

**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**

**2P51RR000164-45
TULANE NATIONAL PRIMATE RESEARCH CENTER**

Final

TULANE NATIONAL PRIMATE RESEARCH CENTER

TULANE UNIVERSITY HEALTH SCIENCES CENTER

ANNUAL PROGRESS REPORT

Reporting From: 04/30/2006

Reporting To: 04/29/2007

58.988% AIDS Related

withheld



Patent or Copyright was not awarded this grant year.

PERSONNEL ROSTER

Core Doctoral Scientists

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

Core Doctoral Scientists

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

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
withheld		
		Proprietary Info
		TEXAS A&M: TX, USA
		Proprietary Info
		Proprietary Info
		UNIVERSITY OF ILLINOIS: IL, USA
		Proprietary Info
		LSU HEALTH SCIENCES CENTER: LA, USA
		WANPRC: WA, USA
		Proprietary Info
		LSU HEALTH SCIENCES CENTER: LA, USA
		LSU: LA, USA
		Proprietary Info
		Proprietary Info
		UNIVERSITY OF CA/SF: CA, USA
		Proprietary Info
		SUNY: NY, USA

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
withheld		Proprietary Info
		LOUISIANA STATE UNIVERSITY: LA, USA
		Proprietary Info
		UNIV. OF NORTH CAROLINA/CHARLOTTE: NC, USA
		NIH: MD, USA
		UNIVERSITY OF NEW ORLEANS: LA, USA
		Proprietary Info
		UNIVERSITY OF MISSOURI-COLUMBIA: MO, USA
		Proprietary Info
		Proprietary Info
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		Proprietary Info
		UNIVERSITY OF ILLINOIS: IL, USA
		Proprietary Info
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		Proprietary Info
		LSU: LA, USA
		UNIVERSITY OF WASHINGTON NATIONAL PRIMATE RESEARCH CENTER: WA, USA
		UNIVERSITY OF ALABAMA: AL, USA
		Proprietary Info
		Proprietary Info

Affiliated

Name, Degree

Department

Non-Host Institution: State, Country

withheld

withheld

Proprietary Info

VACCINE RESEARCH CENTER, NIH:
MD, USA

Proprietary Info

Proprietary Info

UNIVERSITY OF
WISCONSIN-MADISON VET SCHOOL:
WI, USA

UNIVERSITY OF NEBRASKA VET
SCHOOL: NE, USA

Proprietary Info

NIAD/NIH: MD, USA

Proprietary Info

YERKES PRIMATE CENTER: GA, USA
UNIVERSITY OF IOWA: IA, USA

Proprietary Info

LSU HEALTH SCIENCES CENTER: LA,
USA

Proprietary Info

Proprietary Info

UNIVERSITY OF TX HEALTH
CENTER: TX, USA

Proprietary Info

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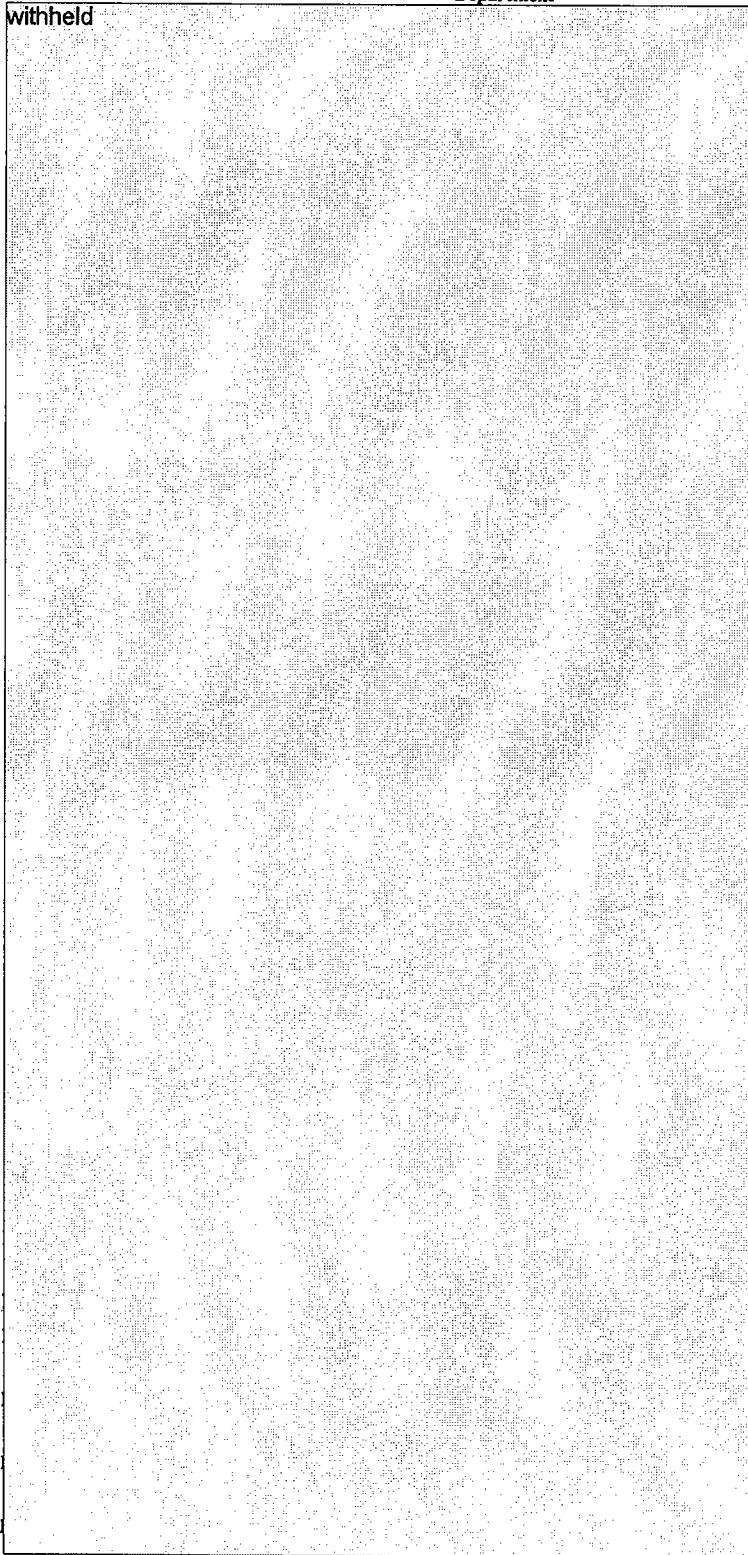
Affiliated

Name, Degree

Department

Non-Host Institution: State, Country

withheld



Proprietary Info

UNIVERSITY OF COLORADO HSC:
CO, USA

PENNINGTON/LSU: LA, USA

Proprietary Info

UNIVERSITY OF ARKANSAS: AR,
USA

Proprietary Info

LSU: LA, USA

Proprietary Info

Proprietary Info

Proprietary Info

Proprietary Info

Proprietary Info

Proprietary Info

ONPRC: OR, USA

NIH: MD, USA

Proprietary Info

Proprietary Info

COLLEGE OF VETERINARY
MEDICINE: CO, USA

Proprietary Info

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
withheld		Proprietary Info
		Proprietary Info
		UNIVERSITY OF CINCINNATI: OH, USA
		UNIVERSITY OF TX/SOUTHWESTERN: TX, USA
		CDC: CO, USA
		Proprietary Info
		Proprietary Info
		Proprietary Info
		NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER: MA, USA
		Proprietary Info
		LSUHSC: LA, USA
		Proprietary Info
		Proprietary Info
		LSU SCHOOL OF VETERINARY MEDICINE: LA, USA
		Proprietary Info
		Proprietary Info
		Proprietary Info
		LSU: LA, USA
		NIAID/NIH: MD, USA
		LSU SCHOOL OF VETERINARY MEDICINE: LA, USA
		Proprietary Info
		UCLA SCHOOL OF MEDICINE: CA, USA
		Proprietary Info

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
withheld		Proprietary Info
		Proprietary Info
		Proprietary Info
		Proprietary Info
		Proprietary Info
		LSU: LA, USA
		Proprietary Info
		NCI FREDERICK: MD, USA
		Proprietary Info
		UNIVERSITY OF VERMONT: VT, USA
		Proprietary Info
		UNIVERSITY OF COLORADO: CO, USA
		Proprietary Info
		UNIVERSITY OF COLORADO HSC: CO, USA
		Proprietary Info

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
withheld		UNIV OF CALIFORNIA/DAVIS: CA, USA SOUTHWESTERN MEDICAL CENTER: TX, USA Proprietary Info LSUHSC: LA, USA Proprietary Info LSUHSC: LA, USA Proprietary Info Proprietary Info Proprietary Info Proprietary Info Proprietary Info Proprietary Info Proprietary Info Proprietary Info UNIVERSITY OF PITTSBURGH: PA, USA Proprietary Info UNIVERSITY OF KANSAS MED CTR.: KS, USA NIH: MD, USA WANPRC: WA, USA LSU HEALTH SCIENCES CENTER: LA, USA Proprietary Info ONPRC: OR, USA Proprietary Info UNIVERSITY OF CALIFORNIA/DAVIS: CA, USA UNIVERSITY OF TX/HOUSTON MEDICAL SCHOOL: TX, USA UNIVERSITY OF WISCONSIN-MADISON: WI, USA Proprietary Info

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
withheld		Proprietary Info
		LSUSVM: LA, USA
		UNIVERSITY OF NEW MEXICO: NM, USA
		Proprietary Info
		Proprietary Info
		Proprietary Info
		UNIVERSITY OF TX MEDICAL BRANCH: TX, USA
		LSUSVM: LA, USA
		Proprietary Info
		NCI-FREDERICK CANCER RESEARCH & DEVELOPMENT: MD, USA
		LSU/HSC: LA, USA
		UNIVERSITY OF NEW MEXICO: NM, USA

Affiliated

Name, Degree

Department

Non-Host Institution: State, Country

withheld

Proprietary Info

ALABAMA STATE UNIVERSITY: AL,
USA

Proprietary Info

NERPRC: MA, USA

ALABAMA STATE UNIVERSITY: AL,
USA

Proprietary Info

UNIVERSITY OF TEXAS: TX, USA

Proprietary Info

UNIVERSITY OF IOWA: IA, USA

YERKES NAT. PRIMATE RES. CTR.:
GA, USA

UNIVERSITY OF CINNCINATI: OH,
USA

Proprietary Info

UNIVERSITY OF TX MEDICAL

BRANCH: TX, USA

Proprietary Info

LOUISIANA STATE UNIVERSITY: LA,
USA

Proprietary Info

COLORADO STATE UNIVERSITY:
CO, USA

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
withheld		<p>CNPRC/UC DAVIS: CA, USA UNIVERSITY OF TEXAS MEDICAL BRANCH: TX, USA Proprietary Info</p> <p>LSUHSC: LA, USA NIH/NIAID: MD, USA Proprietary Info</p> <p>UNIVERSITY OF VERMONT COLLEGE OF MEDICINE: VT, USA Proprietary Info</p> <p>NERPRC: MA, USA Proprietary Info</p> <p>LSUHSC: LA, USA</p> <p>WISCONSIN NATIONAL PRIMATE RESEARCH CENTER: WI, USA OREGON NATIONAL PRIMATE RESEARCH CENTER: OR, USA Proprietary Info</p> <p>NERPRC: MA, USA Proprietary Info</p> <p>UNIVERSITY OF TEXAS MEDICAL BRANCH: TX, USA Proprietary Info</p>

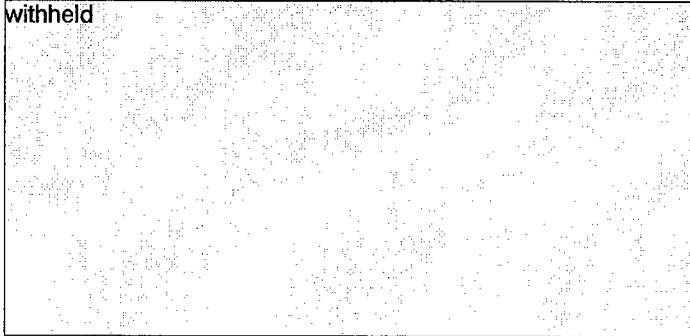
Affiliated

Name, Degree

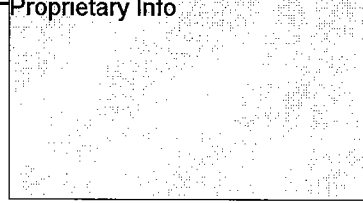
Department

Non-Host Institution: State, Country

withheld



Proprietary Info



UNIVERSITY OF COLORADO: CO,
USA

Proprietary Info



SUBPROJECT DESCRIPTIONS

NPRC MANAGEMENT SUBPROJECTS

INFORMATION TECHNOLOGY SERVICES (0542)

NPRC UNIT: ADMINISTRATIVE

%NPRC \$:

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

SUBPROJECT DESCRIPTION

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 P/OPEN DBMS to MS SQL Server. 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-2007. 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 servers provide e-mail access and access to the animal records system, while Windows 2003 servers act as file servers for both Macintosh and Windows-based desktop clients. Internet access is provided through a DS 3 circuit 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. Technical support calls numbered over 2,800 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 are regularly scheduled and coordinated.

ADMINISTRATIVE SERVICES/BUSINESS OFFICE (0583)

NPRC UNIT: ADMINISTRATIVE

%NPRC \$:

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

SUBPROJECT DESCRIPTION

Because the Center is located Personal Info 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 SERVICES (0584)

NPRC UNIT: ADMINISTRATIVE

%NPRC \$:

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

withheld				
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SUBPROJECT DESCRIPTION

Facilities Services is responsible for maintenance, building construction and renovations, HVAC systems and controls, groundskeeping, chemclave and tissue digester operation, sewerage treatment plant operation, 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 (approximately 110,000 ft²) 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 \$:

INVESTIGATOR

DEGREES STAFF DEPARTMENT

**NON-HOST INSTITUTION: STATE,
COUNTRY**

withheld

Proprietary Info

SUBPROJECT DESCRIPTION

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. We also, participate in a collaborative project with CDC to test for monkey retrovirus seroprevalence in employees at the primate center.

SECURITY (0695)

NPRC UNIT: ADMINISTRATIVE

%NPRC \$:

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

withheld				
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SUBPROJECT DESCRIPTION

Security functions at the Center are now performed by **Proprietary Info** from the **Proprietary Info**
Proprietary Info 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.

INFRASTRUCTURE IMPROVEMENTS TO THE TNPRC (0811)

NPRC UNIT: ADMINISTRATIVE

%NPRC \$:

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

SUBPROJECT DESCRIPTION

The growth in the TNPRC program has produced obvious demands on the infrastructure of the Center. To accommodate this growth we have aggressively pursued funding from multiple sources to renovate and expand existing facilities and have been successful in securing roughly \$50 million from multiple sources to: 1) renovate and expand existing animal facilities and the veterinary clinic, 2) construct a new quarantine building, 3) construct a new veterinary clinic for the breeding facility, 4) upgrade existing security 5) build a regional biosafety laboratory, 6) construct new animal holding facilities, 7) purchase caging; and 8) expand the breeding colony housing capacity. The completion of these construction and renovation projects over the next few years will increase the square footage of our facility by over 70%. Our success in obtaining this funding was facilitated by the development of a TNPRC strategic plan and a campus master plan.

DIRECTORS OFFICE, TNPRC (0585)

NPRC UNIT: ADMINISTRATIVE

%NPRC \$:

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

withheld

SUBPROJECT DESCRIPTION

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.

Three significant goals were achieved during the year: 1) recruitment of additional faculty in the Division of Microbiology (Roy); 2) recruitment of an additional clinical veterinarian; and 3) creation of a TNPRC website.

SCIENTIFIC ADVISORY COMMITTEE (0773)

NPRC UNIT: ADMINISTRATIVE

%NPRC \$:

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
withheld				Proprietary Info
				SUNY, NY USA
				Proprietary Info
				UNIVERSITY OF WASHINGTON NATIONAL PRIMATE RESEARCH CENTER, WA USA
				Proprietary Info
				COLLEGE OF VETERINARY MEDICINE, CO USA NIAID/NIH, MD USA LSU SCHOOL OF VETERINARY MEDICINE, LA USA UNIV OF CALIFORNIA/DAVIS, CA USA UNIVERSITY OF KANSAS MED CTR., KS USA NIAID, NIH, MT USA
				Proprietary Info

SUBPROJECT DESCRIPTION

The TNPRC maintains an external scientific advisory board 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.

The Divisions of Veterinary Medicine and Collaborative Research were reviewed in November of 2006 and a global review occurred in February of 2007.

TRAINING AND EDUCATION (0774)

NPRC UNIT: ADMINISTRATIVE

%NPRC \$:

INVESTIGATOR	DEGREES	STAFF	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
withheld				LSU HEALTH SCIENCES CENTER, LA USA
				LSU, LA USA
				LOUISIANA STATE UNIVERSITY, LA USA
				UNIV. OF NORTH CAROLINA/CHARLOTTE, NC USA
				Proprietary Info
				Proprietary Info
				LSU SCHOOL OF VETERINARY MEDICINE, LA USA
LSU SCHOOL OF VETERINARY MEDICINE, LA USA				
Proprietary Info				
LSU HEALTH SCIENCES CENTER, LA USA				
Proprietary Info				
Proprietary Info				

SUBPROJECT DESCRIPTION

The educational mission of the TNPRC is to provide training for undergraduate, veterinary, and graduate students, post-doctoral fellows, veterinarians, and visiting scientists. In addition to hosting graduate students and post-docs, the educational effort of the TNPRC is further broadened by participation in a T35 training grant in conjunction with the Louisiana State University (LSU) School of Veterinary Medicine, a T32 training grant held together with

the LSU School of Medicine, a Summer Fellowship Program, a Pathology Training Curriculum, and a Veterinary Preceptorship. The summer fellowships entail 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. There is also a Visiting Scientist Program. The basic objective of this program is to provide individuals with a knowledge and understanding of the mission and functions of a National Primate Research Center. A newly instituted Pathology Training Curriculum is directed toward further professional development of staff veterinary pathologists, staff veterinarians, and veterinarians involved in research. Lastly, three Center-wide colloquia address TNPRC diverse educational needs and interests: 1) a monthly seminar on infectious diseases, with invited speakers, 2) a biweekly research lab meeting, and 3) monthly pathology and medicine Grand Rounds.

In the last year the center hosted as many as 9 graduate students and 19 post-doctoral fellows, as well as 4 students in the Preceptorship Program. The Summer Fellowship Program was subscribed somewhat less than in the previous year (7 vs. 12 participants), likely due to aftermath effects of Hurricane Katrina. Three veterinarians participated in the Pathology Training Curriculum. We also welcomed 4 visiting scientists last year. We are pleased with the response of students and investigators of all levels to our educational efforts, and look forward to maintaining this trend in the future.

TULANE RESOURCE ALLOCATION COMMITTEE (0686)

NPRC UNIT: VETERINARY MEDICINE

%NPRC \$: AIDS RELATED RESEARCH

INVESTIGATOR	DEGREES	STAFF	DEPARTMENT
	CODE		

NON-HOST INSTITUTION: STATE, COUNTRY

withheld			
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Proprietary Info

LSU HEALTH SCIENCES CENTER, LA
USA

SUBPROJECT DESCRIPTION

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

The sixth year of operation of the TRAC saw continued 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. A total of 39 investigator requests were made for a total of 405 animals. Approximately of 67% of the animals allocated have been to affiliate (outside) investigators and 38% to core investigators for the last reporting period. Because of the rapid growth of the research program, 29 investigator requests for 292 animals were initially deferred until housing space and/or animals were available for assignment. Three requests (37 animals) were denied in 2006.

RESEARCH SUBPROJECTS

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

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC S: 0.664%

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

withheld

Proprietary Info

SUBPROJECT DESCRIPTION

Malaria, an ancient scourge of mankind, is still one of the biggest killers of children in the world today. The treatment of choice for malaria for over 50 years has been chloroquine (CQ) but the utility of this drug has been compromised by the increasing prevalence of CQ resistance worldwide. Consequently, the development of safe and effective antimalarials is a global health priority. Together with our colleagues at the **withheld** **Propriet** we have developed a series of 4 aminoquinolines active against chloroquine-resistant malaria caused by *Plasmodium falciparum*. We have previously tested a series of these compounds in a monkey model of human malaria, *P. cynomolgi* in the rhesus macaque, a model of human vivax malaria. One of the compounds we tested previously (AQ13) was found to be an efficacious blood schizonticide against a chloroquine resistant isolate in the monkeys, has completed Phase I human trials, and is currently being tested in Phase II trials in Mali. We are now looking at the efficacy of other compounds which can potentially be used in combination with AQ13. Using our monkey models we are now looking at how this class of compounds is metabolized by P450 enzymes in the liver. Because the P450 complement of the rhesus macaque is similar to that of humans, 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.

SURVEY OF ENZOOTIC PATHOGENS AND ARTHROPOD VECTORS (0697)

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC \$: 0.664%

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

Proprietary Info

SUBPROJECT DESCRIPTION

A survey designed to assess the level of endemicity of known enzootic pathogens in the outdoor breeding colonies at the TNPRC, this project serves as a sentinel for the health of the colony. Samples of blood and stool obtained from each animal are examined for parasites of interest. Stool samples are examined by a direct smear and a concentration method. 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 traps and gravid traps. Mosquitoes are speciated and examined by dipstick ELISA test or the newly-developed LAMP test for West Nile virus (WNV). During 2006 we examined 442 stool samples and 590 blood samples. We have also saved and tested 208 serum samples for T. cruzi and have found 34 animals which show evidence of exposure to T. cruzi. We have been able to culture parasites in vitro from some infected animals and are presently re-sampling mothers of infected animals to look for evidence of vertical transmission of this parasite. Many of these animals were born at the Center indicating transmission is taking place here with local triatomid bugs. We spent some months this year attempting the trap the vector at night but have so far been unsuccessful. Other pathogens of interest include Strongyloides fülleborni, Giardia lamblia, Balantidium coli, Trichuris trichiura, and Hymenolepis diminuta, the rat tapeworm. We have expanded our sampling to include milk from mothers with babies by to demonstrate vertical transmission of S. fülleborni. This parasite has been shown to be present in the milk of African women. Its presence in the milk of simian mothers will be an indication that new treatment approaches need to be developed to help reduce the morbidity caused by this organism in our breeding colony.

DIAGNOSTIC PARASITOLOGY CORE (0825)

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC S: 0.664%

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

Withheld				
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NIH/NIAID, MD USA

SUBPROJECT DESCRIPTION

All animals entering quarantine from outside sources are examined for the presence of blood and intestinal parasites before they enter the colony. Additionally, the **Proprietary Info** provides diagnostic support to investigators and clinical veterinarians whenever monkeys are suspected of harboring parasites. Mice in the rodent colony are also periodically checked for mites and pinworms prospectively. The laboratory also collaborates with researchers outside the Center when projects involving non-human primates require diagnostic services.

During the calendar year 2006, the laboratory processed 2,398 clinical samples, including 444 stool samples from animals in quarantine, and 477 stool samples from animals assigned to research projects. The lab also examined 466 blood samples by the Knott's technique and thick and thin blood smears from colony animals. Pathogenic parasites reported included *Giardia lamblia* (1.5%), *Balantidium coli* (17%), *Strongyloides fülleborni* (32%), and *Trichuris trichiura* (28%). The laboratory, recognized as one of the few facilities in the world devoted to parasites of non-human primates, provided pictures of parasites for recent revisions in Flynn's *Parasites of Laboratory Animals*. The laboratory also examined a mite sample from the Tulane vivarium and will continue to aid this facility whenever they request consultation.

In addition to the above samples, the laboratory is also examining blood and fecal samples in direct support of a survey of enzootic pathogens from the breeding colony.

SUPPRESSORS OF CYTOKINE SIGNALING AND IL-10 INHIBITORY EFFECT IN LYME DISEASE (0707)

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC \$: 0.664%

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

withheld

ALABAMA STATE UNIVERSITY, AL
USA**SUBPROJECT DESCRIPTION**

Lyme disease, caused by the spirochete *Borrelia burgdorferi*, is an inflammatory disease. Inflammation, as induced by the spirochete, plays a major role in disease pathogenesis. The anti-inflammatory cytokine IL-10 has been shown to be a key regulator of inflammatory responses in Lyme disease, by controlling the production and function of various pro-inflammatory cytokines. Recently we observed that *B. burgdorferi* together with IL-10 additively induced the expression of the suppressor of cytokine signaling (SOCS)1 and 3 in macrophages. SOCS1/SOCS3 expression correlated with the IL-10-mediated inhibition of several pro-inflammatory cytokines. We hypothesized that the expression of SOCS induced by *B. burgdorferi* and IL-10 in macrophages is functionally important in the IL-10-mediated control of inflammation in macrophages. We used RNAi to silence the SOCS3 gene in mouse J774 macrophages stimulated with either live *B. burgdorferi* (Bb) or lipidated outer surface protein A (L-OspA) alone, or each stimulant together with IL-10. Using a SOCS3 specific pool of 4 siRNA molecules we achieved up to 79% knockdown of SOCS3 gene expression in cells transfected with the SOCS3 siRNA as compared to cells transfected with a nontargeting control siRNA, as assessed by real-time RT-PCR. IL-6 production was increased in culture supernatants with stimulants combined with IL-10 and SOCS3 siRNA as compared to those containing control siRNA. Taken together, these data suggest that SOCS3 may be involved in the IL-10 control of inflammation in macrophages.

REGULATION OF SOCS EXPRESSION IN MACROPHAGES IN RESPONSE TO BORRELIA AND IL-10 (0890)

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC S: 0.664%

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

withheld

ALABAMA STATE UNIVERSITY, AL
USA

SUBPROJECT DESCRIPTION

Inflammation, as induced by the spirochete *Borrelia burgdorferi* in multiple organs, plays a major role in disease pathogenesis, but its regulation is not understood. We recently showed that mouse J774 macrophages incubated with IL-10 and added *B. burgdorferi* spirochetes (freeze-thawed, live or sonicated) or lipidated outer surface protein A (L-OspA) augmented their suppressor of cytokine signaling (SOCS)1 and SOCS3 expression, with SOCS3 being the more abundant. This temporally correlated with the IL-10-mediated inhibition of expression of several pro-inflammatory cytokines. We hypothesized that augmentation of SOCS expression by co-stimulation compared to stimulation with individual stimulants led either to reinforcement of a common signaling pathway or convergence of different signaling pathways for optimal SOCS expression. To begin to address this hypothesis, we used murine cDNA microarray to investigate mediators of SOCS induction in macrophages. J774 macrophages were co-stimulated with IL-10 and sonicated *B. burgdorferi* spirochetes and RNA samples were collected at 2, 4 and 24 hr post-stimulation for microarray analyses. Based on a fold-change cut-off criterion of 3, we observed over 500 up-regulated genes in macrophages, chief amongst which was the SOCS3 gene (log₂ fold change of 5-6). The gene expression data revealed both unique and overlapping sets of genes at all time points. Further Gene Ontology analysis revealed amongst genes with altered microarray profiles, the over-representation of genes encoding mediators from TLR, JAK/STAT and p38 MAPK signaling pathways. These pathways are known to be involved in the induction of SOCS, thus suggesting that more than one pathway maybe involved in SOCS induction in macrophages co-stimulated with IL-10 and sonicated spirochetes.

DNA MICROARRAY AND EXPRESSION CORE (0704)

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC \$: 0.664%

INVESTIGATOR

DEGREES STAFF DEPARTMENT
CODENON-HOST INSTITUTION: STATE,
COUNTRY

withheld

SUBPROJECT DESCRIPTION

The DNA Microarray and Expression core provides bioinformatics expertise to investigators who have already performed their experiments, or performs such experiments de novo. The core upgraded its capabilities and infrastructure last year, and is equipped with a GenePix 4000B dual-laser microarray scanner (scan resolution of 5 nm), supported by GenePix Pro 6.0 image software and Acuity database, operating on a dedicated Dell PC. The core also has access to Spotfire DecisionSite for Functional Genomics and R-code/Bioconductor for data-mining, and will be acquiring Ingenuity Pathways Analysis software. The core has dedicated access to a network drive for data storage, retrieval and distribution.

The core currently provides the following services to the research community: a) Microarray Experimental Design b) Spotted Microarray Experiments c) PCR arrays d) Data Analysis e) RNA Amplification: f) Protein Expression and Purification. In addition the core would like to expand into the following research service areas in future: a) Gene silencing; b) Custom microarray c) Proteomics.

The DNA Microarray and expression core is actively collaborating with other components of TNPRC. We have developed a proposal in collaboration with the Viral Diagnostics core to generate a microarray based detection reagent for microbial pathogens that colonize the rhesus colony at TNPRC.

THE CRUCIAL ROLE OF M. TUBERCULOSIS IN IMMUNOPATHOLOGY (0895)

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC \$: 0.664%

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

withheld

SUBPROJECT DESCRIPTION

The *M. tuberculosis* sigmaH mutant exhibits a unique phenotype in a mouse model of infection via the aerosol route: it is able to reach the same bacterial load as the wild-type (WT) strain in mouse organs, but is unable to induce the typical lung granulomatous histopathology and pulmonary inflammatory response associated with the infection. The lack of immunopathology parallels reduced recruitment of both CD4+ and CD8+ T cells in the lungs infected by the mutant bacilli. SigmaH appears to regulate the thioredoxin regulon, and in its absence, several *M. tuberculosis* proteins involved in recruiting and activating immune effector cells and molecules are likely damaged by the host oxidative burst, rendering the mutant incapable of generating the immunopathology phenotype.

We are comparing the intra-phagosomal transcriptome of *M. tuberculosis* sigmaH mutant and the WT strain to verify the regulation of thioredoxin regulon by sigmaH in the context of in-vivo disease. We are also studying the host macrophage response to the *M. tuberculosis* and its sigmaH mutant, at both transcriptional and protein levels, to gain insights into the signal processing during infection with tubercle bacilli that leads to the development of tissue-damaging immunopathology. In view of our hypothesis, we expect to find differences in the levels of expression of pro-inflammatory cytokines and other mediators and, crucially, of chemokines involved in immune cell recruitment to the lungs. We plan to carry out a pilot study, to observe the in-vivo phenotype of *M. tuberculosis*, as compared to the sigmaH mutant, in an aerosol infection model of rhesus macaques (*Macaca mulatta*).

TOLL-LIKE RECEPTORS IN LYME NEUROBORRELIOSIS (0025)

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC \$: 0.664%

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

withheld

SUBPROJECT DESCRIPTION

Lyme neuroborreliosis is likely caused by inflammatory effects of *B. burgdorferi* on the central and/or peripheral nervous systems. In the central nervous system (CNS), microglia, the resident macrophages, are involved in initiating immune responses that may result in the production of chemokines and inflammatory cytokines. Astrocytes are also known to contribute to the inflammatory activity in the brain. Toll Like Receptors (TLRs) of glial cells may play an essential role in initiating inflammatory responses in the CNS upon interaction with pathogen-associated molecular patterns (PAMP). We hypothesized that the PAMP known to be associated with *B. burgdorferi*, namely, lipoproteins, flagellin, and unmethylated CpG DNA could play this role upon interaction with their cognate TLR on glial cells, i.e. TLR2/TLR1, TLR5, and TLR9, respectively. Microglia and astrocytes were isolated from brain of normal rhesus macaques and stimulated with medium alone, recombinant lipidated outer surface protein A (L-OspA), live *B. burgdorferi*, sonicated *B. burgdorferi*, CpG DNA (ODN M362), or Flagellin (FliC) for 8 or 24 hours. Total RNA was isolated from the stimulated cells and analyzed by real-time PCR. Culture supernatants were collected and assayed for the presence of TNF α , IL6 and IL8 by sandwich ELISA. Stimulated and control astrocytes and microglia were fixed, permeabilized, and blocked for immunofluorescence assays via confocal microscopy. Microglia and astrocytes showed expression of TLR1, 2, 6, 5 and 9. Based on immunofluorescence results we observed that TLR1, TLR2 and TLR5 were upregulated in microglial preparations stimulated by *B. burgdorferi*. Microglia and astrocytes showed constitutive production of IL6 and IL8 that was up-regulated significantly after stimulation with L-OspA, live or sonicated *B. burgdorferi*, or Flagellin. Our results indicate that microglia and astrocytes respond to *B. burgdorferi* by inducing inflammatory cytokine secretion through TLR1/2 and TLR5.

C6 TEST IN RST2-INFECTED HOSTS (0538)

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC \$: 0.664%

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

withheld

Proprietary Info

SUBPROJECT DESCRIPTION

Detection of antibody to C6, a peptide that reproduces the sequence of the sixth invariable region within the central domain of the VlsE protein of *Borrelia burgdorferi*, is used currently for the serologic diagnosis of Lyme disease in humans and in canines. Recent evidence has shown that *B. burgdorferi* isolates taken from infected humans can be categorized into specific genetic subtypes (designated RST1, 2 and 3) by restriction fragment length polymorphisms in the 16S-23S rDNA spacer sequence. Notably, many of these, usually categorized as RST2, retain only segments of the linear plasmid lp28-1 that encodes VlsE. The VlsE genetic region is included in the retained segments, but altered expression of this molecule could affect diagnosis by the C6 ELISA. Human serum samples of patients infected with each of the 3 genotypes and serum from mice infected with three RST2 isolates were tested by the C6 ELISA. Such isolates elicited marked C6 responses in infected mice. The sensitivity of C6 antibody detection in patients infected with RST2 spirochetes was statistically indistinguishable from detection of RST1 and RST3 infections. These findings demonstrate that diagnosis by C6 ELISA remains effective for infection with all *B. burgdorferi* genotypes, including those with incomplete lp28-1 plasmids.

THE C6 TEST IN PATIENTS WITH SOUTHERN TICK-ASSOCIATED RASH ILLNESS (STARI) (0822)

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC \$: 0.664%

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

withheld

Proprietary Info

SUBPROJECT DESCRIPTION

Southern Tick-Associated Rash Illness (STARI), also known as Masters disease, predominantly affects people in the Southeast and South Central United States. These patients exhibit skin lesions that resemble erythema-migrans (EM) the characteristic skin lesion in early Lyme disease. The etiology of STARI remains unknown and no serologic test is available to aid in its diagnosis.

The C6 Lyme ELISA was used to evaluate coded serum specimens from patients with STARI at 2 laboratory sites. The specimens tested at one site consisted of acute and convalescent samples that were obtained from 9 STARI patients from Missouri, and from one patient with documented *B. lonestari* infection who acquired this infection in either North Carolina or Maryland. All of these samples were C6 negative. Seventy acute or convalescent specimens from 63 STARI patients from Missouri were C6-tested at the second site. All but one of these STARI specimens were also negative. In contrast, of 9 acute and 9 convalescent serum specimens obtained from culture-confirmed Lyme disease patients with EM from New York State, 7 were C6-positive at the acute stage, and 8 were positive at convalescence. The C6 test is negative in patients with STARI, providing further evidence that *B. burgdorferi* is not the etiologic agent of this disease.

VECTOR-BORNE DISEASES CORE (0824)

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC S: 0.664%

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

SUBPROJECT DESCRIPTION

The VBD core has continued to maintain an *Anopheles stephensi* colony, which is used to transmit *Plasmodium cynomolgi*, a model of human vivax malaria, to rhesus macaques. The availability of this colony was an essential factor towards the publication, this period, of the first microarray-based study of host response to a primate malaria infection

The tick colony has continued to be instrumental in enabling our division to do research in Lyme borreliosis using the natural mode of infection. 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. 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. This year we have begun the collection of tick saliva, to study its effects on the inflammatory response induced by *B. burgdorferi* spirochetes as they invade the host skin.

THE RELATIVE CONTRIBUTION OF C6 EPIOTOPE(S) TO THE ANTIBODY RESPONSE TO VLSE (0827)

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC S: 0.664%

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

SUBPROJECT DESCRIPTION

Lyme borreliosis (LB) is a disease for which antibody-based detection assays are often required for diagnosis. The variable surface molecule VlsE, and IR6, one of its invariable regions, are commonly targeted by the antibody response in infected individuals. A series of ELISAs was performed to comparatively examine the antibody responses of North American LB patients (n = 37) to VlsE and invariable segments of this molecule. Both IgM and IgG responses to full-length VlsE, and peptides reproducing invariable regions 2, 4 and 6, as well as the invariable domains at the amino and carboxyl termini of VlsE were assessed. The proportion and specificity of reactivity to the invariable segments were tested by using cognate peptides as competitors for VlsE binding by patient serum antibodies. IR6 epitopes (by the C6 peptide) were found to dominate the response to invariable segments. IR6 (C6)-specific antibodies were detected in 78% of the serum specimens, whereas less than 40% of patients generated antibodies that bound the N- or C-terminal domains; less than 12% of patients responded to either IR2 or IR4. Interestingly, 15 of 37 patients generated IgG antibodies that reacted with C6 but not with VlsE. Conversely, IgM responses were frequent for VlsE but not for invariable segments. A representative number of the serum specimens (n = 8) that contained IgG antibodies reacting both with C6 and VlsE was assessed in competition experiments using C6 as competitor. Only half of these specimens contained IgG antibodies whose binding to VlsE could be inhibited more than 50% by competition with added C6 peptide. The median percent inhibition was 45.5%. These findings indicate that IR6 epitopes are largely concealed from the VlsE molecular surface and that full-length VlsE-based diagnosis likely detects antibodies to conformational and/or variable region epitopes.

PATHOGENESIS OF LYME NEUROBORRELIOSIS IN THE RHESUS MONKEY: STUDIES EX VIVO (0830)

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC \$: 0.664%

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

SUBPROJECT DESCRIPTION

Lyme neuroborreliosis is a disease of the nervous system caused by the spirochete *B. burgdorferi*, resulting in cognitive deficits that may be due to impaired neuronal function. Various cytokines and chemokines have been detected in the cerebrospinal fluid of Lyme neuroborreliosis patients and we and others have assumed that inflammation plays a role in pathogenesis. We hypothesized that *B. burgdorferi* spirochetes induce cytokines, chemokines and immune mediators in the central nervous system that contribute to inflammation and neuroglial damage. To test our hypothesis we set up an ex vivo model consisting of fresh brain slices from the cortex of normal rhesus monkeys, and allowed live spirochetes to penetrate the tissue. In order to obtain a global overview of the immune response mounted by brain cells against spirochetes, tissues stimulated with spirochetes or medium alone were subjected to Real Time-PCR (human) array analysis for transcripts of common inflammatory mediators. We then identified the actual cells that were producing immune mediators in situ, by blocking protein export from the cells with brefeldin A, followed by immunofluorescence staining with appropriate antibodies and confocal microscopy. Apoptosis was quantified by the TUNEL assay. A transcriptional fold increase of 2.31 ($p=0.016$) for the chemokine IL-8, and 7.43 ($p=0.005$) for the cytokine TNF-alpha was quantified by PCR array. We detected IL-6 in astrocytes, IL-1b in microglia and endothelial cells, IL-8 in astrocytes, microglia and endothelial cells and MCP-1 in endothelial cells. The immune mediator COX-2 was detected in astrocytes, microglia and endothelial cells. Concomitant apoptosis of oligodendrocytes and neurons was also observed in spirochete-stimulated tissues. These results provide proof of concept for our proposed hypothesis for Lyme neuroborreliosis pathogenesis, that *B. burgdorferi* is able to induce in brain tissues an inflammatory environment that leads to neuroglial damage.

PATHOGENESIS OF LYME NEUROBORRELIOSIS IN THE RHESUS MONKEY: STUDIES IN VITRO (0921)

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC S: 0.664%

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

Withheld

SUBPROJECT DESCRIPTION

Background: Many neurodegenerative disorders including Alzheimer's disease, cerebral ischemia and the AIDS-dementia complex are thought to result from inflammation in the central nervous system (CNS). Lyme neuroborreliosis is likewise considered to be a consequence of inflammation elicited in the CNS. The bacterial spirochete *Borrelia burgdorferi* (Bb) causes Lyme disease and is known to induce the production of inflammatory mediators in glial cells of the CNS. We hypothesized that neuronal cells, by virtue of proximity, may become impaired in this environment, eventually leading to the neurocognitive symptoms seen in neuroborreliosis.

Methods: In order to determine the neuronal and glial cell responses to *Borrelia burgdorferi* infection we have designed an in-vitro model where Bb is co-cultivated with cells from primary rhesus cortex either alone or in combination with SH-SY5Y neuroblastoma cells. **Results:** Using sandwich ELISA we observe robust expression and release of the inflammatory cytokines / chemokines IL-6 and 8, and induction of TNF- α , albeit on a much lower scale in the cortex cells stimulated with Bb. When these same stimulations of primary glial cells with Bb are combined with the neuronal cell lines SH-SY5Y or HCN-1, increases in cellular apoptosis consistently occur. The neuronal cell lines independently stimulated with *Borrelia* express negligible amounts of inflammatory cytokine and they are resistant to apoptosis in this environment. Confocal images of the mixed cultures however, stained for TUNEL and with cell specific markers, indicate that it is almost exclusively the neuronal type cells that are dying in response to *Borrelia*. **Conclusion:** These findings suggest a bystander effect in which the neurotoxic surroundings generated by glial cell responses to Bb in the CNS may impact the neuronal cell damage responsible for symptoms observed in neuroborreliosis.

B. BURGENDORFERI VLSE IN RABBITS (0922)

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC \$: 0.664%

INVESTIGATOR	DEGREES	STAFF	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
		CODE		
withheld				CDC, CO USA
				LSU, LA USA
				UNIVERSITY OF TX/HOUSTON MEDICAL SCHOOL, TX USA

SUBPROJECT DESCRIPTION

Borrelia burgdorferi, the Lyme disease pathogen, employs several immune-evasive strategies to survive in mammals. Unlike mice, major reservoir hosts for *B. burgdorferi*, rabbits are considered to be non-permissive hosts for persistent infection. Antigenic variation of the VlsE molecule is one of the strategies of probable evasion known to function in mice. The invariable region 6 (IR6) and carboxyl-terminal domain (Ct) of VlsE elicit dominant antibody responses that are not protective, perhaps to function as decoy epitopes that protect the spirochete. We sought to determine if either of these characteristics of VlsE differed in rabbit infection, contributing to its reputed non-permissiveness. VlsE recombination was observed in rabbits that were given inoculations with either cultured or host-adapted spirochetes. Early observations showed a lack of anti-IR6 response in most rabbits, so the anti-Ct and IR6 responses were monitored for 98 weeks. Anti-IR6 antibody appeared as late as 20 weeks post-inoculation, and the anti-Ct response, evident within the first 2 weeks post-inoculation, oscillated for prolonged periods of time. These observations, together with the recovery of cultivable spirochetes from tissue of one animal at 98 weeks post-inoculation, provokes our suggestion that the rabbit is capable of harboring a long-term *B. burgdorferi* infection.

GENE EXPRESSION IN BORRELIA BURGdorFERI (0061)

NPRC UNIT: BACTERIOLOGY/PARASITOLOGY

%NPRC \$: 0.664%

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

SUBPROJECT DESCRIPTION

We are focused on understanding regulation of gene expression in the Lyme disease spirochetes at the onset of vertebrate infection. The alternative Sigma factor, RpoS, plays a significant part during these events by regulating the expression of multiple genes including ospA and ospC that have been shown to play important roles within the tick vector and during spirochetal transmission into the vertebrate host. The regulation of rpoS itself has been shown to be complex in *B. burgdorferi* and likely involves the relA/spoT gene as well as a signal transduction pathway composed of histidine kinase (Hk2)/response regulator (RRP2) and the sigma factor RpoN. We have knocked out the relA/spoT gene and are still attempting to complement the knockout with a wildtype copy of this gene. In the meantime, we are also examining the mechanism underlying the variable expression of RpoS in different strains by targeting the factors HK2, RRP2 and RpoN. We have generated an antibody against the RRP2 protein and are currently do the same for RpoN and HK2. We will use these reagents to address the issue of differential expression of RpoS.

MICROGLIA AND SIV NEUROPATHOGENESIS (0718)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC \$: 0.664% AIDS RELATED RESEARCH

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

withheld

Proprietary Info

SUBPROJECT DESCRIPTION

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.

SUBPROJECT DESCRIPTION

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 an inverted (DMIRE2), that allow for confocal microscopy of fixed preparations and also living cells. We have a separate workstation to run the Leica software for the analysis of the data collected. We also have Volocity Software for the rendition of the data in 3 dimensions. 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 workstation for investigators use in image analysis. 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. e) Multicolor imaging. Several fluorochromes can be imaged at the same time

MATH MODEL OF EXTRAVASATION OF LEUKOCYTES IN SIV INFECTION IN RHESUS MACAQUES (0833)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC S: 0.664% AIDS RELATED RESEARCH

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

withheld

Proprietary Info

SUBPROJECT DESCRIPTION

The trafficking of leukocytes through the blood brain barrier in the presence of disease, as in the case of human AIDS, is too complicated to understand intuitively. We have developed a protocol utilizing the techniques of immunohistochemistry and confocal microscopy to achieve simultaneous detection and visualization of cell populations and signals involved in the neuropathogenesis of AIDS. However, the number of cells and cytokines produced during neuroinvasion are far too numerous to accurately gain an understanding of their activities in response to infection. Therefore, we have begun developing a mathematical model to track the leukocyte extravasation at the BBB in order to accommodate the major activities of the cytokines and to establish a sequence in which these cells arrive to deliver the virus into the brain. Although the pathogenesis is still unclear, we propose that SIV-infected macrophages producing IL-6 are the first cells to arrive, followed by T-cells producing IL-6 and IFN- γ , and finally macrophages producing TNF- α or β . This study discusses the techniques carried out to develop this model and attempts to qualitatively examine this system of infection to ultimately propose points of interference that could lead to advancements in the treatment of HIV and possible prevention of such infections into the brain.

IMMUNOPATHOLOGIC ALTERATIONS IN RHESUS MACAQUES WITH GLOBOID CELL LEUKODYSTROPHY (0847)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC S: 0.564%

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

Globoid cell leukodystrophy or Krabbe's disease, is a severe disorder of the central and peripheral nervous system caused by the absence galactocerebrosidase (GALC) activity. In this report, the clinical neuropathological, histochemical and immunohistological features observed in Krabbe-affected rhesus macaques are described. Clinical signs in affected animals include pronounced muscle tremors of head and limbs, difficulty ambulating, ataxia, hypermetria and respiratory difficulties. Histopathologically, all animals presented with evidence of demyelination in the peripheral and central nervous system and accumulation of mononuclear and multinuclear globoid cells in the cerebral and cerebellar white matter associated with severe gliosis. Using immunohistochemistry and multilabel confocal microscopy with multiple cell-type specific markers, it was determined that globoid cells were CD68+, HAM56+, LN5+, CD163+, IBA-1+ and Glut-5+ suggesting that both peripheral blood derived monocyte/macrophages and resident parenchymal microglia give rise to globoid cells. Interestingly, many of the globoid cells as well as parenchymal microglia with a more amoeboid morphology expressed HLA-DR indicating immune activation. Furthermore, a marked increase in expression of iNOS was observed in the affected white matter and colocalized with globoid cells and activated microglia. This raises the possibility that dysregulation of monocyte/macrophage/microglia may contribute to the pathogenesis of Krabbe's disease.

CD163, A MARKER OF PERIVASCULAR MACROPHAGES IS UPREGULATED ON MICROGLIA IN SIVE (0906)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC S: 0.664% AIDS RELATED RESEARCH

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

withheld

SUBPROJECT DESCRIPTION

Macrophages and microglia are the major cell types infected in the central nervous system of humans infected with HIV and macaques infected with SIV. Microglia are the resident macrophages of the brain and have been shown to be quite sensitive to even minor disturbances of central nervous system (CNS) homeostasis, and are readily activated. Activation of microglia induces changes in cellular morphology and in the expression of cell surface receptors. CD163 is a member of the scavenger receptor family with cysteine-rich domains (SCRC) identified as a receptor of haptoglobin-hemoglobin (Hp-Hb) complex and exclusively expressed by cells of monocyte-macrophage lineage. We examined the expression of CD163 in vitro and in vivo by multiple techniques and at varying times after SIV infection in animals with or without SIVE. Our data show that CD163 is expressed by cells of monocyte/macrophage lineage including perivascular macrophages but not parenchymal microglia in normal and acutely SIV-infected animals or animals with terminal AIDS without encephalitis. CD163 expression was detected in activated microglia (HLA-DR+) surrounding SIVE lesions in chronically infected macaques with severe encephalitis in the presence of haptoglobin-haemoglobin complex (Hp-Hb) in the tissue suggesting breakdown of the blood-brain-barrier. CD163 expression was also induced in microglia in vitro by stimulation with Hp-Hb complex indicating that the interaction of the Hp-Hb complex is required to trigger the upregulation of CD163. To confirm that activation of microglia was associated with the presence and upregulation of CD163 RNA we treated microglia isolated from rhesus macaque brain with Hp-Hb for 0, 6, 12, 18 and 48 h and performed quantitative real-time PCR. We observed a 2.5 fold increase of CD163 RNA in the microglia treated with haptoglobin-hemoglobin within 18hrs of exposure. We conclude that CD163 is a selective marker of perivascular macrophages in normal macaques and during the early phases of SIV infection. However, latter in infection CD163 also labels microglia that have been activated probably as a result of vascular compromise.

PRIMATE CENTER IMAGE DATABASE COLLABORATIVE (0903)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC \$: 0.664%

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

TNPRC is a collaborating member in the National Primate Centers' Image Database Project. Over 3800 archived gross images have been scanned and annotated in a TNPRC database which incorporates clinical records. Ongoing additions to the TNPRC gross image database occur through acquisition of digital gross photos from necropsy specimens. Monthly participation in conference calls with other participating centers are used to define uniform terminology and technical standards for images and attached records. The TNPRC is spearheading a multi-center virtual slide conference as part of this project using digital microscope slide scanner and webconferencing technology. The virtual slide conference will increase interactions between the primate center pathologists and disseminate information regarding nonhuman primate pathology.

MONKEY AND MOUSE MOLECULAR BEACON GENOTYPING FOR KRABBE (0920)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC \$: 0.664%

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

withheld

SUBPROJECT DESCRIPTION

Colonies of rhesus macaques and mice which carry mutations in the galactocerebrosidase gene are important for research into the pathogenesis and treatment of globoid cell leukodystrophy. Current genotyping methods require extended technical time to complete. A rapid, accurate genotyping method with minimal sample was needed.

METHOD: Molecular beacons were designed for rhesus macaque and mouse DNA and coupled with a rapid DNA extraction method from hair roots. **RESULTS/DISCUSSION:** The new method can be completed in under 4 hours with minimal technical time. Comparisons with previous techniques show the method is reliable and unambiguous.

A RHESUS MONKEY MODEL OF MALARIA DURING PREGNANCY (0073)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC \$: 0.664%

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

withheld

Proprietary Info

Proprietary Info

Proprietary Info

SUBPROJECT DESCRIPTION

We developed a rhesus monkey model to examine the effects of malaria (*Plasmodium coatneyi*) during pregnancy. This project, supported by an NIH R01, explores maternal immunologic responses. In a prospective study of rhesus monkeys inoculated with *Plasmodium coatneyi* or saline on an infection/gestational timeline, we determined the serum levels of tumor necrosis factor-alpha (TNF-alpha), soluble tumor necrosis factor receptor type I (sTNFR-I), and soluble tumor necrosis factor receptor type II (sTNFR-II) in peripheral blood throughout primigravid pregnancy, malaria infection, and a combination of the two. Our goal was to determine the association between levels of TNF-alpha and of its 2 soluble receptors and the course of pregnancy and/or malaria and infant outcome. We found that any detectable level of TNF-alpha was always associated with fetal death and that the sTNFRs may be important for fetal protection, possibly through neutralizing the toxic effects of TNF-alpha. Our findings also showed that increased levels of sTNFR-II were associated specifically with malaria and not with normal pregnancy or even pregnancy with low birth weight due to other causes. In contrast, increases in sTNFR-I levels during the later half of normal pregnancies indicate that sTNFR-I may be important in regulating TNF-alpha levels in preparation for normal labor and delivery.

IMMUNE FUNCTION AND BIODEFENSE IN CHILDREN, ELDERLY, AND THE IMMUNOCOMPROMISED (0840)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC \$: 0.664%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
Withheld				ONPRC, OR USA

SUBPROJECT DESCRIPTION

The immediate goal of this project is to develop a model of West Nile virus (WNV) infection and immunity in rhesus macaques (RM) with a long term goal of developing an improved and safer vaccine against WNV induced morbidity and mortality in the elderly. Although not exclusively a disease of the aged, it appears that older individuals may be more at risk due to declining capabilities of their immune systems. We will test whether the aged immune response lacks features of a mature intact immune system and determine if the mosquito contributes components that suppress immune response to WNV. Initially cellular immune function of rhesus monkeys greater than 17 years of age that were naturally exposed to WNV will be compared to normal exposed adult monkeys. Later WNV infection will be done at ONPRC with and without mosquito components to assess the immunologic and pathologic effects of the mosquito on disease transmission and viral persistence. Identification of infected cells and cellular immune participants will identify vulnerable cellular targets in aged individuals that may be important as sources of persistent infection, diagnostic sentinels and targets of therapy. Immunological characterization of 20 aged rhesus monkeys and 12 adult control monkeys from TNPRC is in progress and murine infection studies and dendritic cell experiments continue at ONPRC. Salivary gland extract in vivo and in vitro experiments and monkey infection studies are scheduled for year 2 of this project.

NIH/NIAID BIODEFENSE PROGRAM (0691)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC S: 0.664%

INVESTIGATOR	DEGREES	STAFF	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
withheld				TEXAS A&M, TX USA
				Proprietary Info UNIVERSITY OF TX MEDICAL BRANCH, TX USA
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				Proprietary Info

SUBPROJECT DESCRIPTION

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, B and 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, B and 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.

NONHUMAN PRIMATE CORE FOR THE CENTER FOR AIDS RESEARCH (0692)

NPRC UNIT: COMPARATIVE PATHOLOGY
%NPRC \$: 0.664% **AIDS RELATED RESEARCH**

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

SUBPROJECT DESCRIPTION

The objective of the nonhuman primate core is to provide highly integrated clinical management and laboratory investigations using nonhuman primate models of AIDS to CFAR investigators. The Core will enhance and facilitate the ability of CFAR investigators to perform studies in nonhuman primates and promote scientific collaborations between the TNPRC and CFAR colleagues in Philadelphia. The core consists of clinical and laboratory components. The clinical component will acquire, house and care for the nonhuman primates and assist investigators with experimental design. The core will also be responsible for the daily clinical care of animals and animal procedures such as immunizing the animals, blood draws, fluid collection, bronchoalveolar lavage, biopsies, etc.

The laboratory component of the core will perform routine hematology, clinical chemistry, ova and parasite examination of feces, microbiology, and pathologic examination of all necropsies and biopsies in support of the animal studies. The core will also provide flow cytometry and immunology services, SIV and SHIV viral stocks and isolation, and specialized pathology services including in situ hybridization, immunohistochemistry, confocal microscopy and image analysis. The core also includes animals and animal support for developmental studies. It is our expectation that the combination of nonhuman primate resources and specialized research expertise with nonhuman primate models of AIDS will enhance the AIDS research mission of the CFAR and result in new and stronger collaborations as well as attracting new investigators to use nonhuman primate models of AIDS.

SYSTEMIC ARTERIOPATHY IN SIV-INFECTED RHESUS MACAQUES (MACACA MULATTA) (0918)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC \$: 0.664% AIDS RELATED RESEARCH

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

SUBPROJECT DESCRIPTION

Severe disseminated vasculopathy was observed in two simian immunodeficiency virus (SIV)-infected rhesus macaques (*Macaca mulatta*). These animals developed clinical signs of AIDS, including lymphadenopathy, weight loss, diarrhea and collapse. Grossly, both animals showed emaciation, lymphadenopathy, vegetations on the mitral valve, renal infarcts and a dilated intestine; one animal had multifocal hemorrhages in multiple organs. Histologically, both cases had disseminated arteriopathy characterized by intimal thickening and fibrosis with varying degrees of vasculitis. The lesion was prominent in the kidney, intestine, pancreas, liver, heart, lymph nodes, spleen and testis. Occasional venules had intimal thickening. Both cases had cytomegalovirus (CMV) infection with intranuclear inclusions; CMV antigen and nucleic acid; some inclusions were observed in endothelial cells within some of the vascular lesions in one of the two. These data suggest that CMV caused the unusual lesions.

FOCAL ADHESION KINASE ACTIVATION IN THE BLOOD-BRAIN BARRIER (0841)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC \$: 0.664% AIDS RELATED RESEARCH

INVESTIGATOR	DEGREES	STAFF	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
withheld		CODE		LSU HEALTH SCIENCES CENTER, LA USA

SUBPROJECT DESCRIPTION

It is possible to isolate individual brain microvessels intact from recently sacrificed macaques. Using confocal microscopy, we demonstrate imaging of such vessels with a focus on signal transduction mechanisms of tight junction disruption. Using similar techniques, combined with detection of other cell types, allows us to visualize the effects of virus and viral-infected cells on activation processes necessary for tight junction disruption in the blood-brain barrier (BBB) in real time.

Brain microvessels stained for focal adhesion kinase (FAK) and zo-1 (a tight junction marker) demonstrate a "zipper" of tight junction protein extending the length of the vessels, but little or no FAK staining. In vessels incubated with SIV-infected cells, we noticed that the staining of zo-1 was lacking from some areas of vessel and not from others: of the same vessels. These areas are rich in FAK expression. Additionally, Western blot studies show that FAK is upregulated following incubation with SIV-infected mononuclear cells. Combined, these indicate that FAK is important in the regulation of tight junction protein expression.

TRANSDUCERS AND ACTIVATORS OF TRANSCRIPTION IN SIV INFECTED RHESUS MACAQUES (0835)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC \$: 0.664% AIDS RELATED RESEARCH

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

The gastrointestinal (GI) tract is a major target for HIV/SIV infection due to the presence of a large population of CD4+ CCR5+ T lymphocytes of the memory phenotype. Intestinal disease and inflammation are common sequelae to HIV/SIV infection. Nevertheless, the molecular mechanisms that lead to GI dysfunction following CD4+ T cell depletion remain unclear. We investigated changes in proinflammatory cytokine mediated signal transduction pathways associated with intestinal inflammation in SIV-infected rhesus macaques. We examined jejunum and colon collected at necropsy from 12 SIV-infected macaques with diarrhea (group 1), 10 non-SIV infected macaques with diarrhea (group 2) and 7 control uninfected macaques (group 3). All group 1 and group 2 macaques had chronic diarrhea, wasting and colitis but only group 1 animals also had significant enteritis. Gene expression analysis for interleukin-6 (IL-6), and suppressor of cytokine signaling-3 (SOCS-3) was performed using quantitative real-time SYBR Green one-step RT-PCR. The activation state and DNA binding capability of STAT3 was assessed using immunoprecipitation/western blotting and biotin streptavidin pull down assay, respectively. A significant increase in IL-6 and SOCS-3 gene expression along with constitutive activation of STAT3 was observed in the colon of all group 1 and group 2 macaques compared to controls. However, in the jejunum, together with constitutive activation of STAT3 statistically significant increases in IL-6 and SOCS-3 gene expression was observed only in group 1 macaques. Further, in the colon, histopathology severity scores correlated significantly with gene expression for IL-6 (groups 1 & 2) and SOCS-3 (group 2). In the jejunum, a significant correlation was observed for IL-6 and SOCS-3 only in group 1 animals. Similarly phosphorylated STAT3 (p-STAT3) was immunohistochemically localized to the lymphocyte (CD3+) and macrophage (CD68+) population in the intestinal lamina propria. In contrast, fewer CD3+ lymphocytes expressing p-STAT3 were detected in the SIV-infected macaque compared to the non-SIV infected animal. Despite high SOCS-3 expression, STAT3 remained constitutively active and provides a likely mechanism by which high IL-6 concentrations in the inflamed GI tract could induce and maintain intestinal inflammation and favor viral replication and disease progression.

PAUCITY OF CD4+CCR5+ T CELLS IN NATURAL SIV HOSTS:A PROTECTIVE ROLE AGAINST AIDS (0722)

NPRC UNIT: COMPARATIVE PATHOLOGY

%NPRC \$: 0.664% AIDS RELATED RESEARCH

INVESTIGATOR	DEGREES	STAFF	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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NIH, MD USA
 NEW ENGLAND NATIONAL
 PRIMATE RESEARCH CENTER, MA
 USA

Proprietary Info

SUBPROJECT DESCRIPTION

In contrast to lentiviral infections of humans and macaques, SIV infection of natural hosts is non-pathogenic despite high levels of viral replication. However, the mechanisms underlying this absence of disease are unknown. Here we report that natural hosts for SIV infection express remarkably low levels of CCR5 on memory CD4+ T-cells isolated from blood, lymph nodes, and mucosal tissues. As this immunological feature is found in five different species of natural SIV hosts (sooty mangabeys, African green monkeys, mandrills, solatus, and chimpanzees) but absent in four non-natural/recent hosts (humans, rhesus, pigtail, cynomolgous macaques, and baboons), it may represent a key feature of the co-evolution between the virus and its natural hosts that led to a non-pathogenic infection. Beneficial effects of low CCR5 expression on CD4+ T-cells may include the reduction of target cells for viral replication and/or a decreased homing of activated CD4+ T-cells to mucosal tissues.

