB screening and vaccinations. Databases have been established for injury reporting/risk assessment and health education. The Nurse Specialist works closely with several affiliated physicians to provide case management of employee illnesses and injuries. There is a focus on simian Herpes B virus prevention and SIV/SHIV transmission prevention. Currently we are also, working on a collaborative project with CDC to test for monkey retrovirus seroprevalence in employees at the primate center.

SECURITY (0695)

NPRC UNIT: ADMINISTRATIVE

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
AERTKER, MIKE W	MENG	C	DIRECTORS OFFICE	

AXIS I CODES: 28(SECURITY) **AXIS II CODES:**92(ADMINISTRATION/OPERATIONS)

ABSTRACT

Security functions at the Center are now performed by P.O.S.T. Certified police officers from the Tulane University Health Sciences Police Department. Officers are on-site 24 hours a day to respond to incidents, conduct routine patrols, provide after-hours escorts and liaise with local law enforcement agencies.

DIRECTORS OFFICE, TNPRC (0585)

NPRC UNIT: ADMINISTRATIVE

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LACKNER, ANDREW A	DVM, PHD	C	DIRECTOR	
Lname J	MENG	C	DIRECTORS OFFICE	

AXIS I CODES: 28(ADMINISTRATIVE) **AXIS II CODES:**92(ADMINISTRATIVE)

ABSTRACT

The Director's Office provides oversight and overall responsibility for the scientific, administrative and operational functions of the Center. The Director, with input from the Executive Committee, faculty and the Board of Scientific Advisors, develops and implements the scientific direction and planning for the Center. This includes determining future funding opportunities, long range strategic planning, establishing collaborative agreements with other institutions and representing the Center's interests with our host institution and funding institutions. The Director's Office is also responsible for allocation of resources to the various departments at the Center.

Administrative and Operational oversight is also provided from the Director's Office with primary responsibility for supervision of Administrative Services, Facilities Services and IT Services. Each of these units has a manager who reports to the Director's Office.

SCIENTIFIC ADVISORY COMMITTEE (0773)

NPRC UNIT: ADMINISTRATIVE

%NPRC $:

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LACKNER, ANDREW A	DVM, PHD	C	DIRECTOR	
L	MD	A		FRED HUTCHISON CANCER RESEARCH CENTER, WA USA
	PHD	A	CENTER FOR INFECTIOUS DISEASES	SUNY, NY USA
	PHD	A		ACRES, LA USA
	DVM	A	ANIMAL RESOURCES	SCRIPPS RESEARCH INSTITUTE, CA USA
names	DVM, PHD	A		COLLEGE OF VETERINARY MEDICINE, CO USA
	MD	A		NIAID/NIH, MD USA
	DVM, PHD	A		LSU SCHOOL OF VETERINARY MEDICINE, LA USA
	DVM	A	MICRO, MOLEC. GENETICS & IMM.	UNIVERSITY OF KANSAS MED CTR., KS USA
	DVM, PHD	A	BIOMED. SCIENCE/VET DIAGNOSTI	TUFTS UNIV. SCHOOL OF VET MED, MA USA

AXIS I CODES: 28(ADMINISTRATIVE REVIEW) **AXIS II CODES:**92(ADMINISTRATIVE REVIEW)

ABSTRACT

The TNPRC maintains an external scientific advisory committee comprised of outstanding scientists from around the country with expertise in areas of research being conducted at the Primate Center. The term for committee members is 3 years. This Committee conducts regular reviews of all Center programs. Two complementary types of reviews are conducted. The first is a general overview of all components of the institution. This occurs every 18 to 24 months. The second type of review is focused on single research divisions. These reviews are much more in depth. Two research Divisions are reviewed each year. Together these complementary reviews provide thorough oversight of all center programs.

TRAINING AND EDUCATION (0774)

NPRC UNIT: ADMINISTRATIVE

%NPRC $:

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LACKNER, ANDREW A	DVM, PHD	C	DIRECTOR	
	PHD	A	PHYSIOLOGY	LSU MEDICAL CENTER, LA USA
	DVM, PHD	C	COLLABORATIVE RESEARCH	
	DVM	C	VETERINARY MEDICINE	
	PHD	C	GENE THERAPY	
names	PHD	A	MICROBIOLOGY/IMUN OLOGY	TUHSC, LA USA
	PHD	A		, ARGENTINA
	PHD	A	PARASITOLOGY/VETER INARY SCIENC	LSU SCHOOL OF VETERINARY MEDICINE, LA USA
	DVM, PHD	A		LSU SCHOOL OF VETERINARY MEDICINE, LA USA
	DVM	G	VETERINARY MEDICINE	
	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	MD	A		LSU HEALTH SCIENCES CENTER, LA USA
	PHD	C	BACTERIOLOGY AND PARASITOLOGY	
	DVM, PHD	C	COMPARATIVE PATHOLOGY	

AXIS I CODES: 28(TRAINING/EDUCATION) **AXIS II CODES:**51, 92(TRAINING/EDUCATION)

ABSTRACT

The educational mission of the TNPRC is to "provide training for graduate students, postdoctoral fellows, undergraduates and visiting scientists." In the last year the TNPRC hosted 3 graduate students, 12 postdoctoral fellows, 3 veterinary fellows and 9 undergraduate and veterinary students as part of our summer fellowship program. Our educational mission has been augmented by our recent participation in a T35 training grant in conjunction with the Louisiana State University (LSU) School of Veterinary Medicine and a T32 training grant in conjunction with the LSU School of Medicine.
The summer fellowship program entails one-on-one participation in a research project with an end of summer seminar session by the students to demonstrate their understanding of the work.

The basic objective of the visiting scientists' program is to provide individuals with a sound knowledge and understanding of the mission and functions of a National Primate Research Center.

Teaching of graduate courses and individual classes at Tulane is viewed as an important component in the effort to strengthen the inclusion of TNPRC faculty in academic and research functions at Tulane.

Lastly, three Center-wide colloquia have been organized 1) a monthly seminar on infectious diseases, with invited speakers, 2) a biweekly research lab meeting, and 3) monthly pathology and medicine Grand Rounds.

BUILDING C RENOVATIONS (0646)

NPRC UNIT: VETERINARY MEDICINE

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BLANCHARD, JAMES L	DVM, PHD	C	COLLABORATIVE RESEARCH	
[illegible]	DVM	C	VETERINARY MEDICINE	
[illegible]	DVM, PHD	C	DIRECTOR	

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

ABSTRACT

Grants awarded to the Tulane National Primate Research Center partially provide for renovation and expansion of existing animal housing and administrative space to meet the current and projected demand for additional BSL-2 animal housing, laboratory, and support space for investigators whose research is focused on infectious diseases using non-human primate models. The upgrade and additional construction will allow for support of active and pending research projects that are administered by outside collaborating scientists as well as core faculty.
In addition, the facility will allow centralization of the Division of Veterinary Medicine faculty and staff and its programs freeing up space that is presently being borrowed from research Divisions. The enhanced facility will also provide support space for the training programs for both veterinary residents in nonhuman primate medicine and in support of IACUC mandated personnel training.

BUILDING D RENOVATIONS-ANIMAL RESOURCES IMPROVEMENTS (0647)

NPRC UNIT: VETERINARY MEDICINE

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BLANCHARD, JAMES L	DVM, PHD	C	COLLABORATIVE RESEARCH	

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

ABSTRACT

G20 funds were obtained to renovate Building D. The facility has not been renovated in over 20 years. The proposed modifications will increase the number of animal rooms from 5 to 14 and increase the number of cages from 160 to 340. The renovated areas will be BSL-2 plus and will accommodate a number of research projects including malaria, SIV and other infectious diseases. The entire HVAC system will be replaced and new mechanical systems monitoring will be installed. The building will be equipped with rolling racks. The project has been substantially completed. Interior finishing remains as well as installation and activation of HVAC systems. The anticipated completion date is May 2004.

TULANE RESOURCE ALLOCATION COMMITTEE (0686)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BOHM, RUDOLF P	DVM	C	VETERINARY MEDICINE	
	MENG	C	DIRECTORS OFFICE	
	DVM, PHD	C	COLLABORATIVE RESEARCH	
		A		ADARC, NY USA
names	PHD	A	OB/GYN	TULANE UNIVERSITY HEALTH SCIENCES CENTER, LA USA
	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	MD	A		LSU HEALTH SCIENCES CENTER, LA USA
	MPH	C	VETERINARY MEDICINE	
	DVM	C	VETERINARY MEDICINE	
	DVM, PHD	C	COMPARATIVE PATHOLOGY	

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

ABSTRACT

The Tulane Resource Allocation Committee (TRAC) is composed of core and affiliate members who are responsible for the equitable allocation of animal resources.

The third year of operation of the TRAC saw refinement of operations of the committee, development of policy statements, and better reporting and analysis of allocation data. Analysis of breeding colony demographic, morbidity, and mortality data as well as allocation data assist in colony management decision making. In the last year, approximately 43% of animal allocation has been to affiliate (outside) investigators and 57% to core investigators.

AIDS MODULAR BUILDING (0737)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BOHM, RUDOLF P	DVM	C	VETERINARY MEDICINE	
L name 1	DVM, PHD	C	DIRECTOR	

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

ABSTRACT

This G20 will allow the TNPRC to purchase equipment (manufactured modular BSL-2 primate housing equipment) to help meet the current need for BSL2 animal housing for the AIDS research program. The proposed modular housing will provide space for approximately 100 animals assigned to AIDS research projects. The manufactured modular housing equipment will provide much needed additional BSL-2 space particularly during renovation of existing facilities.

D BUILDING RENOVATION-CAGING (0738)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $:

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BOHM, RUDOLF P	DVM	C	VETERINARY MEDICINE	
[name]	DVM, PHD	C	DIRECTOR	

AXIS I CODES: 11 **AXIS II CODES:**66

ABSTRACT

The research program at the Tulane National Primate Research Center (TNPRC) has been heavily invested in infectious disease research for close to three decades. In addition to infectious disease, research programs in parasitology, gene therapy, behavior and reproductive biology are represented at the Center. The NPRC program provides resources and opportunities for research using nonhuman primates to core faculty and to faculty affiliated with outside institutions.

Recent changes in leadership at the Tulane National Primate Research Center have resulted in a dramatic increase in grant funding over the past 18 months. The rapid increase in funding has resulted in a shortage of appropriate BSL-2 nonhuman primate housing space to support the research program which in some cases has resulted in a waiting time of up to 8.5 months for investigators to begin research studies.

This proposal will improve the infrastructure at the TNPRC and expedite research activities by adding to our existing BSL-2 caging capacity in conjunction with ongoing construction and renovation. The purchase of additional caging for Building D, which is currently under renovation, will complement the Center's long term plan to renovate and expand nonhuman primate housing facilities and supplements ongoing construction funded through other sources.

RESEARCH SUBPROJECTS

TESTING OF EXPERIMENTAL 4 AMINOQUINOLINES IN MONKEY MODELS OF HUMAN MALARIA (0627)

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
COGSWELL, FRANK B	PHD	C	BACTERIOLOGY AND PARASITOLOGY	
[name]	MD	A	TROPICAL MEDICINE	TULANE UNIVERSITY HEALTH SCIENCES CENTER, LA USA

AXIS I CODES: 1A, 7C, 17 **AXIS II CODES:**50C, 66

ABSTRACT

Chloroquine (CQ) has been the treatment of choice for malaria for over 50 years and is one of the few drugs for which there is evidence of safety during pregnancy. However, the value of CQ as an antimalarial has been compromised for several decades by the increasing prevalence of CQ resistance in Southeast Asia, sub-Saharan Africa, South America and elsewhere. The development of economical antimalarials that are safe and effective, therefore, is a global health priority. Together with our colleagues at the Dept. of Tropical Medicine, TSPHTM, we have developed a series of 4 aminoquinolines active against chloroquine-resistant malaria caused by Plasmodium falciparum. In this project we are testing these compounds in monkey models of human malaria, specifically, P. cynomolgi in the rhesus macaque, a model of human vivax malaria, and human P. falciparum in the Saimiri monkey. One of the compounds (AQ13) was found to be an efficacious blood schizonticide, even against a chloroquine resistant isolate in the monkeys, and is now in Phase I human trials. Using the monkey models we are not only able to assess efficacy but have the ability to look at pharmacokinetic parameters, including absorption, bioavailability, AUC, rate of excretion, and other factors which may be predictive of the ability of these compounds to be used for treatment of human malaria. In the coming year we expect to test between 10 and 20 of these compounds in our monkey models.

SURVEY OF ENZOOTIC PATHOGENS AND ARTHROPOD VECTORS (0697)

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
COGSWELL, FRANK B	PHD	C	BACTERIOLOGY AND PARASITOLOGY	
L names	PHD	A		LOYOLA UNIVERSITY, LA USA
	PHD	A	TROPICAL MEDICINE	TULANE UNIV. SCH OF PUB HEALTH, LA USA

AXIS I CODES: 1A, 1C, 7C, 16C, 17 **AXIS II CODES:** 66

ABSTRACT

Arthropod vectors commonly found in Louisiana can potentially carry a variety of pathogens. This project is designed to assess the level of endemicity of known enzootic pathogens in the outdoor breeding colonies at the TNPRC. Samples of blood and stool obtained from each animal are examined for parasites of interest. Stool samples are examined by direct smear and ZnSO4 flotation. Blood samples are examined by thick and thin blood smears for Plasmodium species and the Knott's test for filariasis. Plasma is examined by ELISA for evidence of Trypanosoma cruzi and DNA is saved for future studies. Potential vectors are trapped weekly by CDC light trap and gravid traps. Mosquitoes are speciated and examined by RT-PCR or a dipstick ELISA test for West Nile virus (WNV), Eastern Equine Encephalitis and St. Louis Encephalitis virus. Only one mosquito pool (Culex salinarius) was positive for WNV this year. Since the project was funded in November 2003 we have examined 972 animals, or approximately 1/5 of the colony. Potentially the most important vector-borne parasite found was Plasmodium inui in the Macaca nemestrina colony. Other pathogens of interest found include Strongyloides fulleborni, Giardia lamblia, Balantidium coli, and Trichuris trichiura. We have also found Hymenolepis diminuta, the rat tapeworm, reported for the first time in macaques here at the Center.

TRANSCRIPTOME PROFILES OF HOST GENE EXPRESSION IN MONKEY MODELS OF HUMAN MALARIA (0698)

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
COGSWELL, FRANK B	PHD	C	BACTERIOLOGY AND PARASITOLOGY	
[name]	MS	A	GENE THERAPY	TULANE UNIVERSITY SCHOOL OF MEDICINE, LA USA

AXIS I CODES: 1A, 7C, 13, 16D **AXIS II CODES:** 59, 66

ABSTRACT

Malaria, caused by protozoan parasites of the genus Plasmodium, is the most serious parasitic disease of humans. P. vivax is the most common of the four human malaria parasites and infection is widespread in Asia, Latin America, the Middle East, North Africa, and the South Pacific. P. cynomolgi, used in this study, is a simian parasite closely related to, and a good model of, P. vivax. Two rhesus macaques were inoculated with sporozoites of P. cynomolgi and RNA was isolated from peripheral blood mononuclear cells (PBMCs) harvested before infection (baseline), after 8 days (liver phase), at the peak parasitemia, at the first relapse, and at the second relapse. Samples were run on a human microarray chip containing over 22,000 genes. Sample clustering, using over 3,000 differentially expressed genes, showed that samples from both monkeys clustered similarly, with baseline samples being very distinct from other samples and the first and second relapse samples being the most similar. Hierarchical clustering of the genes showed dramatic gene expression level changes in both monkeys, especially down regulation of many genes during the initial liver stages and at the peak parasitemia. Interestingly, the number of enriched genes involved in defense and immunity increased throughout the time course. In this study we were able to use the monkey malaria model effectively to study the transcriptome profile of host gene expression, since we infected malaria-naïve animals, and neither concomitant infections nor nutritional status were confounding factors as would be expected in human patients from malaria-endemic areas.

LIPOPROTEINS OF BORRELIA DIFFERENTIALLY INDUCE IL-6 AND IFN-G IN SPLEENS OF MICE (0705)

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
DENNIS, VIDA A	PHD	C	BACTERIOLOGY AND PARASITOLOGY	
names	PHD	G	BACTERIOLOGY AND PARASITOLOGY	
	PHD	C	BACTERIOLOGY AND PARASITOLOGY	
	DVM	C	VETERINARY MEDICINE	

AXIS I CODES: 1D, 7A, 19 **AXIS II CODES:**39, 64, 66

ABSTRACT

Lipoproteins of Borrelia burgdorferi (Bb) are key contributors to the enhanced inflammatory response to Bb observed in vitro in the lymph node cells (LNC) of disease-susceptible (C3H/HeJ) mice. C3H cells produced markedly higher levels of the proinflammatory cytokines, interferon-gamma (IFN-g) and interleukin-6 (IL-6) than did disease-resistant (C57BL/6J) cells, when the cells were stimulated with Bb, lipidated outer surface protein A (L-OspA) and synthetic lipohexapeptide, Pam3Cys. In addition, IFN-g and IL-6 were more efficiently inhibited by the anti-inflammatory cytokine, IL-10 in cells of C57 than in those of C3H mice. In this study, we investigated if the same phenomenon of differential production of proinflammatory cytokines occurred with spleen cells obtained from C3H and C57 mice after one-week of infection with Bb. Spleen cells from C3H mice infected with Bb produced higher levels of both IFN-g and IL-6 when stimulated in vitro with L-OspA and Pam3Cys than those of C57 mice. The concentration of IFN-g in L-OspA and Pam3Cys cultures of C3H mice respectively, were 1700 pg/ml and 3081 pg/ml. IL-6 concentrations were 3080 pg/ml and 4059 pg/ml for L-OspA and Pam3Cys, respectively. L-OspA did not induce IFN-g in C57 cell cultures, whereas Pam3Cys induced only 35 pg/ml of this cytokine. For IL-6, L-OspA and Pam3Cys respectively induced 495 pg/ml and 995 pg/ml in C57 cultures. We examined whether exogenous IL-10 added at the time of stimulation was able to affect the concentration of IFN-g and IL-6 after L-OspA or Pam3Cys stimulation. Added recombinant IL-10 (10 ng/ml) significantly dampened production of IFN-g and IL-6 with the same efficiency in spleen cell cultures of both strains of mice. Spleen cells obtained ex vivo after one-week of infection further revealed similar levels of IL-10R bearing cells from C57 (37.18%) and C3H mice (38.37%). Our results indicate the differential production of proinflammatory cytokines in the spleens of C3H and C57 mice as observed in LNC. The findings also show that exogenous IL-10 dampens the production of proinflammatory cytokines by spleen cells when these cells are stimulated with L-OspA or Pam3Cys. These results are consistent with a major role played by IL-10, as induced by B. burgdorferi lipoproteins, in controlling inflammation in Lyme borreliosis.

TOLL RECEPTOR EXPRESSION ON LYMPH NODE CELLS OF BORRELIA INFECTED MICE (0706)

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
DENNIS, VIDA A	PHD	C	BACTERIOLOGY AND PARASITOLOGY	
	PHD	G	BACTERIOLOGY AND PARASITOLOGY	
names	PHD	C	BACTERIOLOGY AND PARASITOLOGY	
	DVM	C	VETERINARY MEDICINE	

AXIS I CODES: 1D, 7A, 19 **AXIS II CODES:** 39, 64, 66

ABSTRACT

We recently demonstrated that lymph node cells (LNC) of disease-susceptible C3H/HeJ mice produced more interferon (IFN)-g and interleukin-6 (IL-6), as induced by lipidated outer surface protein A (L-OspA) and Borrelia burgdorferi (Bb) spirochetes, than those of disease-resistant C57/BL6 mice. To determine whether this difference in responsiveness to lipoproteins were due to differences in the TLR-2 signaling pathway, TLR2 mRNA expression was studied in LNC of mice one week after infection with Bb. LNC were stimulated with L-OspA, Bb and phorbol-12-myristate-13-acetate (PMA)/ionomycin for 30 min, 2 hr and 4 hr and TLR2 mRNA transcript was assessed by reverse-transcriptase polymerase chain reaction (RT-PCR). TLR2 PCR levels were normalized for the amount of mRNA encoding GAPDH, a housekeeping gene, detected in the same sample. Overall, the level of mRNA for TLR2 in L-OspA- Bb- or PMA/ionomycin-induced LNC was not significantly different between C3H and C57 mice. Also, no difference was seen in TLR2 transcript in LNC of normal C3H and C57 mice. Given that TLR1 and TLR6 have been shown to be involved in lipoproteins signaling, we also stimulated LNC with L-OspA, Bb and PMA/ionomycin for 30 min, 2 hr and 4 hr to evaluate the level of TLR1 and TLR6 mRNA transcripts. No difference in the level of expression of TLR1 and TLR6 transcripts in LNC was seen between C3H and C57 mice. These results suggest that differences in the differential production of proinflammatory cytokines in C3H and C57 mice infected with Bb may be due to other downstream molecules in the lipoprotein-signaling pathway.

EFFECT OF IL-17 ON BORRELIA BURGDORFERI-INDUCED IL6 AND TNFA IN J774 CELLS (0707)

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
DENNIS, VIDA A	PHD	C	BACTERIOLOGY AND PARASITOLOGY	
	PHD	G	BACTERIOLOGY AND PARASITOLOGY	
names	PHD	C	BACTERIOLOGY AND PARASITOLOGY	
	DVM	C	VETERINARY MEDICINE	

AXIS I CODES: 1D, 7A, 19 **AXIS II CODES:**39, 64, 66

ABSTRACT

Interleukin-17 is a recently described T-cell-derived cytokine that has been shown to be expressed in the synovium of patients with arthritis. IL-17 has been shown to contribute to the pathogenesis of arthritis as well as having synergistic effects with other proinflammatory cytokines in inducing joint pathology. Studies have also demonstrated that IL-17 induces the production of proinflammatory cytokines by several cell types such as stromal cells, synoviocytes, chondrocytes and macrophages. In this study we investigated the effect of exogenous IL-17 on the production of the macrophage-derived proinflammatory cytokines IL-6 and TNF-a. To study the effect of exogenous IL-17 on cytokine production, mouse J774 cells were stimulated with lipidated outer surface protein A (L-OspA), Borrelia burgdorferi (Bb) and LPS in the presence or absence of mouse recombinant IL-17 (rIL-17) (0.1, 1 and 10 ng/ml). The results demonstrated that IL-6 was significantly reduced by 54% in L-OspA and Bb-treated cultures in the presence of 10 ng/ml of rIL-17. rIL-17 at all concentrations did not significantly affect the production of LPS by macrophages. J774 cells produced a marginal amount of TNF-a in response to L-OspA (28 pg/ml). However, Bb induced up to 400 pg/ml of TNF-a that was reduced by all three concentrations of rIL-17. The most significant effect was with 10 ng/ml of rIL-17 that rendered a 90% reduction in TNF-a production. There was no effect of rIL-17 on LPS-induced TNF-a production. These results indicated that exogenous IL-17 affects the production of TNF-a and IL-6 by J774 cells when these cells are stimulated with L-OspA or Bb. The significance of this finding in relationship to Lyme borreliosis remains to be investigated.

DIFFERENTIAL ACQUIRED IMMUNE RESPONSES TO BORRELIA LIPOPROTEINS IN INFECTED MICE (0708)

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
DENNIS, VIDA A	PHD	C	BACTERIOLOGY AND PARASITOLOGY	
	PHD	G	BACTERIOLOGY AND PARASITOLOGY	
names	PHD	C	BACTERIOLOGY AND PARASITOLOGY	
	DVM	C	VETERINARY MEDICINE	

AXIS I CODES: 1D, 7A, 19 **AXIS II CODES:**39, 64, 66

ABSTRACT

We investigated the effect of Borrelia burgdorferi lipoproteins (outer surface protein A) and the synthetic lipohexapeptide tripalmitoyl-S-glyceryl-Cys-Ser-4(Lys) (Pam3-Cys) on isolated lymph node (LN) cells from Lyme disease-susceptible (C3H/HeJ) and -resistant (C57BL/6J) mice. Mice were either infected with B. burgdorferi for 1 week or left uninfected. Lipoprotein-stimulated LN cells from infected C3H/HeJ mice produced significantly higher levels of the inflammatory cytokines IL-6 and IFN-g than did cells from C57BL/6J mice. Cells from uninfected mice did not respond. No TNF-a or IL-1b were produced by LN cells from infected mice of either strain in response to lipoprotein or B. burgdorferi spirochetes. Unlike with IL-6 or IFN-g, LN cells from either strain failed to produce IL-10 in response to lipoproteins. However, the LN cells were able to produce this cytokine in response to B. burgdorferi spirochetes or after incubation with phorbol-12-myristate-13-acetate/ionomycin, anti-CD3 antibody alone or anti-CD3 combined with anti-CD28 antibodies. Addition of exogenous IL-10 to lipopeptide-stimulated cultures significantly reduced IFN-g and IL-6 production in a dose-dependent fashion. This inhibition was more effective with cells from disease-resistant C57BL/6J mice than with cells from disease-susceptible C3H/HeJ mice. The proclivity to disease of the C3H/HeJ mouse could be simultaneously based on the phenomena of enhanced inflammatory responsiveness to lipoproteins and diminished ability to respond to IL-10. An investigation of the determinants of these two phenomena could be used as a blueprint to elucidate the pathogenesis of Lyme disease in humans.

ANTIBIOTIC TREATMENT OF CHRONIC LYME DISEASE IN RHESUS MONKEY (0024)

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
PHILIPP, MARIO T	PHD	C	BACTERIOLOGY AND PARASITOLOGY	
names	DVM, PHD	A		UNIV OF CALIFORNIA/DAVIS, CA USA
	DVM, PHD	C	COMPARATIVE PATHOLOGY	
	MD	A		YALE, CT USA
	DVM, PHD	A	COMPARATIVE MEDICINE	UNIVERSITY OF CALIFORNIA, CA USA
	DVM	C	VETERINARY MEDICINE	

AXIS I CODES: 1A, 7A, 9, 13, 19, 21 **AXIS II CODES:** 35, 39, 64, 66, 91

ABSTRACT

The preferred antibiotic treatment of chronic Lyme disease, and that of chronic neuroborreliosis in particular, is still not fully defined. In an effort to develop improved and more reliable remedies for chronic Lyme disease, an eclectic treatment regimen has been designed. It includes two antibiotics that are highly effective against both acute and chronic Lyme disease: ceftriaxone (2 g, IV, once a day, 30 days) and doxycycline (100 mg/kg, bid, per os, 60 days). The goal of this project is to assess the efficacy of this combination regimen, originally devised for humans, in rhesus macaques. More specifically, to monitor the elimination of a Borrelia burgdorferi infection from all organs commonly targeted by this spirochete, and especially from the central nervous system. Twenty four rhesus macaques were needle inoculated with B. burgdorferi and four control animal were sham inoculated. After monitoring the animals for infection and signs of disease, over a six-months period, antibiotics were administered. After completing the treatment animals were kept for an additional 6 months, to allow for spirochetal re-population, in case the treatment had not been fully efficacious. Animals were sacrificed and tissue specimens were obtained from multiple organs. These specimens were cultured in vitro for spirochetal recovery. Only one lung specimen from an untreated animal yielded cultivable spirochetes. Initial analysis by real-time PCR analysis in search of spirochetal DNA (in collaboration with U.C. Davis) yielded residual flagellin and OspA DNA in several organs of both treated and untreated animals. A microscopic pathology survey of several organ tissues specimens is being conducted, in search of inflammatory lesions that are characteristic of B. burgdorferi-infected organs. The DNA PCR results are especially relevant as they indicate that antibiotic treatment does not fully eliminate spirochetes. To confirm these results we are examining both heart and brain tissues from all of the animals for presence of spirochetal RNA. This is done in collaboration with Yale University.

PATHOGENESIS OF LYME BORRELIOSIS IN RHESUS MONKEY (0025)

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
PHILIPP, MARIO T	PHD	C	BACTERIOLOGY AND PARASITOLOGY	
[illegible]	PHD	C	BACTERIOLOGY AND PARASITOLOGY	
[illegible]	PHD	G	BACTERIOLOGY AND PARASITOLOGY	
[illegible]	PHD	G	COMPARATIVE PATHOLOGY	

AXIS I CODES: 1A, 7A, 9, 13, 19, 21 **AXIS II CODES:** 35, 39, 64, 66, 91

ABSTRACT

Brain invasion by Borrelia burgdorferi, the agent of Lyme disease, results in an inflammatory and neurodegenerative disorder called neuroborreliosis. In humans, neuroborreliosis has been correlated with enhanced concentration of glial fibrillary acidic protein in the cerebrospinal fluid, a sign of astrogliosis. Rhesus monkeys infected by us with B. burgdorferi showed evidence of astrogliosis, namely astrocyte proliferation and apoptosis. We formulated the hypothesis that astrogliosis could be caused by spirochetal lipoproteins. We established primary cultures of rhesus monkey astrocytes and stimulated the cells with recombinant lipidated outer surface protein A (L-OspA), a model B. burgdorferi lipoprotein, and tripalmitoyl-S-glyceryl-Cys-Ser-Lys4-OH (Pam3Cys), a synthetic lipopeptide that mimics the structure of the lipoprotein lipid moiety. L-OspA elicited not only astrocyte proliferation but also apoptosis, two features observed during astrogliosis. Astrocytes produced both IL-6 and TNF- alpha in response to L-OspA and Pam3Cys. Proliferation induced by L-OspA was diminished in the presence of an excess of anti-IL-6 antibody, and apoptosis induced by this lipoprotein was completely suppressed with anti-TNF-alpha antibody. Hence, IL-6 contributes to, and TNF-alpha determines, astrocyte proliferation and apoptosis, respectively, as elicited by lipoproteins. We now demonstrated that cells from the human mixed neuronal/epithelial cell line SK-N-SH co-cultivated with B. burgdorferi also produce IL-6 and TNF-alpha, and undergo apoptosis. This result suggests a mechanism for the pathogenesis of neuroborreliosis that is similar to what is believed to be the pathogenetic basis of other neurodegenerative diseases, e.g. Alzheimer's disease and AIDS-dementia complex, namely, inflammatory responses, induced in this case by spirochetes and/or lipoproteins in the CNS milieu, can mediate neuronal apoptosis and thus lead to cumulative neurodegeneration.

A DNA VACCINE TO PREVENT TRANSMISSION OF HUMAN MALARIA (0534)

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
PHILIPP, MARIO T	PHD	C	BACTERIOLOGY AND PARASITOLOGY	
	MD	A	MOLECULAR MICROBIOLOGY & IMMUN	JOHNS HOPKINS UNIVERSITY SCHOOL OF PUBLIC HEALTH, MD USA
names	PHD	A		JOHNS HOPKINS U, MD USA
	DVM	C	VETERINARY MEDICINE	

AXIS I CODES: 1A, 7A, 9, 13, 19, 21 **AXIS II CODES:**35, 39, 64, 66, 91

ABSTRACT

Malaria transmission-blocking vaccination can effectively reduce and/or eliminate transmission of parasites from the human host to the mosquito vector. The immunity achieved by inducing an antibody response to surface antigens of male and female gametes and parasite stages in the mosquito. Our laboratory has developed DNA vaccine constructs, based on Pfs25 (a Plasmodium falciparum surface protein of 25 kDa), that induce a transmission-blocking immune response in mice (C. A. Lobo, R. Dhar, and N. Kumar, Infect. Immun. 67:1688-1693, 1999). To evaluate the safety, immunogenicity, and efficacy of the Pfs25 DNA vaccine in nonhuman primates, we immunized rhesus macaques (Macaca mulatta) with a DNA vaccine plasmid encoding Pfs25 or a Pfg27-Pfs25 hybrid or with the plasmid (empty plasmid) alone. Immunization with four doses of these DNA vaccine constructs elicited antibody titers that were high but nonetheless unable to reduce the parasite's infectivity in membrane feeding assays. Further boosting of the antibody response with recombinant Pfs25 formulated in Montanide ISA-720 increased antibody titers (30-fold) and significantly blocked transmission of P. falciparum gametocytes to Anopheles mosquitoes (90% reduction in oocyst numbers in the midgut). Our data show that a DNA prime-protein boost regimen holds promise for achieving transmission-blocking immunity in areas where malaria is endemic and could be effective in eradicating malaria in isolated areas where the level of malaria endemicity is low.

A POSSIBLE TEST FOR ELIMINATION OF A BORRELIA BURGDORFERI INFECTION (0538)

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
PHILIPP, MARIO T	PHD	C	BACTERIOLOGY AND PARASITOLOGY	
names	PHD	A		ALFRED I. DUPONT HOSPITAL FOR CHILDREN, DE USA
	MD	A		NIAID, MD USA
	DVM	C	VETERINARY MEDICINE	
	MD	A		NEW YORK MEDICAL COLLEGE, NY USA

AXIS I CODES: 1A, 7A, 9, 13, 19, 21 **AXIS II CODES:** 35, 39, 64, 66, 91

ABSTRACT

Management of Lyme disease would benefit from a test to assess therapy outcome. Such a test could be employed to ascertain if treatment of early Lyme disease was successful and would be helpful to clinicians assessing patients with lingering posttreatment symptoms. We reported recently that levels of the antibody to C6,a Borrelia burgdorferi-derived peptide that is used as an antigen in the C6-Lyme diagnostic test, declined after successful antibiotic treatment of Lyme borreliosis patients. We assessed retrospectively the change in anti-C6 antibody titers in 131 patients with either early localized disease (erythema migrans) or disseminated disease. All of these patients were treated with antibiotics and were free of the clinical signs shown at presentation within 12 weeks after the initiation of treatment. Decreases in reciprocal geometric mean titers (rGMT) of the anti-C6 antibody were quantified for the subpopulation of 45 patients whose baseline rGMT were 80 and whose second serum specimens were obtained at least 6 months after the baseline specimen. Eighty percent of this patient group (36 of 45) experienced a 4-fold decrease in their rGMT (P 0.0003). These results suggest that a change in the anti-C6 antibody titer may serve as an indicator of therapy outcome for patients with localized or disseminated Lyme borreliosis. An additional comprehensive prospective study in patients with culture-confirmed B. burgdorferi infection and single or multiple erythema migrans is in progress in collaboration with name, of the New York Medical College.

AN IMMUNE EVASION MECHANISM FOR SPIROCHETAL PERSISTENCE IN LYME BORRELIOSIS (0631)

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
PHILIPP, MARIO T	PHD	C	BACTERIOLOGY AND PARASITOLOGY	
Lyme	PHD	G	BACTERIOLOGY AND PARASITOLOGY	

AXIS I CODES: 1A, 7C **AXIS II CODES:** 39, 59, 64, 66, 91

ABSTRACT

Borrelia burgdorferi, the Lyme disease spirochete, persistently infects mammalian hosts despite the development of strong humoral responses directed against the pathogen. Here we describe a novel mechanism of immune evasion by B. burgdorferi. In immunocompetent mice, spirochetes that did not express ospC (the outer-surface protein C gene) were selected within 17 d after inoculation, concomitantly with the emergence of anti-OspC antibody. Spirochetes with no detectable OspC transcript that were isolated from immunocompetent mice reexpressed ospC after they were either cultured in vitro or transplanted to naive immunocompetent mice, but not in OspC-immunized mice. B. Burgdorferi persistently expressed ospC in severe combined immune-deficient (SCID) mice . Passive immunization of B. burgdorferi–infected SCID mice with an anti-OspC monoclonal antibody selectively eliminated ospC -expressing spirochetes but did not clear the infection. OspC-expressing spirochetes reappeared in SCID mice after the anti-OspC antibody was eliminated. We hypothesized that selection of surface-antigen nonexpressers is an immune evasion mechanism that contributes to spirochetal persistence. We are currently examining other surface antigens of B. burgdorferi, as well as organs other than the skin, to ascertain if this mechanism involves only OspC, or is of a general, and therefore more significant nature.

A NOVEL 3-DIMENSIONAL CELL CULTURE APPROACH FOR STUDYING NEUROBORRELIOSIS (0699)

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
PHILIPP, MARIO T	PHD	C	BACTERIOLOGY AND PARASITOLOGY	
names	PHD	A	MICROBIOLOGY AND IMMUNOLOGY	TULANE UNIV. HSC, LA USA
	PHD	A	EAS/WYLE LAB/LIFE SCI RES. LA	NASA, TX USA

AXIS I CODES: 1A, 7A, 9, 13, 19, 21 **AXIS II CODES:** 35, 39, 64, 66, 91

ABSTRACT

Lyme neuroborreliosis is thought to be chiefly associated with inflammation elicited in the central nervous system (CNS) by Borrelia burgdorferi. This is the spirochete that causes Lyme disease. We have hypothesized that spirochetal lipoproteins are the molecular basis of Lyme disease inflammation. These lipoproteins are known to induce production of pro-inflammatory cytokines such as TNF-alpha, IL-6 and IL-1beta, in cells of the immune system, as well as glial cells of the CNS. We propose that these inflammatory effects result in neuronal/glial cell loss, which, in turn, causes the neurocognitive symptoms seen in neuroborreliosis.

There is currently persuasive evidence in the literature suggesting that the 3-dimensional growth conditions provided by culture in a high-aspect-ratio rotating wall Vessel (HARV) may drive the phenotype of transformed cell lines toward a state more representative of an untransformed cell. As primary neuronal cultures are difficult to generate, we have engaged in exploring this phenomenon by cultivating the neuronal cell line SH-SY5Y in the simulated microgravity environment of a Synthecon HARV bioreactor. We have shown decreased expression of the proto-oncogene N-myc and the RNA binding protein HuD in 3-dimensional culture as compared to that observed in more traditional cell culture methods. We have also observed diminished cellular proliferation in the HARV cultures, coupled with distinct morphological differences as revealed by scanning electron microscopy. Because N-myc is a transcription factor known to be instrumental in both malignant transformation and cellular differentiation, this combination of findings has encouraged us to pursue a novel approach in the study of Lyme neuroborreliosis. We will use in vitro assays, incorporating the use of 3-dimensional culture to elucidate the cellular milieu of astrocyte, neuronal and glial cell combinations responsible for the pathogenesis seen in neuroborreliosis. We also anticipate further investigation into the role of IL-6, TNF-alpha and IL-1beta regarding CNS cell apoptosis resulting from typical Lyme disease stimulants, i.e. B. burgdorferi and its lipoproteins.

LIPIDATION-DEPENDENT OSPA VACCINATION OF TLR-2-DEFICIENT MICE (0700)

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
PHILIPP, MARIO T	PHD	C	BACTERIOLOGY AND PARASITOLOGY	
Unnamed	PHD	A	PATHOLOGY	UNIVERSITY OF UT, UT USA

AXIS I CODES: 1A, 1D, 7A, 17 **AXIS II CODES:**39, 64, 66

ABSTRACT

Toll-like receptor 2 (TLR2) is a transmembrane signal transducer for tripalmitoyl-S-glyceryl-cysteine (Pam3Cys)-modified lipoproteins, including OspA from the Lyme disease spirochete Borrelia burgdorferi. The Pam3Cys modification provides adjuvant activity for inducing humoral responses, suggesting that TLR2 could function as the adjuvant receptor for the OspA vaccine. The importance of TLR2 in the humoral response to OspA was confirmed, because overall levels of immunoglobulin G (IgG) were reduced in TLR2-deficient mice, when compared with those in wild-type mice. However, the levels of production of IgG1 were similar in both mouse strains, and the levels of induction of protective immunity were comparable. Unlipidated OspA was not immunogenic in wild-type or TLR2-deficient mice, indicating the lipid modification was active in the absence of TLR2. These findings indicate that the Pam3Cys modification of bacterial lipoprotein has adjuvant properties independent of TLR2 signaling.

IXODES SCAPULARIS TICKS FROM LOUISIANA CAN TRANSMIT LYME DISEASE (0701)

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
PHILIPP, MARIO T	PHD	C	BACTERIOLOGY AND PARASITOLOGY	
L name J	DVM	C	VETERINARY MEDICINE	

AXIS I CODES: 1A, 7C **AXIS II CODES:**39, 59, 64, 66, 91

ABSTRACT

The principal vector of Borrelia burgdorferi, the Lyme borreliosis spirochete, in the Northeast and Midwestern regions of the United States is the blacklegged tick Ixodes scapularis. Because of a favorable environment, I. scapularis is also plentiful in the South; however, a correlation with Lyme borreliosis cases does not exist in this region of the United States. Concern existed that something intrinsic to ticks found in Louisiana could mitigate their ability to transmit B. burgdorferi. Therefore, we set out to assess the ability of I. scapularis ticks from Louisiana to become infected with and transmit B. burgdorferi using mice as hosts. In the laboratory, mating adult female ticks collected in southeastern Louisiana were fed on the ears of rabbits. After oviposition and egg hatching, the resulting larvae were fed on mice that had been needle-inoculated with two different strains of B. burgdorferi sensu stricto, B31 and JD1. Larvae were found to be positive for spirochetes. Additional fed larvae were allowed to molt into the nymphal stage. Flat nymphs remained infected with B. burgdorferi. Infected nymphs were allowed to feed on naõ¨ve mice, all of which became infected as shown by culture of ear biopsy specimens. Naive larvae were then fed on these same mice to assess transmissibility. The resulting engorged larvae harbored spirochetes. We have demonstrated that the I. scapularis ticks found in Louisiana are fully competent to carry and transmit B. burgdorferi infection.

C6-TESTING IS AS SENSITIVE AND SPECIFIC AS TWO-TIER DIAGNOSIS OF LYME DISEASE (0702)

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
PHILIPP, MARIO T	PHD	C	BACTERIOLOGY AND PARASITOLOGY	
Lname J	PHD	A	VECTOR-BORNE INFECTIOUS DIS.	CDC, CO USA

AXIS I CODES: 1A, 7A, 9, 13, 19, 21 **AXIS II CODES:** 35, 39, 64, 66, 91

ABSTRACT

In a study of US patients with Lyme disease, immunoglobulin (Ig) G and IgM antibody responses to recombinant Borrelia burgdorferi antigen VlsE1 (rVlsE1), IgG responses to a synthetic peptide homologous to a conserved internal sequence of VlsE (C6), and IgM responses to a synthetic peptide comprising the C-terminal 10 amino acid residues of a B. burgdorferi outer-surface protein C (pepC10) were evaluated by kinetic enzyme-linked immunoassay. At 99% specificity, the overall sensitivities for detecting IgG antibody to rVlsE1 or C6 in samples from patients with diverse manifestations of Lyme disease were equivalent to that of 2-tiered testing. When data were considered in parallel, 2 combinations (IgG responses to either rVlsE1 or C6 in parallel with IgM responses to pepC10) maintained high specificity (98%) and were significantly more sensitive than 2-tiered analysis in detecting antibodies to B. burgdorferi in patients with acute erythema migrans. In later stages of Lyme disease, the sensitivities of the in parallel tests and 2-tiered testing were high and statistically equivalent.

EVALUATION OF C6 PEPTIDE ELISA IN DOGS VACCINATED WITH RECOMBINANT OSPA VACCINE (0703)

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
PHILIPP, MARIO T	PHD	C	BACTERIOLOGY AND PARASITOLOGY	
L. name J	PHD	A	RESEARCH AND DEVELOPMENT	IDEXX LABS, INC., ME USA

AXIS I CODES: 1A, 7A, 9, 13, 19, 21 **AXIS II CODES:** 35, 39, 64, 66, 91

ABSTRACT

A 25-amino acid synthetic peptide (C6 peptide) derived from an immunodominant conserved region (designated IR6) of the VlsE protein of Borrelia burgdorferi has been identified and used to construct immunoenzyme-based diagnostic procedures. These have excellent sensitivity and specificity. Previous reports have demonstrated the usefulness of the C6 peptide as an antigen for the serodiagnosis of human and canine Lyme disease. Results indicated that assays based on the C6 peptide were nonreactive to sera from vaccinated nonexposed animals and humans. The purpose of the current study was to confirm these results in a controlled trial by testing sera from experimentally vaccinated dogs known to be uninfected. Nine specific-pathogen-free beagles were assigned to one of three vaccine groups, each containing three dogs. Each group received one of three commercial Lyme vaccines: RECOMBITEK Lyme (Merial), LymeVax (Fort Dodge Animal Health) and Galaxy Lyme (Schering-Plough Animal Health). Each animal was administered a total of five doses of vaccine over a period of 39 weeks. Serum samples were collected prior to vaccination, then on a weekly basis from weeks 3 to 18 and from weeks 33 to 43. Selected samples were tested by the immunofluorescence assay (IFA) and Western blot (WB) assay using whole-cell B. burgdorferi antigen extracts, and the results were compared to those obtained with two immunoenzyme-based procedures formatted using the C6 peptide. Serum specimens from all animals were reactive in the IFA and WB assay at week 5 and became highly reactive following the administration of multiple doses of vaccine. All serum specimens were uniformly nonreactive in the C6 peptide immunoenzyme procedures at all time points throughout the study.

GENE EXPRESSION IN BORRELIA BURGDORFERI (0061)

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
RAMAMOORTHY, RAMESH	PHD	C	BACTERIOLOGY AND PARASITOLOGY	

AXIS I CODES: 3, 7A **AXIS II CODES:** 66, 74G, 74H

ABSTRACT

P35 (bba64) is an immunodominant antigen of Borrelia burgdorferi. Its expression has been previously shown to be regulated by pH, temperature and growth phase. Furthermore, a DNA-binding protein has been shown to specifically bind to the 5' regulatory sequence of the P35 gene as assessed by an electromobility shift assay. The presence of this DNA-binding protein positively correlates with the expression of the P35 gene thereby suggesting that this protein is a positive regulator of this gene. To study the role of this DNA-binding activity in vivo, we have constructed transcriptional fusions containing the P35 5' regulatory sequence and the green fluorescent protein gene (marker). In a second construct, we have mutated the binding site for the DNA-binding protein. Currently, we are in the process of transferring these constructs to the E. coli-B. burgdorferi shuttle vector pBVS2 and analyzing the expression of the marker gene in B. burgdorferi.

DNA MICROARRAY AND EXPRESSION CORE (0704)

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
RAMAMOORTHY, RAMESH	PHD	C	BACTERIOLOGY AND PARASITOLOGY	

AXIS I CODES: 3, 7A **AXIS II CODES:** 66, 74G, 74H

ABSTRACT

We had proposed to set up an in-house microarray core to provide for the research needs of TNPRC investigators. In its inaugural operation, the DNA Microarray and Expression Core (DMEC) had proposed to offer the analysis of RNA expression in nonhuman primates through the use of a limited microarray and by RT-PCR (reverse-transcription-PCR). The comprehensive services of DMEC in the area of microarray experimentation would include consultation in matters of design of experiments, development and standardization of protocols, performance of microarray experiments, interpretation of results and maintenance of data. The RT-PCR service will be set up as an integral part of the microarray core and provide a routine quality control tool for the rapid assessment of microarray results. The DMEC will extend the RT-PCR-densitometry services to individual investigators interested in further quantifying specific mRNAs.

During the past year, the following progress has been made in this area. A Shared Instrumentation Grant proposal was submitted to NCRR to obtain funding for this core. Unfortunately, the proposal was not funded. The main reason cited was a shortage of expertise in the area of microarray experimentation and analysis. Therefore, the bulk of our efforts have been dedicated to overcoming our deficiency. Toward this end, we have familiarized ourselves with the instrumentation housed in the Tulane Gene Therapy Center in New Orleans. We have also followed the developments in this field, attended meetings and invited [name] (University of Nebraska), an expert in this area for consultation. [name] is dedicated to designing a rhesus microarray chip the first version of which will be soon available for general use. Our current plan is to incorporate this chip in our experiments when it becomes available. Currently, we continue to offer our RT-PCR-densitometry services to TNPRC investigators.

MICROGLIA AND SIV NEUROPATHOGENESIS (0718)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
ALVAREZ, XAVIER A	PHD	C	COMPARATIVE PATHOLOGY	
L name	PHD	A	VIRAL PATHOGENESIS	BETH ISRAEL DEACONESS MED. CTR., MA USA

AXIS I CODES: 1A, 1B, 19, 21 **AXIS II CODES:** 31, 63I, 64

ABSTRACT

The focus of this study is on the perivascular macrophage as target of productive SIV infection in the central nervous system (CNS). Increasing evidence underscores the role of CNS macrophages, some of which are HIV infected, contributing to neurologic disease. We propose that CNS perivascular macrophages are a primary cell productively infected early and terminally, in animals with AIDS and SIV encephalitis (SIVE). We have established previously, using combinations of immune markers expressed by cells of the myeloid lineage, phenotypic differences between perivascular macrophages and parenchymal microglia and identified perivascular macrophages as a primary target of productive SIV infection. The working hypothesis that guides this proposal is that bone marrow monocyte/macrophages that are potential CNS perivascular macrophages, can be identified in SIV infected macaques and studied as they traffic to the CNS. We hypothesize that the immune system controls the level of SIV infection of perivascular macrophage precursors in the bone marrow; their activation traffic through the blood, and accumulation in the CNS. Lastly, we hypothesize that the traffic and accumulation of SIV infected perivascular macrophages, after the development of AIDS, and not SIV that enters the CNS early after infection, correlate with neuronal damage and injury.

HIV INFECTION OF MICROGLIA (0719)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
ALVAREZ, XAVIER A	PHD	C	COMPARATIVE PATHOLOGY	
names	PHD	A	NEUROLOGY	UNIVERSITY OF PENNSYLVANIA, PA USA
	MD	A	NEUROLOGY	UNIV. OF PENNSYLVANIA, PA USA

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

ABSTRACT

Among CNS cells, macrophage and microglia are the principal cells harboring or replicating virus. The life cycle of HIV within such macrophages and microglia has been studied extensively, and most investigators believe that the HIV genome can integrate effectively into non-dividing cells such as microglia and brain macrophages. Macrophage infection can be long-lived and produce little cytopathology, making these cells ideal potential reservoirs for the virus in a treated individual. Whhile most steps in the infection of macrophages parallel those in lymphocytes, virus assembly and egress are different, and involve intracytoplasmic assembly and routing into multivesicular bodies (MVBs) in preference to budding at the plasma membrane. Subsequent release of virus is believed to take place via an exocytotic pathway involving direct fusion of plasma and MVB limiting membranes. The principal hypothesis that we are currently examining is that the interactions between gag and annexin 2 (Anx2), and possibly other cellular components involved in the assembly of MVBs, are critical to the life cycle of HIV in macrophages, and specifically to virus assembly within these cells.

PNEUMOCOCCUS INFECTION ACTIVATES NFKB IN SIV-INFECTED BAL MACROPHAGES (0643)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BAGBY, GREGORY	PHD	A	PHYSIOLOGY	LSU MEDICAL CENTER, LA USA
	PHD	C	COMPARATIVE PATHOLOGY	
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	MD	A		LSU HEALTH SCIENCES CENTER, LA USA
	DVM	C	VETERINARY MEDICINE	
	DVM, PHD	C	COMPARATIVE PATHOLOGY	

AXIS I CODES: 1A, 1D, 2, 7B **AXIS II CODES:**31, 631, 64, 66, 83, 87

ABSTRACT

Simian Immunodeficiency Virus (SIV) infection of macaques is an important animal model for the acquired immunodeficiency syndrome (AIDS) that recapitulates most features of HIV infection, including CNS disease. Alcohol has been shown to exacerbate other disease states, notably pneumonia. Activation of NFKB is known to be an initial step in the development of disease.

To determine if SIV infection of macaques exacerbates the activation of NFKB and its subsequent translocation from the cytoplasm to the perinuclear area we obtained bronchio-alveolar lavage (BAL) fluids from rhesus macaques before and after infection with pneumococcus. We also examined lung tissues obtained from the same macaques at necropsy. In situ hybridization and immunohistochemistry was performed on these tissues to determine if there is colocaliztion of the virus and NFKB within nucleus of cells.

These experiments can be only performed in the rhesus macaque model due to obtaining samples before infection with SIV and at timed intervals thereafter. Immunohistochemistry and in situ hybridization indicate that inoculation of an SIV-infected macaque with pneumococcus leads to an increase in NFKB activation and increased numbers of SIV-infected cells within the lungs when compared with cells derived from the same lung in the same animal previously.

IN VITRO CELL TROPISM OF SIV NOT PREDICTIVE OF IN VIVO TROPISM OR PATHOGENESIS (0770)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BORDA, JUAN	DVM, PHD	C	COMPARATIVE PATHOLOGY	
	PHD	C	COMPARATIVE PATHOLOGY	
names	PHD	A		HARVARD UNIVERSITY, MA USA
	PHD	A		NEPRC, MA USA
	DVM, PHD	C	DIRECTOR	
	DVM	A		NERPRC, MA USA

AXIS I CODES: 1A, 7B, 19 **AXIS II CODES:** 31, 63I, 64, 66, 83

ABSTRACT

SIVmac239/316 is a molecular clone derived from SIVmac239 that differs from the parental virus by nine amino acids in env. This virus, unlike the parental SIVmac239 is able to replicate well in alveolar macrophages in vitro. We have not however, observed macrophage-associated inflammatory disease in any animal infected with SIVmac239/316. Therefore, we sought to examine the cell tropism of this virus in vivo in multiple tissues utilizing in situ hybridization combined with immunohistochemistry and multilabel confocal microscopy for viral nucleic acid and multiple cell-type specific markers for macrophages and T lymphocytes. Tissues examined included brain, heart, lung, lymph nodes, spleen, thymus, small and large intestine. Matched tissues from macaques infected with the parental SIVmac239 and uninfected macaques were also examined. Many infected cells were detected in the tissues of animals infected with SIVmac239 and SIVmac239/316 although there appeared to be fewer positive cells in animals infected with SIVmac239/316. Surprising, in light of the in vitro observations, nearly every SIV-infected cell in animals inoculated with SIVmac239/316 was a T lymphocyte rather than a macrophage. This was true both during early infection (first 2 months) and in terminal disease. In contrast, as previously described, SIVmac239 was found in both T cells and macrophages in tissues as early as 21 days after infection. These studies indicate that during both acute and chronic SIVmac239/316 infection T lymphocytes rather than macrophages are the principal targets in vivo. These data combined with the absence of macrophage-associated lesions in SIVmac239/316 infected animals indicate that in vitro cell tropism is not predictive of in vivo tropism or disease pathogenesis.

IMMUNOGLOBULIN-A NEPHROPATHY W/CRESCENTIC GLOMERULONEPHRITIS IN PIGTAIL MACAQUE (0775)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BORDA, JUAN	DVM, PHD	C	COMPARATIVE PATHOLOGY	–
	PHD	C	COMPARATIVE PATHOLOGY	
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	DVM	A		NERPRC, MA USA

AXIS I CODES: 1A, 27 **AXIS II CODES:**63I, 64

ABSTRACT

A 4-year-old female pigtailed macaque (Macaca nemestrina), experimentally coinfected with simian immunodeficiency virus (SIVmac251) and Mycobacterium bovis(bacillus Calmette-Guerin), was euthanatized I year after infection because of weight loss and labored breathing. On gross examination, both kidneys were found to be markedly enlarged (right: 54.7 g and left: 51.7 g; normal 20 g). Renal lesions were evaluated by histopathologic, immunohistochemical, and ultrastructural methods. Light microscopy revealed that the glomeruli were diffusely hypercellular with expansion of the mesangial matrix, and crescent formation affected approximately 60% of the glomeruli. By immunohistochemical evaluation, it was found that the crescents were composed principally of macrophages, as seen by CD68 (KP1), MRP8, MAC387, and HAM56 expression. Electron microscopic examination of the glomeruli revealed extensive intramembranous, subendothelial, and mesangial electron-dense deposits and multifocal fusion of the visceral epithelial foot processes. Immunofluorescence, used to determine the composition of the electron-dense deposits, revealed diffuse granular mesangial and capillary staining for immunoglobulin A (IgA). The renal changes described in this case report are most consistent with the findings of crescentic gloerulonephritis with IgA immune complex deposition in the glomerular basement membrane and mesangium as described in humans with IgA nephropathy.

DENDRITIC CELL-MEDIATED ANTI-TUMOR IMMUNITY (0637)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
CURIEL, TYLER J	MD	A	MEDICINE	TULANE HSC, LA USA
	PHD	C	COMPARATIVE PATHOLOGY	
names		A	GENE THERAPY CENTER	UNIVERSITY OF ALABAMA, AL USA
	DVM, PHD	C	DIRECTOR	
	MD, PHD	A	PATHOLOGY	TULANE UNIVERSITY SCHOOL OF MEDICINE, LA USA

AXIS I CODES: 1D, 19 **AXIS II CODES:**76B

ABSTRACT

B7-H1 is a member of the B7 family with pleiotropic effects on T cell-mediated immune responses after ligation with its receptors. PD-1 is the identified receptor for B7-H1. We now demonstrate that a fraction of blood monocyte-derived myeloid dendritic cells (MDC) express B7-H1 on the cell surface. This expression could be upregulated by interleukin (IL)-10 and vascular endothelial cell growth factor (VEGF), two cytokines frequently associated with progressive growth of ovarian carcinomas. Consistent with this finding, virtually 100% of MDC isolated from the tissues or draining lymph nodes of ovarian carcinomas express B7-H1. Blocking interaction of B7-H1 with a non-PD-1 receptor enhanced MDC-mediated stimulation of T cells, and was accompanied by a downregulation of T cell interleukin 10 (IL-10), and an upregulation of IL-2 and interferon gamma. Importantly, T cells stimulated with MDC in vitro in the presence of a B7-H1 neutralizing monoclonal antibody (mAb) had increased potency in inhibition of autologous human ovarian carcinoma growth in transplanted NOD/SCID mice. Our findings support the concept that upregulation of B7-H1 on MDC by tumor microenvironmental factors downregulates T cell anti-tumor immunity. The blockade of the B7-H1 pathway is potentially therapeutic.

A RHESUS MONKEY MODEL OF MALARIA DURING PREGNANCY (0073)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
DAVISON, BILLIE B	DVM	C	COMPARATIVE PATHOLOGY	
L	DVM	A	PATHOLOGY	CHARLES RIVER/SIERRA BIOMEDICAL, NV USA
	PHD	C	BACTERIOLOGY AND PARASITOLOGY	
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	PHD	A	TROPICAL MEDICINE	TULANE UNIVERSITY HEALTH SCIENCES CENTER, LA USA
	MD	A	TROPICAL MEDICINE	TULANE UNIVERSITY HEALTH SCIENCES CENTER, LA USA
	PHD	A		OCHSNER MED FDN, LA USA
	MPH	C	VETERINARY MEDICINE	

AXIS I CODES: 1A, 2, 7C, 23 **AXIS II CODES:** 60, 63H, 64, 65, 66, 71, 77, 93

ABSTRACT

Pregnant women are 4-12 times more likely to develop symptomatic malaria than their nonpregnant counterparts. The factors responsible for the increased severity of malaria during pregnancy are unknown. In holoendemic areas, malaria is the most common cause of maternal death during pregnancy and is a major cause of fetal complications and low birth weight.

A study utilizing 32 rhesus monkeys of differing parities through 3 sequential pregnancies with malaria (Plasmodium coatneyi) began in 2000. It began with 8 malaria-infected primigravida , 8 saline-inoculated primigravid controls, 8 saline-inoculated secundigravid controls and 8 age-matched malaria-infected nulligravid females serving as nonpregnant controls. With repeated pregnancies, inoculations and deliveries of infants, 72 pregnancies are now complete. In this crossover study design, each group of 8 monkeys in their successive pregnancies represents a different level of gravidity and level of immunity to malaria. The resulting nursery reared infant's development, growth, CBCs, and FACs analysis have been monitored for at least 1-3 years.

Throughout pregnancy, parasitemia, CBCs, FACS data, hormone levels, and clinical signs are monitored. Fetal growth and development is evaluated by ultrasonography. The infants, placental tissues, cord blood, maternal blood, and amniotic fluid are collected during cesarean section for histologic and immunologic evaluation. Malaria appears to cause a general widespread immunosuppression throughout gestation involving granulocytes, monocytes, and lymphocytes. Gravidity plays a role, not only with respect to the clinical severity of malaria, but its influence on normal pregnancy and the development of the fetal immune system. The level of malaria immunity is also a major factor in determining outcome. Reproductive immunology has focused on Th1-type responses as detrimental to pregnancy, and although these are extremely important, our data reveal a much more complicated picture with Th2 and B-cell involvement. Our data indicates that not only Th1 inflammatory type cell responses are unfavorable for pregnancy outcomes but maternal B lymphocyte responses may also be detrimental. Placental function and the macrophages in the local placental environment also play a role. Pregnancy-induced immunosuppression combined with malaria-induced immunopathology are important factors contributing to poor fetal outcome.

CELLULAR RESPONSES ASSOCIATED WITH MALARIA IN PREGNANT MONKEYS (0636)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
DAVISON, BILLIE B	DVM	C	COMPARATIVE PATHOLOGY	
L nav c J	MD	A	TROPICAL MEDICINE	TULANE UNIVERSITY HEALTH SCIENCES CENTER, LA USA

AXIS I CODES: 1A, 2, 3, 7C, 23 **AXIS II CODES:** 60, 65, 66, 71, 77, 93

ABSTRACT

We have developed a rhesus monkey model to examine the effects of malaria during pregnancy by using time bred pregnant rhesus monkeys inoculated with Plasmodium coatneyi during the first trimester. This project is supported by an NIH R01 and explores the hypothesis of "pregnancy induced immunosuppression" as the mechanism for the increased susceptibility to severe clinical malaria. Along with the maternal immunologic responses, we are examining the effects of gravidity, and preexisting immunity on the severity of clinical malaria and fetal outcome. Much of the FACS ananlysis and a portion of the work on fetal outcome is being supported by a subcontract through Mississippi state university and the CDC.

We have now begun to analyze the FACS data of the secundigravid and tertigravid nonimmune monkeys as well as the primi and secundigravid monkeys with second exposures to Plasmodium. The results indicate that pregnancy suppresses both cell mediated immunity (CD4, CD8) and humoral immunity or B cell responses to malaria infection. Surprisingly, the data indicate a very strong influence of gravidity on both the cellular and humoral immune responses.

In our model, malaria has been associated with not only impaired fetal growth but impaired infant growth and persistent immunologic alterations in the infants during the first year of life. Babies born to malaria infected mothers have higher absolute numbers of B (CD20+) and lower numbers of T (CD2+) lymphocytes than babies born to controls. The absolute number of CD4+ lymphocytes is lower and the absolute number of CD8+ lymphocytes is higher during the first 4 months. In addition to its value for malaria research, this model is relevant for the examination of the hypothesis known as "fetal programming" which states that the origins of adult disease are related to the fetal environment in utero.

PROMPT TREATMENT OF PARASITEMIA DURING PREGNANCY LIMITS PLACENTAL PATHOLOGY (0714)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
DAVISON, BILLIE B	DVM	C	COMPARATIVE PATHOLOGY	
	PHD	A	TROPICAL MEDICINE	MAHIDOL UNIVERSITY, THAILAND
	PHD	A	CLINICAL TROP MED	MAHIDOL UNIVERSITY, THAILAND
	PHD	A	NUFFIELD DEPT OF CLIN. MED	CENTRE FOR TROP MED, UK
names	MD, PHD	A	EPIDEMIOLOGY AND MICROBIOLOGY	UNIVERSITY OF NC/CHAPEL HILL, NC USA
	MD, PHD	A	SHOKLO MALARIA RES. UNIT	MAHIDOL UNIVERSITY, THAILAND
	PHD	A	TROP. MED/CLINICAL MEDICINE	JOHN RADCLIFFE HOSPITAL, UK
	PHD	A	PATHOBIOLOGY/TROP ICAL MEDICINE	TULANE SCHOOL OF PUBLIC HEALTH, LA USA
	PHD	A	INFECTIOUS DISEASES/TROP MED	ACADEMIC MEDICAL CENTRE, THE NETHERLANDS

AXIS I CODES: 5A, 5C, 5D, 7C, 12, 23 **AXIS II CODES:** 50, 60, 65, 66, 71

ABSTRACT

Placental histopathology was studied in a cohort of 204 women living in an area of low P. falciparum and P. vivax malaria transmission. Detection of malaria antenatally was active, by weekly peripheral blood smears, and all infections were treated. Significant histopathological placental malaria changes (increased malaria pigment, cytotrophoblastic prominence and presence of parasites) were found only in a minority of women who had P. falciparum infections in pregnancy. These changes were significantly more frequent in women with evidence of peripheral blood infection close to delivery and only in these cases, were placental inflammatory cells increased. Antenatal P. vivax infection was associated only with the presence of malaria pigment in the placenta. All placental infections were associated with patent peripheral parasitemia. This study indicates that prompt treatment of peripheral parasitemias during pregnancy limits placental pathology. The effect on birthweight reduction does not result from irreversible placental changes but from the acute insult of infections. These findings emphasize the importance of treating malaria in pregnancy promptly with effective antimalarial drugs.

A RAPID LATERAL FLOW TEST FOR TB IN NONHUMAN PRIMATES (0715)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
DIDIER, PETER J	DVM, PHD	C	COMPARATIVE PATHOLOGY	
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	PHD	A	IMMUNOLOGY	SEQUELLA, INC., MD USA

AXIS I CODES: 1D, 7A, 9, 18, 19 **AXIS II CODES:** 64, 66, 91

ABSTRACT

The overall objective of this SBIR project is to develop and bring to market an improved diagnostic test for tuberculosis (TB) in nonhuman primates. The format of the test is a lateral flow assay that can use whole blood, serum, or plasma, and can detect antibodies to specific antigens within 15 minutes. The objective of this Phase II research is to validate the lateral flow diagnostic test in terms of sensitivity, specificity, and utility, and to meet the requirements for USDA licensure. In Phase I of this study, test antigens were selected using sera from monkeys inoculated with M. tuberculosis. In this study (Phase II), monkeys will receive environmental mycobacteria that could produce false positive reactions (M. kansasii and M. avium). To validate the test, in year two, monkeys will be inoculated with M. bovis.

INDUCTION OF SIV-SPECIFIC CD8+ INTRAEPITHELIAL LYMPHOCYTES (0587)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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		A	BASIC RESEARCH LAB	NCI, MD USA
		A	BASIC RESEARCH LAB	NCI, MD USA

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

ABSTRACT

The vaginal and rectal mucosa are the first line of cellular immune defense to HIV-1 entry. Thus, intraepithelial lymphocytes (IEL) likely are an important factor in maintaining an immune response to HIV infection. The objective of this study was to assess whether vaccination at mucosal sites or infection would induce SIV-specific T-cells within the intraepithelial layer of sufficient frequency to be visualized by direct staining with a tetrameric complex specific for the immunodominant Gag epitope (Gag181-189) of SIV. In Mamu A*01+ infected macaques, either immunized with the NYVAC/SIVgpe vaccine or during acute and chronic SIVmac251 infection, Gag-specific tetramer-positive cells were found following separation or directly by tetramer staining in tissues. The frequently isolated SIV-specific IEL's were further characterized by assessing their expression of activation markers CD69 and CD25 and the intracellular expression of cytokines such as IFN-gamma and IL-10.

Ag-specific cells directed to the Gag181-189 epitope were readily demonstrated within the IEL population. These cells were detected in immunized animals as well as in macaques acutely or chronically infected with SIVmac251. Furthermore, very high percentage of the total CD8+ population as well as of the Gag-specific CD8+ IEL's expressed the activation marker CD69. Percentage of these cells expressing CD25 was low. When stimulated, a very high percentage of the CD8+ IEL's and almost all of the Gag-specific CD8+ IEL's expressed IFN-gamma, a cytokine that mediates protective responses. Intracellular expression of IL-10, a cytokine believed to be involved in tolerance was low and only 0.03-0.28% of the Gag-specific CD8+ IEL's expressed it. Thus, IEL's may important in determining the success of an SIV vaccine in guarding against mucosal transmission.

PROSPECTIVE IN VIVO MR SPECTROSCOPY STUDY OF THE SIV/MACAQUE MODEL OF NEUROAIDS (0689)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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	PHD	A	NEURORADIOLOGY	MA GEN HOSPITAL/HARVARD MED SCHOOL, MA USA
		A	NEURORADIOLOGY	MASSACHUSETTS GENERAL HOSPITAL, MA USA
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	PHD	A	NEURORADIOLOGY	MA GEN HOSPITAL/HARVARD MED SCH, MA USA
	DVM, PHD	C	DIRECTOR	
	PHD	A	NEURORADIOLOGY	MA GEN HOSPITAL/HARVARD MED SCH, MA USA
	PHD	A	NEUROSCIENCES	UC-SAN DIEGO, CA USA
	DVM	A		NERPRC, MA USA

AXIS I CODES: 1A, 7B, 9, 21 **AXIS II CODES:**31, 63C, 64, 66

ABSTRACT

The neurological complications of HIV infection remain poorly understood. In clinical studies, in vivo magnetic resonance spectroscopy (MRS) demonstrates brain injury caused by HIV infection even when the MRI is normal. Our goal was to better understand the dynamics of cerebral injury by performing a longitudinal in vivo MRS study of the SIV/macaque model of neuroAIDS. We serially imaged 8 SIVmac251-infected rhesus macaques to terminal AIDS or the endpoint of 2 years. During the acute period of infection, we observed stereotypical brain MRS changes, dominated by elevation of the Cho/Cr ratio. Subsequently, brain metabolic patterns diverged. Strikingly, we found an elevation of basal ganglia Cho/Cr four weeks post-inoculation in the 2 animals destined to develop encephalitis ($p = 0.022$). Thus, this metabolite ratio may be an early marker of animals destined to progress to SIVE. Additionally, we found a significant positive correlation between a change in frontal lobe Cho/Cr and plasma viral load (P 0.001, $R = 0.80$), and a negative correlation between NAA/Cr in the basal ganglia and the plasma viral load (P 0.02, $R = -0.73$). Our findings that markers for cerebral inflammation and neuronal injury correlate with viral levels in the periphery supports the use of drugs capable of controlling the propagation and trafficking of virus into the CNS, and may help explain the reduction in incidence of HIV-associated dementia in the era of HAART despite the inability of most of those drugs to effectively enter the CNS.

MRS: AN IN VIVO TOOL FOR MONITORING CEREBRAL INJURY IN SIV-INFECTED MACAQUES (0595)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
GRECO, J.B.		A	NEURORADIOLOGY	MASSACHUSETTS GENERAL HOSPITAL, MA USA
		A	NEURORADIOLOGY	MASSACHUSETTS GENERAL HOSPITAL, MA USA
	PHD	A	NEURORADIOLOGY	MASSACHUSETTS GENERAL HOSPITAL, MA USA
		A	NEURORADIOLOGY	MASSACHUSETTS GENERAL HOSPITAL, MA USA
names	PHD	A	NEURORADIOLOGY	MA GEN HOSPITAL/HARVARD MED SCH, MA USA
	DVM, PHD	C	DIRECTOR	
	PHD	A	NEURORADIOLOGY	MA GEN HOSPITAL/HARVARD MED SCH, MA USA
	PHD	A	NEUROSCIENCES	UC-SAN DIEGO, CA USA
		A	NEURORADIOLOGY	MASSACHUSETTS GENERAL HOSPITAL, MA USA
	DVM	A		NERPRC, MA USA

AXIS I CODES: 1A, 7B, 9, 21 **AXIS II CODES:** 31, 63C, 64, 66

ABSTRACT

PURPOSE: To quantify the relationship between astrogliosis and Cho/Cr and MI/Cr ratios measured by MRS in the simian immunodeficiency virus (SIV) infected macaque model of neuroAIDS.
MATERIALS AND METHODS: Eleven rhesus macaques were studied including 7 infected with SIV during the first month of infection. Animals were studied by in vivo 1H MRS, and post mortem frontal lobe samples were investigated by 1H MRS of brain extracts, and GFAP immunohistochemistry. ANOVA was used to determine significant changes in neuropathological and MRS measures. Spearman rank correlation was used to assess relationships between plasma viral load, neuropathological and MRS markers.
RESULTS: GFAP, and in vivo MRS Cho/Cr and MI/Cr attained their highest levels near the time of peak plasma viral loads at 11 days after infection. The subsequent time course of these measures diverged. Peak GFAP levels were significant ($p = 0.009$), and significant correlation was found between plasma viral load and GFAP ($Rs = 0.64$, p 0.05). Solution 1H MRS of brain extracts revealed no significant increases in Cho/Cr and MI/Cr near the time of peak viremia, and there were no significant correlations with their in vivo counterparts.
CONCLUSIONS: Brain in vivo 1H MRS Cho/Cr more closely tracks changes in GFAP than MI/Cr during transient astrogliosis induced by AIDS virus infection. Changes in Cho/Cr and MI/Cr detected in vivo in relation to astrogliosis are principally due to contributions other than low molecular weight, water soluble metabolites. Potential contributors may include macromolecules that are upregulated during the astrogliotic process.

ANTIBODY RESPONSES AND PROTECTION FROM PYELONEPHRITIS FOLLOWING VACCINATION WITH(0709)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
KAACK, M BERNICE	PHD	C	COMPARATIVE PATHOLOGY	
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	MD	A		WASHINGTON U, MO USA
	PHD	A	SCHOOL OF MEDICINE	WASHINGTON UNIV, MO USA
	PHD	A		WASHINGTON U, MO USA

AXIS I CODES: 1A, 1D, 27 **AXIS II CODES:**91

ABSTRACT

Purpose: A critical early step in the establishment of E. coli pyelonephritis is bacterial attachment via the tip protein of P fimbriae. This adhesin, PapG, binds to glycolipid receptors present on vaginal and kidney epithelial surfaces. In this study, we investigated the efficacy of vaccination with purified PapDG protein complex in preventing pyelonephritis caused by E. coli.

Materials and Methods: Mature cynomolgus monkeys were intraperitoneally vaccinated with 100 μg of purified PapDG protein, and following three identical boosters, serum antibody titers to PapDG were measured by ELISA. Both vaccinated and unvaccinated animals were urethrally inoculated with 1 x 108 CFU of E. coli strain DS17, which was isolated from a child with acute pyelonephritis. The course of infection was monitored by catheterized urine cultures, and by histologic examination of the kidneys and bladder and culture of kidney tissue 28 days after infection.

Results: Intraperitoneal administration of purified PapDG vaccine resulted in the development of specific antibody responses in cynomolgus monkeys. In contrast to control monkeys, vaccinated monkeys did not show histologic evidence of pyelonephritis after subsequent urethral challenge with pyelonephritogenic E. coli expressing P fimbriae.

Conclusion: Purified PapDG is a tractable vaccine candidate that, in our small study, demonstrated the ability to elicit adequate serum antibody levels to prevent E. coli-mediated pyelonephritis.

HERPES GLYCOPROTEIN TRANSPORT AND VIRUS-INDUCED CELL FUSION (0638)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
KOUSOULAS, KONSTANTIN G	DVM, PHD	A		LSU SCHOOL OF VETERINARY MEDICINE, LA USA
names	PHD	C	COMPARATIVE PATHOLOGY	
	PHD	A		LSU, LA USA

AXIS I CODES: 1B, 19, 21 **AXIS II CODES:**63I, 64, 66, 83

ABSTRACT

Intracellular transport and egress of alphaherpesviruses require the coordinate function of multiple proteins and glycoproteins. Recently, we showed that gK is expressed on infected cell surfaces and that gK cell-surface expression required the presence of the UL20 protein [J. Virol. 77 (2003), 499]. Overexpression of gK by gK-transformed cells blocked transport of enveloped virions from perinuclear spaces and inhibited virus-induced cell fusion caused by gK syncytial mutants [J. Virol.69 (1995), 5401]. Therefore, we investigated whetheraltered synthesis and transport of gK was responsible for the observed gK-mediated interference phenomena. HSV-1 infection of the gK-transformed cell line Vero (gK9) caused a profound entrapment of gK in the endoplasmic reticulum and total inhibition of gK cell surface expression. In addition, gK drastically inhibited intracellular transport and maturation of gD and caused substantial defects in Golgi-dependent glycosylation of gB. Visualization of intracellular organelles via confocal microscopy revealed a profound collapse of the Golgi apparatus into the endoplasmic reticulum. These results were analogous to those observed in the presence of brefeldin A, a known Golgi disruptor. Therefore, virion entrapment within perinuclear spaces and inhibition of glycoprotein transport are due to gK-mediated collapse of the Golgi apparatus.

PROXIMITY OF ENTEROENDOCRINE CELLS TO LYMPHOCYTES IN THE GUT MUCOSA (0690)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LACKNER, ANDREW A	DVM, PHD	C	DIRECTOR	
[illegible]	PHD	C	COMPARATIVE PATHOLOGY	

AXIS I CODES: 1A, 16C, 21 **AXIS II CODES:** 63I

ABSTRACT

The involvement of serotonin (5-hydroxytryptamine; 5-HT) in immunoregulation has been well documented. Gut mucosa is a large reservoir of 5-HT most of which is attributed to gut endocrine cells. In this study, we examined the anatomical relationship among 5-HT immunoreactive cells and T- and B- lymphocytes in the gut mucosa of rhesus monkeys (Macaca mulatta). 5-HT, CD3 and CD20 immunoreactive cells were immunofluorescently labeled and visualized by confocal microscopy. 5-HT immunoreactive cells were primarily found within the epithelium of the intestine and were present at all levels of the gastrointestinal tract. Many 5-HT immunoreactive cells were in contact with, or very close proximity to CD3+ and CD20+ lymphocytes. These results provide morphological evidence to suggest interactions between 5-HT secreting enteroendocrine cells and lymphocytes in the gut mucosa. This further supports a possible role of 5-HT in mucosal immune responses.

NIH/NIAID BIODEFENSE PROGRAM (0691)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LACKNER, ANDREW A	DVM, PHD	C	DIRECTOR	
	DVM	A		TEXAS A&M, TX USA
	DVM	C	VETERINARY MEDICINE	
	PHD	A		UNIVERSITY OF ALABAMA, AL USA
	MD	A		DUKE UNIVERSITY, NC USA
names	PHD	A		UNIVERSITY OF ALABAMA, AL USA
	MD	A		UNIVERSITY OF TX MEDICAL BRANCH, TX USA
	PHD	A		DUKE UNIVERSITY, NC USA
	MD	A		UNIVERSITY OF TEXAS MEDICAL BRANCH, TX USA
	MD, MSC	A		TULANE UNIVERSITY HEALTH SCIENCES CENTER, LA USA

AXIS I CODES: 1A, 2, 7A, 7B, 11 **AXIS II CODES:** 64, 66, 77, 91

ABSTRACT

The TNPRC is involved in the NIH/NIAID biodefense and emerging infectious diseases research agenda through participation in two of the Regional Centers of Excellence in Biodefense and Emerging Infectious Diseases (RCE) in regions IV and VI and construction of a Regional Biodefense Laboratory (RBL). The TNPRC serves as part of the nonhuman primate core for each the two RCEs. Studies in nonhuman primates will be critical to the development of therapeutics and vaccines for NIAID Category A – C agents. The TNPRC is ideally suited to meet this critical need particularly because of our expertise with infectious disease studies and model development in nonhuman primates housed at BSL-3. The specific objectives of the RBL are to: 1) provide an infrastructure to support regional and national research on Category A – C agents with a focus on work requiring nonhuman primates; 2) provide highly integrated clinical care and laboratory investigations to the biodefense research community to obtain the maximum amount of information possible from every animal; 3) provide oversight on experiments using animals to assure compliance with federal animal welfare and biosafety regulations. These objectives will be facilitated by the participation of the TNPRC in the nonhuman primate cores of the RCE applications from regions IV and VI.

IMMUNOBIOLOGY OF SIV-ASSOCIATED LYMPHOMAS (0056)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LEVY, LAURA S.	PHD	A	MICROBIOLOGY/IMMUNOLOGY	TULANE MEDICAL SCHOOL, LA USA
L name J	DVM, PHD	C	COMPARATIVE PATHOLOGY	

AXIS I CODES: 1A, 1D, 7B, 9, 17, 19 **AXIS II CODES:** 31, 39, 64, 66, 76B

ABSTRACT

We are continuing our collaborative project with Dr. Laura Levy in examining lymphomas in SIV-infected and uninfected rhesus macaques. Lymphomas occur with increased frequency (3-6%) in HIV-infected individuals. These AIDS-associated lymphomas (AAL) exhibit characteristics that distinguish them from lymphomas in the general population. Lymphomas also occur in SIV-infected macaques. We have evidence suggesting that the incidence of lymphomas in macaques may be indirectly related to the rate of disease progression. We are currently examining rhesus macaques of Chinese origin, who have a slower progression to disease and the incidence of lymphomas in this subspecies may in fact be higher due to the prolonged course of infection. Currently, all SAIDS-associated lymphomas (SAL) are being examined by multiparameter flow cytometry, immunohistochemistry, and in situ hybridization, and viably frozen cells are cultured by Dr. Levy for further characterization. In general, results show that lymphomas occur in SIV-infected rhesus macaques at an incidence similar to that of AAL, and that the incidence of SAL in cynomolgus macaques(another species that progresses relatively slowly) is 8-fold higher. Analysis of SAL from both species of macaques demonstrated significant similarity to the hallmark pathobiological features of AAL. The tumors occur in long-term survivors of SAIDS, exhibit extranodal anatomic distribution, represent clonal expansions of B-cell origin, lack SIV in tumor cells, and are infected with RhLCV (a herpesvirus closely related to EBV). These findings indicate that the HIV-infected human and the SIV-infected macaque share a common pathobiology and mechanism of lymphomagenesis.

IMMUNOBIOLOGY OF SIV-ASSOCIATED LYMPHOMAS (0056)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650% AIDS RELATED RESEARCH

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LEVY, LAURA S.	PHD	A	MICROBIOLOGY/IMMUNOLOGY	TULANE MEDICAL SCHOOL, LA USA
L name 1	DVM, PHD	C	COMPARATIVE PATHOLOGY	-

AXIS I CODES: 1A, 1D, 7B, 9, 17, 19 **AXIS II CODES:** 31, 39, 64, 66, 76B

ABSTRACT

We are continuing our collaborative project with Dr. Laura Levy in examining lymphomas in SIV-infected and uninfected rhesus macaques. Lymphomas occur with increased frequency (3-6%) in HIV-infected individuals. These AIDS-associated lymphomas (AAL) exhibit characteristics that distinguish them from lymphomas in the general population. Lymphomas also occur in SIV-infected macaques. We have evidence suggesting that the incidence of lymphomas in macaques may be indirectly related to the rate of disease progression. We are currently examining rhesus macaques of Chinese origin, who have a slower progression to disease and the incidence of lymphomas in this subspecies may in fact be higher due to the prolonged course of infection. Currently, all SAIDS-associated lymphomas (SAL) are being examined by multiparameter flow cytometry, immunohistochemistry, and in situ hybridization, and viably frozen cells are cultured by Dr. Levy for further characterization. In general, results show that lymphomas occur in SIV-infected rhesus macaques at an incidence similar to that of AAL, and that the incidence of SAL in cynomolgus macaques (another species that progresses relatively slowly) is 8-fold higher. Analysis of SAL from both species of macaques demonstrated significant similarity to the hallmark pathobiological features of AAL. The tumors occur in long-term survivors of SAIDS, exhibit extranodal anatomic distribution, represent clonal expansions of B-cell origin, lack SIV in tumor cells, and are infected with RhLCV (a herpesvirus closely related to EBV). These findings indicate that the HIV-infected human and the SIV-infected macaque share a common pathobiology and mechanism of lymphomagenesis.

CHARACTERIZATION OF AN IN VITRO RHESUS MACAQUE BLOOD-BRAIN BARRIER (0594)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MACLEAN, ANDREW	PHD	C	COMPARATIVE PATHOLOGY	
	PHD	C	COMPARATIVE PATHOLOGY	
	DVM, PHD	C	DIRECTOR	
names	DVM, PHD	C	COMPARATIVE PATHOLOGY	
	PHD	A	VIRAL PATHOGENESIS	BETH ISRAEL DEACONESS MED. CTR., MA USA

AXIS I CODES: 1D, 7B, 9, 21 **AXIS II CODES:** 31, 52, 64, 66, 77, 87

ABSTRACT

Monocyte/macrophages and activated lymphocytes traffic through normal brain, and this trafficking is increased in inflammatory conditions such as HIV encephalitis (HIVE). HIVE is characterized in part by perivascular accumulations of macrophages. The earliest events in this process are poorly understood and difficult or impossible to address in humans. From the SIV-infected macaque model of neuroAIDS it appears there is an immigration of monocytes into the brain early in disease, coincident with peak SIV viremia. The chemotactic signals that facilitate the first mononuclear cells to traverse the blood-brain barrier have not been described. Here we describe the use of an in vitro model of the rhesus macaque blood-brain barrier involving autologous astrocytes and microvascular brain endothelial cells to examine very early events in leukocyte recruitment to the CNS. We have previously published complementary in vivo work demonstrating the presence of MCP-3/CCL7 (and other chemokines) within the brain of SIV-infected macaques. Here we demonstrate that MCP-3/CCL7 is a significant chemokine produced by astrocytes and that it is likely to play a major role in the basal level of monocyte/macrophage trafficking to the CNS and thus entry of SIV/HIV into the brain.

ALCOHOL AND SIV ENCEPHALITIS: PBMC CHEMOTAXIS MODULATION FOLLOWING SIV INFECTION (0642)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MACLEAN, ANDREW	PHD	C	COMPARATIVE PATHOLOGY	
	PHD	A	PHYSIOLOGY	LSU MEDICAL CENTER, LA USA
	MD, PHD	A		LSUHSC, LA USA
names	MD	A		LSU HEALTH SCIENCES CENTER, LA USA
	DVM, PHD	C	COMPARATIVE PATHOLOGY	
	PHD	A	VIRAL PATHOGENESIS	BETH ISRAEL DEACONESS MED. CTR., MA USA

AXIS I CODES: 1D, 7B, 9, 21 **AXIS II CODES:** 31, 52, 64, 66, 77, 87

ABSTRACT

Simian Immunodeficiency virus (SIV) infection of macaques is an important animal model for the acquired immunodeficiency syndrome (AIDS) that recapitulates most features of HIV infection, including CNS disease. Alcohol has been shown to exacerbate neurological diseases in humans, and it is known that there is a higher incidence of HIV infection among chronic alcohol abusers. However, it is not known if this translates into a higher incidence of neurological complications associated with HIV infection. Numbers of SIV infected PBMCs found within the brain of monkeys with terminal AIDS correlates with severity of disease. These experiments can best be performed using the SIV-infected macaque model as it is not possible to obtain pre-inoculation samples from HIV-infected individuals.

To examine if chronic alcohol abuse leads to increased PBMC migration into the CNS following SIV infection we determined chemotactic indices. These were obtained by measuring the ability of PBMCs freshly obtained from macaques to migrated in a directed manner to the chemokines MIP-1a and MIP-1b before and after SIV infection. The results obtained from this technique showed that there is an increase in migration of PBMCs towards the above chemokines following SIV infection and that this is exacerbated by chronic alcohol administration.

MCP-3 PRODUCTION BY ASTROCYTES: IMPLICATIONS FOR SIV NEUROINVASION (0772)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MACLEAN, ANDREW	PHD	C	COMPARATIVE PATHOLOGY	
names	PHD	C	COMPARATIVE PATHOLOGY	
	DVM, PHD	C	DIRECTOR	
	PHD	A	VIRAL PATHOGENESIS	BETH ISRAEL DEACONESS MED. CTR., MA USA

AXIS I CODES: 1D, 7B, 9, 21 **AXIS II CODES:** 31, 52, 64, 66, 77, 87

ABSTRACT

Monocyte/macrophages and activated lymphocytes traffic through normal brain, and this trafficking is increased in inflammatory conditions such as HIV encephalitis (HIVE). HIVE is characterized in part by perivascular accumulations of macrophages. The earliest events in this process are poorly understood and difficult or impossible to address in humans. From the SIV-infected macaque model of neuroAIDS it appears there is an immigration of monocytes into the brain early in disease, coincident with peak SIV viremia. It is not known if the first cell crosses the blood-brain barrier during normal trafficking or indeed how normal trafficking occurs; the chemotactic signals that facilitate the first mononuclear cells to traverse the blood-brain barrier have not been described. We have used an in vitro model of the rhesus macaque blood-brain barrier involving autologous astrocytes and microvascular brain endothelial cells to examine very early events in leukocyte recruitment to the CNS. We have previously published complementary in vivo work demonstrating the presence of MCP-3/CCL7 (and other chemokines) within the brain of SIV-infected macaques. We demonstrated that MCP-3/CCL7 is a significant chemokine produced by astrocytes and that it is likely to play a major role in the basal level of monoycte/macrophage trafficking to the CNS and thus entry of SIV/HIV into the brain.

HIGH LEVELS OF SIVMND-1 REPLICATION IN CHRONICALLY INFECTED MANDRILLUS SPHINX (0723)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
PANDREA-VASILE, IVONA	MD, PHD	C	COMPARATIVE PATHOLOGY	
	MD, PHD	C	MICROBIOLOGY & IMMUNOLOGY	
	DVM	A		CIRMF, GABON
	PHD	A		CIRMF, GABON
	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	PHD	A		CENTRE INTERNATIONAL DE RECHERCHES MEDICALES, GABON
	PHD	A		CIRMF, GABON
	PHD	A		CENTRE INTERNATIONAL DE RECHERCHES MEDICALES, GABON
	DVM	A		CIRMF, GABON
	MD	A		CENTRE INTERL DE RECHERCHES MED, GABON

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

ABSTRACT

Viral loads were investigated in SIVmnd-1-chronically infected mandrills and the results were compared with those previously observed in other non-pathogenic natural SIV infections. Four naturally and 11 experimentally SIVmnd-1-infected mandrills from a semi-free ranging colony were studied during the chronic phase of infection. Four SIVmnd-1-infected wild mandrills were also included for comparison. Twelve uninfected mandrills were used as controls. Viral loads in all chronically infected mandrills ranged from 105 to 9x105 copies/ml and antibody titers ranged from 200 to 14,400, and 200 to 12,800 for anti-V3 and anti-gp36, respectively. There were no differences between groups of wild and captive mandrills. Both parameters were stable during the follow-up, and no clinical signs of immune suppression were observed. Chronic SIVmnd-1 infected mandrills presented slight increases in CD20+ and CD28+/CD8+ cell counts, and a slight decrease in CD4+/CD3+ cell counts. A slight CD4+/CD3+ cell depletion was also observed in old uninfected controls. Similar to other non-pathogenic models of lentiviral infection, these results show a persistent high level of SIVmnd-1 replication during chronic infection of mandrills, with minimal effects on T cell subpopulations.

EARLY IN VIVO REPLICATION PROFILES OF SIVAGM IN AFRICAN GREEN MONKEYS (0766)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
PANDREA-VASILE, IVONA	MD, PHD	C	COMPARATIVE PATHOLOGY	
	MD, PHD	C	MICROBIOLOGY & IMMUNOLOGY	
	PHD	A		INSTITUTE DE PASTEUR, FRANCE
	DVM, PHD	A		CENTRE PASTEUR, SENEGAL
names	PHD	A		PATEUR INSTITUTE, FRANCE
	PHD	A		CENTRE INTERNATIONAL DE RECHERCHES MEDICALES, GABON
	PHD	A		CENTRE INTERNATIONAL DE RECHERCHES MEDICALES, GABON
	DVM	A		CIRMF, GABON
	MD	A		CENTRE INTERL DE RECHERCHES MED, GABON

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

ABSTRACT

To better understand which factors govern the level of viral load in vivo during early lentiviral infection in primates, we developed a model that allows distinguishing between the influence of host and viral factors on viremia. Herein we report that two species of AGMs (Chlorocebus sabaeus and C. pygerythrus) infected with their respective wild type SIVagm viruses (SIVagm.sab92018 and SIVagm.ver644) consistently showed reproducible differences in viremia during primary infection, but not at later stages of infection. Cross-infections of SIVagm.sab and SIVagm.ver into, respectively, C. pygerythrus and C. sabaeus revealed that the extent of early virus replication was primarily dependent on viral determinants and not the host species or the individual, whereas the host environment had a greater impact on the viremia starting from the post-acute infection phase on. Current studies investigate if these differences in viral pathogenicity are due to differences on co-receptor usage between the two viruses. These experiments are in progress. Preliminary results suggest that SIVagm.sab92018 may have a larger spectrum of co-receptor usage compared to SIVagm.ver644.

SUBSTANCE P AND THE PATHOGENESIS OF CRYPTOSPORIDIOSIS IN AIDS (0694)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
ROBINSON, PREMA	PHD	A		BAYLOR UNIVERSITY, TX USA
names	DVM, PHD	C	COMPARATIVE PATHOLOGY	
	DVM, PHD	C	DIRECTOR	

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

ABSTRACT

Cryptosporidiosis, caused by the protozoan parasite, Cryptosporidium parvum, is self-limited in normal hosts but can cause life threatening, chronic diarrhea in AIDS patients. No safe and effective treatment has been successfully developed for cryptospofidiosis associated with advanced AIDS. Substance P (SP), a neuropeptide, is a pain transmitter and can cause C1- ion secretion in human intestinal explants. We have previously studied SP expression in jejunal biopsies of AIDS patients with natural severe cryptosporidiosis and normal volunteers experimentally challenged with C. parvum (mild disease). SP expression was stronger in AIDS patients compared to normal volunteers with mild self-limited cryptosporidiosis. We hypothesize that SP is a key mediator of chronic intestinal symptoms in AIDS associated cryptosporidiosis. We also hypothesize that SP expression will be elevated in intestinal tissues of immunodeficient hosts because of cryptosporidiosis infection, HIV infection alone will not cause increased SP expression. To verify these hypotheses, we propose to use an immunodeficient animal model of cryptosporidiosis, ie. primates with AIDS (after experimental SIV infection) and cryptosporidiosis as an opportunistic naturally occurring infection. The goal of this project is to test the hypothesis that SP mediates severe symptoms of cryptosporidiosis in immunodeficient hosts.

IMMUNOGENICITY STUDIES OF RABIES VIRUSES EXPRESSING HIV-1 OR SIV (0589)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
SCHNELL, MATTHIAS J.	MS, PHD	A	CENTER FOR HUMAN VIROLOGY	THOMAS JEFFERSON UNIVERSITY, PA USA
	PHD	A	MICROBIOLOGY	THOMAS JEFFERSON UNIVERSITY, PA USA
	DVM, PHD	C	DIRECTOR	
names		A	BIOCHEMISTRY	THOMAS JEFFERSON UNIVERSITY, PA USA
		A	MICROBIOLOGY	THOMAS JEFFERSON UNIVERSITY, PA USA
	PHD	A		DUKE UNIVERSITY MEDICAL CENTER, NC USA
	PHD	A		THOMAS JEFFERSON UNIVERSITY, PA USA
	MD	A	DIVISION OF INFECTIOUS DISEASE	THOMAS JEFFERSON UNIVERSITY, PA USA

AXIS I CODES: 1A, 7C, 19 **AXIS II CODES:**31, 66, 91

ABSTRACT

Rabies virus (RV), a single-stranded RNA virus of the Rhabdovirus family, has recently been developed as a novel vaccine candidate for HIV-1. As a live-attenuated vaccine in mice, RV has been shown to induce vigorous and long lasting immune responses to both HIV-1 Env and Gag. Further, the single RV glycoprotein (G) can be functionally replaced by HIV-1 Env if the gp160 cytoplasmic tail domain (CD) is replaced by that of RV G. These surrogate, or G-deleted (DG), viruses expressing Env assume an HIV-1-like cell tropism and are therefore targeted to CD4+/HIV-1 co-receptor positive cells. This report describes a proof of principle study of the safety, replication capacity and immunogenicity of G-deleted RV expressing Env in rhesus macaques. The results show these viruses can productively infect rhesus peripheral blood mononuclear cells (PBMCs) and vaccinated animals seroconvert to the RV ribonucleic acid particle (RNP). An animal vaccinated with a G-deleted virus expressing the SHIV-89.6P envelope developed high titer virus neutralizing antibodies and Env-specific cellular immune responses post-challenge with SHIV-89.6P. Importantly, there was no evidence of CD4+ T-cell loss and plasma viral loads were controlled to undetectable levels by six weeks post-challenge. The animal has remained healthy with no signs of disease up to twenty-two weeks post-challenge.

EVALUATION OF FUSION INHIBITORS AS MICROBICIDES FOR SHIV (0048)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
VEAZEY, RONALD S.	DVM, PHD	C	COMPARATIVE PATHOLOGY	
	PHD	A		SCRIPPS RES INST, CA USA
	MD, PHD	A	MICROBIOLOGY	UNIVERSITY OF PA, PA USA
	DVM	C	VETERINARY MEDICINE	
names	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	PHD	A		CORNELL UNIVERSITY, NY USA
	PHD	A		POPULATION COUNCIL, NY USA
	PHD	A	INFECTIOUS DIS. & MEDICINE	ST. GEORGE HOSPITAL MED SCHOOL, UK
	PHD	A		MERCK & CO, NJ USA

AXIS I CODES: 1A, 2, 7B, 9, 23 **AXIS II CODES:**31, 50B, 66, 83, 93, 94

ABSTRACT

Development of an effective microbicode that could prevent sexual transmission of HIV-1 when applied to the vagina prior to intercourse could potentially slow the AIDS pandemic, and save millions of lives. We are continuing to test microbicides in the SIV macaque model of vaginal transmission to determine whether fusion inhibitors may be effective in preventing vaginal transmission of human immunodeficiency virus type 1 (HIV-1) to humans. Briefly, we are applying a solution of the inhibitor to the vagina of anesthetized macaques, followed by vaginal inoculation with SHIV-162P, a CCR5-utilizing virus that is highly relevant in HIV-1 transmission., To date, we tested several such compounds and have demonstrated that the HIV-1 mAb b12 successfully prevents vaginal transmission of SHIV162P (1). We are continuing to test various compounds in this system including agents that bind chemokine receptors, CD4, and gp120 fusion inhibitors in this system for efficacy and safety so that an effective microbicide may be developed for use in humans.

ONTOGENY OF THE NEONATAL MACAQUE IMMUNE SYSTEM (0051)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
VEAZEY, RONALD S.	DVM, PHD	C	COMPARATIVE PATHOLOGY	
	PHD	A	MICRO/IMMUNO/PARASIT	LSU HEALTH SCIENCES CENTER, LA USA
names	DVM, PHD	C	DIRECTOR	
	MD	A	RETROVIRAL PATHOGENESIS	NCI FREDERICK, MD USA
	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	

AXIS I CODES: 1A, 7B, 16C, 19 **AXIS II CODES:** 31, 60, 64, 71

ABSTRACT

Children with HIV infection often have higher viral loads and progress to AIDS more rapidly than adults. Since the intestinal tract is a major site of early viral replication and CD4+ T cell depletion in adults, we examined the effects of SIV on both peripheral and intestinal lymphocytes from 13 neonatal macaques infected with SIVmac239. Normal neonates had more CD4+ T cells, and fewer CD8+ T cells in all tissues than adults. Surprisingly, neonates had substantial percentages of CD4+ T cells with an activated, memory phenotype (effector CD4+ T cells) in the lamina propria of the intestine as compared to peripheral lymphoid tissues, even when examined on the day of birth. Moreover, profound and selective depletion of jejunum lamina propria CD4+ T cells occurred in neonatal macaques within 21 days of infection, which was preceded by large numbers of SIV-infected cells in this compartment. Furthermore, neonates with less CD4+ T cell depletion in tissues tended to have higher viral loads. The persistence of intestinal lamina propria CD4+ T cells in some neonates with high viral loads, suggests that increased turnover and/or resistance to CD4+ T cell loss may contribute to the higher viral loads and increased severity of disease in neonatal hosts.

EMERGENCE OF SIV-SPECIFIC CYTOTOXIC T CELLS IN SIV INFECTION (0052)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
VEAZEY, RONALD S.	DVM, PHD	C	COMPARATIVE PATHOLOGY	
	PHD	A		BETH ISRAEL DEACONESS MEDICAL CENTER, MA USA
	DVM, PHD	C	DIRECTOR	
names	MD	A	RETROVIRAL PATHOGENESIS	NCI FREDERICK, MD USA
	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	MD	A		BETH ISRAEL DEACONNESS MEDICAL CENTER, MA USA
	PHD	A	VIRAL PATHOGENESIS	BETH ISRAEL DEACONESS MED. CTR., MA USA

AXIS I CODES: 1A, 2, 7B, 16C, 19 **AXIS II CODES:**31, 64, 66

ABSTRACT

Although the dynamics of HIV and SIV-specific CTLs have been well documented in the blood, little is known regarding CTL development in other tissues. In this study, 6 MamuA*01+ macaques were inoculated with SIVmac251. Two macaques were euthanized at 21 days of infection, and SIV gagp11c tetramer responses were measured in the blood, axillary and mesenteric lymph nodes, spleen, bone marrow, and thymus. The other four macaques were followed throughout disease progression, and intestinal biopsies and blood were examined at regular timepoints after inoculation. Two animals were euthanized when clinical signs of AIDS developed and tissues were examined as above. Peak early tetramer responses were detected in the blood (3.9 to 19% of CD3+CD8+ T cells) between day 14-21 p.i.. After day 49, tetramer responses in the blood diminished and remained relatively stable through day 200, ranging from 0.7-6.5% of CD3+CD8+ T cells. In contrast, tetramer positive T cells increased in the intestine in later stages of infection (100-200 days p.i.) in 3 of 4 infected animals (peak values from 10.6% to 28.8%). Percentages of tetramer positive cells were consistently higher in the intestine than in the blood in all 4 animals after day 100. In the animals with AIDS, the highest CTL response was detected in the lamina propria of the jejunum (10% of CD3+CD8+T cells) followed by the spleen (8.4%), colon LPL (7.2%), jejunum IEL (5.6%), bone marrow (4.6%), blood (3.3%), mesenteric lymph node (2.7%) axillary lymph node (1.4%) and thymus (0.0%). In contrast, the two animals euthanized at day 21, demonstrated the highest SIV-specific CTL responses in the blood (4.4 and 6.9%) of all tissues examined. The spleen had the next highest percentage (3.7% and 3.7%) followed by the bone marrow (3.6%, 4%), intestinal lamina propria (LPLs; 2.6%, 2.3%) mesenteric lymph node (1.2%, 1.4%), and axillary lymph nodes (1%, 0.9%). Minimal SIV-specific CTLs were detected in the thymus (0.07%, 0.05%) and intestinal epithelium (IELs; 0% and 0.6%). Combined, these data suggest that while high CTL responses develop in both peripheral and mucosal lymphoid tissues in primary SIV infection, mucosal CTL responses may dominate later in the course of disease.

THE EFFECTS OF ALCOHOL ON SIV PATHOGENESIS (0545)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
VEAZEY, RONALD S.	DVM, PHD	C	COMPARATIVE PATHOLOGY	
	PHD	A	PHYSIOLOGY	LSU MEDICAL CENTER, LA USA
names	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	MD	A		LSU HEALTH SCIENCES CENTER, LA USA
	DVM	C	VETERINARY MEDICINE	

AXIS I CODES: 1A, 7B, 19 **AXIS II CODES:**31, 64, 66, 77, 87

ABSTRACT

Increasing evidence indicates that alcohol consumption adversely affects immune function, and may increase the likelihood of HIV transmission and progression to disease. There is a clear association between alcohol use and the risk of contracting HIV infection, yet it remains to be determined whether this is due to immunologic or behavioral mechanisms. Although studies in humans are limited, alcohol has been shown to markedly affect cell-mediated and humoral immune responses. Moreover, consumption of even small amounts of alcohol by humans has been shown to increase HIV replication and affect the production of certain cytokines in cells obtained after alcohol consumption. Alcohol use also causes marked changes in gastrointestinal structure and function, and may adversely affect mucosal immune responses. Since the gastrointestinal tract has recently been shown to be important in the transmission and pathogenesis of AIDS, examining mucosal immune responses during alcohol consumption is crucial for determining the effects of alcohol as a cofactor in transmission and disease progression. We hypothesize that chronic alcohol use; 1) results in an increase in viral target cells specifically in the intestinal tract, resulting in increased susceptibility to infection, and increased viral loads in primary SIV infection, and; 2) results in increased turnover of viral target cells in the intestinal tract, resulting in sustained local viral replication and an increased rate of disease progression. Currently, we are comparing the cellular and molecular changes in the peripheral and mucosal lymphoid tissues of macaques receiving alcohol to those that are not, both before and after SIV infection. Alcohol will be administered to groups of macaques and cells from multiple peripheral and mucosal lymphoid tissues will be serially examined before and during SIV infection. Changes in viral target cells, naïve and memory T cell immunophenotyping, chemokine receptor expression, cytokine and SIV-specific cytotoxic T cell (CTL) production, and levels of cellular activation and proliferation are being analyzed in these tissues by various state-of the-art techniques, and compared with viral loads in plasma and tissues by quantitative methods.

MECHANISMS OF CD4 DEPLETION AND PROLIFERATION IN SIV (0546)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
VEAZEY, RONALD S.	DVM, PHD	C	COMPARATIVE PATHOLOGY	
	DVM, PHD	C	DIRECTOR	
names	MD	A	RETROVIRAL PATHOGENESIS	NCI FREDERICK, MD USA
	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	

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

ABSTRACT

The intestine has been shown to play a fundamental role in SIV pathogenesis. Intestinal lamina propria lymphocytes are a major early target for viral replication, and high level replication of virus in this compartment coincides with a profound loss of intestinal CD4+ T cells within days of SIV infection. However, little is known regarding the capacity for CD4+ T cell restoration and turnover in the intestine following this depletion. In this study, eight rhesus macaques were intravenously inoculated with either SIVmac251 (n=6) or SIVmac239 (n=2) and rates of CD4+ and CD8+ T cell turnover were compared in the intestine, blood, and lymph nodes throughout the course of infection. As expected, CD4+ T cells were markedly depleted by 21 days of infection in all macaques. Ki-67 expression on CD4+ T cells before infection ranged from 1.4 to 32% of total intestinal CD4+ T cells (mean 11.7%) indicating a wide variation in baseline intestinal CD4+ T cell turnover. Within 10 days of infection, percentages of CD4+ T cells expressing Ki-67 were reduced (mean 5.1%) suggesting that actively dividing CD4+ T cells were being eliminated in acute infection. However, by 21 days of infection, marked increases in Ki-67 expression were evident in intestinal CD4+ T cells of most macaques. Mean Ki-67 expression at day 28 was 37% of CD4 cells and mean levels ranged from 33 to 43% of CD4+ T cells throughout 200 days of infection. Although much variation was evident, Ki-67 expression appeared to correlate with CD4+ T cell restoration. Some animals partially restored intestinal CD4+ T cells at different timepoints, coinciding with a decrease in Ki-67 expression on intestinal CD4+ T cells. However, CD4+ T cells were never restored to preinfection levels in any macaque. In contrast, CD8+ T cell proliferation, while briefly elevated in primary (17-50 days p.i.) infection, returned to just above pre-infection levels thereafter. Proliferating CD4+ T cells in the blood also transiently increased in primary infection, but declined thereafter. Combined, these data suggest that intestinal CD4+ T cell turnover is ongoing throughout SIV infection and that much of this turnover occurs through local tissue expansion rather than through recirculation and homing of proliferating cells.

EVALUATION OF RANTES ANALOGUES FOR PROTECTION FROM SHIV (0547)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
VEAZEY, RONALD S.	DVM, PHD	C	COMPARATIVE PATHOLOGY	
	DVM	C	VETERINARY MEDICINE	
names	MD	A	PHARMACOLOGY	JOHNS HOPKINS UNIVERSITY, MD USA
	MD	A		CASE WESTERN RESERVE UNIVERSITY, OH USA
	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	MD	A	MEDICINE	CASE WESTERN RESEARCH UNIVERSITY, OH USA
	MD	A	MEDICINE	CASE WESTERN RESEARCH UNIVERSITY, OH USA

AXIS I CODES: 1A, 2, 7B, 9, 23 **AXIS II CODES:**31, 50B, 66, 83, 93, 94

ABSTRACT

Worldwide, most HIV-1 infections in both women and men result from mucosal transmission. In developing countries, the majority of women are infected via the vaginal route of transmission. Although homosexual transmission via anal intercourse among males still accounts for most new infections in developed countries, the incidence of heterosexual transmission in women is rapidly increasing in the U.S. A compound that could be safely applied to the vaginal mucosa immediately before intercourse that would consistently and safely prevent infection with HIV-1 could save millions of lives. Certain chemokine analogs have recently been demonstrated to have remarkable efficacy in blocking CCR5 expression and preventing HIV-1 infection of cells in vitro. However, several factors may affect the ability of a compound to prevent viral transmission across an intact mucosal surface. For example, cell cultures do not contain the abundant numbers of activated T cells, macrophages, and Langerhans cells that are normally found in the vaginal mucosa. Moreover, the effects of repeated application of a compound on the vaginal or rectal mucosa must be carefully examined, since continued use may induce mucosal inflammation. Since HIV-1 optimally infects and replicates within activated (CCR5+) cells, inflammation in the mucosa may lead to increased rates of transmission. We have begun testing RANTES analogs in the rhesus macaque vaginal infection model of HIV-1 transmission. We have recently demonstrated that PSC RANTES may effectively bloch transmission of SHIV162P when applied to the vagina in large doses 15 min before virus exposure. Additional ongoing studies are designed to titrate the lowest dose that is effective and safe for repeated use in the vagina.

EVALUATING MUCOSAL IMMUNE RESPONSES IN THE VAGINA (0633)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
VEAZEY, RONALD S.	DVM, PHD	C	COMPARATIVE PATHOLOGY	
	DVM, PHD	C	DIRECTOR	
	MD	A		CASE WESTERN RESERVE UNIVERSITY, OH USA
names	MD	A	RETROVIRAL PATHOGENESIS	NCI FREDERICK, MD USA
	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	PHD	A		CORNELL UNIVERSITY, NY USA

AXIS I CODES: 1A, 2, 7B, 23 **AXIS II CODES:** 31, 66, 83, 93

ABSTRACT

Worldwide, the vast majority of HIV-1 cases occur through heterosexual transmission. Although the initial events involved in vaginal transmission are uncertain, studies suggest that dendritic cells in the vaginal epithelium may be involved in trapping viral particles on the surface and transporting them to CD4+ T lymphocytes in the mucosa. As part of our microbicide testing and development programs, we are evaluating the normal immune components of the female reproductive tract as well as the fluctuations in the normal thickness and integrity of the vaginal mucosa in response to both hormonal and chemical (microbicide) influences. We have started with an examination of the expression of relevant chemokine receptors on T cell subsets in the vagina. Lymphocytes were isolated from the lymph nodes, blood, and vagina from 5 uninfected and 9 SIV-infected macaques, and examined by flow cytometry. Numerous CD4+ T cells were observed in the vaginal mucosa of uninfected female macaques. Between 32% and 60% of the T cells in the vaginal mucosa were CD4+, whereas 40% to 77% expressed CD8. Most CD4+ and CD8+ lymphocytes in the vaginal mucosa exhibited an activated (CD69+), "memory" (CD45RA—,CD62L—) phenotype. Patterns of chemokine receptor expression also differed between vaginal lymphocytes compared to peripheral lymphocytes. From 9% to 67% of the CD4+ T cells in the vagina of naive macaques expressed CCR5, whereas 84-99% co-expressed CXCR4. In acutely infected macaques, profound and rapid depletion of CD4+ T cells occurred in the vaginal mucosa. Furthermore, 4 of the 5 macaques euthanized with AIDS demonstrated marked CD4+ T cell depletion. Surprisingly, one SIV-infected macaque had substantial numbers of CD4+ T cells remaining in the vaginal mucosa. However, none of the remaining CD4+ T cells in this macaque co-expressed CCR5. This study demonstrates there are large numbers of activated, CD4+ T cells co-expressing CCR5 residing within the vaginal mucosa and that these cells are selectively targeted for infection and elimination in early SIV infection.

EVALUATION OF FUSION INHIBITORS AS TREATMENT FOR HIV (0635)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
VEAZEY, RONALD S.	DVM, PHD	C	COMPARATIVE PATHOLOGY	
	MD, PHD	A	MICROBIOLOGY	UNIVERSITY OF PA, PA USA
names	DVM	C	VETERINARY MEDICINE	
	PHD	A		CORNELL UNIVERSITY, NY USA
	PHD	A		MERCK & CO, NJ USA
	MD	A	MICROBIOLOGY	NORTHWESTERN UNIVERSITY, IL USA

AXIS I CODES: 1A, 2, 7B, 9, 12B **AXIS II CODES:** 31, 50B, 66, 83

ABSTRACT

With the rapid and spreading emergence of multi-drug resistant strains of HIV, new classes of anti-HIV therapies are needed to combat HIV infections and the prevention of AIDS. We are currently testing fusion inhibitors in SIV-infected rhesus macaques to determine whether they may affect viral loads, and whether they may be useful as single or combinational therapies against SIV and SHIV-infected macaques. We have demonstrated that certain compounds have remarkable efficacy in reducing viral loads in SIV-infected macaques and are currently testing whether these changes correlate with reductions in chemokine receptor expression, and/or result in viral envelope mutations that may result in drug resistance. These compounds are being tested for efficacy, drug resistance, and safety in nonhuman primates.

PATHOGENESIS OF SIV IN NATURAL AFRICAN MONKEY HOSTS (0722)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
VEAZEY, RONALD S.	DVM, PHD	C	COMPARATIVE PATHOLOGY	
	MD, PHD	C	MICROBIOLOGY & IMMUNOLOGY	
	DVM	C	VETERINARY MEDICINE	
	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	MD, PHD	C	COMPARATIVE PATHOLOGY	

AXIS I CODES: 1A, 7B **AXIS II CODES:** 31, 64, 66, 77, 83

ABSTRACT

Feral African green monkeys (AGM) represent the largest reservoir of simian immunodeficiency virus (SIV). Similar to SIV-infected sooty mangabeys and mandrills, naturally-infected AGMs are generally believed to be resistant to disease progression as only a few cases of immunodeficiency have been reported in these "natural hosts". Determining the mechanisms by which AGMs have evolved to resist disease progression may be useful in designing vaccine and therapeutic strategies to combat HIV-1 infection in humans. Despite numerous investigations on this model, the reason(s) SIV-infected AGMs do not develop AIDS remain unclear. Recently we demonstrated decreased CCR5 expression on CD4+ T cells of SIV-infected sooty mangabeys and hypothesized that this may play a role in the lack of disease progression in this natural host. Here, we report similar low-level expression of CCR5 on CD4+ T cells of AGM monkeys, further suggesting that decreased CCR5 expression is associated with the lack of disease progression. The expression of CCR5 on CD4 and CD8 T cells in peripheral blood of 23 uninfected AGM and 24 age-matched normal rhesus macaques were compared by a four-color flow cytometry. Percentages, absolute numbers, and mean channel fluorescence were compared. AGMs had significantly (p0.05) higher percentages and absolute numbers of CD8+ cells (54.5±12.4 %; 2505±978) than macaques (37.9±9.24%; 1120±526) and fewer CD4+ T cells 19.5±9.9% (35.5±8.9%). Furthermore, CCR5 expression on CD4+ T cells of AGM was significantly (p0.05) lower than macaques, both by percentage (2.8±2.1% versus 13.71±7.9%) and absolute numbers of CD4+CCR5+ T cells (15±9, versus 125±76 respectively). Surprisingly, the decreased CCR5 expression was selective for CD4+ T cells as CD8+ T cells of AGMs expressed higher levels of CCR5 (38.4±13.9%; 1087±696) than macaques (23±11.7%; 246±158). In conclusion, normal, uninfected AGMs have significantly reduced expression of CCR5 specifically on their CD4+ T cells, as compared to normal rhesus macaques. Significantly lower levels of CCR5 expression on CD4+ T cells of SIV-infected AGMs may play a role in the diminished immune responses and the lack of disease progression in this natural host species.

INTRAMARROW GENE TRANSFER IN NEONATAL RHESUS MONKEYS (0599)

NPRC UNIT: GENE THERAPY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BUNNELL, BRUCE A	PHD	C	GENE THERAPY	
L name J	PHD	A		CNPRC, CA USA

AXIS I CODES: 1A, 9, 17 **AXIS II CODES:**31, 39, 55, 66, 77

ABSTRACT

The experiments conducted during the past year were performed to investigate whether an alternative vector pseudotype, namely the cat endogenous virus, RD114, envelope protein would provide a significant increase in gene transfer to long term progenitor cells. The determination of the most effective gene transfer system was made by the analysis of FACS, PCR, and hematopoietic progenitor cell assays designed to measure transduction levels of HSC. We utilized the data on the percentages of EGFP-expressing cells gathered from the FACS analysis of bone marrow aspirates and PBMC performed at monthly intervals following infusion of the retrovirus vector preparations. Although the detection of EGFP by FACS is essential information, the "true" transduction efficiency was more effectively analyzed by PCR because typically a fraction of the cells that are transduced by a retrovirus vector do not express the vector sequences. We analyzed immunoselected CD34+ cells from bone marrow aspirates and colonies from hematopoietic progenitor cell assays. Methylcellulose assays were performed to analyze the specific populations of erythroid and myeloid hematopoietic progenitor cells that were transduced using the in situ transduction procedure. Blood and bone marrow was collected at monthly intervals post-transfer from all animals. The cells were cultured in methylcellulose medium containing growth factors allowing the identification and isolation of clonogenic hematopoietic progenitors. Assessment of hematopoietic progenitors revealed that the HIV-1/VSV-G-MND vector system transduced erythroid and myeloid progenitors in all groups of animals. In animals that received wither vector pseudotyped with the RD 114 envelope the percentage of methylcellulose progenitors that were positive ranged between 10-20%, but this level declined to 0-8% by four months of age. These data suggest that long term progenitor cells may not have been transduced. Flow cytometric analysis of the bone marrow aspirates indicated EGFP positive cells were detected 1 month after administration of producer cells. The percentage of EGFP positive cells ranged from 0-2% but declined to undetectable levels thereafter.

MARROW STROMAL CELL-MEDIATED GENE THERAPY OF KRABBES DISEASE (0748)

NPRC UNIT: GENE THERAPY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BUNNELL, BRUCE A	PHD	C	GENE THERAPY	
[named]	MD	A		OHIO STATE UNIVERSITY, OH USA

AXIS I CODES: 1A, 7B, 9 **AXIS II CODES:** 39, 44, 55, 58, 77

ABSTRACT

The goal of this proposal is the development of novel gene therapy strategies for Krabbe's disease focusing on MSCs in a rhesus monkey. Adult MSCs from Krabbe's patients provide the potential of performing autologous stem cell therapy, if they are susceptible to gene transfer and then be induced to differentiate into mature neuronal cells. We will analyze whether GALC gene-corrected to MSCs can undergo differentiation into CNS cells and ultimately, generate mature neurons with normal GALC enzyme activity, and ameliorate disease pathology. To this end, adult mesenchymal stem cells (MSC) will be obtained from a rhesus macaque animal model of Krabbe's disease. Once isolated these cells will be expanded in culture, undergo delivery of the GALC gene by transduction ex vivo. The engraftment and differentiation potential of the gene corrected cells will be analyzed in vitro and in vivo. Thus, our plans are two-fold. First, we will isolate marrow stromal cells from GALC deficient monkeys and investigate these cells in terms of growth and expansion characteristics in vitro in comparison to MSCs isolate from unaffected rhesus monkey. In addition, we will assess the efficiency of transduction of two viral vector systems expressing a reporter gene, enhanced green fluorescent protein (EGFP) or GALC, HIV-1-derived lentivirus and adeno-associated virus (AAV) vector systems. This system provides a CNS environment to induce the engineered stem cells to undergo differentiation. Our proposed work will combine gene therapy strategies with the plasticity of MSC to develop cures for genetic disorders of the CNS.

BIOLOGY OF NON-HUMAN PRIMATE MARROW STROMAL CELLS (0601)

NPRC UNIT: GENE THERAPY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
PROCKOP, DARWIN	MD	A	GENE THERAPY	TULANE UNIVERSITY HSC, LA USA
	PHD	C	GENE THERAPY	
names	DVM	C	VETERINARY MEDICINE	
	PHD	G	GENE THERAPY	
	PHD	C	GENE THERAPY	

AXIS I CODES: 1A, 9, 16, 17 **AXIS II CODES:**39, 55, 74, 77

ABSTRACT

The overall aim of the project is to develop procedures whereby adult stem cells from the bone marrow stroma can be used for trials of gene therapy in non-human primates. The adult stem cells, referred to as mesenchymal stem cells or marrow stromal cells (MSCs), are of interest for cell and gene therapy because they can readily be obtained from a patient, expanded in culture, genetically engineered with or without the use of viruses, and then returned for therapy of the same patient. They are also of interest because they home to damaged tissues and differentiate to replace the damaged cells in the tissues. The cells are currently being tested in many small animal models of human diseases and several promising clinical trials with the cells have been initiated in rare diseases in children. However, extensive trials of the cells in non-human primates are clearly essential for some of the currently proposed applications to common diseases such as osteoporosis, cardiac failure, Parkinsonism, leukodystrophies, and Alzheimer's disease. The goals of the proposal are:

Specific Aim 1. Isolate and expand primate MSCs with the improved protocol our laboratory has recently developed to isolate and expand cultures of human MSCs that are highly enriched for the earliest progenitor cells (RS cells). We have successfully isolated rhesus MSCs. We are presently characterizing these cells.

Specific Aim 2. Compare the primate MSCs in culture with human MSCs in their ability to expand rapidly and to differentiate into osteoblasts, chondrocytes, adipocytes, and neural cells.

Specific Aim 3. Compare the primate MSCs to human MSCs in vivo in their ability to engraft into multiple tissues after systemic or intracranial infusion into immunodeficient mice.

Specific Aim 4. When a recently purchased microPET instrument becomes operational, assay the engraftment of the primate cells first into immunodeficient mice and then into the same primates from which the cells were derived using real-time imaging with the microPET.

VIROLOGICAL AND GENETIC CHARACTERIZATION OF NEWLY DERIVED HIV-1 GROUP N STRAINS (0620)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
APETREI, CRISTIAN	MD, PHD	C	MICROBIOLOGY & IMMUNOLOGY	
	PHD	A		INSTITUTE DE PASTEUR, FRANCE
names	PHD	A		CENTRE INTERNATIONAL DE RECHERCHES MEDICALES, GABON
	PHD	A		PASTEUR DU CAMEROON CTR, AFRICA
	PHD	A		UNIVERSITY OF MANCHESTER, UK
	PHD	A		CENTRE INTERNATIONAL DE RECHERCHES MEDICALES, GABON
	MD	A		CENTRE INTERL DE RECHERCHES MED, GABON

AXIS I CODES: 7B **AXIS II CODES:**31, 66, 74G, 74H, 75B

ABSTRACT

Introduction: Three HIV-1 lineages (named groups M, N and O) have been identified that were very probably introduced into the human population as a result of independent cross-species transmissions of SIVcpz from chimpanzees, Pan troglodytes, in Central Africa. For the HIV-1 group N lineage only two strains (YBF30 and YBF105) have been characterized at the molecular level.

Objective: To better understand HIV-1 group N's epidemiology and to define this lineage's relationship to HIV-1 groups O and M, and to SIVcpz strains.

Methods: DNA amplification, sequencing and phylogenetic analyses were performed to genetically characterise viruses from three individuals confirmed to be infected by group N viruses. The newly derived group N strains were designated YBF106, YBF115 and YBF116.

Results: A full-length genome sequence was obtained for YBF106. gag, pol and env sequences were obtained for YBF116. Fragments of sequence for pol (integrase) and env (gp41) were obtained for YBF115. Phylogenetic analysis confirmed the monophyletic clustering of the group N strains and the recombinant nature of this lineage with part of its genome more closely related to HIV-1 group M and part to SIVcpz strains. The newly derived HIV-1 group N sequences confirm the existence and circulation of an unusual AIDS-inducing virus in Cameroon

Conclusions: The observation that the most closely related SIVcpz strains to HIV-1 group N also have a Cameroonian origin, supports the hypothesis of a single zoonotic transfer of a SIVcpz from chimpanzees to humans in this geographical region. Although it was postulated that the recombination event which gave rise to HIV-1 group N occurred in chimpanzee, the alternative hypothesis of a HIV-SIV recombinant being generated in a human superinfected with a group M ancestor and a SIVcpz strain cannot be discounted. Importantly, despite the devastating outcome of progression to AIDS in people known to be infected with group N, the extremely low prevalence of these infections suggests this rare HIV-1 group is not an emerging threat to human health at this time.

VIRAL DIAGNOSTIC CORE (0751)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
APETREI, CRISTIAN	MD, PHD	C	MICROBIOLOGY & IMMUNOLOGY	

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

ABSTRACT

The viral diagnostics core (VDC) was established in late 2003 following the approval of the program during the base grant review process.. This core is designed to supply testing for the specific pathogen free colony which is being developed. Diagnostic tests for 4 pathogens (SIV, STLV, SRV and herpes B) will be provided. The core is not yet functional, since essential renovations for the laboratory are in progress. Equipment has been ordered and will be installed in the newly renovated laboratory. Standard Operating Procedures are being developed for the VDC. New diagnostic tests are developed and standardized. Advertising for technical support is ongoing.
A new peptide ELISA for the detection of SIVmac/SIVsm has been optimized and will detect infection by different lineages of SIV in macaques and sooty mangabeys. Peptide ELISA for the detection of and differentiation among different types of STLV is currently under development. We are working on extablishing the most suitable peptide for the use in the diagnostic of SRV. We are also testing different commercial kits for the diagnosis of Herpes B virus infections.

AIDS IN A BLACK MANGABEY FOLLOWING CROSS-SPECIES TRANSMISSION OF SIVSM (0764)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
APETREI, CRISTIAN	MD, PHD	C	MICROBIOLOGY & IMMUNOLOGY	
	PHD	C	COMPARATIVE PATHOLOGY	
	DVM	A	PATHOLOGY	CHARLES RIVER/SIERRA BIOMEDICAL, NV USA
	DVM	C	VETERINARY MEDICINE	
names	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	DVM, PHD	A	VIROLOGT	BIOMEDICAL PRIMATE RES. CTR., THE NETHERLANDS
	PHD	A	VIROLOGY	BIOMEDICAL PRIMATE RES. CTR., THE NETHERLANDS
	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	MD, PHD	C	COMPARATIVE PATHOLOGY	
	PHD	A	VIROLOGY	BIOMEDICAL PRIMATE RES. CTR., THE NETHERLANDS
	DVM, PHD	C	COMPARATIVE PATHOLOGY	

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

ABSTRACT

Introduction. A unique opportunity for the study of the role of serial passage and cross-species transmission was offered by a series of studies carried out at the Tulane National Primate Research Center (TNPRC) in the 1980s. Methods. With the aim to develop an animal model for leprosy, 3 black mangabeys (BkM) were inoculated with lepromatous tissue that had been serially passaged in four sooty mangabeys (SMs). All 3 BkM became SIVsm-infected by day 30 post-inoculation (pi) of lepromatous tissue. One (#G140) was found dead 2 years pi from causes unrelated to SIV, 1 (G139) survived for 10 years, whereas the third (#G138) was euthanized with AIDS after 5 years.

Results and discussion. Necropsies revealed a high number of giant cells in tissues of #G138, but no SIV-related lesions were found in the remaining 2. Four-color immunofluorescence revealed high levels of SIVsm associated with both giant cells and T lymphocytes in #G138 and no detectable SIV in the remaining 2. Serum viral load (VL) showed a significant increase (1 log) during the late stage of the disease in #G138, as opposed to a continuous decline in VL levels in the remaining two BkMs. The study took on new significance when phylogenetic analysis unexpectedly showed that all 4 SMs were infected with different SIVsm lineages prior to the beginning of the experiment. Furthermore, the strain infecting the BkMs originated from the last SM in the series and therefore the virus infecting BkMs has not been serially passaged. In conclusion, we present the first compelling evidence that cross-species transmission of SIV may induce AIDS in heterologous African non-human primate species. The results showed that cross-species transmitted SIVsm was well controlled in 2 BkMs for 2 and 10 years, respectively. Finally, this case of AIDS in an African NHP suggests that the dogma of SIV non-pathogenicity in mangabeys and other African non-human primate hosts should be reconsidered.

CHARACTERIZATION OF NEW SIVSM STRAINS FROM BUSH MEAT SAMPLES FROM SIERRA LEONE (0765)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
APETREI, CRISTIAN	MD, PHD	C	MICROBIOLOGY & IMMUNOLOGY	
names	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	PHD	A		UNIVERSFTY OF MANCHESTER, UK

AXIS I CODES: 1D, 7B **AXIS II CODES:**31, 56, 66

ABSTRACT

HIV-2 originated from simian immunodeficiency viruses (SIVs) that are natural infections of sooty mangabeys (Cercocebus atys). In order to further investigate the relationship between HIV-2 and SIVsm, eight new SIVsm strains from monkeys sold in markets as bush meat were characterized. Gag, pol and env sequences showed that while the viruses of all eight sooty mangabeys belonged to the SIVsm/HIV-2 family, they were highly divergent strains in spite of the fact that most of the samples originated from the same geographical region. Three of the newly found viruses were genetically divergent, showing as much genetic distance from each other as from the entire SIVsm/HIV-2 family. No simian correspondent of the epidemic groups of HIV-2 (A and B) was found in Sierra Leone. Also, phylogenetic studies point on Sierra Leone as the origin of sooty mangabeys in colonies in the United States.

POTENTIAL FOR TRANSMISSION OF BLOOD BORNE PATHOGENS BY SYRINGES IN CAMEROON (0767)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
APETREI, CRISTIAN	MD, PHD	C	MICROBIOLOGY & IMMUNOLOGY	
	MD	A		UNIVERSITY OF CA/SF, CA USA
	PHD	A		MONTEFIORI MEDICAL SCHOOL, NY USA
	PHD	A		MED RES STATION, CAMEROON
	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	

names

AXIS I CODES: 5A, 5B, 6, 7B **AXIS II CODES:**31, 66, 67, 83

ABSTRACT

Background. HIV-1 infection emerged in Central Africa 50/60 years ago from a simian source (SIVcpz from chimpanzees). At least 3 cross-species transmission events have occurred, generating groups M, N and O. All three HIV-1 groups are co-circulating in Cameroon. The mechanism of HIV emergence is unknown. One theory explaining the mechanism and the timing of HIV-1 emergence proposes that multiple unsterile injections facilitated the cross-species transmission and fueled the spread of HIV in humans. In this regard, we have investigated the risks of HIV transmission by injections in a rural Anglophone region of Cameroon.

Methods: To examine the extent of contamination of injections in Kumba Cameroon, we observed the circumstances of a sample of injections (N=1500+) administered in a range of clinical settings in a three month period in 2001–2002. Plasma, cells, and matched syringe washes from these injections were collected and tested by Determine (Abbott,) rapid test and Inno-Lia Immunoblot (Innogenetics). HIV RNA was extracted from positive and indeterminate samples and from syringe washings. PCR assays were performed to amplify gag, pol and env genes. HBV (HBsAg) and HCV seroprevalence was tested by ELISAs (Ortho), whereas their presence in needle washes was investigated by PCR.

Results: A high prevalence of blood-borne viral pathogens was observed in this rural area of Cameroon, with prevalences of 16.92%, 10.75% and 10.12% for HIV, HBsAg and HCV, respectively in adults. False negative rapid test (Determine) results were characterized by early seroconversion profiles by Inno-Lia and positive PCR being thus due to a high incidence of HIV rather than to the circulation in the area of divergent strains. All sequenced viruses were group M, belonging mainly to the CRF_02 (IbNg) (50%). Subtypes A, D, F2 and CRF11_cpx were also present. Only syringe washes from i.v. injections (32 % of the total) tested positive by PCR, and sequence analyses showed that the viral form was CRF_02.

Conclusions: A high prevalence of blood-borne viruses in rural Cameroon was found. In this region, the reliability of serological surveys may be influenced by high incidence of HIV. The limited diversity of the strains present in the syringe washes may be related to biological properties of CRF_02. Reuse of blood draw syringes and lack of testing of blood for transfusion may have fueled the massive expansion of CRF_02 in West Central Africa and contributed to SIV human infection.

CHARACTERIZATION OF A NEW SIV FROM AGILE MANGABEY (CERCOCEBUS AGILIS) (0768)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
APETREI, CRISTIAN	MD, PHD	C	MICROBIOLOGY & IMMUNOLOGY	
names	PHD	A		CENTRE PASTEUR, CAMEROON
	PHD	A		PASTEUR INSTITUTE, FRANCE
	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	PHD	A		PASTEUR DU CAMEROON CTR, AFRICA

AXIS I CODES: 1A, 1D, 7B **AXIS II CODES:**31, 56, 66

ABSTRACT

Background: Primate lentiviruses co-evolved with their host species and have extensive evidence of cross-species transmission. Two species of mangabeys were described to date to harbor SIVs: sooty mangabeys (SIVsm) and red-capped mangabeys (SIVrcm). These two viruses cluster in two different lineages. SIVagi isolated from agile mangabeys in Cameroon were philogenetically and biologically characterized in order to investigate the evolution of lentiviruses in mangabeys.

Methods: Blood from 10 captive household pet agile mangabeys was tested for anti-SIV antibody using ELISA and Western Blot. V3 and gp36 reactivity for SIVs from major lineages were tested by peptide EIA. Virus cultures were done on agilis PBMCs, human PBMCs and cell lines. Co-receptor use of the isolated strain was investigated and CCR-5 sequencing was done to investigate delta-24 genotype of the tested monkeys. gag and pol fragments were amplified and phylogeneticly analyzed.

Results: Two out the ten monkeys (20%) had antibody. Peptide assays showed no reaction on the V3 peptides and SIVrcm gp36 reactivity for both samples. Cultures of the PBMCs of one of these monkeys (703) were positive. This virus strain had grown on human PBMCs. No monkeys had the delta-24 bp deletion. However, preliminary data suggests that the SIVagiCam703 used CCR-2 for viral entry, similar to the SIVrcm. Phylogenetic analysis showed that SIVagi clusters within SIVrcm lineage in both analyzed regions.

Conclusions: Agile monkeys are naturally infected with a distinct SIVagi. This virus was cross-transmitted from SIVrcm, which is supported by phylogenetic analyses. This cross-species transmission seems to be recent, as the cross-transmitted virus still uses the CCR-2 co-receptor for virus entry, in spite of the low frequency of CCR-5 delta-24 in the agile mangabeys. SIVagi represent new piece in the puzzle of lentiviral diversity and pathogenesis. Long-term follow-up is necessary to characterize the pathogenic potential of this cross-transmitted virus in agile monkeys.

SIVSM DIVERSITY IN PRIMATE CENTERS IN THE UNITED STATES AND ITS IMPLICATIONS (0769)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
APETREI, CRISTIAN	MD, PHD	C	MICROBIOLOGY & IMMUNOLOGY	
	DVM	C	VETERINARY MEDICINE	
	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	MD	A	IMMUNOLOGY	NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, MA USA
	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	DVM	A		YERKES NPRC, GA USA
	MD, PHD	C	COMPARATIVE PATHOLOGY	
	MPH	C	VETERINARY MEDICINE	
	PHD	A		YERKES NAT. PRIMATE RES. CTR., GA USA
	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	DVM, PHD	C	COMPARATIVE PATHOLOGY	

AXIS I CODES: 1A, 1D, 7B **AXIS II CODES:**31, 56, 66

ABSTRACT

Five different SIVsm lineages are co-circulating in the TNPRC colony. Pathogenic studies of SIVsm cross-transmission to rhesus macaques (Rhs) only involved viruses from lineage 1. SIVb670/SIVH5 are the prototypes of this lineage. SMs from TNPRC originated from the Yerkes National Primate Research Center (YNPRC) colony, from where they were transferred in early 1980s. We further studied diversity in the TNPRC and investigated if a similar viral diversity is observed in the source colony of YNPRC. We have analyzed if such a diversity impact on SIVsm monitoring and pathogenesis. Viral DNA was extracted from 10 SMs naturally infected with SIVsm originating from the YNPRC colony. PCR amplifications with specific primers were carried on of different genomic regions of SIVsm. These were: gag and pol regions which are targeted by different types of plasma viral load assays, and two env fragmants overlapping the V3 region in the gp120 and the immunodominant region of the gp41 TM. Our analysis shown that at least 4 SIVsm lineages co-circulate in the YNPRC, the most prevalent being lineages 1 and 2 as defined in Ling et al, 2003. This high viral variability may impact on the quality of viral load monitoring by real-time PCR and bDNA, as mismatches occur in the genomic targets of the primers used in these assays. No difference in serologic expression by Western blot was observed between viruses belonging to different lineages. No correlates of viral pathogenesis could be established to date for viruses belonging to different lineages. Most of the experiments involving SIVsm transmission to Rhs have involved viruses belonging to lineage 1. The pathogenic potential of primary isolates from the remaining lineages should be investigated in order to conclude that SIVsm is intrinsically pathogenic to Rhs. Monitoring of SIVsm infections should take into account this high viral diversity.

EXPERIMENTAL TRANSMISSION OF HTLV-I TO NONHUMAN PRIMATE (0108)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BEILKE, MARK A	MD	A	MEDICINE	TULANE UNIVERSITY HEALTH SCIENCES CENTER, LA USA
L name J	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	

AXIS I CODES: 1A, 1D, 7B, 19, 21 **AXIS II CODES:**31, 35, 39, 64, 66, 77

ABSTRACT

HTLV-I is an important pathogen worldwide causing a life-long chronic infection that may lead to adult T-cell leukemia/lymphoma (ATLL) and a variety of neuromuscular diseases. In certain geographic regions, coinfection in HIV-I positive individuals is high (5-10%), and is hypothesized to increase HTLV viral expression and the risk for HTLV-associated diseases. To test this hypothesis, rhesus macaques experimentally infected with HTLV-I and SIV/SM B670 were utilized. HTLV-I infection was established in 3/3 rhesus macaques inoculated with an HTLV-I clinical isolate, based on the presence of viremia, positive culture, PCR, and seroconversion. Over the course of over a year, viremia fell to undetectable levels, at which time a secondary SIV infection was then produced by inoculation of 50-100 TCID50 SIV/SM B670. HTLV expression subsequently increased. Peripherial PBMC were culture positive. Quantitation of viral gene tax DNA by real time PCR assays showed absolute increases to several hundred copies per 106 circulating PBMC, and peaking between 1.5 – 2 months post coinfection. These findings were coincident with an absolute increase in circulating CD2+ and CD8+ T-lymphocytes, 1.4 to 2.1 fold over preinoculation levels, while maintaining normal levels of CD4+ T-lymphocytes, and the striking production of up to 5% "flower cells" lymphocytes in the circulation. These findings were sustained for several months and then followed a rapid, progressive decline of CD4+ T-lymphocytes, typical for terminal SIV disease. These findings suggest that coinfection with SIV can cause a reactivation of HTLV-I virus expression, although transiently. The emergence of "flower cells" in 3 of 3 coinfected animals during infection suggests the possibility that HTLV/SIV coinfection may increase the risk for development of leukemia and lymphoma in dually infected individuals.

In a final experiment, two of the last three chronically HTLV-I infected monkeys were identically coinfected with SIV. These animals have been followed clinically and virologically for several months. We are in the process of correlating these clinical findings with viral activation and cellular changes.

ANTIMICROSPORIDIAL DRUG DISCOVERY (0567)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
DIDIER, ELIZABETH S	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	PHD	A		TULANE UNIVERSITY SPHTM, LA USA
	DVM, PHD	C	COMPARATIVE PATHOLOGY	
names	PHD	A	MICROBIOLOGY AND IMMUNOLOGY	XAVIER UNIVERSITY, LA USA
	PHD	A		SOUTHERN RESEARCH INSTITUTE, AL USA
	PHD	A		SOUTHERN RES INSTITUTE, AL USA
	PHD	A		NIH, MD USA
	MD, PHD	A		GWU, DC USA
	PHD	G	MICROBIOLOGY AND IMMUNOLOGY	

AXIS I CODES: 1D, 2, 7C, 16C, 27 **AXIS II CODES:**31, 50B, 63I, 66, 77

ABSTRACT

Introduction: Microsporidia are single-celled parasites that are recognized as causes of opportunistic and emerging infections in persons with AIDS, organ transplant recipients, travelers, and malnourished children. Persons with microsporidiosis usually
develop persistent diarrhea, and effective therapies are lacking.

Methods: Over 400 compounds were assayed in vitro against two microsporidian species which infect humans, Encephalitozoon intestinalis and Vittaforma corneae. These drugs included protease inhibitors, chitin assembly inhibitors, benzimidazoles which interfere with microtubule assembly, fumagillin-related compounds, fluoroquinolones, and triazines. Compounds that inhibited microsporidia replication by 70% at doses not toxic to the host cells were then tested for their ability to prolong survival in V. corneae-infected athymic mice. Athymic mice (groups of 8 each) were inoculated ip with 1 X 107 V. corneae spores, and drugs were administered beginning one day later. Controls received either parasites only or drug only (toxicity control). Statistically significant increases in survival times were determined by analysis of variance.

Results and Discussion: Drugs that significantly (P 0.05) prolonged survival of the V. corneae-infected athymic mice included fumagillin (at 5, 10, or 20 mg/kg sq daily), the fumagillin analogue, TNP-470 (at 20 mg/kg ip daily), doxycycline (at 40 mg/kg ip daily), kanamycin (at 50, 100, or 200 mg/kg ip daily), lomefloxacin (at 100 mg/kg ip daily), norfloxacin (50 and 100 mg/kg ip daily), and gatifloxacin (25 and 50 mg/kg ip daily).

ENTEROCYTOZOON BIENEUSI MONKEY MODEL (0568)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
DIDIER, ELIZABETH S	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	DVM, PHD	C	COMPARATIVE PATHOLOGY	
names	PHD	A	MICROBIOLOGY AND IMMUNOLOGY	XAVIER UNIVERSITY, LA USA
	DVM, PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	PHD	G	MICROBIOLOGY AND IMMUNOLOGY	

AXIS I CODES: 1D, 2, 7B, 7C, 16B, 16C **AXIS II CODES:** 31, 63I, 66, 77

ABSTRACT

Introduction: Enterocytozoon bieneusi is the most common microsporidian infecting AIDS patients. No small animal models exist nor can E. bieneusi be grown in culture. The purpose of this study was to determine if SIV-infected rhesus macaques (Macaca mulatta) can be infected with E. bieneusi to study the pathogenesis of this infection, test the efficacy of antimicrosporidial lead compounds, and establish primary epithelial cell cultures for attempts to propagate E. bieneusi.

Methods: Eight SIVDelta/B670 -infected rhesus macaques with depressed peripheral CD4+CD29+ T cell levels were inoculated orally with approximately 4 X 106 E. bieneusi spores enriched from duodenal lavage fluid of an AIDS patient. Monkeys were monitored over time for shedding of spores in feces, peripheral CD4+CD29+ T cell levels, and at necropsy, lesions associated with E. bieneusi or other pathogens were identified. E. bieneusi was found to infect gall bladder epithelium in the rhesus macaques. Therefore, gall bladders from other rhesus macaques, with or without SIV infection, were obtained after necropsy, washed with tissue culture medium, gently scraped to release epithelium, and explanted onto tissue culture dishes in attempt to generate primary epithelial cell cultures.

Results and Discussion: E. bieneusi spores were detected in feces of all monkeys but no correlation could be identified between quantity or consistency of spore shedding relative to peripheral CD4+CD29+ T cell levels or other clinical signs (eg. weight loss, diarrhea, systemic SIV load). To date, five of the eight monkeys have died and E. bieneusi-associated lesions, primarily in gall bladder, were detected in three of these five monkeys. Other opportunistic pathogens (eg. Mycobacterium avium, Candida albicans, adenovirus) also were detected which may have camouflaged the E. bieneusi infection in the remaining two monkeys that died. These results indicate that rhesus macaques can be infected with E. bieneusi, but coinfection with other opportunistic pathogens may confound interpretation of pathogenesis and drug testing studies. Primary cultures of gall bladder epithelium have been generated including one cell line that seems to have become transformed. After 21 passages over eight months, the "continuous" cell line exhibits a cobblestone appearance, brush border, large vacuoles (that appear to be secreting a mucin-like substance), prominent nucleoli, and cytokeratin (with some expression of vimentin being detected). Several primary cultures could be passaged up to 10 times before dying out. E. bieneusi organisms have been seeded onto monolayers of both the continuous and non-continuous host cell monlayers, but long-term culture has not yet been achieved.

GENE TARGETS OF ANTIMICROSPORIDIAL DRUGS (0623)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
DIDIER, ELIZABETH S	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
L	PHD	C	COMPARATIVE PATHOLOGY	
	PHD	A		TULANE UNIVERSITY SPHTM, LA USA
	DVM, PHD	C	COMPARATIVE PATHOLOGY	
names	PHD	A	MICROBIOLOGY AND IMMUNOLOGY	XAVIER UNIVERSITY, LA USA
		G	MICROBIOLOGY AND IMMUNOLOGY	
		G		TUHSC, LA USA
	PHD	G	MICROBIOLOGY AND IMMUNOLOGY	
J	MD, MPH	A		EINSTEIN UNIVERSITY SCHOOL OF MEDICINE, NY USA

AXIS I CODES: 2, 7C **AXIS II CODES:**31, 39, 50B, 66

ABSTRACT

Introduction: Compounds currently being evaluated for preclinical evaluations of antimicrosporidial activity include the fumagillin-related antibiotics which target methionine aminopeptidase 2 and and fluoroquinolones which target topoisomerase IV. The purpose of these studies was to clone, sequence, and express these two putative drug target genes to better characterize and understand their mechanisms of antimicrosporidial activities.

Methods: The Encephalitozoon cuniculi genome was published in November 2001 and primers were chosen to amplify the E. cuniculi MetAP2 gene. These primers also successfully amplified the MetAP2 genes of Encephalitozoon hellem and Encephalitozoon intestinalis. Amplicons were cloned into the vector pGEM-T and subcloned into the pQE30 Qiagen expression system. In addition,immunohistochemistry and confocal microscopy were performed on E. cuniculi organisms developing within RK-13 host cells using antibody generated against human MetAP2 which cross-reacts with the microsporidian MetAP2 and an antiserum generated against the microsporidian polar tube proteins. The partial sequence of the topoisomerase IV gene in Vittaforma corneae has been determined and gene walking experiments were performed to further characterize this gene.

Results and Discussion: Genes for MetAP2 of E. cuniculi, E. hellem, and E. intestinalis have been successfully expressed and an assay for protease activity was developed for the recombinant MetAP2 from E. cuniculi. Studies also will be conducted to determine if the protease activity is inhibited by fumagillin and if this protease assay can be used to screen test compounds for antimicrosporidial activity. In the immunohistochemistry studies, expression of MetAP2 was first detected in E. cuniculi on day 3 and staining intensity increased steadily during the next 3 days. By confocal microscopy, staining was first localized as two foci on either side of the nucleus in the same region of polar filament development. Over the next few days in culture, MetAP2 staining was dispersed throughout the cytoplasm of intact spores and in germinated spores, MetAP2 staining was detected along the entire length of the everted polar filament, suggesting a close relationship between MetAP2 expression and polar filament development. A segment of the V. corneae topoisomerase IV gene was found to be most closely related to that of Borelia burgdorferi by Blastx matching and Clustalw alignments. Homology PCR using primers derived from the B. burdorferi gene therefore is underway to attempt to clone the entire gene of topoisomerase IV from several species of microsporidia. The gene walking experiments failed to provide additional information about this gene and genomics library is currently being generated so that the entire topoisomerase IV gene can be further characterized.

IMMUNE RESPONSES TO MICROSPORIDIA (0626)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
DIDIER, ELIZABETH S	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	PHD	C	COMPARATIVE PATHOLOGY	
	DVM, PHD	C	COMPARATIVE PATHOLOGY	
names	PHD	A	MICROBIOLOGY AND IMMUNOLOGY	XAVIER UNIVERSITY, LA USA
	PHD	A	MICROBIOLOGY, IMMUNOLOGY, PARA	LSUHSC, LA USA
	DVM, PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	PHD	G	MICROBIOLOGY AND IMMUNOLOGY	

AXIS I CODES: 1A, 2, 7C, 19 **AXIS II CODES:**31, 63I, 64, 66, 74C, 77

ABSTRACT

Introduction: Microsporidia cause chronic infections in many laboratory animals (eg. rodents, lagomorphs) and cause disease in immunocompromised hosts including AIDS patients and SIV-infected rhesus macaques. Resistance is dependent on T lymphocytes and presently, macrophages are the only cells known to be capable of killing microsporidia. Previous studies identified a role for reactive nitrogen intermediates (RNI) for macrophage-mediated killing of microsporidia in vitro, but iNOS - /- (knockout) mice infected with Encephalitozoon cuniculi failed to develop lethal disease. The purpose of this study was to further explore the roles of macrophages and CD8+ T cells inresistance to microsporidia.

Methods: RAW264.7 macrophages were incubated with Encephalitozoon cuniculi. Total RNA was extracted various time points later and assayed for cytokine mRNA expression.

Results and Discussion: Increased expression of IFN-gamma was observed at 12 hr after introduction of the microsporidia to the macrophages. Confocal microscopy and western blot immunodetection are underway to corroborate these findings. Studies then will be performed to determine if inhibition of IFN-gamma inhibits or augments microsporidia replication in the macrophages in vitro.

ENVIRONMENTAL STUDIES ON MICROSPORIDIA (0749)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
DIDIER, ELIZABETH S	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	PHD	A	MICROBIOLOGY AND IMMUNOLOGY	XAVIER UNIVERSITY, LA USA
	PHD	A	FACILITIES AND WATER	EPA, OH USA
	PHD	G	MICROBIOLOGY AND IMMUNOLOGY	
	PHD	A		AGRICULT EXPMTL STATION, CT USA

AXIS I CODES: 1D, 7C, 9, 16C **AXIS II CODES:** 31, 39, 54B, 56, 63I, 66, 94

ABSTRACT

Introduction: Microsporidia are obligate intracellular parasites recognized as causing chronic diarrhea and systemic disease in a wide range of mammals including humans (AIDS patients, organ transplant recipients, travelers, and malnourished children) and non-human primates (Saimiri sciureus and Macaca mulatta). Species of microsporidia that infect humans and non-human primates have been detected in drinking water sources, and recently, Encephalitozoon intestinalis and Enterocytozoon bieneusi, were included on USEPA's drinking water Contaminant Candidate List and Occurrence Priorities List and were included as Biodefense Category B pathogens of concern for waterborne transmission by the NIH. The purpose of these studies was to develop methods for capture and identification of microsporidia in environmental and clinical specimens and to assess microsporidian spore viability as a measure for risk of transmission to humans and animals.

Methods: A multiplex immunomagnetic bead separation (IMBS) method was developed using a pan-microsporidian antiserum for capture of most, if not all of the species of microsporidia that infect humans. The IMBS was standardized against serial dilutions of micropsporidia suspended in saline and river water sediment follow by direct and nested PCR using rDNA primers. Viability and infectivity of the microsporidia were determined by fluorescent staining (Sytox Green plus Calcofluor White, or Cell Tracker dyes) and an in vitro focus-forming assay.

Results and Discussion: In the IMBS titration assay, 1 X 107 magnetic beads could capture an upper limit of approximately 5 X 107 E. intestinalis or V. corneae spores. PCR using SSUrDNA primers was applied to the magnetic beads after performing the capture assay against the serial dilutions of microsporidia diluted in saline. By direct PCR and nested PCR, lower limits of one spore could be detected in saline and river water sediment, respectively. Viability staining procedures correlated directly with infectivity of spores in a focus forming assay and spores either still attached or detached from the magnetic beads by treatment with 0.3% Tween 20 followed by washing with tissue culture medium, were still infectious for RK-13 cell cultures suggesting that the IMBS capture procedures did not affect viability of the spores. E. intestinalis spores subjected to freezing showed significant decreases in viability and infectivity in vitro, but spores incubated at temperatures ranging from 4 degrees C to 37 degrees C remained viable at least 5 days. Longer incubation times still need to be tested. After dehydration and rehydration, at least 25% of the spores remained viable, suggesting that microsporidia are environmentally resistant and pose a risk for waterborne transmission. In addition, the multiplex IMBS procedure has been used to successfully capture E. bieneusi spores from feces of infected rhesus macaques (Macacca mulatta), suggesting that this method should be useful for improving diagnosis of microsporidiosis.

MICROSPORIDIOSIS IN AN EGYPTIAN FRUIT BAT (0750)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
DIDIER, ELIZABETH S	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
L names ┘	DVM	A		NORTHWEST ZOOPATH, WA USA
	PHD	G	MICROBIOLOGY AND IMMUNOLOGY	

AXIS I CODES: 1D, 7C, 9 **AXIS II CODES:** 39, 56, 59, 64, 66

ABSTRACT

Introduction: An Egyptian fruit bat was found dead and submitted for necropsy and histopathology diagnosis to Northwest Zoopath, Inc. Systemic microsporidiosis was diagnosed as the cause of death and paraffin-embedded tissues were sent to our lab for species identification.

Methods: DNA was extracted from paraffin-embedded tissue sections and PCR was performed using primers that amplify the SSUrDNA and the rDNA ITS of Encephalitozoon species and Enterocytozoon bieneusi. Amplicons were subjected to nucleotide sequencing and BLAST analysis.

Results and Discussion: No PCR amplicons were obtained with the E.bieneusi-specific primers. Amplicons were generated using the Encephalitozoon primers. The nucleotide sequences generated from the fruit bat microsporidian rDNA ITS region suggested that this microsporidian was related to both E. cuniculi and E. hellem. Amplicons generated from SSUrDNA primers generated a Blast value of 3e-85 for E. hellem. E. hellem has been reported to cause infections in humans and psittacines, and this is the first report for E. hellem infecting an Egyptian fruit bat.

TUBERCULOSIS MODEL DEVELOPMENT IN SIV-INFECTED RHESUS MONKEYS (0755)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
GORMUS, BOBBY J	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	PHD	A		BAYLOR U, TX USA
	DVM, PHD	C	COLLABORATIVE RESEARCH	
	DVM, PHD	C	COMPARATIVE PATHOLOGY	
	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	PHD	A	MOLEC GENET&BIOCHEM	U PGH SCH MED, PA USA

AXIS I CODES: 1A, 1D, 7A, 9, 24 **AXIS II CODES:** 31, 64, 66, 77

ABSTRACT

Introduction. We completed the immunologic, pathologic and microbiologic studies in the 12 rhesus monkeys that were inoculated with SIVB670. Six were co-infected with low dose (200cfu) M. tuberculosis H37Rv 404 days post-inoculation with simian immunodeficiency virus (SIV), and 6 remained as SIV-only-infected controls. We have previously shown that 200cfu H37Rv produces asymptomatic tuberculosis in SIV-negative (normal) rhesus monkeys.

Methods. Longitudinally, plasma samples were obtained for SIV load assay by real time RT-PCR, blood mononuclear cell (PBMC) subsets were monitored by Flow Cytometry and bronchoalveolar lavage (BAL) cells and PBMC were stimulated with M. tuberculosis antigens culture-filtrate protein (CFP) or were incubated with medium only. Supernatants and pelleted cells were studied for cytokine secretion (ELISA) and cellular cytokine mRNA levels (real time RT-PCR), respectively. Tuberculin skin testing was done at 4 and 8 weeks and chest radiographs were taken at 0, 10 and 20 weeks post-M. tuberculosis inoculation. Weighed samples of organs from the 6 necropsied SIV/M. tuberculosis co-infected rhesus monkeys were homogenized and serial dilutions were cultured on 7H10 agar plates to determine M. tuberculosis burdens.

Results and Discussion. Three co-infected animals with initially highest SIV loads (7 X 104 to 1.9 X 106 copies/ml plasma) developed clinical tuberculosis and/or severe tuberculosis in the lungs, pleura, bronchial nodes, kidney, spleen and liver, whereas the 3 animals with lowest SIV loads (9 X 102 to 5 X 103 copies/ml) contained a few lung granulomas, but were clinically latent. There was no effect of M. tuberculosis inoculation on the SIV loads or CD4 percentages in any of the 6 co-infected monkeys, suggesting that neither progressive nor latent tuberculosis enhances the progress of chronic AIDS by these criteria.

In bronchoalveolar lavage (BAL) cells or blood mononuclear cells (PBMC), IFN-gamma mRNA and secreted protein levels were elevated significantly but little IL-4 mRNA or protein was detected in response to CFP-stimulation. The results are similar to those reported in humans. In BAL cells, moderate levels of TNF-a mRNA and protein were made in response to CFP in co-infected monkeys with progressive or latent tuberculosis. CFP-stimulation of PBMC resulted in enhanced TNF-a mRNA and protein production in SIV-only and co-infected monkeys. The possible immunopathologic role of TNF-a in tuberculosis activation in SIV-positive monkeys remains unclear.

The results showed that organs from rhesus monkeys with highest SIV loads at the time of M. tuberculosis inoculation had higher M. tuberculosis burdens than monkeys with lower initial SIV load and there is more extra-pulmonary spread in SIV/M. tuberculosis co-infected monkeys than we have previously observed in SIV-negative rhesus monkeys co-infected with 200cfu H37Rv M. tuberculosis.

We conclude that viral load is an important factor in the activation/progression of tuberculosis in chronically SIV-infected rhesus monkeys that are subsequently co-infected with low doses of M. tuberculosis. We further conclude that our model of SIV/M. tuberculosis co-infection is an important model for the study of M. tuberculosis/HIV interactions in humans [pending support]

TUBERCULOSIS MODEL DEVELOPMENT IN RHESUS MONKEYS (0756)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
GORMUS, BOBBY J	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
names	PHD	C	COMPARATIVE PATHOLOGY	
	DVM, PHD	C	COLLABORATIVE RESEARCH	
	DVM, PHD	C	COMPARATIVE PATHOLOGY	

AXIS I CODES: 1A, 1D, 7A, 9, 24 **AXIS II CODES:** 64, 66, 77

ABSTRACT

Introduction. Rhesus monkeys were inoculated intrabronchially with graded doses of Mycobacterium tuberculosis strains Erdman and H37Rv in an effort to produce a model of asymptomatic tuberculosis infection.

Methods. Animals were observed for clinical tuberculosis, tuberculin skin testing was done and blood mononuclear cells (PBMC) and bronchoalveolar lavage (BAL) cells were stimulated in vitro with M. tuberculosis culture filtrate protein (CFP) and resulting mRNA levels coding for the cytokines IFN-gamma, IL-4 and TNF-alpha were determined. Animals were studied histopathologically and microbiologically after necropsy.

Results and Discussion. Erdman strain produced active disease within 7-11 weeks regardless of dose (20-150 colony-forming units, cfu). Low doses of H37Rv (30-200cfu) resulted in asymptomatic infections; high doses (2-6 X 106 CFU) produced active disease within 11 weeks. Over a 4 month period of postinoculation study, MTB culture-filtrate protein (CFP)-stimulated BALC and blood PBMC from monkeys with active disease (30 cfu-Erdman-inoculated) or asymptomatic infection (200 cfu-H37Rv-inoculated) produced similar significant quantities of mRNA encoding for IFN-g or TNF-a, but insignificant quantities of IL-4 mRNA. These results are similar to humans. Differences were observed in antigen-induced in vitro blastogenic responses and serum anti-lipoarabinomannan antibody responses in animals with active compared to asymptomatic MTB infections. The results indicate that rhesus monkeys are a good model for the study of asymptomatic tuberculosis infections using doses of H37Rv equal to or less than 200cfu intrabronchially. These conclusions were supported by histopatholofic results and by culture of M. tuberculosis or polymerase chain reaction (PCR)-detection of M. tuberculosis DNA in organs of animals with no clinical indication of disease.

We conclude that low dose H37Rv inoculation of rhesus monkeys will provide a model for the study of asymptomatic tuberculosis that is similar to latent disease in humans. Since the simian immunodeficiency virus (SIV) inoculated rhesus monkey is the best-characterized model for AIDS, we are presently using the low dose H37Rv model to investigate interactions between SIV and M. tuberculosis in SIV infected rhesus monkeys.

EVALUATION OF A MULTI-ENVELOPE HIV VACCINE (0688)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
HURWITZ, JULIA L		A		ST. JUDES CHILDREN'S RESEARCH HOSPITAL, TN USA
names	DVM, PHD	C	COLLABORATIVE RESEARCH	
	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	

AXIS I CODES: 1A, 1D, 2, 7B, 9, 19 **AXIS II CODES:**31, 39, 62, 64, 66, 94

ABSTRACT

We characterized the elicitation of broad immune activity with a multi-envelope HIV vaccine. Six rhesus macaques were immunized with a multi-envelope vaccine using recombinant DNA, vaccinia virus (VV) and protein. DNA was administered IM, VV was administered SC and protein was administered IM as a formulation with alum. All animals showed a take of VV, defined by transient swelling at the site of inoculation. We found that six of six animals responded to immunization by production of HIV-specific antibodies and each showed significant booster effects with VV and protein immunizations. Antibodies were scored in multiple, different ELISA assays. Data from tests with the commercial HIV ELISA (Abbott Laboratories, Commercial Standard Kit, Abbott Park, IL) showed antibody activity from all six animals, which peaked the assay (OD405 2.0) for many months. The most recent samples (Feb 2004) continue to score at peak assay levels. Samples were also tested for reactivity against other envelope preparations. Every monkey exhibited antibody activity toward every envelope, regardless of clade origin, and regardless of whether the envelope sequence was included in the poly-envelope vaccine. To measure T-cell responses elicited by vaccination, interferon-gamma ELISPOT assays were performed with macaque peripheral blood lymphocytes, against peptide pools spanning the entire sequence of envelope UG, a component of the recombinant DNA, VV and purified protein vaccines. All animals except for one demonstrated significant responses to at least one of the UG peptide pools. Experiments were also performed to dissect the contribution of CD4+ and CD8+ T cell populations to the IFN-gamma secretion measured by ELISPOT formation. We found that both envelope-specific CD4+ and CD8+ T cell populations contributed to IFN-gamma activity. T-cell assays are now being performed with a number of different envelope target antigens, as we continue to examine the magnitude and durability of vaccine-induced immunity.

DEVELOPMENT OF CORE SERVICE FOR SIV CELLULAR IMMUNE ASSAYS (0575)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MARTIN, LOUIS N	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	DVM, PHD	C	COMPARATIVE PATHOLOGY	
	PHD	A	PHYSIOLOGY	LSU MEDICAL CENTER, LA USA
names	DVM, PHD	C	DIRECTOR	
	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	MS, PHD	A	CENTER FOR HUMAN VIROLOGY	THOMAS JEFFERSON UNIVERSITY, PA USA
	DVM, PHD	C	COMPARATIVE PATHOLOGY	

AXIS I CODES: 1A, 1D, 2, 7B, 9, 19 **AXIS II CODES:** 31, 64, 66

ABSTRACT

The Cellular Immunology Core Laboratory was approved during the base grant review process in 2003 and is currently staffed by one Medical Research Specialist. This core provides immunology services to specific research projects of in-house and outside investigators as requested. Current services include sample preparation under controlled parameters for optimal assay analysis, planning and performance of ELISPOT assays, data preparation and presentation for ELISPOT results obtained after outside analysis, intracellular cytokine staining preparation, as well as preparation and maintenance of viral stocks for use as antigenic stimulants in these assays. Considerable preliminary efforts were made, prior to and including this past year, on the optimizing of the ELISPOT Assay using both SIV recombinant peptide pools and actual SIV recombinant viral types, as well as comparative analysis of commercially available ELISPOT Assay kits.

In May and June of 2003, three different ELISPOT commercial assay kits [B-D ELISPOT Human Interferon-gamma, MabTech ELISPOT for Human/Monkey Interferon gamma, and R & D Systems Non-human Primate IFN gamma ELISPOT] were compared with the previously used assay kit [U-Cytech Monkey IFN gamma ELISPOT Assay]. The MabTech Assay kit was determined to provide the highest sensitivity and was used as the assay for analysis of all samples. Using this assay, ninety-eight (98) samples were run for three TNPRC investigators with twenty-one (21) samples awaiting analysis and forty-eight (48) samples were run for one outside collaborating investigator with twenty-three (23) samples awaiting analysis. One hundred and seven (107) sample preparations of PBMCs for use in ELISPOT assays were prepared for three TNPRC investigators and an additional sixty-six (66) were prepared for an outside collaborator. Specialized staining for stem cells was prepared on thirty-two (32) combinations of four samples of one animal for an outside collaborator. Coulter SIV Core Antigen quantitation was run on seventeen samples and SIV screening was run using this assay kit for six samples; all samples were for an outside collaborator.

THE EFFECT OF SINGLE EXON TAT IN PATHOGENESIS (0559)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MARX, PRESTON A	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
Lname_1	MD, PHD	A	INFECTIOUS DISEASE	ST MICHAELS MED CTR, NJ USA

AXIS I CODES: 1A, 7B, 19 **AXIS II CODES:** 31, 59, 64, 66, 83

ABSTRACT

Human and simian immunodeficiency virus (HIV/SIV) Tat proteins are specified by two coding exons. Tat functions in the transcription of primate lentiviruses. A plethora of in vitro data currently suggests that the second coding exon of Tat is largely devoid of function. However, whether the second exon of Tat contributes functionally to viral pathogenesis in vivo remains unknown. To address this question directly, we compared infection of rhesus macaques with an SIV, engineered to express only the first coding exon of Tat (SIVtat1ex), to counterpart infection with wild-type SIVmac239 virus, which expresses the full 2-exon Tat. This comparison showed that the second coding exon of Tat contributes to chronic SIV replication in vivo. Interestingly, in macaques, we observed a cytotoxic T lymphocytes (CTL) response to the second coding exon of Tat, which appears to durably control SIV replication. When SIV mutated in an attempt to escape this second Tat-exon-CTL, the resulting virus was less replicatively fit and failed to populate the host in vivo. Our study provides the first evidence that the second coding exon in Tat embodies an important function for in vivo replication. We suggest the second coding exon of Tat as an example of a functionally constrained "epitope" whose elicited CTL response cannot be escaped by virus mutation without producing a virus that replicates poorly in vivo.

STUDIES OF SIVRCM AND RELATED PRIMATE LENTIVIRUSES IN WEST AFRICA (0561)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MARX, PRESTON A	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
names	PHD	A		MED RES STATION, CAMEROON
	PHD	A		U ALABAMA, AL USA
	PHD	A		PASTEUR DU CAMEROON CTR, AFRICA
	PHD	A		INTL RECHERCHES CTR, FRANCE

AXIS I CODES: 1A, 1D, 5A, 5B, 7B, 19 **AXIS II CODES:**31, 64, 66, 75, 83

ABSTRACT

SIVrcm is a relatively new SIV found in red cap mangabeys in their native Gabon. SIVrcm is unique among SIVs in that it uses CCR2 as its primary co-receptor instead of CCR5. We are interested in developing a SIVrcm infection model in Rhesus macaques to learn about the role of a CCR2 tropic virus in macaques. Six Indian rhesus macaques have been serially inoculated and successfully infected with SIVrcm. the sixth SIVrcm passaged monkey was euthanized with severe pneumonia, but the etiologic agent of this infection is unknown. Three additional Indian rhesus were infected with SIVrcm derived from the 6th passaged monkey to further test the pathogenesis of SIVrcm. Thus far, all 3 monkeys are all healthy after 9 months. To determine if CD8+ T lymphocytes play a role in controlling SIVrcm infection in Rhesus macaques, we will treat 2 SIVrcm infected rhesus with CD8 monoclonal antibody to deplete these cells that may control the infection.

LONGITUDINAL FOLLOW UP OF SIVMAC PATHOGENESIS IN MACAQUES OF CHINESE ORIGIN (0564)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MARX, PRESTON A	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
L	MD	A	RETROVIRAL PATHOGENESIS	NCI FREDERICK, MD USA
names	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	PHD	A		DUKE UNIVERSITY MEDICAL CENTER, NC USA
J	DVM, PHD	C	COMPARATIVE PATHOLOGY	

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

ABSTRACT

Two sub-species of Rhesus (Rh) macaques, 10 belonging to the Chinese (Ch) sub-species and 4 from the Indian (Ind) sub-species were infected intravenously with 100TCID50 SIVmac239. The animals have been followed for clinical and virological manifestations of disease for 4 years. Our previous studies showed that plasma viral loads in Ch Rh were lower in the acute and chronic phases compared in Ch Rh when compared to Ind Rh. It was found that SIVmac viral loads in Ch Rh were closer to virus loads seen in untreated HIV infected humans. Ch Rh had higher CD4/CD8 ratios, stronger antibody responses and interestingly, slower depletion of intestinal memory CCR5+CD4+ T lymphocytes compared to Ind Rh. In 4 years, 7 of 10 Ch Rh developed SIVAIDS within 1.5~ 3.4 years at the average of 2 years. One Ch Rh developed B-cell origin lymphoma at 570 days post-infection, the first such report in this sub-specie. Three of the four Ind Rh developed AIDS within 6 months. To test our hypothesis that the relatively slow disease development was because SIVmac239 is not adapted to the Ch Rh subspecies, we inoculated 3 Ch Rh with the end-stage SIVmac239 isolated from a Ch Rh with AIDS. The data show that the plasma viral loads increased two fold (3.3X107 copies/ml vs 1.4X107 copies/ml) and reached the peak earlier (at day 7~12 instead of day 12~14 post-infection) compared to the first generation of SIVmac239 infection. T The animals will be followed for AIDS or AIDS-related diseases as well as virus loads. If this is the case, we will prepare more virulent virus stocks for researchers who may interested in short-term AIDS research using Ch Rh AIDS model. An analysis of the virus mutation and variation is in progress.

NONINVASIVE DETECTION OF NEW SIV LINEAGES IN CAPTIVE SOOTY MANGABEYS (0604)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MARX, PRESTON A	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	MD, PHD	C	MICROBIOLOGY & IMMUNOLOGY	
names	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	PHD	A		U ALABAMA, AL USA
	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	DVM	A		YERKES NPRC, GA USA

AXIS I CODES: 1A, 7B, 19 **AXIS II CODES:** 31, 39, 56, 66, 77

ABSTRACT

We developed a noninvasive method for SIVsm virion RNA detection in feces of captive sooty mangabeys (SMs) (Cercocebus atys). Employing this method to investigate the natural history of SIVsm in endangered SMs in the wild is useful for understanding diversity and evolution of SIVsm and HIV-2. Fecal samples collected from 61 wild SMs and 14 wild west African chimpanzees (Pan troglodytes verus) were studied. Samples were collected in rural Sierra Leone in 1993. One SM sample tested positive by reverse transcriptase-PCR. No viral sequences were detected in 14 feces of chimpanzees. Phylogenetic analysis of env sequence obtained from SM #13 showed that it clustered within the SIVsm group that includes SIVsmH4, B670 and PBj, identifying a previously unknown SIV connection from West Africa and American based colonies of SM. The virus, designated as SIVsmSL93g, indicates that the SIVB670-SIVsmH4-SIVPbj cluster originated in Northern Sierra Leone. The discovery of this strain in wild SM also indicates that noninvasive methods can be used for SIV detection from monkey feces collected in the field.

VIRUS CHALLENGE STOCK PRODUCTION AND STORAGE (0757)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MARX, PRESTON A	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	DVM, PHD	C	COMPARATIVE PATHOLOGY	
	PHD	A	PHYSIOLOGY	LSU MEDICAL CENTER, LA USA
	MD	A	NEUROLOGY	UNIV. OF PENNSYLVANIA, PA USA
		A		ST. JUDES CHILDREN'S RESEARCH HOSPITAL, TN USA
names	DVM, PHD	C	DIRECTOR	
	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	MS, PHD	A	CENTER FOR HUMAN VIROLOGY	THOMAS JEFFERSON UNIVERSITY, PA USA
	PHD	A	SW MEDICAL CENTER	UNIVERSITY OF TEXAS, TX USA
	DVM, PHD	C	COMPARATIVE PATHOLOGY	

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

ABSTRACT

The core for the production and storage of SIV and SHIV challenge stocks was approved during the base grant review process in 2003. The purpose of core is to provide SIV and SHIV challenge stocks to NIH funded programs at the TNPRC and also to NIH investigators outside the primate center. Thus, the core prevents the unnecessary duplication of effort and expense among investigators at the TNPRC. The core also maintains records on the pedigree on all virus stocks. The core presently maintains 65 virus stocks prepared in tissue culture lines, primary human PBMCs and rhesus macaque PBMCs. Although the core has only been in existence for part of 2003, 5 TNPRC and 5 outside NIH investigators have requested and been provided with 73 vials of virus for inoculations and in vitro experiments

TOPICAL ESTROGEN PROTECTS AGAINST SIV VAGINAL TRANSMISSION (0758)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MARX, PRESTON A	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	PHD	A		ORGANON, INC, NJ USA
names	PHD	A		ONPRC, OR USA
	MD, PHD	A	INFECTIOUS DISEASE	ST MICHAELS MED CTR, NJ USA
	PHD	A	SW MEDICAL CENTER	UNIVERSITY OF TEXAS, TX USA

AXIS I CODES: 1A, 7B **AXIS II CODES:** 31, 64, 66, 83, 93, 94

ABSTRACT

Accumulating data suggest that the state of the vaginal epithelium affects a woman's risk of HIV vaginal transmission. Several human and non-human primate studies have shown that the rate of HIV or SIV vaginal transmission is decreased when estrogen is dominant. In this study, we examined the safety and protective efficacy of vaginal estriol cream in ovariectomized macaques against SIV vaginal transmission. Vaginal estriol applied twice weekly resulted in minimal serum estriol levels and had no effect on serum LH levels, which decline in the presence of systemic estrogen. Vaginal epithelia cornified and thickened significantly in response to estriol therapy. Twelve macaques on vaginal estriol and eight control animals on placebo cream were challenged vaginally with pathogenic SIVmac251. 1 of 12 estriol treated became infected after this single challenge, while 6 of 8 control animals became infected ($p=0.0044$). These data demonstrate that topical vaginal estriol can strongly protect against SIV vaginal transmission, while having no detectable systemic effect. These results support the study of topical vaginal estriol in preventing HIV vaginal transmission in at-risk women.

STRUCTURE AND FUNCTION OF CC-CHEMOKINE RECEPTOR 5 (0759)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MARX, PRESTON A	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	PHD	A		WNPRC, ~~WA~~ USA
	PHD	A		LOS ALAMOS NATIONAL LABS, NM USA
names	PHD	A		NORTHWESTERN UNIVERSITY SCHOOL OF MEDICINE, IL USA
	PHD	A		LOS ALAMOS NATIONAL LABS, NM USA
	PHD	A		NIAID/NIH, MD USA
	MD	A	MICROBIOLOGY	NORTHWESTERN UNIVERSITY, IL USA

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

ABSTRACT

A chemokine receptor from the seven transmembrane domain G protein-coupled receptor super-family is an essential coreceptor for the cellular entry of human immunodeficiency virus type 1 (HIV-1) and simian immunodeficiency virus (SIV) strains. To investigate non-human primate CC-chemokine receptor 5 (CCR5) homologue structure and function, we amplified CCR5 DNA sequences from peripheral-blood cells obtained from 24 representative species and subspecies of the primate suborders Prosimii (family Lumuridae) and Anthropoidea (families Cebidae, Callitrichidae, Cercopithecidae, Hylobatidae and Pongidae) by polymerase chain reaction using primers flanking the gene's coding region. The full-length CCR5 receptors were inserted into pCDNA3.1 and multiple clones were sequenced to permit discrimination of both alleles. When compared to the human CCR5 sequence, Lemuridae, Cebidae, and Cercopithecidae shared 87%, 91 to 92%, and 96 to 99% amino acid sequence homology, respectively. Amino acid substitutions tended to cluster in the amino and carboxyl termini, the first transmembrane domain, and the second extracellular loop, with a pattern of species-0specific changes that characterized the CCR5 receptor from primates within a given family. At variance with humans, all primate species examined from the suborder Anthropoidea had amino acid substitutions in positions 13 (N to D) and 129 (V to (), of which the former change is critical for CD4-independent binding of SIV to CCR5. Within Cebidae, Cercopithecidae, and Pongidae (including humans) CCR5 nucleotide similarities were 95.2% to 97.4%, 98.0% to 99.5%, and 98.3% to 99.3%, respectively. Despite this low genetic diversity, the phylogeny of the selected primate CCR5 receptor homologue sequences agrees with current primate systematics, apart from some intermingling of species of the Cebidae and Cercopithecidae. Constructed HOS.CD4 cell lines expressing the entire CCR5 homologue protein from each of the Anthropoidea species and subspecies were tested for their ability to support HIV-1 and SIV entry and membrane fusion. Other than Cercopithecus pygerythrus, all CCR5 homologues tested were able to support both SIV and HIV-1 entry. Our results suggest that the shared structure and function of primate CCR5 homologue proteins would not impede the movement of primate immunodeficiency viruses between species.

HIGHLY EFFECTIVE CONTROL OF AIDS VIRUS CHALLENGE IN MACAQUES (0760)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MARX, PRESTON A	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	PHD	A		NIAID/NIH, MD USA
names	PHD	A		DUKE UNIVERSITY MEDICAL CENTER, NC USA
	PHD	A		NIAID/NIH, MD USA
	MD, PHD	A		GLADSTONE INSTITUTE, UCSF, CA USA
	PHD	A		YALE UNIVERSITY, CT USA
	PHD	A		YALE U SCH MED, CT USA
	PHD	A		YALE UNIVERSITY, CT USA

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

ABSTRACT

Previous studies have shown that vaccination and boosting of rhesus macaques with attenuated vesicular stomatitis virus (VSV) vectors encoding Env and Gag proteins of SIV/HIV hybrid viruses (SHIV) protects rhesus macaques from AIDS after challenge with the highly pathogenic SHIV89.6P. In the current study we compared the effectiveness of a single prime-boost with VSV vectors expressing SHIV Env, Gag, and Pol proteins to a VSV vector prime followed with a single boost with modified vaccinia Ankara (MVA) expressing the same SHIV proteins. After challenge with SHIV89.6P, MVA-boosted animals controlled peak challenge viral loads to less than 2x106 copies/ml, significantly lower than in VSV-boosted animals, and lower than reported in other vaccine studies employing the same challenge. MVA-boosted animals have shown excellent preservation of CD4+ T cells while 2 of 4 VSV-boosted animals have shown significant loss of CD4+ T cells. The improved protection in MVA-boosted animals correlates with stronger pre-challenge CD8+ T cell responses to SHIV antigens and with stronger post-challenge SHIV neutralizing antibody production.

HYBRID ORIGIN OF SIV IN CHIMPANZEES (0761)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MARX, PRESTON A	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	PHD	A		UNIVERSITY OF NOTTINGHAM, UK
	PHD	A		DUKE UNIVERSITY, NC USA
names	PHD	A		DUKE UNIVERSITY, NC USA
	PHD	A		U ALABAMA, AL USA
	PHD	A		UNIVERSITY OF MONTPELLIER, FRANCE
	PHD	A		UNIVERSITY OF NOTTINGHAM, UK

AXIS I CODES: 1D, 7B **AXIS II CODES:** 31, 56, 66

ABSTRACT

The ancestry of HIV-1 has been traced to SIVcpz infecting chimpanzees (Pan troglodytes) in west central Africa, but the origin of SIVcpz itself remains unknown. Research in West Africa has shown that the West African sub-species of chimpanzee, Pan troglodytes verus does not appear to be naturally infected with SIV. In contrast, chimpanzee sub-species in Central and Estern Africa are naturally infected with SIV. These data suggest that SIVcpz may have emerged in chimpanzees relatively late, after the sub-species divergence. Such questions are important because SIVcpz is the ancestor of HIV-1.

Detailed phylogenetic analysis of the gene sequences of SIVrcm, a virus discovered by the Marx research group in Central Africa, showed that SIVrcm and another SIV from Cercopithecus nictitans, recombined genetically to form a new virus, SIVcpz in chimpanzees in Central Africa. These results are consistent with a late origin of SIVcpz and show how new viruses may emerge in non-human primates that are important to human diseases.

SIV VAGINAL TRANSMISSION IN THE ABSENCE OF A CERVIX (0762)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MARX, PRESTON A	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
L name J	MD, PHD	A	INFECTIOUS DISEASE	ST MICHAELS MED CTR, NJ USA

AXIS I CODES: 1A, 7B, 19 **AXIS II CODES:** 31, 59, 64, 66, 83

ABSTRACT

The role of the cervix in vaginal transmission of SIV and HIV is controversial. Monkey studies have repeatedly shown that the most likely target for the sexual transmission of SIV is vaginal tissue, not cervical tissue. Despite this, funding has been provided to test the use of diaphragms in prevention of HIV vaginal transmission in women. In this study, we are using four female rhesus macaques that have undergone complete hysterectomies to prove that vaginal tissue alone, without the presence of the cervix, will allow the transmission of the SIV virus with the onset of AIDS as a result. We feel that this study has the potential to shed light on the lack of value of diaphragms for prevention of HIV transmission to women, thereby avoiding unnecessary risk of exposure in women using diaphragms alone for both birth control and prevention of disease transmission.

To date, each monkey has undergone a complete hysterectomy, including removal of the cervix. The healing period following surgery is now complete, and the monkeys will be challenged next week (3/16/04) with 600 TCID50 of SIVmac251 by the vaginal route. Following this challenge, the monkeys will be followed for a maximum of six months to assess viral infection through direct contact of the virus with only the vaginal epithelium.

MOLECULAR EVIDENCE FOR DEEP PHYLOGENETIC DIVERGENCE IN MANDRILLUS SPHINX (0763)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MARX, PRESTON A	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	PHD	A		CIRMF, GABON
	PHD	A		NEW YORK UNIVERSITY, NY USA
	PHD	A		CENTRE INTERNATIONAL DE RECHERCHES MEDICALES, GABON
names	PHD	A		CIRMF, GABON
	PHD	C	MICROBIOLOGY/IMMUNOLOGY	
	PHD	A		INTL RECHERCHES CTR, FRANCE

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

ABSTRACT

Mandrills (Mandrillus sphinx) are forest primates indigenous to western central Africa. Phylogenetic analysis of 267 base pairs (bp) of the cytochrome b gene from 53 mandrills of known and 17 of unknown provenance revealed two phylogeographical groups, with haplotypes differentiated by 2.6% comprising seven synonymous transition. The distribution of the haplotypes suggests that the Ogooue River, Gabon, which bisects their range, separates mandrill populations in Cameroon and northern Gabon from those in southern Gabon. The haplotype distribution is also concordant with that of two known mandrill simian immunodeficiency virus, suggesting that these two mandrill phylogroups have followed different evolutionary trajectories since separation.

HIV AND THE MUCOSAL IMMUNE SYSTEM: NEW VACCINE STRATEGIES (0678)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
SESTAK, KAROL	DVM, PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	PHD	C	COMPARATIVE PATHOLOGY	
	PHD	A	MICROBIOLOGY/IMUNOLOGY	TUHSC, LA USA
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names	MD	A	RETROVIRAL PATHOGENESIS	NCI FREDERICK, MD USA
	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	PHD	A		DUKE UNIVERSITY MEDICAL CENTER, NC USA
	PHD	A		UPPSALA INNOVATION CENTER, SWEDEN
	DVM, PHD	C	COMPARATIVE PATHOLOGY	

AXIS I CODES: 1A, 7B, 16C, 19 **AXIS II CODES:** 31, 64, 66, 77, 91

ABSTRACT

Intensive efforts to develop an effective systemic vaccine to contain the HIV/AIDS epidemic have met with limited success. This lack of success combined with the fact that primary infection often occurs via mucosal surfaces, and that the mucosa contains large numbers of activated CD4+ T-cells has shifted attention to the role of the mucosal immune system in HIV transmission and AIDS pathogenesis. This shift has been accelerated by the observation that activated CD4+ T cells in the intestinal mucosa are the initial targets for SIV infection and destruction. Furthermore, preservation of mucosal CD4+ T cells in animals immunized intrarectally has been shown to be an important correlate of vaccine effectiveness (10). We predict that a mucosal AIDS vaccine that incorporates both T helper and CTL epitopes in conjunction with immuno-enhancing molecules designed to stimulate the immune response towards generating HIV/SIV specific CTL, will be highly efficient in controlling the virus infection in its primary reservoir, e.g. gut-associated lymphoid tissue (GALT), and may protect the host against subsequent challenge.

Currently, we are working on the production of a mucosal vaccine. Synthetic peptides containing the HIV/SIV immunogens were commercially prepared and shipped to our collaborators (name group) overseas for incorporation into immunostimulating complexes (ISCOMs). It is expected that vaccine production will be completed in summer 2004. Meanwhile, we are optimizing immunological assays that will be later used to measure immune responses. Also, we are in process of challenge virus (SHIV-Ku and SHIV-162P) preparation with help of Dr. Marx's retrovirus core facilities. It is expected that by the end of year 2004 at least half of the animals assigned for this project will be virus inoculated (both controls and vaccinates).

COLONIC SPIRAL BACTERIOSIS OF COLONY-RAISED RHESUS MACAQUES (0679)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
SESTAK, KAROL	DVM, PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	DVM, PHD	C	COMPARATIVE PATHOLOGY	
names	DVM, PHD	A		UNIVERSITY OF NEBRASKA VET SCHOOL, NE USA
	DVM, PHD	C	DIRECTOR	

AXIS I CODES: 7A, 16C, 16F **AXIS II CODES:**64, 66, 77

ABSTRACT

Colonic spirochetosis (CS) of humans and non-human primates is an inflammatory bowel disease characterized by intimate attachment of spirochetes and flagellated microbes on the apical membrane of colonic enterocytes. We reported recently that two Helicobacter species were present either alone or in combination with two Brachyspira species in the colons of rhesus macaques with CS (Duhamel et al., Anaerobes 9: 45-55, 2003). The purpose of the present study was to further confirm the association of Helicobacter species in rhesus macaques with CS. Formalin-fixed and paraffin-embedded colons obtained from control macaques (n=5) and macaques (n=22) with CS were examined by (i) light and ultrastructural microscopy, (ii) avidin-biotin-alkaline phosphatase complex method using Brachyspira, Campylobacter and Helicobacter antisera, and (iii) comparative analysis of cloned PCR products obtained using DNA extracts amplified with 16S rRNA primers specific for each bacterial genus. Taken together the data confirm the association of multiple Brachyspira and Helicobacter species in CS, and further suggest inflammatory bowel disease of colony-raised research macaques is a polymicrobial disease.

A PRIMATE MODEL FOR EVALUATION OF ROTAVIRUS VACCINES (0681)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
SESTAK, KAROL	DVM, PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	PHD	C	COMPARATIVE PATHOLOGY	
	DVM, PHD	C	COMPARATIVE PATHOLOGY	
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	PHD	A		CHILDREN'S HOSPITAL, OH USA
	PHD	A		CHILDREN'S HOSPITAL, OH USA
	PHD	A	MICROBIOLOGY AND IMMUNOLOGY	TULANE UNIVERSITY HEALTH SCIENCE CENTER, LA USA
	PHD	G	COMPARATIVE PATHOLOGY	
	PHD	A		CHILDREN'S HOSPITAL, OH USA

AXIS I CODES: 1A, 7B, 16C, 19 **AXIS II CODES:** 64, 66, 77, 91

ABSTRACT

Rotavirus specific IgG and IgA seroconversions along with fecal shedding of viral protein and the appearance of memory CD4+ and CD8+ T lymphocytes in peripheral blood was observed following natural rotavirus infection of juvenile rhesus macaques. Seroconversion against group A rotaviruses was detected at the age of 4-6 months when rotavirus was isolated from stool specimens of asymptomatic animals. A new simian rotavirus strain TUCH (Tulane University and Cincinnati Children's Hospital) was isolated and identified as serotype G3. Genomic RNAs extracted from TUCH rotavirus was electrophoretically clearly distinct from prototype rotaviruses including the simian RRV and SA11 strains. Further characterization revealed that these viruses belonged to subgroup 1 and serotype G3, both typical of simian rotaviruses. Interestingly, however, their VP6 protein showed less than or equal to 95% homology with all published sequences and their VP4 protein did not belong to any established P genotype (less than or equal to 86.2% homology with all published VP4 sequences representative of 20 P genotypes). The CD4+ and, to a lesser extent, CD8+ T lymphocyte-mediated immunological memory to rotavirus was associated with interleukin-6 (IL-6) and interferon-g (IFN-g) production in vitro. Re-stimulation of peripheral T lymphocytes by double-layered rotavirus particles (containing VP6 on their surface) resulted in higher production of IL-6 and IFN-g than it did by triple-layered particles (containing VP4 and VP7 on their surface) (p 0.05). Increased production of both IL-6 and IFN-g cytokines by T helper lymphocytes was noted (p 0.05) when rotavirus was presented via dendritic (HLA-DR+) cells. This is the first report demonstrating cell-mediated immune responses to rotavirus in nonhuman primates.

When a filtered stool preparation of TUCH rotavirus was orally administered to caesarian-derived, colostrum-deprived, 3-day and 14-day old macaques, both developed severe diarrhea and shed rectally viral antigens. Further studies are currently in progress with more juvenile macaques in order to determine the window of opportunity for clinical illness and also to test new rotavirus vaccine candidates.

EVALUATION OF RECOMBINANT ATTENUATED RSV VACCINES IN THE AFRICAN GREEN MONKEY (0109)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
TRAINA-DORGE, VICKI L	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
L name	PHD	A		MEDIMMUNE VACCINES INC., CA USA

AXIS I CODES: 1A, 1D, 7B, 24 **AXIS II CODES:**33, 50B, 66, 78

ABSTRACT

Towards the goal of developing live attenuated RSV vaccines to prevent severe respiratory tract infection caused by RSV, recombinant RSV containing a deletion of single or multiple NS1, NS2, SH and M2-2 genes have been obtained. In this study, rA2,A2deltaNS2, rA2deltaNS1NS2, rA2deltaSHNS2, rA2deltaM2-2NS2 were evaluated in African green monkeys for their levels of replication in the upper and lower respiratory tracts, immunogenicity and protection against wild type RSV challenge. Replication of rA2deltaNS2 and rA2deltaSHNS2 was not attenuated in both the upper and lower respiratory tracts. However, rA2deltaNS1NS2 was over-attenuated; it did not replicate in the respiratory tracts of the infected monkeys and did not provide sufficient protection against wt RSV challenge. rA2deltaM2-2NS2 was slightly more attenuated than rA2deltaM2-2 and provided partial protection against wt RSV challenge. rA2deltaM2-2, and possibly rA2deltaM2-2NS2, exhibited designed phenotypes that could be further evaluated as potential live attenuated RSV vaccine candidates.

EXPERIMENTAL STLV-I INFECTION AND STLV/SIV COINFECTION IN THE NONHUMAN PRIMATE (0579)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
TRAINA-DORGE, VICKI L	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	

AXIS I CODES: 1A, 7B, 7D, 17, 19 **AXIS II CODES:**31, 39, 64, 66, 76, 77

ABSTRACT

Naturally occurring old world primate STLV-I viral isolates have been identified and isolated from African green monkeys, rhesus macaques, sooty mangabey monkeys, and baboons. Viral isolates were cultured in vitro and transformed cell lines were produced. Extensive characterization and nucleotide sequencing of each isolate are being performed and comparisons made.

Ten rhesus macaques were recipients of three STLV isolates: STLV-IAGM, STLV-IRhesus, or STLV-ISM. All animals seroconverted, became PCR and culture positive. Over a year period, the animals developed lymphocytosis, with absolute increases in CD8+ T-lymphocytes. These animals eventually became only transiently PCR positive and culture negative, and suggested virus latency, possibly due to CD8 immune suppression. To test this hypothesis, we conducted an in vivo CD8 depletion study on seven of these animals and monitored them over a six to eight week period for any changes in viral expression.

The monoclonal anti-CD8 antibody cM-807 was administered to each animal at 5mg/kg subcutaneously (d0) and intravenously (d2, and d7) over a seven day period. Blood was drawn weekly over a 6 week monitoring period. Plasma isolated from those samples were tested by indirect ELISA for virus-specific antibody levels. Baseline reciprocal antibody titers for all seven animals ranged from 6400. One animal remained antibody negative. PBMC were isolated from the weekly blood samples and nucleic acids isolated and tested for STLV-I proviral DNA with end-point PCR. At baseline, 6 of 7 animals were PCR negative and one was weakly positive for proviral DNA. Following depletion and within a 28-day monitoring period, all animals had converted to PCR positive. Two had transient increases that were negative by day 28, whereas 5 of 7 remained PCR positive throughout the entire monitoring period. Clinical findings are being correlated with viral activation and cellular changes, both at a cellular and a molecular level.

SIMIAN VARICELLA VIRUS INFECTION AND LATENCY IN THE NONHUMAN PRIMATE (0580)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
TRAINA-DORGE, VICKI L	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
names		A		UNIVERSITY OF COLORADO HSC, CO USA
	PHD	A	DEPT. NEUROLOGY	UNIVERSITY OF COLORADO HSC, CO USA

AXIS I CODES: 1A, 1D, 7B, 17, 21 **AXIS II CODES:**39, 50, 66

ABSTRACT

Simian varicella virus (SVV) infection in primates shares clinical, pathological, immunological, and virological features with varicella-zoster virus infection of humans. Natural varicella infection was simulated by exposing four SVV-seronegative monkeys to monkeys inoculated intratrachaelly with SVV, in which viral DNA and RNA persist in multiple tissues for more than one year (T.M. White, R. Mahalingam, V. Traina-Dorge, and D.H. Gilden, J. Neurovirol. 8:191:205, 2002). The four naturally exposed monkeys developed mild varicella 10 to 14 days later, and skin scrapings taken at the time of the rash contained SVV DNA. Analysis of multiple ganglia, liver, and lung tissues from the four naturally exposed monkeys sacrificed 6 to 8 weeks after resolution of the rash revealed SVV DNA in ganglia at multiple levels of the neuraxis but not in the lung or liver tissue of any of the four monkeys. This animal model provides an experimental system to gain information about varicella latency with direct relevance to the human disease.

ANIMAL MODELS TO DESIGN AND EVALUATE IMPROVED VZV VACCINES (0753)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
TRAINA-DORGE, VICKI L	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
Lname_1	PHD	A	MICROBIOLOGY	UNIVERSITY OF ARKANSAS, AR USA

AXIS I CODES: 1A, 1D, 7B, 17, 18, 21 **AXIS II CODES:** 66, 77

ABSTRACT

Varicella zoster virus (VZV) causes varicella (chicken pox) in children, a common disease in childhood. Following resolution of the primary disease, the virus establishes latent infection in neural ganglia and may reactivate later in life, particularly in the elderly, causing herpes zoster (shingles) and postherpeutic neuralgia. Reactivation VZV infections cause significant morbidity, especially in children, the elderly, and in immunosuppressed individuals. An FDA approved live attenuated VZV Oka vaccine is currently available and in widespread use in healthy children and susceptible adults, however, it is not recommended for immunocompromised individuals. Studies to assess this and other VZV vaccines are limited due to lack of suitable animal models for testing. VZV is known to infect nonhuman primates, however, it does not cause disease. A strong non-human primate animal model however, does exist for the simian varicella virus, SVV. In nonhuman primates, SVV not only produces infection but produces acute infection and latency in nonhuman primates similar to that observed for VZV in humans.

This study proposes to expand the simian varicella model by fully characterizing the immunological and cellular response to the VZV Oka vaccine in nonhuman primates and evaluating protection against SVV challenge. A study with six African green monkeys comprising two groups of three monkeys each was started. The three animals in the experimental group were vaccinated subcutaneously with 2 x 1ml of VZV Oka vaccine strain in vero cells at 1 x 104pfu SVV. The animals will be monitored for immunological changes, protection against SVV challenge and viral latency.

MOLECULAR EPIDEMIOLOGY OF STLV-I IN WILD AND CAPTIVE SOOTY MANGABEYS (0754)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
TRAINA-DORGE, VICKI L	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
names	MD, PHD	C	MICROBIOLOGY & IMMUNOLOGY	
	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	

AXIS I CODES: 1A, 1D, 7B **AXIS II CODES:** 56, 59, 64, 66, 76, 77

ABSTRACT

Serological and molecular surveys to evaluate prevalence and diversity of simian T cell lymphotropic virus (STLV) within the long established Tulane National Primate Research Center (TNPRC) captive sooty mangabey (SM; Cercocebus atys) colony were conducted. Serological analysis determined that 22 of 39 animals (56%) were positive for STLV-I. Cellular DNA isolated from each infected animal was amplified by PCR for both STLV-I envelope (env) and LTR, nucleotide sequencing conducted, and phylogenetic comparisons with known HTLV-I and STLV-I isolates were made. A second group of 13 SM monkey samples obtained from Sierra Leone, Africa, as bush meat samples, were included in the study. Three of those wild SM samples (23%) were positive for STLV-I by PCR. All TNPRC colony STLV-I virus isolates clustered together along with the previously published STLV-Ism strain from Yerkes National Primate Research Center (YNPRC) and the newly isolated African SM isolates. These data confirm an African origin for the TNPRC viruses and suggest a Sierra Leone origin for the SM colonies in the United States. A high viral diversity was seen within TNPRC STLV-Ism strains showing further subdivision into three distinct subclusters. Given the genetic stability of this virus family, these data also suggest at least three founder sooty mangabeys were infected at the time of their importation. High viral diversity of STLV-Ism in the TNPRC colony matches the already reported high diversity of SIVsm, however, lack of correlation between lineage distribution of the strains of SIVsm and STLV-Ism suggests the intra-colony transmission of the two viruses followed different mechanisms. Given the geographical clustering of STLV strains in Africa, study of HTLV-I diversity in Sierra Leone will be necessary to confirm STLV-Ism potential for cross-species transmission to humans, as reported for SIVsm and HIV-2.

SIV-MACAQUE MODEL FOR BREAST MILK TRANSMISSION OF HIV (0731)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
AMEDEE, ANGELA M	PHD	A	MICRO/IMMUNO/PARASIT	LSU HEALTH SCIENCES CENTER, LA USA
L name J	DVM	C	VETERINARY MEDICINE	

AXIS I CODES: 1A, 1D, 7B, 17, 22 **AXIS II CODES:** 31, 66, 71, 77, 93

ABSTRACT

Mother to infant transmission of HIV is associated with high maternal viral load and advanced disease state; however, the mechanism of transmission remains undefined. Using SIV infected rhesus macaques we have isolated a genotype of SIV derived from SIVDeltaB670 that is expressed at higher levels in breast milk and is capable of being transmitted orally to an infant more readily than the parental strain. Four of six lactating female macaques inoculated IV with the isolate (SIV/CK35) transmitted virus to their infant via breast milk by 21 days post inoculation. Transmission of the parental strain at such an early time point only occurred in 2 of 17 animals. At 7 days post inoculation, animals inoculated with SIV/CK35 had higher milk viral loads than animals inoculated with the parental strain. Additionally, four juveniles were orally inoculated to assess the potential of the SIV/CK35 virus stock as an oral inoculum. All four animals became infected within 4 days of inoculation. Our findings suggest that this virus has a phenotypic advantage in the milk, which increases its potential for transmission. This genotype will be valuable in defining the viral and host factors involved in breast milk transmission.

IMPROVING PERSONNEL SAFETY BY CORRECTING RISK PERCEPTIONS IN PRIMATE BIOMEDICINE (0662)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BAKER, KATE C	PHD	C	VETERINARY MEDICINE	
names	CRNP	C	DIRECTORS OFFICE	
	MPH	C	VETERINARY MEDICINE	

AXIS I CODES: 1A **AXIS II CODES:** 36, 51, 66, 94

ABSTRACT

Physical hazards and zoonotic risks associated with nonhuman primates in the laboratory setting vary with species differences in pathogens and behavioral characteristics, housing settings, handling techniques, procedures performed, and personnel attitudes. Employee safety is influenced by numerous features of the workplace, including availability of protective gear, management support, standards development, and personnel training. However, in addition to these factors, people also develop their perceptions of on-the-job dangers based upon their own individual experiences and beliefs, and employees cite misjudgment about the primate involved as the most frequent reason given for the occurrence of animal-inflicted exposures. A disparity between beliefs and reality has the potential to increase risks of exposures by fostering misguided complacency about risk in certain circumstances. The aim of this project is to directly address the culture of risk perception in order to bring personal beliefs in line with actual risks. It aims to test whether improving the accuracy of risk perceptions improves laboratory safety practices. This study involves four steps: risk perception surveys, tabulation of exposure patterns, development and delivery of training material, and assessment of preliminary outcome measures. By systematically assessing perceptions, making a detailed determination of which situations actually pose the greatest risk of exposure, and tailoring training to this information, this study aims to enhance preventative behavior and the effectiveness of the Occupational Health and Safety program at the Tulane National Primate Research Center.

ENVIRONMENTAL ENRICHMENT PROGRAM (0687)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BAKER, KATE C	PHD	C	VETERINARY MEDICINE	
	DVM, PHD	C	COLLABORATIVE RESEARCH	
	DVM	C	VETERINARY MEDICINE	
	PHD	C	GENE THERAPY	
	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	PHD	C	BACTERIOLOGY AND PARASITOLOGY	
	DVM, PHD	C	COMPARATIVE PATHOLOGY	

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

ABSTRACT

The Environmental Enrichment and behavioral research programs were expanded in 2003. An additional environmental enrichment technician position was created to support an enhanced enrichment program. Considerable progress was made in expanding the use of social housing for research animals and in the behavioral monitoring and intervention program for nonhuman primates, which now includes a wider variety of enrichment strategies and treats a wider variety of behavioral issues. Environments were enhanced with additional structures in corrals and corncribs and an increased variety of portable objects. Positive reinforcement training methods were incorporated into several research projects and was applied to management problems with individual animals.

The Environmental Enrichment and Behavioral Research Coordinator conducts collaborative research with scientists and graduate students in the Department of Pharmacology at the Tulane University School of Medicine, the Tulane University Center for Gene Therapy, the Department of Psychology at Southeastern Louisiana University, and the Department of Animal Resources at the Yerkes National Primate Research Center.

TAILORING BEHAVIORAL MANAGEMENT TO REARING AND RESEARCH (0733)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BAKER, KATE C	PHD	C	VETERINARY MEDICINE	

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

ABSTRACT

The USDA Draft Policy on Environmental Enhancement for Nonhuman Primates outlines the USDA's current interpretation of the Animal Welfare Act. It has been developed to provide more specific guidelines to facilities and their inspectors as to what measures sufficiently address the psychological needs of captive primates. While the USDA based the Draft Policy on a review of the scientific literature, this research is not currently sufficient for guiding the implementation of several elements of the Draft Policy. This project will provide direct benefit to the primate well-being and management of the Tulane National Primate Research Center colony, as well as Center's ability to adjust to the changing regulatory climate in an optimal manner. Rhesus macaques are being studied due to their widespread use in biomedicine, due to their availability as subjects at Tulane, and the need for enhanced management of monkeys with the backgrounds and research settings to be explored in this project. Focus is placed on social grouping and human interaction as enrichment. Using behavioral, physiological, and clinical data, we are 1) comparing the effects of continuous full contact, continous protected contact, and intermittent full contact for pair-housing rhesus macaques, and 2) comparing the effects of several quantities and forms of human/primate interaction on the behavioral well-being of singly-housed individuals. Subject are drawn from the following populations: those mother-reared in a social setting, those mother-reared without other social partners, nursery-reared individuals, and subjects used in research that includes frequent invasive access. To date, baseline data have been collected on 24 subjects. This project aims to provide the scientific underpinning for decisions relating to the changing regulatory climate governing the behavioral management on non-human primates.

ABNORMAL BEHAVIOR & ONSET OF INITIAL SOCIALIZATION AMONG NURSERY-REARED MACAQUES (0732)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BAKER, KATE C	PHD	C	VETERINARY MEDICINE	
L name	MPH	C	VETERINARY MEDICINE	

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

ABSTRACT

The socialization of nursery-reared macaques typically involves initial social exposure at approximately one month of age. However, in a biomedical environment, the onset of socialization may be delayed for a variety of reasons. This ongoing study examined the prediction that these delays are associated with broadened expression of abnormal behaviors among immature, socially-housed rhesus macaques. In order to control for the types of research procedures experienced and the reason for delayed socialization, all subjects were drawn from one research project that imposed restrictions on early socialization. Subjects included 14 (6:8) six-month-olds first socialized at 2-6 mo., 24 (15:9) 18-month-olds socialized at 3-7 mo., and 14 (6:8) 30-month-olds socialized at 9-18 mo. Three five-minute surveys were conducted on each subject, noting the presence of 16 abnormal behaviors. Associations between age at socialization and frequency of abnormal behavior within each cohort were determined by simple regression procedures. Among the 6- and 30-mo. cohorts, no relationship was detected between age at socialization and number of abnormal behaviors. However, among the 18-month-old subjects, onset of socialization was positively related to breadth of the abnormal behavior repertoire. Initial results suggest that decisions regarding early socialization need to strike a careful balance between the rationale for delayed socialization and the promotion of normal development. Continued research will permit an examination of a wider range in subject ages and initial socialization ages.

NALTREXONE HCL TO DECREASE INCIDENCE & SEVERITY OF SELF-INJURY IN MACAQUES (0746)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BAKER, KATE C	PHD	C	VETERINARY MEDICINE	
Unnamed	DVM	C	VETERINARY MEDICINE	

AXIS I CODES: 1A, 12B **AXIS II CODES:** 50B, 72

ABSTRACT

Few pharmacological interventions for self-injurious behavior (SIB) in laboratory primates have been thoroughly evaluated. This preliminary report on the effect of naltrexone HCl involves a case study of two caged subadult male rhesus macaques, as part of an ongoing long-term evaluation involving a large number of subjects. Naltrexone HCl was compounded into a palatable syrup at 10mg/ml. Physical exams, complete blood counts, blood chemistry, urinalysis, and behavioral testing totaling 45 h were performed before beginning treatment and at regular intervals throughout the duration of the study. Animals were dosed at 0.032mg/kg orally once every 24 hours. Individuals were reassessed and dosing intervals were gradually increased every two to four weeks, with a maximum interval of 96 hours. Dramatic reductions in the frequency of self-biting were observed within the first week of treatment for both subjects. In one subject, the greatest reduction (2.5-fold) was observed with dosing levels of every 24 and 48 hours. In the other subject, dosing every 72 hours was associated with a 30-fold reduction, a greater level of improvement than either daily or more intermittent dosing. However, variability in levels of acute environmental stress was associated with increased in SIB in both subjects. The rapid reduction in self-biting suggests that naltrexone holds promise as an intervention for SIB in macaques, but further research on these and additional subjects are permitting us to differentiate between the effect of varying dosing levels, environmental influences, and long-term efficacy.

SPECIFIC PATHOGEN FREE RHESUS MONKEY COLONY FOR AIDS RESEARCH (0648)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BLANCHARD, JAMES L	DVM, PHD	C	COLLABORATIVE RESEARCH	
names	DVM	C	VETERINARY MEDICINE	
	DVM, PHD	C	MICROBIOLOGY AND IMMUNOLOGY	

AXIS I CODES: 1A, 7, 11 **AXIS II CODES:** 31, 66

ABSTRACT

The SPF breeding colony has grown to a population of approximately 900 animals. The first round of testing required the removal of 19% of animals because of positive viral testing results. Fifteen per cent of these cases were due to B virus. Corral renovations are on target with completion of all 4 corrals funded by the first 2 years of the grant. Additional corrals have been renovated by the Center and new pens have been built to hold yearling monkeys entering the SPF colony in 2003 - 2004. Viral testing continues to be done at the Simian Retrovirus Diagnostic Lab and the National b virus lab in Georgia. No unexpected results were seen in SRV and STLV tests.

The total number of animals projected for the entire SPF breeding colony at the end of five years from this and other SPF colonies will approach 2000 animals.

NATIONAL INSTITUTE ON AGING (NIA): AGING COLONY MAINTENANCE (0501)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.620% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BOHM, RUDOLF P	DVM	C	VETERINARY MEDICINE	

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

ABSTRACT

The NIA set aside program maintains aged rhesus monkeys at several facilities to provide for allocation to NIA funded investigators.

The current census of the NIA colony is 28, which is comprised of Indian rhesus macaques of both sexes ranging in age from 13-30 years of age. The animals are housed among their original conventional breeding colony cohorts in several enclosures.

EFFICACY OF MOXIDECTIN IN TREATMENT OF STRONGYLOIDES INFECTION IN RHESUS MONKEYS (0663)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BOHM, RUDOLF P	DVM	C	VETERINARY MEDICINE	
[illegible]	DVM	C	VETERINARY MEDICINE	

AXIS I CODES: 1A **AXIS II CODES:** 50, 66, 77

ABSTRACT

Strongyloides infection has always been a health concern for nonhuman primates and may make them less useful for certain experimental protocols. We are observing increasing levels of resistance of strongyloides to ivermectin, which is our current anthelmintic of choice. We are concerned about the impact that a resistant parasite population could have on research results, but we are also concerned for all the clinical cases of diarrhea that we attributed to strongyloides infections. In our attempts to maintain a healthy breeding and research colony, we are looking for a new anthelmintic that will alleviate strongyloides infections. We seek to compare the efficacy of moxidectin (Cydectin) to ivermectin.

As of 2/9/04, we have performed fecal examinations on 533 animals from the conventional and SPF breeding colony. One hundred twenty two animals had more that 24 eggs/gram of strongyloides ova, which are our criteria for acceptance to study. Sixty one animals have been treated with moxidectin at .5mg/kg topically. Sixty one animals were treated with ivermectin at .4 mg/kg IM. At this point there has been no statistically significant difference in the two groups. Each group has achieved statistical difference in pre/post treatment eggs/gram. We will conclude this study when we have treated 75 animals with ivermectin and 75 animals with moxidectin.

WANPRC BREEDING COLONIES (0677)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BOHM, RUDOLF P	DVM	C	VETERINARY MEDICINE	
L	DVM	A		WNPRC, WA USA
	DVM	A		WANPRC, WA USA
names	DVM	A		WANPRC, WA USA
	DDS, PHD	A	DEAN, DENTAL SCHOOL	UNIVERSITY OF WA, WA USA
1	PHD	A		WNPRC, WA USA

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

ABSTRACT

The nonhuman primate breeding colonies of the Washington National Primate Research Center (WaNPRC) are maintained at the TNPRC. Animals derived from these colonies are used to support the research program at the WaNPRC. The colony consists of approximately 779 Macaca nemestrina and 516 Papio spp. housed in outdoor social groups. Veterinary care and husbandry are performed as per TNPRC standard operating procedures. Inventory procedures are performed a minimum of twice annually for all breeding colony animals and consist of blood sampling, physical examination, anthelmintic treatment, tattooing, and TB testing. Blood samples are drawn at the time of inventory for viral screening or genetic testing. Other samples are taken as necessary. Ill animals are removed from the colony and housed indoors for diagnosis and treatment.

ESTABLISHMENT OF SPF COLONY FOR NON AIDS RESEARCH (0734)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BOHM, RUDOLF P	DVM	C	VETERINARY MEDICINE	

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

ABSTRACT

The presence of retroviral infection in nonhuman primate research animals makes them unsuitable for a number of research studies. In addition, the presence of B-virus in nonhuman primates used in research is a significant occupational safety and health concern. The specific pathogen free (SPF) program was created to provide rhesus monkeys seronegative SIV, SRV, STLV1, and b-virus for research. Yearling M. mulatta are housed with peers from their natal groups while viral screening occurs during years 1-3 and are then moved into larger breeding groups. Animals testing positive for viral agents are removed from the SPF program. Yearling rhesus macaques are currently being removed from the conventional breeding colony for inclusion in the SPF program.
This program provides SPF animals for studies other than AIDS research.

ELECTRICALLY STIMULATED AND NONSTIMULATED SPINAL FUSION CAGES (0505)

NPRC UNIT: VETERINARY MEDICINE
%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
COOK, STEPHEN D	PHD	A	ORTHOPAEDICS	TULANE UNIVERSITY MEDICAL CENTER, LA USA
names	DVM	C	VETERINARY MEDICINE	
	DVM	C	VETERINARY MEDICINE	

AXIS I CODES: 1A, 26 **AXIS II CODES:** 46, 48, 86

ABSTRACT

Titanium cages have been effective for single level fusions of the lumbar spine in patients with degenerative disc disease. Direct current bone stimulation has been used successfully with posterolateral fusions and may improve anterior fusion rates as an adjunctive therapy with interbody fusion cages. Objectives were to assess the in vivo feasibility and safety of a deployable titanium cage design with autogenous bone graft in lumbar interbody fusion in a non-human primate model. The results were directly comparable to those obtained previously using an earlier cage design with and without adjunctive electrical stimulation to accelerate anterior bone fusion.
Animals were randomly assigned to two groups: titanium fusion cage without electrical stimulation and femoral allograft bone ring. Each animal received an appropriately sized cage or bone ring in the lumbar disc space with autogenous iliac crest bone graft inserted through a retroperitoneal approach. Animals were sacrificed at 26 weeks postoperative. Radiographs were obtained to study the progression of healing. Post-retrieval studies include computed tomography imaging, nondestructive mechanical bend testing, and histologic analysis.
The results from completed work on this study have shown that anterior lumbar interbody fusion was achieved with autogenous bone graft and insertion of a titanium fusion cage in a primate model. The fusion cage was equivalent to or better in all outcome variables than the femoral allograft rings in achieving fusion regardless of the use of electrical stimulation. Adjuvant direct current stimulation increased the incidence and extent of interbody fusion, although the observed effects were not always dose-related. The current study determined that radiographic fusion was achieved with the deployable titanium cage design and the use of autogenous bone graft. Imaging, mechanical testing and histologic data are unavailable.

TIMED BREEDING CORE (0507)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
HARRISON, RICHARD M	PHD	C	VETERINARY MEDICINE	
	DVM	C	COMPARATIVE PATHOLOGY	
	PHD	C	VETERINARY MEDICINE	
	MPH	C	VETERINARY MEDICINE	
	DVM, PHD	A	MICROBIOLOGY AND IMMUNOLOGY	TULANE UNIVERSITY HEALTH SCIENCES CENTER, LA USA
	DVM, PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	PHD	A		CHILDREN'S HOSPITAL, OH USA

AXIS I CODES: 1A, 2, 15, 23 **AXIS II CODES:** 60, 71, 74E, 77

ABSTRACT

The timed-breeding program at the Tulane National Primate Research Center uses exogenous progesterone administration to control the time of ovulation. The progesterone (USP grade) is dissolved in oil and administered by intramuscular injection at a dose of 5 mg/0.25 ml oil daily for 10 days. The female is placed with the male 14 days after the last injection. Ultrasonography conducted 24 or 31 days after placing the female with the male confirms that pregnancy occurs 4 days after introduction to the male. This procedure allows for efficient use of the males and provides a conception date + 24 hours. In the 2003-2004 breeding season 45 Indian-origin and 13 Chinese-origin rhesus monkeys were used in this project. Excluding the monkeys who have not been examined to determine pregnancy, 76% of the Indian-origin and 60% of the Chinese-origin monkeys are pregnant. All the pregnant monkeys were assigned to projects supported by outside funding agencies. These included (1) effects of maternal malaria on fetal development and infant growth, (2) a nonhuman primate rotavirus illness model and (3) safety and toxicity of mesenchymal stem cells administered to the CNS of non-human primates. This timed-breeding procedure does not require determination of menstrual cycle stage prior to initiation of progesterone administration. This procedure has been used to synchronize cycles in groups of monkeys. Publications in this period include a report of 4 years breeding success, conception rates for age and number of previous pregnancy and an abstract describing synchronization of menstrual cycles.

ASSISTED REPRODUCTIVE TECHNIQUES IN PIGTAIL MACAQUES (0523)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
HARRISON, RICHARD M	PHD	C	VETERINARY MEDICINE	
names	DVM	C	COMPARATIVE PATHOLOGY	
	PHD	C	VETERINARY MEDICINE	
	DVM	C	VETERINARY MEDICINE	

AXIS I CODES: 1A, 9, 23 **AXIS II CODES:** 60, 63H, 77

ABSTRACT

A number of embryo transfers were performed to assess the possibility of utilizing pigtail macaques (Macaca nemestrina) as recipients for rhesus macaque (Macaca mulatta) embryos. A total of 250 oocytes were collected from rhesus females during 11 follicular aspirations. Forty-eight hours after in vitro fertilization 192 of these had cleaved at least once. A total of 15 embryo transfers of two embryos each were performed into rhesus recipients resulting in 8 pregnancies, of which two were lost during the second trimester. Among the remaining 6 pregnant rhesus females two were carrying sets of twins resulting in the birth of 8 infants. Twelve transfers of rhesus embryos were attempted into pigtail females resulting in one pregnancy and the birth of one infant. Fetal growth and development were monitored by monthly ultrasound examinations at which time biparietal measurements were taken and compared to those derived from 22 pregnant control females. IVF-derived singletons tended to develop faster than twins and naturally conceived controls during the initial months of pregnancy and weighed more at birth than twins. There were significant morphological changes in the placenta of the rhesus developing in the pigtail female. These included an irregular shape, elevated placenta-to-birth-weight ratio, as well as an abnormal length and diameter of the umbilical cord These results demonstrate that pigtail females can carry rhesus fetuses to term, but further studies are necessary to determine the cause of lower pregnancy rates and the nature of placental abnormalities.

ENDOCRINOLOGY CORE LABORATORY (0739)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
HARRISON, RICHARD M	PHD	C	VETERINARY MEDICINE	
	DVM, PHD	C	COLLABORATIVE RESEARCH	
	PHD	A		AARON DIAMOND AIDS RESEARCH CENTER, NY USA
names	PHD	C	VETERINARY MEDICINE	
	MPH	C	VETERINARY MEDICINE	

AXIS I CODES: 1A, 15, 23 **AXIS II CODES:**66, 93

ABSTRACT

Estradiol levels in serum collected during the follicular phase of the menstrual cycle was assayed using a competitive binding radioimmunoassay (RIA) procedure utilizing a commercial kit (Diagnostic Products Corporation, DPC, Los Angeles). The assay was used to determine the preovulatory peak of estradiol and allows the investigators to determine the optimal day to conduct embryo transfers. In the period from May 2003 through February 2004, daily samples were collected from day 8 in 5 rhesus and day 10 in 9pigtails until the peak was determined or until it was clear that there would not be a normal peak. Studies were also conducted in the rhesus monkeys to collect urine from pans under their cages for determination of estradiol levels in the urine and compare that to estradiol levels in the blood (10 rhesus). These data were not conclusive. Current studies are looking at estrone in the urine, an estrogen analyzed by other investigators, and comparing that to estradiol levels in the blood. We expect to find a relationship between serum estradiol and urinary estrone and will be able to predict serum estradiol peaks without daily blood collections.

The Endocrinology Core Laboratory also conducts RIAs for other investigators and in this report period these includes estradiol and progesterone assays in an aging study (62 rhesus) and progesterone assays in an anti-HIV microbicide study (15 rhesus).

PROGESTERONE ADMINISTRATION TO SYNCHRONIZE MENSTRUAL CYCLES IN NONHUMAN PRIMATES (0741)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
HARRISON, RICHARD M	PHD	C	VETERINARY MEDICINE	
names	PHD	C	VETERINARY MEDICINE	
	MPH	C	VETERINARY MEDICINE	

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

ABSTRACT

Exogenous administration of progesterone has been used successfully at TNPRC for timed-breeding studies. The purpose of this study was to determine if a modification of the progesterone administration schedule could be used to synchronize the menstrual cycles in a group of 16 rhesus (Macaca mulatta) monkeys. The monkeys were housed in individual cages, received daily intramuscular injections of 5 mg progesterone in 0.25 ml of oil beginning on the 16th day of their normal cycle. No two monkeys started injections on the same day. All monkeys received the daily injections until all had received a minimum of 10 injections. At that time administration of progesterone ceased. All monkeys began menses on day 2 or 3 following the last injection. On day 18 after the last progesterone administration all monkeys were in the luteal phase of their cycle. In two separate timed- breeding studies, following progesterone administration for a period of 10 days, serum progesterone levels were 14.6 + 5.7 ng/ml and 15.0 + 4.9 (mean + std dev) 21 days after progesterone administration. (n=10 in each study). This procedure for synchronization of menstrual cycles in rhesus monkeys can be used in assisted reproductive technology studies involving oocyte collections, embryo transfers, and artificial inseminations.

FEMALE REPRODUCTIVE AGING (0740)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
KUBISCH, H. MICHAEL	PHD	C	VETERINARY MEDICINE	
	PHD	A		UNIVERSITY OF NEW ORLEANS, LA USA
		A		UNIVERSITY OF NEW ORLEANS, LA USA
names	DVM, PHD	C	COMPARATIVE PATHOLOGY	
	PHD	C	VETERINARY MEDICINE	

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

ABSTRACT

A dramatic decline in fertility is evident in human females past their middle thirties. This "reproductive senescence" is marked by a sharp decline in embryo implantation and pregnancy rates, and may be attributed to a reduced number of available oocytes and their quality. The ideal animal model for studies of human reproductive senescence would possess similar physiological and genetic characteristics. Old World primates exhibit ovarian morphology and physiological control and timing of menstrual cycles that closely resemble those of humans. The current study investigated the use of the rhesus macaque as a potential model for reproductive aging. Ovaries were collected at autopsy from 62 females of various ages (ranging from 1 to 25 years old) and preserved for histologic analyses. General ovarian morphology was examined through basic staining techniques and demonstrated significant changes in follicle profile and tissue morphology with increasing age, becoming most pronounced as the females approached menopause. Across age groups, percentages of primordial and primary follicles all demonstrated significant differences (P0.0001 for both). Samples from females approaching or undergoing the menopausal transition (aged 20-25) demonstrated evidence of ovarian senescence, having scattered and atretic follicles, occasional primordial follicles and reduced amounts of stromal tissue. Radioimmunoassays of serum collected at the time of euthanasia were inconclusive. This was likely due to the fact that the single samples were collected at unknown periods of the females' cycles. This study demonstrates the value of the rhesus monkey as a model for reproductive aging because the ovary undergoes similar follicular reservoir depletion patterns as in humans. Future studies utilizing the rhesus macaque model will be invaluable for understanding the mechanism underlying reproductive aging so that assisted reproductive technologies can be developed to address this phenomenon.

INTERFERON-TAU SECRETION ON PREGNANCY RATE AFTER TRANSFER OF BOVINE BLASTOCYSTS (0743)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
KUBISCH, H. MICHAEL	PHD	C	VETERINARY MEDICINE	

AXIS I CODES: 1A, 9, 23 **AXIS II CODES:**60

ABSTRACT

Three separate trials of bovine embryo transfers were performed consisting of 32, 41 and 33 transfers, respectively, to examine the effects of a) the developmental stage of in vitro-derived blastocysts, b) the amount of interferon-t (IFN-t) they secreted during culture and c) the cyclic stage of the recipient at the time of transfer on the probability of establishment of pregnancy. One blastocyst was transferred into the ipsilateral uterine horn to the CL. At the time of transfer, blastocysts were classified into one of three developmental stages (early blastocyst, blastocyst and expanded blastocyst) and the cyclic stage of each cow was assessed (-12h, on time, + 12 h, + 24 hr, 24 h). Prior to the second and third trials, blastocysts were individually cultured for 24 h in50 μl medium droplets and the IFN-t concentration in the droplet was determined. Logistic regression analyses revealed that expanded blastocysts had a significantly higher likelihood of establishing pregnancy (p=0.009), and that there was a significant interaction with the cyclic stage of the recipient in this group with lower rates of pregnancy resulting from decreasing synchrony with the recipient (p=0.033). IFN-t secretion during culture was significantly higher in expanded blastocysts than in the other two groups (P0.05). A significant effect of the pre-transfer level of IFN-t secretion was found only in the 'Blastocyst" group where transfer of embryos with lower IFN-t production prior to transfer resulted in higher pregnancy rates (p=0.047). These results demonstrate that IFN-t secretion may be a useful tool to predict pregnancy outcome, but only within certain developmental stages.

GENETIC TRANSFORMATION OF RAT EMBRYOS (0744)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
KUBISCH, H. MICHAEL	PHD	C	VETERINARY MEDICINE	
names	MD	A		UNIVERSITY OF MISSISSIPPI MEDICAL CENTER, MS USA
	DVM, PHD	A		UNIVERSITY OF MISSISSIPPI MEDICAL CENTER, MS USA

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

ABSTRACT

The objectives of this study are to assess the effects of suppression of 11b-hydroxysteroid dehydrogenase 2 as well as over-expression of aldosterone synthase in rats. To this end, one-cell rat embryos were injected under the zona pellucida with a lenitivrus carrying either a 11b-hydroxysteroid dehydrogenase 2 siRNA under control of the U6 promoter or the aldosterone synthase gene driven by either the synapsin 1 or myosin heavy chain promoter. Injection of the 11b-hydroxysteroid dehydrogenase 2 siRNA has resulted in 19% of pups derived from transfer of embryos injected with this vector to be positive. The F1 generation of 1founder dam has to date been analyzed and the transgene was detected in several offspring. To date, none of the first round of pups generated from embryos injected with the aldosterone synthase vector were positive, although litter sizes tended to be unusually small, perhaps indicating some type of embryonic lethality. Current efforts are directed towards determining the cause of these observations.

EXPERIMENTAL INFECTION OF RHESUS MACAQUES WITH WEST NILE VIRUS (0771)

NPRC UNIT: VETERINARY MEDICINE
%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
RATTERREE, MARION S	DVM	C	VETERINARY MEDICINE	
names	DVM	C	VETERINARY MEDICINE	
	PHD	A	INFECTIOUS DISEASE/CLINICAL BI	ABBOT LABORATORIES, IL USA
	DVM, PHD	C	COMPARATIVE PATHOLOGY	
	MD	A	DEPARTMENT OF PATHOLOGY	UNIVERSITY OF TX MEDICAL BRANCH, TX USA
	BS	A	DEPARTMENT OF PATHOLOGY	UNIVERSITY OF TX MEDICAL BRANCH, TX USA
	MD	A	DEPARTMENT OF PATHOLOGY	UNIVERSITY OF TX MEDICAL BRANCHG, TX USA

AXIS I CODES: 1A **AXIS II CODES:**66, 77

ABSTRACT

In order to better understand the pathogenesis of West Nile virus (WNV) infection in humans, 5 rhesus macaques (Macaca mulatta) were inoculated intradermally with a New York 1999 strain of WNV. Following infection, the animals were bled daily for 10 days, and subsequently at weekly intervals; samples are currently being tested to determine the level and duration of viremia, immune response, duration of infectious virus and viral RNA in the blood and other parameters Spinal taps were also done on the animals at various intervals after infection to detect IgM and possible virus in the CNS. The animals developed a brief viremia and good immune response after infection, but remained asymptomatic. Two months post-infection, the animals were euthanized and necropsy was performed. Samples of brain and other tissues were taken for histopathologic examination as well as for culture and RT-PCR to test for possible chronic CNS infection These studies are still in progress.

PILOT SUBPROJECTS

IN SITU STAINING WITH MACAQUE MHC CLASS I AND II TETRAMERS (0640)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.636% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
KURODA, MARCELO	PHD	A		BETH ISRAEL DEACONESS MEDICAL CENTER, MA USA
names	PHD	C	COMPARATIVE PATHOLOGY	
	PHD	G	COMPARATIVE PATHOLOGY	

AXIS I CODES: 1A, 1B, 19 **AXIS II CODES:** 31, 63I, 64

ABSTRACT

The central importance of virus-specific CD4+ T lymphocytes in containing HIV-1 replication has recently been appreciated. Studies have shown that control of viral replication in vivo is associated with vigorous HIV-1-specific CD4+ T lymphocyte proliferative responses. It will be important to characterize these lymphocytes in greater depth to determine how they contribute to containing HIV-1 replication. However, our ability to study these lymphocyte populations has been limited by the technologies available to carry out such analyses. By providing a reproducible and precise quantitative assay for CTL responses, the tetramer assay has dramatically increased the level of sophistication that can be brought to bear on the study of antigen-specific CD8+ T lymphoctes. The application of the tetramer technology to the study of CD4+ T lymphocyte responses should similarly increase our ability to evaluate the role of these cells in disease pathogenesis. In the studies, we will improve the MHC class I/peptide tetramer in situ staining technology and develop MHC class II/peptide tetramer for in situ staining to detect simian human immunodeficiency virus (SHIV)-specific CD4+ T lymphocytes in rhesus monkeys.

PEPTIDES INDENTIFIED THROUGH PHAGE DIRECT IMMUNOGENIC ANTIGEN TO DENDRITIC CELLS (0713)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.636%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MOHAMADZADEH, MANSOUR	PHD	A	MICROBIOLOGY AND IMMUNOLOGY	TULANE UNIVERSITY HEALTH SCIENCE CENTER, LA USA
[illegible]	PHD	C	COMPARATIVE PATHOLOGY	
	PHD	A	MICROBIOLOGY AND IMMUNOLOGY	TULANE UNIVERSITY HEALTH SCIENCES CENTER, LA USA

AXIS I CODES: 1D **AXIS II CODES:**63

ABSTRACT

To show that dendritic cell (DC) – binding peptides bind to monocyte-derived DCs, monocytes were isolated from peripheral blood cells of rhesus macaques. Data clearly show that all three peptides #3, #12 and #18 did bind to myeloid (M) DCs. Moreover, in order to demonstrate whether DC-peptides may change the phenotype or the function of DCs the cells were then cultured with allogenic CD4+ T cells for four days. T cell proliferation was determined by 3H thymidine up-take. Results show that DC-peptide did not change FACS-phenotype and accessory function of MDCs and these cells induce the proliferation and action of CD4+ T cells in vitro. Additionally, the coding region of SIVmac239 gag P 17 – P27 was fused in frame to DC peptide #3 or control peptide using a vector-encoded C-terminal histidine tag (pET24d). Following SDS-PAGE and Western blotting, full-length recombinant fusion proteins were detected

Future Studies:
To demonstrate p17-p27-fusion protein (FP) function, DCs will be pulsed with p17-p27-FP, p17-p27-cFP, or nothing. DC, Pulsed and unpulsed with immunogenic fusion proteins will then be co-cultured with autologous CD4+ or CD8+ T cells from infected monkeys. T cell proliferation and activation induced by DCs pulsed with fusion proteins will be studied in vitro. These first results will highlight the efficacy of DC-based immunotherapy in order to be used in vivo.

PERFLOROCARBON-ENHANCED GENE DELIVERY TO PRIMATE LUNG (0603)

NPRC UNIT: GENE THERAPY

%NPRC $: 0.636%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
WEISS, DANIEL	MD, PHD	A		UNIVERSITY OF VT/BURLINGTON, VT USA
	DVM, PHD	C	COLLABORATIVE RESEARCH	
names	DVM	C	VETERINARY MEDICINE	
	PHD	C	GENE THERAPY	
	DVM, PHD	C	COMPARATIVE PATHOLOGY	

AXIS I CODES: 1A, 2, 9, 24 **AXIS II CODES:** 39, 55, 77

ABSTRACT

Current techniques of gene delivery to airway epithelium, including catheter or bronchoscopic-directed instillation and aerosol administration, do not reliably result in reproducible, widespread, diffuse delivery of large amounts of gene transfer vectors to distal airways. However, more uniform vector distribution can be achieved if the vector is propelled by a liquid instilled throughout the lung. Perfluorochemical (PFC) liquids are chemically inert fluorinated short carbon chains, immiscible with aqueous solutions that have remarkable properties of gas solubility and have been safely instilled into airways of mechanically ventilated patients to support gas exchange. PFC liquids also appear to have anti-inflammatory effects both in vitro and in vivo and can decrease inflammatory responses associated with acute lung injury.

We have developed a model using a single intratracheal instillation of PFC liquid immediately following intratracheal instillation of gene transfer vector to lungs of spontaneously breathing rodents. Use of PFC liquids increases total transgene expression mediated by adenoviral, adeno-associated virus, and cationic liposomal vectors. Distribution of expression is enhanced throughout the lung, particularly in distal airway and alveolar epithelium. Moreover, use of PFC liquids enhances adenoviral-mediated transgene expression in two models of lung injury, GM-CSF knockout mice with chronic alveolar filling similar to that found in the clinical disease alveolar proteinosis and in rats with acute bleomycin-induced lung injury. Preliminary data also suggests that PFC liquids suppress acute inflammatory responses associated with adenoviral vector administration to lungs of spontaneously breathing rats

We have determined that PFC liquids can enhance lung gene transfer and gene expression in a larger, more clinically relevant animal model using non-human primates (rhesus macaques). We are assessing whether the use of PFC liquids will decrease both inflammatory and immune responses to these vectors and additionally allow more effective secondary gene transfer.

COMPARATIVE PATHOGENESIS OF SIVSM VIRUSES OF DIFFERENT GENETIC LINEAGES (0710)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.636% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
APETREI, CRISTIAN	MD, PHD	C	MICROBIOLOGY & IMMUNOLOGY	
names	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	MD, PHD	C	COMPARATIVE PATHOLOGY	
	DVM	C	VETERINARY MEDICINE	
	DVM, PHD	C	COMPARATIVE PATHOLOGY	

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

ABSTRACT

This pilot project is designed to evaluate the pathogenic potential of different SIVsm lineages in rhesus macaques (Rhs). It will explore the hypothesis that SIVsm may not be intrinsically pathogenic in Rh but were adapted by experimental or accidental serial passages. The main objective is to test the intrinsic pathogenicity of SIVsm strains naturally occurring at in TNPRC belonging to 5 different genetic lineages by experimental infections of Rhs. Our hypothesis that different strains of SIVsm have different pathogenicity in Rhs resulted from observations of SIVsm diversity in the TNPRC sooty mangabey colony showing that five different SIVsm lineages are co-circulating within this colony. A critical review of literature published during the last 18 years suggests that data might be over interpreted with regard to pathogenesis. None of these studies are taking into account SIVsm genetic diversity. This project was awarded in September 2003. Six animals were assigned for the project in November. All of them are currently infected with SIVsm (three lineages). At this point (day 120 post-infection) it is premature to draw any conclusion concerning their pathogenicity in Rhs. However, after a peak of viral replication of 108 copies/ml (by bDNA), a significant drop in VL was observed at the set point, which values of 6x103 copies in most of the animals. The depletion of target cells (CD4+ CCR5+ CD45Raneg) was limited during the primary infection and partially recovered after the peak of viral replication. Four new monkeys will be included during the second year of the project. Based on preliminary results and on current evaluations of SIVsm in the TNPRC colony, an RO-1 application will be submitted with the following specific aims: (1) to construct infectious molecular clones of SIVsm strains belonging to different lineages and to investigate their in vivo pathogenesis. (2) to use this high viral diversity in vaccine protocols in order to evaluate the correlates of vaccine protection against challenge with heterologous viruses belonging to a different subtype.

DEVELOPMENT OF STRATEGIES FOR VECTOR-MEDIATED GENE TRANSFER INTO RHESUS MONKEYS (0711)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.636%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
KUBISCH, H. MICHAEL	PHD	C	VETERINARY MEDICINE	
L name l	PHD	C	GENE THERAPY	

AXIS I CODES: 1D **AXIS II CODES:**58, 92(REPRODUCTION)

ABSTRACT

This study is designed to assess the suitability of various viral vectors to accomplish germline transformation of rhesus monkeys. Such genetically modified animals could prove immensely valuable for the generation of disease models, investigations into the action and control of specific genes or modulation of expression levels of endogenous genes. To this end several viral constructs were designed to be used as vectors that carry the green fluorescent protein (EGFP) as a reporter gene. The lentivirus FUGW, with the ubiquitin promoter driving EGFP expression, is used to provide a baseline as this vector has been shown to readily transform rat embryos. In addition several adeno-associated virus (AAV) vectors are being used which utilize the CMV early promoter to drive gene expression. To date 57 one-cell zygotes have been injected under the zonal pellucida with the FUGW vector. Reporter gene expression has been assessed in 30 of these, the remainder is currently still in culture. After one week in culture, 13 positive morulae and 7 positive embryos with arrested development were found. EGFP expression in all embryos was mosaic indicating either delayed vector integration or differential control of expression among individual blastomeres. The vector AAV2 was similarly injected into 25 zygotes, which resulted in 6 morulae with mosaic evidence of transgene expression. The vector AAV2/1 was used to inject 15 zygotes and reporter gene expression was subsequently detected in 3 blastocysts, 2 morulae and 3 arrested 8-cell embryos. Overall these results show that AAV and FUGW vectors appear to transform rhesus embryos, although it is at present unclear if these vectors integrate efficiently and if so at what stage of development.

COLLABORATIVE SUBPROJECTS

ANTI-HIV MICROBICIDE: CELLULOSE ACETATE (0651)

NPRC UNIT: COLLABORATIVE RESEARCH

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BLANCHARD, JAMES L	DVM, PHD	C	COLLABORATIVE RESEARCH	
names	PHD	A		AARON DIAMOND AIDS RESEARCH CENTER, NY USA
	PHD	A		ADARC, NY USA
	PHD	A		NEW YORK BLOOD CENTER, NY USA
	DVM	C	VETERINARY MEDICINE	

AXIS I CODES: 1A, 2, 23 **AXIS II CODES:** 31, 50, 62

ABSTRACT

Cellulose acetate phthalate (CAP), a pharmaceutical excipient designed as a coating material for tablets or granules, has been demonstrated to be effective against herpes simplex virus type 2 (HSV-2) infection in mice, and to protect four of six rhesus monkeys from vaginal challenge with simian immunodeficiency virus SIVmac251. Formulated CAP applied vaginally to rhesus macaques was not irritating as determined by colposcopy. Serum chemistries, vaginal biopsies, bacterial cultures and vaginal pH were all within normal limits. No obvious changes in peripheral CD4:CD8 ratios or levels of inflammatory cytokines/chemokines in plasma and vaginal fluids were detected. Thus, CAP appears to be safe in vivo. Magnetic resonance imaging (MRI) revealed that CAP was evenly distributed after application and 20 min thereafter, but was found absent 24h after application. To assess whether CAP confers protection against primary viral strains that are transmitted in humans, infections with simian/human immunodeficiency viruses (SHIVs) expressing the envelopes of X4 and R5 HIV-1 strains (SHIVSF33A and SHIVSF162P3, respectively) were performed. Replication of SHIVSF33A and SHIVSF162P3 in vitro can be efficiently blocked by CAP, with ID50 concentrations of 180 and 25 mg/ml respectively. Preliminary findings in rhesus macaques challenged with a mixture of X4-SHIVSF33A and R5-SHIVSF162P3 suggest that CAP is efficacious against both X4 and R5 SHIV viruses in vivo, and should therefore be considered as a viable topical microbicide candidate in the prevention of HIV-1 infection.

LOCATION & CHARACTERIZATING DECL THYMIC EMIGRANTS IN THYMECTOMIZED MACAQUES (0652)

NPRC UNIT: COLLABORATIVE RESEARCH

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BLANCHARD, JAMES L	DVM, PHD	C	COLLABORATIVE RESEARCH	
names	DVM	C	VETERINARY MEDICINE	
	MD	A	DIRECTOR	AARON DIAMOND AIDS RES, NY USA
	PHD	A		AARON DIAMOND AIDS RES, NY USA

AXIS I CODES: 1A, 2, 3, 7B, 16C **AXIS II CODES:** 31, 64, 66, 77

ABSTRACT

The goal of this study is to define the role of the thymus in peripheral T-cell homeostasis and to assess the significance of thymic output in SIV infection by surgical removal of the thymus in juvenile rhesus macaques.Nine (9) juvenile rhesus macaques were thymectomized and 8 underwent sham surgery. Blood was drawn periodically in the 9 months following surgery and for the subsequent 6 months following SIV infection, and assayed for plasma viral loads, lymphocyte subsets and the concentration of T-cell receptor excisional circles (TREC).

In the 9 months post surgery, there were no statistically differences in the decay rates of CD3+, CD4+, CD8+, CD3+CD45RA+, CD4+CD45RA+, CD8+CD45RA+ and Ki67+ proliferating T cells in blood between thymectomy and sham groups. We found that TREC decay rates in peripheral CD4+ (-0.0046) and CD8+ (-0.0065) T cells of thymectomized macaques, however, were significantly higher than those in sham controls (p0.05). Based on the decay slope of TREC post thymectomy, we have calculated an absolute thymic production rate of ~5.5 x 106 to 1.1 x 107 TREC-bearing cells per day, which is quantitatively insignificant among the total T-cell pool of ~1011 in rhesus monkeys. After infection with SIV, no significant differences in peak or setpoint viral loads and in decay rates of the same lymphocyte subsets studied above were noted between infected thymectomized and sham groups. Infection increased the decay of TREC in peripheral T cells in both groups. However, slopes adjusted for the pre-infection difference in decay between two groups demonstrated no significant difference in TREC decay between the groups after infection.

TRANSMISSION & PATHOGENESIS OF X4 & R5 SHIVS (0653)

NPRC UNIT: COLLABORATIVE RESEARCH

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BLANCHARD, JAMES L	DVM, PHD	C	COLLABORATIVE RESEARCH	
	PHD	A		AARON DIAMOND AIDS RESEARCH CENTER, NY USA
names	DVM	C	VETERINARY MEDICINE	
	PHD	A		ADARC, NY USA
	PHD	A		AARON DIAMOND AIDS RESEARCH CTR, NY USA

AXIS I CODES: 1A, 2, 3, 7B, 16C **AXIS II CODES:** 31, 64, 66, 77

ABSTRACT

The identification of the major viral coreceptors CCR5 and CXCR4 provided insight into the mechanism of viral entry; however, the paradox of the "phenotypic switch" observed in HIV infection remains unsolved. To study the mechanism of CCR5 viral dominance, we generated pathogenic chimeric envelope SHIVs that are specific for CCR5, SHIVSF162P3, or CXCR4, SHIVSF33A. When inoculated singly into naïve rhesus macaques, SHIVSF162P3 and SHIVSF33A transmitted and replicated with comparable efficiencies. Results obtained from individually infected macaques served as baseline data for coinfection experiments designed to model natural HIV-1 infection with a mixture of CCR5- and CXCR4 using viruses.

Naïve rhesus macaques were inoculated either intravenously (IV) or intravaginally (IVAG) (seven macaques per group) with a mixture of SHIVSF162P3 and SHIVSF33A isolates. Immediately after inoculation both CXCR4- and CCR5-specific viruses were readily amplified from the plasma of coinfected animals with no obvious barrier to CXCR4 viral transmission or replication noted. Within three to six weeks, a time coincident with the onset of acquired anti-viral immunity, CCR5 viruses dominated in macaques with high viral set-points. Animals with low viral set-points did not consistently replicate either virus. To investigate whether CTLs differentially control CXCR4 and CCR5 viral replication in dually-infected macaques, animals were experimentally depleted of CD8+ T cells and the genotype of replicating virus was noted. A dramatic change in the genotype of circulating virus was observed, such that in the absence of CD8+ T cells a burst of CXCR4 virus replication was observed. Furthermore, CD8+ T-cell depletion resulted in an increase in the absolute level of plasma viremia, albeit to varying degrees in each animal.

SPECIMENS TO OUTSIDE COLLABORATORS (0683)

NPRC UNIT: COLLABORATIVE RESEARCH

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BLANCHARD, JAMES L	DVM, PHD	C	COLLABORATIVE RESEARCH	
	PHD	A	BACTERIOLOGY	VETERINARY RESEARCH INSTITUTE, CZECH
	PHD	A	MICROBIOLOGY	YALE UNIVERSITY, CT USA
	PHD	A	MICRO/IMMUNO/PARASIT	LSU HEALTH SCIENCES CENTER, LA USA
	PHD	A	PHYSIOLOGY	LSU MEDICAL CENTER, LA USA
	PHD	A	MICRO & IMMUNO	UPSTATE MEDICAL SCHOOL, NY USA
	PHD	A	DEPARTMENT OF BIOLOGY	UNIV. OF NORTH CAROLINA/CHARLOTTE, NC USA
names		A		UNIVERSITY OF NEW ORLEANS, LA USA
	PHD	A		TULANE UNIVERSITY, LA USA
	PHD	A		BAYLOR COLLEGE OF MEDICINE, TX USA
	PHD	A	VIRAL PATHOGENESIS	BETH ISRAEL DEACONNESS, MA USA
	MD	A		ABGENIX, INC., CA USA
	PHD	A		BETH ISRAEL DEACONNESS HOSPITAL, MA USA
	PHD	A	MICROBIOLOGY/IMUNOLOGY	TUHSC, LA USA
	MD	A	OPHTHALMOLOGY	TULANE SCHOOL OF MEDICINE, LA USA
	PHD	A	ORTHOPAEDICS	TULANE UNIVERSITY MEDICAL CENTER, LA USA
	PHD	A		UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL, MA USA
	MD	A		ST. JUDE CHILDEN'S RESEARCH HOSPITAL, TN USA
	PHD	A	INFECTIOUS DISEASE/CLINICAL BI	ABBOT LABORATORIES, IL USA
	PHD	A	TULANE CANCER CENTER	TULANE UNIVERSITY, LA USA
	PHD	A		EUROPEAN VETERINARY LAB, THE NETHERLANDS
	DVM, PHD	A		UNIVERSITY OF NEBRASKA VET SCHOOL, NE USA
	PHD	A		WISTAR INSTITUTE, PA USA
	PHD	A		WA NATIONAL PRIMATE RES. CENTER, WA USA
	PHD	A	MICROBIOLOGY/IMMUNOLOGY	TULANE UNIVERSITY MEDICAL CENTER, LA USA

		A		ADARC, NY USA
	MD	A	NEUROLOGY	UNIV. OF PENNSYLVANIA, PA USA
	PHD	A	BIOLOGICAL SCIENCES	LOUISIANA STATE UNIVERSITY, LA USA
	PHD	A	DE BIOCHIMIE MEDICALE	CENTRE MEDICALE UNIVERSITAIRE, SWITZERLAND
	PHD	A	OB/GYN	TULANE UNIVERSITY HEALTH SCIENCES CENTER, LA USA
	PHD	A		ONPRC, OR USA
		A		ST. JUDES CHILDREN'S RESEARCH HOSPITAL, TN USA
	PHD	A		UNIVERSITY OF WASHINGTON, WA USA
	PHD	A	BIOLOGICAL SCIENCES	UNIVERSITY OF CINCINNATI, OH USA
	PHD	A		WEILL MEDICAL COLLEGE, NY USA
names	PHD	A		MEDIMMUNE, INC., MD USA
	MD	A	PEDIATRICS INFECTIOUS DISEASES	UCLA SCHOOL OF MEDICINE, CA USA
	PHD	A		NORTHWESTERN UNIVERSITY SCHOOL OF MEDICINE, IL USA
	PHD	A	PHARMACOLOGY	TULANE UNIVERSITY, LA USA
	PHD	A		HARVARD UNIV. SCHOOL OF PUBLIC HEALTH, MA USA
		A		AUDUBON CENTER, LA USA
	MD	A		BETH ISRAEL DEACONESS MEDICAL CENTER, MA USA
	PHD	A	BIOCHEMISTRY	TULANE SCHOOL OF MEDICINE, LA USA
	MD	A	RETROVIRAL PATHOGENESIS	NCI FREDERICK, MD USA
	PHD	A		SCIENTIFIC DEVICE, IL USA
	PHD	A	CHEMICAL ENGINEERING	FLORIDA STATE UNIVERSITY, FL USA
	PHD	A	VACCINE RESEARCH CENTER	NIH, MD USA
	PHD	A		DUKE UNIVERSITY MEDICAL CENTER, NC USA
	PHD	A	DEPT OF RESEARCH	BETH ISRAEL DEACONNESS MED CTR, MA USA
	MD	A	MAGEE-WOMENS RES. INST	PITTSBURGH DEVE. CENTER LAB, PA USA
	DVM, PHD	A	MICROBIOLOGY AND IMMUNOLOGY	TULANE UNIVERSITY HEALTH SCIENCES CENTER, LA USA
	MD	A		CHILDREN'S HOSPITAL, LA USA
	PHD	A	MICROBIOLOGY	UNIVERSITY OF PENNSYLVANIA, PA USA
		A		UNIVERSITY OF WISCONSIN HOSPITAL, WI USA

PHD	A		BETH ISRAEL DEACONNESS MED CTR, MA USA
PHD	A		BAYLOR UNIVERSITY, TX USA
PHD	A		YALE U SCH MED, CT USA
PHD	A	PATHOBIOLOGY	UNIVERSITY OF WA, WA USA
	A		LA STATE POLICE CRIME LAB, LA USA
DVM, PHD	A		UNIVERSITY OF PENNSYLVANIA, PA USA
MD	A		BETH ISRAEL DEACONNESS MEDICAL CENTER, MA USA
MS, PHD	A	CENTER FOR HUMAN VIROLOGY	THOMAS JEFFERSON UNIVERSITY, PA USA
PHD	A	HUMAN VACCINE INSTITUTE	DUKE UNIVERSITY, NC USA
MD, PHD	A	INFECTIOUS DISEASE	ST MICHAELS MED CTR, NJ USA
	A	FORENSIC LAB	LAS VEGAS METRO POLICE, NV USA
PHD	A	SW MEDICAL CENTER	UNIVERSITY OF TEXAS, TX USA
PHD	A	INSECT PATHOLOGY	LSU, LA USA
PHD	A		UNIVERSITY OF NC, NC USA
MD	A	DEPARTMENT OF PATHOLOGY	UNIVERSITY OF TX MEDICAL BRANCH, TX USA
PHD	A	DE ANATOMIA APATOLGIA	INSITUTO DE MEDICINA TROPICAL, CUBA
PHD	A	SECT. PARASITOLOGY	ACADEMIC MEDICAL CENTER, THE NETHERLANDS
PHD	A		AGRICULT EXPMTL STATION, CT USA
DVM, PHD	A	LAB ANIMAL DIAGNOSTIC CTR	BIORELIANCE CORP, MD USA
PHD	A		CHANNING LABS, MA USA
PHD	A		CHILDREN'S HOSPITAL, OH USA
	A	VET. GENETICS LAB	UNIV. OF CA/DAVIS, CA USA
MD, MPH	A		EINSTEIN UNIVERSITY SCHOOL OF MEDICINE, NY USA
PHD	A	MOLECULAR VIROL & IMMUNO	OHIO STATE UNIVERSITY, OH USA
PHD	A		HARVARD, BETH ISRAEL DEACONESS MED. CTR., MA USA
PHD	A		UNIV. OF PENNSYLVANIA, PA USA
PHD	A		STANFORD UNIVERSITY, CA USA
DVM, PHD	A	SCHOOL OF VET MED/PEDIATRICS	UNIV PA CHILDREN HOSP OF PHIL, PA USA
PHD	A	FCRDCM	NATIONAL CANCER INSTITUTE, MD USA

names

AXIS I CODES: 1D, 13, 14, 15, 16B, 16C, 16D, 16E, 23, 26, 27 **AXIS II CODES:**30, 31, 66

ABSTRACT

One of the primary missions of the TNPRC is to be a national resource. In the current reporting year, 19,549 samples were shipped to 68 institutions. The samples included blood, serum, CSF, semen, DNA preparations,

viral and bacterials stocks, histology slides, bronchoalveolar-lavage flued, and tissue such as cervix, liver, kidney and brain.

CRYPTOCOCCUS NEOFORMANS INFECTION OF RHESUS MONKEYS (0650)

NPRC UNIT: COLLABORATIVE RESEARCH

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BUCHANAN, K	PHD	A		TULANE UNIVERSITY, LA USA
	DVM, PHD	C	COLLABORATIVE RESEARCH	
names	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	
	DVM	C	VETERINARY MEDICINE	

AXIS I CODES: 1A, 9, 24 **AXIS II CODES:** 31, 64, 66

ABSTRACT

Cryptococcus neoformans is an encapsulated yeast-like organism and the causative agent of cryptococcosis. This opportunistic organism does not typically cause symptomatic disease in healthy hosts, but in individuals with decreased cell mediated immunity, such as AIDS (acquired immunodeficiency syndrome) patients, the organism can disseminate from the lungs, via the bloodstream, to the brain, resulting in a life threatening infection. Much of the studies on pathogenesis of cryptococcosis and host defense against C. neoformans have utilized animal models without the immunodeficiency associated with AIDS. Consequently, an animal model incorporating AIDS-like immunodeficiency would be helpful in studying cryptococcosis and host defense against C. neoformans. In this study, we show that a model infection is possible using SIV- (simian immunodeficiency virus) infected Rhesus monkeys. As a proof of concept of this model, 5 previously SIV-infected animals were infected with C. neoformans via two routes-intravenous and bronchially-or a combination of these two routes. The animals were monitored for signs of cryptococcal infection by culturing bronchoaveolar lavage (BAL) and cerebrospinal fluid (CSF) samples. All animals showed signs of infection within 2 weeks post-infection, with varying presentations in individual animals. Signs of infection included: presence of viable C. neoformans yeast in CSF and BAL fluid and/or cryptococcal antigen in CSF and serum. At termination of the experiment (6 weeks), those monkeys that received C. neoformans i.v. demonstrated severe granulomatous inflammation in the brain due to cryptococcal meningoencephalitis; whereas, monkeys that were infected in the lungs exhibited granulomatous inflammation in the lungs due to pulmonary cryptococcosis. The results of this study indicate that the SIV-infected Rhesus model is an excellent means of studying cryptococcal infection in the context of AIDS-like disease.

EFFECT OF AN ANTIRETROVIRAL DRUG AGAINST SIV INFECTION IN RHESUS MACAQUES (0696)

NPRC UNIT: COLLABORATIVE RESEARCH

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LIFSON, JEFFREY	MD	A	RETROVIRAL PATHOGENESIS	NCI FREDERICK, MD USA
names	DVM, PHD	C	COMPARATIVE PATHOLOGY	
	DVM	A		TRIANGLE PHARMACEUTICALS, INC., NC USA

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

ABSTRACT

While antiretroviral drugs have done much to extend the lives of people infected with Human Immunodeficiency Virus (HIV), severe adverse effects and rising levels of drug resistance can limit their usefulness and are driving efforts to develop new anti-HIV medications. In this study we examined the antiretroviral activity of an nucleoside analog called "Antiviral 1" in three Simian Immunodeficiency Virus (SIV) infected rhesus macaques. Animals were inoculated with 100TCID50 of highly pathogenic strain SIVmac251 via intravenous route. Treatment with AA-1 was started on day 62 post inoculation with SIVmac251 and it was given everyday for 28 consecutive days. The dose for AA-1 was 50 mg/kg/day. Cellular immune response, CBC, serum chemistries, viral RNA copies were measured at day 0, 30, 55, 62, 76, 90, 120 and 133-post inoculation and body weight was measured once a week. Body weight and CBC of all three animals were well within the normal range. AST and ALT levels of serum chemistry were two times higher in post treatment than that of pre-inoculation. Viral RNA copies of two macaques were range from 90, 000 to 150, 000 whereas one macaque had 25 millions copies at the end of the study (133days PI). Two animals restored CD4 cells count during and after treatment. Animal which had low CD 4 count also had highest viral load at the end of the study. It is concluded that AA-1 had some effect on cellular immune response and viral load in SIV infected rhesus macaques. Study with more animals need to be done in order to access the effects of this anti retroviral drug.

ANTI-HIV IMMUNOTOXINS (0747)

NPRC UNIT: COLLABORATIVE RESEARCH

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
PINCUS, SETH	MD	A		CHILDREN'S HOSPITAL, LA USA
[illegible]	DVM, PHD	C	COMPARATIVE PATHOLOGY	
[illegible]		A		NATIONAL CANCER INSTITUTE, MD USA

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

ABSTRACT

Introduction: When tested in tissue culture, anti-HIV immunotoxins (ITs) are the most effective anti-HIV agents. Experiments in SCID mice confirm their efficacy. The next step in the development of these agents for human use is testing in non-human primates. Because the ITs must be directed against the HIV Env protein, SHIV infection is the relevant model. These experiments tested the safety, tolerability, and immunogenicity of two different ITs: HY-KDEL and HY-diS. Evidence of efficacy was also sought. Four SHIV 162p-infected macaques, obtained from another study, received weekly IV injections of the ITs. Doses started at 8μg/kg, and doubled each week to a dose of 64μg/kg. Animals were monitored for clinical signs of toxicity, CBC, chem panel, and virus load. No clinical or laboratory evidence of toxicity was observed. A mild anemia developed in all animals (mean hgb dropped from 12.5 to 11.4), but this may have been as attributable to the bleeding of the animals for monitoring as to the IT treatment. All animals showed a drop in proviral DNA loads during the course of the trial. However, this cannot necessarily be attributed to treatment, since there were no control animals. Evidence of immunogenicity was seen in all animals, HY-disHY-KDEL. The two ITs tested were safe and well tolerated at doses higher than the expected therapeutic dose (comparable ITs are effective in human leukemia at doses of 35 μg/kg). Immunogenicity may be a problem. Future studies will examine tolerability at sustained high doses (32-64μg/kg three times per week) and efficacy.

This work was supported by the Research Institute for Children at the Children's Hospital in New Orleans, LA.

THE MUCOSAL DENDRITIC CELL-T CELL MILIEU AND SIV SPREAD (0656)

NPRC UNIT: COLLABORATIVE RESEARCH

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
POPE, MELISSA	PHD	A		POPULATION COUNCIL, NY USA
names	DVM, PHD	C	COLLABORATIVE RESEARCH	
	MD	A	DIRECTOR	AARON DIAMOND AIDS RES, NY USA
	DVM	C	VETERINARY MEDICINE	

AXIS I CODES: 1A, 7B, 18, 22 **AXIS II CODES:**31, 64, 66

ABSTRACT

This study has been critical in defining dendritic cells (DCs) in healthy and infected macaques and in refining procedures to isolates these cells from blood, skin, mucosal tissues, and lymph nodes. Through these experiment we have confirmed how similar macaque DCs are to their human counterparts and that they interact with T cells and SIV in analogous ways as human DCs do with HIV. Specifically, we have shown that the DC-T cell environment represents a site in which virus can propagate in vitro and in vivo. This supports the hypothesis that DCs are central to the capture of virus following mucosal transmission and in establishing and spreading infection. Combined with studies examining attenuated SIV delta nef we are continuing to dissect how DCs facilitate virus replication and how the virus can exploit these features to it's own advantage

AT-2 SIV VACCINATION AFTER DENDRITIC CELL MOBILIZATION (0658)

NPRC UNIT: COLLABORATIVE RESEARCH
%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
POPE, MELISSA	PHD	A		POPULATION COUNCIL, NY USA
	DVM	C	VETERINARY MEDICINE	
names	DVM	C	VETERINARY MEDICINE	
	MD	A	DIRECTOR	AARON DIAMOND AIDS RES, NY USA
	DVM	C	VETERINARY MEDICINE	

AXIS I CODES: 1A, 7B, 18, 22 **AXIS II CODES:**31, 64, 66

ABSTRACT

While both immature and mature monocytes-derived dendritic cells capture and present AT-2 SIV to primed T cells in vitro, mature dendritic Cells activate both CD4 and CD8 T cell but immature dendritic cells predominantly activate CD4 T cells. This supports the rationale for targeting activated dendritic cells with antigen for induction of the most effective immunity. In the last year, we have also identified and characterized the peripheral dendritic cells and mucosal dendritic cells in macaque blood and lymph nodes. These populations appear comparable in naïve and delta nef-infected, wild type-challenged animals. Peripheral dendritic cells and mucosal dendritic cells respond to various stimuli comparable to human dendritic cells and can be mobilized in vivo following treatment with Flt3L. To this end, we have also found that as little as 7 days of Flt3L treatment significantly increases dendritic cell numbers. The peak of the increase in dendritic cell numbers post treatment is under investigation. A study applying AT-2 SIV to the tonsils of naïve macaques revealed that SIV-specific T cells are primed and that pretreatment with immunostimulatory oligodeoxynucleotides (ISS-ODNs; that activate P Dendritic Cells), tends to increase the responses seen.

HIV,TB AND MALARIA VACCINE DEVELOPMENT (0693)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
HAYNES, BARTON	MD	A		DUKE UNIVERSITY, NC USA
	PHD	A		BETH ISRAEL DEACONNESS HOSPITAL, MA USA
names	PHD	A		ALBERT EINSTEIN SCHOOL OF MEDICINE, PA USA
	DVM, PHD	C	DIRECTOR	
	MD	A		BETH ISRAEL DEACONESS MEDICAL CENTER, MA USA

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

ABSTRACT

The overall objective is to perform preclinical studies that are needed to successfully express and test HIV and malaria antigens in an attenuated Mycobacterium tuberculosis (MTB) vector. We ultimately aim to develop a trivalent vaccine for HIV, tuberculosis and malaria in an attenuated MTB. Specific objectives include: (1) Test attenuated strains of MTB for virulence in mice and macaques and test for their ability to protect macaques against challenge with virulent MTB (project 1); (2) Test attenuated MTB-MSP-119 and MSP-142 malaria agents, and test the attenuated MTB-MSP19 and MSP-142vectors for their ability to protect against Plasmodium knowlesi challenge in rhesus macaques (project 2) as proof of principal; (3) Test BCG and attenuated MTB as a vector for expression of HIV antigens of African HIV isolates that induce broadly reactive MHC Class I restricted CTL in mice and rhesus macaques (project 3); 4) Test BCG and attenuated MTB as a vector for expression of HIV envelope constructs that induce broadly reactive neutralizing antibodies to African HIV primate isolates (project 4). Taken together these studies will perform the research needed to determine the feasibility of attenuated MTB expressing HIV and malaria genes as a vaccine for AIDS, Tuberculosis and malaria.

TRANSIENT POST-INOCULATION ANTIRETROVIRAL THERAPY AS A VACCINE FOR SIV (0548)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
VEAZEY, RONALD S.	DVM, PHD	C	COMPARATIVE PATHOLOGY	
names	PHD	A		GILEAD SCIENCES, CA USA
	MD	A	RETROVIRAL PATHOGENESIS	NCI FREDERICK, MD USA
	DVM	C	VETERINARY MEDICINE	

AXIS I CODES: 1A, 7B, 19 **AXIS II CODES:** 31, 50B, 64, 66, 91

ABSTRACT

Like HIV infection of humans, infection of rhesus macaques with pathogenic SIV strains typically results in persistent progressive infection, leading to clinically significant immunosuppression. In previous studies, we administered short term antiretroviral treatment, shortly after i.v. inoculation with SIVsmE660, in an effort to allow immunological sensitization under conditions not characterized by overwhelming cytopathic infection compromising the developing immune response. Control of off treatment viremia was associated, at least in part, with CD8+ lymphocytes, based on in vivo CD8 depletion studies. In the present study, six rhesus macaques were infected intraveously with 100 MID(50) of SIVmac239; four then received 30 days of treatment with tenofovir (PMPA; 20-30 mg/kg, subcutaneously) starting 24 hours post-inoculation. Tenofovir treated animals showed low (500 copy Eq/mL) or undetectable (100 copy Eq/mL) plasma SIV RNA levels during treatment, with undetectable plasma viremia following discontinuation of treatment. Plasma SIV RNA remained 100 copy Eq/mL, even after depletion of CD8+ lymphocytes, six weeks after discontinuation of PMPA treatment. In contrast to untreated infected control animals that showed substantial depletion of CD4+ T cells from Gut Associated Lymphoid Tissues (GALT), tenofovir treated animals showed sparing of GALT CD4+ T cells both during the treatment period and in the off treatment follow up period. However, in contrast to earlier results with animals infected with SIVsmE660, in the present study, the animals did not develop readily measurable cellular anti-SIV immune responses, and did not resist homologous rechallenge with SIVmac239, administered 44 weeks after the initial infection. Comparative analysis of virologic and immunologic parameters in this model system may provide important insights for understanding the basis of effective immunological control of SIV infection.

EVALUATION OF A REVERSE-TRANSCRIPTASE SHIV IN RHESUS MACAQUES (0634)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC $: 0.650%. **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
VEAZEY, RONALD S.	DVM, PHD	C	COMPARATIVE PATHOLOGY	
Lname I	PHD	A	MICROBIOLOGY	YALE UNIVERSITY, CT USA

AXIS I CODES: 1A, 7B **AXIS II CODES:** 31, 39, 50B, 66, 77, 83

ABSTRACT

Although the SIV macaque model of HIV infection in humans is crucial for examining numerous aspects of HIV-1 transmission and pathogenesis, it is somewhat limited in its utility for analyzing responses to certain therapeutic agents, particularly reverse transcriptase (RT) or protease inhibitors. This is due to the facts that ; 1) there are many differences in the sequence of the reverse transcriptase (rev) gene of HIV and SIV, and; 2) point mutations that frequently occur in HIV rev that induce drug resistance do not occur in the SIV rev. Therefore, a hybrid virus that contained the RT of HIV-1 virus but retained the high level replicative capacity of an SIV in macaques could serve as a useful model for studying new reverse transcriptase inhibitors as well as the effects of treatment interruption and combinational drug strategies. Our collaborator [name] at Yale University has created such a virus. This virus contains the most of the genetic structure of the pathogenic molecular clone SIVmac239, with the exceptions of the RT gene, which was derived from HIV-1. The SIVmac239 clone replicates to high titers and causes AIDS in rhesus macaques. If this RT-SHIV virus also results in persistently high viral titers, a new model for treatment strategies may emerge. We have inoculated two rhesus macaques with this virus, and are currently monitoring viral loads and performing viral sequence analysis to determine if this may be a useful model for therapies. We will also monitor the virus to determine whether in may undergo changes in the RT gene. If this virus is replicates to as high levels as SIVmac239 we may also use this virus in studies of viral pathogenesis and microbicide development. To date, we have inoculated 4 macaques with this virus and demonstrated that it is infectious and maintains viral loads for at least 1 year after intravenous inoculation (n=2) and several months after intravaginal inoculation (n=2).

A PRIMATE MODEL FOR LIVER REGENERATION BY MARROW-DERIVED CELLS (0600)

NPRC UNIT: GENE THERAPY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LARUSSA, VINCENT	PHD	A	PHARMACOLOGY	TULANE UNIVERSITY, LA USA
	DVM, PHD	C	COLLABORATIVE RESEARCH	
names	DVM	C	VETERINARY MEDICINE	
	PHD	C	GENE THERAPY	
	DVM	C	VETERINARY MEDICINE	

AXIS I CODES: 1A, 9, 16, 17 **AXIS II CODES:** 39, 55, 74, 77

ABSTRACT

To better understand mechanisms of marrow stem cell engraftment for liver regeneration, and to determine the validity of findings from rodent models mentioned, we have developed a partial hepatectomy model in rhesus monkeys (Macaca mulatta) that is safe and effectively induces liver regeneration and believed to facilitate migration of donor stem cells from extra-hepatic sites after hematopoietic reconstitution. In addition, laparoscopic-guided liver biopsy allows observations of changes in the liver remnant as regeneration develops and provides excellent tissue specimens for analysis. We want to use our combined bone marrow transplant / hepatectomy model that is capable of supporting donor hematopoietic stem cell engraftment and donor liver stem cell engraftment with liver regeneration. Our goal is to examine the engraftment potential of both CD34+Lin- hematopoietic stem cell preparations from male donor marrow and peripheral blood as well as novel NGFR+ cells believed to represent non-clonogenic (hematopoietic and non-hematopoietic) and clonogenic non- hematopoietic progenitor cells that express nerve growth factor receptor, NGFR from male donor marrow.

Specific Aim 1: We shall first determine whether liver-regenerating cells can be mobilized with G-CSF. Male donor, CD34+/-, Lin- cells from G-CSF mobilized PBPC will be used in a dose responsive manner (10, 100, 1000, 10,000, 100,000/KG) to ensure liver engraftment by SRY+ CD34+/-, Lin- donor cells co-transplanted with autologous G-CSF mobilized PBPC containing 2X10 6 CD34+ cells/KG recipient body weight.

Specific Aim 2: Will involve examination for competitive-liver repopulation by donor CD34+, Lin- or non-hematopoietic NGFR+ marrow cells against autologous CD34+, Lin- marrow cell population since the engrafting population is believed to be a marrow derived stem cell and not in the autologous CD34+ PBPC population which is used only to assure hematopoietic engraftment.

Specific Aim 3: Will examine competition between donor hematopoietic CD34+, Lin- against female recipient NGFR+ marrow cells as well as donor NGFR+ marrow cells with female recipient CD34+, Lin- marrow cells.

Over the past year, our group has begun to work out the logistics of performing irradiation and transplantation in adult rhesus.

SAFETY OF MESENCHYMAL STEM CELL ADMINISTRATION TO THE CNS OF RHESUS MACAQUES (0602)

NPRC UNIT: GENE THERAPY

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
PHINNEY, DONALD G	DVM, PHD	A	MICROBIOLOGY AND IMMUNOLOGY	TULANE UNIVERSITY HEALTH SCIENCES CENTER, LA USA
names	PHD	C	GENE THERAPY	
	DVM	C	VETERINARY MEDICINE	

AXIS I CODES: 1A, 9, 16, 17 **AXIS II CODES:**39, 55, 74, 77

ABSTRACT

The overall aim of these studies is to investigate the safety and toxicity of mesenchymal stem cell (MSC) administration directly to the central nervous system of Rhesus macaques. Once the risk assessment of MSCs is complete, their efficacy as therapeutic agents will be directly tested in macaques afflicted with Krabbe's disease, a lysosomal storage disease that causes neurodegeneration in the central and peripheral nervous system. These studies are a necessary step toward development of MSCs as cellular vectors to clinically treat CNS neurodegeneration in human lysosomal storage diseases, and possibly more common disorders like Parkinson's and Alzheimer's disease. We have begun to perform Intracerebral transplants of rhesus MSCs to assess their engraftment and differentiation potential.

COINCIDENT AIDS/RELAPSING MALARIA (0752)

NPRC UNIT: MICROBIOLOGY/IMMUNOLOGY

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
GARRY, ROBERT	PHD	A	MICROBIOLOGY/IMMUNOLOGY	TULANE UNIVERSITY MEDICAL CENTER, LA USA
	PHD	A	MICRO/IMMUNO/PARASIT	LSU HEALTH SCIENCES CENTER, LA USA
	PHD	C	BACTERIOLOGY AND PARASITOLOGY	
	PHD	A	TROPICAL MEDICINE	TULANE UNIVERSITY HEALTH SCIENCES CENTER, LA USA
	MD	A	TROPICAL MEDICINE	TULANE UNIVERSITY HEALTH SCIENCES CENTER, LA USA
	PHD	C	MICROBIOLOGY AND IMMUNOLOGY	

AXIS I CODES: 1A, 1D, 7B, 7C, 17, 19 **AXIS II CODES:** 31, 64, 66, 69, 77, 94

ABSTRACT

Human immunodeficiency viruses and various Plasmodium species have emerged to high prevalence in the same regions of the world, causing intense morbidity and mortality. Yet, little data regarding their interactions are available. We propose an experiment that will guide further definitive studies to establish a primate model of lentivirus and malaria parasite co-infection. The pattern of co-infection we will model is adults living in regions of the world, such as Southeast Asia, that are endemic for P. vivax malaria and are experiencing the most explosive increase in new HIV-1 infections. Our studies will combine well established primate moels for AIDs and malaria: 1) SIV, a lentivirus that establishes a severe immunodeficiency diseae in rhesus macaques and 2) Plasmodium cynomolgi, which causes a relapsing disease resembling malaria induced by P. vivax, the most wide-spread human Plasmodium species. In Specific Aim 1 we propose to conduct a limited pilot study of co-infection with SIV and P. cynomolgi in rhesus macaques. The studies proposed in Specific Aim 2 will examine immunological parameters including lymphocyte subsets, chemokine and cytokine expression, and humoral and cellular immune responses to selected SIV and P. cynomolgi proteins to determine which, if any, of these parameters correlate with progression of SIV disease (Simian AIDS) or P. cynoimolgi malaria in co-infected, singly infected and control animals. The hypotheses underlying the proposed studies are that therelapsing malaria induced by P. cynomolgi will alter the course of simian AIDS induced by SIV in the rhesus monkey and that imunosuppressaion induced by SIV will alter P. cynomolgi growth or relapse. Other hypotheses underlying these studies are that infection with P. cynomolgi will alter immune responses to SIV in the rhesus monkey and that immunosuppression induced by SIV will alter immune responses to the malaria parasite. Results of the proposed experiment will direct further studies that may lead to strategies for improving health care of individuals in regions of the world where there are dual epidemics of AIDS and malaria.

THE PATHOGENESIS OF SHIV-C STRAINS IN MACAQUES (0514)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
CHEN, ZHIWEI	PHD	A		AARON DIAMOND AIDS RES, NY USA
names	MD	A	DIRECTOR	AARON DIAMOND AIDS RES, NY USA
	DVM	C	VETERINARY MEDICINE	

AXIS I CODES: 1A, 7B, 23 **AXIS II CODES:** 31, 64, 66

ABSTRACT

In this study, based on the subtype C viruses, which were selected from the epidemic areas, including India and southwestern China, we have generated two SHIV-C strains. The biological properties of the chimeric viruses have been examined in vitro. They replicated well in human PBMC and used CCR5 but not CXCR4 as a co-receptor. We have established infection and pathogenesis in both macaques species via the intravenous and intravaginal routes.

Both intravenous and intravaginal infection with SHIV-C of M. nemestrina and M. mulatta were achieved. Infected animals are monitored for low CD4+ T cells, virus load in plasma and clinical signs associated with SAIDS.

TESTING OF HIV VACCINE REGIMENS USING A SHIV/MACAQUE MODEL (0515)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
CHEN, ZHIWEI	PHD	A		AARON DIAMOND AIDS RES, NY USA
names	DVM, PHD	C	COLLABORATIVE RESEARCH	
	MD, PHD	A		ADARC, NY USA
	MD	A	DIRECTOR	AARON DIAMOND AIDS RES, NY USA
	PHD	A		ADARC, NY USA

AXIS I CODES: 1A, 7B, 23 **AXIS II CODES:** 31, 64, 66

ABSTRACT

Experimental infection of Asian macaques with selected SIV strains causes a fatal AIDS-like disease. However, because the env genes of simian and human immunodeficiency viruses show significant sequence diversity, the SIV-macaque model has only limited utility for in vivo analyses of phenotypic and immunologic properties of HIV-1 env. HIV-1 itself establishes only a transient infection in Asian macaques without any clinical signs of disease. For these reasons, our group and others have generated recombinant chimeric simian/human immunodeficiency viruses (SHIV). Using our newly generated SHIV/macaque model, we will be able to test various HIV vaccine regimens against infection.

16 macaques were immunized three times intramuscularly (IM) with different SIVgag constructs at 4 sites, left and right triceps and left and right caudal thigh respectively. Immune responses are monitored in plasma and cells.

IMMUNOGENICITY STUDY OF SARS VACCINE IN MONKEYS (SPID) (0724)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
CHEN, ZHIWEI	PHD	A		AARON DIAMOND AIDS RES, NY USA
	DVM	C	VETERINARY MEDICINE	
	MD	A	DIRECTOR	AARON DIAMOND AIDS RES, NY USA

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

ABSTRACT

Immunization with live-attenuated or inactivated vaccine has consistently provided significant protection in animals against challenge with corresponding pathogenic animal coronavirus. However, the promise of this approach has been hampered by serious concerns over the risk of using a live Severe Acute Respiratory Syndrome (SARS) virus in humans, regardless of the degree of attenuation. Thus, we have turned our attention to studying safer alternative vaccine strategies using plasmid DNA and vaccinia viral vectors. In addition to testing of a single immunogen, we will also examine combinations of immunogens to maximize both humoral and cellular immune responses against SARS. We will test the "prime-boost" concept: an initial series of immunizations with one immunogen to prime the immune system and to induce T-cell-mediated responses, including CTL; a subsequent boost with the second immunogen to stimulate B-cell responses, including neutralizing antibodies. In this project, we will develop new immunogens suitable for the priming phase, based on both DNA constructs and modified vaccinia Ankara (MVA), and test them for immunogenicity in macaques. We will also evaluate new immunogens in macaques for boost using soluble proteins, including pseudovirions.

Eight Rhesus macaques, 4 animals per group were immunized intramuscularly at four sites, right and left triceps , right and left cranial thigh with SARS DNA and hepatitis C envelope DNA respectively on day 0 and day 28. Blood, nasal washes, and intratracheal washes were performed in all animals to analyse immune responses.

STUDIES ON ANTIVIRAL EFFECT OF CCR5-TARGETED INHIBITORS OF HIV-1 ENTRY (0727)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
CHEN, ZHIWEI	PHD	A		AARON DIAMOND AIDS RES, NY USA
names	DVM, PHD	C	COLLABORATIVE RESEARCH	
	DVM	C	VETERINARY MEDICINE	
	MD	A	DIRECTOR	AARON DIAMOND AIDS RES, NY USA

AXIS I CODES: 1A, 2, 7B, 17 **AXIS II CODES:** 31, 64, 66

ABSTRACT

To investigate the antiviral properties of a compound developed as a specific antagonist of the human immunodeficiency virus type 1 (HIV-1) entry into immune cells (CD4+ T-cells), mediated via a co-receptor called CCR5. This compound blocks the CCR5 co-receptor, inhibiting HIV-1 entry to CD4+ cells. This is a new class of drug developed specifically to block the co-receptor-CCR5.

A fusion inhibitor peptide (IZN17), a potent HIV-1 inhibitor in vitro was administered intravenously (IV) 10mg/kg pre and post SIV/SHIV infection. Two animals previously infected with SIV were used to establish safety and decay rate of this fusion inhibitor. We found that the half life IZN17 was very short (less than an hour) and were unable to sustain a high plasma concentration after IV injection of IZN17, 10mg/kg. Two additional previously SIV infected animals were injected with 40 mg total of IZN17 subcutaneously (SQ) to achieve a higher concentration and longer half-life of this drug. Based on this, 3 animals infected with SHIVSF33A with high virus load were treated daily for ten days with IZN17 20mg/animal/day. Currently, plasma virus load, CD4/CD8, and virus inhibition are being analyzed.

TESTING OF VAGINAL MICROBICIDES IN SHIV/MACAQUE MODELS (0730)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
CHEN, ZHIWEI	PHD	A		AARON DIAMOND AIDS RES, NY USA
names	MD	A	DIRECTOR	AARON DIAMOND AIDS RES, NY USA
	DVM	C	VETERINARY MEDICINE	

AXIS I CODES: 1A, 7B, 23 **AXIS II CODES:** 31, 64, 66

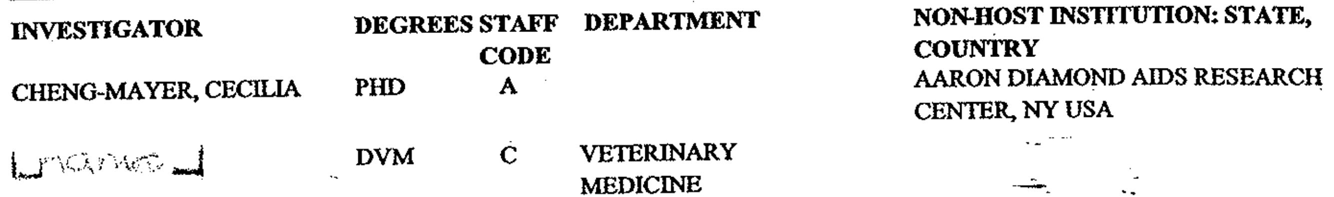
ABSTRACT

Entry efficiency of human immunodeficiency virus (HIV) into genital tissue determines the rate of sexual transmission and influences the course of HIV disease. Blockage of HIV entry into genital mucosa is one of the major strategies in preventing HIV transmission. Since it is not practical to test this strategy in humans, we use a SHIV/macaque model for this purpose. Specifically, we have used a newly developed CCR5-dependent SHIV/macaque model to evaluate the in vivo efficacy of two specific vaginal microbicides in blocking HIV-1 infection via the vaginal route. As the vaginal microbicides were based on inhibitors of both HIV-1 envelope and CCR5 co-receptors, this study provides a new strategy in preventing HIV-1 sexual transmission.

PHENOTYPIC AND GENOTYPIC DETERMINANTS OF SHIV PATHOGENESIS (0725)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650% **AIDS RELATED RESEARCH**



INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
CHENG-MAYER, CECILIA	PHD	A		AARON DIAMOND AIDS RESEARCH CENTER, NY USA
[illegible]	DVM	C	VETERINARY MEDICINE	

AXIS I CODES: 1A, 7B, 16, 23 **AXIS II CODES:** 31, 64, 66, 91

ABSTRACT

As a part of an ongoing effort to define the molecular determinants of viral pathogenesis, we have utilized the chimeric enveloped simian/human immunodeficiency virus (SHIV)/ rhesus macaque model system. We have previously reported the pathogenic consequences of infection with viral isolates that possess distinct phenotypic properties. As a continuation of these studies we performed similar in vivo experiments using molecular clones derived from the isolates SHIVSF162P and SHIVSF33A.

Macaques were exposed to molecularly cloned SHIVs by either the intravenous (IV), intra-vaginal (IVAG) or intrarectal (IR) inoculation routes, and subsequently monitored for levels of plasma viremia, changes in T cell subsets, anti-viral immune responses and viral evolution. These studies are designed to identify discrete sequences within the coding the region of the envelope protein that are responsible for increased viral replication and cytopathicity of SHIVs in addition to analyzing viral determinants that allow for increased evasion of host immune responses.

IN VIVO EVALUATION OF A LUMBAR INTERVERTEBRAL DISC PROSTHESIS (0736)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
COOK, STEPHEN D	PHD	A	ORTHOPAEDICS	TULANE UNIVERSITY MEDICAL CENTER, LA-USA
Lname 1	DVM	C	VETERINARY MEDICINE	

AXIS I CODES: 1A, 26 **AXIS II CODES:** 46, 48, 86

ABSTRACT

Discectomy is a common surgical procedure performed on patients with degenerative disc disease to relieve low back pain. However, removal of the disc alone does not restore normal disc height and results in changes to the biomechanics and compressive stability of the lumbar spine. Replacement of the disc with a prosthetic implant has the ability to restore disc height and normal load distributions to the spine. This study will assess the in vivo feasibility, efficacy, and safety of a new lumbar intervertebral disc replacement and determine the benefit of utilizing a carbon material rather than traditional cobalt chromium metal alloy material on endplate cartilage preservation. The stability of the disc prosthesis without further degeneration will be evaluated using imaging and histologic methods.

8 adult baboons will be utilized. Each animal will receive two intervertebral disc prostheses in the L4-5 and L5-6 disc spaces of the lumbar spine. One prosthetic design will be evaluated in the form of two materials, cobalt chromium metal (control) and pyrolytic carbon (experimental). The prostheses will be placed in the disc spaces through an anterolateral (retroperitoneal) approach. Animals will be evaluated for 26 weeks postoperative and sacrificed. Radiographs will be obtained to assess implant placement, disc height, and endplate morphology and to monitor the implant functionality over time. Histologic analysis of specimens will be performed post-retrieval. Preliminary results show that the lumbar disc may be successfully replaced with an artificial disc replacement in the baboon model. At 12 weeks postoperative, 13 of 14 disc prostheses remain functional. Radiographs showed that one metal control implant migrated anteriorly out of the disc space in the immediate postoperative period without further clinical complication. It was determined that the prosthesis was undersized for the disc space. Imaging and histologic analyses will be conducted at the conclusion of the study.

SALMONELLA AS A VACCINE TOOL AGAINST HIV (0726)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
GURNER, DEBORAH	MD, PHD	A		ADARC, NY USA
	DVM	C	VETERINARY MEDICINE	
names	MD	A	DIRECTOR	AARON DIAMOND AIDS RES, NY USA

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

ABSTRACT

The objective of this study is to evaluate a new vaccine strategy for use against HIV. Attenuated Salmonella typhimurium, which is wholly non-pathogenicserves as a plasmid delivery vehicle in an effective bacterial transduction. The bacteria are first transformed with plasmid vectors bearing viral antigens of interest (in this case, env, gag, pol, and nef). The different bacteria are then pooled together to constitute a polyvalent inoculum, which is administered orally. These bacteria enter the lymphatic system via the gut and invade macrophages. Because they are attenuated, however, they perish promptly after reaching the cytoplasm, releasing the plasmids they carry. This genetic material is then imported into the host cell nucleus and expressed in situ. The antigens are thus manufactured by native macrophages, which go on to present them to the host immune system. We therefore have reason to believe that a measurable (and perhaps protective) immune response will be induced.

STUDY OF VIRAL DYNAMICS IN ACUTE SIV/SHIV INFECTION (0729)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
GURNER, DEBORAH	MD, PHD	A		ADARC, NY USA
names	DVM	C	VETERINARY MEDICINE	
	PHD	A		AARON DIAMOND AIDS RES, NY USA

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

ABSTRACT

Early viral kinetics can be characterized by the "basic reproductive ratio" (R0), the average number of cells infected by the progeny of an infected cell when almost all cells are uninfected. For a vaccine to prevent infection, R0 has to be driven below 1. Thus, the accurate determination of R0 is important to establish targets for successful vaccination. R0 for HIV-1/SIV has only been estimated from virus in plasma; however, most infection occurs in tissue. To obtain an accurate estimate of R0, we studied viral and infected cell dynamics in blood and lymph nodes (LN) in acute SIV infection.

Five (5) rhesus macaques were inoculated with 100 TCID50 of SIVmac251 intravenously. Blood was drawn biweekly for the first 3 wks and weekly thereafter. In each monkey, 3 to 5 lymph nodes from different sites were obtained at 3 time points (day 4/5, day 7/8, and day 11) to study the initial exponential growth of the virus. SIV-RNA and SIV-DNA in plasma, PBMC and LN were measured by real time PCR. Infected cell number in PBMC and LN was estimated by end-point dilution nested PCR.

Plasma virus was detectable on day 4 or 5 after the virus inoculation. Plasma virus increased exponentially during the first 2 wk, reached its peak of 2.5 x 107 to 3.7 x 108 copies/ml between days 13 and 18. The infected cell number in PBMC increased exponentially, Infected cells in LN were detectable in some monkeys on day 4 or 5, and in all by day 7 or 8.. The R0 values of SIVmac251 in acute infection in plasma and LN were estimated in 5 rhesus macaques. The values in LN are larger than the estimates in plasma SIV and provide a quantitative target for vaccine efficiency.

LEPTIN IN BABOON PREGNANCY (0521)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
HENSON, MICHAEL C	PHD	A	OB/GYN	TULANE UNIVERSITY HEALTH SCIENCES CENTER, LA USA

AXIS I CODES: 1A, 23 **AXIS II CODES:** 60, 65, 71, 74E, 74F, 77, 93

ABSTRACT

Introduction: Leptin, produced by both adipose tissue and the placental trophoblast, has been proposed to regulate numerous aspects of human conceptus development. Although recent animal studies have suggested an additional role for the polypeptide in fetal lung maturation, no direct evidence has been reported in primates. Therefore, we employed the baboon (Papio sp.), a well-characterized primate model for human pregnancy, to determine the presence and ontogeny of leptin receptor in fetal lung with advancing gestation.

Methods: Lungs were collected from fetal baboons, early in gestation (days 58-62; n = 4), at mid gestation (days 98-102, n = 4), and late in gestation (days 158-165, n = 4). Term  184 days. mRNA transcripts for leptin and two isoforms of the leptin receptor (LEP-RL and LEP-RS) were assessed by quantitative, competitive RT-PCR. Proteins were evaluated by immunoblotting. Cell types expressing leptin receptor were identified in late pregnancy by in situ hybridization and immunohistochemistry. Fetal serum leptin concentrations were determined by RIA.

Results: Fetal leptin levels (mean ± SEM) ranged from 5.7 ± 1.1 ng/ml in mid pregnancy to 8.4 ± 3.0 ng/ml in late pregnancy (P 0.05). Although leptin mRNA transcripts were detectable in fetal lung, no changes in transcript abundance were apparent with advancing gestation. However, transcripts for both LEP-RL and LEP-RS receptor isoforms increased several-fold (P 0.05) in fetal lung between mid and late gestation, while leptin receptor protein was detectable only in late pregnancy. Leptin receptor was localized in type II/distal pulmonary epithelial cells.

Discussion: In summary, leptin is present in the fetal baboon and its receptor is enhanced during late gestation in fetal lung. This increase, combined with the location of leptin receptor in surfactant-producing cells, suggests a role for the polypeptide in promoting primate fetal lung maturation.

IN VITRO HIV/SIV ASSAYS USING RHESUS MACAQUE BLOOD (0517)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
HO, DAVID D	MD	A	DIRECTOR	AARON DIAMOND AIDS RES, NY USA
	PHD	A		AARON DIAMOND AIDS RESEARCH CENTER, NY USA
	DVM	C	VETERINARY MEDICINE	
	PHD	A		AARON DIAMOND AIDS RES, NY USA
names	PHD	A		AARON DIAMOND AIDS RESEARCH CENTER, NY USA
	PHD	A		ADARC, NY USA
	PHD	A		ADARC, NY USA
	PHD	A		AARON DIAMOND AIDS RES, NY USA
	PHD	A		POPULATION COUNCIL, NY USA
	PHD	A		AARON DIAMOND AIDS RESEARCH CENTER, NY USA
	PHD	A		AARON DIAMOND AIDS RES, NY USA

AXIS I CODES: 1A, 7B, 16C **AXIS II CODES:** 31, 64, 66

ABSTRACT

We are using blood from uninfected and SIV/SHIV infected animals to optimize our assays to test promising fusion inhibitors, study dendritic cell biology and effects of microbicides in vitro. In addition, blood from long term infected animals will be used to document immune correlates and virus dynamics. PBMC from uninfected animals is used for SIV/SHIV virus challenge stock production, co-receptor assays and for testing susceptibility of individual animals to infection using in vitro viral growth kinetics assays.

STUDY OF ANTI-CD40 ANTIBODY AS AN IMMUNOTHERAPY IN SIV INFECTION (0728)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MOHRI, HIROSHI	PHD	A		AARON DIAMOND AIDS RES, NY USA
[illegible]	MD	A	DIRECTOR	AARON DIAMOND AIDS RES, NY USA
	DVM	C	VETERINARY MEDICINE	

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

ABSTRACT

ABSTRACT

Highly active anti-retroviral treatment (HAART) has dramatically improved the quality of life and the survival of HIV-1 infected patients. However, the life-long treatment with these drugs will be daunted by their side effects as well as by the emergence of drug-resistance. Thus, developing an alternative treatment, such as immunotherapy is essential. Activation of CD40 signaling by agonistic antibody that we plan to test its efficacy in this study is a promising strategy to enhance specific immunity in the situation that CD4+ T cell function is damaged, such as in HIV-1 infection. Replacing helper T cells with anti-CD40 antibody may also provide an opportunity to enhance therapeutic as well as preventive vaccination.

Four SIV infected macaques were treated with 0.1 mg/kg Anti-CD40 antibody at two time points, day 0 and day 35. Currently, we are assessing the therapeutic effect on damaged CD4+ T cells.

CHRONIC ALCOHOL & AIDS IMPACT ON MUSCLE WASTING (0745)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MOLINA, PATRICIA E	MD, PHD	A		LSUHSC, LA USA
names	PHD	A	PHYSIOLOGY	LSU MEDICAL CENTER, LA USA
	PHD	A	COLLEGE OF MEDICINE	UNIVERSITY OF PENNSYLVANIA, PA USA
	DVM	C	VETERINARY MEDICINE	

AXIS I CODES: 1A, 7B, 9, 14, 20, 26 **AXIS II CODES:** 31, 46, 57, 64, 66, 77

ABSTRACT

Muscle wasting is a common feature of both chronic alcohol consumption and AIDS. Involuntary weight loss greater than 10% in an HIV-infected individual is a hallmark of AIDS according to the CDC. The AIDS wasting syndrome and the resulting decline in body cell mass remains a major cause of morbidity and mortality, despite the significant improvement in control of HIV-infection with the use of highly active anti-retroviral therapy. Excess alcohol consumption is associated with a 50% incidence of skeletal muscle myopathy resulting from decreased muscle protein synthesis as well as accelerated muscle proteolysis. The effects of alcohol consumption on muscle metabolism appear to be multifactorial. The hypothesis to be tested by the specific aims described in this proposal is that chronic alcohol administration accelerates the progression and exacerbates the severity of muscle wasting associated with simian immunodeficiency virus (SIV) infection by altering the balance between protein anabolic and catabolic mechanisms. The general aim of the studies proposed is to determine the impact of chronic alcohol administration on the temporal progression of whole body, tissue and molecular alterations in body composition, muscle mass and muscle protein synthesis and breakdown, in SIV-infected rhesus monkeys. The studies will (a) determine body composition throughout the course of SIV infection in chronically alcohol-administered monkeys and in parallel, the in vivo rates of muscle protein synthesis and breakdown, as well as (b) the rate-controlling molecular mechanisms involved in both synthetic (eukaryotic initiation factors, myostatin) and degradation (ubiquitin-proteasome) pathways and (c) the recognized endocrine (IGF-I, GH, insulin & testosterone) nutritional (amino acids) and immune (pro-inflammatory cytokines) modulators of muscle mass. The results from these studies will provide detailed knowledge of how alcohol and SIV independently as well as in concert thereby impair the host's cellular metabolic and synthetic mechanisms involved in the regulation of muscle mass.

ALCOHOL, SIV INFECTION AND HOST DEFENSE (0502)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
NELSON, STEVE	MD	A		LSU HEALTH SCIENCES CENTER, LA USA
L names	PHD	A	PHYSIOLOGY	LSU MEDICAL CENTER, LA USA
	DVM	C	VETERINARY MEDICINE	

AXIS I CODES: 1A, 7B, 16, 19 **AXIS II CODES:** 31, 64, 66, 77, 87

ABSTRACT

Alcohol abuse and human immunodeficiency virus (HIV) infection are common and frequently coexist in the same individual. Alcohol consumption has long been known to suppress critical aspects of both innate and specific immunity thereby increasing host susceptibility to infections. HIV infection primarily exerts its pathogenic effects on immune cells expressing CD4 membrane receptor which leads to progressive depletion of the CD4+cells, compromised immunosurveillance, opportunistic infections, and death. Currently, there is little information on how these two immunosuppressive states interact to alter host defense mechanisms directed against both the primary viral infection and/or secondary opportunistic infections. The focus of this project is to determine the impact of alcohol on the progression and sequelae of SIV infection in rhesus monkeys as it relates to the primary infection itself and the development of secondary infections. It is our hypothesis that alcohol functions as a cofactor to accelerate the progression of SIV infection as well as to increase host susceptibility to opportunistic infections which, in turn, will further accelerate progression of SIV infection. This research tests this hypothesis by addressing 3 Specific Aims: 1) To determine the effect of alcohol consumption on primary infection with SIV, progression of SIV infection, and the subsequent development of opportunistic infections. 2) To examine in vivo the separate and combined effects of alcohol consumption and SIV infection on the innate immune system of the lung. 3) To determine the in vivo effect of alcohol consumption on indices of SIV disease progression in response to experimental intrapulmonary infection. Addressing these specific aims in the context of a well-defined and accepted nonhuman primate model of HIV infection will provide novel and important information on the effects of alcohol on altering host defenses to both primary infection with HIV and its progression.

KINETICS OF SIV REPLICATION AFTER INTESTINAL RESECTION (0659)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
POLES, MICHAEL	MD, PHD	A		AARON DIAMOND AIDS RESEARCH CENTER, NY USA
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	MD	A	DIRECTOR	AARON DIAMOND AIDS RES, NY USA

AXIS I CODES: 1A, 7B, 16C **AXIS II CODES:** 31, 64, 66

ABSTRACT

This study quantitatively examines the relative contribution of gastrointestinal mucosal SIV replication to the total amount of replicating virus in the macaque's body. Three macaques which were previously infected with SIV/SHIV and which will have to be sacrificed due to advanced SIV/SHIV disease will be chosen for study. Following anesthesia, these macaques underwent surgical removal of their large intestine and then 75% of their small intestine as a terminal procedure. During the surgery, blood samples were taken from the macaques to determine the amount of SIV virus it contained. Blood samples were studied every five minutes during the surgery and for one hour following surgery, then every 15 minutes for the next 2- 3 hours while the animal was anesthetized.

Three end stage SIV and SHIVSF162p3 infected animals have been used thus far. Sequential pre and post blood samples following colectomy and 75% jejunectomy were collected and analyzed. Results are pending.

BLOCKING VIRUS SPREAD BY DCS WITH CARRAGEENAN-BASED COMPOUNDS (0657)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
POPE, MELISSA	PHD	A		POPULATION COUNCIL, NY USA
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	MD	A		ADARC, NY USA

AXIS I CODES: 1A, 7B, 18, 22 **AXIS II CODES:**31, 64, 66

ABSTRACT

Studies have been initiated to assess the ability of carrageenans to impede AT-2 SIV capture by monocytes-derived dendritic cells and skin-derived dendritic cells (human cells). The phenotype of immature and mature dendritic cells is unchanged following exposure to the carrageenans. Furthermore, pretreatment of cells with carrageenan reduced the amount of virus protein detected
by immunofluorescent microscopy of AT-2 SIV-pulsed dendritic cells, suggesting that carrageenan interfered with virus capture.

VACCINE EFFICACY OF MODIFIED HIV ENVELOPES (0519)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
STAMATATOS, LEONIDAS	PHD	A	SEATTLE BIOMED RES. INST	ADARC, WA USA
names	DVM, PHD	C	COLLABORATIVE RESEARCH	
	DVM	C	VETERINARY MEDICINE	
	DVM	C	VETERINARY MEDICINE	
	MD	A	DIRECTOR	AARON DIAMOND AIDS RES, NY USA

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

ABSTRACT

We continue to design novel HIV envelope immunogens to elicit broad neutralizing antibody responses in rhesus macaques. Our approach is to modify, by eliminating specific glycosylation sites or hypervariable loops, the gp120 subunit of the HIV envelope. The immunogencity of such modified constructs is compared to the unmodified envelope immunogen. We use the DNA-prime followed by recombinant protein-boosting immunization methodology. We monitor the antibody as well as the cellular responses elicited by our various immunogens. To test the protective potential of the immune responses elicited during vaccination, we challenged the animals with the SHIVSF162P4 virus. To specifically evaluate the protective potential of neutralizing antibodies, following the end of the vaccination schedule, macaques are depleted of their CD8+ cells and then challenged with virus. Following challenge we monitor plasma and lymph node viremia, antibody and cellular anti-viral responses, rate of CD4+ T cell-depletion and rate of progression to disease.

A total of 18 animals immunized with the SF162gp140, the DV2gp140, or control vector using the 'DNA-prime plus protein-boost' immunization protocol, were challenged with SHIVSF162P4. We monitored the viral load, CD4+ T cell numbers, cellular-mediated anti-viral responses, as well as the development of neutralizing antibodies. Partial protection, low and sustained virus load and longer survival rate was observed in immunized groups.

DEHYDROEPIANDROSTERONE-SULFATE AS A BIOMARKER OF SENESCENCE IN MALE NHPS (0671)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
SVEC, FRANK		A	MEDICINE	LSU HEALTH SCIENCES CENTER, LA USA
		A	ANTHROPOLOGY	BOSTON UNIVERSITY, MA USA
	PHD	A	ANTHROPOLOGY	YALE UNIVERSITY, CT USA
names	MA	C	VETERINARY MEDICINE	
		A	BIOSTATISTICS	TULANE UNIVERSITY SPHTM, LA USA.
	MPH	C	VETERINARY MEDICINE	
		A	MEDICINE	LSU HEALTH SCIENCES CENTER, LA USA

AXIS I CODES: 1A, 1D, 15, 23 **AXIS II CODES:**34, 74E

ABSTRACT

Numerous studies have suggested important and varying roles for DHEA and DHEA-S in primate physiological functions. Despite these numerous claims, DHEA's specific actions and significance are still equivocal. A decline of these androgens in adult humans may have functional significance, yet there is no clear relationship between functional impairments of aging and the decline in DHEA levels. This current study attempts to address the natural history of adrenal androgens by presenting non-human primate evidence of the endocrinology of aging; the age-related pattern of adrenal androgen decline in three species of the subfamily Cercopithecinae, Macaca mulatta, Macaca nemestrina, and Papio cynocephalus ssp. is compared. It is concluded that DHEA and DHEA-S represent lineage specific markers of senescence among primates and that parallel age-related patterns of DHEA and DHEA-S likely reflect lineage specific effects, or rather, phylogenetic similarities of endocrine senescence. The use of relative adrenal androgen levels to approximate species' life expectancies is discussed.

LEPTIN, BODY COMPOSITION, ADRENAL & GONADAL HORMONES AMONG CAPTIVE MALE BABOONS (0672)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
SVEC, FRANK		A	MEDICINE	LSU HEALTH SCIENCES CENTER, LA USA
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	PHD	A	ANTHROPOLOGY	YALE UNIVERSITY, CT USA
	MA	C	VETERINARY MEDICINE	
		A	BIOSTATISTICS	TULANE UNIVERSITY SPHTM, LA USA
	MPH	C	VETERINARY MEDICINE	
		A	MEDICINE	LSU HEALTH SCIENCES CENTER, LA USA

AXIS I CODES: 1A, 1D, 15, 23 **AXIS II CODES:**34, 74E

ABSTRACT

Morphometric and hormonal measures were collected from 21 captive savanna baboons (Papio cynocephalus) maintained at the Tulane National Primate Research Center in order to determine age-related patterns in leptin levels over the life course as well as their relationships to body composition and adrenal and gonadal steroids. Comparison of leptin levels between peri-pubertal, adolescent, young adult and fully mature males show lower levels among adolescent as compared to young adult males ($p = 0.05$ by Kruskal-Wallis ANOVA). In addition, abdominal fat varied among age groups ($p = 0.003$ by Kruskal-Wallis ANOVA) with the peri-pubertal animals lower than the adolescents, young adults, and prime adults. However leptin was not related to any measure of body composition, including abdominal fat, or to adrenal hormones (dehydroepiandrosterone, dehydroepiandrosterone-sulfate, and cortisol) or gonadal hormones (testosterone and estradiol). Age-related changes in leptin appear similar to those reported for captive rhesus macaques, while the failure to find an association between leptin and abdominal fat is interestingly different. These results confirm elevated levels of leptin in captive baboons compared to their wild counterparts and suggest that they result from changes in fetal development.

ALCOHOL AND HIV INFECTION: ADDITIVE NEUROPHYSCHOLOGICAL EFFECTS (0529)

NPRC UNIT: VETERINARY MEDICINE

%NPRC $: 0.650% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
WINSAUER, PETER J	PHD	A	PHARM/EXPERIMENTAL THERAPEUTIC	LSUHSC, LA USA
	PHD	A	PHARMACOLOGY AND EXP. THERAPY	LSU HEALTH SCIENCES CENTER, LA USA
	PHD	A	PHARM/EXPERIMENTAL THERAPEUTIC	LSUHSC, LA USA
	DVM	C	VETERINARY MEDICINE	

AXIS I CODES: 1A **AXIS II CODES:** 31, 60

ABSTRACT

Alcohol and Human Immunodeficiency Virus (HIV) infection have been shown to produce similar neuropathological profiles, including loss of neurons in the frontal cortex. Additionally, 50-75% of HIV-infected adults are diagnosed with neurological problems, and 20% develop Acquired Immunodeficiency Syndrome (AIDS) dementia. There is also experimental evidence indicating that chronic alcohol consumption potentiates AIDS-related neuropathy. For example, HIV-positive patients who are long-term abusers of alcohol generally have greater neurologic deficits, and chronic alcohol abuse has been reported to produce abnormalities earlier in the HIV process. Alcohol abuse and HIV infection also have additive effects on abnormal brain electrophysiological measurements. However, the relationship between the effects of alcohol and AIDS-related neuronal and cognitive dysfunction require further examination. The studies proposed will test the overall hypothesis that alcohol unmasks neuropsychological deficits in rhesus monkeys infected with simian immunodeficiency virus (SIV). This component will systematically explore the significant interaction that occurred between ethanol and SIV during behavioral testing in the previous funding period and begin to examine the potential role of GABAA and NMDA receptors in that interaction. An important aspect of this research will be the regimen for ethanol administration and the use of SIV, which will control for ethanol consumption in infected subjects while avoiding many uncontrolled variables that frequently compromise clinical studies with humans. These experiments will investigate whether chronic alcohol administration will 1) potentiate neuropsychological deficits produced by SIV in monkeys responding under a complex neuropsychological procedure such as repeated acquisition, 2) produce tolerance to the rate-decreasing and error-increasing effects of alcohol and cross tolerance to behavioral effects of three different, site-specific, positive GABAA modulators in both sham- and SIV-inoculated monkeys, 3) produce cross tolerance to behavioral effects of NMDA receptor antagonists in both sham- or SIV-inoculated monkeys, and 4) reduce effectiveness of antiviral therapy in SIV-infected monkeys.

RESEARCH SERVICES

NAME	NON-HOST INSTITUTION: STATE, COUNTRY	# SPECIES: SPECIMEN
	VETERINARY RESEARCH INSTITUTE	MACACA MULATTA: CELLS
	YALE UNIV SCHOOL OF MED: CT	MACACA MULATTA: TISSUES
	LSU HEALTH SCIENCE CENTER: LA	MACACA MULATTA: TISSUES
	LSU HEALTH SCIENCE CENTER: LA	PAPIO: TISSUES
	LSU MEDICAL CENTER: LA	MACACA MULATTA: TISSUES
	SUNY UPSTATE MEDICAL SCHOOL: NY	MACACA MULATTA: TISSUES
	UNIVERSITY NORTH CAROLINA CHARLOTTE: NC	MACACA MULATTA: OTHERS
	UNIVERSITY NORTH CAROLINA CHARLOTTE: NC	MACACA MULATTA: CELLS
	UNO ACRES: LA	MACACA NEMESTRINA: TISSUES
	TULANE UNIVERSITY MEDICAL SCHOOL: LA	MACACA MULATTA: TISSUES
	TULANE UNIVERSITY MEDICAL SCHOOL	PAPIO: TISSUES
	BAYLOR COLLEGE OF MEDICINE: TX	MACACA MULATTA: TISSUES
	BETH ISRAEL DEACONNESS MEDICAL CENTER: MA	MACACA MULATTA: TISSUES
	BETH ISRAEL DEACONNESS MEDICAL CENTER: MA	PAPIO: TISSUES
	ABGENIX, INC.: CA	MACACA FASCICULARIS: TISSUES
	AARON DIAMOND AIDS RESEARCH CENTER: NY	MACACA MULATTA: TISSUES
	TULANE MEDICAL CENTER: LA	MACACA MULATTA: CELLS
	TULANE DEPT OPHTHALMOLOGY: LA	MACACA MULATTA: TISSUES
	TULANE DEPT OPHTHALMOLOGY: LA	MACACA NEMESTRINA: TISSUES
	TULANE UNIVERSITY MEDICAL SCHOOL: LA	MACACA NEMESTRINA: TISSUES
	UNIVERSITY OF MASS MEDICAL SCHOOL: MA	MACACA MULATTA: TISSUES
	UNIVERSITY OF MASS MEDICAL SCHOOL: MA	MACACA NEMESTRINA: TISSUES
	ST. JUDE CHILDREN'S HOSPITAL: TN	MACACA MULATTA: TISSUES
	ABBOTT LAB: IL	MACACA MULATTA: TISSUES
	TULANE UNIVERSITY CANCER CENTER: LA	MACACA MULATTA: TISSUES
	EUROPEAN VETERINARY LAB	MACACA MULATTA: CELLS
	UNIVERSITY NEBRASKA - LINCOLN: NE	MACACA MULATTA: TISSUES
	UNIVERSITY NEBRASKA - LINCOLN: NE	MACACA NEMESTRINA: CELLS

UNIVERSITY NEBRASKA - LINCOLN: NE	PAPIO: TISSUES
WISTAR INSTITUTE: PA	MACACA MULATTA: OTHERS
UNIV ERSITY WASHINGTON PRIMATE CENTER: WA	MACACA MULATTA: TISSUES
TULANE UNIVERSITY MEDICAL SCHOOL: LA	MACACA MULATTA: TISSUES
TULANE UNIVERSITY MEDICAL SCHOOL: LA	MACACA NEMESTRINA: TISSUES
ADARC: NY	MACACA MULATTA: TISSUES
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AARON DIAMOND AIDS RESEARCH CENTER: NY	MACACA MULATTA: TISSUES
CENTRE MEDICALE UNIV	MACACA MULATTA: TISSUES
TULANE UNIVERSITY MEDICAL SCHOOL: LA	PAPIO: TISSUES
OREGON NATIONAL PRIMATE RESEARCH CENTER: OR	MACACA MULATTA: TISSUES
AARON DIAMOND AIDS RESEARCH CENTER: NY	MACACA MULATTA: TISSUES
ST. JUDE CHILDREN'S HOSPITAL: TN	MACACA MULATTA: TISSUES
ST. JUDE CHILDREN'S HOSPITAL: TN	MACACA NEMESTRINA: CELLS
ST. JUDE CHILDREN'S HOSPITAL: TN	MACACA NEMESTRINA: CELLS
UNIVERSITY WASHINGTON, HSB K: WA	MACACA NEMESTRINA: TISSUES
UNIVERSITY CINCINNATI: OH	MACACA MULATTA: CELLS
WEILL MEDICAL COLLEGE: NY	MACACA MULATTA: TISSUES
[Private funding]	PAPIO: TISSUES
UCLA SCHOOL OF MEDICINE: CA	MACACA MULATTA: TISSUES
NORTHWESTERN UNIVERSITY SCHOOL MEDICINE: IL	MACACA MULATTA: TISSUES
TULANE UNIVERSITY: LA	MACACA MULATTA: TISSUES
HARVARD, SPH: MA	MACACA MULATTA: TISSUES
AUDUBON CENTER: LA	MACACA MULATTA: TISSUES
BETH ISRAEL DEACONNESS: MA	MACACA MULATTA: TISSUES
BETH ISRAEL DEACONNESS: MA	MACACA NEMESTRINA: CELLS
TULANE UNIVERSITY MEDICAL SCHOOL: LA	MACACA MULATTA: TISSUES
NIH SAIC FREDERICK: MD	MACACA MULATTA: TISSUES
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VACCINE RESEARCH CENTER, NIH: MD	MACACA MULATTA: TISSUES
DUKE UNIVERSITY MEDICAL CENTER: NC	MACACA MULATTA: TISSUES

BETH ISRAEL DEACONNESS: MA	MACACA MULATTA: TISSUES
PITTSBURGH DEVE. CENTER LAB: PA	MACACA NEMESTRINA: TISSUES
PITTSBURGH DEVE. CENTER LAB: PA	PAPIO: TISSUES
TULANE UNIVERSITY MEDICAL SCHOOL: LA	MACACA MULATTA: TISSUES
CHILDREN'S HOSPITAL: LA	MACACA MULATTA: TISSUES
CHILDREN'S HOSPITAL: LA	PAPIO: CELLS
UNIVERSITY PENN: PA	MACACA MULATTA: TISSUES
UNIVERSITY WISCONSIN HOSPITAL: WI	MACACA FASCICULARIS: CELLS
UNIVERSITY WISCONSIN HOSPITAL: WI	MACACA MULATTA: TISSUES
BAYLOR COLLEGE OF MEDICINE: TX	MACACA MULATTA: TISSUES
BAYLOR COLLEGE OF MEDICINE: TX	MACACA NEMESTRINA: CELLS
YALE UNIVERSITY SCHOOL MEDICINE: CT	MACACA MULATTA: TISSUES
UNIVERSITY OF WASHINGTON: WA	MACACA NEMESTRINA: TISSUES
LOUISIANA STATE POLICE CRIME LAB: LA	MACACA MULATTA: TISSUES
LOUISIANA STATE POLICE CRIME LAB: LA	MACACA NEMESTRINA: TISSUES
UNIVERSITY PENN: PA	MACACA MULATTA: CELLS
BETH ISRAEL DEACONNESS MEDICAL CENTER: MA	MACACA MULATTA: TISSUES
THOMAS JEFFERSON MEDICAL SCHOOL: PA	MACACA MULATTA: TISSUES
DUKE UNIVERSITY: NC	MACACA MULATTA: TISSUES
ST. MICHAEL'S MEDICAL CENTER: NJ	MACACA MULATTA: TISSUES
LAS VEGAS METRO POLICE DEPARTMENT: NE	CERCOPITHECUS AETHIOPS: TISSUES
LAS VEGAS METRO POLICE DEPARTMENT: NE	ERYTHROCEBUS PATAS: TISSUES
LAS VEGAS METRO POLICE DEPARTMENT: NE	PAPIO: TISSUES
LAS VEGAS METRO POLICE DEPARTMENT: NE	MACACA NEMESTRINA: TISSUES
LAS VEGAS METRO POLICE DEPARTMENT: NE	MACACA MULATTA: TISSUES
UNIVERSITY TEXAS SOUTHWEST MEDICAL CENTER: TX	MACACA MULATTA: TISSUES
LSU LAB INSECT PATHOLOGY: LA	MACACA MULATTA: OTHERS
LSU LAB INSECT PATHOLOGY: LA	MACACA MULATTA: CELLS
AARON DIAMOND AIDS: WA	MACACA MULATTA: TISSUES
AARON DIAMOND AIDS: WA	MACACA NEMESTRINA: CELLS

UNIVERSITY OF NORTH CAROLINA: NC	MACACA MULATTA: TISSUES
UNIVERSITY OF NORTH CAROLINA: NC	MACACA NEMESTRINA: CELLS
UNIVERSITY TEXAS: TX	MACACA MULATTA: TISSUES
UNIVERSITY TEXAS: TX	PAPIO: TISSUES
UNIVERSITY TEXAS: TX	MACACA NEMESTRINA: TISSUES
INSTITUTI DE MEDICINA TROPICAL	MACACA MULATTA: CELLS
ACADEMIC MEDICAL CENTER	MACACA MULATTA: CELLS
CONNECTICUT AGRI. EXPER. STATION: CT	MACACA MULATTA: TISSUES
[Private funding]	MACACA MULATTA: TISSUES
CHANNING LABS: MA	MACACA NEMESTRINA: TISSUES
CINCINNATI CHILDREN'S HOSPITAL: OH	MACACA MULATTA: TISSUES
UNIVERSITY CALIFORNIA - DAVIS: CA	MACACA MULATTA: TISSUES
UNIVERSITY VERMONT COLLEGE MEDICINE: VT	MACACA: CELLS
BETH ISRAEL DEACONNESS MEDICAL CENTER: MA	MACACA MULATTA: CELLS
HARVARD, BETH ISRAEL DEACONNESS MEDICAL CENTER: MA	MACACA MULATTA: TISSUES
STANFORD UNIVERSITY: CA	MACACA NEMESTRINA: TISSUES
UNIVERSITY PENN CHILDREN'S HOSPITAL: PA	MACACA MULATTA: TISSUES
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NATIONAL CANCER INSTITUTE: MD	MACACA MULATTA: TISSUES

PUBLISHED: ABSTRACTS, BOOKS & JOURNALS

‡ NPRC Cited *NPRC Personnel

SPIDs		Reference
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‡ NPRC Cited *NPRC Personnel

SPIDs	Reference
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0564	‡ [In press publication]
0715	‡ [In press publication]
0681	‡ [In press publication]
Books	
0568, 0749	‡ [In press publication]
0567, 0626	‡ [In press publication]
0749	‡ [In press publication]
0626	‡ [In press publication]
Journals	
0519	‡ [In press publication]
0505	‡ [In press publication]
0749	‡ [In press publication]
0567, 0623	‡ [In press publication]
0073	‡ [In press publication]
0626	‡ [In press publication]
0689	‡ [In press publication]
0600	‡ [In press publication]
0756	‡ [In press publication]
	‡ [In press publication]
0748	‡ [In press publication]

0580 ‡ [In press publication]

0657 ‡ [In press publication]

0743 ‡ [In press publication]

0561 ‡ [In press publication]

‡ [In press publication]

0073, 0714 ‡ [In press publication]

0567 ‡ [In press publication]

0599 ‡ [In press publication]

0703 ‡ [In press publication]

0760 ‡ [In press publication]

0709 ‡ [In press publication]

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0521 ‡ [In press publication]

0758 ‡ [In press publication]

‡ [In press publication]

0658 ‡ [In press publication]

0603 ‡ [In press publication]

0626 ‡ [In press publication]

SOURCE OF INVESTIGATORS' SUPPORT

NON-FEDERAL

FOUNDATION

INVESTIGATOR ORGANIZATION	GRANT/CONTRACT		TOTAL FUNDING	SPID
BAKER, KATE C				
[private funding]		$	18,461	0662
BUNNELL, BRUCE A				
[private funding]		$	50,000	0748
[private funding]	701M2	$	95,148	0748
CHEN, ZHIWEI				
IAVI		$	0	0514,0515
[private source]				0517
DAVISON, BILLIE B				
PREMA-EU	ICA4-CT-2001-10012			0714
HO, DAVID D				
[private]	PALLOTTA	$	0	0517,0659
[private funding]	4-02	$	0	0517,0658
LACKNER, ANDREW A				
[ ]		$	100,000	
MARTIN, LOUIS N				
[ ] private funding		$	604,269	
PANDREA-VASILE, IVONA				
[				0723
]				0766
PINCUS, SETH				
[private funding]				0747
POPE, MELISSA				
[private funding]	PG50999	$	0	0656,0658
RATTERREE, MARION S				
[private]		$	31,431	
	FOUNDATION	$	899,309	

INDUSTRY

INVESTIGATOR ORGANIZATION	GRANT/CONTRACT		TOTAL FUNDING	SPID
AYE, PYONE P				
[ ]		$	42,211	
PHILIPP, MARIO T				
[ ] private funding		$	215,000	
RATTERREE, MARION S				
[ ]		$	42,900	
TRAINA-DORGE, VICKI L				

[private source]

INDUSTRY	$	300,111	0754

OTHER NON FEDERAL

INVESTIGATOR ORGANIZATION	GRANT/CONTRACT		TOTAL FUNDING	SPID
BUNNELL, BRUCE A				
[ ]		$	45,000	
	HEF2001-206	$	44,124	0600,0601,0602
COOK, STEPHEN D				
[ ]		$	0	0505,0736
NELSON, STEVE				
[ ]	MILLENIUM	$	702,000	0643
PHINNEY, DONALD G				
[ ]	HEALTH EXCELLENCE FUND	$	646,415	0507,0602
SESTAK, KAROL				
[private funding]		$	50,000	0507,0681
[private]		$	0	0620
WINSAUER, PETER J				
	ARC FUNDS	$	0	0529
	OTHER NON FEDERAL	$	1,487,539	

private funding

FEDERAL

INVESTIGATOR ORGANIZATION	GRANT/CONTRACT		TOTAL FUNDING	SPID
FEDERAL - NON PHS				
[ ]				
DOD		$	720,000	0748
SESTAK, KAROL				
USDA	2002-35204-11650	$	49,360	0568
[ ]				
DOD	DAAD 19-01-045	$	134,879	0691
DOD	DAMD 170210198	$	260,750	0691
	FEDERAL - NON PHS	$	1,164,989	
FEDERAL - PHS				
AMEDEE, ANGELA M				
NIH	5R01DE012916-05	$	202,381	0731
[ ]				
NIH	5U24RR018114-02	$	956,922	0677
BAGBY, GREGORY				
NIH	3T32AA007577-05S1	$	54,009	0643,0774
NIH	5T32AA007577-05	$	273,978	0502,0545,0745,0774
NIH	3T32AA007577-04S1	$	51,896	0545,0643,0774

Name / Sponsor	Grant		Amount	Code
NIH	1R21AI049118-01A2	$	306,638	0683
NIH	1R21AI056923-01	$	228,000	
NIH	5R03AI052809-02	$	76,000	
NIH	5R01AI044935-04	$	244,933	0755
NIH	5R01AI026815-17	$	334,125	0024
NIH	5U42RR014905-05	$	1,290,605	
NIH	5R24RR014034-04	$	295,490	
NIH	5T35RR007067-04	$	53,623	
NIH	5T32RR007038-16	$	278,935	
NIH	1R13RR018354-01	$	31,918	
NIH	5R24RR015395-02	$	327,656	0740
BEILKE, MARK A				
NIH	5R01AI049744-02	$	359,125	0108
NIH	5R01AR040445-14	$	376,250	
NIH	4R37AI027044-15	$	338,625	
BLANCHARD, JAMES L				
NIH	G20RR017029	$	699,655	0646
NIH	G20RR016930-01	$	699,950	0647
NIH	5U42RR016026-03	$	806,832	0648
BOHM, RUDOLF P				
NIH	5U24RR018111-02	$	1,747,006	0648,0734
NIH	5R01AI047181-03	$	162,500	0683
NIH	5R01AI032976-10	$	227,500	0683
BUNNELL, BRUCE A				
NIH	5R01AI047693-04	$	344,972	0599
NIH	5R01AI052057-02	$	774,821	0048
NIH	5U01AI048494-04	$	368,686	
NIH	5R01AI048053-04	$	310,275	
NIH	5R37AI033292-12	$	498,748	
NIH	1R01AI055332-01	$	771,584	0048
NIH	5R21CA096951-02	$	150,500	
NIH	5R01CA025215-23	$	379,564	0683
NIH	5P30AI036211-10	$	856,457	0683
NIH	5R01HL064560-05	$	609,000	0683
CHENG-MAYER, CECILIA				
NIH	5P01HD041761-03	$	325,603	0651
NIH	5R01CA072822-15	$	311,500	0651
NIH	5R01AI046980-04	$	480,367	0517,0653
NIH	5R37AI041945-07	$	432,899	0517,0725

Name / Agency	Grant	$	Amount	Codes
NIH	1R43AI056847-01	$	298,424	0681
NIH	1R43AI051918-01A1	$	125,499	
NIH	1U01AI056452-01	$	1,027,810	0678,0683
NIH	1R21AI055013-01	$	297,000	0678,0683
NIH	5R01CA094084-02	$	258,100	
NIH	5R01CA086881-04	$	226,013	0637
NIH	5R01CA094084-03	$	258,100	
NIH	5R01HL067962-03	$	385,581	0637
CURIEL, TYLER J				
NIH	5R21AI044322-02	$	0	0637
DAVISON, BILLIE B				
NIH	5R01AI042400-04	$	326,543	0073,0507,0636,0714
NIH	5R01GM045668-11	$	259,875	0683
NIH	5R37AI025328-17	$	443,111	
NIH	5R01AI050421-03	$	382,500	0770
DIDIER, ELIZABETH S				
NIH	R01 AI39968	$	250,000	0626
NIH	N01-AI75327	$	193,046	0567,0568,0623
NIH	R01-AI46307	$	64,173	0567,0623,0749
DIDIER, PETER J				
NIH	1R01RR014177-03	$	0	0715
NIH	5R01AI040880-07	$	391,152	0048,0635
NIH	5T32AI007632-04	$	314,975	
NIH	1T32AI055400-01	$	228,826	
NIH	5R01AI050469-03	$	396,250	0048,0635
NIH	5R01AI049200-03	$	327,000	0024
NIH	1R21AI055618-01	$	245,250	
NIH	1R01AI055749-01	$	109,001	
NIH	2R01AI032947-11	$	408,750	0024
NIH	1R21AI054630-01	$	245,250	0024
NIH	2R01AI041440-06	$	408,750	
NIH	5R21AI054233-02	$	255,000	0692
NIH	5R01AI035513-10	$	498,250	0692
NIH	5U01AI027668-17	$	1,478,841	0547
GARRY, ROBERT				
NIH	1R21AI054238-01A1	$	222,750	0683
NIH	1R01RR018229-01A1	$	540,471	0752
NIH	1R01AI054626-01	$	259,875	0683

NIH	5T32NS007321-15	$	215,585	
NIH	5R37AG006127-17	$	467,307	0580
NIH	5P01NS032623-15	$	1,107,873	0580
NIH	5R01HL027255-21	$	228,541	0744
NIH	1R01HL075321-01	$	284,000	
NIH	5R01HL027737-22	$	186,875	0744
GONZALEZ, R. GILBERTO				
NIH	5R01NS034626-07	$	0	0595,0689
NIH	2T35HL007789-11	$	183,177	
NIH	2T32NS007180-22	$	209,006	
NIH	5P01NS027405-15	$	1,192,392	
NIH	5R01NS035743-08	$	278,700	0719
NIH	5R01MH067734-02	$	482,127	0683
NIH	1R01AI052373-01A1	$	306,805	0753
NIH	5R01AI050529-03	$	595,597	0561,0604,0761
NIH	5R21AI046278-02	$	0	0517
HAYNES, BARTON				
NIH	5P01AI052816-02	$	3,057,151	0693
NIH	1U54AI057157-01	$	4,207,052	0691
NIH	5P30AI051445-02	$	2,164,111	
NIH	5P01AI035351-09	$	1,004,634	
NIH	1P01AI052816-01A1	$	1,632,606	0693
HO, DAVID D				
NIH	U01AI048013	$	737,625	0727
NIH	5P30AI042848	$	0	0514,0515,0517,0519,0652,0656,0657,0658,0659
NIH	5R01AI049784-03	$	758,178	0692
NIH	5R01AI045378-05	$	466,665	0692
NIH	5P30AI045008-05	$	1,425,153	0692
HURWITZ, JULIA L				
NIH	5P01AI045142-05	$	1,191,222	0688
NIH	5R44AI045267			0109
NIH	5R01AI043890-06	$	422,500	
NIH	2R01AI043890-05A1	$	224,620	
NIH	5R01AI049809-03	$	294,690	0769

Investigator / Sponsor	Grant Number		Amount	Codes
NIH	5R01AI033325-12	$	248,500	0626
NIH	1T35RR017504-01A1	$	47,883	0774
NIH	1R21AI060463-01	$	191,458	0683
NIH	5R01AI051996-02	$	700,144	0683
NIH	1R01AI051996-01A1	$	718,554	0683
KUBISCH, H. MICHAEL				
NIH	R29HD036421	$	111,711	0743
NIH	5D43TW001587-04	$	144,751	
NIH	5R01AI047089-04	$	301,600	0534
NIH	5R01AI046760-04	$	363,325	
KURODA, MARCELO				
NIH	5R01AI048400-03	$	464,530	0640
LACKNER, ANDREW A				
NIH	5R01NS030769-13	$	365,152	0595,0770,0772
NIH	1C06RR017563-01A1	$	2,499,064	0646
NIH	5R01MH061192-06	$	293,022	0595,0689,0770,0772
NIH	5R01DK050550-10	$	480,651	0587,0589,0690,0770,0772
NIH	1G20RR018397-01	$	697,400	0737,0738
NIH	5R01HL066443-03	$	304,454	
NIH	5R01GM038032-17	$	272,960	0745
NIH	5R01AA011290-08	$	280,282	0745
NIH	5R21HL072088-02	$	183,250	0748
NIH	5P51AI051649	$	1,547,262	0547,0633
NIH	3P30AI036219-10S1	$	750,000	0547
NIH	2R01AI020729-21	$	663,778	0683,0693
LEVY, LAURA S.				
NIH	5R01CA083823-04	$	224,978	
NIH	5R01CA074731-05	$	258,805	0056
NIH	5R01NS009626-34	$	392,980	0683
NIH	2R01NS009626-33	$	389,427	0683
MACLEAN, ANDREW				
NIH	5R21AA013828-02	$	160,000	0594,0642,0643,0772
NIH	5R01AI046307-05	$	432,300	0567
MARX, PRESTON A				
NIH	N01AI025458	$	197,947	0757
NIH	5R01AI041952-07	$	580,288	0559

NIH	5R01AI044596-06	$	629,175	0559,0561,0723,0758,0762,0763,0764,0765,0767,0769
NIH	5R24RR016986-02	$	602,611	0604
NIH	5R01MH062962-03	$	335,502	0595,0689
NIH	5R01MH062962-02	$	335,502	0595,0689
NIH	5R01AG018440-03	$	321,480	0595,0689
NIH	5R01HL065937-04	$	240,000	0604,0769
MOHAMADZADEH, MANSOUR				
NIH	5R21DA016029-02	$	148,500	0713
MOLINA, PATRICIA E				
NIH	5R01AA013543-02	$	370,054	0642,0643,0745
NIH	3R01AA013543-01S1	$	12,350	0745
NIH	1R13AI053895-01	$	0	0678
NIH	5P01AI052048-03	$	1,364,201	0048,0633,0635
NIH	5R01AI045463-06	$	486,773	
NIH	5R01AI041420-08	$	423,750	0048,0633,0635
NIH	1R21AI054159-01	$	291,740	
NIH	4R37AI036082-11	$	404,985	
NIH	1R03HD045768-01	$	74,250	0713
NIH	5P40RR001240-24	$	120,000	
NIH	1R13RR018632-01	$	71,413	
NIH	1G20RR018389-01	$	699,384	
NIH	P51RR000166	$	0	0677
NIH	5R01AI046149-04	$	317,677	0589
NIH	1R21AI052773-01A1	$	366,883	0755
NIH	5R01AI049497-03	$	172,765	
NIH	1U01AI057313-01	$	237,679	
NIH	9R44RR019845-02A1	$	986,376	0715
NIH	5P20RR016443-03	$	2,123,599	
NIH	5R01AI051220-02	$	712,734	
NIH	5P51RR000166-42	$	13,155,676	0677
NELSON, STEVE				

Name / Agency	Grant		Amount	Codes
NIH	5P50AA009803-10	$	1,755,879	0642,0643
NIH	5P01HD041761-03	$	1,114,849	0651
NIH	1K08AI060380-01	$	112,779	0683
NIH	5R01AI046254-06	$	306,289	
NIH	5R01AI052731-02	$	398,000	
NIH	5R01AI044595-06	$	352,032	0760
NIH	5U01CA086739-04	$	86,179	0567
PHILIPP, MARIO T				
NIH	5R01AI049976-03	$	148,000	0538
CDC	U50CCU606604	$	167,241	0025,0699,0705,0706,0707,0708
NIH	5P01HD041752-03	$	1,515,688	0657
PHINNEY, DONALD G				
NIH	5R01NS039033-03	$	259,875	0507,0602,0683
PINCUS, SETH				
NIH	1R01AI059376-01	$	279,580	0747
NIH	5R01AI041899-07	$	274,750	
NIH	5R01NS044513-02	$	298,300	
NIH	5R01NS041864-04	$	318,000	0589
NIH	5R21AA013849-02	$	157,000	
POPE, MELISSA				
NIH	1R01DE015512-01	$	520,051	0048,0657
NIH	5R01AI040877-07	$	751,768	0517,0656,0658
PROCKOP, DARWIN				
NIH	5R01AR048323-03	$	371,250	
NIH	1R01HL073755-01	$	450,544	0601
NIH	1R01HL073252-01	$	371,250	
NIH	1P40RR017447-01	$	814,806	0601
RAMAMOORTHY, RAMESH				
NIH	5R01AI049293-02	$	200,000	0061
NIH	5R24RR016001-04	$	693,540	0683
ROBINSON, PREMA				
NIH	1R01NS042604-01A2	$	249,336	0694
NIH	1R21AI054205-01	$	209,680	0694
NIH	2R37AI040357-08	$	163,500	0683
NIH	2R01AI045510-05	$	637,975	0760
NIH	5R01CA091760-03	$	303,579	0683

NIH	3R01CA091760-02S1	$	100,000	0683
NIH	5R01RR013154-07	$	380,000	0683
NIH	5K02AI049275-03	$	98,658	0683
NIH	1R21AI053343-01A1	$	317,000	0683
NIH	5R01AI048394-03	$	496,777	0052,0683
SCHNELL, MATTHIAS J.				
NIH	5R21AI051170-02	$	292,865	0575,0683
NIH	5R01AI049153-03	$	357,750	0589,0757
SESTAK, KAROL				
NIH	5R43AI056847-01	$	281,040	0507
NIH	1R21AI054146-01A1	$	247,500	0678
NIH	2R01AI035522-11A1	$	194,802	0683,0757
NIH	5R01DE012926-05	$	290,579	0683,0758
STAMATATOS, LEONIDAS				
NIH	5R01AI051217-03	$	586,676	
NIH	5R21AI053810-02	$	268,500	
NIH	5R01AI047708-05	$	324,527	0519
NIH	1R01HL075766-01	$	759,317	0769
NIH	1R21AI054260-01	$	400,000	
NIH	5U01HL069748-03	$	562,169	0599
NIH	3U01HL069748-03S1	$	59,650	
NIH	1R01HL073220-01	$	323,250	
NIH	1R13HL072168-01	$	20,000	
NIH	5R01AI050175-03	$	360,250	0683,0771
NIH	5R01AI041326-07	$	356,625	
NIH	5R01AI050471-02	$	396,250	
NIH	5R01DK058993-04	$	334,000	
NIH	5R21AI052792-02	$	231,900	
NIH	2R01AI041326-06A2	$	178,313	
VEAZEY, RONALD S.				
NIH	5R29HD036310			0051
NIH	5R01AI049080-03	$	355,049	0052,0546,0634,0722
NIH	5R01AA013563-02	$	554,215	0545,0642,0643
NIH	5U54AI057156-02	$	9,407,383	0691
NIH	1D43TW006590-01	$	150,000	
NIH	1U54AI057156-01	$	4,242,615	0691
NIH	5R01AI031431-11	$	372,500	
NIH	5R01AI021242-19	$	372,500	

NIH	5R01AR043521-10	$	371,669	0700
NIH	5R01AI032223-10	$	375,000	0700
WEISS, DANIEL				
NIH	5K08HL003864-05	$	0	0603
NIH	5U01AI058303-02	$	447,860	0697
NIH	1U01AI058303-01	$	274,734	0697
NIH	5K01RR000150-05	$	100,991	0689
NIH	1UC6AI058609-01	$	13,656,935	0691
NIH	5M01RR005096-14	$	2,476,907	
NIH	5K12HD043451-02	$	447,022	
NIH	1R01NS048316-01	$	341,094	0683
NIH	2R01NS037654-06A1	$	386,866	0594,0718,0772
NIH	5R01NS040237-05	$	315,970	0594,0718,0772
NIH	2P30DK047757-11	$	1,056,542	
NIH	5P01HL059407-05	$	1,395,686	0683
NIH	5R01HL049040-12	$	356,625	
NIH	5R01NS038690-05	$	414,414	0683
NIH	5T32RR007063-08	$	133,006	
NIH	5R01NS038690-04	$	405,071	
NIH	5R01DK063973-02	$	560,649	
NIH	5R01DK046637-10	$	318,753	
NIH	5T32DK007748-07	$	184,889	
NIH	5R01HD037356-05	$	490,411	0635
NIH	5R01AI052764-02	$	254,877	0759
NIH	5R01AI046964-04	$	467,304	0517,0652
NIH	5R01AI052312-02	$	512,751	
NIH	5R01AI046919-03	$	515,866	0547
NIH	1R01CA092562-01A2	$	264,330	0637
	FEDERAL - PHS	$	154,242,003	
	FEDERAL	$	155,406,992	
TOTAL FUNDING:		$	**158,093,951**	

names

RESOURCE SUMMARY: SUBPROJECTS

The following only includes information associated with subprojects.

	Mgmt. A	Research B	Pilot C	Collab. D	Total (excludes
Number of Subprojects	13	114	5	35	167
Number of Investigators	29	236	15	131	335
Number of Published	0	53	1	26	78
Number In Press	0	28	1	5	34
%AIDS of NPRC Dollars	0.000%	38.320%	1.272%	18.200%	57.792%
%Non-AIDS of NPRC Dollars	0.000%	35.750%	1.908%	4.550%	42.208%
Total Percent of NPRC Funds Awarded	0.000%	74.070%	3.180%	22.750%	100.000%

RESOURCE SUMMARY: ADMINISTRATIVE

PERSONNEL

	On Subprojects	Not On Subprojects
Core Personnel		
DOCTORAL LEVEL SCIENTISTS (C)	40	0
Core Personnel	40	0
Non-Core Personnel		
AFFILIATED (A)	286	0
GRADUATE STUDENT/POST DOCTORAL SCIENTIST (G)	9	0
Non-Core Personnel	295	0
Personnel Total:	335	0

ACCESS BY NON-NPRC PERSONNEL

GEOGRAPHICAL USAGE BY INVESTIGATORS AT NON-HOST INSTITUTIONS

Foreign Investigators by Country	**38**
AFRICA	1
ARGENTINA	1
CAMEROON	2
CUBA	1
CZECH	1
FRANCE	5
GABON	9
SENEGAL	1
SWEDEN	1
SWITZERLAND	1
THAILAND	3
THE NETHERLANDS	6
UK	6
USA Investigators by State	**249**
AL	6
AR	1
CA	14
CO	4
CT	7
DC	1
DE	1
FL	1
GA	2
IL	4
KS	1
LA	51
MA	28
MD	20
ME	1
MO	4
MS	2
NC	10
NE	1
NJ	3
NM	2
NV	2
NY	24
OH	10
OR	1
PA	20
TN	2
TX	11
UT	1
VT	1
WA	12
WI	1
Total Investigators at Non Host Institutions:	**287**

RESEARCH SERVICES

Scientists Provided with Services	83
Services Provided	

RESEARCH SERVICES BY COUNTRY

Research Services to Foreign Investigators by Country	**5**
CUBA	1
CZECH	1
SWITZERLAN	1
THE NETHER	2
Research Services to USA Investigators by State	**78**
CA	4
CT	3
IL	3
LA	18
MA	8
MD	5
NC	4
NE	2
NJ	1
NY	7
OH	2
OR	1
PA	7
TN	2
TX	4
VT	1
WA	5
WI	1
Research Services to Unknown Locations	**1**
Total Research Services (Numbers do not total due to errors in investigator locations):	**83**

INFRASTRUCTURE TABLE

GRANT REPORTED UNITS	**%NPRC USE**
ADMINISTRATIVE	12.442%
BACTERIOLOGY/PARASITOLOGY	4.584%
COLLABORATIVE RESEARCH	6.536%
COMPARATIVE PATHOLOGY	6.187%
GENE THERAPY	3.046%
MICROBIOLOGY/IMMUNOLOGY	7.208%
PHYSICAL PLANT AND I&M	37.870%
VETERINARY MEDICINE	22.127%
TOTAL NPRC:	**100.00%**

RESEARCH TABLE

UNITS GENERATED BY SUBPROJECTS	**%NPRC USE**
ADMINISTRATIVE	0.000%
BACTERIOLOGY/PARASITOLOGY	12.350%

COLLABORATIVE RESEARCH	5.850%
COMPARATIVE PATHOLOGY	25.972%
GENE THERAPY	3.886%
MICROBIOLOGY/IMMUNOLOGY	25.336%
VETERINARY MEDICINE	26.606%
TOTAL NPRC:	**100.000%**

RESOURCE SUMMARY: PUBLICATION/SUPPORT

PUBLICATIONS

	Cited	Not Cited	Total
Published			
Abstracts	12		12
Journals	62	51	113
In Press			
Abstracts	4		4
Books	4		4
Journals	29		29
Total	111	51	162

INVESTIGATOR SUPPORT

NON-FEDERAL	$ 1,487,539
FOUNDATION	$ 899,309
INDUSTRY	$ 300,111
NON-FEDERAL	**$ 2,686,959**
FEDERAL	
NON-PHS	
DOD	$ 1,115,629
USDA	$ 49,360
NON-PHS	**$ 1,164,989**
PHS	
AA	$ 3,669,663
AG	$ 788,787
AI	$ 87,850,098
AR	$ 1,119,169
CA	$ 2,821,648
CDC	$ 167,241
DA	$ 148,500
DE	$ 1,013,011
DK	$ 2,935,484
GM	$ 532,835
HD	$ 4,079,534
HL	$ 6,903,369
MH	$ 1,446,153
NS	$ 7,140,041
RR	$ 33,331,719
TW	$ 294,751
PHS	**$ 154,242,003**

TOTAL SUPPORT	**$ 158,093,951**

COLONY STATISTICS

Base Breeding Colony Only

Note: These animals are supported by NCRR Comparative Medicine.

1Genus Species	May-03	2Live Births	3Other Additions	Exper. Use	4Other Reduct.	5Sold or Trans.	6Trans. in Center	Apr-04
CERCOCEBUS ATYS								
Adult Females	11	0	0	0	1	0	0	10
Adult Males	23	0	0	0	2	0	0	21
Infants/Juveniles	0	3	0	0	2	0	0	1
CERCOCEBUS T LUNULATIS								
Adult Females	3	0	0	0	0	0	0	3
Adult Males	1	0	0	0	0	0	0	1
Infants/Juveniles	4	0	0	0	0	0	0	4
CERCOPITHECUS AETHIOPS								
Infants/Juveniles	0	1	0	0	0	0	0	1
ERYTHROCEBUS PATAS								
Adult Females	1	0	1	0	0	0	0	2
Adult Males	2	0	0	0	0	0	0	2
MACACA FASCICULARIS								
Infants/Juveniles	16	0	0	16	0	0	0	0
MACACA MULATTA								
Adult Females	349	0	60	92	33	10	55	219
Adult Males	55	0	37	8	10	5	15	54
Infants/Juveniles	358	180	64	32	45	2	272	251
MACACA MULATTA (SPF)								
Adult Females(SPF)	11	0	2	0	2	0	1	10
Infants/Juveniles(SPF)	91	7	74	0	9	0	6	157
MACACA NEMESTRINA								
Adult Females	4	0	2	0	0	0	0	6
Adult Males	0	0	1	0	0	0	0	1
Infants/Juveniles	4	3	4	0	1	0	0	10
PAPIO								
Adult Females	1	0	4	0	4	0	0	1
Adult Males	0	0	1	0	0	0	0	1
PAPIO CYNOCEPHALUS								
Adult Males	0	0	1	0	0	0	0	1
	934	**194**	**251**	**148**	**109**	**17**	**349**	**756**

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.

1Genus Species	May-03	2Live Births	3Other Additions	Exper. Use	4Other Reduct.	5Sold or Trans.	6Trans. in Center	Apr-0
CAVIA PORCELLUS								
Adult Females	0	0	3	1	1	0	0	1
Gender Undetermined	2	0	0	1	0	0	0	1
MUS MUSCULUS								
Adult Females	63	1	253	265	0	0	0	52
Adult Males	0	0	243	171	0	0	0	72
ORYCTOLAGUS CUNICULUS								
Adult Females	11	0	1	11	0	0	0	1
Adult Males	1	0	0	1	0	0	0	0
	77	**1**	**500**	**450**	**1**	**0**	**0**	**127**

Non-Base Breeding Colony Only

Note: These animals are supported by NCRR Comparative Medicine.

1Genus Species	May-03	2Live Births	3Other Additions	Exper. Use	4Other Reduct.	5Sold or Trans.	6Trans. in Center	Apr-04
MACACA MULATTA								
Adult Females	324	0	91	24	25	5	40	321
Adult Males	41	0	20	6	9	0	7	39
Infants/Juveniles	542	388	122	20	49	4	348	631
MACACA MULATTA (SPF)								
Adult Females(SPF)	51	0	1	0	12	0	0	40
Adult Males(SPF)	7	0	0	0	2	0	0	5
Infants/Juveniles(SPF)	778	52	362	18	52	2	66	1,054
MACACA NEMESTRINA								
Adult Females	304	0	35	8	22	10	0	299
Adult Males	30	0	7	2	2	4	0	29
Infants/Juveniles	377	179	46	0	69	54	0	479
MACACA NEMESTRINA (SPF)								
Adult Females(SPF)	0	0	1	0	1	0	0	0
PAPIO								
Adult Females	181	0	0	3	6	4	0	168
Adult Males	21	0	0	2	0	5	0	14
Infants/Juveniles	292	119	0	0	52	4	0	355
PAPIO ANUBIS								
Adult Females	2	0	0	0	1	0	0	1
PAPIO CYNOCEPHALUS								
Adult Males	1	0	0	0	0	0	0	1
	2,951	738	685	83	302	92	461	3,436

Research Colony Only

Note: These animals are supported by NCRR Comparative Medicine.

1Genus Species	May-03	2Live Births	3Other Additions	Exper. Use	4Other Reduct.	5Sold or Trans.	6Trans. in Center	Apr-04
CERCOPITHECUS AETHIOPS								
Adult Females	11	0	0	0	1	2	0	8
Infants/Juveniles	7	0	6	0	3	0	0	10
ERYTHROCEBUS PATAS								
Adult Females	1	0	0	0	0	0	1	0
MACACA FASCICULARIS								
Adult Females	0	0	4	0	0	0	0	4
Adult Males	0	0	9	0	0	0	0	9
Infants/Juveniles	0	0	20	0	8	0	0	12
MACACA MULATTA								
Adult Females	310	0	173	0	81	2	18	382
Adult Males	153	0	24	0	46	0	13	118
Infants/Juveniles	212	22	70	0	24	0	23	257
MACACA NEMESTRINA								
Adult Females	12	0	8	0	1	0	3	16
Adult Males	12	0	2	0	10	0	1	3
Infants/Juveniles	5	0	0	0	1	0	4	0
PAPIO								
Adult Females	5	0	3	0	0	0	4	4
Adult Males	1	0	2	0	0	0	1	2
Infants/Juveniles	1	0	0	0	1	0	0	0
PAPIO ANUBIS								
Adult Females	1	0	0	0	0	0	0	1
PAPIO CYNOCEPHALUS								
Adult Males	1	0	0	0	0	0	1	0
SAIMIRI SCIUREUS								
Adult Males	3	0	0	0	0	0	0	3
	735	**22**	**321**	**0**	**176**	**4**	**69**	**829**

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

PATHOGENESIS OF LYME BORRELIOSIS IN RHESUS MONKEY

SPID(s): 0025

Brain invasion by Borrelia burgdorferi, the agent of Lyme disease, results in an inflammatory and neurodegenerative disorder called neuroborreliosis. In humans, neuroborreliosis has been correlated with enhanced concentration of glial fibrillary acidic protein in the cerebrospinal fluid, a sign of astrogliosis. Rhesus monkeys infected by us with B. burgdorferi showed evidence of astrogliosis, namely astrocyte proliferation and apoptosis. We formulated the hypothesis that astrogliosis could be caused by spirochetal lipoproteins. We established primary cultures of rhesus monkey astrocytes and stimulated the cells with recombinant lipidated outer surface protein A (L-OspA), a model B. burgdorferi lipoprotein, and tripalmitoyl-S-glyceryl-Cys-Ser-Lys4-OH (Pam3Cys), a synthetic lipopeptide that mimics the structure of the lipoprotein lipid moiety. L-OspA elicited not only astrocyte proliferation but also apoptosis, two features observed during astrogliosis. Astrocytes produced both IL-6 and TNF- alpha in response to L-OspA and Pam3Cys. Proliferation induced by L-OspA was diminished in the presence of an excess of anti-IL-6 antibody, and apoptosis induced by this lipoprotein was completely suppressed with anti-TNF-alpha antibody. Hence, IL-6 contributes to, and TNF-alpha determines, astrocyte proliferation and apoptosis, respectively, as elicited by lipoproteins. We now demonstrated that cells from the human mixed neuronal/epithelial cell line SK-N-SH co-cultivated with B. burgdorferi also produce IL-6 and TNF-alpha, and undergo apoptosis. This result suggests a mechanism for the pathogenesis of neuroborreliosis that is similar to what is believed to be the pathogenetic basis of other neurodegenerative diseases, e.g. Alzheimer's disease and AIDS-dementia complex, namely, inflammatory responses, induced in this case by spirochetes and/or lipoproteins in the CNS milieu, can mediate neuronal apoptosis and thus lead to cumulative neurodegeneration.

Publications:

RAMESH, GEETA;ALVAREZ, ALIDA L;ROBERTS, E DONALD;DENNIS, VIDA A;LASATER, BARBARA L;ALVAREZ, XAVIER*;PHILIPP, MARIO T Pathogenesis of Lyme neuroborreliosis: Borrelia burgdorferi lipoproteins induce both proliferation and apoptosis in rhesus monkey astrocytes. Eur J Immunol 33 2539-50 2003

A DNA VACCINE TO PREVENT TRANSMISSION OF HUMAN MALARIA

SPID(s): 0534

Malaria transmission-blocking vaccination can effectively reduce and/or eliminate transmission of parasites from the human host to the mosquito vector. The immunity achieved by inducing an antibody response to surface antigens of male and female gametes and parasite stages in the mosquito. Our laboratory has developed DNA vaccine constructs, based on Pfs25 (a Plasmodium falciparum surface protein of 25 kDa), that induce a transmission-blocking immune response in mice (C. A. Lobo, R. Dhar, and N. Kumar, Infect. Immun. 67:1688-1693, 1999). To evaluate the safety, immunogenicity, and efficacy of the Pfs25 DNA vaccine in nonhuman primates, we immunized rhesus macaques (Macaca mulatta) with a DNA vaccine plasmid encoding Pfs25 or a Pfg27-Pfs25 hybrid or with the plasmid (empty plasmid) alone. Immunization with four doses of these DNA vaccine constructs elicited antibody titers that were high but nonetheless unable to reduce the parasite's infectivity in membrane feeding assays. Further boosting of the antibody response with recombinant Pfs25 formulated in Montanide ISA-720 increased antibody titers (30-fold) and significantly blocked transmission of P. falciparum gametocytes to Anopheles mosquitoes (90% reduction in oocyst numbers in the midgut). Our data show that a DNA prime-protein boost regimen holds promise for achieving transmission-blocking immunity in areas where malaria is endemic and could be effective in eradicating malaria in isolated areas where the level of malaria endemicity is low.

Publications:

COBAN, CEVAYIR*;PHILIPP, MARIO T;PURCELL, JEANETTE E;KEISTER, DAVID B;OKULATE, MOBOLAJI;MARTIN, DALE S;KUMAR, NIRBHAY Induction of Plasmodium falciparum transmission-blocking antibodies in nonhuman primates by a combination of DNA and protein immunizations. Infect Immun 72 253-9 2004

MICROBICIDES FOR HIV

SPID(s): 0048, 0547, 0634

The development of a microbicide that could be applied to the vagina and prevent the transmission of HIV-1 could save lives. Unfortunately, compounds that destroy HIV-1 are also likely to damage mucosal tissues. Alternatively, fusion inhibitors that attach to viral or host cell receptors may provide a safe and effective mechanism to prevent HIV-1 infection. We have recently published that vaginal administration of the broadly neutralizing monoclonal antibody (MAb) b12 can protect macaques from SHIV infection by the vaginal route of transmission. We are currently exploring the possibility of producing this monoclonal antibody in plants so that it may be cost more effective as a microbicide that could be distributed to places where the epidemic is rampant.

Publications:

ALEXANDER, LOUIS;ILLYINSKII, PETR O;LANG, SABINE M;MEANS, ROBERT E;LIFSON, JEFFREY*;MANSFIELD, KEITH;DESROSIERS, RONALD C Determinants of increased replicative capacity of serially passaged simian immunodeficiency virus with nef deleted in rhesus monkeys. J Virol 77 6823-35 2003

Veazey RS, Shattock RJ, Pope M, Jones J, Hu Q, Ketas T, Kirijan CJ, Klaase PJ, Marx PA, Burton DR, and Moore JP. Prevention of virus transmission to macaque monkeys by a vaginally applied monoclonal antibody to HIV-1 gp 120. Nature Medicine, 198:1551-1562, 2003

HIGHLY EFFECTIVE CONTROL OF AIDS VIRUS CHALLENGE IN MACAQUES

SPID(s): 0760

Previous studies have shown that vaccination and boosting of rhesus macaques with attenuated vesicular stomatitis virus (VSV) vectors encoding Env and Gag proteins of SIV/HIV hybrid viruses (SHIV) protects rhesus macaques from AIDS after challenge with the highly pathogenic SHIV89.6P. In the current study we compared the effectiveness of a single prime-boost with VSV vectors expressing SHIV Env, Gag, and Pol proteins to a VSV vector prime followed with a single boost with modified vaccinia Ankara (MVA) expressing the same SHIV proteins. After challenge with SHIV89.6P, MVA-boosted animals controlled peak challenge viral loads to less than 2x106 copies/ml, significantly lower than in VSV-boosted animals, and lower than reported in other vaccine studies employing the same challenge. MVA-boosted animals have shown excellent preservation of CD4+ T cells while 2 of 4 VSV-boosted animals have shown significant loss of CD4+ T cells. The improved protection in MVA-boosted animals correlates with stronger pre-challenge CD8+ T cell responses to SHIV antigens and with stronger post-challenge SHIV neutralizing antibody production.

Publications:

[In press publication]

ADMINISTRATIVE INFORMATION

INFRASTRUCTURE

COMMITTEE MEMBERS

PRINCIPAL INVESTIGATOR
Paul K. Whelton, MD, MSc

Scientific Advisory Committee

DIRECTOR
Andrew A. Lackner, DVM, PhD

Executive Committee

ADMINISTRATION & OPERATIONS

- Associate Director for Administration and Operations
  Michael W. Aertker, MSE
  - Administrative Services
  - Facilities Services
  - Information Technology
  - Science Information Services
  - Occupational Health & Safety
  - Security

RESEARCH & SCIENCE DIVISIONS

- Bacteriology & Parasitology
  Mario T. Philipp, PhD
- Collaborative Research
  James L. Blanchard, DVM, PhD
- Comparative Pathology
  Ronald S. Veazey, DVM, PhD
- Gene Therapy
  Bruce A. Bunnell, PhD
- Microbiology & Immunology
  Preston A. Marx, Jr., PhD

VETERINARY RESOURCES

- Associate Director for Veterinary Resources and Chair of Veterinary Medicine
  Rudolf P. Bohm, DVM
  - Clinical & Research Medicine
    Rudolf P. Bohm, DVM
  - Environmental Enrichment
    Kate Baker, PhD
  - Reproductive Biology
    H. Michael Kubisch, PhD
  - Research Resources
    Marion S. Ratterree, DVM
  - Animal Resources
    [name]

INFRASTRUCTURE

Director's Overview

The last year has seen continued dramatic growth, improvement and accomplishment for the TNPRC in all areas. Particularly dramatic has been the increase in grant funding (≈100%) , total employment (200 to over 240), numbers of funded core investigators and resource usage. This has been driven by a number of factors including increased usage of the Center by affiliate investigators around the country. Of particular note is the participation of the TNPRC and its investigators in the University of Pennsylvania Center for AIDS Research (CFAR) and two of the Regional Centers of Excellence in Biodefense and Emerging Infectious Diseases (RCEs) all funded by NIAID. The two RCEs we are involved in are the Southeast Regional Center of Excellence in Biodefense lead by Barton Haynes at Duke and the Western Regional Center of Excellence in Biodefense and Emerging Infectious Diseases lead by [name] at the University of Texas Medical Branch at Galveston, Texas. In addition, the TNPRC competed for and received an award for construction of a regional biodefense laboratory (RBL) to support the NIH biodefense research agenda. The RBL will be a state of the art biosafety level 3 laboratory focused on nonhuman primate infectious disease research to support the RCEs.

Of additional note is the recent recertification of the TNPRC animal care program by the AAALAC at the exemplary level. This is the highest-level certification offered by AAALAC or received by the TNPRC in more than 20 years of continuous AAALAC certification. This achievement is emblematic of the significant improvements that have occurred at the TNPRC in the recent past.

The improvements in the scientific program at the Center have been facilitated by increased involvement of the host institution and the ability of core scientists to obtain Tulane faculty appointments. Over the last year, all new and several existing core scientists have been successful in obtaining Tulane faculty appointments. These appointments have been in a variety of departments and schools including Pharmacology, Medicine, Pathology and Microbiology & Immunology at the School of Medicine, Tropical Medicine at the School of Public Health and Tropical Medicine and Psychology at Tulane College.

The growth in our program produces obvious demands on the infrastructure. To address these demands we have been very aggressive in pursuing construction and renovation funds. Currently, we have roughly $30 million in funded construction projects at various stages of design or construction largely funded by competitive NIH grants. These include:

- A building administration renovation
- B building BSL3 flow cytometry laboratory
- C building veterinary clinic and office renovation
- D building animal holding renovation
- E building BSL3 renovation

- Breeding facility drainage and security
- Employee locker and break rooms
- Security building
- Regional biodefense laboratory

In addition, a formal master plan for the TNPRC campus is underway.

Additional changes and accomplishments over the last year include:

- Enhancement of our Occupational Health and Safety program
- Expansion of our specific pathogen free rhesus macaque colony

FACULTY ADDITIONS AND DELETIONS

Additions:

Erin Ribka, DVM was hired as a Clinical Veterinarian the Division of Veterinary Medicine.

Ivona Vasile-Pandrea, MD, PhD was hired as a Pathologist in the Division of Comparative Pathology. Dr. Vasile-Pandrea was reported as a post-doc in last year's report.

Juan Borda, DVM, PhD was hired as a Pathologist in the Division of Comparative Pathology. Dr. Borda was reported as a post-doc in last year's report.

[name] was hired as a Post-doc in the Division of Gene Therapy.

[name] was hired as a Post-doc in the Division of Bacteriology and Parasitology.

[name] was hired as a Post-doc in the Division of Comparative Pathology.

[name] was hired as a Post-doc in the Division of Comparative Pathology.

[name] was hired as a Post-doc in the Division of Comparative Pathology.

[name] was hired as a Veterinary Resident in the Division of Veterinary Medicine.

[name] was hired as a Nurse Practitioner for the TNPRC.

Paul Telfer, PhD was hired in the Division of Microbiology and Immunology.

[name] was hired as a Veterinary Pathologist in the Division of Comparative Pathology.

[name] was hired as a Post-doc in the Division of Comparative Pathology.

Binhua Ling was hired as a Research Instructor in the Division of Microbiology and Immunology. Dr. Ling was reported as a post-doc in last year's report.

Deletions:

[ ] left TNPRC in June 2003.

[ ] left TNPRC in April 2003.

Gui-Bo Yang, PhD left TNPRC in August 2003.

Marlene Orandle, PhD left TNPRC in January 2004.

[ ] left TNPRC in March 2004.

[ ] left TNPRC in March 2004.

FACILITIES SERVICES

The Division of Facilities Services is organized into three units, consisting of Engineering, Facility Maintenance and Central Glassware/Laundry. The Division's responsibilities include all HVAC operations, steam supply, potable water supply, sewerage treatment operations, electrical, plumbing, and maintenance of all buildings including new renovations and construction projects. The Division of Facilities Services also oversees the disposal of all hazardous waste and waste products.

The Facilities Services Manager is responsible for all daily operations, oversees and contributes to all renovations and construction projects, reviews all requests for service and also reviews all construction and renovation projects with architects and planners to ensure they fall within the Center's guidelines and infrastructure. The Manager also oversees relevant local, state, and federal statutes to assure compliance and communications with university and local emergency preparedness officials to ensure adequate planning.

The Engineering Unit has the responsibility for delivering adequate heating and air conditioning, potable water and waste water treatment, steam for heating and autoclave units, five cage wash facilities, multiple deionized water supply stations, modified security, monthly fire extinguisher inspection and documentation, and eye wash/emergency shower stations testing and documentation. Operations are staffed twenty-four hours a day with three eight-hour shifts. Services are reduced when possible for energy conservation purposes. Operational guidelines now assure two engineers per shift unless operations dictate otherwise. Continuing education and training are essential

for all engineering staff so they can achieve and carry out all daily and monthly operations as governed by local, state and federal guidelines. The Engineering Unit also continues to revise and establish new SOP's for their operations.

The Engineering Unit has 3 Licensed Engineers and 5 Unlicensed Jr. Operating Engineers. From May 1, 2003 – April 30 2004, 13,580 hours were expended by the Engineering Unit. (See Table 1).

The Facility Maintenance Unit's responsibilities include all day-to-day maintenance operations for all eight primary buildings and twenty-three satellite buildings at the Center. Approximate square footage of the 8 major building surpasses [ ] ft^2 with an additional [ ] ft^2 for the satellite buildings. Outdoor animal corral housing totals [ ] ft^2 and includes corncribs. "Y" areas and baboon housing exceeds [ ] ft^2. This equals a total area of [ ] ft^2 that must be maintained by the Facility Maintenance Unit. During the period of May 1 2003, through April 30 2004, a total of 631 work orders consuming 14,905 work hours were completed. Fourteen Job Orders were started consisting of 3,922 hours of labor which contributed to the completion of several of these Job Orders. (See Table 2) (See Table 4 for Improvements and Additions to Facilities)

The Central Glassware/Laundry Unit is responsible for daily uniform cleaning of all laboratory glassware that is used throughout the Center's divisions and laboratories. Central Glassware/Laundry has 3 [illegible] employees that totaled 5,950 hours of labor. 4,743 hours were directly related to the laundry, which maintains all Center uniforms and divisions' other needs such as lab coats and miscellaneous items. 1,207 hours were indirectly related to picking up contaminated glassware, cleaning and storing the sterilized glassware until needed by each division. (See Table 3).

Table 1
Engineering Unit

Daily Operation of all HVAC and Related Equipment	7,876
General Maintenance –autoclaves, cage washers & heaters	679
General Maintenance – freezers	407
Inspection/repair – eyewash, filters, fire extinguishers, and safety showers	1,087
Security	679
Sewer Plant	407
Steam/air conditioning	1901
Water – potable, distilled & deionized	544
TOTAL HOURS	**13,580**

Table 2
Maintenance and Service Provided

UNIT	HOURS	UNIT	HOURS

Unit	Hours	Unit	Hours
Center Resources	594	Grounds	2,459
Director's Office	1,598	Job Orders	3,922
Facilities Services	519	Microbiology	528
Gen. Building Maintenance	4069	Parasitological	27
Gen. Electrical Maintenance	441	Pathology	349
Gen. Plumbing Maintenance	293	Vehicle Maintenance	900
Gene Therapy	151	Veterinary Medicine	5,782
Business Office	529	Custodial	548
ChemClav Tissue Agrilyzer	429		
		TOTAL HOURS	**23,138**

Table 3
Central Glassware/ Laundry

UNIT	HOURS
Laundry	4,743
Glassware	1,207
TOTAL HOURS	**5,950**

Table 4
Improvements & Additions to Facilities

Item	Cost
Construction of New Change Room/Enrichment Building	$107,417
Construction of New Break Room/Storage/Office Building	$129,483
Renovation of Existing Storage Building	$11,902
Construction of New Storage Building	$35,305
Security Police Vehicle	$10,056
Used Vehicle Purchase for Facilities Services	$6,043
Purchase and Installation of New Huebch 40 lb. and 50 lb. Washer and Dryer	$8,240
Purchase of Utility Trailers for Facilities Services	$2,612
Repair and Refurbishing 1203 Cage Units	$5,550
Purchase of DR All-Terrain Field and Brush Mower	$2,568
Installation of New Irrigation System	$14,625
Construction of Carpentry and Welding Building	$24,894
Painting and Floor Patch H Building	$64,125
Replacement of Two Hot Water Tube Bundles	$5,340
Purchase and Installation of ChemClav and Tissue Agrilyzer	$285,759
Painting and Floor Patch in B Building	$9,825
Painting and Floor Patch in Gene Therapy Building	$4,725
Purchase of Golf Cart for Facilities Services	$2,255
Purchase of Golf Cart for Security	$3,304
Rental (six months) Security Office	$7,963
Renovation Occupational Health and Safety Suite	$8,711

Item	Amount
Installation of New Shades for Office and Laboratory Windows	$12,805
Center Security Upgrade – New Barrier Gates & 7ft. Fencing in the Breeding Colony Area	$70,485
Center Security Upgrade – Barrier Gates & Fencing for Campus Area	$8,400
Access Security Doors for Campus Buildings	$196,000
Renovation of Roof/Perching #G001-G010	$182,980
Replacement of Roof Fabric on 13 Pigtail Corrals	$139,255
Construction of Z Building	$146,415
Fabrication of Troughing and Brackets Z Building	$68,676
Renovation of Y Building	$56,180
Renovation of Facilities/Services Offices and Break Room	$24,557
Replacement of Entry and Exit Security Gates	$7,735
Renovation of G001-G004 Corrals	$41,186
Renovations of E-Building	$15,999
Renovations of Clinical Pathology Rooms B-233/B-235/B-237	$122,448
Renovations of Administration Building	$1,109,516
New HVAC Control Computer/ Including All Software Licensing	$4,300
Cell Sorter Room B-415A	$252,514
TOTAL	**$3,210,153**

INFORMATION TECHNOLOGY

Mission Statement

The mission of Information Technology is to provide technology support for the faculty and staff of the Tulane National Primate Research Center, including maintaining an animal records system database, assisting with desktop and network computing, and assisting with multimedia presentation development and production.

Overview

The Information Technology Unit is responsible for maintaining most computer related technology. This includes support for the animal records system, nicknamed "Blacksmith". This database system is continually revised, with new modules being added often. The database migration project, which was started at the end of 2002, was placed on hold due to the urgency of requests for electronic billing and transfer of billing data to the Tulane Accounts Management System (TAMS). This migration project is now back on track, and it's completion is anticipated for mid-year 2004. IT is responsible for desktop support for over 200 desktop computers, 30 laser printers, three Windows 2000 Servers and two Solaris servers. It is responsible for maintaining a 100BaseT Ethernet LAN in coordination with Tulane University's Infrastructure Technology Services. Finally, IT is responsible for multimedia presentation support, including slide presentations, posters and video productions. The IT staff is comprised of ___ positions including: two database support and development staff, a multimedia coordinator, two desktop support staff, and the IT Manager (unit supervisor).

percentage of effort

Animal Records System

One of our most significant accomplishments is "Blacksmith", the TNPRC animal records system. This system was developed in-house using the PI/open database system and the Blacksmith 4GL development package and DBMS interface. It was specifically designed with non-human primate data management in mind. The system allows for the following data management: demographic data, weight histories, animal-location histories, protocol assignment histories, clinical treatment data, clinical observation data, clinic animal samples (blood draws, urinalysis, fecal/parasitic analysis, etc...), surgical data, clinical lab data, parasite lab data, viral lab data, genetic lab data, pathology data (necropsies), environmental enrichment data, vivarial assistance scheduling, protocol tracking, and billing.

At the end of 2002, the database team along with an outside consulting group began an intense data migration project. It was determined that a much desired data migration was necessary immediately, due to the discovery that support for the existing PI/open database had been terminated by IBM after its acquisition of support contracts for PI/open software. The decision was made to purchase Oracle 9i DBMS and begin the process of transferring the animal records system design into this system. The project involves testing every aspect of all files, reports and entry screens to ensure proper function of the animal records system. Blacksmith will still be used to interface to the animal records system on Oracle. This will give the faculty and staff an identical

interface to the animal records system (still nicknamed Blacksmith). For those users the migration project will initially have no obvious impact. In the long term, applications will begin to be developed using Oracle-based tools and allow for improved data integration with other systems. The migration project was originally expected to be completed in May of 2003. However, due to a large amount of database requests, the project was put on-hold. We have recently restarted the project. We now anticipate that it will be completed by mid-2004.

Key projects, which were completed during 2003, or which are still in progress include the following:

Grants Management module, for maintenance of research funding data, from inception of grant or contract proposal, to award statement and yearly budget maintenance. This project is about 80% completed. However, it needs to be thoroughly tested, which requires cooperation of a very busy Business Office. We also anticipate that this will be completed by third quarter of 2004.

Electronic transfer of Billing data from the Blacksmith system into the Tulane Account Management System (TAMS), reducing error created through re-entry of data into two different systems, as well as reducing time of entry. Currently, perdiem, vivarial assistance and supplies, surgery time and supplies, and clinical lab charges have been intergrated. We are in the planning stages for incorporating the following: flow cytometry, histology, and facility services charges.

Continued work on the Collaborative Research contact management and sample tracking system.

Electronic transfer of data from various new clinical lab testing machines for hematology and blood chemistry data. This project is still underway, because of continued difficulty to coordinate with hardware and software vendors. We anticipate that this project will be completed by mid-2004.

Desktop Support

Desktop support is responsible for maintaining the computer hardware and software needs of the facility. This includes desktop computers running Windows 98, Windows 2000, Windows XP and Macintosh 9.x, and X operating systems. It also includes support for a Sun Microsystems Sparc 1000 server running Solaris 2.5, a Sun Microsystems SunFire 280R running Solaris 9, and four other servers running Windows 2000 Server software. Finally, desktop support staff is responsible for associated peripheral and network device support, including over 30 black and white and color laser printers, multiple scanning devices, video recording and playback devices and other assorted backup devices. Desktop support staff has the task of troubleshooting network problems, as well as coordinating network wiring, network cable termination, and coordinating network design issues with Tulane Infrastructure Services.

Hardware support includes assembling of Windows-based desktop computers. During 2003, over 40 new Windows-based computers were assembled and distributed at TNPRC. Some of these were additions to the overall computer count. Most were replacements of broken, out-dated equipment. Hardware support requires tedious testing and replacing of various components. Software support can also be time consuming. IT staff assist with the installation of various software packages (both public domain and TNPRC approved site licensed software) and troubleshoot software related problems.

Desktop support staff responded to over 2200 support requests (hardware and software). Some of the requests required approximately 15 minutes to complete, while others took hours and even days to finally sort out. The amount of calls is at times overwhelming.

Throughout 2003, IT desktop support maintained a computer-based time clock system for the Divisions of Veterinary Medicine and Facility Services. IT assisted with software configuration and maintenance, as well as coordinating hardware repairs. A migration of data and transfer of control of this system to a Kronos system at Tulane University is in the planning stages and should be completed by mid-2004.

Other projects include a network tape backup system incorporating a 2-terabyte RAID storage device for backing up desktop computer across the network. These devices have allowed us to backup desktop computers throughout the facility, maintain storage of high-resolution graphic images generated by the digital scopes in the Division of Pathology, as well as act as a general file server for all divisions at TNPRC.

Finally, the TNPRC phone system is officially the responsibility of IT. We are responsible for all issues related to the phone system, including new equipment purchases, configuration and management of both analog and digital telephones, and coordination of hardware and software maintenance. This responsibility also includes the management of Nextel cell phone/radios, which includes purchase of new phones and coordination of maintenance and repair of existing units.

Media Lab

The Media Lab has continued to experience growth during 2003. The Media Lab staff provides multimedia production support by assisting with the following: slide presentation production, 35mm slide creation, 35mm slide scanning, document and image scanning, color document and image creation, video production (including filming and editing), and research poster creation. In addition to these tasks, the Media Lab has taken on the responsibility of producing identification badges for all TNPRC personnel. This project involved the purchase of a card printer (Eltron P310 PVC Card Printer). Media Lab has a morning set aside each week for employee photos for ID badges. These badges were necessary for improved security.

For video production, the Media Lab has S-VHS videotape editing equipment along with digital video camcorders and computer-based video acquisition and editing capability. Most video editing is now done on a Macintosh G4 using iMovie and Adobe Premier. The Media Lab has a high-quality digital photo camera and a digital 8mm video camera. This equipment is either loaned out to different TNPRC Divisions for their own visual documentation needs or scheduled for use with varying research related activities. The portable Sharp Notevision video projector is used for small group presentation in the TNPRC Conference Room. Media Lab staff has access to both Windows and Macintosh computers for use in presentation creation. A professional flatbed scanner and a slide scanner provide ability to digitize documents and slides for electronic publication and research presentation. A manual binding machine is available for binding business and research documents. The lab also maintains an inventory of poster supplies such as mat board, poster paper, glue, Velcro, along with other supplies and equipment for use in producing scientific research posters. Most research posters are now printed on single sheet photo paper. The Media Lab creates poster images on-site. For mid-sized poster

images, an HP large format printer was purchased. However, the large posters are printed at a local photo-copy center.

Another key area for IT and multimedia has been the coordination of video-conferenced research seminars. Two systems are currently in place. CI Workspace is an IP-based video conferencing system, developed by Tulane faculty and staff, which works over the public internet. It is a Mac-based application, though they are currently in the process of porting this application across multiple OS platforms. This system has been tested successfully for connection to many different countries around the world. Our use has been limited to seminars on Tulane's downtown campus and video-conference meetings with scientists at the Aaron Diamond AIDS Research Center in New York. The second system is also IP-based, using a Polycom video conferencing workstation. We have used this system for receiving the CFAR AIDS research seminar series presented by the University of Pennsylvania. We are also looking into the use of Vbrick system technology to send and receive video broadcasts from Tulane University for possible transmission over their TUCAN cable television network. 2004 should prove to be a year for increased use of video conferencing technology.

OCCUPATIONAL HEALTH AND SAFETY PROGRAM

The TNPRC's Occupational Health and Safety Program follows Occupational Safety and Health Administration (OSHA) Guidelines. While the supervisor of each lab or facility is responsible for safety in the his/her workplace, the Occupational Health Nurse Specialist works closely with the TNPRC Safety Committee to ensure that TNPRC provides a safe workplace for all employees. The TNPRC Occupational Health Program has the following goals:

- To prevent occupational exposures, accidents, injuries and illnesses via ongoing safety training and risk assessment techniques.

- To use an educational program to improve employee knowledge of zoonotic diseases, demonstrate safe work techniques, provide instruction in emergency response, provide information on regulatory controls and yearly updates on safety policies and procedures.

- To maximize employee health outcomes by careful orientation to potential hazards, provision of case management for worker's compensation, attention to appropriate injury and post-exposure follow-up care , evaluation of employee health status using a health assessment questionnaire and annual allergy risk assessments for animal workers.

- To provide appropriate preventive healthcare via education, vaccinations, and quarterly workplace inspections.

- To collaborate with the Tulane Office of Environmental Health & Safety, Tulane Infectious Disease Specialists and TNPRC Administration to maximize employee health outcomes.

Hazard Identification and Risk Assessment

Risk Assessment and History Forms (RAHF) are required from all faculty, staff and students using the TNPRC animal facilities, including IACUC members. The TNPRC Occupational Health Nurse is a voting member on the IACUC and notifies, reviews and maintains the RAHF's. The Nurse is also Chair of the TNPRC Safety Committee and works closely with each Department to ensure employee safety. The nurse maintains a computer database of occupational injuries for future risk assessment purposes. This database permits the generation of injury reports for trend calculations and subsequent implementation of preventive measures and training.

Office of Environmental Health and Safety (OEHS) identifies hazardous conditions and practices in collaboration with the TNPRC Safety Committee, which meets monthly. The Safety Committee and OEHS evaluate the impact of these problems and recommend methodologies to correct or prevent these conditions or practices from causing danger to individuals, equipment, buildings or the environment. Departments are required by the University's Personal Protective Equipment Hazard Assessment/Certification Program to submit PPE Assessment Questionnaires. Hazards to which an employee may be exposed are assessed and need for PPE is determined.

Hazards are also identified at the time of IACUC protocol review or prior to submission of the protocol if a new agent is involved. The TNPRC Safety Committee and the Tulane Environmental Health and Safety (OEHS) Department provide advice on the handling of biological and other agents to the IACUC and protocols are approved only after the investigator acknowledges the required safeguards. The investigator and members of the Division of Veterinary Medicine then develop protocols for proper handling of the agent.

Medical Evaluation and Preventive Medicine for Personnel

In order to meet the needs of the research program and ensure the effectiveness of the TNPRC's Occupational Health Program, a full time Safety Officer/ Occupational Health Nurse position was created and filled in 2002. Currently, [name] holds this position. [name] is a Registered Nurse with experience in occupational health and safety, human subjects research, infection control and biological safety in academic environments. The addition of [name] has led to a reevaluation of existing programs.

All employees are given a semi-annual tuberculin test unless the individual is known to have positive reaction, in which case he is given a chest X-ray as prescribed by the Occupational Health Physician at Tulane University. Persons

working near the radiology facility or radioactive materials are issued dosimetry badges.

All injuries, including bites and scratches, are reported to the on-site Occupational Health Nurse and OSHA documents are maintained at TNPRC and at the University. For health related concerns and exposures, employees are seen in the TNPRC Occupational Health Clinic and referred to the appropriate physician if needed. Many injuries can be treated with first aid and evaluated and followed up by the Nurse Specialist. Physician coverage is provided by the Occupational Health Clinic at Tulane University Medical Center or the local Redi-Med Clinic. [name] (Infectious Disease Specialist) works closely with the on site Occupational Health Nurse in the event of exposures to infectious diseases such as SIV or B-virus. Employees with minor injuries can be referred to [name] who has contracted with the TNPRC to see employees at a local occupational health facility. [name] has access to [name] and other infectious disease physicians at Tulane for consultation. In addition, all physicians have been provided with information packets that contain the latest literature on diagnostic algorithms and B virus treatment.

In 2004, SIV testing is being offered to employees who are potentially exposed to this retrovirus. This will be performed at Centers for Disease Control and Prevention (CDC) as part of their Simian Retrovirus Seroprevalence Study or at UC Davis Primate Center if the employee does not wish to participate in the study.

Permission for vaccination, skin tests, and other special medical or prophylactic procedures are a condition for employment in laboratories handling infectious or toxic substances. The necessity for vaccination, skin test, and work in areas with infectious or toxic substances is determined by TNPRC's Safety Committee, the IACUC, and the Occupational Health Nurse. Annual Right to Know seminars are provided by the Office of Environmental Health and Safety. Hepatitis B and Tetanus vaccinations will soon be offered on site to all employees at risk for occupational exposure.

Employees are encouraged to become CPR certified and there is defibrillator (AED) equipment on site in the event of an emergency.

For work in BSL-3 containment areas, employees are fit tested for respirators by Tulane Occupational Health and Safety personnel.

Bite/wound kits are located in every clinic, necropsy areas, laboratories and in the breeding colony work trucks and break area. If an injury occurs, the employee follows the instructions for cleaning the wound as stated in the kit. A first report of injury is filled out and faxed to Risk Management by the Occupational Health Nurse, and a blood sample is drawn. The employee is then put on a schedule to have a second sample drawn in two weeks. Prophylactic medication is provided according to Treatment Standing Orders from the Tulane ID physician [name]. The animal involved in the incident is bled for a serum sample and swabs are taken for culture. The samples from the human and animal are sent to the B-virus Reference Laboratory ([name] Atlanta, GA). Viral culture

swabs are collected from nonhuman primates by a veterinarian who performs a physical examination at the time of sample collection. Any abnormal examination findings are noted in the animal's record, on the accident report and relayed to the nurse. The serum is checked for antibody to herpes-B virus within 48 hours. Culture results are reported to the nurse within 2 to 5 days. Depending on the severity of the injury the employee may be referred to the Tulane Occupational Health Clinic, [name] locally, or to one of the hospital emergency facilities in the area. Physicians at the local emergency facilities have received a packet of information about herpes-B virus and contact numbers for consultation. Employees are advised to report any symptoms that can be related to B-virus infection to the on-site Occupational Health Nurse. In addition, the Occupational Health Nurse follows up with patients after an exposure.

The Occupational Health RN is on-call 24/7 in the event of injuries or exposures and can access Tulane Medical Center physicians or the local emergency room after hours for coordination of treatment.

Personnel Training

The Tulane OEHS provides and maintains mandatory occupational and environmental health training documentation. The TNPRC Occupational Health Nurse Specialist is on-site and is active in providing training on zoonotic diseases and in maintaining documentation of both orientation training and continuing education for all employees. There is a quarterly health information educational series in place with speakers presenting on health-related topics such as Tuberculosis control, B-virus treatment protocols and blood-borne pathogens prevention. The OEHS Safety Policies and Procedures Manual and supplementary documents are developed and maintained by OEHS. Occupational Health Standard Operating Procedures (SOPs) are being developed by the Occupational Health Nurse who works closely with Tulane Infectious Disease Specialists to implement these SOPs.

Employees Working with Non-Human Primates

Each new employee is given a brief explanation of the hazards of working with nonhuman primates prior to being hired. Before working with nonhuman primates the employee is required to view a series of films and pamphlets that detail important aspects of nonhuman primate care and use including hazards. Periodic training seminars are provided by the Division of Veterinary Medicine, Occupational Health Nurse and TNPRC investigators. New personnel are assigned to specific areas where the "on the job" training is supervised by a veterinarian, the Animal Care Technician Supervisor and Quality Assurance Specialist to assure compliance with SOPs.

DIVISION OF BACTERIOLOGY AND PARASITOLOGY

Research in the Division of Bacteriology and Parasitology and pertinent research of other divisions is supported infrastructurally by three Research Cores: the Vector-Borne Diseases Core, the Diagnostic Parasitology Core, and the DNA Microarray and Expression Core. The Vector-Borne Diseases Core produces infected and uninfected Ixodid ticks for research on Lyme disease and other tick-borne diseases, Anopheline mosquitoes and sporozoites for malaria research, and Aedes mosquitoes for filariasis research. Monkey and mouse infection sera also are generated and supplied by this core. The Diagnostic Parasitology Core is responsible for providing diagnostic laboratory support to TNPRC research programs and the Preventive Medicine program of the Division of Veterinary Medicine. Thus far the DNA Microarray and Expression Core has performed cytokine expression experiments for TNPRC investigators. The microarray section is under development.

Vector-Borne Diseases Core. The *Anopheles stephensi* colony was used to transmit *Plasmodium cynomolgi*, a model of human vivax malaria, to seven rhesus macaques in 2003. The colony was also exploited to provide material to train mosquito dissectors in the Advanced Medical Entomology course (TRMD 780) at the Tulane School of Tropical Medicine. The colony is maintained at approximately 900 individuals and is then expanded when studies require infective stage sporozoites. We have produced up to 5,000 mosquitoes at a time this year when operating at full capacity. A new insectary is currently being designed and funds have been budgeted for its construction. The new facility will allow us to house multiple species and maintain temperature and humidity in a more closely controlled environment.

The tick colony has been instrumental in enabling our division to continue research in Lyme borreliosis using the natural mode of infection. We now routinely infect mammals (mice and monkeys) via tick bite. The technique of capillary feeding of nymphal ticks, which we have available, allows us to infect ticks with spirochetal clonal isolates. This is often essential to insure defined host-responses to infection. We also are able to infect larval ticks by immersion in tissue-culture fluid that contains spirochetes. Unfortunately, this simplified method does not work with nymphs. The availability of ticks and of these infection techniques has contributed to secure a fundable score for an NIH-RO1 grant subcontract, in collaboration with the [name] of the University of Texas at Houston. This subcontract will address the role of key virulence factors in infectivity to ticks, and to mice via ticks. The tick section of the core has currently available numerous specimens of all of the developmental stages of *Ixodes scapularis*. Larvae, nymphs, and adults are stored at 4°C in a staggered fashion. Therefore, we usually have all of the stages available at most times throughout the year. This includes 5-10 jars of larvae (with about 1000 larvae each) and several hundred uninfected nymphs for experimental needs as they arise.

Diagnostic Parasitology Core. During the year 2003-4, the DP Core processed 1,330 clinical samples, including 105 stool samples from animals in quarantine, and 1,214 stool samples from animals assigned to research projects. The Core also examined 196 blood

samples by the Knott's technique, and 203 thick and thin blood smears from colony animals. Pathogenic parasites reported included *Giardia lamblia* (52), *Balantidium coli* (119), *Strongyloides fulleborni* (417), and *Trichuris trichiura* (324). The DP Core, recognized as one of the few facilities in the world devoted to parasites of non-human primates, also examined a number of whole worm and histological specimens containing parasites in support of the Division of Comparative Pathology, TNPRC.

In addition to clinical samples, during the last year the Core has examined and graded 553 stool samples in support of a research project by Dr. Jason Dufour (Division of Veterinary Medicine) on Ivermectin-resistant *Strongyloides fulleborni*. The Core is supporting a research project by Dr. Karol Sestak (Division of Microbiology and Immunology) on the origins of idiopathic diarrhea in colony animals. The Core is also examining blood and fecal samples in direct support of a survey of enzootic pathogens from the breeding colony, a project of Dr. Frank Cogswell (Division of Bacteriology & Parasitology).

In addition to samples from colony animals, the Core examined monkey blood smears from Taiwan ([name] National Pingtung University of Science and Technology) and sent worm specimens to *Museum National d'Histoire Naturelle Origine, Structure et Evolution de la Biodiversité (UMR CNRS)* Paris. The Core also examined and speciated helminths from monkeys for the *Universidad Nacional*, Heredia, Costa Rica, examined monkey fecal and blood samples for [name] University of Washington, and examined soil samples for LA Office of Public Health in support of a child endangerment action.

DNA Microarray and Expression Core. In its inaugural operation, the DNA Microarray and Expression Core (DMEC) had proposed to offer the analysis of RNA expression in nonhuman primates through the use of a limited microarray and by RT-PCR (reverse-transcription-PCR). The comprehensive services of DMEC in the area of microarray experimentation would include consultation in matters of design of experiments, development and standardization of protocols, performance of microarray experiments, interpretation of results and maintenance of data. The RT-PCR service will be set up as an integral part of the microarray core and provide a routine quality control tool for the rapid assessment of microarray results. The DMEC will extend the RT-PCR-densitometry services to individual investigators interested in further quantifying specific mRNAs.

During the past year, the following progress has been made in this area. A Shared Instrumentation Grant proposal was submitted to NCRR to obtain funding for this core. Unfortunately, the proposal was not funded. The main reason cited was a shortage of expertise in the area of microarray experimentation and analysis. Therefore, the bulk of our efforts have been dedicated to overcoming our deficiency. Toward this end, we have familiarized ourselves with the instrumentation housed in the Tulane Gene Therapy Center in New Orleans. We have also followed the developments in this field, attended meetings and invited [name] (University of Nebraska), an expert in this area for consultation. [name] is dedicated to designing a rhesus microarray chip the first version of which will be soon available for general use. Our current plan is to incorporate

this chip in our experiments when it becomes available. Currently, we continue to offer our RT-PCR-densitometry services to TNPRC investigators.

DIVISION OF COLLABORATIVE RESEARCH

The Division of Collaborative Research (DoCR) was formed in July 2002 to more formally meet the needs of the research community interested in performing research using nonhuman primates. A central mission of the National Primate Research Center Program is to provide access to primate resources for NIH funded investigators. The DoCR provides a central contact and assistance point for non-core investigators interested in accessing the resources of the TNPRC. The DoCR also functions to track and quantify the use of TNPRC resources being used to meet the needs of these investigators.

The Division is staffed by personnel with expertise in veterinary medicine, budgeting, database management, IACUC issues, sample preparation, and shipping. This covers the full spectrum of duties required to adequately supply and track requests for assistance/collaboration with off-site investigators. The Division has two members with DVM, PhD degrees and a faculty and staff of 7 with a combined total of more than 120 years of experience in the field of nonhuman primate research.

The database developed for DoCR tracks investigators, contact information, type and number of samples sent, and biographical and funding information about each collaborator. The database can be used to track the total number of inquires received, those that result in significant interactions with Center investigators including collaborative grant proposals, and those that result in additional funding at the Center. It can also track the total amount of NIH funded research projects the Center supports through collaborations with non-core scientists.

In this reporting year the Center received 94 inquiries involving over 200 non-core scientists. These contacts resulted in the development of 51 budgets for grant or contract arrangements, 10 of which resulted in some level of funding for the Center.

The Division has processed and shipped over 34,000 samples in over 400 individual shipments. The DoCR also tracked over 7,000 addition samples shipped by other Divisions at the Center. This represents support of research programs at 68 institutions in 19 states and 9 foreign countries. Ninety individual investigators at these facilities received samples including biological agents, blood, tissues, and preserved materials from 9 species of monkeys.

The Center has always had a significant role in fostering collaborations with non-core scientists. In the past this was done informally on a case-by-case basis by core faculty. Initial contacts that did not lead to collaborations were not recorded. The Division of Veterinary Medicine played a significant part in the collaborative process due to the need by many investigators for guidance on study design, animal use, special techniques, and IACUC protocol issues. Most collaborative projects that began in Veterinary Medicine or other Divisions have remained in those Divisions although several have been transferred

to DoCR for a variety of reasons. For these existing collaborative research projects the DoCR will facilitate reporting of these interactions by maintaining a recently created database to better document the depth and breadth of these interactions.

In addition to providing veterinary and research planning expertise, the Center has devoted space to the collaborative research projects for many years. This had been accomplished primarily through the use of individual investigators labs. This concept of providing lab space dedicated to the support of collaborative projects has been formalized by the allocation of space to the DoCR. We currently have nearly [ ] square feet of equipped laboratory space for the Division with two [ ] technicians. This space supports the research of over 30 investigators including 10 non-core scientists.

percentage of effort

DIVISION OF COMPARATIVE PATHOLOGY

The Division has significant service functions that consist of providing diagnostic, clinical, and anatomic pathology support for the medical care of the animal colonies, as well as anatomic and clinical pathology, tissue collection, histology, molecular pathology, and confocal microscopy service to investigators throughout the center and to collaborators and affiliates based at other institutions. The pathologists also frequently serve as a source of information and expertise by providing consultation on primate diseases, pathology, and research to investigators throughout the United States and the world.

The service components of the Division are divided into four research and diagnostic support Cores: Anatomic Pathology, Clinical Pathology, Molecular Pathology, and Confocal Microscopy and Image Analysis. The Anatomic Pathology Core consists of the necropsy and histology laboratories and is responsible for post-mortem examinations, tissue collection, tissue fixation, processing, slide preparation, and cryotomy for both research and diagnostic purposes. The Clinical Pathology core provides bacteriology, hematology, and clinical chemistry analyses for the colony health maintenance and for research support. Previously, this division also performed the occupational and safety services of the center, including tuberculin testing, blood collection and serum banking for employees, but this service was transferred to the newly created Occupational Health and Safety Office in 2003. The Molecular Pathology Core provides assistance with PCR, probe preparation, immunohistochemistry, and *in situ* hybridization for both Core scientists and affiliate investigators. Demands for this service have grown tremendously in the last two years, requiring an additional [ ] square feet of laboratory space devoted towards this core. Renovations and modernization of this new laboratory space were completed in Feb 2003. The Confocal Microscopy and Image Analysis Core was established late in 2001 and has continued to provide service support to numerous investigators and research projects. This Core provides assistance with fluorescence microscopy, confocal microscopy, image analysis, and photomicrography to core and affiliate scientists.

A national search for additional pathologists was concluded in 2003 to fill the vacancy left by [name] departure, and to meet the increasing pathology service demands on the Division. As a result of this search, three new pathologists were hired to

accommodate the increased needs of the service work in the Division. Ivona Pandrea, MD, PhD, who is a certified MD pathologist, was hired to perform anatomic pathology service, particularly so that we could bring human pathology expertise to the Division of Comparative Pathology. Dr. Pandrea also has expertise in AIDS research, particularly in the field of SIV infection in "natural" nonhuman primate hosts. Dr. Juan Borda, DVM, PhD, was also promoted to the rank of Research Assistant Professor and is also performing diagnostic pathology service. Dr. Borda has over 14 years of nonhuman primate pathology experience, and he is also developing his own research program in renal pathology and AIDS in the nonhuman primate model. Dr. Borda was previously a Postdoctoral Fellow in Dr. Lackner's laboratory at the New England Primate Research Center. Finally, Wayne Buck, DVM, PhD, Diplomate ACVP, accepted a position in the Division and will be joining the faculty in April 2004. [name] will bring expertise in both diagnostic veterinary pathology and Postdoctoral training to the Division. These three pathologists, along with Dr. Pete Didier, who has been a pathologist at the TNPRC since 1988, will be responsible for all of the pathology service work in the Division. Once the Division is fully staffed (April 2004) each pathologist will devote [ ] effort to service work and [ ] toward their own research programs.

Anatomic Pathology Core: The Anatomic Pathology Core provides necropsy and histopathology support for colony health maintenance, as well as for essentially all ongoing research projects at the TNPRC. The core is currently staffed by three Veterinary Pathologists, one of whom is Board Certified in Veterinary Pathology, a Human Pathologist, a Medical Research Specialist and a Medical Research Technician. Dr. Veazey, while not currently on active Pathology service duty, is also a veterinary Pathologist and provides consulting and training for cases. In addition, the Director, Dr. Andrew Lackner is also a board certified Veterinary Pathologist and is available for consultation.

It is a center policy that a cause of death is determined, if possible, for all animals that die at the center, whether of natural or experimental causes. This allows us to monitor and document all disease processes that occur within the colony and provides an opportunity to discover new diseases that may be useful models. Complete sets of tissues are collected from every animal. Most major research areas at the center depend heavily on pathology support as an integral part of the research. The Division's service load in 2003 continued at high levels in all areas. In 2003, the pathologists performed 772 necropsies. In addition, 54 biopsies and 40 miscellaneous (non-primate) cases were accessioned for diagnostic purposes in 2003. Mortality statistics for the Center are shown in the tables below. Note that it is our policy to count all intercurrent abortions, stillbirths, intrauterine deaths, and neonatal deaths as perinatal deaths for statistical purposes.

Three Medical Research Technicians staff the Histology Service Laboratory. In addition to diagnostic specimens, technicians assigned to various research projects also produce histology slides for various Divisions and affiliate scientists. The totals are combined for this report. The utilization of histopathology in the Division is summarized in the table below.

Calendar Year Totals.

THE NUMBER OF NECROPSIES BY SPECIES AND DISPOSITION, Jan 1, 2003 to Dec 31, 2003

	Experimental	Spontaneous	Perinatal*	Total
Chinese-origin *Macaca mulatta*	59	8	9	76
Indian-origin *Macaca mulatta*	298	96	78	472
Macaca nemestrina	21	65	66	152
Macaca fascicularis	8	0	0	8
Chlorcebus aethiops	0	0	1	1
Papio species	6	17	33	56
Cercocebus torquatus atys	3	1	2	6
Saimiri sciureus	0	1	0	1
Total	395	185	188	772

Fiscal Year Totals.

The number of necropsies by species and disposition for March 1, 2003 – February 29, 2004

	Experimental	Spontaneous	Perinatal*	Total
Chinese-origin *Macaca mulatta*	59	8	9	76
Indian-origin *Macaca mulatta*	280	92	81	453
Macaca fascicularis	8	0	0	8
Macaca nemestrina	29	53	61	143
Chlorcebus aethiops	6	0	1	7
Papio species	13	23	34	70
Cercocebus torquatus atys	3	1	2	6
Total	398	177	188	763

*Perinatal totals include deaths at <30 days of age, stillbirths, abortions and intrauterine deaths.

Histopathology Summary Jan 25, 2003 To Jan 24, 2004
(No. of Blocks, Slides Produced)

	Pathology	Vet. Med.	Bacteriol/ Parasitol.	Gene Therapy	AIDS related	Outside invest.	Micro.	Totals
NECROPSY	285	3418	9	0	4853	385	0	8,950
BIOPSY	246	23	0	0	26	2	38	335
MISCELL.	185	15	0	0	67	0	0	267
SPECIAL STAINS	525	36	5	0	9	34	6	615
DUPLICATES	4959	110	358	0	1579	399	104	7,509
BLOCK ONLY	422	929	0	0	438	99	24	1,912
CRYOSECTIONS	3915	0	295	255	0	808	0	5,273
TOTALS	10,537	4,531	667	255	6,972	1,727	172	24,861

The **Molecular Pathology Core Laboratory** is staffed by a Medical Research Specialist, a Medical Technician, and a Laboratory Supervisor. This core provides molecular pathology services to specific research projects as requested. Current services include the generation of labeled RNA and DNA probes (for cytokines, EGFP, and SIV) via *in vitro* transcription or random primed labeling, *in situ* hybridization on paraffin and frozen sections, and molecular manipulation of genetic and plasmid material to provide the necessary templates. This section of the pathology division also provides a significant amount of consulting regarding molecular techniques to investigators. The table below indicates the actual number of tests that were performed in the laboratory from February 15, 2003 to February 14, 2004, but the laboratory also provides considerable time teaching and training other scientists, technicians, and postdoctoral fellows in molecular biology techniques.

Molecular Pathology Core Laboratory Summary, February 15, 2003 to February 14, 2004

Technique Performed	TNPRC Scientists	Affiliate Scientists	Totals
In situ hybridization	271	3	248
Apoptosis (various techniques)	52		52
Cytospins	48		48
DNA/RNA Digests	55		55
DNA Preps	146		146
Immunohistochemistries	715		125
PCR Reactions	621	45	666
Probe Labeling	40	3	45
TOTALS:	**1332**	**48**	**1385**

The **Clinical Pathology Core Laboratory** is staffed with two Medical Research Specialists and a Laboratory Supervisor, all three of whom are ASCP registered Medical Technologists. The Laboratory Supervisor is [name] The two Medical Research Specialists are [names] a laboratory technician, retired November 30, 2003. [name] was hired in August 2003 as the replacement for [name]

The primary responsibility of this unit is to perform hematology, clinical chemistry, and bacteriology for the medical care of the animal colony and in support of research projects. Work was done for 40 different investigators in the time period from February 1, 2003 through January 31, 2004. This represents service to 88 separate projects (29 base grant, and 58 grant or contract supported projects.

The Clinical Pathology Laboratory also provided occupational health and safety functions for the Center from June 2003 to December 2003 during the transition period cause by the absence of a nurse at the Center. These functions have since been transferred back to the Occupational Health and Safety Office. In 2003 the Clinical Laboratory staff performed

198 tuberculin tests, and 61 venipunctures; (15 employee accident/injury, 6 follow-up bleeds and 40 new employee baseline). Serum was also banked and recorded from all cases and documentation provided to the IACUC.

The Clinical Pathology Laboratory also provided service to the vivarium by separating and diluting mouse serum. Serum separation and banking were also done for several investigators and veterinarians. The total number of routine cultures includes 919 cage cultures. These are environmental swabs taken to verify sterility procedures in the cage washers. We do not have the ability to enter these in the computer database at this time. The utilization of the Clinical Laboratory is summarized in the table below.

Clinical Pathology Laboratory Summary; February 15, 2003 to February 14, 2004

	NECROPSY	GRANTS/ CONTRACTS	BASE GRANT	TOTALS
BACTERIOLOGY				
Routine & Clinical Cultures	118	237	1,005	**1,360**
Colon & Rectal Cultures	585	846	2,547	**3,978**
Sensitivities	-	128	175	**303**
Acid Fast Smears	-	-	34	**34**
Total Bacteriology Units	703	1,211	3761	**5,675**
CLINICAL CHEMISTRIES				
Total Chemistry Units		27,899	15,750	**43,649**
HEMATOLOGY				
Complete Blood Counts (6 units)		25,150	7,250	**32,400**
Platelet Counts		5,030	1,450	**6,480**
Reticulocyte Counts		138	29	**167**
Total Hematology Units		30,318	8,729	**39,047**
URINALYSIS		19	11	**30**
OCCULT BLOOD		2	5	**7**
FUNGUS CULTURE			1	**1**
YEAST CULTURE			1	**1**
BIOPSY/APSIRATES		9	14	**23**
CSF CELL COUNTS				**14**
SMEARS REVIEWED				**1,705**
EXTRA SLIDES MADE				**1,232**

BACTERIOLOGY SUMMARY FOR 03/01/03 - 02/29/04

Organism	Count	Organism	Count
AEROMONAS HYDROPHILIA	7	NEGATIVE CULTURE	104
ALCALIGENES, NOS	1	NEISSERIA, NOS	1
ALPHA HEMOLYTIC STREPTOCOCCUS, NOS	57	NO AFB FOUND	33
BACILLUS, GRAM NEGATIVE	2	NO CAMPYLOBACTER ISOLATED	890
BACILLUS, GRAM POSITIVE	23	NO ENTERIC PATHOGENS ISOLATED	1,278
BACTERIUM, GRAM NEGATIVE	1	NO YERSINIA ISOLATED	1,282
BETA HEMOLYTIC STREPTOCOCCUS, NOS	39	PASTEURELLA MULTOCIDA	2
BORDETELLA BRONCHOSEPTICA	1	POSITIVE	6
CAMPYLOBACTER COLI	429	PROTEUS MIRABILIS	17
CAMPYLOBACTER JEJUNI SS. JEJUNI	21	PROTEUS VULGARIS	16
CANDIDA ALBICANS	1	PROVIDENCIA STUARTII	1
CHROMOBACTERIUM VIOLACEUM	2	PSEUDOMONAS AERUGINOSA	9
CITROBACTER FREUNDII	4	PSEUDOMONAS, NOS	9
COCCUS , GRAM POSITIVE	4	SERRATIA MARCESCENS	1
CORYNEBACTERIUM, NOS	52	SHIGELLA FLEXNERI (GROUP B)	60
CRYPTOCOCCUS, NOS	2	STAPHYLOCOCCUS AUREUS	11
E. COLI FIMBRIAE	1	STAPHYLOCOCCUS, HEMOLYTIC, COAGULASE NEG	38
EIKENELLA CORRODENS	2	STAPHYLOCOCCUS, HEMOLYTIC, COAGULASE POS	139
ENTEROBACTER CLOACAE	6	STAPHYLOCOCCUS, NON-HEMOLYTIC, COAGULASE,NEG	54
ENTEROBACTER, NOS	3	STENOTROPHOMONAS MALTOPHILIA	2
ESCHERICHIA COLI	25	STREPTOCOCCUS FECALIS	35
GAMMA HEMOLYTIC STREPTOCOCCUS, NOS	14	STREPTOCOCCUS GROUP A,NOS	2
KLEBSIELLA OXYTOCA	2	STREPTOCOCCUS GROUP D, NOS	5
KLEBSIELLA, NOS	6	STREPTOCOCCUS PNEUMONIAE	2
LACTOBACILLUS, NOS	6	YEAST, NOS	3
MICROBIAL SWAB: NORMAL FLORA	31	YERSINIA ENTEROCOLITICIA	41
MORAXELLA, NOS	37	YERSINIA PSEUDOTUBERCULOSIS	16
MORGANELLA MORGANII	6	TOTAL:	4,848
NEGATIVE	6		

The Confocal Microscopy and Image Analysis Core. This Core provides state-of-the-art confocal microscopy, multilabel fluorescent labeling and detection, and image analysis support to every Division in the TNPRC, and to numerous affiliate research scientists at several institutions. The Core has a Leica TCS SP2 laser scanning confocal microscope system equipped with 3 lasers, with 6 laser lines available, capable of simultaneously collecting information in four channels (3 fluorescent and one for differential interference contrast). The system is attached to two microscopes, an upright (DMRE) and inverted (DMIRE2), that allow for confocal microscopy of fixed preparations as well as living cells. The confocal system offers such benefits as: a) Multi-dimensional imaging, as it is possible to obtain images in four dimensions; length (x axis), width (y axis), depth (z axis) and time (t); b) resolution improvement; c) contrast improvement, and; e) multicolor imaging. The image analysis system for transmitted light is based in the Leica DMRE microscope, a Spot camera and the latest ImagePro software in a dedicated work station for investigators requiring image analysis.

Dr. Xavier Alvarez is responsible for maintaining the equipment and assisting investigators with proper preparation of samples, use of equipment and analysis of results. The equipment has been used for a variety of purposes including: colocalization of green fluorescent protein (GFP) expressing SIV and T cell markers; localization of SIV-specific cytotoxic T cells using tetramer technology in tissues; colocalization of GFP and brain cell markers; colocalization of malaria parasites, Hofbauer cells and cytokine producing cells; colocalization of Borrelia, brain cell markers and cytokine producing astrocytes; colocalization of SIV by in situ hibridization and dendritic cell markers; and colocalization of *M. tuberculosis*, SIV and cell markers simultanously.

This core provides services to specific research projects ranging from tissue to publication or presentation of results, from both live and fixed tissues. Encompassing services are: generation of preliminary results for grant applications, training of researcher capturing the images, and assistance with the final micrographs or movie. This period has been very productive with high quality results leading to eight published papers, of which four of the confocal images generated were selected for the covers of the journals. This section of the pathology department also provides a significant amount of consulting and training of labeling by molecular techniques, molecular probes and antibodies to in house and affiliated investigators. The table below indicates an estimation of the number of tests that were performed and the amount of data generated (all pictures are computer generated therefore an estimation of load handled are the gigabites accumulated) We generate 8-10 gigabytes per week from the Leica TCS. The summary is from February 28, 2003 to March 1, 2004. Included in the table are the numbers of investigators/technicians trained in the use of the confocal microscope.

Confocal Microscopy Core Facility Summary, February 28, 2003 to March 1, 2004

Service/Technique Performed	TNPRC Scientists Slides	Affiliate Scientists Slides	Totals
3 color fluorescent in situ hybridization-SIV and 2 antigens	200	4	204
3 color fluorescent apoptosis and 2 antigens	40	20	60
3 color GFP and 2 antigens	60	60	120
2 and 3 color Immunohistochemistries	400	200	600
2-3 color SIV-gag Tetramer and 2 antigens	50		50
2 color 3chanels live microscopy	12		12
Bites generated 300 GB			
TOTALS:	**762**	**284**	**1046**

Profile of usage of the Confocal Microscopy Core Facility Summary, February 28, 2003 to March 1, 2004

User	TNPRC Scientists	Hours used	Affiliate Scientists	Hours used	Slots Total
PI-solo	1	63	1	14	22
PI-assisted	3	56			16
Post Doctoral Fellow-solo	4	494	1	14	141
Post Doctoral Fellow-assisted	6	203			58
Technician-solo	2	371	1	175	178
Technician-assisted	4	77			22
Pathologist-assisted	2	161			46
Manager-solo	1	49			14
TOTALS:	**23**	1474	**3**	203	**479**

GENE THERAPY OVERVIEW

Bruce A. Bunnell, Ph.D. is the Chair of the Division of Gene Therapy. The Division has grown to include TNPRC employees. The division also hosts two Research Associates that are employed by Division Affiliate Scientists. The mission of the Division is two-fold. The

primary mission of the Division of Gene Therapy has been to establish a strong independent research program. The Division is currently performing novel research in the areas of stem cell biology and recombinant virus vector mediated gene transfer on the nonhuman primate model. Dr. Bunnell's group also has extensive experience in fetal gene transfer and has in collaboration with Veterinary Medicine, developed stereotaxic delivery techniques for the central nervous system.

Dr. Bunnell's research group has focused a significant portion of their efforts on the isolation and characterization mesenchymal stem cells (MSC) from the bone marrow and adipose tissue of rhesus macaques (*Macaca mulatta*) that are able to differentiate into several mesodermal lineages, as well as neural lineage cells. MSCs were isolated from bone marrow (BMSCs) and adipose tissue (AMSCs) by an adherent tissue culture protocol. Upon isolation, cells were characterized for their biologic and lineage differentiation efficiency *in vitro* and *in vivo*. Dr. Bunnell's group has determined that MSCs isolated from either bone marrow or adipose tissue may be a viable source of stem cells for therapy of inherited genetic diseases in many organ systems. The successful isolation of rhesus MSCs will provide the opportunity to perform preclinical transplantation studies and therapeutic interventions in a nonhuman primate model of Krabbe's disease.

In addition, Dr. Bunnell has assumed responsibility for the colony of rhesus macaques that have the only genetic disease captured in nonhuman primates, the Krabbe's monkeys. Dr. Bunnell, in collaboration with scientists from the Division of Veterinary Medicine, has been focused on expansion of the numbers of affected animals in an attempt to make animals available for research projects. Dr. Bunnell is presently developing vector and stem cell-based therapies for testing in the Krabbe's model.

The Division of Gene Therapy has several ongoing collaborations with scientists outside the TNPRC. Dr. Bunnell has continued his collaborations with Drs. Prockop and Phinney from the Tulane Center for Gene Therapy on the isolation and characterization of rhesus mesenchymal stem cells. Dr. Vincent LaRussa has begun a series of studies aimed at testing the ability of hematopoietic cells to become liver cells.

In collaboration with [name] the Division of Gene Therapy will be testing recombinant lentivirus vectors that have been developed for Krabbe's Disease in the nonhuman primate model.

The Division also has a long-standing collaboration with [name] from the State University of New York at Syracuse; we are investigating the role of dendritic cells, since they play a central role in the presentation of antigens to naïve T-cells and the induction of primary cellular immune response to HIV. We have determined that dendritic cells, made to stably express lentivirus gene products with lentivirus vectors can efficiently elicit antiviral immune responses. We are presently optimizing the conditions necessary for the lentivirus vectors to stably express SIV genes in monocyte-derived dendritic cells from rhesus macaques. We will then evaluate whether dendritic cells transduced with SIV genes migrate to draining lymphoid tissues, thereby increasing their likelihood of interacting with SIV-specific cytotoxic T-

lymphocyte (CTL) precursors. We will determine next if rhesus macaques injected with the transduced cells generate anti-SIV CTL *in vivo*.

In collaboration with Dr. Dan Weiss, University of Vermont and [name], University of Pittsburgh we have been studying methods of improving gene transfer to the lung, with a focus on cystic fibrosis. One of the current limitations to successful lung gene therapy is effective vector delivery to target airway and alveolar epithelial cells. Perflurochemical liquids instilled into the lung improve gene transfer after intratracheal administration of adenovirus vectors in rodents. We studied rhesus monkeys to determine whether this method would similarly enhance gene expression in primates. Animals received recombinant adeno-associated virus (AAV) alone, AAV with perflubron, or perflubron alone. Monkeys that received AAV with perflubron showed gene expression in more cells and with a more widespread distribution.

A new collaboration that has been undertaken this year is with [name] from the University of Pennsylvania. We have been investigating the ability of alternative AAV serotypes to provide gene transfer to the rhesus CNS. We have performed a study mapping the transduction patterns of vectors derived from AAV1, 2 and 7 in the rhesus CNS. In collaboration with TNPRC Scientists from the Divisions of Veterinary Medicine, Pathology and the Confocal Microscopy core, we have successfully performed stereotaxic delivery of the vectors and assessed gene transfer and expression of these vector systems. All vector systems showed a broad spectrum of high levels of gene transfer and expression.

MICROBIOLOGY AND IMMUNOLOGY DIVISION

The mission of the Microbiology and Immunology (M&I) Division is to develop and use non-human primate models of human infectious diseases and to improve the quality of the NHP colony at the Tulane National Primate Research Center (TNPRC). The M&I personnel consist of 8 doctorate level faculty, 13 research technologists, 1 postdoctoral fellow, 1 visiting scientist and 52 affiliate scientists. The faculty increased by 1 in the past year when Dr. Binhua Ling was promoted from post-doctoral fellow in the division to Instructor. Dr. Preston A. Marx is the division chair since 2001. The mission also includes the support of the National Institutes of Health funded affiliate scientists at other institutions. Our goals emphasize the acquisition of National Institutes of Health funding to build strong faculty research programs and collaborative research programs with affiliate scientists. Divisional facilities include laboratories for conducting research on pathogenic viruses, bacteria and protozoas.

Faculty research programs cover a broad area of microbial diseases and Non-Human Primate models. The largest program is Acquired Immune Deficiency Syndrome (AIDS). AIDS vaccines, vaginal microbicides, HIV and SIV phylogenetics and AIDS pathogenesis represent the most significant areas of effort in AIDS. Other viral programs include Human/Simian T cell Leukemia Virus (HTLV/STLV), Simian Varicella Virus (SVV), Varicella Zoster virus (VZV), SVV-VZV hybrid viruses, Rotaviruses and Respiratory Syncytial Virus (RSV). Diseases caused by the eukaryotic organisms belonging to the Microsporidia group are represented. Finally, research on intestinal bacterial diseases of rhesus involving Campylobacter and Helicobacter are ongoing.

Division Goals

Future goals can be divided into 3 areas, (a) faculty development and recruiting, (2) new research programs and, (3) upgrading research space.

New research areas will take advantage of the Tulane award for construction of a[ ]sq. ft. Regional Biocontainment Laboratory (RBL). The RBL will contain BL3 NHP and rodent housing and BL3 laboratories. Three new cores are being established for Viral Diagnostics, Cellular Immunology and Standardized Virus Stock Production. The viral diagnostic core will provide testing for adventitious retroviruses and Herpes B virus. A real time PCR lab will also be part of this core.

The division participated in a successful Center for AIDS Research (CFAR) proposal with the University of Pennsylvania. The CFAR will bring a large group of highly productive affiliate scientists to the TNPRC. New expertise, especially in the areas of HIV/SIV co-receptors, new vaccines and pathogenesis, will greatly enhance our program. The CFAR will simulcast seminars, which will greatly expand our exposure to current state of the art research at other institutions.

Faculty recruitment will focus on positions in immunology and vaccine vector development.

DIVISION OF VETERINARY MEDICINE

TNPRC Animal Colonies. The TNPRC animal colonies are comprised of the research colony, preassignment/holding colony, and the breeding colonies. The breeding colonies are further broken down into the conventional/source breeding colony and the SPF colonies. The SPF colonies consist of the AIDS SPF and Center SPF breeding colonies.

As of March 1, 2004, nine species of nonhuman primates are represented at the TNPRC for a total population of 4,857 animals. Data in the "Colony Statistics" section of this report includes projections through April 30 as requested by NCRR. Thus, the numbers in the tables and those described below are not identical.

Of the animals in the colony, the African species are *Cercocebus torquatus atys*, *Cercocebus torquatus lunulatus*, *Chlorcebus aethiops*, *Erythrocebus patas*, and *Papio spp*. Macaque species consist of *Macaca mulatta*, *Macaca nemestrina* and *Macaca fasicularis*. The TNPRC has both Chinese origin and Indian origin *M. mulatta*. These regional variants have been maintained as separate populations in the breeding colony. The Center has a small number of *Saimiri sciureus* maintained for malaria research.

Research colony. The research colony (n=821) is comprised of animals assigned to active research projects with approved IACUC protocols and funding. The research colony currently consists of *M. mulatta* (Indian n=621; Chinese n=130), *M. nemestrina* (n=19), *M. fasicularis* (n=25), Papio *spp.* (n=5), *C. aethiops* (n=18), *S. sciureus* (n=3), and *E. patas* (n=1). Support for

animals in the research colony is provided through sources other than the base grant except for animals assigned to the pilot study program.

Preassignment colony. Animals assigned to the preassignment colony (n=202) are held for anticipated assignment to research programs. The preassignment/holding colony currently consists of *M. mulatta* (Indian n=144; Chinese n=45), *M. nemestrina* (n=3), *C. aethiops* (n=1), *Papio spp.* (n=5), and *E. patas* (n=4). Animals assigned to the colony are those that have been released from prior assignment or derived from the breeding colonies. Animals are evaluated individually by veterinarians by physical examination, viral screening and clinical laboratory analysis to determine fitness for assignment to research protocols. This group of animals is supported by base grant funding until the time that they are assigned to the research colony.

Holding colony. Animals assigned to the holding colony (n=106) are being used or will be used as foster mothers, foster grandparents, timed breeders, or have had indeterminate viral test results, which require follow-up testing. The holding colony currently consists of *M. mulatta* (Indian n=103; Chinese n=3).

Breeding colonies. The breeding colonies make up the largest population (n=3,728) of nonhuman primates at the TNPRC. The WaNPRC breeding colonies which are supported by the WaNPRC are housed at the TNPRC and consist of M. nemestrina (n=779) and Papio spp. (n=516). The balance of animals (n=2,433) constitutes the TNPRC breeding colonies. With exception of the animals housed for treatment of disease, the animals assigned to the breeding colony are housed in outdoor enclosures in social groups.

The conventional/source breeding colony is made up of *M. mulatta* (Indian n=933; Chinese n=194), *C.t.atys* (n=32), *C.t.lunulatus* (n=8), *M. nemestrina* (n=14). A National Institute of Aging (NIA) set aside colony (n=28) is part of the conventional/source colony. The conventional/source colony is negative for Type D simian retrovirus (SRV) as a result of a test and removal program.

The AIDS SPF colony (Indian origin *M. mulatta* n=1059) has been derived using funding from two resource grants (U42,U24) to create and expand the number of SPF animals to be assigned exclusively to AIDS research programs. The Center SPF (*M. mulatta*, Indian n=53; Chinese n=112) colony will be used to supply animals for research programs other than AIDS. All animals assigned to the TNPRC SPF colonies are derived from the conventional /source colonies.

Breeding Colony Management. The Breeding Colonies of the TNPRC provide nonhuman primates to core investigators and affiliate investigators for research. Nonhuman primates are housed in stable social groups in large fenced corrals that allow for the establishment of a normal social distribution similar to that found in feral troops. The breeding colony management program is designed and administered by veterinarians, the breeding colony manager, environmental enrichment coordinator, and the breeding colony epidemiologist. In addition, the Tulane Resource Allocation Committee (TRAC) facilitates breeding colony management by determining appropriate allocation of animals for assignment to research protocols based on

statistical analysis of colony demographics. All animals in the colony are tracked via a centralized, computer based animal records system.

The demand for animals from the SPF and conventional/source colonies has increased dramatically. In addition, there has been an increase in the number of requests from investigators for more thoroughly characterized nonhuman primates with regard to viral status and genetic background. The breeding management, viral screening and genetic testing programs are in place to maximize the use of this valuable animal resource. Our long range goal is to rapidly expand the SPF breeding colonies while decreasing the size of the source/conventional colony.

Conventional Breeding Colony. The Conventional Breeding Colony provides nonhuman primates for assignment to research protocols. In addition, the conventional colony is the source for animals populating the SPF colonies.

Screening of the conventional breeding colony is performed annually for the presence of simian Type D retrovirus (SRV). Pooled blood samples from corral members are used for PCR testing with follow-up individual PCR screening in positive test pools. In addition, antibody screening for SRV was performed in all animals in the conventional colony in 2003. PCR and antibody positive animals were removed from the conventional colony (n= 9 of 1346 animals tested in 2003-2004). All assays are performed by the Simian Retrovirus Laboratory at the University of California, Davis.

Specific Pathogen Free Breeding Colony. Derivation of a Specific Pathogen Free (SPF) breeding colony of rhesus monkeys was instituted in 2001 through a U42 grant from NCRR and continued expansion in 2002-2003 with the award of a U24 grant from NCRR. The Center SPF colony was created in 2002 to create a group of SPF rhesus that could be used in nonAIDS research programs. Expansion of the three SPF colonies will have the dual benefit of reducing health risks to personnel and producing animals free from viral infections that impact research protocols. The SPF colony members are individually tested four times a year by PCR and antibody testing for STLV I, SIV, simian retrovirus type D, and herpes B-virus. Screening for simian immunodeficiency virus (SIV), Type D simian retrovirus (SRV) and simian T lymphotrophic virus I (STLV I) is performed at the University of California Simian Retrovirus Reference Laboratory. Herpes B-virus testing is performed by The National B Virus Resource Center at Georgia State University. In the 2004 birth season, the Expanded SPF program was created using 12 animals born to the Conventional SPF colony. The animals will be seronegative for the four viruses of the Conventional SPF colony. In addition, five other viral agents are excluded. These agents are simian foamy virus, SV40, rhesus rhadinovirus, lymphocryptovirus and cytomegalovirus. Several gastro intestinal tract pathogens will also be monitored for prevalence. The present census of the SPF colonies continues to match our long term projections for the colony. Plans are to add no fewer than 300 animals per year to the SPF colonies.

In 2003-2004, 18 SPF animals were assigned to affiliate investigators and one animal was assigned to a core investigator for AIDS research studies.

Analysis of the Breeding Colonies. The regular analysis of the breeding and research colonies has resulted in more efficient use of animals at the Center. A decision was made to increase the use of animals on multiple projects simultaneously when possible and to enhance collaboration between individual investigators so that maximal use of animals would occur. Monthly assessments of animal availability have been invaluable in tracking the use of animals assigned to research projects. A monthly statistical analysis and quarterly report of breeding colony demographics and production have been developed by the Animal Colony Epidemiologist for use by the Division of Veterinary Medicine and the Tulane Resource Allocation Committee. These reports provide valuable information used in decision-making processes for animal assignment and colony management. Information from quarterly statistical analyses aids in the creation of management strategies that will expand the present colony while at the same time attempt to decrease inbreeding. The quarterly colony analysis will also help determine the number and type of animals that require genetic testing to achieve established colony goals. In addition, the analysis will permit us to closely monitor the results of changes made to the breeding colony management plan.

Arthropod vector surveillance and control/ Vector borne disease surveillance. We have continued to collect mosquitoes on a weekly basis from the breeding corral area using CDC light traps and gravid traps. Mosquito pools were examined for West Nile Virus (WNV), St. Louis Encephalitis Virus (SLE), and Eastern Equine Encephalitis Virus (EEE) using a dipstick format. On June 25, 2003 we detected a mosquito pool (*Culex salinarius*) positive for WNV. No further positive pools have been detected. We are now using a PCR-based test which should be more sensitive.

During 2003 we examined 400 rhesus macaques, 189 pigtail macaques and 183 baboons for vector-borne parasites in the blood. Each animal had thick and thin blood smears made for malaria parasites, a Knott's test for filarid parasites and plasma taken for serologic evidence of exposure to *Trypanosoma cruzi*. Blood samples to date have been negative for parasites.

We will continue blood sampling until all animals in the breeding corrals have been examined for parasites of interest. We will also continue weekly monitoring of mosquito populations in the vicinity of the breeding corrals.

Resource Allocation. The Tulane Resource Allocation Committee (TRAC) was created to evaluate all proposed research projects that request utilization of the resources of the Center. The Committee, composed of ten members, includes research scientists, veterinarians, program coordinators and the animal colony epidemiologist. The Chair of the Committee is the Associate Director for Veterinary Resources and Chair of the Division of Veterinary Medicine. Several members represent facilities and programs from outside the Center. Requests are reviewed after both IACUC approval and funding is in place. Once TRAC approval is in place, the Division of Veterinary Medicine assigns the animal or space resource as it becomes available.

From March 2003 to March 2004, 544 animals have been requested by core and affiliate investigators for assignment to research projects. When compared to 2002-2003, this number demonstrates an increase of 119 animals (↑28%) requested. Of the total assignments, 200 animals

were made available to core investigators and 153 were made available to outside investigators. Of the total assignments from March 2003 to March 2004, 57% were to core investigators and 43% were to affiliate investigators. During the past reporting period, five investigator requests (52 animals) were deferred because no animals were available for assignment. A program to utilize animals previously assigned to infectious disease studies (SIV) was instituted in 2003. The animals are offered to core and affiliate scientists with appropriate approved IACUC protocols after release from the infectious disease study. Specific information related to TRAC activity can be found in the tables below.

The total number of nonhuman primates requested, allocated, and assigned by investigator status
(March 2003 to March 2004)

	Number of	Number of Animals						
Status	Requests	Requested[a]	Amended[b]	Allocated[c]	Assigned[d]	Assignment Pending[e]	Deferred[f]	Review Pending[g]
Core	32	308	269	249	200	49	0	20
Affiliate	29	236	228	184	153	31	31	13
Total	61	544	497	433	353	80	31	33

[a] Reflects the number of animals initially requested
[b] Reflects the number of animals in final request after changes by PI
[c] Reflects the number of animals allocated for assignment by the TRAC
[d] Reflects the number of animals that have been assigned from allocation
[e] Reflects the number of animals that remain to be assigned when they become available
[f] Reflects the number of animals that have been requested, but not currently approved for allocation
[g] Reflects the number of animals that have been requested on applications not yet reviewed by the TRAC

The total number of animals requested, allocated, and assigned by species*
(March 2003 to March 2004)

	Number of Animals						
Species	Requested	Amended	Allocated	Assigned	Assignment Pending	Deferred	Review Pending
M.fasiscularis	37	36	36	16	20	0	0
M.mulatta	473	435	371	312	59	31	33
M.nemestrina	10	10	10	10	0	0	0
C.aethiops	23	15	15	15	0	0	0
Papio sp.	1	1	1	0	1	0	0
Total	544	497	433	353	80	31	33

*Refer to previous table footnotes for explanation of categories

The number of animals requested, allocated, and assigned by investigator status and species.
(March 2003 to March 2004)

	Number Requested		Number Amended		Number Allocated		Number Assigned		Number Pending		Number Deferred		To be Reviewed	
Species	Core	Affiliate	Core	Affiliate	Core	Affiliate	Core	Affiliate	Core	Affiliate	Core	Affiliate	Core	Affiliate
M.fasicularis	20	17	20	16	20	16	0	16	20	0	0	0	0	0
M.mulatta	255	218	224	211	204	167	175	137	29	30	0	31	20	13
M.nemestrina	10	0	10	0	10	0	10	0	0	0	0	0	0	0
C.aethiops	23	0	15	0	15	0	15	0	0	0	0	0	0	0
Papio sp.	0	1	0	1	0	1	0	0	0	1	0	0	0	0
Total	308	236	269	228	249	184	200	153	49	31	0	31	20	13

The number of *M.mulatta* allocated and assigned from the TNPRC Infectious Disease Use Program*
(March 2003 to March 2004)

Status	Allocated	Assigned	Assignment Pending
Core	26	23	0
Affiliate	4	4	0
Total	**29**	**27**	**0**

* Animals released from infectious disease studies that were allocated and assigned to core and affiliate investigators

The number of *M.mulatta* allocated and assigned from NIA holding colony
(March 2003 to March 2004)

Status	Requested	Amended	Allocated	Assigned	Assignment Pending
Core	0	0	0	0	0
Affiliate	55	48	48	32	16
Total	55	48	48	32	16

Serum bank. The TNPRC Rhesus Monkey Serum Bank is maintained by the Division of Veterinary Medicine and stores serum and plasma samples collected during routine inventory procedures for the breeding colony. The serum bank also includes samples collected during routine monitoring of viral status for our SPF colony. The purpose of the serum bank is to provide samples for retrospective analysis of the colony and for investigator use, if required, to alleviate the need to access animals from the colony for serum samples on multiple occasions. The samples have been catalogued and entered into the Center's database.

PROGRESS IN CORE SERVICE UNITS

The Veterinary Resources Program is administered through the Division of Veterinary Medicine. Six individual units work in conjunction to accomplish Division objectives. The units are the Office of the Associate Director for Veterinary Resources and Chair Division of Veterinary Medicine, Clinical and Research Medicine, Research Resources, Animal Resources, Environmental Enrichment, and Reproductive Biology. The Division currently has approximately 100 approved positions which provide for the care of approximately 5000 nonhuman primates.

Faculty Additions/Deletions
Deletions: [ ]
Additions: Erin Ribka, D.V.M.

Office of the Associate Director for Veterinary Resources and Chair of the Division of Veterinary Medicine

The Office of the Associate Director for Veterinary Resources and Chair of the Division of Veterinary Medicine is the central administrative unit of the Division. The Office of the Associate Director for Veterinary Resources provides centralized administration and coordination of the Center's animal resources and certain support services. This entails (1) providing for all aspects of care, husbandry and management of the animal colony, (2) provision of clinical veterinary medical care to the animal colony, (3) development and implementation of the nonhuman primate enrichment program to remain in compliance with USDA regulations, (4) maintenance and development of the animal records database, (5) provision of animal care and colony management to insure the availability of the resources and services needed to support Center research activities, (6) provision of veterinary care, research support, and animal care support, for investigators, and (7) collection of biological specimens (blood, tissues, etc.) for non-TNPRC investigators.

UNIT OF CLINICAL AND RESEARCH MEDICINE

The Unit of Clinical and Research Medicine in the Division of Veterinary Medicine provides preventive and clinical health care for the animal colonies of the TNPRC. Collaborative research activities and independent clinical research studies which focus on the diagnosis and treatment of spontaneous clinical disease in nonhuman primate populations are provided through the Unit. This unit is also responsible for providing research support to core and affiliate scientists, providing legally-mandated veterinary consultation for investigators planning studies that will use nonhuman primates and assisting the TNPRC in complying with relevant regulatory requirements. With the addition of Dr. Erin Ribka in 2003, the unit consists of six clinical veterinarians and seven veterinary technicians.

Training Programs

The Unit of Clinical and Research Medicine provides for the administration and oversight of the Laboratory Animal Medicine Preceptorship Program, Laboratory Animal Medicine Residency Program and the Division of Veterinary Medicine Training Committee

Laboratory Animal Medicine Preceptorship Program. Veterinary students enrolled in the professional curriculum and post graduate veterinarians participate in the program. Three individuals participated in the Laboratory Animal Medicine Preceptorship Program in 2003-2004. These included two fourth year veterinary students from the Louisiana State University School of Veterinary Medicine. [name] a veterinarian from Bombay, India received extensive training in our Program from March 2003-March 2004. Our training program exposes veterinary students and graduate veterinarians to all aspects of the research environment including regulatory issues, research support, colony health surveillance, clinical medicine and surgery. In addition, the Division of Pathology at TNPRC provided instruction in pathological findings of spontaneous and experimental disease in nonhuman primates to these students.

Laboratory Animal Medicine Residency Program. The integration of the Division of Veterinary Medicine into the American College of Laboratory Animal Medicine (ACLAM) accredited Laboratory Animal Medicine Residency program at the LSU School of Veterinary Medicine provides for a [illegible] resident position at the TNPRC that will focus on nonhuman primate medicine and surgery. The in house residency program runs concurrently with the Laboratory Animal Medicine Preceptorship Program (described above) which provides opportunities for students outside of the Tulane/LSU system. Only a few ACLAM accredited residency programs exist that offer a similar exposure to nonhuman primates. The duration of the program is two years and provides eligibility for board certification by ACLAM. Residents spend 9 months of each year at the TNPRC with the balance spent at the LSU SVM for didactic course work including pathology of laboratory animals. Currently, the TNPRC has four ACLAM board certified veterinarians on faculty that provide training for residents. [name] started in July 2003 and is the first resident to participate in our ACLAM accredited residency program.

Training Committee. The Training Committee of the Division of Veterinary Medicine provides training to employees of the Division in addition to new employee training directed by the TNPRC IACUC. The Training Committee consists of veterinarians, management personnel, quality assurance personnel and the TNPRC Occupational Health and Safety Nurse. A series of training modules using PowerPoint presentations for topics such as occupational health and safety topics, use of personal protective equipment, disease control measures, animal observations, and environmental enrichment were created and presented at Division meetings in 2003-2004.

PREVENTIVE MEDICINE

The preventive medicine program provides for regular clinical assessments of the breeding and research colonies as well as quarantine procedures for ill and imported animals.

Quarantine. All nonhuman primates are acquired lawfully from established USDA registered primate importers. Quarantine and conditioning of nonhuman primates is done in Building F quarantine area. All imported nonhuman primates are quarantined for a minimum of 90 days. During this time they are TB tested using standard techniques and mammalian tuberculin every two weeks. In addition, several complete blood counts, selected blood chemistries, multiple stool cultures, thick and thin blood films, and Knotts tests and viral testing are performed on a routine basis. Physical examinations are performed by veterinarians on a regular basis. Animals completing the 90-day quarantine period without problems are moved into the research or breeding colonies. A reference chest radiograph is evaluated before transfer and filed for future reference. Animals arriving in quarantine are kept in groups in which they arrive and shipments are not mixed in individual rooms.

In 2003-2004, 187 nonhuman primates of three different species were imported to the TNPRC and participated in the quarantine program.

Breeding colonies. The health status of the breeding colonies is monitored on a daily basis. Animals are observed during feeding for injuries or illness. A minimum of twice yearly they are gathered for tuberculin testing, ultrasound pregnancy examinations, examination of infants, tattooing of infants, updating of genealogical records, weights, and collection of demographic data. Necropsy of animals dying or culled from these colonies is performed and provides critical information related to breeding colony morbidity and mortality.

Ill animals from the breeding colonies are moved to several different facilities on the main campus for diagnosis and treatment of disease. The facilities are designated based on the viral status of the particular animal.

Research colony. Animal caretakers observe all animals daily during feeding and cleaning operations. These caretakers have been trained by senior technicians and the veterinary staff to observe animals closely for signs that indicate a change in normal behavior or well-being. Should such a change be seen, the caretaker will notify his supervisor immediately. The supervisor will, in turn, verbally notify one of the staff veterinarians and indicate the animal's identification number, location, and abnormal finding on the daily observation sheet for entry into the animal records database. In addition, the senior technical staff, veterinary staff, and the Quality Assurance Specialist make unannounced inspections.

Unit of Research Resources

The Unit of Research Resources provides facilities, technical support, and equipment necessary to provide for research programs utilizing surgery or imaging as a component of their programs. The Unit provides oversight for Radiology (fluoroscopy, plain films, ultrasound, MRI), Surgery and the Dispensary/Central Supply. These areas are utilized by nearly every research division and the veterinary staff at the Center.

Radiology. Radiology support is provided with a Continental 150KV, 300 ma fluoroscopy unit with image intensification. An appropriate darkroom is available and the area is supported with

an automatic 60 second film processor. Routine soft tissue and orthopedic studies are performed in addition to fluoroscopically guided vascular catheterization procedures, angiography, and renal function studies. In 2003-2004, 471 radiographic procedures were performed for clinical and research protocols. Over the same reporting period, 45 MRI procedures were performed for clinical and research protocols.

Surgery. Surgery is performed in either of two operating rooms in Building B. From May 1, 2003-February 29, 2004, 10 surgeons performed 134 major surgical procedures. Six hundred and eighty-eight minimally invasive endoscopic procedures were performed utilizing either rigid endoscopic video assisted techniques or flexible fiber optic gastrointestinal scopes. In addition, 336 peripheral lymph node biopsies and other minor surgical procedures were performed in support of research protocols. Detailed information on specific procedures is located in the tables below.

Surgical Procedures

Procedure	Number
lymph node biopsy	288
c-section	25
gastric catheter implant	21
embryo transfer	2
Mesenteric lymph node biopsies	20
stereotaxic intracerebral injections	19
hysterectomy	4
enucleation	3
Repair perforated intestines	2
venous catheterization	18
Cruciate repair	1
Repair AV fistula	1
intest. resec. and anastomosis	10
corneal transplant	1
lumbar fusion	3
trauma repair	9
inguinal hernia repair	3
exploratory laparotomy	31
fracture repair	5
limb amputation	2
skin biopsy	2
Total	**470**

Rigid Endoscopic Surgical Procedures

Procedure	Number
Colposcopy	93
Follicular aspiration (ovary)	13
Lung/thymic biopsy	9
Total procedures	**115**

Flexible Endoscopic Procedures

Procedure	Number
Bronchoalveolar lavage	169
Duodenal biopsy	392
Colonic biopsy	12
Total procedures	**573**

Dispensary/Central Supply. The Dispensary/Central Supply provides for the ready availability of supplies needed for the treatment of clinically ill animals, for routine husbandry practices, and for necessary protective clothing and equipment used by Division of Veterinary Medicine and research personnel.

Unit of Animal Resources

The Unit of Animal Resources is a service unit that provides routine husbandry care for the animal colonies at the Center. The Unit also has responsibility to provide support to the Units of Clinical and Research Medicine, Environmental Enrichment and Research Resources, and to core and affiliate scientists. The Unit assists the Center in complying with relevant regulatory requirements including but not limited to those of the USDA, PHS, and the US Fish and Wildlife Service.

Routine husbandry practices include the reporting of any abnormal clinical sign or activity by animals to the appropriate veterinary medical staff and faculty. Animal Care Technicians provide support during diagnostic and therapeutic procedures and the administration of the preventive medicine program. The unit closely coordinates its activities with research personnel to provide assistance, equipment and support for their work. The Unit of Animal Resources provides after hours care, which includes administration of treatments, collection of biologic samples for research activities and observation of animals. The TNPRC facilities are accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC).

The Unit staff consists of a Vivarium manager, a Breeding Colony Manager, a Quality Assurance Specialist, Animal Care Supervisors, and Animal Care Technicians. The Unit provides support for the TNPRC Breeding Colony, the Washington National Primate Research Center's (WANPRC) breeding colony housed at the TNPRC, and the research colony.

Unit of Environmental Enrichment

The Environmental Enrichment and behavioral research programs were expanded in 2003. An additional environmental enrichment technician position was created to support an enhanced enrichment program. Considerable progress was made in expanding the use of social housing for research animals. Over 200 monkeys were moved from single housing to a social setting. Also, a larger proportion of group integrations and reintroductions were monitored with sustained behavioral observation. Characterization of the hierarchies was accomplished for many corral groups. The intervention program for nonhuman primates was also expanded. A wider variety of enrichment devices and novel objects were incorporated in order to boost novelty for primates with behavioral problems. Behavioral pathology is also addressed with positive human interaction and pharmacological intervention. Environments were enhanced with additional structures in corrals and corncribs and an increased variety of portable objects. A systematic program for the monitoring of behavioral well-being and the success of ameliorative

interventions was put into place. Assessments of the success of a variety of enrichment techniques were conducted through the use of videotaping and behavioral data collection and analysis. Positive reinforcement training methods were incorporated into several research projects and was applied to management problems with individual animals.

The effectiveness of the program depends on a team approach, with collaboration between Enrichment Program staff, veterinary staff, animal caretakers, Physical Plant staff, and research staff. New enrichment devices/strategies and redesign of other devices/strategies continue to be sought and developed through collaborations with Center and outside personnel. As a member of the IACUC, the Program Coordinator is able to provide investigators with enrichment and housing options as well as tailor the enrichment implementation to specific research projects. The Enrichment Technicians provide an invaluable liaison between animal care staff, veterinarians, and Physical Plant staff ensuring daily program implementation. The Environmental Enrichment Unit contributes to the training and continuing education program for care staff and delivers presentations center-wide concerning nonhuman primate behavior, elements of the enrichment program and regulations concerning well-being.

Enrichment technicians conduct behavioral assessments of animals with behavioral problems, develop treatment plans in coordination with the Environmental Enrichment Coordinator and Veterinary staff, oversee treatment of psychologically challenged nonhuman primates. A system was created to flag all nonhuman primates with chronic behavioral problems. The flagging system alerts animal care technicians to the need for extra monitoring and the constant availability of the devices or techniques being used to treat individual animals. The incidence of self-injurious behavior (SIB) remains low. Those monkeys exhibiting SIB have been successfully managed through a combination of behavioral and clinical interventions. Through retrospective case-control analyses, significant factors have been identified and enable staff to target those individuals at most risk for developing SIB and apply prevention strategies. Data from the enrichment program is maintained in the enrichment tracking database that is linked to the IACUC tracking database as part of the centerwide computer system.

The continuing use of our foster mother protocol and introduction of cesarean-delivered infants to their biological mothers has resulted in fewer infants from our breeding colony that must be raised in the nursery. Infants who must be nursery-reared continue to receive enriched homecages and social opportunities through age-matched peer play groups and housing with older, culled animals from the breeding colony as appropriate for the monkey's age, research status, viral status, and medical status.

The purchase of modified cage dividers has permitted the use of protected contact housing for nonhuman primates. This technique has expanded the pool of caged research subjects who can be provided social contact without interfering with research protocols. Modified cage dividers also enable the implementation of staged, gradual social introduction to reduce the stress of social introduction and minimize risks of injury.

Unit of Reproductive Biology

Assisted Reproductive Technologies (ART)

The ART Core is administered through the Unit of Reproductive Biology in the Division of Veterinary Medicine. The program is focused on several areas of embryo production and embryo manipulation. The significance of ART in rhesus monkeys for biomedical research is growing with rapid advances in production, preservation and manipulation of embryos. These advances may ultimately facilitate genetic modification of embryos, the identification of embryos with specific genotypes, production of identical twins by embryo splitting or the production of rhesus infants by year-round transfer into pigtail females.

During the past year the focus of activities has been:

Production Of Embryos. These efforts were hampered by a scarcity of female rhesus monkeys. Nevertheless 10 oocyte aspirations were performed which resulted in 202 oocytes. Of these 159 were successfully fertilized by in vitro fertilization. Efforts were directed towards refinement of culture medium and cryopreservation. The standard medium containing 20% fetal calf serum has been replaced with a defined medium which should make embryo production more consistent because it will eliminate the variation inherent in the use of serum. We are currently determining whether embryos from a defined culture system can be frozen as successfully as those produced with serum.

We continued to develop the techniques to perform blastomere biopsies. This will be of tremendous benefit in identifying embryos of specific genotypes or sex. Work to date has shown that nearly 20% of biopsied embryos can reach the blastocyst stage following blastomere removal. We are currently in the process of determining whether such embryos can be successfully cryopreserved.

Continued work was directed towards developing a protocol that would facilitate cryopreservation of rhesus semen. We have tried two separate freezing protocols on three rhesus males. Overall, motility was acceptable immediately after thawing, but decreased significantly and rapidly within hours. We are currently testing and modifying additional protocols that are based on observations in other species.

In Vitro Maturation. The ART core in collaboration with researchers at the University of New Orleans ([names]) has begun to investigate the possibility of utilizing ovaries of dead monkeys for the retrieval of immature oocytes. This would represent a significant improvement for embryo production as it could generate large numbers of additional oocytes at very little cost. Preliminary work at the ART Core has indicated that a large number of oocytes can be retrieved from such ovaries and that some of the retrieved oocytes can be fertilized successfully after in vitro maturation. Efforts are now directed towards identifying conditions that will increase the efficiency of in vitro maturation of ovary-derived oocytes.

Support of Research. During the past year, the core has provided support for the following research projects:

a) *Development of strategies for vector-mediated gene transfer into rhesus monkeys.*
This is a TNPRC pilot study aimed at investigating novel approaches to the generation of germline modifications of rhesus monkeys. A number of rhesus zygotes have been injected with either a lentivirus (FUGW) or one of several strains of adeno-associated virus (AAV). Work to

date has shown that all of the vectors tested can readily infect rhesus zygotes as judged by the expression of a reporter gene (GFP). However, in all instances, gene expression was mosaic and subsequent efforts will be directed towards determining whether this is the result of differential control of GFP expression or a reflection of mosaic integration into the genome.

b) *New approaches to the generation of genetically valuable rhesus monkey.*
This is a Resource Development grant with the aim of investigating the possibility of using pigtail females as recipients of rhesus embryos. To date one rhesus infant has been produced. After gestation in a pigtail surrogate, although the efficiency appears significantly below what we routinely obtain in embryo transfers with rhesus embryos into rhesus recipients. Moreover, examination of placental tissues has shown evidence of possible immunological incompatibility between infant and dam. Efforts are currently under way to develop an in vitro fertilization system for pigtail monkeys. Production of pigtail embryo and their subsequent transfer into pigtail females will establish a baseline for the efficiency of performing embryo transfers into this species.

c) *Consulting/collaborations with outside PIs*
The Core has provided discarded embryos and blood samples to [names] at the University of New Orleans to aid in the generation of preliminary data on the cytogenetic analysis as well as mitochondrial DNA damage in rhesus embryos. This work could be of significant value because it may fill a crucial need to develop models of damage in embryos that is prevalent in human embryos, but whose causes are poorly understood. The Core has also collaborated with [names] at the University of Mississippi Medical Center in Jackson on establishing protocols for virus-mediated transformation of rat embryos. This work, which is supported by several NIH and Veterans Affairs' grants, is aimed at using interference RNA to suppress expression of 11β-hydroxysteroid dehydrogenase 2. To date, several transgenic rat pups have been produced that are currently under investigation to determine the effects of iRNA expression.

Timed breeding program. The timed-breeding program at the Tulane National Primate Research Center uses exogenous progesterone administration to control the time of ovulation. The progesterone (USP grade) is dissolved in oil and administered by intramuscular injection at a dose of 5 mg/0.25 ml oil daily for 10 days. The female is placed with the male 14 days after the last injection. Ultrasonography conducted 24 or 31 days after placing the female with the male confirms that pregnancy occurs 4 days after introduction to the male. This procedure allows for efficient use of the males and provides a conception date ±24 hours. In the 2003-2004 breeding season 45 Indian-origin and 13 Chinese-origin rhesus monkeys were used in this project. All the pregnant monkeys were assigned to projects supported by outside funding agencies. These included (1) effects of maternal malaria on fetal development and infant growth, (2) a nonhuman primate rotavirus illness model and (3) safety and toxicity of mesenchymal stem cells administered to the CNS of non-human primates. This timed-breeding procedure does not require determination of menstrual cycle stage prior to initiation of progesterone administration. This procedure has been used to synchronize cycles in groups of monkeys. Publications in this period include a report of 4 years breeding success, conception rates for age and number of previous pregnancy and an abstract describing synchronization of menstrual cycles.

Pregnancy rates from 2003 are shown in the tables below.

Pregnancy Rates, Timed Breeding Program

Indian-origin M. mulatta

Number	Round 1	Round 2	Round 3	Overall*
Females	45	26	4	45
Pregnant	17	10	2	29
Pending UTS	0	0	0	0
% Pregnant	37.78	38.46	50.00	64.44

Indian-origin & Chinese-origin M.mulatta

Number	Round 1	Round 2	Round 3	Overall*
Females	58	37	7	58
Pregnant	18	12	2	32
Pending UTS	1	1	0	2
% Pregnant	31.03	32.43	28.57	55.17

*Overall: The number of females is the number of unique animals bred.