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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

5P51RR000169-42

CALIFORNIA NATIONAL PRIMATE RESEARCH CENTER

Final

UNIVERSITY OF CALIFORNIA - DAVIS

ANNUAL PROGRESS REPORT

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

46.455% AIDS Related

Dallas M Hyde 6/16/04

Signature Date

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Patent or Copyright was not awarded this grant year.

PERSONNEL ROSTER

Core Doctoral Scientists

Name, Degree	Department	Non-Host Institution: State, Country
AMARAL, DAVID G, PHD	MED:PSYCHIATRY	
BARRY, PETER A, PHD	CTR FOR COMPARATIVE MED	UC DAVIS: CA, USA
CAPITANIO, JOHN P, PHD	PSYCHOLOGY	
[illegible]		
GERSHWIN, LAUREL J, DVM, PHD	VM PATH/MICRO	
HYDE, DALLAS M, PHD	VM ANAT/PHYSI&CELL B	
KANTHASWAMY, SREE, PHD	CNPRC AND VETERINARY GENETICS	
LASLEY, BILL L, PHD	VM:POPULAT HLTH&REPRODU	
LERCHE, NICHOLAS W, DVM, MPVM	VM:PATHO/MICROBIOL/IMM UNO	
LUCIW, PAUL A, PHD	MED:PATHOLOGY	
MARTHAS, MARTA L, PHD	VM:PATHO/MICROBIOL/IMM UNO	
MASON, WILLIAM A, PHD	PSYCHOLOGY	
MCCHESNEY, MICHAEL B, MD	MED:PATHOLOGY	
MCDONALD, RUTH J, MD, PHD	MED PEDIATRICS	
MENDOZA, SALLY P, PHD	PSYCHOLOGY	
MILLER, CHRISTOPHER J, DVM, PHD	VM:PATH/MICRO/IMMUNO	
PINKERTON, KENT E, PHD	VM ANAT/PHYSI&CELL B	
PLOPPER, CHARLES G, PHD	VM ANAT/PHYSI&CELL B	
ROBERTS, JEFFREY A, DVM	PRIMATE CENTER	
[illegible]		
[illegible]		
TARANTAL, ALICE F, PHD	MED:PEDIATRICS	
VANDEVOORT, CATHERINE A, PHD	MED:OBSTETRICS/GYNECOLOGY	

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
[illegible]	OBST AND GYNECOLOGY	WISCONSIN NATIONAL PRIM RESEARCH CENTER: WI, USA
ABEL, KRISTINA, PHD		UC DAVIS: CA, USA
[illegible]		ORTHO DIAGNOSTICS: NJ, USA
		UC DAVIS: CA, USA
ANDERSON, DAVID E., PHD	MED: MICROBIO AND IMMNUO	UC DAVIS: CA, USA
[illegible]		UC SAN FRANCISCO: CA, USA
		OSWALDO CRUZ INSTITUTE, BRAZIL
[illegible]		HENRY DOORLY ZOO: NE, USA
		COVANCE LABS: MD, USA
[illegible]		UC DAVIS: CA, USA
		MCLEAN HOSPITAL: MA, USA

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
		ORPRC: OR, USA
		UNIVERSITY OF TEXAS, MEDICAL BRANCH: TX, USA
	CALIF AIR RESOURCES BOARD	UC SAN FRANCISCO: CA, USA
BARNES, CAROL, PHD	PSYCHOLGY AND NEUROLOGY	UNIVERSITY OF ARIZONA: AZ, USA
	CENTER FOR COMP MED	UC DAVIS: CA, USA
	PSYCHIATRY AND BEHAV. SCIENCES	UC DAVIS: CA, USA
BEAMAN, BLAIN L, PHD	NIEHS	
		CDC MEASLES BRANCH: GA, USA
	PSYCHIATRY AND BEHAV. SCIENCES	UC DAVIS: CA, USA
	ANIMAL SCIENCES	UC DAVIS: CA, USA
	UNKNOWN	UNKNOWN: CA, USA
		UNIV OF TEXAS: TX, USA
		ISIS PHARMACEUTICALS, INC. CARLSBAD: CA, USA
	MECH ENGINEERING	UNIV OF MINNESOTA: MN, USA
		TRPRC: LA, USA
		PHARMACIA & UPJOHN: NY, USA
		WORLDWIDE PRIMATE: FL, USA
		UC DAVIS: CA, USA
		TRPRC: LA, USA
	MED PHARM TOX:MED	UC DAVIS: CA, USA
		PFIZER-KALAMAZOO: MI, USA
	NIEHS	PENN STATE UNIV: PA, USA
	CENTER FOR COMP MED	UC DAVIS: CA, USA
		GENENTECH: CA, USA
		COLUMBIA UNIVERSITY: NY, USA
BRITTEN, KENNETH H, PHD	NEUR/PHYSI&BIO	
		MASS INSTITUTE OF TECHNOLOGY: MA, USA
BUCKPITT, ALAN R, PHD	VM MOLE BIOSCIENCES	
BUNNELL, BRUCE A., PHD	PHARMACOLOGY	TULANE UNIVERSITY HEALTH SCIENCES CENTER: LA, USA
	RADIOLOGY	UC MEDICAL CENTER: CA, USA
		CINCINNATI ZOO: OH, USA
	PRIMATE CENTER	
		MEDICAL COLLEGE OF GEORGIA: GA, USA
	MAGEE WOMEN'S INSTITUTE	UNIV OF PITTSBURGH: PA, USA
		UC DAVIS: CA, USA
		HOGLE ZOO: UT, USA

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
[ ]	VET MED TEACHING HOSPITAL	UC DAVIS: CA, USA
CHAFFIN, CHARLES L, PHD		MED COLLEGE: GA, USA
[names]		GENENTECH: CA, USA
		SIERRA BIOMEDICAL LABS: NV, USA
[names]		NIMH: MD, USA
		LYON UNIVERSITY, FRANCE
	CENTER FOR HEALTH AND ENVIRON.	UC DAVIS: CA, USA
[names]	ENVIR TOX	
		UNIVERSITY OF OKLAHOMA: OK, USA
CHOMEL, BRUNO B, PHD, DVM	SCH OF VET MED:POP HLT REPR	UNIV OF CALIF DAVIS: CA, USA
[ ]		JOHNS HOPKINS: CA, USA
COFFMAN, ROBERT L.		DYNAVAX TECHNOLOGIES CORPORATION AND UC DAVIS: CA, USA
[.		UCLA SCHOOL OF MEDICINE: CA, USA
		MERCK: NJ, USA
	POP HLTH REPRO	UC DAVIS SCHOOL OF VETERINARY MED: CA, USA
N		UNIV OF MARYLAND: MD, USA
	PSYCHIARTRY	
a	NIEHS	PACIFIC NORTHWEST NATIONAL LAB: WA, USA
m		COVANCE LABS, UK
e		UNIVERSITY OF CL. BERNARD-LYON, FRANCE
s		BALTIMORE ZOO: MD, USA
	DEPT OF PEDIATRICS	UNIV OF CALIF IRVINE: CA, USA
	NIEHS	
	MOLECULAR CELL BIO	UC DAVIS: CA, USA
	NIEHS	LOUISIANA STATE UNIV: LA, USA
]		USAMRICD: MD, USA
DANDEKAR, SATYA, PHD	MED:PATHOLOGY	
		TRPRC: LA, USA
[Names]	NPB	CTR FOR NEUROSCIENCE: CA, USA
		UCSF: CA, USA
[Names]		MRMC/FDA: OH, USA
DISBROW, ELIZABETH A., PHD	RADIOLOGY	UC SAN FRANCISCO: CA, USA
[ ]		MANNHEIMER FOUNDATION: FL, USA
DOUGLAS, GORDON C, PHD	MED:CELL BIO AND HUMAN ANAT	UC DAVIS: CA, USA

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
		UNIVERSITY OF LOUISIANA/NEW IBERIA: LA, USA
DUNAIF, ANDREA, MD	ENDOCR/METAB/MOL MED	NORTHWESTERN UNIVERSITY MEDICAL SCHOOL: WA, USA
		SAN FRANCISCO ZOO: CA, USA
		NIAID: MD, USA
		OAKLAHOMA STATE UNIVERSITY: OK, USA
	DYNAVAX	UCSD: CA, USA
		BIOMEDICAL RESEARCH FOUNDATION: LA, USA
		OAKLAND ZOO: CA, USA
		LOVELACE RESPIRATORY RESEARCH INSTITUTE: NM, USA
		MERCK: NJ, USA
ESSER, URSULA, PHD	MEDICAL PATHOLOGY	
		HARVARD UNIVERSITY: MA, USA
	VM: ANAT/PHYSIO & CELL B	
FELBER, BARBARA K, PHD		NCI: MD, USA
		ADVANCED BIOSYSTEMS: VA, USA
		PFIZER-GROTON: CT, USA
		OREGON STATE: OR, USA
	MED: SURGERY	UCD MED CENTER: CA, USA
		SNBL: MD, USA
		UNIV OF PITTSBURGH: PA, USA
		NIMH: MD, USA
		UC BERKELEY: CA, USA
		CA STATE DEPT HEALTH SERVICES: CA, USA
FULLER, CHARLES A, PHD	PSYCHOLOGY	NCI: MD, USA
	HEMATOLOGY AND ONCOLOGY	UC SAN FRANCISCO: CA, USA
GAGE, FRED	INSTITUTE OF AGING	SALK INSTITUTE: CA, USA
	CCM	UC DAVIS: CA, USA
		STANFORD UNIVERSITY: CA, USA
GERSHWIN, MERRIL E.		UC DAVIS: CA, USA
		AARON DIAMOND AIDS RESEARCH CENTER: NY, USA
	OB/GYN	
	NIEHS	
GOLUB, MARI S, PHD	PRIMATE CENTER	
		COLUMBUS ZOO: OH, USA

Affiliated

Name, Degree	Department	Non-Host Institution : State, Country
GOTHARD, KATI, PHD	PHYSIOLOGY	UNIVERSITY OF ARIZONA: AZ, USA
	NUTRITION	WASHINGTON NPRC: WA, USA
GREGORY, CLARE R	VET MED SURGERY	UNIV OF MIAMI: FL, USA
HAASE, ASHLEY, MD		UNIV OF MINNESOTA: MN, USA
HACIA, JOSEPH G, PHD	BIOCHEM AND MOL BIO	UNIVERISITY OF SOUTHERN CALIFORNIA: CA, USA
HAGERMAN, PAUL J	MED:BIO CHEM	UC DAVIS: CA, USA
		UNIVERSITY OF ILLINOIS: IL, USA
		HARVARD UNIVERSITY: MA, USA
		TSUKUBA PRIMATE CENTER, JAPAN
	NIEHS	MICHIGAN STATE UNIVERSITY: MI, USA
		AARON DIAMOND AIDS RESEARCH CENTER: NY, USA
		OREGON ZOO: OR, USA
	NIEHS	US EPA: WA, USA
HAVEL, PETER J, DVM, PHD	NUTRITION	
HECKER, JAMES G, PHD, MD	DEPT OF ANESTHESIOLOGY	UNIV OF PENNSYLVANIA: PA, USA
		UC SAN FRANCISCO: CA, USA
	CENTER FOR HEALTH & ENVIR.	
		CENTER FOR DISEASE CONTROL: GA, USA
		PFIZER-ANN ARBOR: MI, USA
		MERCK: CA, USA
	PATH., MICROBIO AND IMM.	UC DAVIS: CA, USA
	PSYCHOLOGY	
		LOVELACE CLINIC: NM, USA
	CENTER FOR COMP MED	UC DAVIS: CA, USA
		FOCUS TECHNOLOGIES: VA, USA
HORTON, JONATHON C, MD, PHD		UCSF: CA, USA
		SHARED ENTERPRISES, UNKNOWN
	CENTER FOR COMPARATIVE MEDICIN	
		BIORELIANCE: MD, USA
	NIEHS	PENN STATE UNIV: CA, USA
		GENESIS BIOSYSTEMS: TX, USA
JOAD, JESSE P, MD	MED PEDIATRICS	
		GENENTECH: CA, USA

Affiliated

Name, Degree	Department	Non-Host Institution : State, Country
JONES, EDWARD G, MD, PHD	CTR FOR NEUROSCIENCE	
	VM INTERNATL LAB MOL	
		CSL, AUSTRALIA
		UC DAVIS: CA, USA
KAN, Y.W., MD	HOWARD HUGHES MEDICAL INSTITUT	UC SAN FRANCISCO: CA, USA
		BLOOD CENTERS OF THE PACIFIC: CA, USA
KEARNS-JONKER, MARY, PHD	CARDIOTHORACIC SURGERY	CHILDREN'S HOSPITAL LOS ANGELES: CA, USA
		SCHERING CORPORATION: CA, USA
		SAN DIEGO ZOO: CA, USA
	NUTRITION	
		BIOCOR ANIMAL HEALTH: NE, USA
		AVENTIS-PASTEUR: PA, USA
		WESTERN HUMAN NUTRITION RESEARCH CENTER: CA, USA
	NIEHS	CENTERS FOR HEALTH SCIENCES: NC, USA
		MCLEAN HOSPITAL: MA, USA
		UNIVERSITY OF MINNESOTA: MN, USA
		SCHERING PLOUGH: NJ, USA
	CALIF AIR RESOURCES BOARD	UC IRVINE: CA, USA
		UCLA: CA, USA
		NMRC: MD, USA
KOEHLER, JANE		UCSF: CA, USA
KOHN, DONALD B, MD	IMMUNOLOGY AND BMT	CHLDRNS HOSP LOS ANGELES: CA, USA
		ADVANCED BIOSYSTEMS: VA, USA
		SCHERING PLOUGH: NJ, USA
KRUBITZER, LEAH A, PHD	PSYCHOLOGY	
		UNIV OF IOWA: IA, USA
	BIOLOGICAL CHEM:UCD CANCER CTR	
LANDAY, ALAN L.		UNKNOWN: CA, USA
		HARVARD UNIVERSITY: CT, USA
		SACRAMENTO ZOO: CA, USA
	PUL MED	UCD TSR&TP: CA, USA
		NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER: MA, USA

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
		U NEW ORLEANS: LA, USA
		ECOLE VETERINARIE DE LYON, FRANCE, FRANCE
		OREGON NPRC: OR, USA
		COLUMBIA UNIVERSITY: NY, USA
	VM:ANAT/PHYSIO & BELL BIO	UCD SCHOOL OF VETERINARY MEDICINE: CA, USA
	CENTER FOR NEUROSCIENCE	UC DAVIS: CA, USA
LONNERDAL, BO, PHD	NUTRITION	
	CENTER FOR NEUROSCIENCE	UC DAVIS: CA, USA
LOZOFF, BETSY, MD	PEDIATRICS	UNIV OF MICHIGAN AT ANN ARBOR: MI, USA
LU, FA	MED:PATH/MICRO/IMMUN	
		METABOLEX CORP.: CA, USA
		LOS ANGELES ZOO: CA, USA
		TOLEDO ZOO: OH, USA
		FRESNO ZOO: CA, USA
LYONS, LESLIE, PHD	VM:POP HLTH & REPRO	UC DAVIS: CA, USA
		NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER: MA, USA
	PSYCHIATRY AND BEHAV. SCI	UC DAVIS: CA, USA
		TULANE NATIONAL PRIMATE RESEARCH CENTER: LA, USA
MATSELL, DOUGLAS G, MD	DIVISION OF NEPHROLOGY	UNIVERSITY OF BRITISH COLUMBIA, BRITISH COLUMBIA
MATSUMURA, FUMII	UNKNOWN	UNKNOWN: CA, USA
		SOUTHWEST BIOMEDICAL FOUNDATION: TX, USA
		YERKES NPRC: GA, USA
		LARGE SCALE BIOLOGY: CA, USA
	MED:ORAL BIO/MICRO/IMMUN	UNIV OF ALABAMA AT BIRMINHAM MED CTR: AL, USA
	PSYCHOLOGY AND PHYSIOLOGY	UNIVERSITY OF ARIZONA: AZ, USA
MEYERS, STUART A	VM:ANAT/PHYSIO/CELL BIO	
		SIERRA BIOMEDICAL LABS: NV, USA
	VM ANAT/PHYSI&CELL B	
	ENVRION. TOXICOLOGY	UC DAVIS: CA, USA
		DISNEY WORLD: FL, USA
		UNIV TEXAS SOUTHWESTERN MED CTR: TX, USA
	PATH., MICROB, IMM, VIROLOGY	UC DAVIS: CA, USA
		DUKE UNIVERSITY: GA, USA

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
MORRISON, JOHN, PHD	NEUROBIOLOGY	STANFORD UNIVERSITY: CA, USA MOUNT SINAI SCHOOL OF MEDICINE: NY, USA NIAID: MD, USA TSUKUBA PRIMATE CENTER, JAPAN LOWRY PARK ZOO: FL, USA UNIV OF PITTSBURGH: PA, USA STANFORD UNIVERSITY: CA, USA ALLERGAN: CA, USA NORTHWESTERN UNIVERSITY: IL, USA
NORTH, THOMAS W, PHD	CTR FOR COMPARAT MED	
O NEILL, EDUARDO		CARRIBBEAN PRIMATE CENTER, PUERTO RICO
	CENTER FOR NEUROSCIENCE	NINDS: MD, USA SHIN NIPPON BIOMEDICAL LABS USA, LTD.: WA, USA
	SCHOOL OF VETERINARY MEDICINE	
	PATH., MICROBIO., AND CELL BIO	UC DAVIS VET MED: CA, USA
		CDC: GA, USA
OVERSTREET, JAMES W, MD, PHD	MED:OBSTETRICS & GYNEC	
PACHNER, ANDREW R, MD	NEUROSCIENCES	UMDNJ-NEW JERSEY MEDICAL SCHOOL, NEWARK: NJ, USA
PAPPAGIANIS, DEMOSTHENES, PHD	MED:MICROB & IMMUN	UC DAVIS: CA, USA NIH-ROCKY MOUNTAIN: MT, USA
	INTERNAL MEDICINE	STANFORD UNIVERSITY SCHOOL OF MEDICINE: CA, USA
	VM MED&EPIDEMIOLOGY	
	VET GENETICS LAB	UC DAVIS: CA, USA
PEREZ, RICHARD V, MD	MED:SURGERY	UCD MED CENTER: CA, USA HARVARD SCHOOL OF PUBLIC HEALTH: MA, USA
PESSAH, ISAAC N., PHD	UNKNOWN	UNKNOWN: CA, USA MERCK: CA, USA
POLLARD, RICHARD B.		UC DAVIS: CA, USA
POSTLETHWAIT, EDWARD M, PHD	NIEHS	UNIV OF ALABAMA: AL, USA
	UCD SCHOOL OF MEDICINE	UC DAVIS: CA, USA NCRR: MD, USA
	CELL BIO AND HUMAN ANATOMY	

Affiliated

Name, Degree	Department	Non-Host Institution : State, Country
		WALTER REED ARMY INSTITUTE OF RESEARCH: MD, USA
	PATH, MICROBIO, AND CELL BIO	UC DAVIS VET MED: CA, USA
	MOLECULAR BIOSCIENCES	
RAPP, PETER R, PHD	NEUROBIOLOGY AND AGING	MT SINAI SCHOOL OF MEDICINE: NY, USA
	NIAID	UCSD: CA, USA
RECANZONE, GREGG HOWARD, PHD	CTR FOR NEUROSCIENCE	
		TOLEDO ZOO: OH, USA
	CENTER FOR COMPARATIVE MEDICIN	UC DAVIS: CA, USA
		UNIVERSITY OF PITTSBURGH: PA, USA
	MED PATHOLOGY	
	ENVIR TOX	UCD: CA, USA
		UNIV OF TEXAS: TX, USA
		VALLEY BIOSYSTEMS: CA, USA
		UNIVERSITY OF KENTUCKY: KY, USA
		LABS OF VIRGINIA, YEMASSEE: VA, USA
		TRPRC: LA, USA
	RES CORE:SIMIAN RETROVIR LAB	
	ANIMAL SCIENCES	UC DAVIS: CA, USA
	MOLECULAR BIO	CITY OF HOPE NATIONAL MED CTR: CA, USA
		CDC MEASLES BRANCH: GA, USA
	ENDOCRINOLOGY	UCDMC: CA, USA
		CARRIBBEAN PRIMATE CENTER, PUERTO RICO
		FOLSOM ZOO: CA, USA
	MED PATHOLOGY	UC DAVIS: CA, USA
SCHELEGLE, EDWARD, PHD	VM ANAT/PHYSI&CELL B	
	RES: ENDO: CTR	UC DAVIS: CA, USA
		GENENTECH: CA, USA
		UNIV OF TEXAS: TX, USA
	OMS	NIH: MD, USA
		HARVARD UNIVERSITY: NJ, USA
	NIEHS	
		PHARMACIA & UPJOHN: NY, USA
		3 SPRINGS SCIENTIFIC, UNKNOWN
		UC IRVINE: CA, USA

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
[Names]	CENTER FOR NEUROSCIENCE	UC DAVIS: CA, USA
	INST. VIR.& IMMUN.	UC SAN FRANCISCO: CA, USA
		WISCONSIN RPRC: WI, USA
	RES.ENDO:CTR FOR HLTH & ENV	UC DAVIS: CA, USA
		UNIVERSITY OF ARIZONA: AZ, USA
	DIVISION OF NEURAL SYSTEMS	UNIVERSITY OF ARIZONA: AZ, USA
		BIOCOR ANIMAL HEALTH: NE, USA
		DUKE UNIVERSITY MEDICAL CENTER: GA, USA
	ANTHROPOLOGY	UC DAVIS: CA, USA
		SOUTHWEST PRIMATE CENTER: TX, USA
		SOUTHWEST BIOMEDICAL FOUNDATION: TX, USA
SODORA, DONALD L, PHD		SOUTHWESTERN MED CTR: TX, USA
SOLNICK, JAY V, MD, PHD	MED:INTERNAL MED	
[names]		METABOLIX: MA, USA
	GENETIQUE DES VIRUS	INSTITUT COCHIN DE GENETIQUE MOLECULAIRE, FRANCE
SPARGER, ELLEN, PHD, DVM	ASSOCIATE ADJUNCT PROFESSOR	SCHOOL OF VETERINARY MEDICINE, UC DAVIS: CA, USA
[Names]	NIEHS	LOUISIANA STATE UNIV: LA, USA
		BIOQUAL: MD, USA
	USC MEDICAL CENTER	
		PRIMATE PRODUCTS: CA, USA
		YUNNAN ANIMAL INSPECTION AND QUARANTINE, CHINA
		CDC: GA, USA
SUTTER, MITCHELL L	CENTER FOR NEUROSCIENCE	
[Names]	FAMILY AND COMMUNITY MEDICINE	UNIVERSITY OF MISSOURI, COLUMBIA: MI, USA
		SHIN NIPPON BIOMEDICAL LABS: WA, USA
		CENTER FOR DISEASE CONTROL: GA, USA
	VM:ANAT PHYS AND CELL BIO	UC DAVIS: CA, USA
		NUCLEAR ENERGY INSTITUTE: DC, USA
		CNPRC PATHOLGY SERVICE: CA, USA

Affiliated

Name, Degree	Department	Non-Host Institution : State, Country
[Names]	INHALATION EXPOSURE FACILITY	
		AVENTIS-PASTEUR, TORONTO, CANADA
	DEPT OF PSYCHIATRY	
		UC SAN FRANCISCO: CA, USA
		UNIVERSITY OF WASHINGTON: WA, USA
		INSERM, FRANCE
		GENESIS BIOTECH, TAIWAN
TUSZYNSKI, MARK H, MD, PHD		UCSD: CA, USA
[ ]	NIEHS	PENN STATE UNIV: PA, USA
USREY, WILLIAM M	CENTER FOR NEUROSCIENCE	
VAN-ROMPAY, KOEN K A, DVM, PHD	PRIMATE CENTER	
[ ]	VM ANAT/PHYSI&CELL B	
	VM: INTERNATL LAB MOL	CD DAVIS: CA, USA
		UC SAN FRANCISCO: CA, USA
		CENTER FOR COMPARATIVE MEDICINE: CA, USA
		FOCUS TECHNOLOGIES: VA, USA
[Names]	POP HLTH REPRO	UCD-VM: CA, USA
		NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT: MD, USA
		WNPRC: WI, USA
		WHALE BRANCH ANIMAL SERVICES: VA, USA
		IDEXX: ME, USA
		LIVERMORE: CA, USA
		NE RPRC: MA, USA
[ ]	ANAT AND NEUROBIO	LOUISIANA STATE UNIV MED CTR: LA, USA
WIEHLE, RONALD, PHD		ZONAGEN: TX, USA
[ ]	PATH., MICROBIO AND CELL BIO	UC DAVIS VET MED: CA, USA
[Names]	PATH MICROB IMM:VM	UCD: CA, USA
		CA DEPT OF HEALTH SERVICES, BERKELEY: CA, USA
WINE, JEFFREY J	PSYCH, MOL CELL PHYSIO	STANFORD UNIVERSITY: CA, USA
[Names]	BIOLOGICAL SCIENCES	UC DAVIS: CA, USA
		UNIVERSITY OF WISCOSNSIN/WNPRC: WI, USA
[ ]	OBS AND GYN	UC DAVIS: CA, USA

Affiliated

Name, Degree	Department	Non-Host Institution: State, Country
		NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT: MD, USA
	INTERNAL MED	UCD: CA, USA
		YUNNAN ANIMAL INSPECTION AND QUARANTINE, CHINA
YILMA, TILAHUN D, DVM, PHD	VM INTERNATL LAB MOL	
YOUNG, GLENN M	FOOD SCI & TECH	UC DAVIS: CA, USA
ZAHORSKY-REEVES, JOANNE, MD		LOS ANGELES CHILDREN'S HOSPITAL: CA, USA
ZERN, MARK A.		UC DAVIS: CA, USA
		PFIZER: NE. USA

Graduate Student/Postdoctoral Scientists

Name, Degree	Department	Non-Host Institution: State, Country
	CENTER FOR NEUROSCI	UC DAVIS: CA, USA
	ANAT/PHYS/CELL BIO	UCD SCHOOL OF VETERINARY MEDICINE: CA, USA
	CENTER FOR COMPARATIVE MEDICIN	
	IMMUNOLOGY GRADUATE PROGRAM	UC DAVIS: CA, USA
	PRIMATE CENTER	
FANNUCHI, MICHELLE	VM: ANAT/PHYSIO & CELL B	
	MED:BIO CHEM	UC DAVIS: CA, USA
	PRIMATE CENTER	
	DEPT OF PSYCHIATRY	
		CNPRC: CA, USA
		UC SAN FRANCISCO: CA, USA
	NEURO, PHYSIO, BEHAVIOR	
	PRIMATE CENTER	
	PSYCHIATRY AND BEHAV. SCIENCES	
	PSYCHIATRY AND BEHAV. SCIENCES	
	PRIMATE CENTER	
	VM:POP HLTH AND REPRO	UC DAVIS: CA, USA
	SCHOOL OF MEDICINE	

Graduate Student/Postdoctoral Scientists

Name, Degree	Department	Non-Host Institution: State, Country
[redacted]	PSYCHOLOGY	UC DAVIS: CA, USA
[redacted]	DEPT OF PSYCHIATRY VIROLOGY AND IMMUNOLOGY	
[redacted]	NEURO, PHYSIO, BEHAVIOR	
[redacted]	MEDICAL PATHOLOGY	UC DAVIS: CA, USA
[redacted]	NEUROLOGY DEPT.	COLUMBIA UNIVERSITY: NY, USA
[redacted]	NUTRITION	UC DAVIS: CA, USA
[redacted]	PRIMATE CENTER	
[redacted]	NEUROSCIENCE	
[redacted]	CENTER FOR COMPARATIVE MEDICIN	

SUBPROJECT DESCRIPTIONS

NPRC MANAGEMENT SUBPROJECTS

G20 PURCHASE AND INSTALLATION OF BIO-ISOLATION UNITS (0259)

NPRC UNIT: MODERNIZE & IMPROVE - AID

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
HYDE, DALLAS M	PHD	C B	VM ANAT/PHYSI&CELL	

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

ABSTRACT

This is a G 20 grant for purchase and installation of bio-isolation cages to be utilized in housing of experimentally infected non-human primates. The isolation afforded by these cages will allow housing of animals with otherwise incompatible infectious agents in the same room. This will increase the efficient use of space that would otherwise be restricted to animals infected with common agents. Furthermore, the isolators increase containment of the agents and increase personnel safety. The detailed design and cost estimates for this project have been completed and submitted to the NIH architect for review and approval. The Primate Center is awaiting approval to proceed

G20 RENOVATION OF OFFICE/LABORATORY SPACE TO ANIMAL HOUSING (0261)

NPRC UNIT: MODERNIZE & IMPROVE - AID

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
HYDE, DALLAS M	PHD	C B	VM ANAT/PHYSI&CELL	

AXIS I CODES: 1A, 11 **AXIS II CODES:** 31, 36, 66

ABSTRACT

This is a G 20 grant to renovate 3600 square feet of office, laboratory, and outdoor chain link animal housing to indoor animal housing capable of housing up to 200 non-human primates. The project will return 2700 square feet of office and laboratory space in three 900 sf buildings to the original function as animal housing. An additional 900 square feet of outdoor space located between two of the buildings will be incorporated into the renovated area to increase the housing capacity.

This project is currently in the design phase. An architectural consultant has prepared preliminary design documents and construction costs. Final construction documents and costs estimates will be submitted to NIH for review and approval in 2003. Construction will begin in 2004.

C06 EXTRAMURAL RESEARCH FACILITIES CONSTRUCTION (0290)

NPRC UNIT: MODERNIZE & IMPROVE - AID

%NPRC $: 5.586% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
HYDE, DALLAS M	PHD	C B	VM ANAT/PHYSI&CELL	

AXIS I CODES: 1A, 11 **AXIS II CODES:** 31, 41, 60, 64, 71

ABSTRACT

The CNPRC is proposing to replace the Building, designated L animal location that currently houses the Brain, Mind and Behavior (BMB) Unit on the CNPRC campus with a new foundation and a metal frame building with overall dimensions of 7,433 sq. ft. The new structure will accommodate several existing programs of research that are focused on Child Health and Disease. All four Research Units at the CNPRC have research currently in progress in the area of Childhood Health, and this is an area of research focus that will continue to expand Center-wide. As an initial step, construction of the proposed facility will permit consolidation of existing programs in the BMB Unit, and will serve the long-term objective of expanding and integrating the research effort in pediatric health-related issues by current staff scientists, new faculty recruits, and by developing additional collaborations with staff scientists in other units that share this investigational focus. The specific aim of this application is to provide high quality testing and laboratory space for the biobehavioral research in the BMB Unit that is focused on Childhood Health and Disease. The building will include 1,646 sq. ft. of behavioral testing space, three rooms of animal housing space totaling 1,100 sq. ft. (including mother-infant, nursery and juvenile housing), one wet laboratory of 231 sq. ft., one wet laboratory of 467 sq. ft. and one wet laboratory of 472 sq. ft.. In addition, there will be a surgical suite (comprising an animal preparation area, a surgeon preparation suite and a surgery to accommodate extended neurosurgical procedures), a room for shared equipment (freezer, refrigerator, centrifuge), and a small preparation room for technician use.

G20 MODULAR ANIMAL HOUSING UNITS FOR PRIMATE NURSERY (0260)

NPRC UNIT: MODERNIZE & IMPROVEMENT

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
HYDE, DALLAS M	PHD	C B	VM ANAT/PHYSI&CELL	

AXIS I CODES: 1A, 11 **AXIS II CODES:** 64, 66, 67, 71

ABSTRACT

This is a G 20 grant to purchase two modular animal buildings for expansion of research programs using the infant rhesus model. The modular units will provide necessary separation of infants cohorts that are either allergen naïve or have been exposed to both dust mite allergen and ozone. These units will be sited immediately adjacent to the CNPRC Respiratory Exposure facility to optimize transport of infant monkeys to the exposure chambers. These modular units will allow necessary expansion of asthma research program targeting development of strategies for prevention and treatment of this debilitating disease.

This project has been awaiting completion of environmental analysis and review. That process is now complete. Site and infrastructure planning for the buildings is ongoing. Detailed building design will commence in May 2003. Detailed site plans and costs estimates will be submitted to the NIH architect for review and approval in 2003. Site construction and installation of the modular buildings will begin in 2004.

PRODUCTION OF PEDIGREED SPF RHESUS MACAQUES (0168)

NPRC UNIT: PRIMATE SERVICES

%NPRC $: 2.169% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LERCHE, NICHOLAS W	DVM, MPVM	C	VM:PATHOMICROBIOL/IMMUNO	
name 3	DVM	C	PRIMATE CENTER	

AXIS I CODES: 1A, 1D, 7B **AXIS II CODES:**31, 58, 66

ABSTRACT

The SPF has expanded recruitment of Indian origin rhesus into the SPF colony.. There is a specific need for rhesus macaques in AIDS research that are free of certain specific pathogens and are of Indian origin. The goal of this project is to produce pedigree SPF (Specific Pathogen Free) Indian origin rhesus macaques and establish a long term breeding colony of SPF animals. Animals selected for the SPF macaque colony are screened for Cercopithecine herpesvirus 1 (CHV1) Type D retrovirus, Simian Immunodeficiency Virus (SIV), Simian T- Lymphotrophic Virus (STLVI) and Simian Foamy Virus (SFV). All animals are of known pedigree and geographic origin. Animals are also typed for two MHC loci, MaMu A*01 and MaMu B*01. Macaques with the MaMuA*01 allele are thought to be important for research in vaccinology and the biology of cytotoxic lymphocytes. Identification of animals that are know homozygous MaMa A*01 has allowed development of specific breeding strategies for A*01 positive animals. Breeding strategies utilize both natural matings and assisted reproductive technology. This year 74 infant rhesus were recruited from known Indian origin animals in the CRPRC colony. All animals were screened for the five selected agents and MHC typed. Eighteen rhesus were allocated to AIDS investigators in 2002. The remaining animals have been placed in social housing. Female SPF animals are retained for long term breeding and males made available for AIDS investigators needs. A total of 36 adult rhesus are assigned to this project for assisted reproductive technology procedures and 104 SPF animals have been retained for future SPF breeding.

HORMONAL RESPONSE TO A SELECTIVE ESTROGEN RECEPTOR MODULATOR AND TO ESTROGEN (0307)

NPRC UNIT: RESEARCH CORES

%NPRC $: 0.045%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
HAVEL, PETER J	DVM, PHD	A	NUTRITION	
		A		
		A		

AXIS I CODES: 1A **AXIS II CODES:** 93

ABSTRACT

In order to provide options to hormone replacement therapy, [ ] has developed a novel [ ] proprietary [ ] This compound is expected to decrease post menopausal hot flashes and bone loss and improve cardiovascular and breast and uterine cancer risk. Three pilot studies were run for the testing of this compound. The goal of this pilot study is to determine the hormonal response to daily estrogen administration. This paradigm will be used to test

Pilot 1 Objective: To determine the hormonal responses to daily estrogen administration in 6 rhesus monkeys.

Pilot 2 Objective: To determine the hormonal responses to administration of the novel [ ] proprietary [ ] developed by [ ] for improving post-menopausal symptom in women to the hormonal responses to daily estrogen adminstration measured in a pilot study 1 in 8 rhesus monkeys.

Pilot 3 Objective: To determine the hormonal responses to administration of the novel [ ] proprietary [ ] at a higher dose than the dose used in pilot study 2 to the hormonal responses daily estrogen adminstration measured in a pilot study 1 in eight rhesus monkeys .

Results: Pilot study 1 demonstrated that the leptin response to estrogen administration was marked and consistent and would serve as a biomarker for modulation of the estrogen receptor by the novel compound.

Pilot study 2 demonstrated that the dose of the [ ] administered was not high enough to induce the leptin response that was documented in pilot study 1 following estrogen administration.

Pilot study 3: In order that the results remain proprietary, [ ] analyzed the collected plasma and RNA.

private funding

private funding

proprietary

private funding

FLIGHT ATTENDANT MEDICAL RESEARCH (0324)

NPRC UNIT: RESPIRATORY DISEASES

%NPRC $: 0.003%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
JOAD, JESSE P	MD	A	MED PEDIATRICS	

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

ABSTRACT

No abstract available.

RESEARCH SUBPROJECTS

ANATOMY OF PRIMATE AMYGDALOID COMPLEX (0001)

NPRC UNIT: BRAIN, MIND, & BEHAVIOR

%NPRC $: 0.946%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
AMARAL, DAVID G	PHD	C	MED:PSYCHIATRY	
		A	PSYCHIATRY AND BEHAV. SCIENCES	UC DAVIS, CA USA
		G	PSYCHIATRY AND BEHAV. SCIENCES	

AXIS I CODES: 1D, 21 **AXIS II CODES:**63C

ABSTRACT

The amygdaloid complex is a heterogeneous anatomical region located in the primate temporal lobe. It has been implicated in the mediation of emotional behavior, especially fear, and in the coordination of species typical social behavior. Our laboratory is conducting a multidisciplinary research program aimed at understanding the structure, physiology and function of the non-human primate amygdala. We are using these data as the basis for understanding the pathology associated with disorders of social interaction such as autism.

During this project period, we have completed an analysis of cortical inputs to the amygdala (Stefanacci and Amaral, 2002). This is the second of two papers that have defined all of the potential sensory inputs to the macaque monkey amygdala. We have also initiated a new series of studies designed to evaluate the development of these connections. Essentially all of the cortical inputs to and from the amygdala are established by two weeks of age. Another new program of research is using electron microscopy to examine the synaptic organization of the amygdala's projections to the neocortex. Finally, we have also begun studies to examine the morphological organization of the normal human and autistic amygdala in postmortem material.

NEUROBIOLOGY OF PRIMATE SOCIAL BEHAVIOR (0002)

NPRC UNIT: BRAIN, MIND, & BEHAVIOR

%NPRC $: 1.588%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
AMARAL, DAVID G	PHD	C	MED:PSYCHIATRY	
		A	PSYCHIATRY AND BEHAV. SCIENCES	UC DAVIS, CA USA
	PHD	C	PSYCHOLOGY	
	PHD	G	DEPT OF PSYCHIATRY	
		G	PSYCHIATRY AND BEHAV. SCIENCES	
	PHD	C	PSYCHOLOGY	
		G	SCHOOL OF MEDICINE	
	PHD	C	PSYCHOLOGY	

AXIS I CODES: 1A, 21

AXIS II CODES: 36, 60, 63C

ABSTRACT

The primate amygdaloid complex is an important component of the brain system involved in mediating appropriate species-specific behaviors such as threat and defense. Large lesions of the inferior temporal lobe including the amygdala, produce the so-called "Kluver-Bucy Syndrome" which has been characterized as an inability to attribute emotional significance to perceived stimuli. Significant changes in social behavior have also been reported. Critical reading of the literature, however, indicates that the experimental basis for this characterization is tenuous. Previous studies have often suffered from the lack of discrete lesions, comprehensive histological analysis or ethologically appropriate and sophisticated behavioral assessment. This project uses sophisticated neurobiological and behavioral methods to reassess the role of the primate amygdala in normal social interaction. The research is carried out in the context of a long-standing program of neuroanatomy which has demonstrated that the amygdala receives sensory information from widespread regions of the neocortex. The overarching hypothesis guiding this program is that the amygdala is a high level perceptual apparatus that interprets ongoing sensory information in order to orchestrate appropriate species-specific responses. These studies will provide important insights into the neurobiology of normal social behavior and may contribute to an understanding of the pathologies of social communication in disorders such as autism. An important new area advanced this year has been the completion of amygdala lesions in neonatal macaques. The operates were returned to their mothers for rearing and their social development has been extensively studied.

FUNCTIONAL ORGANIZATION OF THE HIPPOCAMPAL FORMATION (0003)

NPRC UNIT: BRAIN, MIND, & BEHAVIOR

%NPRC $: 1.064%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
AMARAL, DAVID G	PHD	C	MED:PSYCHIATRY	
	BA	A	PSYCHIATRY AND BEHAV. SCIENCES	UC DAVIS, CA USA
		G	PSYCHIATRY AND BEHAV. SCIENCES	

AXIS I CODES: 1D, 21 **AXIS II CODES:**41

ABSTRACT

The hippocampal formation is an important component of the brain system involved in producing long term memories. It is clear that the system that carries out this function in the human brain is structured very similarly to the non-human primate brain but is different in important ways from the rodent brain. This program of research involves various types of morphological studies to evaluate the intrinsic organization as well as the extrinsic connections and chemical neuroanatomy of the macaque monkey and human hippocampal formation. These studies range from intracellular labeling of single neurons in the in vitro hippocampal slice preparation (Amaral and Amaral, 2002) to connectional studies of the hippocampus and related regions (Amaral 2002) to studies of the human hippocampal formation and related structures. It is fair to state at this point that we and others have identified all of the major connections of the hippocampal formation. The retrosplenial cortex, which provides about 20% of the input to the hippocampal formation has been an area of intense work in the laboratory.

NEUROBEHAVIORAL RELATIONS IN SENESCENT HIPPOCAMPUS (0295)

NPRC UNIT: BRAIN, MIND, & BEHAVIOR

%NPRC $: 0.607%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BARNES, CAROL	PHD	A	PSYCHOLGY AND NEUROLOGY	UNIVERSITY OF ARIZONA, AZ USA
	PHD	C	MED:PSYCHIATRY	
	PHD	A	RADIOLOGY	UC MEDICAL CENTER, CA USA
	PHD	A	PHYSIOLOGY	UNIVERSITY OF ARIZONA, AZ USA
	PHD	A	PSYCHOLOGY AND PHYSIOLOGY	UNIVERSITY OF ARIZONA, AZ USA
	PHD	A	NEUROBIOLOGY AND AGING	MT SINAI SCHOOL OF MEDICINE, NY USA
	PHD	A	DIVISION OF NEURAL SYSTEMS	UNIVERSITY OF ARIZONA, AZ USA
		G	NEUROLOGY DEPT.	COLUMBIA UNIVERSITY, NY USA
	PHD	A	BIOLOGICAL SCIENCES	UC DAVIS, CA USA

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

ABSTRACT

The objective of this research program is to understand the basis of memory impairments that result from normal aging. Over the past 19 years we have discovered links between spatial memory deficits and age-related changes in hippocampal connectivity and plasticity at the cellular and network levels. While empirical focus on the hippocampus is justified because of this structures critical role in memory, the extent to which changes in upstream cortico-hippocampal inputs contribute to these age-related behavioral deficits is unknown. The perirhinal cortex is at the highest level of the ventral visual processing stream. It carries polymodal sensory information to the hippocampus, is extensively reciprocally connected with it, and is critical for memory in its own right. Whether it transmits degraded information to the aged hippocampus, resulting in deficits in visual perception or stimulus associations is thus a major question addressed in the present grant. A complementary question is whether the breakdown during aging in the connectivity and plasticity mechanisms of hippocampal circuits leads to defective associative binding among neocortical areas, and hence less robust stabilization of episodic memories. Understanding how the bi-directional interactions between these structures are altered by the aging process, and how such failures in network communication may contribute to behavioral deficits, could provide insights into the neural mechanisms of memory at all ages. To begin the process of integrating the past two decades of rodent work towards an understanding of human aging, the scope of the project will be expanded to include young and aged monkeys in addition to rodents. The animals will be behaviorally tested on a battery of tasks that are adaptable to both species and known to be sensitive to lesions of the hippocampus and to the perirhinal cortex. In the monkeys, high resolution quantitative structural MRI and eventual microscopic stereological analysis will be used to begin to define structural changes associated with physiological changes and memory impairments in the aged non-human primate. Electrophysiological experiments will focus on ensemble recordings from hippocampus and perirhinal cortex of behaving young and old monkeys, and on synaptic connectivity and plasticity of the hippocampal - perirhinal cortex in young and old rats. The combination of ensemble recordings in the awake, behaving, aged non-human primate, and functional electrophysiological characterization of connections in behaviorally-screened young and old rats, should lead to insights into the respective involvement of hippocampal and neocortical association areas to age-associated memory deficits. This is a prerequisite for successful development of therapeutic or preventative treatments for cognitive decline in the elderly.

SIMIAN AIDS SOCIAL STRESS, ENDOCRINE, & IMMUNE FUNCTION (0004)

NPRC UNIT: BRAIN, MIND, & BEHAVIOR

%NPRC $: 1.258% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
CAPITANIO, JOHN P	PHD	C	PSYCHOLOGY	
	PHD	C	CTR FOR COMPARATIVE MED	UC DAVIS, CA USA
	PHD	A		UCLA SCHOOL OF MEDICINE, CA USA
	PHD	C	PSYCHOLOGY	
	PHD	C	PSYCHOLOGY	

E Names]

AXIS I CODES: 1A, 15 **AXIS II CODES:**31, 36, 64, 72

ABSTRACT

Objective: To determine whether personality, social stress and social stability interact to affect SIV disease progression following establishment of viral set point, and to generate pilot data on whether drugs that block the action of stress-response systems can ameliorate the effects of social stress on SIV disease progression.

Results: Personality characteristics are associated with differences in physiologic measures that are important for disease processes. In a series of studies, we demonstrated that the personality characteristic "Sociability", which represents a tendency to affiliate, is associated with greater heart rate responsiveness during social interaction with unfamiliar animals, greater immune responsiveness following relocation stress, and generally higher plasma levels of epinephrine and norepinephrine. DHEAS declines and cortisol rises at the end of disease. The androgen dehydroepiandrosterone-sulfate (DHEAS) is secreted from the adrenal in response to ACTH, just as is cortisol. While cortisol is considered immunosuppressive, DHEAS is purported to increase immunocompetence. Using banked samples, we contrasted the first three monthly time points after SIV inoculation with the last three preceding euthanasia and found a significant decrease in CD4+ numbers and DHEAS, an increase in cortisol, and an increase in the cortisol/DHEAS ratio. These data are pertinent to the pilot study we will conduct following the current study to determine whether DHEA abrogates the effects of a social stressor on viral load.

BIOBEHAVIORAL CHARACTERIZATION FOR MANAGEMENT AND RESEARCH PURPOSES (0136)

NPRC UNIT: BRAIN, MIND, & BEHAVIOR

%NPRC $: 0.360%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
CAPITANIO, JOHN P	PHD	C	PSYCHOLOGY	
[Names]	PHD	C	PSYCHOLOGY	
	PHD	C	PSYCHOLOGY	

AXIS I CODES: 1A, 15 **AXIS II CODES:**36, 65, 71, 72, 74E, 77

ABSTRACT

Objective: to implement an assessment program that will identify animals differing in biobehavioral organization, and to provide this information to colony managers to aid in decision-making in the areas of health, reproduction, and enrichment. A battery of assessments was developed to achieve this goal. Three to four month old animals are observed under a number of standardized conditions: free behavior in the cage (response to separation), a preferential looking task (recognition memory), video playback task (social responsiveness), and a human intruder task (emotionality). In addition, the animals' responses to novel objects are recorded, and a temperament rating is made. Blood samples are taken to assess hypothalamic-pituitary-adrenal (HPA) responsiveness.

Results: In Year 4, 264 animals were assessed: 219 from the [C] field cages, 9 from corncrib cages, and 36 nursery-raised (NR) animals. Analysis in Year 4 has focused on the measurement of HPA function. Using data from the past 3 years involving nearly 800 animals, we identified a pattern of HPA response characteristic of nursery-reared monkeys based on the cohort of animals tested in 2001, and we have replicated this result with the 2002 and 2003 cohorts. Moreover, using cluster analysis, we have identified three patterns of HPA regulation in all of our animals, including an abnormal pattern that is characterized by very high cortisol concentrations and a failure to suppress cortisol in response to dexamethasone. Ongoing studies are aimed at determining whether this pattern persists into young adulthood, and whether it is associated with poor health outcomes. These results indicate that early rearing has profound influences on biobehavioral processes that could be significant for physical and behavioral health.

DIFFERENTIAL FACIAL ENCODING IN MONKEY AMYGDALOID NUCLEI (0306)

NPRC UNIT: BRAIN, MIND, & BEHAVIOR

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
GOTHARD, KATI	PHD	A	PHYSIOLOGY	UNIVERSITY OF ARIZONA, AZ USA

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

ABSTRACT

This application is to support a period of advanced training in multidisciplinary approaches to the study of the neural substrate of social cognition in monkeys. The candidate will acquire new theoretical knowledge in animal behavior, computational methods and practical skills in primate neurophysiology. The combination of behavioral, neurophysiological and computational techniques has great potential for the study of social cognition in monkeys. Additional training is needed by the candidate to achieve this potential since the species studied, the questions addressed, and the analytical methods that will be used are new to her. This training will complement her earlier experience in electrophysiological recordings in freely behaving rats. The candidate will work with a small group of talented co-mentors/consultants who will provide a sound background in primate social behavior, electrophysiology and computational methods. The candidate will also attend advanced classes and national workshops on statistical and computational methods suitable for analyzing neuronal ensemble data obtained with multielectrode arrays. UC Davis and the California Regional Primate Research Center (CRPRC) are uniquely suited for the training and research goals of the candidate. The CRPRC houses social troops of 60-120 rhesus monkeys in large outdoor enclosures where the animals develop in a socially naturalistic environment. The departments of Computer Science, Center for Animal Behavior, Center for Neuroscience and the Medical and Veterinary Schools offer advanced courses in the areas of neuroscience, animal behavior and computational science. The candidate's immediate goal is to use modern neurophysiological techniques to determine the responses of neural ensembles in different nuclei of the monkey amygdala to images of monkey faces and facial expressions. This project will complement and benefit from an ongoing research program at the CRPRC directed by the sponsor, Dr. David Amaral. The specific aims of the research proposed in this application are to determine 1) whether neuronal ensembles recorded from different nuclei of the monkey amygdala differentiate between monkey faces and facial expressions, and 2) whether ensemble responses to facial expressions are modulated by social context. The candidate's long-term career goal is to use the experience afforded by this award to develop an independent research program that combines behavioral, neurophysiological and computational methods to study the role of structures such as the amygdala and orbitofrontal cortex in emotional and social behavior in primates.

RHESUS MACAQUE PSYCHOTROPIC DOSAGE ADMINISTRATION (0250)

NPRC UNIT: BRAIN, MIND, & BEHAVIOR

%NPRC $: 0.071%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
JONES, EDWARD G	MD, PHD	A	CTR FOR NEUROSCIENCE	

AXIS I CODES: 1A, 21 **AXIS II CODES:**72, 82

ABSTRACT

Postmortem studies of human brains from patients with schizophrenia have implicated changes in gene expression in the inhibitory GABA(gamma amino butyric acid) and excitatory glutamate neurotransmitter systems. The importance of these findings is limited because of the possible confounds of treatment. medications. Therefore, it is important to determine the effects of these medications on gene expression in well-controlled experiments in primates. The aim of the experiments, now completed, was to determine the effects of commonly used psychotropic medications for the treatment of affective disorder schizophrenia and schizoaffective disorder on mRNA and protein expression in the brain. Chronic dosing experiments with these compounds were conducted on the monkeys. 4 additional monkeys served as controls The antipsychotics chosen were haloperidol and olanzapine, representing the most commonly used conventional and atypical antipsychotics for the above disorders. The antidepressants chosen were fluoxetine and nortriptyline. Fluoxetine is the most commonly used serotonin-re-uptake inhibitor. The most common mood stabilizer was lithium. All the animals have now been terminated and the brains removed and frozen for microarray studies of gene expression levels.

SOMATOSENSORY CORTEX & THALAMUS (0310)

NPRC UNIT: BRAIN, MIND, & BEHAVIOR

%NPRC $: 1.064%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
KRUBITZER, LEAH A	PHD	A	PSYCHOLOGY	

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

ABSTRACT

Our goal is to examine in human and non-human primates, the contribution of the somatosensory system to complex primate behaviors such as manual dexterity, bilateral coordination of the hands, multimodal integration, and sensorimotor integration required for goal directed reaching. The evolution of these abilities in humans is intertwined with the evolution of our sensory and motor systems. In order to understand how these sophisticated behaviors are generated, we must uncover the details of the organization of our sensory systems, and the neural circuitry that subserves complex functions. Studies of cortical fields in the lateral sulcus (LS; SII, PV, VS, 7b, and RL) indicate that they are involved in tactile discrimination, tactile recognition, attention, and integration of unilateral and bilateral inputs across the hands. Areas in posterior parietal cortex (PP; areas 5, 7a, LIP and VIP) are involved in generating motor coordinates for directed movements, attention, and multimodal integration. Our studies are aimed at uncovering the topographic organization of cortical fields, receptive field size, stimulus preference, and detailed topographic connection patterns of fields in LS and PP in monkeys, and determining if similar fields exist in humans. Our proposal combines several data collection techniques. In non-human primates we will record extracellularly from clusters of neurons in cortical fields in LS and PP in response to quantifiable, reproducible stimuli such as small indentations on the glabrous surface of the hand, displacement of hairs, light strokes along the glabrous surface of the hand in different directions, pressure, muscle manipulation, and digit, wrist and hand movements. In some of these same monkeys, the detailed patterns of intracortical, callosal, and thalamic connections will be determined by placing anatomical tracers into electrophysiologically defined subdivisions, and then mapping target structures using multiunit electrophysiological recording techniques. Recently, it has been established that the fMRI technique can be used effectively in humans to determine the topographic organization of fields, and the number of subdivisions within a region of cortex. In parallel with our electrophysiological and connection studies in monkeys, we will utilize fMRI techniques to explore similar regions of the neocortex in humans. Our stimulus selection and areas of interest will be guided by our results in monkeys. Thus, we will begin with stimulation like that described above, and direct our efforts to areas in the LS and PP cortex. Applying the framework of cortical fields and patterns of connections established in our monkey model to humans, we can expand our stimulus repertoire to include more sophisticated tasks which involve bilateral manipulation, goal directed reaching, and multimodal integration. This study represents one of the first efforts to combine results from human and non-human primate studies, and promises to provide a richer understanding of somatosensory cortex, and its contribution to higher perceptual and cognitive processing.

IRON DEPRIVATION AND BRAIN DEVELOPMENT IN MONKEYS (0228)

NPRC UNIT: BRAIN, MIND, & BEHAVIOR

%NPRC $: 3.912%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LOZOFF, BETSY	MD	A	PEDIATRICS	UNIV OF MICHIGAN AT ANN ARBOR, MI USA
[Name]	PHD	A	PRIMATE CENTER	
	PHD	C	MED:PEDIATRICS	

AXIS I CODES: 1A, 2, 17, 21 **AXIS II CODES:**36, 41, 65, 78

ABSTRACT

Iron deficiency is a worldwide public health problem that impacts the survival and brain development of infants. Human studies have documented these effects, but animal models are needed to understand their pathophysiology and develop preventive and ameliorative strategies. This study asks the important question of how prenatal, in utero, iron deprivation compares to postnatal infant iron deprivation in terms of its impact on brain development. The study is planned in two cohorts; the treatment and evaluation of the first cohort was be completed in July 2003. To date we have established that a 10 ppm iron diet leads to a borderline iron deficiency anemia in pregnant rhesus monkeys by the third trimester. Fetuses and newborns, however, do not demonstrate anemia as has been observed in the offspring of iron deficient human mothers. However prenatal iron deficiency leads to a lag in postnatal weight gain and an apparently smaller head circumference by 4 months of age. Both the prenatally and postnatally deprived groups demonstrated behavioral differences from controls during infant development. During the past year we have established the pregnancies for the second cohort and completed serum assays and MRI scans.

SOMATOSENSORY CORTEX IN THE EXPRESSION OF AFFECTIVE SOCIAL RELATIONSHIPS (0301)

NPRC UNIT: BRAIN, MIND, & BEHAVIOR

%NPRC $: 0.425%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MENDOZA, SALLY P	PHD	C	PSYCHOLOGY	
	PHD	A	PSYCHOLOGY	
	PHD	C	PSYCHOLOGY	
	PHD	G	PSYCHOLOGY	UC DAVIS, CA USA

AXIS I CODES: 1A, 21, 25C **AXIS II CODES:** 36

ABSTRACT

OBJECTIVE: To understand the neurobiology of social behavior by tracing transmission of somatosensory information from the body surface to neuronal regions concerned with processing tactile information essential for social behavior interactions.

The propensity to seek contact and to form strong positive relationships is exemplified in the extreme by the South American titi monkey. In nature and in the laboratory, these monogamous primates spend up to 90% of their day in physical contact with other members of their family group. Animals sit side-by-side with their lateral surface in close contact with another monkey. Contact between titi monkeys also includes active contact, such as grooming or grasping. A unique aspect of social contact in titi monkeys is tail-twining. Very often all members of a family group (3-5 individuals) sit in a row and combine their tails in a single twine.

Using multiunit electrophysiological recording this research examines the role of several somatosensory cortical areas involved in social contact. The research involves two steps: The first is to map, in individual animals, the flow of somatosensory information from the body surface to regions of the neocortex that utilize somatosensory information in regulation of social behavior. This phase of the research relies on electophysiological recording in anesthetized monkeys. To evaluate the extent to which cortical regions are involved in social behavior, focal lesions will be performed and the effects of the lesion on social motivation and social cognition will be evaluated. . These studies are unique in that they take advantage of an overt behavior, directly mediated by the somatosensory system, to examine the role of cortical mechanisms.

RESULTS:

The results of our electrophysiological recordings indicate that somatosensory representation of body parts relevant to social behavior, such as the lateral surface of the body is magnified titi monkeys. Focal lesions of somatosensory cortex were performed in two monkeys. Animals were trained in a reaching task and observed for handedness in spontaneous social and grasping behaviors. Unilateral lesions (on the side of the cortex contralateral to the dominant hand) were made to parietal somatosensory cortex, an area implicated in motivated reaching and hypothesized to be important to social expression as well. Testing after the lesions were performed revealed a transitory shift in hand preference, but little lasting influence on social behavior. We have traced somatosensory pathways to areas of the frontal lobe that are hypothesized to play a direct role in social expression. Future research will include focal lesions of the prefrontal cortex which receives rich inputs from primary and secondary somatosensory cortex to examine the role of this area in regulation of affective social relationships.

This research was made possible by the availability of a research colony of titi monkeys and the extensive veterinary and surgical capabilities of the CNPRC. This is one of the only research facilities in the world that can bring together the scientific expertise on titi monkey biology and behavior with the neuroscience expertise essential to the project.

ANIMAL MODELS OF AUTISM (0312)

NPRC UNIT: BRAIN, MIND, & BEHAVIOR

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
PESSAH, ISAAC N.	PHD	A	UNKNOWN	UNKNOWN, CA USA
	PHD	C	MED:PSYCHIATRY	
	PHD	A	PSYCHIATRY AND BEHAV. SCI	UC DAVIS, CA USA

AXIS I CODES: 1D, 21 **AXIS II CODES:**36, 44, 50A

ABSTRACT

Autism is a neurodevelopmental disorder that appears to have both genetic and environmental components to its etiology. Epidemiological studies have indicated that various viral infections during early stages of pregnancy may lead to autism. Work carried out in a mouse model system has demonstrated that influenza infection during the late first trimester of pregnancy leads to behavioral abnormalities including social and sensorimotor gating deficits, both of which are known to exist in autism. We hypothesize that maternal influenza infection during the late first trimester of pregnancy is a cause of autism symptomatology in the exposed offspring. In order to test this hypothesis, we will expose pregnant rhesus monkeys to influenza infection during the late fist trimester of their pregnancy, and following birth, test the exposed offspring in a number of behavioral paradigms designed to assess motor, social, cognitive, and sensory skill development. Through these tasks, we will be able to detect behavioral abnormalities in the offspring including social and sensorimotor deficits similar to those observed in the mouse mode, as well as other abnormalities present in the autistic syndrome. This study is significant because of its potential for establishing a cause of autism symptomatology that would then lead to studies on its neuropathology and potential remedies. In addition, this study is significant because vaccinations against influenza infection are now readily available, and it is therefore imperative to establish whether influenza vaccination should be recommended during pregnancy as a preventive measure against adverse behavioral outcomes in exposed offspring.

AUDITORY-VISUAL INTERACTIONS IN AUDITORY SPATIAL PERCEPTION (0296)

NPRC UNIT: BRAIN, MIND, & BEHAVIOR

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
RECANZONE, GREGG	PHD	A	CTR FOR NEUROSCIENCE	
Names]	BS	A	CENTER FOR NEUROSCIENCE	UC DAVIS, CA USA
	BS	A	CENTER FOR NEUROSCIENCE	UC DAVIS, CA USA

AXIS I CODES: 1A, 21, 25A, 25B **AXIS II CODES:**45

ABSTRACT

Most real world objects contain several sensory attributes, for example they make sounds, reflect light, have a particular mass, density and texture, and may have a distinct odor. Although each of these sensory attributes are initially processed independently, at some point in the nervous system they are combined to give rise to a unified percept. In the laboratory, one can manipulate the spatial and temporal features of stimuli of different modalities to create illusions. One common such illusion is the ventriloquism effect, wherein a small spatial disparity between visual and auditory stimuli is perceived as a single event occurring at the location of the visual stimulus. This study investigates how auditory and visual stimuli are combined in the central nervous system to give rise to both unified percepts, as well as illusions such as the ventriloquism effect.

OBJECTIVE: To determine the neural correlate of auditory and visual integration in the primate brain. Multi-modal integration is a critical component of complex sensory perceptions, and dysfunction of this integration system can plausibly lead to auditory and/or visual hallucinations, such as those experienced by schizophrenic individuals.

RESULTS: The data collected to date indicate that multi-modal areas of the cerebral cortex respond in a manner that is consistent with the percept, including the illusions, and are not consistent with the actual stimulus parameters. Studies in unimodal areas show the opposite, namely neurons in these areas are responsive to the actual stimulus parameters and are not dependent on the percept. CNPRC has provided the animal subjects and routine veterinary care, as well as surgical technicians and the surgery suite.

DYNAMIC TUNING IN MOTION AND DEPTH PROCESSING (0282)

NPRC UNIT: COLLABORATIVE RES PROGRAM

%NPRC $: 0.123%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BRITTEN, KENNETH H	PHD	A	NEUR/PHYSI&BIO	

AXIS I CODES: 1A, 21, 25B **AXIS II CODES:**36

ABSTRACT

Stereoscopic depth is relevant but not sufficient for ego-centric depth perception. This project aims to understand the relation between retino-centric and head-centric disparity as the latter represents head-centric depth in principle. A neuronal implementation of this transformation through gain-fields is developed.

PRIMATE CIRCADIAN RHYTHMS IN THE MARTIAN ENVIRONMENT (0187)

NPRC UNIT: COLLABORATIVE RES PROGRAM

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
FULLER, CHARLES A	PHD	A	PSYCHOLOGY	
	PHD	A	PSYCHOLOGY	
	PHD	G	NEURO, PHYSIO, BEHAVIOR	

AXIS I CODES: 1A, 21, 28(REGULATORY BIOLOGY)

AXIS II CODES: 85, 92(CIRCADIAN RHYTHMS)

ABSTRACT

The Circadian Timing System (CTS) coordinates the temporal aspects of physiology and behavior in animals. Disruptions in circadian timing have adverse effects on performance and health. Adaptation to altered acceleration environments, such as space flight, results in profound changes in many physiological systems, including the CTS and sleep regulation. Understanding responses to altered gravitational environments is critical to the development of effective countermeasures for astronauts on long duration space flights and planetary expeditions, as well as for our understanding of how gravity affects humans on Earth. Mars not only has less gravity than Earth, but its day length is longer and its ambient light is deficient in the short wavelengths most effective in circadian entrainment.

OBJECTIVE: To determine if organisms can entrain their circadian rhythms to a martian day length under a simulated martian lighting spectrum, and to determine how properties of circadian rhythms change in altered acceleration environments.

RESULTS: Male and female rhesus monkeys were able to entrain to a martian day length of 24.67 hours under both white and reddish light. By varying light intensity we also were able to show entrainment under very dim light conditions, light levels that would likely be lower than those experienced in a Mars habitat. Increased gravity, produced by acceleration, produced transient effects on rhythms that were largely compensated after acclimation. Circadian period was variably affected by gravity. However, sensitivity to light appeared to be diminished in hypergravity, a result previously seen in nocturnal rodents. This suggests that changes may be needed in lighting environments in space and in the reduced gravity of Mars. Studies of entrainment to the martian day were conducted at the CNPRC with support from CNPRC personnel.

NIEHS CENTER FOR HEALTH EFFECTS OF AGROCHEMICALS (0338)

NPRC UNIT: COLLABORATIVE RES PROGRAM

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MATSUMURA, FUMII		A	UNKNOWN	UNKNOWN, CA USA

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

ABSTRACT

The major goal of the NIEHS Center for Environmental Health Sciences at UCD is to maintain a strong program in the toxicology of agrochemicals and related xenobiotics, particularly relating to human health and the mechanistic aspects of toxicology. A team of 20 Center investigators whose interests are specifically aligned with Center goals has been assembled. Collectively these investigators are in charge of almost $12 million per year (direct costs) in research grants. The Center members include new and experienced scientists, many fields of interest, and strong histories of collaboration. To build an infrastructure which facilitates relationships within and between groups, the Center has been reorganized to form seven facility/service cores: (1) Administrative, (2) Analytical Biochemistry, (3) Cell/Tissue Culture, (4) Cellular and Molecular Imaging, (5) Field Studies (6) Functional Genomics and Molecular Biology, and (7) Primate/Animal Models. In addition, to promote focused research efforts, intellectual stimulation and synergistic interactions, five research cores have been formed: (1) Epidemiology, (2) Molecular Neurotoxicology, (3) Reproductive and Developmental Toxicology, (4) Respiratory Toxicology, and our newest core, (5) Toxicogenomics. The composition of these cores changed to provide flexibility to the Center?s research directions. The Pilot Projects Program is used to bring in new investigators and research ideas. An Affiliate Scientist category was developed to recognize interactions with UCD faculty through a less formal mechanism than full membership, and 11 new Affiliate members were appointed. The new COEP has been carefully guided by the Center Director, and under the leadership of the new coordinator, [illegible], the COEP Mini-Grants Program has been an effective program to identify new ideas. From those ideas came a successful long-term program that currently supports four outreach programs for agricultural workers, three K-12 programs, and an alumni/corporate outreach program. In addition, during the current project period, the COEP conducted a national symposium on aging and a town-hall meeting, and sponsored the International Congress on Ecosystem Health in 1999 and the Dioxin 2000 Twentieth International Symposium on Halogenated Environmental Organic Pollutants and POPS. The COEP also serves as an Environmental Health Information Center for the public, answering questions via phone and e-mail, and disseminating information via websites, list servers, newsletters, and annual community events attended by approximately 1,000 people/year. The CEHS program is reviewed annually by the External Advisory Committee consisting of experts in this area of science, the Internal Advisory Committee consisting of eminent scientists with administrative experience at UCD, and the Executive Committee composed of CEHS faculty. The UCD has made a strong commitment of support (approximately 40%/year) by providing salaries and benefits for all Center investigators, providing space, and purchasing equipment for the CEHS.

PIG TO RHESUS MONKEY TRANSPLANTATION: AN ANIMAL MODEL (0339)

NPRC UNIT: COLLABORATIVE RES PROGRAM

%NPRC $: 0.094%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
ZAHORSKY-REEVES, JOANNE	MD	A		LOS ANGELES CHILDREN'S HOSPITAL, CA USA

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

ABSTRACT

No abstract available.

G20 AIDS RESEARCH FACILITY IMPROVEMENT GRANT (0258)

NPRC UNIT: MODERNIZE & IMPROVE - AID

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
HYDE, DALLAS M	PHD	C B	VM ANAT/PHYSI&CELL	

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

ABSTRACT

This is a G 20 grant for multiple renovations in, and adjacent to, the CNPRC [redacted], which is heavily used in AIDS related research. These renovations include necropsy improvements to replace two existing necropsy tables with new longer, adjustable tables that will accommodate staff of different heights and replacement of a necropsy room fume hood with a combination fume hood/biosafety cabinet; installation of an environmental monitoring system in the animal housing area of the [redacted] to monitor temperature, humidity, light status and air changes per hour; and purchase of two modular units to provide additional space for - 80* C freezers. The necropsy improvement and environmental monitoring projects have been submitted to the NIH architect for review and approval. The NIH architect returned questions for clarification. UC Davis Operations & Maintenance planners have replied to the questions and the Primate Center is awaiting approval to proceed.

The purchase of the modular buildings and associated site improvements for freezer storage has been awaiting completion of environmental impact analysis and review. That process is now complete and site utilities and building design has begun.

animal locations

RHESUS MACAQUE AS A MODEL FOR HUMAN INFECTIONS CAUSED BY YERSINIA SPECIES (0248)

NPRC UNIT: PILOT STUDY

%NPRC $: 0.068%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
YOUNG, GLENN M		A	FOOD SCI & TECH	UC DAVIS, CA USA
Names	PHD	C	CTR FOR COMPARATIVE MED	UC DAVIS, CA USA
		A		

AXIS I CODES: 7A, 16C **AXIS II CODES:**64, 66, 91

ABSTRACT

Objective: To determine if Rhesus macaques are susceptible to infection by Yersinia enterocolitica.

Background: Yersinia enterocoltica is a bacterium that causes a severe gastrointestinal syndrome in humans and causes of systemic disease in infants with a high rate of mortality. This bacterium is also closely related to Yersinia pestis, which is the causative agent for the plague. Therefore, these studies have the added benefit of promoting the skills of people at the primate center in a direction that will eventually allow us to perform studies on the plague bacterium as well.

Results: Before animals were infected, we wanted to determine whether the animals had previously been exposed to any pathogenic Yersinia. Accordingly, one corral of animals was tested for sero-conversion (the presence of reactive IgG antibody) to a set of antigens common to all pathogenic Yersinia called Yops. It was expected that none, or only a few animals, would display sero-conversion toward Yops. Interestingly and unexpectedly, the results showed that 80% of animals older than 18 months displayed sero-conversion suggesting that most animals are exposed to one of the species of pathogenic Yersinia. From our results we can not conclude whether the animals were exposed to one of the gastrointestinal pathogens (Y. enterocolitica or Y. pseudotuberculosis) or possibly to the plague bacterium (Y. pestis). All three species can be carried by wild animals including rodents that would pass through the outdoor living quarters at the CNPRC. Subsequently, the first challenge experiments were completed using 3 animals less than 18 months old. All of the animals displayed symptoms of gastrointestinal disease. These results set up the possibility to perform a preliminary test of a candidate live attenuated vaccine strain of Y. enterocolitica. These experiments are in progress and the results will be available within the next few months.

REGULATION OF TROPHOBLAST MIGRATION, INTEGRIN EXPRESSION, AND SHEAR STRESS (0279)

NPRC UNIT: REPROD & GENETIC SCIENCES

%NPRC $: 0.042%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
DOUGLAS, GORDON C	PHD	A	MED:CELL BIO AND HUMAN ANAT	UC DAVIS, CA USA

AXIS I CODES: 1D, 23 **AXIS II CODES:**71, 93

ABSTRACT

This project investigates the effect of cigarette smoke constituents on certain aspects of early placental development that are vital to successful pregnancy. Placental trophoblast cells will be cultured in the presence of selected constituents found in cigarette smoke. We will measure the rate of cell migration as well as the levels of adhesion molecule expression. From these studies we hope to be able to define the mechanism of action of cigarette smoke constituents on these important placental trophoblast functions. They will also provide new information about normal placental development.

MACAQUE IN VITRO IMPLANTATION MODEL (0309)

NPRC UNIT: REPROD & GENETIC SCIENCES

%NPRC $: 0.213%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
DOUGLAS, GORDON C	PHD	A	MED:CELL BIO AND HUMAN ANAT	UC DAVIS, CA USA

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

ABSTRACT

Implantation involves trophoblast attachment to, and penetration of, the endometrial epithelium. The factors that regulate these processes in human and non-human primates are poorly understood, largely due to the lack of suitable in vitro systems. We have recently found that macaque blastocysts attach to monolayers of MDCK epithelial cells. This in vitro implantation model offers advantages not frequently met in other systems. Attachment was followed by development of the inner cell mass (ICM) and penetration of the epithelial monolayer by trophoblasts. Other preliminary data show that expression of integrins by isolated macaque trophoblasts is regulated by contact with immobilized chemokines. Also, trophoblasts migrate in a haptotactic manner towards the chemokine, RANTES (Regulated on Activation, Normal T-cell Expressed and Secreted). RANTES and other chemokines are present in both human and macaque endometrium. Our long-term objective is to understand the mechanisms that regulate trophoblast penetration of the endometrial epithelium. We suggest that a novel in vitro implantation model that utilizes macaque blastocysts and polarized MDCK cells would allow many important questions relating to the regulation of implantation to be addressed. In this R03 application we propose experiments that will validate this model. Validation criteria will include acquisition of a migratory trophoblast phenotype and development of an inner cell mass and extraembryonic mesoderm. In addition, we will use this system to test the hypothesis that interaction of blastocysts with immobilized chemokines on the epithelial surface results in trophoblast activation and the acquisition of a polarized migratory phenotype. Specific Aim 1 uses immunocytochemistry, in situ hybridization, and quantitative image analysis to characterize the expression of migratory phenotypic markers (integrins, chemokine receptors) during trophoblast penetration of polarized MDCK cells. Specific Aim 2 characterizes blastocyst development (as defined by the appearance of an amniotic cavity, appearance of an epiblastic plate, and differentiation of extraembryonic mesoderm) during co-culture with MDCK cells. Specific Aim 3 will use neutralizing antibodies and immobilized recombinant chemokines to characterize the role of chemokines in regulating expression of trophoblast migratory phenotypic markers and blastocyst development.

FETAL ANDROGEN EXCESS AND POLYCYSTIC OVARIAN SYNDROME (0230)

NPRC UNIT: REPROD & GENETIC SCIENCES

%NPRC $: 0.236%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
DUNAIF, ANDREA	MD	A	ENDOCR/METAB/MOL MED	NORTHWESTERN UNIVERSITY MEDICAL SCHOOL, WA USA
[illegible]	PHD	A	OBST AND GYNECOLOGY	WISCONSIN NATIONAL PRIM RESEARCH CENTER, WI USA
[illegible]	PHD	C	MED:PEDIATRICS	

AXIS I CODES: 1A, 15, 23 **AXIS II CODES:**49, 58, 60, 63H, 71, 74E, 93

ABSTRACT

The Northwestern University Specialized Center of Research on Sex and Gender Factors Affecting Women's Health is a multidisciplinary NIH-funded program and includes investigators from two National Primate Research Centers (California and Wisconsin), Pennsylvania State University, the University of Chicago, and the Mayo Clinic. Overall, projects are focused on the etiology of polycystic ovary syndrome, and include objectives to determine the gene region associated with this syndrome in humans, and how such genes result in reproductive abnormalities and an increased risk for diabetes. This Specialized Center of Research encompasses human and nonhuman primate studies, and uses the monkey model to explore the syndrome proposed to be associated with prenatal androgen excess. The nonhuman primate research team is evaluating whether fetal androgen excess induces ovarian, luteinizing hormone (LH), and beta-cell defects in female rhesus monkeys with an induced male phenotype. Studies, to date, indicate that elevated circulating testosterone levels in fetuses are comparable to those found in males, and that prenatal androgenized fetuses and infants exhibit basal and GnRH-stimulated LH hypersecretion. In terms of metabolic consequences, the prenatal androgenized fetuses have also been shown to exhibit hyperinsulinemia. Thus, results from initial studies support the hypothesis of fetal androgen excess reprogramming LH hypersecretion and insulin release, and provide the first direct evidence of fetal precursors to adult polycystic ovary syndrome traits.

SCREEN FOR FRAGILE X MUTATIONS IN PRIMATES (0249)

NPRC UNIT: REPROD & GENETIC SCIENCES

%NPRC $: 0.766%

INVESTIGATOR	DEGREES STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
HAGERMAN, PAUL J	A	MED:BIO CHEM	UC DAVIS, CA USA
	G	MED:BIO CHEM	UC DAVIS, CA USA

AXIS I CODES: 1A **AXIS II CODES:**58

ABSTRACT

Fragile X syndrome, the most common inherited form of mental retardation, arises in individuals with more than 200 CGG repeats in the 5 untranslated region of the fragile X mental retardation 1 (FMR1) gene. In humans, approximately 1 in 260 women, is a carrier of the expanded (55 to 200) CGG repeat. We hypothesize that approximately 1 animal in 300 females will have a premutation expansion.

Although CGG repeat numbers comparable to those found in the normal human population are found in various non-human primates, neither the within-species size variation nor the propensity for expansion of the CGG repeat has been described for any non-human primate species. There is no adequate animal model for the behavioral and cognitive phenotype of Fragile X. There is no animal model that has an expanded repeat or that exhibits expansion of the CGG repeats in succeeding generations, as observed in humans.

M. mullata may be useful as an animal model for the study of fragile X syndrome: the allele distribution has been determined for FMR1 (homologue) CGG repeats of 266 unrelated founder females of M. mullata monkeys. All of these females with progeny (266), resident at the California Regional Primate Research Center, were analyzed for FMR1 (homologue) allele size by PCR amplification and Southern blot analysis. Among 530 X chromosomes, at least 26 distinct repeat lengths were identified, ranging from 16 to 54 (mean is 28) CGG repeats. Three animals carried borderline premutation alleles with 54 CGG repeats, within the region of marginal instability for humans. These are MMU 24660, a female, and two of her offspring: 34220 (male) and 35122 (female). They could become founders of a breeding population that would be of fundamental importance for fragile X mental retardation research. We plan to focus our future studies on the extent of expansion of higher number of CGG repeats in succeeding generations of founder female MMU 24660.

NON-VIRAL DNA AND MRNA GENE DELIVERY TO THE RHESUS CNS FOR NEUROPROTECTION (0237)

NPRC UNIT: REPROD & GENETIC SCIENCES

%NPRC $: 0.463%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
HECKER, JAMES G	MD, PHD	A	DEPT OF ANESTHESIOLOGY	UNIV OF PENNSYLVANIA, PA USA
	PHD	G	PRIMATE CENTER	
	PHD	G	PRIMATE CENTER	
	PHD	C	MED:PEDIATRICS	

C Names]

AXIS I CODES: 1A, 21 **AXIS II CODES:**32, 55, 62, 86, 94

ABSTRACT

The objectives of these studies are to characterize and quantify nonviral gene delivery of nucleic acids complexed with cationic lipids to the central nervous system (CNS) of the monkey, including the extent of expression of candidate neuroprotective genes such as heat shock protein 70 (Hsp70). These experiments will lead to the development of DNA and mRNA as "gene medicines" for transient expression in a variety of clinical applications, such as pre-operatively to minimize stress responses and to protect the brain. In addition to pre-operative prevention of CNS damage, such methods and treatments can be used to deliver mRNA and DNA encoding therapeutic gene sequences using nonviral techniques after stroke, brain trauma, or spinal cord injury. As a first step towards clinical use, it is essential to ensure that the nonviral delivery techniques are well-tolerated. These methods and delivery agents have previously been explored in rodents and safety shown. It is equally important to examine the duration and intensity of expression, and to determine what other tissues, if any, demonstrate expression after delivery to the cerebrospinal fluid in the CNS. A preliminary study has shown high levels of gene expression and no evidence of adverse effects. The intent of the current studies is to further explore efficiency of gene transfer and safety by extending the length of time of the analysis. Our approach in these studies is modeled on FDA and NIH-sponsored short courses on the planning involved in acquiring appropriate pre-clinical data for eventual FDA approval prior to studies in humans, and will also minimize the total number of animals which are necessary for such approval.

FETAL MONKEY MODEL FOR GENE THERAPY FOR SICKLE CELL DISEASE (0128)

NPRC UNIT: REPROD & GENETIC SCIENCES

%NPRC $:

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
KAN, Y.W.	MD	A	HOWARD HUGHES MEDICAL INSTITUT	UC SAN FRANCISCO, CA USA
	MD	A	HEMATOLOGY AND ONCOLOGY	UC SAN FRANCISCO, CA USA
	PHD	G	PRIMATE CENTER	
	MD	A	IMMUNOLOGY AND BMT	CHLDRNS HOSP LOS ANGELES, CA USA
	PHD	G	PRIMATE CENTER	
	PHD	C	MED:PEDIATRICS	

AXIS I CODES: 1A, 7B, 17 **AXIS II CODES:** 55, 62, 63H

ABSTRACT

OBJECTIVE: To explore in vivo transduction methods for obtaining long-term globin-expressing erythroid cells in rhesus monkeys.

RESULTS: Studies in progress in the rhesus monkey model focus on using in utero gene delivery techniques and postnatal analysis. Self-inactivating lentiviral vectors with erythroid promoters and using the enhanced green fluorescent protein as a reporter gene are under investigation. Fetuses were transferred in the early first trimester under ultrasound-guidance, then monitored sonographically during gestation, with fetal and maternal blood samples collected for analysis (flow cytometry, quantitative PCR, hematopoietic progenitor assays, antibody responses, hematology). Newborns were delivered by cesarean-section at term for assessments of transduction and transgene expression (blood, marrow; flow cytometry, quantitative PCR, hematopoietic progenitors). Normal prenatal and postnatal growth and development has been observed for all animals. Hematology and clinical chemistry assessments were also within normal limits at all time points when compared to controls at comparable ages. Lineage specificity of the lentiviral vectors has been shown in erythroid progenitors from blood and marrow collected and analyzed. Studies in the rhesus monkey are crucial for identifying efficient methods for fetal gene transfer for congenital disorders such as sickle cell disease, and to determine whether these approaches are safe for use in humans.

USE OF GENE THERAPY TO INDUCE TRANSPLANT TOLERANCE (0231)

NPRC UNIT: REPROD & GENETIC SCIENCES

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
KEARNS-JONKER, MARY	PHD	A	CARDIOTHORACIC SURGERY	CHILDREN'S HOSPITAL LOS ANGELES, CA USA
	PHD	G	PRIMATE CENTER	
	PHD	C	MED:PEDIATRICS	

AXIS I CODES: 1A, 7B, 9, 17 **AXIS II CODES:**55, 62, 64, 88

ABSTRACT

OBJECTIVE: Xenograft transplantation for patients with end-stage diseases represents a potential solution to the shortage of human organ donors. Humans reject grafts from porcine donors due to pre-existing natural xenoantibodies directed at the gal alpha1,3gal carbohydrate which is synthesized by alpha1,3-galactosyltransferase. This enzyme is not expressed in humans, apes, or old world monkeys. These species, therefore, produce xenoantibodies directed at the gal carbohydrate which is expressed on pig cells. In gal-/- knockout mice, we recently reported that permanent tolerance to gal+ hearts can be induced by the use of lentiviral vectors to achieve chimerism. The objective of the current studies in rhesus monkeys is to test whether chimerism for the gal epitope can be generated, a key step to a clinical application of a similar ex vivo gene therapy for use in humans.

RESULTS: Autologous bone marrow was isolated from rhesus monkeys, transduced with lentiviral vectors expressing porcine alpha1,3-galactosyltransferase, and transplanted into monkeys that received brief, low dose irradiation over two days. Chimerism was examined monthly by flow cytometry and immune responses directed at the gal carbohydrate were assessed by ELISA. Gal chimerism was detectable in certain lineages up to 1 year post-transplantation. Anti-gal IgM xenoantibody production was inhibited for five months and cytotoxic xenoantibodies were not produced following primary immunization with porcine hepatocytes. Results indicate that chimerism sufficient to delay the production of cytotoxic anti-gal antibodies after immunization with porcine hepatocytes can be achieved in rhesus monkeys.

LENTIVIRAL VECTOR TRANSFER TO HEMATOPOIETIC STEM CELLS (0235)

NPRC UNIT: REPROD & GENETIC SCIENCES

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
KOHN, DONALD B	MD	A	IMMUNOLOGY AND BMT	CHLDRNS HOSP LOS ANGELES, CA USA
	PHD	G	PRIMATE CENTER	
E-Name 2	PHD	C	MED:PEDIATRICS	

AXIS I CODES: 1A, 7B, 17 **AXIS II CODES:** 31, 55, 62, 64, 88

ABSTRACT

Many synthetic genes have been developed which can inhibit infection or replication of HIV-1 using a gene transfer/gene therapy approach, including genes encoding antisense RNA, ribozymes, dominant-negative mutant HIV-1 genes, RNA decoys, and intracellular antibodies against HIV-1 proteins or essential cellular co-factors. The limitation in targeting mature lymphocytes for gene therapy, the predominant host cell for HIV-1 infection, is the limited life-span of these mature cell populations. In these studies, we are assessing whether conditioning therapy [ ] is necessary for transplant of autologous transduced hematopoietic stem cells. [ ] produces a specific loss of early stem cells and has been used as a stem cell cytotoxic conditioning agent prior to bone marrow transplantation in humans. These studies focus on transplanting a fixed quantity of autologous hematopoietic stem cells transduced with anti-HIV genes in rhesus monkeys with and without pathogenic SHIV infection Novel lentiviral vectors are currently being tested in vitro which will then be used to transduce rhesus hematopoietic stem cells ex vivo in preparation for autologous transplant. These studies will assess the current "best" conditions for transduction and transfer of rhesus hematopoietic stem cells with anti-HIV genes, and subsequent expression in myeloid and lymphoid cells in vivo. Future studies focus on determining whether antiretroviral chemotherapy protects cells expressing anti-HIV genes from infection, and if these cells become infected after drug treatment is withdrawn.

EFFECT OF ENVIRONMENTAL ESTROGENS AS ENDOCRINE DISRUPTORS IN NON-HUMAN PRIMATES (0190)

NPRC UNIT: REPROD & GENETIC SCIENCES

%NPRC $: 2.435%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LASLEY, BILL L	PHD	C	VM:POPULAT HLTH&REPRODU	
[redacted]	PHD	A	CENTER FOR HEALTH & ENVIR	
[redacted]	MD, PHD	A	MED:OBSTETRICS & GYNEC	

AXIS I CODES: 1A, 2, 15, 23 **AXIS II CODES:** 54, 65, 71, 93

ABSTRACT

Many compounds that are found in the environment have unsuspected biological properties. A large group of these environmental hazards are categorized as endocrine disruptors because they interfere with hormone action. One such compound, nonylphenol, is known to have estrogenic properties in laboratory rodents and is considered to have similar adverse effects in humans. Nonylphenol is widely used as a "wetting agent" for many pesticides that are used in agricultural settings. Thousands of gallons of nonylphenol are being added to the environment every year in combination with pesticides that are known to be environmental hazards. While the pesticides are known toxicants and are being studied and regulated, little attention has been focused on the vehicles, such as nonylphenol. In collaboration with [redacted], we demonstrated a delayed effect on secondary sex development in prepubertal rhesus macaques. We also administered nonylphenol in the follicular phase of the menstrual cycle, then follow up with treatment of a gonadotropin releasing factor (GnRH) in the luteal phase of adult cynomolgus macaques. The resulting data indicated a rise in circulating FSH levels resulting from increased pituitary sensitivity to GnRH. These data reveal a latent effect of nonylphenol on the functioning of the hypothalamo-pituitary-ovarian axis in adult female primates.

EFFECT OF ALA-MAGAININ II ON IMPLANTATION IN THE RHESUS MACAQUE (0191)

NPRC UNIT: REPROD & GENETIC SCIENCES

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LASLEY, BILL L	PHD	C	VM:POPULAT HLTH&REPRODU	
[illegible]	PHD	A	CENTER FOR HEALTH & ENVIR	
[illegible]	MD, PHD	A	MED:OBSTETRICS & GYNEC	

AXIS I CODES: 1A, 2, 15, 23 **AXIS II CODES:**54, 65, 71, 93

ABSTRACT

The objective of this study is to characterize the endocrine changes associated with intravaginal administration of ala-magainin II, with respect to delay of implantation and alterations in chorionic gonadotropin (CG) by measuring the Bioactive/Immunoactive (B/I) ratio of serum mCG. We used TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin or dioxin), demonstrate that spontaneous and induced early fetal loss (EFL) are associated with alterations in the bioactivity of trophoblastic gonadotropin (CG). These results would help determine if a toxicant that targets the trophoblast would have adverse effects on the physical nature of CG (B/I ratio of serum mCG). If true, then the B/I ratio of CG may be an early and general indicator of adverse effects of toxicant in early pregnancy which results in EFL. In the past, we have used dioxin as a model toxicant and are currently investigating the subcellular mechanism associated with its toxicity at the level of the trophoblast cell in both in vivo and in vitro studies. At the same time we have found that ala-Magainin II, a synthesized analogue of Magainin 2 induces a delay in implantation at low doses (0.5 mg/animal) and prevents pregnancy altogether at higher doses (1.0 mg/animal). Magainin 2 is one of two closely related cationic peptides, isolated from the skin of African clawed frog Xenopus laevis that has anti-tumor effects. Therefore, we hypothesize that ala-magainin II will also target the trophoblast cell and cause alterations in CG that are similar to that observed in spontaneous losses as well as in TCDD-induced EFL. The result of the study was negative indicating that trophoblast targets of toxicity do not necessarily alter the CG B/I ratio. The significance of this is the demonstration that changes in the B/I ratio of CG more likely indicate adverse effects on the developing early embryo and not the placenta. We have subsequently used bromodichloromethane, another trophoblast toxicant, to substantiate this claim.

ASSESSING THE ROLE OF ESTRADIOL ON SERUM LIPIDS IN NON-HUMAN PRIMATES (0192)

NPRC UNIT: REPROD & GENETIC SCIENCES

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LASLEY, BILL L	PHD	C	VM:POPULAT HLTH&REPRODU	
[illegible]	PHD	A	CENTER FOR HEALTH & ENVIR	
[illegible]	MD, PHD	A	MED:OBSTETRICS & GYNEC	

AXIS I CODES: 1A, 2, 15, 23 **AXIS II CODES:**54, 65, 71, 93

ABSTRACT

Although the cause of the majority of reproductive failure in humans is unknown, it is currently believed that a substantial proportion of these may be environmentally induced. Previous studies in our laboratory have shown that toxicants like TCDD induce changes in specific lipids. Since, the potential interaction of TCDD and estrogen is well known we believe that TCDD acts by antagonizing estrogen-induced rise in maternal lipids during embryonic development. Therefore we hypothesized that estradiol induces specific types of lipids that are key to normal development and these "essential lipids" are blocked by TCDD-like toxicants. Furthermore, since TCDD blocks the accelerated rise in critical circulating neurogenic fatty acids in chickens, we speculated that it may have the same effect in mammals. In order to characterize the changes in lipids associated with increasing endogenous estradiol, we administered TCDD at 4 ug/Kg BW during the early peri-implantation phase of the cynomologus monkey. Embryos were collected at GD 28 and evaluated for neural development changes. The results from this study demonstrated both a reduction in critical free fatty acids and defects in the neural tube of the treated embryos. These data will enable us to design future studies to understand the mechanism by which toxicants like TCDD act in altering lipid metabolism that may have neuro-developmental consequences.

EFFECT OF PHYSICAL STRESS ON THE RHESUS MACAQUE (0245)

NPRC UNIT: REPROD & GENETIC SCIENCES

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LASLEY, BILL L	PHD	C	VM:POPULAT HLTH&REPRODU	
	MD, PHD	A	MED:OBSTETRICS & GYNEC	
		A	RES.ENDO:CTR FOR HLTH & ENV	UC DAVIS, CA USA

AXIS I CODES: 1A, 2, 15, 23 **AXIS II CODES:**54, 65, 71, 93

ABSTRACT

The effect of physical stress has been long recognized to have adverse effects on ovarian function in women and nonhuman primate animal models. Recently, we demonstrated that acute physical stress had a latent effect on the hormonal dynamics of the subsequent ovarian cycle and was associated with stress fractures in young women and increased bone resorbtion in mature women. We also produced evidence to indicate that the adverse effects of physical stress can have different effects at different time of the menstrual cycle. A study was designed to determine if the luteal follicular transition was a sensitive period for physical stressors and to determine if stress-induced perturbations on ovarian function resulted in increased bone resorption in the subsequent menstrual cycle. Mature rhesus macaques are being subjected to capture and restraint for one, two or three consecutive days during the luteal-follicular transition. Daily urine samples were collected to monitor ovarian function and bone resorption. All samples have been collected and hormonal analyses is currently underway.

URINARY ESTROGEN COMPONENTS TO ACCURATELY ASSESS DECLINING OVARIAN FUNCTION (0292)

NPRC UNIT: REPROD & GENETIC SCIENCES

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LASLEY, BILL L	PHD	C	VM:POPULAT HLTH&REPRODU	
[illegible]		A	RES: ENDO: CTR	UC DAVIS, CA USA

AXIS I CODES: 1A, 2, 15, 23 **AXIS II CODES:** 54, 65, 71, 93

ABSTRACT

While the direct measurement of estrone conjugates (E1C) provide an accurate assessment of the dynamics of ovarian estrogen production in normally cycling primates, this measurement has not been useful in monitoring declining estrogen production in older humans or non-human primates. In the present study we separated and quantified all of the estrogenic metabolites before and following ovariectomy. As expected E1C levels fell only 60% following removal of the ovarian source of estrogen. Similarly total estrone fell seventy percent following ovariectomy. In contrast total estradiol fell 90% and provided the most accurate measurement of decreased ovarian estrogen production.

EFFECT OF BROMODICHLOROMETHANE ON PLACENTAL DEVELOPMENT (0293)

NPRC UNIT: REPROD & GENETIC SCIENCES

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LASLEY, BILL L	PHD	C	VM:POPULAT HLTH&REPRODU	
[illegible]	PHD	A	CENTER FOR HEALTH AND ENVIRON.	UC DAVIS, CA USA
[illegible]	MD, PHD	A	MED:OBSTETRICS & GYNEC	

AXIS I CODES: 1A, 2, 15, 23 **AXIS II CODES:**54, 65, 71, 93

ABSTRACT

Several epidemiology reports have suggested that by-products of drinking water purification results in late term abortion in human populations. While studies in rats supported the possibility of trihalmethanes being abortifacients, the rodent model does not provide an adequate model for this kind of study. We used human trophoblast cells to demonstrate proof of concept and demonstrated that bromodichloromethane (BDCM) targeted the human placenta to suppress the secretion of chorionic gonadotropin and block transformation of the cytotrophoblast to the syncytiotrophoblast. In subsequent studies we exposed early pregnancy cynomologus macaques to BDCM by gastric lavage. These studies are designed to provide pharmacokinetic data for BDCM in the nonhuman primate model and determine if exposures similar to that experience by humans would have an adverse effect on placental development in vivo.

A NONHUMAN MODEL OF OBSTRUCTIVE RENAL DYSPLASIA (0023)

NPRC UNIT: REPROD & GENETIC SCIENCES

%NPRC $: 0.205%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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	PHD	C	MED:PEDIATRICS	
-1	MD	A	OBS AND GYN	UC DAVIS, CA USA

AXIS I CODES: 1A, 27 **AXIS II CODES:**44, 60, 63H, 71

ABSTRACT

OBJECTIVE: To study the prenatal pathogenesis of obstructive renal disease in a nonhuman primate model that parallels the disease observed in humans.

RESULTS: This nonhuman primate model shows all the classic features of human fetal renal dysplasia. An important feature of this model is the disruption of normal glomerular development and architecture, which is associated with significant podocyte apoptosis and is evident as early as the pre-vascularized S-shaped nephron. These results demonstrate the importance of this model for exploring the pathophysiology of congenital obstructive uropathy, highlight the potential role of podocyte injury in determining long-term renal function associated with this condition, and clearly parallel human disease. Although the pathogenesis of renal dysplasia resulting from urinary tract obstruction is not well-defined, it is clear that the earlier the obstruction occurs during in utero nephrogenesis, the more severe the histopathological changes. Efforts to intervene in the human fetus have been hampered by an inaccuracy in diagnosis and by an inability to validate in utero features that predict poor outcome. Thus, this model is currently being used to explore these issues, and future studies will assess novel cell and gene-based therapies for potential human application.

FUNDAMENTAL CRYOBIOLOGY OF MACAQUE SPERMATOZOA (0225)

NPRC UNIT: REPROD & GENETIC SCIENCES

%NPRC $: 1.240%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
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		A	MECH ENGINEERING	UNIV OF MINNESOTA, MN USA
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	MD, PHD	A	MED:OBSTETRICS & GYNEC	
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AXIS I CODES: 1D, 23 **AXIS II CODES:** 73, 77, 92(REPRODUCTIVE SYSTEM)

ABSTRACT

Non-human primates, especially genetically unique macaques, are highly relevant models of human disease. Their preservation as important biomedical resources is critical. The main objective of this project is to develop a clear understanding of the fundamental cryobiology of macaque sperm and to develop a rational and reliable method for cryopreservation of macaque sperm. New information is likely to be applicable to development of cryopreservation methods for sperm of all non-human primates and it can be transferred and used in other centers. Macaque sperm displays 3 major phase transitions (Tm1=10°C, Tm2=30°C, Tm3=45°C) indicating that the sperm plasma membrane has critical temperatures at which the liquid crystalline and gel phases of the membrane lipids co-exist in temperature-dependent proportions. Initial purification and analysis of membrane rafts in comparison to lipid content of whole sperm plasma membrane indicate that although sperm membranes are rich in cholesterol in contrast to somatic cells, rafts isolated using sucrose density centrifugation demonstrate relatively greater enrichment of cholesterol and sphingomyelin. Experiments have also determined that macaque sperm behave as linear osmometers with a mean cell volume of 36.8 ± 0.5 μm3 at 22°C with 77.2 % being osmotically inactive. Sperm motility was more sensitive than membrane integrity to deviations from isotonicity. In addition, rhesus sperm motility and membrane integrity were more sensitive to hyperosmolal than hyposmolal conditions. Although most spermatozoa were able to recover initial volume after osmotic stress, they were not able to recover initial motility. The results of the funded studies contribute to the literature on sperm preservation and membrane biophysics of gametes.

CENTER FOR FETAL MONKEY GENE TRANSFER FOR HEART, LUNG, AND BLOOD DISEASES (0206)

NPRC UNIT: REPROD & GENETIC SCIENCES

%NPRC $: 1.612%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
TARANTAL, ALICE F	PHD	C	MED:PEDIATRICS	
	PHD	G	PRIMATE CENTER	
	MD	A	IMMUNOLOGY AND BMT	CHLDRNS HOSP LOS ANGELES, CA USA
	PHD	G	PRIMATE CENTER	
	PHD	C	VM ANAT/PHYSI&CELL B	

AXIS I CODES: 1A, 4, 7B, 13, 17, 24 **AXIS II CODES:**55, 60, 62, 63E, 63H, 71, 88

ABSTRACT

OBJECTIVE: To determine the optimal gestational age(s) to perform gene transfer, the efficiency of direct intraorgan routes of administration versus systemic approaches, the potential effects of gene transfer on prenatal and postnatal development, the potential for germ line transmission, and the possible risks for the mother.

RESULTS: The effect of the timing of fetal gene delivery and the route of administration on gene transfer efficiency was explored by comparing systemic delivery to direct organ-targeted approaches. Intraperitoneal and intrahepatic administration was shown to result in a 400-fold higher level of the transgene in the omentum, peritoneum, and diaphragm when compared to abdominal organs, whereas intraportal injection resulted in a 200-fold reduction in the level of gene marking. Intrapulmonary and intramyocardial transgene deliveries were also assessed in order to determine whether gene transfer could be limited to the developing lung and heart, respectively. Efficient gene transfer occurred in the lung parenchyma and myocardium, few vector copies were found in non-thoracic tissues, and there was no evidence of gene transfer to the germ cells. Normal prenatal and postnatal lung and heart function was also found. These studies are important because they show that organ-targeted prenatal gene transfer and subsequent transgene expression both prenatally and postnatally does not alter organ structure or function in a nonhuman primate model. Current findings suggest that direct in utero organ-targeting will most likely be the best means for obtaining maximum therapeutic effect for the treatment of congenital or acquired diseases of the heart, lung, and blood.

ANNUAL GENE THERAPY SYMPOSIUM FOR HEART, LUNG, AND BLOOD DISEASES (0232)

NPRC UNIT: REPROD & GENETIC SCIENCES

%NPRC $: 0.057%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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	MD, PHD	A	DEPT OF ANESTHESIOLOGY	UNIV OF PENNSYLVANIA, PA USA
Names	MD	A	IMMUNOLOGY AND BMT	CHLDRNS HOSP LOS ANGELES, CA USA
	PHD	C	VM ANAT/PHYSI&CELL B	
J	PHD	A	MOLECULAR BIO	CITY OF HOPE NATIONAL MED CTR, CA USA

AXIS I CODES: 13, 17, 24, 28(SYMPOSIUM) **AXIS II CODES:**51, 55, 62, 71, 92(ANNUAL SYMPOSIUM)

ABSTRACT

The intent of these annual interdisciplinary scientific symposia is to provide a novel and informal scientific setting for the dissemination and exchange of ideas and research findings by bringing together students, fellows, and junior/senior investigators who do not typically interact at other meetings. Presentations focus on unpublished works-in-progress, workshops on cutting edge technologies, and speakers who address key thematic issues. Each year, a competitive process supports the attendance and participation of approximately 18 students and postdoctoral fellows. Each student or fellow has the opportunity to present his or her work in a brief oral presentation followed by a poster session. The focus topic for the 2nd Annual Gene Therapy Symposium was the 'Fetus and Infant'. The importance of gene therapy to correct or treat congenital or acquired diseases in fetuses and infants is based on the fact that this developmental period could provide the optimal time for gene transfer because it may be possible to prevent clinical disease with early treatment. In addition, the growth that occurs in fetuses and infants could result in an amplification of genetically-modified cells. The functional immaturity of the fetal immune system may also eliminate a barrier that has significantly hampered the development of effective gene therapy strategies in adults. By performing gene transfer in early gestation fetuses, the generation of potent cellular and humoral immune responses may be avoided, so that prolonged transgene expression may be obtained. The fetus and infant also have other unique features such as a significantly higher percentage of stem cells when compared to adults. For example, because of the capacity of hematopoietic stem cells for self-renewal, proliferation, and differentiation into all hematopoietic lineages, transduction of even a small population of primitive cells could lead to significant percentages of erythroid and myeloid cells expressing the therapeutic gene at birth.

RHESUS MONKEY MODEL FOR FETAL:MATERNAL MICROCHIMERISM (0313)

NPRC UNIT: REPROD & GENETIC SCIENCES

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
TARANTAL, ALICE F	PHD	C	MED:PEDIATRICS	
Ename_2	PHD	G	PRIMATE CENTER	

AXIS I CODES: 1A, 1D, 17, 23 **AXIS II CODES:**71, 93

ABSTRACT

OBJECTIVE: To demonstrate that fetal DNA can be detected in the maternal circulation of rhesus monkeys, with gestational changes and postnatal clearance characteristics that parallel those found in humans.

RESULTS: A real-time PCR TaqMan assay for the rhesus Y chromosome and esilon-globin genes was used to assess fetal DNA in maternal serum throughout all stages of gestation. Data analysis showed a consistent increase with each subsequent trimester in the concentration of fetal sequences. Overall, results indicated that fetal DNA concentrations increased with advancing gestation, similar to findings in humans. In further studies it was shown that using these real-time PCR assays, fetal CD34+ cells were found to circulate and persist long-term in the maternal compartment. This model will be crucial for addressing a number of unanswered questions such as the origin of these cells and the role of fetal cells and DNA in maternal health and disease. Finally, the sexing of rhesus monkey embryos prior to sexual differentiation was investigated using this technique. Specimens were obtained from gravid monkeys in early gestation, and fetal gender and the quantity of circulating fetal DNA determined by real-time PCR analysis of rhesus Y-chromosomal DNA sequences. Predicting the sex of the embryo in the early first trimester was found to be in 100% concordance with fetal sex determination by ultrasound once sexual differentiation had been achieved. Thus, this assay provides a noninvasive method for routine gender screening.

RHESUS MESENCHYMAL STEM CELLS FOR FETAL GENE DELIVERY (0314)

NPRC UNIT: REPROD & GENETIC SCIENCES

%NPRC $: 0.927%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
TARANTAL, ALICE F	PHD	C	MED:PEDIATRICS	
	PHD	A	BIOCHEM AND MOL BIO	UNIVERISITY OF SOUTHERN CALIFORNIA, CA USA
	MD	A	IMMUNOLOGY AND BMT	CHLDRNS HOSP LOS ANGELES, CA USA
	PHD	G	PRIMATE CENTER	

AXIS I CODES: 1D, 7B, 17 **AXIS II CODES:** 55, 62, 63H, 71, 92(STEM CELLS)

ABSTRACT

OBJECTIVE: To explore the transduction kinetics of HIV-1-derived lentiviral vectors containing the CMV, EF1lpha, or PGK promoters expressing the enhanced green fluorescent protein (EGFP) in fetal rhesus monkey bone marrow-derived mesenchymal stem cells (rhMSC).

RESULTS: Studies focused on the effects of transduction with a range of titers on growth, cell cycle, and differentiation. Flow cytometric analysis indicated an approximate 8- to 10-fold greater quantity of EGFP-expressing rhMSC when cells were transduced with the CMV or EF1lpha promoter compared to PGK, although quantitative PCR revealed no differences at the DNA level. The CMV promoter initially expressed 10- to 100-fold higher levels of EGFP when compared to EF1lpha or PGK, respectively, at increasing titer, although a significant decline in transgene expression was observed post-transduction and with advancing passage, whereas a significant increase in the level of expression was observed over time with the EF1lpha promoter. At high titers, a transient arrest at the S phase of the cell cycle was observed for both vector constructs. Transduced rhMSC differentiated towards an osteogenic lineage was comparable to untransduced rhMSC, and showed equivalent levels of alkaline phosphatase activity. These findings suggest that the self-inactivating HIV-1-derived lentiviral vectors used in these studies can efficiently transduce rhMSC in vitro without inhibiting differentiation potential, although the cell cycle was transiently altered at high titers.

PROTOCOLS FOR FREEZING AND MATURING MONKEY OOCYTES (0132)

NPRC UNIT: REPROD & GENETIC SCIENCES

%NPRC $: 1.582%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
VANDEVOORT, CATHERINE A	PHD	C	MED:OBSTETRICS/GYNECOLOGY	
Names	PHD	A		MED COLLEGE , GA USA
	PHD	A		U NEW ORLEANS, LA USA
	PHD	C	MED:PEDIATRICS	

AXIS I CODES: 1A, 23 **AXIS II CODES:**71, 77

ABSTRACT

This project is developing protocols for freezing and in vitro maturation of monkey oocytes. These methods will have direct relevance to human oocytes as well as allow preservation of genetically valuable and/or endangered non-human primates.

The approach to protocol development begins with testing conditions that have been successful in other species with alterations based on differences in biology between the species. We have found that mature, MII oocytes are extremely sensitive to cooling and non-reversible changes occur in the spindle. However, immature oocytes can be exposed to cooling (0 degrees C) without these effects and can be subsequently matured in vitro at a similar rate to fresh immature oocytes. Our preliminary results show that vitrification (ultrarapid freezing) as a method to potentially avoid spindle damage in mature oocytes does not seem to support survival of the cumulus cells surrounding the oocytes. These cumulus cells are required for oocyte maturation, therefore, we are exploring methods for cryoprotectant addition and slow cooling that may improve survival. In parallel studies, we are making progress on media for in vitro maturation (IVM) of oocytes. In past experiments we have improved the blastocyst development rate of about 60% for IVM oocytes (collected after 7 days FSH, no hCG), to 10%. New methods for live cell imaging (Delta vision microscope) have allowed tracking of the changes in cumulus-oocyte interactions during the in vitro maturation process. Our next phase of experiments will evaluate the addition of EGF, IGF2 and aldosterone to the maturation medium.

ANTIPROGESTINS IN CYNOMOLGUS ENDOMETRIOSIS (0291)

NPRC UNIT: REPROD & GENETIC SCIENCES

%NPRC $: 0.646%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
WIEHLE, RONALD	PHD	A		ZONAGEN, TX USA
E. Name	PHD	C	VM:POPULAT HLTH&REPRODU	

AXIS I CODES: 1A, 2, 15, 23 **AXIS II CODES:** 50B, 62, 93

ABSTRACT

Endometriosis affects millions of women worldwide. Most of the associations drawn between the various markers of endometriosis and the symptoms of disease in women (lesions, pain and infertility) have been taken from retrospective studies. The objective of this study is to use the macaque model to prospectively test a new class of antiprogestins, selective progesterone receptor modulators (SPRMs). The effectiveness of this new SPRM (CDB-4124) will be compared to two hormone modulators (gonadotropin releasing hormone agonist [Lupron Depot] and RU 486) in the treatment of surgically induced endometriosis in female cynomolgus macaques. Surgical, histological and endocrine techniques will be used to evaluate the safety and efficacy of CDB-4124 as compared to Lupron Depot and RU 486. Bone markers, bone density and liver function will be monitored to ensure the safety of the test agent. Currently, the in-life phase of the study has been completed and data analysis is in progress. It is expected that CDB-4124 will be an effective treatment for endometriosis without many of the side effects found with current conventional treatments. The results of this study will impact the design and outcome parameters of clinical trials as well as future drug treatments for endometriosis.

ETHANOL EFFECTS ON PRIMATE EMBRYONIC CELLS (0332)

NPRC UNIT: REPROD & GENETIC SCIENCES

%NPRC $: 1.277%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
ZERN, MARK A.		A		UC DAVIS, CA USA
[name]	PHD	C	MED:OBSTETRICS/GYN ECOLOGY	

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

ABSTRACT

No abstract available.

DIETARY FRUCTOSE & 24HR CIRCULATING LEPTIN, ENERGY EXPENDITURE, LIPID LEVELS (0308)

NPRC UNIT: RESEARCH CORES

%NPRC $: 0.173%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
HAVEL, PETER J	DVM, PHD	A	NUTRITION	
	PHD	A		WESTERN HUMAN NUTRITION RESEARCH CENTER, CA USA
	PHD	A	MOLECULAR BIOSCIENCES	

AXIS I CODES: 1A **AXIS II CODES:** 78

ABSTRACT

The prevalence of obesity has increased dramatically during the past two decades. Dietary consumption of fructose has also increased, primarily due to increased consumption of beverages sweetened with sucrose and high fructose corn syrup. Fructose, unlike glucose, does not stimulate insulin secretion and therefore leads to reduced production of leptin, which is regulated by insulin's effects on adipocyte glucose metabolism. Leptin and insulin are important regulators of energy balance via their CNS effects to reduce food intake and increase energy expenditure. In addition, hepatic metabolism of fructose favors lipogenesis, which could lead to hyperlipidemia.

Objective: To show that lower insulin and leptin concentrations on a fructose diet compared with glucose results in increased weight gain, energy intake, lowered energy expenditure, and increased lipid levels. We provided fructose- or glucose-sweetened beverages and ad libitum access to primate "chow" to 18 rhesus monkeys and measured body weight, energy intake and expenditure, and 24-hour leptin, insulin and lipid levels.

Results: Gain of weight was significant in fructose-fed monkeys by the 3rd month of intervention, but was not significant in the glucose group until after the 6th month. The changes in weight were more related to changes in energy expenditure than food intake. Energy expenditure was depressed in the fructose monkeys at 3, 6 and 12 months compared to baseline levels, while it was unaffected in the glucose group until 12 months. There were reductions of meal-induced insulin and leptin responses at 2 months in the fructose group which may have contributed to the decrease in energy expenditure at 3 months and therefore to the early increase in body weight. Both groups exhibited increases in fasting triglyceride levels, however consumption of fructose induced a significant increase of triglycerides during postprandial sampling while glucose did not. Results suggest that dietary fructose could promote obesity and cardiovascular disease.

COMPUTATIONAL IMAGING CORE (0223)

NPRC UNIT: RESEARCH CORES

%NPRC $: 0.179%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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	PHD	C	MED:PSYCHIATRY	
	PHD	A		UNIVERSITY OF TEXAS, MEDICAL BRANCH, TX USA
	PHD	A	ANIMAL SCIENCES	UC DAVIS, CA USA
	DVM	A	PRIMATE CENTER	
	PHD	A	MEDICAL PATHOLOGY	
		G	VM: ANAT/PHYSIO & CELL B	
	MD	A	OB/GYN	
	DVM, PHD	A	NIEHS	MICHIGAN STATE UNIVERSITY, MI USA
	PHD	A	CENTER FOR HEALTH & ENVIR.	
	PHD	A	PATH., MICROBIO AND IMM.	UC DAVIS, CA USA
		A		
		G		
	DVM, MPVM	C	VM:PATHO/MICROBIOL/IMMUNO	
		G		
	MD, PHD	C	MED PEDIATRICS	
	DVM, PHD	C	VM:PATH/MICRO/IMMUNO	
	PHD	A	VM ANAT/PHYSI&CELL B	
	PHD	A	ENVRION. TOXICOLOGY	UC DAVIS, CA USA
		G		
	PHD	A	PATH., MICROBIO., AND CELL BIO	UC DAVIS VET MED , CA USA
		G		
	PHD	C	VM ANAT/PHYSI&CELL B	
	PHD	C	VM ANAT/PHYSI&CELL B	
	PHD	A	NIEHS	UNIV OF ALABAMA, AL USA
	PHD	A	PATH, MICROBIO, AND CELL BIO	UC DAVIS VET MED, CA USA
		A	ENVIR TOX	UCD, CA USA
	PHD	A	ANIMAL SCIENCES	UC DAVIS , CA USA

	PHD	A	VM ANAT/PHYSI&CELL B	
	PHD	C	MED:PEDIATRICS	
	DVM	A		CNPRC PATHOLGY SERVICE, CA USA
	PHD	A	INHALATION EXPOSURE FACILITY	
	PHD	C	MED:OBSTETRICS/GYN ECOLOGY	
	PHD	A	VM ANAT/PHYSI&CELL B	
	PHD	A		CENTER FOR COMPARATIVE MEDICINE, CA USA
		A	PATH MICROB IMM:VM	UCD, CA USA
	PHD	A	INTERNAL MED	UCD, CA USA
	DVM, PHD	A	VM INTERNATL LAB MOL	

AXIS I CODES: 1D, 9 **AXIS II CODES:**63, 63I

ABSTRACT

Our facility provides microscopy, stereology, quantitative fluorescence, digital imaging and consultation services to all campus departments on a recharge basis. Our goal is to assist faculty, staff and students with their research needs for qualitative and quantitative applications. We can assist with the production of publication quality images and offer consultation on experimental approaches for use of our equipment. Instrumentation housed in our facility is available 24 hours per day, 7 days per week for trained users, with consultation, training and support services available from 8-5 Monday through Friday.

Our expanding base of instrumentation offers many possibilities including the creation of 3D images from microscopy specimens; performing quantitative analysis of counts, lengths, areas and/or volumes of cellular and subcellular structures; fluorescence ratio imaging to determine relative concentrations of cellular components such as calcium, sodium or glutathione; imaging and co-localization analysis of fluorescence labeled microscopy specimens; quantitative fluorescence analysis of electrophoretic gels and multiwell plates; and standard brightfield, DIC or epifluorescence microscopy. In addition we can generate publication quality prints, posters and 35 mm film records of virtually any image. To achieve our service goals, the facility houses the following resources:

- Laser scanning confocal microscopy + DIC with 3 channel digital acquisition
- Brightfield, DIC and epifluorescence microscopy with 35 mm film and digital image capture
- Ratio fluorescence microscopy
- A quantitative fluorescence, chemiluminescence, and filmless autoradiography scanner for imaging electrophoretic gels, blots, storage phosphor screens and multiwell plates
- Digital image montaging hardware and software for creating a very high resolution reconstruction of histological specimens
- A 35mm film recorder for creating slides or prints of virtually any image including PhotoShop and PowerPoint presentations
- C.A.S.T. Grid Stereology system for quantifying number, length, area and/or volume of microscopic structures
- PhotoShop, PowerPoint and Illustrator software
- A flatbed scanner for reflective and transparency work
- A variety of color printers to produce publication quality color images
- Poster printing service
- A variety of microtomes for frozen, paraffin, plastic and ultra thin sections
- Equipment includes:

– A Delta Vision Restoration Microscopy System for very high resolution fluorescence imaging of live cells or fixed specimens in 2D, 2D time lapse, 3D or 3D time lapse.
– A fully computer controlled research microscope for fluorescence, DIC and/or brightfield imaging with high

resolution digital capture and a computer controlled stage. The system will be outfitted with software for stereological analysis of fluorescence, DIC or brightfield images.

The investigators listed here have used the CIC services during this reporting period.

ENDOCRINE CORE SERVICES (0221)

NPRC UNIT: RESEARCH CORES

%NPRC $: 0.414%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LASLEY, BILL L	PHD	C	VM:POPULAT HLTH&REPRODU	
	DVM	A	MAGEE WOMEN'S INSTITUTE	UNIV OF PITTSBURGH, PA USA
	DVM	A	VET MED TEACHING HOSPITAL	UC DAVIS, CA USA
		C		
	DVM	A		SAN DIEGO ZOO, CA USA
		A		
	PHD	A	PATH, MICROB, IMM, VIROLOGY	UC DAVIS, CA USA
	PHD	A		STANFORD UNIVERSITY, CA USA
	DVM, PHD	A		SHIN NIPPON BIOMEDICAL LABS USA, LTD., WA USA
	MHS, SCD	A		HARVARD SCHOOL OF PUBLIC HEALTH, MA USA
		C		
	PHD	A	FAMILY AND COMMUNITY MEDICINE	UNIVERSITY OF MISSOURI, COLUMBIA, MI USA
	PHD	C	MED:OBSTETRICS/GYNECOLOGY	
	PHD	A		ZONAGEN, TX USA

AXIS I CODES: 1D, 2, 3, 15 **AXIS II CODES:** 74, 74E

ABSTRACT

The Endocrine Core provides a service of hormone analysis as well as consultation relating to endocrine research for other units, service cores and outside investigators. This core represents the combined services of two semi-independent laboratories; one emphasizing analysis of biological specimens for reproductive hormones and the other for analysis of stress hormones. In addition this core develops and validates steroid, monoamine and protein hormone assays for use in research conducted with non-human primates.

Steroid and protein hormone radioimmunoassays in a variety of species from salivary or blood samples. Routine assays include cortisol, testosterone, estrogen, progesterone, prolactin, ACTH. Other assays could be developed as needed by investigators. We can also offer assistance in experimental design and collection of samples, assessment of stress, and reproductive status.

The investigators listed here have used the Endocrine Core Services during the grant period.

SIMIAN RETROVIRUS LABORATORY (0222)

NPRC UNIT: RESEARCH CORES

%NPRC $: 2.807% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LERCHE, NICHOLAS W	DVM, MPVM	C	VM:PATH/MICROBIOL/IMMUNO	
	DVM	A		HENRY DOORLY ZOO, NE USA
	DVM	A		COVANCE LABS, MD USA
	PHD	C	CTR FOR COMPARATIVE MED	UC DAVIS, CA USA
	DVM	A		WORLDWIDE PRIMATE, FL USA
	DVM	A		UC DAVIS, CA USA
	DVM	A		TRPRC, LA USA
	DVM	A		PFIZER-KALAMAZOO, MI USA
		A	CENTER FOR COMP MED	UC DAVIS, CA USA
		A		MASS INSTITUTE OF TECHNOLOGY, MA USA
	DVM	A		CINCINNATI ZOO, OH USA
	DVM	A	MAGEE WOMEN'S INSTITUTE	UNIV OF PITTSBURGH, PA USA
	PHD	A		UC DAVIS, CA USA
	DVM	A		HOGLE ZOO, UT USA
	PHD	A		SIERRA BIOMEDICAL LABS, NV USA
	PHD	A		NIMH, MD USA
	DVM, PHD	A	SCH OF VET MED:POP HLT REPR	UNIV OF CALIF DAVIS, CA USA
	DVM	A		MERCK, NJ USA
	DVM	A		COVANCE LABS, UK
	DVM	A		BALTIMORE ZOO, MD USA
	PHD	A		USAMRICD, MD USA
	PHD	A		UCSF, CA USA
	DVM	A		MRMC/FDA, OH USA
		A		MANNHEIMER FOUNDATION, FL USA
	DVM	A		UNIVERSITY OF LOUISIANA/NEW IBERIA, LA USA
	DVM	A		SAN FRANCISCO ZOO, CA USA
	DVM, PHD	A		OAKLAHOMA STATE UNIVERSITY, OK USA
	DVM	A		BIOMEDICAL RESEARCH FOUNDATION, LA USA
	DVM	A		OAKLAND ZOO, CA USA
	DVM	A		LOVELACE RESPIRATORY RESEARCH INSTITUTE, NM USA
	PHD	A		PFIZER-GROTON, CT USA
	DVM	A		SNBL, MD USA

PHD	A		UNIV OF PITTSBURGH, PA USA
DVM	A		NIMH, MD USA
PHD	A		UC BERKELEY, CA USA
DVM, PHD	A		STANFORD UNIVERSITY, CA USA
	A		AARON DIAMOND AIDS RESEARCH CENTER, NY USA
	A		COLUMBUS ZOO, OH USA
PHD	A		WASHINGTON NPRC, WA USA
	A		UNIVERSITY OF ILLINOIS, IL USA
DVM	A		HARVARD UNIVERSITY, MA USA
PHD	A		TSUKUBA PRIMATE CENTER, JAPAN
PHD	A		AARON DIAMOND AIDS RESEARCH CENTER, NY USA
DVM	A		OREGON ZOO, OR USA
PHD	G		UC SAN FRANCISCO, CA USA
PHD	A		CENTER FOR DISEASE CONTROL, GA USA
PHD	A		PFIZER-ANN ARBOR, MI USA
PHD	A		BIORELIANCE, MD USA
MD	A		GENESIS BIOSYSTEMS, TX USA
	A		GENENTECH, CA USA
DVM, PHD	A		CSL, AUSTRALIA
PHD	A		UC DAVIS, CA USA
MD	A		BLOOD CENTERS OF THE PACIFIC, CA USA
DVM	A		SCHERING CORPORATION, CA USA
DVM	A		BIOCOR ANIMAL HEALTH, NE USA
DVM	A		MCLEAN HOSPITAL, MA USA
	A		
DVM	A		OREGON NPRC, OR USA
	A		COLUMBIA UNIVERSITY, NY USA
PHD	C	MED:PATHOLOGY	
MD	A		METABOLEX CORP., CA USA
	A		LOS ANGELES ZOO, CA USA
DVM	A		FRESNO ZOO, CA USA
DVM	A		NEW ENGLAND NATIONAL PRIMATE RESEARCH CENTER, MA USA
PHD	A		TULANE NATIONAL PRIMATE RESEARCH CENTER, LA USA
DVM	A		YERKES NPRC, GA USA
PHD	A		TSUKUBA PRIMATE CENTER, JAPAN
PHD	A		ALLERGAN, CA USA
DVM	A		NORTHWESTERN UNIVERSITY, IL USA
MD	A		NINDS, MD USA

	DVM	A		NCRR, MD USA
	DVM	A		WALTER REED ARMY INSTITUTE OF RESEARCH, MD USA
	DVM	A		TOLEDO ZOO, OH USA
	DVM	A		VALLEY BIOSYSTEMS, CA USA
	DVM	A		UNIVERSITY OF KENTUCKY, KY USA
	DVM	A		LABS OF VIRGINIA, YEMASSEE, VA USA
	DVM, MD, PHD	A		CARRIBBEAN PRIMATE CENTER, PUERTO RICO
		A		FOLSOM ZOO, CA USA
		A		UNIV OF TEXAS, TX USA
	MD	A	OMS	NIH, MD USA
		A		3 SPRINGS SCIENTIFIC, UNKNOWN
	PHD	A		UNIVERSITY OF ARIZONA, AZ USA
	DVM, PHD	A		BIOCOR ANIMAL HEALTH, NE USA
		A		SOUTHWEST PRIMATE CENTER, TX USA
	DVM	A		BIOQUAL, MD USA
	DVM	A		PRIMATE PRODUCTS, CA USA
	MS	A		CENTER FOR DISEASE CONTROL, GA USA
	DVM	A		NUCLEAR ENERGY INSTITUTE, DC USA
	PHD	A		UNIVERSITY OF WASHINGTON, WA USA
	PHD	A		GENESIS BIOTECH, TAIWAN
	MS	A		FOCUS TECHNOLOGIES, VA USA
	DVM	A		WHALE BRANCH ANIMAL SERVICES, VA USA
	DVM	A		NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT, MD USA

AXIS I CODES: 1D, 3, 7B **AXIS II CODES:**31, 66

ABSTRACT

The SRL is a research support and service laboratory to provide retrovirologic and serodiagnostic services in support of non-human primate resource development and on-going extramurally-funded biomedical research, and to provide training opportunities for students, technical staff and visiting scientists. This Core provides testing for detection of simian retrovirus infections, monitoring of humans with known occupational exposures to non-human primate retroviruses, serves as a designated reference laboratory for simian type D retroviruses, provides expertise in the interpretation of test results and the development of testing strategies, provides virologic and serodiagnostic assays for four exogenous simian retroviruses, and has an Agent Use Authorization for HIV-1 and HIV-2.

The investigators listed here used the SRL services during the 2003-2004 period.

EARLY POSTNATAL ADMINISTRATION OF CORTICOSTEROIDS AND PULMONARY DEVELOPMENT (0224)

NPRC UNIT: RESPIRATORY DISEASES

%NPRC $: 0.013%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
FANNUCHI, MICHELLE		G	VM: ANAT/PHYSIO & CELL B	
		G	ANAT/PHYS/CELL BIO	UCD SCHOOL OF VETERINARY MEDICINE, CA USA
		A		
	PHD	C	VM ANAT/PHYSI&CELL B	

AXIS I CODES: 1A, 2, 24 **AXIS II CODES:**50B, 60, 74

ABSTRACT

The central hypothesis of the pilot project research was that administration of corticosteroids during early postnatal development of the lung results in alterations in overall lung growth, morphogenesis and cellular differentiation. Although prenatal corticosteroid administration is considered beneficial for maturation of the lungs, benefits of postnatal administration are transient and will result in irreversible changes that may compromise respiratory health later in life. These maturational alterations may also result in infants being more susceptible to injury. The initial stage of this research was to establish the framework to identify critical events during postnatal lung development that may be susceptible to alterations by therapeutic drug exposure. Six 5-day old infant monkeys nursery-reared at the California National Primate Research Center were treated with IM injections of dexamethasone (200 g/kg body weight; Sigma, St. Louis, MO) or an equivalent volume of carrier for 5 days in a row. The animals were necropsied and their lungs evaluated at 90 days of age. To compare the structure of the respiratory bronchioles normal infant rhesus monkeys during the first full week of life, we manually counted the number of generations to the terminal bronchiole in the microdissected left cranial lobe. No differences in the number of airway generations between carrier controls and dexamethasone-treated monkeys were seen. Gamma-glutamyl transpeptidase activity decreased between 5 days and 90 days 3 to 5-fold in all airways evaluated. Glutathione and gamma-glutamyl cysteine synthetase activity assays are currently being evaluated, as are cytochrome P450 3A1 substrate assays. This pilot study will begin to lay the groundwork for studies to answer whether postnatal corticosteroid use alters lung development, and if so, if there is a critical window of susceptibility.

ALLERGY CORE SERVICES (0285)

NPRC UNIT: RESPIRATORY DISEASES

%NPRC $: 0.085%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
GERSHWIN, LAUREL J	DVM, PHD	C	VM PATH/MICRO	
	MD	A	MED PEDIATRICS	
		A		
	PHD	C	VM ANAT/PHYSI&CELL	
		B		
	PHD	C	VM ANAT/PHYSI&CELL	
		B		

AXIS I CODES: 1A **AXIS II CODES:**62, 64

ABSTRACT

Projects this year have included:
1) Development of monoclonal antibodies to rhesus IgE—progress on this project is excellent. Column chromatography has been used to purify monnkey IgE in sufficient quantity to immunize mice for fusions. This project is ongoing.
2) Preparation of rabbit anti-house dust mite antisera
3) Preparation of rabbit anti-Derf 2

Services Offered-

Allergen preparation for immunization and aerosol
Histamine assay
HDM specific IgE, IgG, IgA ELISAs
Leukotriene extraction
Leukotriene C4/D4/E4 ELISA
Leukotriene C4 ELISA
Leukotriene E4 ELISA
Human cytokine ELISAs: IL-5, IL-13, Interferon-g
Thromboxane B2 ELISA
Prostaglandin ELISA
Protein Assay
Creatine Assay
Statistical Analysis of data
OVA-specific rat or mouse IgE ELISA

Custom (rat, mouse, human, or non-human primate) IgE assay development is available.

BORAGE OIL AND GINKGO BILOBA (EGB 761) IN ASTHMA (0321)

NPRC UNIT: RESPIRATORY DISEASES

%NPRC $: 0.039%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
GERSHWIN, MERRIL E.		A		UC DAVIS, CA USA

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

ABSTRACT

Project I: Borage Oil and Ginkbo biloba (EGb 761) in Asthma, ME Gershwin, PI overall; [ ], PI of Oil, Co-Invest; [ ]PI of Ginkbo biloba; [ ] Co-Invest; [ ] [ ] Statistics and Database Management; [ ] Consultant The concept of asthma as a condition in which acute and chronic inflammatory changes in airways play a fundamental role is well established. The role of leukotrienes as a crucial element of these inflammatory processes is supported by abundant laboratory and clinical evidence. There is a potential for herbal medicinal approaches to ameliorate leukotriene-mediated inflammation in asthma based on data from the literature and our laboratory. Studies suggest that dietary gamma-linolenic (GLA), found in borage and evening primrose oil, is unique among the (n=6) polyunsaturated fatty acid family members (linolenic acid, GLA and arachidonic acid) in its potential to attenuate inflammatory processes. For instance, there are randomized, placebo- controlled trials (RCT) demonstrating efficacy of dietary GLA in patients with rheumatoid arthritis and active synovitis. Ginkbo biloba, a flavonoid-rich extract of leaves of the Ginkbo biloba tree, has been studied in one RCT with asthma patients and is recommended by CAM practitioners as a treatment of allergic inflammation and asthma. Ginko biloba may have inhibitory effects on release of inflammatory mediators. Although improvements has been made in management of patients with asthma, may interventions are associated with adverse effects. Because of the possibility of minimal or negligible adverse effects reported with borage oil, and the widespread use of Ginkgo biloba supplements without known adverse effects, we will assess clinical efficacies and/or adverse effects of dietary borage oil containing GLA and Ginkbo biloba in patients with asthma in a 17 month RCT. We also propose to delineate whether or not the clinical course of treatment correlates with suppression of leukotriene B4 (LTB4), LTC4 and LTD4, generated by activated polymorphonuclear cells (PMNs). Additionally, in the Ginkgo biloba arm of study, the vitro/ex vivo inhibition of histamine release will be assayed, since one of its major constituents, quercetin, is known to be structurally related to cromolyn sodium and has been shown in in vitro studies to exhibit similar activities. Furthermore. Anti-inflammatory activities of Ginkbo biloba will be compared to those of some of its individual constituents in a series of in vitro experiments. It is hoped that findings from these studies will evolve relatively non-toxic therapeutic alternatives for attenuating bronchial hyperresponsiveness and inflammation in patients with asthma.

names

GENETIC RESOURCES FOR NON-HUMAN PRIMATES (0305)

NPRC UNIT: RESPIRATORY DISEASES

%NPRC $: 0.757%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LYONS, LESLIE	PHD	A	VM:POP HLTH & REPRO	UC DAVIS, CA USA

AXIS I CODES: 1D

AXIS II CODES: 36, 44, 45, 54A, 58, 59, 64, 65, 77

ABSTRACT

To address human health concerns, we are developing genetic resources for non-human primates. These resources are developed following three aims. Specific Aim 1: Create a warehouse for currently available genetic resources for non-human primates, specifically but not exclusively, for the rhesus macaque. Aim 1 provides a resource distribution component available to all primate researchers. Specific Aim 2: Facilitate the use of genetics and serve the primate research community. Aim 2 provides a service component and will support research initiated by requesting investigators. The data produced will be used as preliminary results for competitive grant proposals. Some program income may be generated from these collaborations. Specific Aim 3: Develop and improve the genetic resources for non-human primates. Aim 3 provides a research component and is independent research. Genetic resources will be developed that are missing for non-human primates and required as a community resource. RESULTS: We have expanded our holdings of DNA samples for the Rhesus macaque half-sib families and the "Founder" animals of the colony. Over 1800 samples are now banked by the core. Human markers that represent the genome screening panel have been tested. To date, 62 markers have been tested in macaques and approximately 60% are efficient for use in rhesus. For SA 2, we have focused on four specific areas: 1) the development of new genetic assays, 2) provide services as a "fee for service" or as a collaborative effort, 3) developing karyotyping analyses and fluorescent in situ hybridization (FISH), and 4) use genetic information to assist colony management, both within and across primate centers. For SA 3, current research areas include: 1) the development of genetic markers for non-human primates, 2) the development of radiation hybrid panels for the rhesus macaque, 3) the development of a linkage-based genetic map for rhesus macaque.

EFF ENVIRONMNTL TOBACCO SMOKE(ETS)ON PERINATAL LUNG DVMT IN NON HUMAN PRIMATES (0027)

NPRC UNIT: RESPIRATORY DISEASES

%NPRC $: 0.806%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
PINKERTON, KENT E	PHD	C	VM ANAT/PHYSI&CELL B	
	PHD	A		UC DAVIS, CA USA
	PHD	A	MED PHARM TOX:MED	UC DAVIS, CA USA
	MD	A	MED PEDIATRICS	
	MD, PHD	C	MED PEDIATRICS	
	DVM, PHD	C	VM:PATH/MICRO/IMM UNO	
	PHD	C	MED:PEDIATRICS	

AXIS I CODES: 1A, 1D, 24 **AXIS II CODES:**54A, 60, 63H, 63I, 64, 71

ABSTRACT

Environmental tobacco smoke (ETS) is a common indoor air pollutant affecting millions of individuals. Exposure to ETS is associated with increased respiratory disease, asthma and middle ear infection in children. Today asthma is the most common disease of childhood. The prevalence of asthma has been increasing in industrialized countries during the last 30 years by 10% of the population being affected (NIH, 1997). To better understand the effects of perinatal exposure to ETS on the immune response in Rhesus macaque monkeys were used. Aged and diluted sidestream cigarette smoke (ADSS) was generated under carefully controlled conditions as a surrogate for ETS. Exposure of mother and infant has been from early gestation (day 40) to postnatal age 13 months. An aged-matched control group has also been followed as well as a third group of monkeys exposed to ADSS beginning at 6 months postnatal age. Lymphocyte profiling and cytokine development will be examined in monkeys at 3, 6, 9 and 12 months of age as a way of elucidating potential immunologic and systemic mechanisms involved in increased risk of asthma during perinatal development. Airway sensitivity to methacholine challenge is being examined at 3, 6 and 12 months of age. Bronchoalveolar lavage and bronchial brushings have been done at 9 months of age. Analysis of these parameters is currently under way. In our preliminary findings we have noted significant changes in the peripheral blood cell analysis with increases in the total number of white blood cells in peripheral blood and a significant decrease in the proportion and number of monocytes following exposure to smoke compared with filtered air control infants. This decrease in blood monocyte number may be due to a significant increase in the recruitment of monocytes to the lungs we observed in an earlier study with infant monkeys. Ongoing studies will continue to examine the number and proportion of lymphocyte phenotypes with increasing exposure to ADSS as well as cytokine profiling by reverse transciptase-polymerase chain reaction (RT-PCR). Our preliminary findings in blood lymphocyte profiling and pulmonary function testing were presented at the American Thoracic Society meeting in Orlando, FL in May 2004.

AFFERENT NERVE ACTIV. IN ISOL. TRACHEA OF INF. MONKEYS EXP. TO OZONE & ALLERGEN (0123)

NPRC UNIT: RESPIRATORY DISEASES

%NPRC $: 3.350%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
PLOPPER, CHARLES G	PHD	C	VM ANAT/PHYSI&CELL B	
		A		
	DVM, PHD	C	VM PATH/MICRO	
	MD	A	MED PEDIATRICS	
	PHD	A	VM ANAT/PHYSI&CELL B	

AXIS I CODES: 1A, 24 **AXIS II CODES:** 54B, 64, 74, 77

ABSTRACT

Twenty-four infant rhesus monkeys were exposed to 11 episodes (starting at 30 days old) of either filtered air (FA), house dust mite

allergen aerosol (HDMA), ozone (O3) or HDMA + O3 (5 days each followed by 9 days of FA). O3 was delivered for 8 hr/day at 0.5 ppm. Twelve monkeys were sensitized to house dust mite allergen (Dermatophagoides farinae) at age 14 and 21 days. HDMA sensitization was confirmed via skin testing. Sensitized monkeys were exposed to HDMA aerosol for 2 hr/day on day 3-5 of either FA (HDMA, n=6) or O3 (HDMA + O3, n=6) exposure. Non-sensitized monkeys were exposed to either FA (FA, n=6) or O3 (O3, n=6). On the eleventh day of the tenth episode the concentration of histamine aerosol required to double breathing frequency (EC200fb) and reduce tidal volume by one half (EC50Vt) was determined. At time of necropsy a 4cm section of distal trachea, along with its vagal innervation, was removed and placed in a partitioned recording chamber in which one side (containing the trachea) was perfused with 35 deg. C Krebs and the other (containing the vagus) was filled with light parrafin oil. Small slips of the vagus were placed on a recording electrode. The luminal surface of the trachea was then gently probed to locate active receptor fields. Conduction velocities were used to characterize nerve fiber type. We previously showed that exposing infant monkeys to ozone and allergen in combination for 6 months increased the baseline activity of A-delta sensory nerves in isolated tracheas. During this funding cycle we examined the baseline activity of A-delta sensory fibers in isolated tracheas of infant rhesus monkeys exposed to ozone and/or allergen for 3 months. In addition, we examined the responsiveness of these sensory nerves to mechanical stimuli (von Frey filaments), bradykinin and poly-L-lysine (a polycationic peptide). We studied a total of 29 receptor fields. The A-delta fibers studied were nonresponsive to bradykinin and poly-L-lysine. The mean mechanical threshold for stimulation was 3.994 mN for the FA group (n = 9), 0.869 mN for the HDMA group (n = 9), 5.450 mN for the ozone group (n = 4) and 3.488 mN for the HDMA plus ozone group. There were no significant differences between groups.

IMMUNE RESP IN NEONATAL HOUSE DUST MITE-SENSITIZED MONKEYS FOL. EXP TO OZONE (0124)

NPRC UNIT: RESPIRATORY DISEASES

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
PLOPPER, CHARLES G	PHD	C	VM ANAT/PHYSI&CELL B	
		G	PRIMATE CENTER	
	DVM, PHD	C	VM PATH/MICRO	
	PHD	C	VM ANAT/PHYSI&CELL B	
	PHD	A	VM ANAT/PHYSI&CELL B	

AXIS I CODES: 1A, 24 **AXIS II CODES:** 54B, 64, 74, 77

ABSTRACT

Indoor allergens such as house dust mite (HDM) are a contributing factor to the development of allergy and asthma in children. There is increasing evidence that air pollutants such as ozone may effect the initiation or severity of atopic diseases. In order to further our understanding of the effects of HDM and ozone on the developing immune system, neonatal Rhesus Monkeys (n=3/group) were exposed for 22 weeks to one of 4 regimens: 1) filtered air (FA), 2) priming doses of HDM + adjuvant parenterally follwed by 3 times weekly aerosolized HMD (HDM), 3) ozone at 0.5 ppm for 8 hrs/day 5 days on and 9 days off (O3, or 4) HDM +O3. We have previously documented that exposure of newborn rhesus monkeys to house dust mite aerosols for a period of 8 weeks resulted in significant recruitment of eosinophils within airway mucosa. Eosinophils were not uniformly distributed within epithelial and interstitial compartments for all conducting airway generations examined. Based on this finding, we proposed that different chemokines are responsible for the trafficking of eosinophils to proximal versus distal airway generations, as well as epithelial versus interstitial compartments. To address this hypothesis, we have used quantitative real-time RT-PCR and immunofluorescence staining to evaluate the expression profile of eosinophil chemokines and chemokine receptors within the infant monkey lung at 24 hours following house dust mite allergen. Overall, the airway mRNA expression level for eosinophil chemokines was as follows: eotaxin-3 eotaxin-1 eotaxin-2 mucosae-associated epithelial chemokine. Immunofluorescence staining for eotaxin-3 within allergen-exposed infant airways revealed protein expression within airway epithelium, as well as nerve fiber bundles within the interstitium. The abundance of CCR3+ cells within large airways correlated well with volume of eosinophils and eotaxin-3 expression by airway epithelium. CCR3+ dendritic cells, but not eosinophils, co-localized within nerve fiber bundles that expressed eotaxin-3. Based on these findings, we conclude that eotaxin-3 plays an important role in the recruitment of eosinophils within large airways following allergen challenge. In addition, eotaxin-3 appears to play a role in the interaction of dendritic cells with neuronal components of the airways.

POSTNATAL REMODELING IN DIST. AIRWAY OF INFANT MONKEYS EXP. TO OZONE & ALLERGEN (0183)

NPRC UNIT: RESPIRATORY DISEASES

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
PLOPPER, CHARLES G	PHD	C	VM ANAT/PHYSI&CELL B	
		A	VM: ANAT/PHYSIO & CELL B	
		G	VM: ANAT/PHYSIO & CELL B	
	DVM, PHD	C	VM PATH/MICRO	
	PHD	A	VM ANAT/PHYSI&CELL B	

Names

AXIS I CODES: 1, 2, 3, 9, 24 **AXIS II CODES:**44, 54, 60, 64

ABSTRACT

We have begun to assess the potential for developmental anomalies produced by childhood exposure to reverse themselves. Previously, we established that cyclic exposure of infant rhesus monkeys to ozone (O3) and/or housed dust mite allergen (HDMA) caused stunting of conducting airways after 5 months exposure. To determine if these changes were reversible, 30-day old infants were exposed for 5 months and housed in filtered air (FA) with or without HDMA (monthly) for 6 more months. After 5 months, airway branching number in 4 axial airway paths was reduced 4-6 generations in O3 + HDMA exposed monkeys. After 6 more months in FA, branching number was still lower in 3 of 4 airway paths. To establish whether growth differed in airway paths with reduced branch number, the distance between individual branches was measured. Compared to animals exposed to FA for 12 months, total path length was shorter in some O3 and O3 + HDMA animals and the distance between individual branches were greater or equal to FA. We conclude that cessation of exposure does not facilitate recovery of airways whose postnatal development was disrupted by previous exposure. We have asked the question of whether the growth anomalies are initiated early during the development of allergic airways disease by exposing animals for only the first two months (ages 30-90 days) of our six-month protocol to either filtered are (FA), ozone (O3), house dust mite (HDMA), or both (O3 + HDMA). We compared lung and airway growth to healthy animals (5, 30, 60, 90, 180 days old) raised in filtered air (FA). By 90 days, bodyweight (5d: 533; 30d: 562; 60d: 935; 90d:1047gms) and lung volume (rt mid lobe); 5d: 3.7; 30d: 3.6; 60d: 4.7; 90d: 6.5ml) both increased in FA and were unaffected by exposure (O3: 1090gm BW; 6.8ml lung volume; HDMA: ;1157 gm; 5.7 ml; O3 +HDMA: 1068gm;6.5ml). After 2 months of exposure, airway branching number in the axial airway path was reduced 2-3 generations by O3 (13.1) and O3 + HDMA (13.3), compared to FA (5d:18; 30d:14.4; 60d:16;90d:15.3). Growth was compromised in airway paths with reduced branch number. Total path length was shorter in O3 (17.3mm) and O3 + HDMA (17.3mm) compared to FA (20.3mm). We conclude that exposure of infants early during postnatal lung development to environmental inflammatory pollutants and allergens 1.) compromises airway growth and development, 2.) these decrements worsen with continued exposure and 3.) the stunting persists even with cessation of exposure.

GLUTATHIONE LEVELS IN AIRWAYS OF INFANT MONKEYS EXP. TO O3 WITH & WITHOUT HDMA (0184)

NPRC UNIT: RESPIRATORY DISEASES

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
PLOPPER, CHARLES G	PHD	C	VM ANAT/PHYSI&CELL B	
Names	PHD	A	VM MOLE BIOSCIENCES	
	PHD	A		GENENTECH, CA USA
		G	VM: ANAT/PHYSIO & CELL B	
Names	DVM, PHD	C	VM PATH/MICRO	
	PHD	A	VM ANAT/PHYSI&CELL B	

AXIS I CODES: 1, 2, 24 **AXIS II CODES:**60, 74H, 77

ABSTRACT

Naphthalene (NA) and 1-nitronaphthalene (1-NN) are ambient air pollutants which undergo bioactivation by pulmonary cytochrome P450 monooxygenases and deplete Glutathione. Reactive metabolites become bound covalently to cellular proteins and this process has been implicated in cellular injury associated with these agents in rodent models. The relevance of rodent models in assessing the importance of chemicals which require bioactivation is not clear because of the 10 to 100 fold lower activities of cytochrome P450 monooxygenases in primates compared to rodent lungs. Besides being a target for bioactivated toxicants, the airway is also one of the most susceptible sites for acute inflammatory response. Inflammation results in a strong suppression of cytochrome P450 dependent metabolism at least in extrahepatic tissues. Recent work has established and validated a primate model for human asthma which involves exposure to house dust mite antigen (HDMA) and ozone (O3). Accordingly these studies were designed to measure the formation of, and identity of reactive metabolite protein adducts in rhesus macaques and to determine whether treatments which produce an asthmatic response alter the rates and or nature of protein adducts generated. Airways were isolated from rhesus monkeys exposed to filtered air, O3, HDMA or a combination of O3 and HDMA (which sensitizes the animals and produces an asthmatic response) and incubated with 14C-labeled NA or 1-NN. Proteins adducted by reactive metabolites were separated by two dimensional gel electrophoresis, proteins were blotted the membranes and the amount of covalent adduct was measured by storage phosphor analysis. Those proteins adducted by reactive metabolites were excised from the gel, digested with trypsin and the peptides analyzed by MALDI TOF and QTOF mass spectrometry. Adducts identified from incubations with either NA or 1-NN included actin, heat shock 60 kDa, mitochondrial stress 70 protein, aldehyde dehydrogenase, 15-hydroxyprostaglandin dehydrogenase, and tubulin β1. Annexin VI and tropomyocin were adducted only by reactive NA metabolites while collagen α3, selenium binding protein, protein disulfide isomerase, and β globin are only adducted in incubations containing 1-NN. These studies show that many of the proteins which are targeted by reactive NA and NN metabolites in rodent models are also adducted in lungs of rhesus macaques, that while many of the proteins are adducted in common by the two toxicants some are unique to the separate agents. The overall levels of bound metabolite did not appear to change with allergen exposure.

INHALATION EXPOSURE FACILITY/PULM FUNCTION TESTING LAB (0226)

NPRC UNIT: RESPIRATORY DISEASES

%NPRC $: 0.456%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
PLOPPER, CHARLES G	PHD	C	VM ANAT/PHYSI&CELL B	
	MD	A	CALIF AIR RESOURCES BOARD	UC SAN FRANCISCO, CA USA
	PHD	A	NIEHS	
	PHD	A	NIEHS	PENN STATE UNIV, PA USA
	PHD	A	VM MOLE BIOSCIENCES	
	PHD	A	NIEHS	PACIFIC NORTHWEST NATIONAL LAB, WA USA
	MD	A	NIEHS	
	PHD	A	NIEHS	LOUISIANA STATE UNIV, LA USA
	MD, PHD	A	DYNAVAX	UCSD, CA USA
		A	VM: ANAT/PHYSIO & CELL B	
		G	VM: ANAT/PHYSIO & CELL B	
	DVM, PHD	C	VM PATH/MICRO	
	PHD	A	NIEHS	
	DVM, PHD	A	NIEHS	MICHIGAN STATE UNIVERSITY, MI USA
	PHD	A	NIEHS	US EPA, WA USA
	DVM, PHD	A	NUTRITION	
	PHD	A	NIEHS	PENN STATE UNIV, CA USA
	PHD	C	VM ANAT/PHYSI&CELL B	
	MD	A	MED PEDIATRICS	
	PHD	A	NIEHS	CENTERS FOR HEALTH SCIENCES, NC USA
		A		
		A	CALIF AIR RESOURCES BOARD	UC IRVINE, CA USA
		A	PUL MED	UCD TSR&TP, CA USA
	MD, PHD	C	MED PEDIATRICS	
	PHD	A	VM ANAT/PHYSI&CELL B	
		G		
	PHD	C	VM ANAT/PHYSI&CELL B	
	PHD	A	NIEHS	UNIV OF ALABAMA, AL USA
	MD	A	UCD SCHOOL OF MEDICINE	UC DAVIS, CA USA

	PHD	A	MOLECULAR BIOSCIENCES	
	MD	A	NIAID	UCSD, CA USA
	PHD	A	VM ANAT/PHYSI&CELL B	
	PHD	A	NIEHS	
	PHD	A	NIEHS	LOUISIANA STATE UNIV, LA USA
	PHD	A	NIEHS	PENN STATE UNIV, PA USA
	PHD	A	VM ANAT/PHYSI&CELL B	
	BS	G	PRIMATE CENTER	
		A		YUNNAN ANIMAL INSPECTION AND QUARANTINE, CHINA

AXIS I CODES: 1A, 24 **AXIS II CODES:**54A, 64

ABSTRACT

The Inhalation Exposure Facility located at the CNPRC is one of the largest in existence on a university campus. It permits unique human health-related pulmonary research opportunities using non-human primates. Capabilities exist for in vivo or in vitro exposure to precisely characterized and controlled atmospheres of gases and aerosols. For health effects of air pollution research, the range of test subjects used for exposure studies can include animals, isolated and perfused lungs, tracheal explants and human or monkey lung cell cultures. This permits an integrated, comparative approach to defining mechanisms of respiratory system injury and repair. A recent addition to the capabilities is a pulmonary function laboratory that offers a comprehensive array of testing for infant through adult non-human primates.

The investigators listed here have used this core facility's services during the granting period.

METABOLIC ACTIVATION OF AIR TOXICS IN ASTHMATIC MONKEYS (0302)

NPRC UNIT: RESPIRATORY DISEASES

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
PLOPPER, CHARLES G	PHD	C	VM ANAT/PHYSI&CELL B	
	PHD	A	VM MOLE BIOSCIENCES	

AXIS I CODES: 1A, 2, 24 **AXIS II CODES:**54A

ABSTRACT

Numerous epidemiologic studies have noted associations between exposures to ambient air pollutants (VOC, particulates, ozone) and asthma incidence and severity. Recent work in juvenile rhesus macaques has shown that a syndrome having many of the hallmark signs of allergic asthma can be induced by intermittent ozone and house dust mite allergen (HDMA) exposures. Several of the structural alterations observed in this model occur in the airways, a primary site for pulmonary xenobiotic metabolism. These studies were conducted to test the hypothesis that exposures resulting in fundamental alterations in the structure and function of the lung also alter the ability to metabolize xenobiotics, with a focus on bioactivated xenobiotics. Accordingly, metabolism of naphthalene and 1-nitronaphthalene was measured in airway subcompartments obtained from monkeys exposed to filtered air, HDMA, ozone, or the combination.. No alterations were noted in reduced glutathione levels or in the rates of metabolism of either substrate to water soluble metabolites in response to exposure. While prior exposures of animals to HDMA, O3 or a combination had no effect on protein covalent binding of naphthalene metabolites, there was an apparent increase in the amounts of reactive 1-nitronaphthalene metabolites bound to proteins in trachea, proximal, and medial airways of exposed monkeys. In contrast to the studies showing substantial exposure related alterations in lung structure and function, aside from the apparent increase in reactive metabolite protein adducts in certain airways of HDMA or ozone exposed animals few changes were noted in the metabolic disposition of these compounds at either substrate concentration.

MECHANISM OF SPECIES DEPENDENT ENVIRONMENTAL LUNG INJURY (0336)

NPRC UNIT: RESPIRATORY DISEASES

%NPRC $: 1.152%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
POSTLETHWAIT, EDWARD M	PHD	A	NIEHS	UNIV OF ALABAMA, AL USA

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

ABSTRACT

A substantial proportion of the US population continues to be exposed to harmful air pollutants such as ozone (O3). Despite the many years and extensive number of research efforts, the mechanisms of exposure-related lung injury, the factors that govern susceptibility, and the long-term health consequences of childhood exposures remain poorly understood. New evidence suggests that episodic O3 exposure of infant nonhuman primates results in profound alterations in lung growth, structure, and function, and exacerbates development of reactive airways disease. Because O3 reactions with constituents of the epithelial lining fluid (ELF) dictate generation of the local dose, we hypothesize that the age-, site-, cell-, and disease-specific susceptibilities to acute versus episodic O3 exposure result from differences in ELF-dependent interactions associated with spatial heterogeneities in the local dose coupled with differential regulation of the airway e pithelial intracellular and ELF a ntioxidant pools. To test this hypothesis, which will further our understanding of the fundamental mechanisms of O3-related disruption of normal lung development, lung injury, and susceptibility; we have brought together an interdisciplinary research team that encompasses expertise in lung surface chemistry, pathobiology and quantitative morphology, dosimetry, and extrapolation modeling. We have designed a highly interactive program that utilizes non-human primates (rhesus monkeys) and involves four interdependent projects and three cores. Our initial goals are to characterize the ELF-mediated generation of the local dose across age, exposure history, and airway sensitization; define the mechanisms of age-dependent susceptibility in the postnatal lung; characterize the determinants of airway remodeling as a function of acute versus episodic exposures; develop non-invasive biomarkers of lung injury utilizing the nose as a sentinel; and, formulate models that predict health outcomes across lung growth and airway sensitization. The program spans from molecular interactions to the intact primate, is highly relevant to the goals of NIEHS, is anticipated to extend into the human population, and will substantially reduce the uncertainties regarding the health effects of oxidant air pollution in our childhood population.

LUNG DEFENSE MECHANISM FOR ENVIRONMENTAL OZONE (0320)

NPRC UNIT: RESPIRATORY DISEASES

%NPRC $: 0.851%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
SCHELEGLE, EDWARD	PHD	A B	VM ANAT/PHYSI&CELL	

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

ABSTRACT

No abstract available.

IL-2SA THERAPY IN SIV INFECTTION (0315)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 0.225% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
ABEL, KRISTINA	PHD	A		UC DAVIS, CA USA

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

ABSTRACT

The effectiveness of antiretroviral therpay in HIV-1 infected patients varies widely among different patients. Thus, there are attempts to boost HAART therapy by using cytokines as immunomodulators in combination with HAART. The purpose of the study is to examine the effect of IL-2 treatment on virus replication in SIV-infected rhesus macaques. Eighteen rhesus macaques will be infected intravaginally with SIVmac251. At the time viral setpoint (6 months post-infection), 9 animals will be treated with IL-2SA and 9 monkeys will receive placebo. IL-2SA will be administered twice daily subcutaneously for a total of 5 consective days. The treatment will be repeated every four weeks for a total of three times. Virus replication will be monitored in CSF and peripheral blood. At six months after the first treatment, all animals will be euthanized and virus replication and CD4 cell numbers will also be assessed in lymphoid tissues. Further, tissues will be examined for histological changes. Virological and immunological parameters will be compared between the IL-2SA treated monkeys and the placebo-treated animals to evaluate the effect of IL-2SA on SIV replication and disease progression.

NON-INVASIVE IMAGING OF T CELL RECRUITMENT TO THE CENTRAL NERVOUS SYSTEM (0326)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 0.068% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
ANDERSON, DAVID E.	PHD	A	MED: MICROBIO AND IMMNUO	UC DAVIS, CA USA
[Name]	PHD	C	MED:PSYCHIATRY	
		A		

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

ABSTRACT

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) white matter characterized by demyelination, axonal injury, focal T cell and macrophage infiltrates and loss of neurological function. An estimated 350,000 people in the US have MS with 10,000 new cases per year.

Autoreactive T cells against brain proteins can be found at low frequencies in the peripheral blood of most individuals. A wide number of animal studies have demonstrated that activated autoreactive T cells can enter the central nervous system (CNS) and initiate an autoimmune disease that resembles multiple sclerosis (MS). While it is clear that activated but not naive T cells can enter the CNS, the relative importance of antigen experience (memory) versus activation state (effector status) has not yet been examined. Thus, it remains possible that unactivated, resting memory T cells (central memory T cells) circulating in the periphery can be recruited to the CNS. In addition, while it is clear that viral infection of the CNS can recruit T cells to the CNS and initiate an autoimmune response, it is unclear whether CNS activation alone (upregulation of proinflammatory cytokines and chemokines) is sufficient to recruit T cells to the periphery, or whether damage within the CNS due to viral cytopathic effect and release of autoantigens is necessary for T cell recruitment.

This proposal will use in vivo imaging to determine if resting memory T cells can infiltrate the CNS, and determine if CNS activation, without disruption of the blood-brain-barrier, influences this process. We hypothesize that CNS activation alone is sufficient to recruit autoreactive resting memory T cells to the CNS without the need for peripheral activation of these T cells. We propose to isolate and expand myelin-reactive T cells in vitro from the peripheral blood of two rhesus macaques.

A NON-HUMAN PRIMATE MODEL FOR CYTOMEGALOVIRUS VACCINES (0218)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 1.302%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BARRY, PETER A	PHD	C	CTR FOR COMPARATIVE MED	UC DAVIS, CA USA
	PHD	C	PSYCHOLOGY	
		G	CENTER FOR COMPARATIVE MEDICIN	
	PHD	G	CENTER FOR COMPARATIVE MEDICIN	

AXIS I CODES: 1A, 1D, 7B, 13, 17, 28(MUCOSAL SURFACE) **AXIS II CODES:** 64, 66, 77, 83, 91

ABSTRACT

OBJECTIVE:

To (a) characterize the roles of the RhCMV interleukin-10 and US28 proteins in the RhCMV replication cycle, and (b) develop novel vaccine designs against human cytomegalovirus by constructing RhCMV variants containing deletions in the viral interleukin-10 and US28 genes.

There are no licensed vaccines for human cytomegalovirus (HCMV). Limited clinical trials have been conducted with live attenuated and recombinant subunit vaccines. Despite partial success protecting from disease in renal transplant recipients, the goal of developing an HCMV vaccine that elicits protective immunity has not been achieved. There are impediments to the development of an HCMV vaccine. Design of an effective HCMV vaccine requires characterization of the correlates of protective immunity and a better understanding of HCMV natural history. Both aspects of HCMV are incompletely resolved and difficult to investigate in humans. Studies have suggested that two measures of humoral immunity, neutralizing antibodies and antibody avidity, and one measure of cellular immunity, CTL, are useful for assessing protective anti-HCMV immunity. The two HCMV proteins associated with protective immune responses, gB and pp65, represent starting points for any rational vaccine. Recent data on HCMV and the closely related rhesus CMV (RhCMV) strongly implicate viral modulation of host immune responses as a critical component of CMV natural history. CMV appears to have evolved strategies that alter lymphoid cell signaling and trafficking. Based on sequence homologies, it is reasonable to infer that HCMV has targeted pro-inflammatory immune responses for disruption during infection. Attenuation of HCMV's ability to modulate host immune responses should limit viral replication and disease sequelae. Accordingly, HCMV vaccines must be directed against both structural and immune modulating ORF to reduce virologic parameters of infection and/or disease. In other words, protective immunity will be enhanced when vaccination is directed against identified immunogens, such as gB and pp65, together with novel vaccine targets represented by immune modulating ORF. A successful outcome of this approach will demonstrate that attenuation of the CMV immunomodulatory ORF by immunization represents a rational vaccine strategy. This would fundamentally alter the paradigm for vaccine approaches to HCMV.

RESULTS:

(a) Viral interleukin-10 has been demonstrated to profoundly affect the functions of dendritic cells at multiple stages. In vitro evidence indicates that viral interleukin-10 should profoundly alter the ability of dendritic cells to elicit fully protective immune responses following viral infection. (b) A modified rhesus CMV (RhCMV) variant has been constructed in which the viral interleukin-10 gene has been deleted. This is currently being analyzed in vitro. A RhCMV variant in which the US28 gene has been constructed by our collaborators at Chemocentryx, Inc. It will soon be evaluated in vivo.

COMPARATIVE IMMUNIZATION FOR SIMIAN HERPESVIRUSES (0219)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BARRY, PETER A	PHD	C	CTR FOR COMPARATIVE MED	UC DAVIS, CA USA
	DVM, PHD	A		OAKLAHOMA STATE UNIVERSITY, OK USA
	DVM, PHD	A	CENTER FOR COMPARATIVE MEDICIN	
	PHD	A	MED PATHOLOGY	

AXIS I CODES: 1A, 9, 17 **AXIS II CODES:**39, 64, 66, 77, 91

ABSTRACT

OBJECTIVES: To develop a vaccine against herpes B virus that can ultimately eliminate B virus from the macaque population at the CNPRC.

Herpes B virus (Cercopithecine herpesvirus 1) is endemic in captive macaque populations and poses a serious threat to humans who work with macaques or their tissues. A vaccine that could prevent or limit B virus infection in macaques would lessen occupational risk. To that end, a DNA vaccine plasmid expressing the B virus glycoprotein B (gB) was constructed and tested for immunogenicity in mice and macaques. Intramuscular (IM) or intradermal (ID) immunization in mice elicited antibodies to gB that were relatively stable over time and predominately of the IgG2a isotype. Five juvenile macaques were immunized by either IM+ID (n=2) or IM (n=3) routes, with two booster immunizations at 10 and 30 weeks. All five animals developed antibodies to B virus gB, with detectable neutralizing activity in the IM+ID immunized animals. These results demonstrated that DNA immunization can be used to generate an immune response against a B virus glycoprotein in uninfected macaques.

POST-EXPOSURE VACCINATION FOR HCMV INFECTION (0229)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 0.213%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BARRY, PETER A	PHD	C	CTR FOR COMPARATIVE MED	UC DAVIS, CA USA

AXIS I CODES: 1A, 7B, 9, 28(IMMUNE SYSTEM) **AXIS II CODES:**64, 66, 71, 91

ABSTRACT

OBJECTIVES: To determine whether post-exposure immunization of monkeys already infected rhesus cytomegalovirus (RhCMV) can alter the frequency of viral shedding at mucosal surfaces.

Preconceptional immunity to HCMV does not fully protect against maternal reinfection with heterologous strains of virus and transplacental transmission of virus to the fetus. In addition, the frequency of fetal sequelae following either reactivation or reinfection of the mother may be greater than once generally believed. These findings highlight that our understanding of both the correlates of protective immunity to HCMV and HCMV natural history are incomplete. Resolution of these issues is paramount to design effective vaccine strategies. Maternal immune responses to HCMV infection can be considered protective because clinical outcomes in the mother are rare. Antiviral immune responses are not protective in that HCMV can disseminate in the presence of antiviral immunity. Reactivated virus can potentially be transmitted horizontally and/or vertically across the placenta. It is the inability of antiviral immunity to restrict HCMV replication that defines the limitation of the immune response. Vaccine strategies may need to be extended to include some seropositive individuals to achieve two potential goals. One goal would be to reduce pathological outcomes of endogenously or exogenously acquired virus. The other would be a reduction in the frequency of HCMV reactivation. HYPOTHESIS: Immunization of HCMV seropositive hosts against HCMV antigens can reduce both the frequency and titer of reactivated virus. This hypothesis will be tested in the rhesus macaque model. We have observed that some macaques are consistently negative for rhesus CMV (RhCMV) DNA in mucosal swabs. In contrast, swabs from other animals are persistently positive for RhCMV DNA. The following Aims will test whether immunization of RhCMV DNA-positive monkeys reduces RhCMV load in mucosal fluids. (1) Longitudinal screening of seropositive animals for rates and titers of RhCMV DNA in mucosal fluids. (2) Genetic immunization of animals with plasmid expression vectors for RhCMV antigens or control plasmids. (3) Post-immunization assessment of RhCMV detection frequency and titer in vaccinated and control animals. The premise of this R03 proposal is that post-exposure immunization can stimulate greater immunological control of cells producing infectious virions. Substantiation of the hypothesis will validate expansion of HCMV vaccine strategies to include populations of seropositive/virus excreting individuals and provide insight into the relationships of early virus-host interactions and chronic outcomes.

RESULTS: Fifteen macaques at the CNPRC were prospectively evaluated over the course of 11 weeks for shedding of RhCMV at mucosal surfaces. Seven animals were genetically immunized with expression plasmids for two RhCMV proteins, and the frequency of RhCMV shedding was evaluated. No changes in shedding were observed following post-exposure immunization.

HEPATITIS B-LIKE VIRUS INFECTION IN NONHUMAN PRIMATES (0325)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 0.068%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
CHOMEL, BRUNO B	DVM, PHD	A	SCH OF VET MED:POP HLT REPR	UNIV OF CALIF DAVIS, CA USA
	PHD	A		LYON UNIVERSITY, FRANCE
	MD, PHD	A		UNIVERSITY OF CL. BERNARD-LYON, FRANCE
		A		
	DVM, MPVM	C	VM:PATHO/MICROBIO L/IMMUNO	
	MD	A		INSERM, FRANCE

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

ABSTRACT

Despite the availability of an effective vaccine, chronic Hepatitis B Virus (HBV) infection remains a major public health problem with an estimated 400 million virus carriers worldwide (including 1.5 million in the USA) which are at high risk to develop cirrhosis and primary liver cancer. Actual anti-HBV treatments have only limited efficacy. Therefore, there is an urgent need to test new therapeutic approaches to fight chronic hepatitis B infection (Zoulim and Trepo 1999). This issue has been hampered by a very narrow host range of HBV, which only infects humans and chimpanzees.

M. fascicularis can harbor HBV-like simian virus, and M. fascicularis can be chronically infected with a HBV-like virus. The objectives of our study are to evaluate the presence of a natural HBV-like virus infection in M Fascicularis. The presence of natural HBV-like virus infection in M fascicularis serum from CNPRC will be investigated in a random group of 100 animals. In addition, a HBV-like virus recently identified in M fascicularis from Mauritius Island will be experimentally inoculated to M fascicularis from the CNPRC to assess its inefectivity.

PATHOGENESIS OF INTESTINAL DYSFUNCTION IN SIMIAN AIDS (0271)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 0.846% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
DANDEKAR, SATYA	PHD	A	MED:PATHOLOGY	
[redacted]	DVM, PHD	A	SCH OF VET MED:POP HLT REPR	UNIV OF CALIF DAVIS, CA USA

AXIS I CODES: 1A, 16 **AXIS II CODES:**31

ABSTRACT

Immunologic and virologic assessments of anti-retroviral therapy in HIV-infected patients are mainly performed on peripheral blood sample. However, blood represents only 2% of the total lymphocytes in the body. Since the gut-associated lymphoid tissue (GALT) harbors the majority of T lymphocytes i the body. Thus, it is an important reservoir of HIV. Our knowledge of HIV suppression and immune restoration in intestinal mucosa during anti-retroviral therapy of HIV infection is limited. The overall objective of this application is to examine the immunologic and virologic effects of anti-retroviral therapy (PMPA) in GALT in comparison to peripheral lymph nodes and blood of simian immunodeficiency virus (SIV)-infected rhesus macaques, a primate model for AIDS. The applicants will test the hypothesis that the level of CD4+ T cell depletion and the stage of viral infection in T cell repopulation (flowcytometry), viral suppression (bDNA assay, PCR and in situ hybridization) and the emergence of viral genomic diversity and drug-resistant variants in intestinal tissue. The Specific aim 1 will be to characterize the phenotype of CD4+ T cells repopulating intestinal mucosa of SIV-infected rhesus macaques following anti-retroviral therapy and to determine the mechanisms of the CD4+ T cell repopulation. The specific aim 2 will be to determine the suppression of viral loads and to examine the emergence of genomic diversity and drug-resistant viral variants in intestinal tissues following anti-retroviral therapy in comparison to peripheral lymph nodes and blood. The specific aim 3 will be to examine whether T cell activation by short-term IL-2 administration will alter the pool of virally infected cells in GALT of SIV-infected animals that are undergoing PMPA therapy. The applicant believes that the proposed studies will provide insights into the immunologic and virologic effects of anti-retroviral therapy in intestinal lymphoid tissue in comparison to peripheral blood and lymph nodes and that this information will be valuable in development of more effective anti-retroviral and immunomodulatory approaches.

DEVELOPMENT OF A LYMPHOCYTE TRAFFICKING MODEL IN RHESUS MACAQUES (0268)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 0.069% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
ESSER, URSULA	PHD	A	MEDICAL PATHOLOGY	
[illegible] names]		G	IMMUNOLOGY GRADUATE PROGRAM	UC DAVIS, CA USA
[illegible]	PHD	G	MEDICAL PATHOLOGY	UC DAVIS, CA USA

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

ABSTRACT

During HIV infection, migration of dendritic cells from mucosal sites and T lymphocyte homing to and from sites of initial and secondary antigenic exposure are orchestrated in a manner still poorly understood. They remain largely unexplored in humans in large part due to the difficulty to assess trafficking in vivo. The simian model for AIDS renders the unique opportunity to develop an animal model to study T lymphocyte migration in SIV-uninfected and SIV-infected animals in vivo. Migratory patterns in healthy macaques will be contrasted with those in SIV-infected animals following initial viral exposure and during later stages of infection and overt disease. Trafficking properties will be characterized following adoptive transfer of autologous, dye-labeled lymphocytes during a set time course. Lymphocytes derived from various primary and secondary lymphoid tissues will be analysed both phenotypically and functionally. Our goal is to define requirements for tissue-specific migration and movement of activated versus naïve T lymphocytes to secondary lymphoid tissue and effector sites, and stimulation of an effective immune response. The overall aim of this project is to link lymphocyte migratory patterns of activated and memory T lymphocytes with parameters of protective immunity in longterm non-progressors as well as vaccinated nonhuman primates. This knowledge will contribute to the design and evaluation of potential AIDS vaccine candidates, and further our understanding of the basic mechanism of protective immunity.

PATHOGENESIS OF MUCOSAL TRANSMISSION/ACUTE SIV INFECTION (0327)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 2.242% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
HAASE, ASHLEY	MD	A		UNIV OF MINNESOTA, MN USA
[name]	VM, PHD	C	VM:PATH/MICRO/IMM UNO	

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

ABSTRACT

The principal aim is to use rhesus macaques infected intravaginally with SIV as a model for HIV-1 transmission and a foundation of designing and evaluating vaccine candidates. Virus-cell relationships will be defined by in situ hybridization and PCR-based techniques and the cellular immune response will be identified and quantified. The proposal involves a consortium of investigators headed by Ashley Haase and includes Christopher Miller, [ ] and [ ] In aim 1, two competing hypotheses will be tested following transmission: SIV replication is confined to the portal of entry for a sufficient time to allow an anamnestic immune defense to prevent dissemination vs. transmission leads to unimpeded spread in DCs and/or macrophages beyond the site of entry. In aim 2, they will examine the hypothesis that latently or chronically infected cells arise quickly after transmission. In aim 3, they will test the hypothesis that the balance between virus reproduction and the scope and breadth of the immune response determines the success or failure of establishing a persistent infection.

names

BARTONELLA MODEL FOR AN AIDS OPPORTUNISTIC PATHOGEN (0256)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 1.429% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
KOEHLER, JANE		A		UCSF, CA USA
Names	DVM, PHD	A	SCH OF VET MED:POP HLT REPR	UNIV OF CALIF DAVIS, CA USA
	DVM, MPVM	C	VM:PATHO/MICROBIOL/IMMUNO	

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

ABSTRACT

The long range objective of the proposed study is to gain insight into the pathogenetic mechanisms of Bartonella species during opportunistic infection of patients co-infected with HIV. Bartonella syndromes in HIV-infected patients include severe, even fatal infections such as bacillary angiomatosis, peliosis hepatitis, relapsing bacteremia, endocarditis, cat scratch disease, neuroretinitis and encephalopathy. From clinical observations, there are two striking manifestations of Bartonella pathogenesis: relapsing and persistent bloodstream infections and vascular proliferative lesions, yet nothing is known about the bacterial pathogenetic mechanisms involved in either, largely because no animal models exist the immediate objective of these studies is to study the mechanisms of Bartonella pathogenesis by developing an animal model, and utilizing this animal model to characterize the host response to infection and mechanisms of virulence gene expression associated with B. henselae and B. quintana. The applicant's first goal is to develop an animal model for AIDS-associated opportunistic Bartonella infections in by infecting animals with B. henselae or B. quintana, with the goal of inducing one or both endpoint disease manifestations: persistent bloodstream infection and angiogenic lesions. The second goal is to utilize the model to study Bartonella pathogenesis (course of infection, pathological changes, humoral immune response). Through development of an animal model and subsequent study of the disease course, pathological manifestations and mammalian host-bacterium interactions, the applicants hope to gain insight into the basis for Bartonella pathogenesis including host immune response and persistent and relapsing infection, which will ultimately lead to improved diagnosis, treatment and prevention of Bartonella infection in HIV-infected patients.

CD1D RESTRICTED T (NKT) CELL INTERACTION WITH CPG ODN (0337)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 4.254% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LANDAY, ALAN L.		A		UNKNOWN, CA USA
[illegible]	DVM, PHD	C	VM:PATH/MICRO/IMMUNO	

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

ABSTRACT

No abstract available.

GENETICALLY DEFINED HERPES/RETROVIRUS SPF MACAQUES (0275)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 4.976% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LERCHE, NICHOLAS W	DVM, MPVM	C	VM:PATHO/MICROBIOL/IMMUNO	
	PHD	C	CTR FOR COMPARATIVE MED	UC DAVIS, CA USA
		A	CCM	UC DAVIS, CA USA
	PHD	C	MED:PATHOLOGY	
	PHD	C	VM:PATHO/MICROBIOL/IMMUNO	
		A	VET GENETICS LAB	UC DAVIS, CA USA
	DVM	C	PRIMATE CENTER	

AXIS I CODES: 1A, 19 **AXIS II CODES:**31, 66, 77

ABSTRACT

Since the start date of 9/30/02, 64 adult non-SPF rhesus macaques (8males, 56 females) imported from China have been assigned to this project. All 64 animals have completed a 90 day quarantine period and have been released to corn cribs for breeding. The objective of this project is to derive SPF animals from non-SPF founder stock. Although not projected until 2004, 3 offspring were produced from these breeding groups in 2003. Four offspring have been produced to date in 2004, and there are currently 19 pregnancies. All offspring will be taken at birth, nursery reared and eventually socialized for pair housing. During the first year all infants will be undergo 4 rounds of testing for SRV, STLV, SIV, SFV, B virus, CMV and RRV at approximately 2, 4 8 and 12 months of age. DNA typing will be performed on breeding adults and offspring to characterize alleles in microsatellite, Class I and Class II loci of the major histocompatibility complex (MHC) and determine haplotypes of offspring.

THE IMMUNOGENICITY OF YEAST-BASED HIVAX2.3-P55 VACCINE IN RHESUS MACAQUES (0263)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 0.141% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
LU, FABIEN X	PHD	A	MED:PATH/MICRO/IMMUN	
[Name illegible]	MD, PHD	A		
	DVM, PHD	C	VM:PATH/MICRO/IMMUNO	

AXIS I CODES: 1A, 7B, 8, 19 **AXIS II CODES:** 31, 64, 83, 91

ABSTRACT

Yeast (Saccharmyces cerevisiae) can be easily made in large scale. Yeast-based candidate HIV vaccines manufactured by [illegible] have been evaluated in mice. The studies undertaken in the murine model have shown that this delivery system is capable of eliciting HIV-specific CD8+ and CD4+ T cell responses. Evaluations of dose response, especially via the subcutaneous route, have revealed that a dose of 25 ng of HIVgag protein delivered in 20 x 10-to-the-6th heat-killed yeast particles is optimal for induction of CD8+ T cell responses in the murine model. However, no large animal immunogenicity or reactogenicity studies have been carried out to determine whether the yeast-based product or this dose will induce immune responses in non-human primates and man. Thus, the purpose of this study is to determine the safety, dose and immunogenicity of recombinant [illegible] antigen derived from yeast (Saccharmyces cerevisiae) in rhesus macaques using one immunization schedule. Eight macaques, divide in two groups (4/4) were immunized subcutaneously with either 50 ng or 2500 ng at week 0, 4, and 12. Animals were observed for more than 14 weeks. Blood samples were evaluated for IFN-gamma-secreting cells by ELISPOT assay and T lymphocyte proliferative activity. Lymph nodes biopsy was done at week 14 and the similar assays were performed on all cell suspensions. The induction of serum ant-HIV1 antibody responses was assessed. All eight of immunized animals were negative for the IFN-gamma spot, proliferation assays and anti-HIV1 antibody.

MOLECULAR BASIS OF NALT-INDUCED MUCOSAL IMMUNITY TO SIV (0264)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LU, FABIEN X	PHD	A	MED:PATH/MICRO/IMMUN	
names	PHD	A	MED:ORAL BIO/MICRO/IMMUN	UNIV OF ALABAMA AT BIRMINHAM-MED CTR, AL USA
	DVM, PHD	C	VM:PATH/MICRO/IMMUNO	—

AXIS I CODES: 1A, 7D, 19 **AXIS II CODES:**31, 64, 83, 91

ABSTRACT

The major goal of our studies has been to develop a nasal vaccine given with a nontoxic molecular mucosal adjuvant which will elicit protective immune responses to simian immunodeficiency virus (SIV) to prevent sexual transmission of HIV in human. We compared mCT E112K with nCT as mucosal adjuvant in rhesus macaques nasally immunized with HIV-1 gp120. Initially, a total of five macaques were given 100 µg of HIV-1 gp120 on five occasions over a six weeks period. Two of these received gp120 mixed with nCT (10 µg) and two other macaques were immunized with gp120 and mCT E112K (25 µg)). One control macaque was given nasal gp120 only. In order to further confirm mucosal adjuvant activity of mCT E112K, an additional three monkeys were nasally immunized with an increased dose of mCT E112K (100 µg) and gp120. As controls, 3 monkeys were given gp120 plus nCT (10 µg) or 1 monkey given gp120 alone. We assessed plasma Ab responses to gp120 as well as mucosal Abs in saliva and vaginal washes. In addition, we quantitated both IgG and IgA anti-gp120 Ab-forming cells (AFCs) in mucosal tissues. Finally, we assessed gp120-specific, CD4+ Th1- and Th2-type cell responses. Significant mucosal S-IgA Abs were seen in saliva of both macaques given nasal gp120 plus nCT. Significant levels of anti-gp120 IgG and IgA Ab responses were induced in plasma of monkeys given nasal gp120 and mCT E112K when compared with those which received nCT as mucosal adjuvant. Our results have revealed that nasal immunization with HIV gp120 with mCT E112K elicits Ag-specific Ab responses in both mucosal and systemic lymphoid tissues. Mutant CT exhibited only minimal expression of NGF-Beta 1 in olfactory tissues. These results offer the promise of development of a protective and safe mucosal adjuvant to be given with HIV components to potentially protect from AIDS.

BETA-CYCLODEXTRAN AS MUCOSAL MICROBICIDE TO PREVENT VAGINAL SIV TRANSMISSION (0265)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LU, FABIEN X	PHD	A	MED:PATH/MICRO/IMMUN	
Names 3	PHD	A		
	DVM, PHD	C	VM:PATH/MICRO/IMMUNO	

AXIS I CODES: 1A, 7D, 19, 23 **AXIS II CODES:**31, 64, 83, 93

ABSTRACT

To prevent heterosexually transmitted HIV, a mucosal anti-HIV microbicide is needed. B-cyclodextrin (BCD) is a cholesterol-sequestering agent that interferes with cell migration and budding of virus from lipid rafts. Mucosal application of BCD followed by vaginal cell-associated HIV-1 challenge in the mouse model is shown to block HIV transmission. BCD as a microbicide to block SIV vaginally transmission in the monkey model has never been tested. We thought the treatment with BCD will protect against repeated mucosal exposure of SIV and possibly result in mucosal and/or systemic immune responses. Female rhesus macaques were assigned in three groups: Group 1(7 animals) was intravaginally inoculated only SIV mac251. Group 2 (6 animals) was exposed vaginally with KY Long Lasting Vaginal Moisturizer and then SIVmac251. Group 3 (9 animals) was exposed vaginally with 5% BCD in KY Long Lasting Vaginal Moisturizer and then SIV mac251. Blood was collected weekly to monitor viral load and immune responses. IFN-gamma ELISPOT assay was performed on samples before and after the day of infection. PCR for various cytokines and flow cytometry analysis of activation markers in PBMC will be performed. Animals that were protected from challenge will be treated in the same manner and challenged again until they become infected. The preliminary results show animals were more susceptible to virus infection upon re-challenge. CD4+T cells counts and CD4:CD8 ratios are consistent with plasma viral load. SIV specific T cells proliferative responses are low or undetectable and are consistent with SIV infection.

DIFFERENTIAL THYMIC PATHOLOGY IN SHIV-INFECTED NEWBORN MACAQUES (0253)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LUCIW, PAUL A	PHD	C	MED:PATHOLOGY	
name 2	PHD	A	CENTER FOR COMPARATIVE MEDICIN	UC DAVIS, CA USA

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

ABSTRACT

Objective: The objective of this project is to establish a non-human primate model to study mechanisms of immune system dysfunction in pediatric AIDS. The mechanisms of thymus dysfunction in HIV-1 infected children are not well defined.

Results: Newborn rhesus macaques were infected with two chimeric simian-human immunodeficiency virus (SHIV) strains, which contain unique HIV-1 env genes and exhibit distinct phenotypes. Infection with either the CCR5-specific, SHIVSF162P3, or the CXCR4-utilizing, SHIVSF33A, resulted in clinical manifestations consistent with simian AIDS. Most prominent to this study was the detection of severe thymic involution in all SHIVSF33A-infected infants, which is very similar to HIV-1-induced thymic dysfunction in children who exhibit a rapid pattern of disease progression. In contrast, SHIVSF162P3 induced only a minor disruption in thymic morphology. Consistent with the distribution of the coreceptors CXCR4 and CCR5 within the thymus, the expression of SHIVSF162P3 was restricted to the thymic medulla, whereas SHIVSF33A was preferentially detected in the cortex. This dichotomy of tissue tropism is similar to the differential tropism of HIV-1 isolates observed in the reconstituted human thymus in SCID-hu mice.

Conslusions: Our results show that the SHIV/monkey model can be used for the molecular dissection of cell and tissue tropism controlled by the HIV-1 env gene and for the analysis of mechanisms of viral immunopathogenesis in AIDS. Furthermore, these findings could help explain the rapid progression of disease observed in some HIV-1-infected children.

LASER SCANNING CYTOMETRY FOR T CELL SUBSETS IN MACAQUES (2)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 0.213% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LUCIW, PAUL A	PHD	C	MED:PATHOLOGY	
E-MAIL	PHD	A	CENTER FOR COMPARATIVE MEDICIN	UC DAVIS, CA USA

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

ABSTRACT

Objective: This project evaluates laser scanning cytometry (LSC) to analyze both viral gene expression (measured by in situ hybridization) and changes in leukocyte populations (measured by cellular immunophenotype) in macaques infected with simian-human immunodeficiency virus (SHIV). Accordingly, this method will help define the cellular mechanism(s) that accounts for simian AIDS in newborns.

Results: We conducted experiments showing that the LSC can be utilized to perform simple immunophenotyping with a level of accuracy and reproducibility similar to data generated using flow cytometry. Although similar experiments have been described using the LSC, we improved upon this analytical platform by describing a unique substrate, LSC phenotyping slides, which facilitate sample preparation and enable increased consistency. These specialized slides are available from Grace BioLabs (Bend, OR) as ExpressLane cell Phenotyping System.

Conclusions: his analytical platform allows for the collection of important experimental and diagnostic information from minute sample volumes, which are typically available from biopsies or pediatric research. However, the complexity of the analysis using LSC remains limited to 2- to 4-color acquisition. Therefore, it is necessary to streamline the numbers of phenotypic markers required for sample characterization by LSC.

THYMOCYTE SUBSETS IN SHIV-INFECTED NEWBORN MACAQUES (0299)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LUCIW, PAUL A	PHD	C	MED:PATHOLOGY	
[illegible]	PHD	A	CENTER FOR COMPARATIVE MEDICIN	UC DAVIS, CA USA

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

ABSTRACT

Objective: The objective is to evaluate T-cell development in normal and in SHIV-infected macaque infants. These studies, based upon a model of human thymopoiesis, will be valuable for defining the mechanisms of immunopathogenesis in HIV-1 infected children with AIDS. This characterization utilizes cell surface phenotype to track the maturation of common lymphoid progenitors through the T-cell lineage. Emphasis has been placed on thymocyte populations, which may be susceptible to viral infection or insult.

Results: To establish labeling and flow cytometry conditions, thymocytes were isolated from a 42-day old rhesus macaque and stained for enumeration of specific T-cell phenotypes as follows: anti- CD1a-PE, CD3-Cy7PE, CD4-Alexa488, CD8a-Cy5PE, CD8-Cy5.5PE CD27- Alexa680APC, CD45RA-Cascade Blue, CD69-Cy7APC and CD195-APC. Data acquisition was preformed on a Cytomation MoFlo flow cytometer equipped with optics for 9-color analysis and analyzed using the FlowJo software package. The 9-color flow cytometry technology enabled us to measure a sufficient number of parameters from each cell (two scattered light and 9 fluorescence measurements) to resolve the underlying heterogenecities of developing thymocytes. In a preliminary comparison of thymocyte populations derived from SHIV-infected and non-infected infant macaques, we observed the most dramatic depletion of CD4SP (CD4+ CD8-) and DP (CD4+ CD8+) thymocytes. Importantly, a high percentage of these thymocyte subsets express the CXCR4 coreceptor rendering them susceptible to SHIV infection.

Conclusions: These results illustrate the ability of this approach, using 9-color flow cytometry, to study the complexities of thymopoiesis and to reveal phenotypically unique thymocytes subsets important to the pathogenesis of pediatric AIDS.

IMMUMNOASSAYS FOR DETECTION OF HERPES B VIRUS (0300)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 0.469% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LUCIW, PAUL A	PHD	C	MED:PATHOLOGY	
BARRY, PETER A	PHD	C	CTR FOR COMPARATIVE MED	UC DAVIS, CA USA
KLEIN, BARRY		A		

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

ABSTRACT

Objective: The objective is to develop immunoassays with (non-pathogenic) herpesvirus papio 2 (HVP-2) for serodiagnosis of macaques infected with the antigenically related herpesB virus. Such diagnostic systems are essential for screening and maintaining specific pathogen-free (SPF) macaques in the breeding colony.

Results: The protocol of [illegible] and coworkers (Oklahoma State University) has been used to screen animals in the re-derivation program developing macaques that are SPF for herpes B virus. This assay utilizes the strong immunological cross-relatedness of the baboon alpha-herpesvirus, HVP-2, to enable a rapid serodetection ELISA assay for evidence of antibodies against herpes B virus. The advantage of the assay is that it substitutes a non-pathogenic virus (i.e., HVP 2) as a source of antigen for the highly pathogenic (to humans) herpes B virus without sacrificing specificity or sensitivity. The assay has been optimized for a high throughput screening assay for both SPF and non-SPF monkeys obviating the need to send samples to extramural laboratories for diagnosis. A multiplex assay, using microbeads conjugated with HVP-2 antigens, has also been developed for rapid serodetection of herpes B virus as well as five other simian viruses.

Conclusions: The ELISA assay has been transferred to the Pathogen Detection Core at the California National Primate Research Center. The multiplex microbead assay is being validated and will also be transferred to this Core.

SIV VACCINES PROTECT INFANT RHESUS MACAQUES AGAINST ORAL SIV EXPOSURE (0163)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 1.574% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MARTHAS, MARTA L	PHD	C	VM:PATHO/MICROBIO L/IMMUNO	
	PHD	A		NIAID, MD USA
	MD	A		NCI, MD USA
	MD	C	MED:PATHOLOGY	
	MD, PHD	A		NIAID, MD USA
	PHD	A		AVENTIS-PASTEUR, TORONTO, CANADA
	DVM, PHD	A	PRIMATE CENTER	

AXIS I CODES: 1A, 7B, 17, 19, 22 AXIS II CODES:31, 64, 66, 71, 77, 91

ABSTRACT

Ideally, a childhood HIV vaccine aimed to prevent HIV transmission from breastfeeding would also protect against later sexual exposure to HIV in adolescence. To test HIV vaccine candidates, we developed an infant rhesus macaque model to better mimic repeated oral HIV exposure during breast-feeding. We recently showed that SIV vaccines protect infant macaques against infection by repeated oral SIV exposure. We now extend this rhesus macaque/multiple, low-dose oral SIV challenge model to evaluate the ability of neonatal vaccination to protect juvenile macaques against repeated oral SIV exposure. Two recombinant poxvirus-based vectors expressing SIV gag, pol and env were evaluated: modified vaccinia Ankara (MVA-SIV) and canarypox (ALVAC-SIV or ALVAC-vector), given at 0, 2 and 3 weeks of age. Two series of multiple, low dose oral SIV inoculations were performed. Infant macaques (4 weeks of age) were fed 3 daily low doses (10,000 TCID 50%) of virulent, uncloned SIVmac251 for 5 days. Fifteen vaccinated animals (7 MVA-SIV; 6 ALVAC-SIV, 2 ALVAC-vector) not infected after this first challenge series were re-challenged as juveniles/adolescents (1 to 4 years of age) weekly (2 doses of 2,000 TCID 50%); five unvaccinated juveniles were challenged as controls. After 20 weeks of oral SIV inoculations only 10 of 15 vaccinated juveniles compared to all unimmunized juveniles were SIV-infected. Kaplan Meier curves for vaccinated and control animals were significantly different (log-rank test: $p = 0.005$; median infection time: 8 weeks for immunized animals versus 1 week for controls); thus, infant vaccines gave durable protection. No immune correlates of protection were identified at the time of SIVmac251 challenge for infant or juvenile macaques. Results of these macaque studies suggest that poxvirus-based anti-HIV vaccines administered shortly after birth have potential to protect human infants against HIV breast milk transmission and oral-genital HIV exposure in adolescence.

IN VITRO AND IN VIVO FUNCTION OF HIV AND SIV NEF GENES (0313)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
LUCIW, PAUL A	PHD	C	MED:PATHOLOGY	

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

ABSTRACT

Human immunodeficiency virus types 1 and 2 (HIV-1 and HIV-2) and the simian immunodeficiency virus (SIV) encode a gene, designated nef (negative effector), that is dispensable for viral replication in vitro (i.e., in tissue culture cells). However, genetic analysis of SIVmac mutants in rhesus macaques has demonstrated that the nef gene is important for maintaining high virus load and for pathogenesis (Kestler et al. 1991). Although numerous studies have been directed at determining the function of the HIV and SIV nef gene in vitro, a critical gap remains in the knowledge of the role of this gene in viral replication and pathogenesis. The goal of this proposal is to elucidate the function of the nef gene both in vitro and in vivo (i.e., a non-human primate model). Recent investigations have revealed that HIV-1 and SIV Nef associates with cellular factors, one of which has protein kinase activity. Accordingly, an important objective within this proposal is to identify these cellular factors and thereby elucidate the mechanisms of HIV and SIV Nef in both human and simian cells. Because SIV is genetically related to HIV and because SIV infection of macaques produces a fatal AIDS-like disease, this highly manipulatable animal model will be utilized to test the in vivo significance of the in vitro studies on nef protein function. HYPOTHESIS The hypothesis is that cellular factors, including a protein kinase, associated with HIV/SIV Nef are critical for Nef function in viral persistence and pathogenesis. SPECIFIC AIM 1: Functional properties of Nef proteins from novel and unique HIV-1 and SIV isolates will be analyzed in vitro. SPECIFIC AIM 2: The mechanism of Nef will be elucidated in in vitro systems; emphasis is directed at characterizing the host cell kinase that associates with this viral protein. SPECIFIC AIM 3: SIVmac mutants in functional domains of Nef will be constructed, characterized in vitro, and analyzed in vivo (i.e., by infection of rhesus macaques) to relate the results of the biochemical analysis of Nef to viral persistence and pathogenesis. SPECIFIC AIM 4: SIV/HIV-1 chimeras (i.e., SHIV) will be constructed by substituting the SIV nef gene with an HIV-1 nef gene, and these chimeric viruses will be tested in rhesus macaques to directly address the function of HIV-1 Nef in vivo. SIGNIFICANCE; The proposed research integrates studies on the function of the nef genes of HIV-1 and SIV. Results of biochemical studies on Nef function of both viruses will be related to in vivo findings in SIV- and SHIV-infected rhesus macaques. A major emphasis of the proposed research is to identify cellular factors which mediate Nef function; accordingly, this knowledge may provide a basis for developing and testing novel anti-viral therapies aimed at inhibiting Nef function and thereby preventing disease progression.

POLIOVIRUS-SIV VACCINES IN PREGNANT AND INFANT MACAQUES (0297)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 0.485% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MARTHAS, MARTA L	PHD	C	VM:PATHOMICROBIOL/IMMUNO	
Names]	PHD	A		UC SAN FRANCISCO, CA USA
	PHD	A		UC SAN FRANCISCO, CA USA

AXIS I CODES: 1A, 7B, 17, 19, 22 **AXIS II CODES:**31, 64, 66, 71, 77, 91

ABSTRACT

The most important means of eliminating pediatric HIV infection is to prevent women from becoming HIV-infected before or during pregnancy. However, there is little information regarding the efficacy of vaccines to prevent vaginal HIV transmission in pregnant women or HIV transmission from mother to infant. The SIV/cynomolgus macaque model has been recently used to demonstrate that a vaccine consisting of live, recombinant Sabin polio virus vaccine expressing multiple SIV antigens is immunogenic and can elicit protection against vaginal challenge with pathogenic SIV. To evaluate the safety and immunogeneicity of an infectious polio-SIV vaccine in pregnancy and infants, we immunized pregnant female cynomolgus macaques and their newborns with two polio-SIV vaccines: infectious polio nucleic acid encoding SIV antigens (polio-SIV RNA) and recombinant polio virus whose genome encodes SIV antigens. Because changes that can affect vaccine-elicited immune responses occur during pregnancy, pregnant macaques must be used. In addition, maternal vaccine antigen-specific immunoglobulin that is transplacentally transferred to a fetus can modulate the infant's specific immune responses to later immunization with the same vaccine antigens. Preliminary results indicate that polio-SIV RNA elicits little if any polio-specific or SIV-specific immune responses in adult or newborn macaques. We are now immunizing adult and infant macaques with infectious recombinant Sabin-SIV virus and have found no adverse events. These preliminary studies suggest that Sabin polio vaccine-based anti-HIV vaccines may be safe to administer to women to prevent genital HIV transmission and to human infants to protect against HIV breast milk transmission.

MEASLES VACCINE DEVELOPMENT IN RHESUS MONKEY (0055)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 0.115% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MCCHESNEY, MICHAEL B	MD	C	MED:PATHOLOGY	
	PHD	A		CDC MEASLES BRANCH, GA USA
	BS	G	VIROLOGY AND IMMUNOLOGY	
	PHD	A	MED PATHOLOGY	
	PHD	A		CDC MEASLES BRANCH, GA USA

AXIS I CODES: 1A, 7B, 9, 19 **AXIS II CODES:**31, 64, 66, 77, 91

ABSTRACT

The live, attenuated measles vaccine is very effective although maternal antibody prevents it s administration prior to 6 months of age. We are investigating the ability of a DNA vaccine encoding the measles viral hemagglutinin, fusion and nucleoprotein to protect newborn infants from measles (disease). New work demonstrates that a measles DNA vaccine protects infant macaques from pathogenic measles virus challenge when the DNA vaccine is adjuvanted with a DNA plasmid expressing an IL-2/IgG heavy chain. We are currently testing the effect of BCG vaccination to augment the measles DNA vaccine. One dose of the measles DNA vaccine is sufficient to protect infants when challenged at 5 months of age. This vaccine strategy models a practical approach to vaccinating newborns in developing countries.

CONSTRUCTION AND PASSAGE OF AN INDIAN CLADE C SHIV (0198)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 0.171% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MCCHESNEY, MICHAEL B	MD	C	MED:PATHOLOGY	
[illegible]	PHD	C	MED:PATHOLOGY	

AXIS I CODES: 1A, 7B, 9, 19 **AXIS II CODES:**31, 58, 64, 66, 77, 83

ABSTRACT

Epidemic HIV infection is emergent in India and the prevalent viral strains are different from those in the U.S. By envelope gene sequence, the viruses in India are clade C types. The goal of this project is to develop a DNA vaccine specific for HIV in India. The SHIV construction strategy has been modified and improved from the one originally proposed, allowing direct cloning of a gp140 fragment of HIV-1 into an SIV env-deleted SIVmac239 genome with appropriate restriction enzymes. However, this strategy did not result in sufficient recombinant DNA to work with. Another multi-step cloning strategy with 4 separate ligations is in progress.

MAINTENANCE OF IMMUNOLOGIC MEMORY TO MEASLES VACCINE (0199)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 0.684%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MCCHESNEY, MICHAEL B	MD	C	MED:PATHOLOGY	
	PHD	A		CDC MEASLES BRANCH, GA USA
Name	BS	G	VIROLOGY AND IMMUNOLOGY	
	PHD	A		CDC MEASLES BRANCH, GA USA

AXIS I CODES: 1A, 7B, 9, 19 **AXIS II CODES:** 64, 66, 77, 91

ABSTRACT

The goal of this proposal is to establish an animal model of long-term immunologic memory to measles vaccine in the rhesus monkey. Measles virus is pathogenic in rhesus monkeys and the immune responses of infected monkeys are similar to those in humans. Vaccination of monkeys with live-attenuated measles vaccine protects them from systemic infection and disease after challenge with pathogenic measles virus. There are two aims and hypotheses for this proposal. 1. Memory B and T cells circulate in the blood and through body tissues differently than do naive cells, and patterns of lymphocyte circulation and retention in tissues are related to the initial route of immunization. 2. The levels of memory B and T cells that persist during long-term memory are determined by the amount of viral antigen produced during the primary immune response.

This year, timed vaccination studies in rhesus monkeys have been/will be completed with 28 experimental animals and 2 additional monkeys obtained from the colony that required medical cull.

SIV TARGET CELLS IN VAGINAL TRANSMISSION (0060)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 0.005% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MILLER, CHRISTOPHER J	DVM, PHD	C	VM:PATH/MICRO/IMMUNO	
	MD	A		UNIV OF MINNESOTA, MN USA
		A		
	MD	A		UNIVERSITY OF WISCOSNSIN/WNPRC, WI USA

AXIS I CODES: 1A, 7D, 19, 23 **AXIS II CODES:**31, 64, 83, 93

ABSTRACT

Understanding the earliest events in vaginal transmission of HIV is critical to the development of interventions to prevent the sexual transmission of HIV. The goal of this project is to identify the earliest target cells after vaginal SIV transmission and characterize the pathway that used by the virus and virus-infected cells to reach the systemic circulation and peripheral lymphoid tissues. We are also characterizing the nature of the SIV variants that are transmitted during vaginal SIV transmission. Further we will identify the initial innate and adaptive immune responses in the mucosal and systemic lymphoid tissues of the inoculated animals. Thus, we have intra-vaginally inoculated 13 female rhesus macaques with SIVmac251. The dose of SIVmac251 used has caused systemic infection in 24 of 25 intra-vaginally inoculated female rhesus monkeys. The animals were culled between 2 hours and 9 days post-challenge. We were able to detect SIV DNA in genital and lymphoid tissues in 7 of the 13 animals and vRNA in 13 of 13 monkeys. We are currently identifying the SIV-infected cells in the tissues and analyzing the adaptive immune responses and mRNA levels of a number of cytokines and chemokines and viral receptors.

PROTECTIVE MECHANISMS WITH ATTENUATED LENTIVIRAL VACCINES (0162)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MILLER, CHRISTOPHER J	DVM, PHD	C	VM:PATH/MICRO/IMMUNO	
C name 3	MD	C	MED:PATHOLOGY	

AXIS I CODES: 1A, 7D, 19, 23 **AXIS II CODES:**31, 64, 83, 93

ABSTRACT

HIV is a sexually transmitted disease and a vaccine capable of preventing sexual transmission of HIV should elicit mucosal immune
responses in the genital tract. The objectives of this study were to determine which immune responses confer protection from intravaginal challenge with SIVmac 239. We have published the results of the PBMC based analysis of immune responses and vRNA levels and immune responses in lymphoid tissue samples have now been analyzed and we are preparing a paper describing the results. In brief, vRNA levels in tissues reflect plasma vRNA levels at 6 months post-SIV challenge. The levels of interferon-gamma mRNA in lymphoid tissues was highest in vaccinated unprotected animals and lowest in vaccinated-protected animals.

In contrast, the number of interferon-gamma ELISPOT+ cells that were elicited by in-vitro SIV peptide stimulation was highest in vaccinated protected animals and lower in vaccinated unprotected animals. Thus interferon-gamma mRNA reflects virus-induced inflammation in lymph nodes and interferon-gamma ELISPOT + cells reflect the capacity of animals to generate SIV–specific
effector T cells. This is the first indication that the level of vaccine-induced inflammation could determine the outcome of
vaccination with a live-attenuated lentiviral vaccine. We have protected animals from vaginal SIV challenge using a proviral SHIV89.6
vaccine and have documented decreased efficacy of this vaccine approach compared to live attenuated virus vaccines. We are also testing the efficacy of a vaccine consisting of combination of DNA plasmids expressing some of the SIV genes and the HIV env gene.

IMMUNOLOGY CORE SERVICES (0286)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 0.950%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MILLER, CHRISTOPHER J	DVM, PHD	C	VM:PATH/MICRO/IMMUNO	
		A		UC DAVIS, CA USA
	PHD	C	MED:PSYCHIATRY	
	MD	A		UC DAVIS, CA USA
	PHD	C	CTR FOR COMPARATIVE MED	UC DAVIS, CA USA
	DVM	A		CINCINNATI ZOO, OH USA
	PHD	C	PSYCHOLOGY	
	PHD	A		GENENTECH, CA USA
	PHD	A		UNIVERSITY OF OKLAHOMA, OK USA
	PHD	A		JOHNS HOPKINS, CA USA
	PHD	A	MED:PATHOLOGY	
		C		
	PHD	A		MERCK, NJ USA
	PHD	A	MEDICAL PATHOLOGY	
	PHD	A		HARVARD UNIVERSITY, MA USA
	MD	A		UNIV OF MINNESOTA, MN USA
	PHD	A		UC SAN FRANCISCO, CA USA
	PHD	A	PATH., MICROBIO AND IMM.	UC DAVIS, CA USA
	PHD	A		UNIVERSITY OF MINNESOTA, MN USA
		A		
	DVM, MPVM	C	VM:PATHO/MICROBIOL/IMMUNO	
	PHD	C	MED:PATHOLOGY	
	PHD	C	VM:PATHO/MICROBIOL/IMMUNO	
	MD	C	MED:PATHOLOGY	
	PHD	A		LARGE SCALE BIOLOGY, CA USA
	MD, PHD	C	MED PEDIATRICS	
	PHD	A	MED:ORAL BIO/MICRO/IMMUN	UNIV OF ALABAMA AT BIRMINHAM MED CTR, AL USA
	PHD	A	VM ANAT/PHYSI&CELL B	
	PHD	A		CDC, GA USA
	PHD	C	VM ANAT/PHYSI&CELL B	
	MD	A		UC DAVIS, CA USA

	PHD	A	CENTER FOR COMPARATIVE MEDICIN	UC DAVIS, CA USA
	PHD	A		UNIVERSITY OF PITTSBURGH, PA US
	PHD	A	MED PATHOLOGY	
	PHD	A		GENENTECH, CA USA
	MD	A	OMS	NIH, MD USA
	PHD	A		HARVARD UNIVERSITY, NJ USA
	MD	A		UC IRVINE, CA USA
		C		
	PHD	A		SOUTHWESTERN MED CTR, TX USA
	DVM, PHD	A	ASSOCIATE ADJUNCT PROFESSOR	SCHOOL OF VETERINARY MEDICINE, UC DAVIS, CA USA
	DVM	A		CNPRC PATHOLGY SERVICE, CA USA
	PHD	A		UC SAN FRANCISCO, CA USA
	DVM, PHD	A	PRIMATE CENTER	
		A		
	MD	A		UNIVERSITY OF WISCOSNSIN/WNPRC, WI USA
	PHD	A	INTERNAL MED	UCD, CA USA
	DVM, PHD	A	VM INTERNATL LAB MOL	
	MD	A		LOS ANGELES CHILDREN'S HOSPITAL, CA USA

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

ABSTRACT

The Immunology Service Core is designed to provide 1) standardized measures of immune response in macaques, 2) advice to outside investigators on experimental design of primate immunology studies, 3) development of new technology for assessing immune responses in this animal model, 4) information on techniques and reagents that are useful for primate immunology, and 5) training of personnel in the use of immunology assays for work with macaques. Because of the large volume of AIDS-related research done by both staff and non-staff scientists at the CNPRC, the emphasis of this core was on antiviral immunity. In addition, assays to nominal test antigens were available for other infectious and non-infectious research at the CNPRC. The Core, which began operation in August 2000, has two services or work areas corresponding to humoral immunity (requires BSL-2 only for initial sample processing) and cellular immunity (requires BSL-2 containment throughout the time of assay). Humoral immune assays include the detection of antibodies to viral antigens by ELISA. In addition, antibody levels to the nominal antigens, tetanus toxoid, cholera toxin and keyhole limpet hemocyanin are measured by ELISA. Cellular assays include the detection of antiviral cytotoxic T lymphocytes (CTL) or natural killer cells (NK) and lymphocyte proliferation to viral and nominal antigens. A mixed lymphocyte reaction is available for genetics and transplantation. Cytokine/chemokine-secreting cells are assayed by ELISPOT and cytokine/chemokine mRNA transcript levels by real-time PCR.

Services Offered

The services offered by the Immunology Core are summarized as follows:

* Sample Processing
* Total IgG, IgA ELISA assays
* Ag Specific IgG, IgA ELISA assays
* Total IgG, IgA ELISPOT assays
* Ag Specific IgG, IgA ELISPOT assays
* Cytotoxic T Lymphocyte assay

* T-cell Proliferation assay
* Ag Specific IFN-g ELISPOT
* B Cell Transformation
* Mixed Lymphocyte Reaction
* SIV gag PCR
* Nucleic acid extraction
* Natural Killer Cell assay
* Real-time PCR to quantify cytokine/chemokine mRNA

All of the investigators listed have used Immunology Core Services for 2003-2004.

HIV VACCINES BASED WITH BOOST WITH WHOLE KILLED VIRUS AND ADENOVIRUS VECTORS (0328)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 1.194% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MILLER, CHRISTOPHER J	DVM, PHD	C	VM:PATH/MICRO/IMMUNO	
CRAWFORD	PHD	A	MED:PATH/MICRO/IMMUN	

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

ABSTRACT

No abstract available.

ANTI-IFNA ANTIBODY ON VIRUS REPLICATION IN CHRONIC CMV & SIV CO-INFECTED RHESUS (0329)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 0.274% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MILLER, CHRISTOPHER J	DVM, PHD	C	VM:PATH/MICRO /IMMUNO	
	PHD	A		UC DAVIS, CA USA
Named	PHD	C	CTR FOR COMPARATIVE MED	UC DAVIS, CA USA

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

ABSTRACT

No abstract available.

PROTECTION AGAINST A CONTAGIOUS RESPIRATORY PATHOGEN WITH OLIGONUCLEOTIDE CPG (0330)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 0.191% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MILLER, CHRISTOPHER J	DVM, PHD	C	VM:PATH/MICRO/IMMUNO	
	PHD	A		UC DAVIS, CA USA
Names	MD	C	MED:PATHOLOGY	

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

ABSTRACT

No abstract available.

HIV-1 VACCINES DESIGNED TO INDUCE MUCOSAL IMMUNITY (0334)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 6.975% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MILLER, CHRISTOPHER J	DVM, PHD	C	VM:PATH/MICRO/IMMUNO	

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

ABSTRACT

The goal of this Program will be to develop an HIV-1 vaccine that is targeted to mucosal surfaces. There are 4 central scientific aims. First, to determine whether delivery of DNA or Sindbis replicon candidate vaccines (vSIN) by mucosal routes is safe and immunogenic. Second, to determine the most appropriate mucosal or systemic routes needed to generate T and B cell responses in the vagina and rectum. Third, to study the inductive phase of vaccination across mucosal surfaces, with special emphasis on antigen presentation and T cell trafficking. And lastly, to improve the methods and assays used to measure mucosally derived or mucosally directed T cell responses. The investigations will focus on the systematic evaluation of optimized PLG-DNA and vSIN vaccines, both of which can be used to produce millions of clinical doses. The constructs will first be studied in the murine model to determine gene expression and relative immunogenicity. The murine system will also be used to evaluate the infection of dendritic and presenting cells at mucosal surfaces, and the trafficking of effector B and T cells after mucosal immunization. Macaque challenge studies will be used to determine the optimum route and sequencing of mucosal vaccination for induction of immune responses in the vagina and rectum. A macaque study also will be designed to determine the relative immunogenicity of HIV vaccine constructs in the macaque, as compared to immunogenicity in humans. The 4 clinical studies in Project 3 and 4 are designed to assess safety and immunogenicity of mucosal vaccination, and to allow for development of techniques that will assess human T cell immunity at mucosal surfaces. The routes, constructs to be used, and design of these clinical trials will be dependent on the results of the studies conducted by Projects 1 and 2. Two essential cores will support all of these Projects. The Vaccine Technology Core will be located at the [redacted] which will supply the necessary constructs, vaccine technology expertise, reagents, and manufacturing capability. An Administrative Core will be responsible for the coordination, communication, and financial management of the Program.

private source

EFFECT OF MICROBICIDES ON MUCOSAL HIV TRANSMISSION (0335)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 3.422% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MILLER, CHRISTOPHER J	DVM, PHD	C	VM:PATH/MICRO/IMMUNO	

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

ABSTRACT

UNAIDS estimates that there are 35-40 million people infected with HIV. Heterosexual transmission of HIV continues to spread this epidemic to an estimated 3-4 million people a year. Development of acceptable female controlled strategies, including microbicides, is a high priority for national and international agencies. The SIV/rhesus macaque vaginal transmission model has been used to test anti-HIV microbicides. We propose to refine the model by developing a multiple low-dose SIV inoculation that more closely mimics the biology of HIV transmission than the current high-dose model. We hypothesize that both the number of target cells infected (dose) and genetic complexity of the viral population that infects those cells, determine the outcome of vaginal SIV exposure. We will determine the mechanism of action for select microbicides, using the high dose IVAG challenge model to rigorously test the ability of a compound to prevent IVAG SIV transmission and acquisition of systemic infection. Once developed, we will use the multiple, low-dose SIV vaginal challenge model to: 1) determine if a microbicide that prevents infection in the high-dose model, allows acquisition of local occult infection with the potential for progression to systemic infection; 2) assess the effect of chronic microbicide use on vaginal pH, bacterial flora, cervicovaginal inflammation and SIV/HIV target cell populations; and 3) define the effect of chronic microbicide use and repeated SIV exposure on genital tract innate and adaptive immunity. It is expected that these studies will allow us to determine the mechanism of action of microbicides in-vivo and test our hypothesis regarding the role of dose and viral population complexity in vaginal SIV transmission. Further, these studies will determine if individuals that consistently and correctly use of microbicides in the face of repeated viral exposure develop anti-viral immune responses or local infection.

RT-SHIV MODEL FOR RESISTANCE TO AIDS THERAPY (0267)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
NORTH, THOMAS W	PHD	A	CTR FOR COMPARAT MED	
[illegible]	DVM, PHD	A	VM MED&EPIDEMIOLOGY	
[illegible]	DVM, PHD	A	PRIMATE CENTER	

AXIS I CODES: 1A, 2, 7B **AXIS II CODES:**31, 50, 77

ABSTRACT

Highly active antiretroviral therapy (HAART) has been a major advance in treatment of AIDS in humans. HAART provides long term suppression of HIV-1 loads to undetectable levels in many patients. Nevertheless, HIV-1 remains in a latent or persistent form in these patients and can reemerge when drug therapy is discontinued. Another major barrier to HAART or other therapeutic approaches is the emergence of drug-resistant and multi-drug resistant variants of HIV-1. A major goal of this project is to establish HAART-like therapy in an animal model. Our goal is not to provide a drug testing system but rather to further develop the animal model system to the point where it can be useful for studies of AIDS therapy that are difficult or impossible to do in humans infected by HIV-1. In particular, we wish to study sites of low-level virus replication and latency/persistence during HAART. For this reason, we will use a chimera of simian immunodeficiency virus (SIV) containing the HIV-1 reverse transcriptase (RT-SHIV), which will enable in vitro and in vivo studies of combinations containing nucleoside analogs and non-nucleoside inhibitors of reverse transcriptase (NNRTI). We will also use this model for studies of drug combinations that include protease inhibitors. Long-term goals are (to) utilize the model to probe sites of virus replication and/or persistence in prolonged HAART, and to evaluate other intervention approaches in attempts to eradicate virus from reservoirs.

MODEL OF COCCIDIOIDOMYCOSIS IN MACACA FASCICULARIS (0251)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 0.114%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
PAPPAGIANIS, DEMOSTHENES	PHD	A	MED:MICROB & IMMUN	UC DAVIS, CA USA
	PHD	G		UC SAN FRANCISCO, CA USA
	DVM, MPVM	C	VM:PATH/MICROBIOL/IMMUNO	

AXIS I CODES: 1A, 7D, 24 **AXIS II CODES:**66, 77, 91

ABSTRACT

Approximately 100,000 human cases of primary coccidioidal infections occur each year in endemic areas of the United States, with 4-5,000 cases of disseminated disease. The U.S. population at risk is estimated at 30 million. Clinical manifestations of Coccidioides immitis infection range from asymptomatic or benign pulmonary infection to progressive pulmonary or systemic extrapulmonary disease involving bone, joints, CNS, and other organ systems. There is an increased incidence of morbidity and mortality in immunocompromised persons. The intent of this study was to develop a primate model of coccidioidomycosis to evaluate the efficacy and safety of experimental vaccines for human disease prevention. Cynomolgus macaques inoculated intratracheally with infectious arthrospores developed a spectrum of clinical and histological disease similar to that seen in humans. Ten animals immunized prior to challenge with a prototype vaccine preparation previously used in primates, were not protected. Immune parameters monitored during the course of infection and recovery provided insights into host immune response, and identified potentially useful correlates immunity for use in evaluating novel experimental vaccine constructs in future studies. The cynomolgus macaque provides a useful experimental model system for evaluating the safety and efficacy of candidate vaccines.

NORTH-CENTRAL CALIFORNIA-CENTER FOR AIDS RESEARCH (0322)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 2.100% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
POLLARD, RICHARD B.	A		UC DAVIS, CA USA

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

ABSTRACT

Two geographically and scientifically linked institutions in North-Central California will establish a Developmental Center for AIDS Research (D-CFAR) that will benefit all of the investigators and clinicians at the respective institutions, as well as the patients living inside and outside that region. This D-CFAR will put into place the appropriate infrastructure and leadership needed to successfully compete for funding as a full CFAR in a 3-year time frame. This North-Central California Developmental CFAR (NCCFAR) will capitalize on the complementary strengths of the institutions, UC Davis and the Virology and Rickettsial Diagnostic Laboratory of the California Department of Health Services (VRDL/CDHS), and fill the gaps needed to develop a full CFAR. At that time a third administratively linked institution, UC Berkeley, will be added to the overall Center. The overall aims of the NCCFAR will be to concentrate efforts during the first years of funding in three specific emphasis areas. The first will be to study prevention strategies along with investigations aimed at developing an effective HIV-1 vaccine. The second will be to gain a better understanding of disease pathogenesis using investigations that span the basic, preclinical and clinical arenas. The third will be to translate knowledge gained from the basic science and preclinical components of the program into developing potential new treatment or prevention modalities. All three of the aims will be carried out in the context of improving the preventative and patient care delivered to local populations. The NCCFAR will be developed using five cores that emphasize the strengths of the relative institutions. The NCCFAR will be organized and led by the Administrative Core at UC Davis. Pilot projects and support for new investigators and science will be funded through a Developmental Core. A basic science Primate Core will be based at the California Regional Primate Facility at UC Davis. A Virology and Immunology Core, located at the VRDL/CDHS, will focus on supplying the basic and clinical virology and immunology infrastructure that will benefit individual investigators, as well as allow for the conduct of complex clinical trials. Lastly, a Clinical Core will be established to conduct clinical trials, perform translational research and supply patient-based samples.

DETERMINANTS OF H PYLORI INFECTION IN RHESUS MONKEY (0227)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
SOLNICK, JAY V	MD, PHD	A	MED:INTERNAL MED	
	PHD	A	MED:PATHOLOGY	
[illegible]	PHD	A	VM:ANAT/PHYSIO & BELL BIO	UCD SCHOOL OF VETERINARY MEDICINE, CA USA
[illegible]	MD	C	MED:PATHOLOGY	

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

ABSTRACT

In vitro studies suggest that H. pylori induces apoptosis in gastric epithelial cells and perhaps in gastric lymphocytes as well. However, the early effects of H. pylori infection on lymphocyte apoptosis have not been examined in experimental animal models, nor have studies been performed using markers specific for T cells and T cell subsets. Gastric T cell apoptosis and Fas ligand expression were examined by flow cytometry after experimental infection of rhesus macaques with H. pylori. Infection induced transient apoptosis of gastric CD4+ and CD8+ T cells, which began as soon as three days after inoculation and declined to baseline within eight weeks. Fas ligand expression showed a similar transient induction, suggesting that it mediates gastric T cell apoptosis. We propose that transient, Fas-mediated apoptosis in gastric lymphocytes is a compensatory response to the initial T cell inflammatory response after acute H. pylori infection.

HIGHLY ATTENUATED SIV VIF DNA VACCINES (0262)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
SPARGER, ELLEN	DVM, PHD	A	ASSOCIATE ADJUNCT PROFESSOR	SCHOOL OF VETERINARY MEDICINE, UC DAVIS, CA USA
[name]	PHD	C	MED:PATHOLOGY	

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

ABSTRACT

Studies in non-human primates with simian immunodeficiency virus (SIV) have demonstrated that live-attenuated viruses are highly effective; however, such vaccines maintain a low level of pathogenicity. The objective of this study was to test the immunogenicity of a SIVdeltavif proviral DNA vaccine administered by the IM and ID routes in rhesus macaques and to test for vaccine efficacy by challenge with pathogenic SIVmac251. Rhesus macaques were inoculated with plasmid DNA containing SIVdeltavif proviral DNA (vif deletion) by intramuscular and intradermal routes. Primary immunization with SIVdeltavif was followed by booster inoculations six weeks and five months later. Vaccinated and unvaccinated macaques were challenged with pathogenic SIVmac251 intravaginally six months post-primary SIVdeltavif vaccination. Inoculation of SIVdeltavif proviral DNA did not produce an infection detectable by presence of viral RNA in plasma or induction of anti-SIV Gag antibody although emergence of SIV Env antibody was observed. CD4 and CD8 T-cell responses to SIV were evident by 2 weeks post-inoculation. Virus-specific CD4 responses increased over the 24 week period following primary and booster proviral DNA inoculations. Virus-specific CD8 responses peaked immediately after either primary or initial booster immunizations. Vaccinated animals did not resist infection by challenge with SIVmac251; ongoing analysis of virus load data will determine if vaccination suppressed challenge virus load. Evidence of increasing SIV-specific CD4 responses prior to final boost suggested persistent SIVdeltavif replication at very low levels in vivo. These results substantiated the immunogenicity and attenuation of SIVdeltavif DNA inoculation and set the stage for evaluation of a SIVdeltavif DNA vaccine utilizing cytokine adjuvants. Large scale preparation of SIVdeltavif DNA has been completed and assayed for a second SIVdeltavif DNA vaccine study testing rhesus IL-15 (expression plasmid recently provided by collaborator [ ] Emory University) as an adjuvant for SIVdeltavif DNA and to be initiated within the next three months.

name

TOPICAL VIRUCIDES TO PREVENT ORAL TRANSMISSION (0288)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
VAN-ROMPAY, KOEN K A	DVM, PHD	A	PRIMATE CENTER	
Name ?	PHD	C	VM:PATHO /MICROBIO L/IMMUNO	

AXIS I CODES: 1A, 2, 7B **AXIS II CODES:**31, 50A, 50B, 64, 66

ABSTRACT

OBJECTIVE: To find better and affordable strategies to prevent mother-to-infant HIV transmission during breast-feeding.

RESULTS: We have previously developed an infant macaque model for breast-milk transmission. Infant macaques are exposed repeatedly to low doses of simian immunodeficiency virus (SIV) by the oral route. This model is currently being used to evaluate the efficacy of tenofovir in doses that work either as topical virucide or that give systemic drug levels. The study is currently ongoing.

SAFER AND MORE EFFICACIOUS RECOMBINANT AIDS VACCINES (0303)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
YILMA, TILAHUN D	DVM, PHD	A	VM INTERNATL LAB MOL	
[illegible]	PHD	A	VM INTERNATL LAB MOL	
[illegible]	PHD	A	VM: INTERNATL LAB MOL	CD DAVIS, CA USA

AXIS I CODES: 1A, 1D, 7D, 17, 19 **AXIS II CODES:**31, 39, 64, 66, 83, 91

ABSTRACT

OBJECTIVE: To enhance both the safety and efficacy of rVVs for SIV by developing a vector with insertional inactivation of the TK and B8R genes and expressing high levels of SIV antigens along with macaque IFN gamma. This vaccine will be tested in rhesus macaques for safety and efficacy against vaginal challenge with virulent SIV.

Our long-term goal is to develop a safe and efficacious vaccine for human immunodeficiency virus using the simian immunodeficiency virus (SIV) infection of rhesus macaques as a model. In our parent grant, we hypothesized that vaccinia virus (VV) recombinants expressing SIV antigens and interferon gamma (IFN gamma) are safe and effective, eliciting protective immune responses against SIV. Since then, we have found that deletion of the VV IFN gamma receptor homolog (B8R) gene enhances VV vector safety without reduction in immunogenicity. Second, we developed a new-generation recombinant VV (rVV) vaccine for rinderpest (v2RVFH) that expresses genes of rinderpest virus under strong synthetic VV promoters. v2RVFH expresses high levels of the glycoproteins and provides cattle with long-term sterilizing immunity. Additionally, we have successfully vaccinated macaques orally with an rVV expressing human IFN gamma, even though the cytokine greatly attenuates the vector. We are developing a new rVV vaccine for SIV that has a number of advantages: 1) levels of expression of SIV antigens will be enhanced with the use of strong synthetic promoters; 2) the pol gene will be expressed in addition to gag, env, and nef; 3) the macaque IFN gamma gene will be used in place of the human IFN gamma gene; and 4) the VV thymidine kinase (a neurovirulence factor) and B8R genes will be insertionally inactivated to increase safety. As an added bonus, the B8R protein will not be able to inactivate the expressed IFN gamma. Our hypothesis is that oral immunization with rVVs having enhanced safety and efficacy will elicit a protective immune response against mucosal challenge with pathogenic virus. The goals of this R21 application are to develop the new rVV vector and, in conjunction with ongoing experiments supported by the parent grant, assess its safety and efficacy in macaques immunized orally with the rVV and challenged mucosally with SIV.

RESULTS: We are currently constructing the vaccine. We hope to start vaccination of rhesus macaques in the next six months.

SAFER AND MORE EFFICACIOUS SMALLPOX VACCINES (0304)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 0.737% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
YILMA, TILAHUN D	DVM, PHD	A	VM INTERNATL LAB MOL	
[redacted]	PHD	A	VM INTERNATL LAB MOL	
[redacted]	PHD	A	VM: INTERNATL LAB MOL	CD DAVIS, CA USA

AXIS I CODES: 1A, 1D, 7D, 17, 19 **AXIS II CODES:** 31, 39, 64, 66, 83, 91

ABSTRACT

OBJECTIVE: To construct a new-generation smallpox vaccine with deletions in two virulence genes and expressing IFN gamma. This vaccine will be compared with the parental smallpox vaccine (Dryvax) in normal rhesus macaques for induction of humoral and cell-mediated immune responses. Safety will be evaluated in SIV-infected rhesus macaques vaccinated with the recombinant vaccine or with parental Dryvax.

One of the most feared bioterrorist agents is variola virus, the causative agent of smallpox. Various strains of vaccinia virus (VV) are highly effective in preventing this disease, but have definite rates of complications. Severe illness or death is rare in people with normal immune responses, but considerably more common in individuals with cell-mediated immune defects. The number of individuals that are at risk from this normally innocuous vaccine has greatly increased with the spread of the human immunodeficiency virus (HIV), and it now becomes important to improve the efficacy and safety of this vaccine. We have worked extensively with VV as a recombinant vaccine for a number of diseases. We have also developed strategies for attenuating VV while enhancing efficacy, with one of the most effective being the incorporation of the interferon gamma (IFN gamma) gene. We have shown that expression of IFN gamma leads to an immune response essential against viral infection with no deleterious effects. We have also studied the effects of inactivating VV immunomodulating genes such as B8R, B13R, and B22R that are virulence factors in VV. Our objective is to develop a safer and more efficacious vaccine for smallpox based on the New York City Board of Health strain of VV that is currently used in the US. The B8R gene will be deleted and the TK virulence gene will be insertionally inactivated with the human IFN gamma gene to increase attenuation of the virus and the protective cell-mediated immune responses. This recombinant VV will be compared to the parental vaccine in both normal and simian immunodeficiency virus-infected macaques (used as a model for HIV-infected humans) to assess efficacy and safety for normal and immunodeficient individuals.

RESULTS: We are currently constructing the vaccine. We hope to start vaccination of rhesus macaques in the next year.

PILOT SUBPROJECTS

HEIRARCHICAL PROCESSING IN THE MOTION SYSTEM (0272)

NPRC UNIT: PILOT STUDY

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BRITTEN, KENNETH H	PHD	A	NEUR/PHYSI&BIO	

AXIS I CODES: 1A, 21 **AXIS II CODES:**36, 41, 68

ABSTRACT

The broad goals of the research program in this laboratory are twofold: understanding the mechanisms of information processing in visual cortex, and connecting the information there with visual perceptual capabilities. The "motion system" of dorsal extrastriate cortex is a good model system for this purpose, because a wealth of data documents its anatomy, physiology, and utility in visual-motion-related behavior. Furthermore, it appears that this system exists in humans as well, from recent imaging work. Therefore, the insights we gain will probably directly further our understanding of human cortical information processing and its disorders. While we know much about the system, the basic processes by which motion information is processed and used remain mysterious. Specifically, we know that cortical areas MT and MST are connected in a serial arrangement, and that both are necessary for normal motion perception. The physiology of these areas suggests a dramatic transformation occurs between the two areas--MST represents much more complex motions than does MT. Work in this laboratory will employ two approaches to further elucidate the mechanisms and consequences of this hierarchy. First, we will employ dual electrode recording to measure the operation of circuit connections and test computational models of the way motion information is transformed. Two specific questions are under study. First, we know that multiple stimuli interact in MT in a mutually divisive manner, and we seek to establish the mechanism for this. Also, we are investigating the manner by which complex RFs in MST are assembled from the simpler ones in MT. Secondly, by recording neuronal activity in awake, behaving monkeys which are performing a complex motion task--discrimination of "heading" based on visual cues--we can infer how the signals in MST and MT are being used in the performance of the task. While we know that activity there is used in performance of the task, what we do not understand is how it is being used. To help with that question, quantitative measurements of neuronal sensitivity to heading stimuli, and of correlation with behavioral choice, will be made. These have in the past proven to be powerful tools for relating neuronal activity to perception.

P450 MEDIATED LUNG TOXICITY (0273)

NPRC UNIT: PILOT STUDY

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BUCKPITT, ALAN R	PHD	A	VM MOLE BIOSCIENCES	

AXIS I CODES: 1A, 24 **AXIS II CODES:**54A, 64, 74, 77

ABSTRACT

Studies in rodents have demonstrated the importance of cytochrome P450 monooxygenases in generating reactive metabolites which produce Clara cell injury. Pulmonary P450 activities in primates are much lower than those in rodents raising the issue of human relevance of rodent data. Few studies on P450 catalyzed activation of cytotoxicants in subcompartments of primate lung have been reported. Accordingly, airway subcompartments of monkeys exposed to filtered air or to allergen/ozone, conditions resulting in asthma, were incubated with naphthalene or 1-nitronaphthalene to define metabolism of these substrates. In control animals, the rates of formation of water soluble metabolites from naphthalene or 1-nitronaphthalene were approximately 100 times less than those observed previously in rodents. Dihydrodiol was the predominant water soluble metabolite of naphthalene generated at all airways levels while covalently bound metabolites accounted for the greatest percentage of 1-nitronaphthalene metabolites. While prior exposures of animals to HDMA, O3 or a combination had no effect on protein covalent binding of naphthalene metabolites, significantly more reactive 1-nitronaphthalene metabolites were generated in trachea, proximal, and medial airways of exposed monkeys. Reduced glutathione levels were not altered in airway levels of exposed animals. We conclude that: 1there are significant quantitative differences between Rhesus and rodents in substrate turnover, 2 the distribution of metabolizing activities for naphthalene but not 1-nitronaphthalene are significantly different for rodents and primates, and 3 prior exposure to allergen or O3 markedly enhances reactive metabolite formation from 1-nitronaphthalene but not naphthalene.

RESPIRATORY SYNCYTIAL VIRUS, RHESUS MACAQUE (0311)

NPRC UNIT: PILOT STUDY

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
GERSHWIN, LAUREL J	DVM, PHD	C	VM PATH/MICRO	
cmarez		G		

AXIS I CODES: 1A, 1D, 24 **AXIS II CODES:**64, 66, 71

ABSTRACT

Respiratory syncytial virus (RSV) is a major cause of lower respiratory tract disease in infants and young children throughout the world. It is a disease for which there is currently no available vaccine. Moreover, there is no single animal model that adequately reproduces all aspects of the human disease. This project was focused on developing a primate model of RSV, which would show symptomatic respiratory disease, by infecting infant Rhesus macaques with astrain of human RSV. We infected six infant rhesus macaques with an isolate of human RSV using aerosol exposure. The ages of the monkeys at infection varied from 1.5 to 5.5 months. All 6 animals infected with human RSV showed clinical symptoms of disease, including increased respiratory rates, fever, and adventitious lung sounds. Viral replication in the lung was documented. The virus was successfully re-isolated and grown in vitro. Serological changes in RSV-specific IgG were observed in two animals two weeks post-infection, but were not detected in animals on day 7 after infection. Histopathological findings in the lung revealed hyperplasia of the BALT in the conducting airways and areas of interstitial pneumonia with infiltration of lymphocytes within the alveolar spaces. These data are consistent with the disease observed in human infants following natural infection. The model will beuseful to address immunological aspects of vaccination against RSV and the potential RSV has for augmentation of theallergic asthmatic response.

This model has been used to test the ability of a cDNA vaccine containing the nucleoprotein gene and the fusion protein gene of bovine RSV to protect infant macaques from experimental infection. Control monkeys received plasmid containing green fluorescent protein. Monkeys were immunized at 1.5 and 2.5 months of age. Eight weeks post-inoculation vaccinees and controls were challenged with human RSV using the protocol previously developed (paragraph above). Viral titers were determined in the lung. Pulmonary histopathology was assessed. Cell mediated and humoral immune responses were measured. RSV specific IgG was induced and remained elevated for 4 months. Cellular responses were greater in vaccinated infants and this correlated to levels of RSV in the lung.

DEVELOPMENT OF A STANDARDIZED PANEL OF MARKERS FOR GENETIC MANAGEMENT (0289)

NPRC UNIT: PILOT STUDY

%NPRC $: 0.068% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
KANTHASWAMY, SREE	PHD	C	CNPRC AND VETERINARY GENETICS	
Name →		A		
		A	ANTHROPOLOGY	UC DAVIS, CA USA

AXIS I CODES: 3 **AXIS II CODES:** 31, 58, 59

ABSTRACT

For an integrated genetic management of NIH-sponsored rhesus macaque colonies, a standardized set of genetic markers for parentage testing and estimating population genetic parameters at all colonies is prerequisite. Our project aims to compile a standardized markerset from existing collections of well-characterized rhesus STR markers currently being used in parentage assessments at the Southwest National Primate Research Center, San Antonio, TX; the Comparative Neurogenomics Laboratory at Bioqual in Rockville, MD and the Molecular Anthropology Laboratory and the Veterinary Genetics Laboratory at UC Davis. Criteria for standard panel of markers entail genetic and technical characteristics. An ideal panel of such markers must satisfy specific criteria to provide for optimal standardized genetic management in addition to parentage identification or confirmation.

INFECTIOUS BASIS FOR ALLOGRAFT REJECTION (0215)

NPRC UNIT: PILOT STUDY

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
PEREZ, RICHARD V	MD	A	MED:SURGERY	UCD MED CENTER, CA USA
	PHD	C	CTR FOR COMPARATIVE MED	UC DAVIS, CA USA
	MD	A	MED: SURGERY	UCD MED CENTER, CA USA
	MD	C	MED:PATHOLOGY	
	PHD	C	MED:PEDIATRICS	

AXIS I CODES: 1A, 13 **AXIS II CODES:**64, 77, 88

ABSTRACT

OBJECTIVE: Occult systemic inflammation, as manifested by increased levels of C-reactive protein (CRP), identifies patients who are at increased risk for renal allograft rejection. The mechanisms linking occult systemic inflammation to these adverse outcomes remain unclear. The objective of this study was to examine the anatomic and physiologic effects of occult pre-transplant systemic inflammation on post-transplant allograft outcome in a nonhuman primate model.

RESULTS: Healthy animals were stratified into quartiles based on serum CRP levels. Five high quartile and six low quartile animals underwent common iliac artery transplantation from male donors. Duplex ultrasound measured graft flow at three weeks post-operatively; luminal narrowing was assessed by graft/femoral peak systolic velocity (PSV) ratio. At six weeks, the grafts were harvested and morphometry studies done. Vessel wall changes were assessed by measuring the intimal medial area. The allografts placed in the high CRP quartile animals had more luminal narrowing by three weeks than those placed in low quartile animals as evidenced by a higher mean graft/femoral PSV ratio. Morphometry studies after graft harvest showed increased vessel wall area in the high quartile group versus the low quartile group. These studies indicate that occult pre-transplant systemic inflammation is associated with increased intimal thickening and stenosis after arterial allograft transplantation in a nonhuman primate model.

GENE EXPRESSION PROFILING OF RHESUS STEM CELLS (0238)

NPRC UNIT: REPROD & GENETIC SCIENCES

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
HACIA, JOSEPH G	PHD	A	BIOCHEM AND MOL BIO	UNIVERISITY OF SOUTHERN CALIFORNIA, CA USA
		A		
	PHD	G	PRIMATE CENTER	
	PHD	C	MED:PEDIATRICS	

AXIS I CODES: 1D, 17 **AXIS II CODES:**59, 62, 71, 92(STEM CELLS)

ABSTRACT

OBJECTIVE: DNA microarray technology provides a sensitive means to measure the intracellular abundance of several thousand different transcripts simultaneously. One powerful application of this technology involves uncovering groups of mRNA transcripts whose relative abundance can be used to identify new classes of cancer (class discovery) as well as assigning cancers to known classes (class prediction). For example, several previously unknown subtypes of diffuse large B-cell lymphoma were uncovered by comparing gene expression profiles of cancer cells from patients with variable responses to chemotherapy. This was not possible using morphological or cytogenetic data alone. The overall goal of these studies is to evaluate gene expression profile analysis of rhesus stem cell populations (hematopoietic and mesenchymal) using similar techniques.

RESULTS: Using oligonucleotide microarray-based gene expression analysis, rhesus mesenchymal stem cells were studied. The Affymetrix U133A oligonucleotide microarrays designed to measure the relative abundance of over 15,000 of the best-characterized human transcripts were used in this analysis. While mismatches between the rhesus macaque RNA samples and the oligonucleotide probes in the Human Genome U133A microarray will cause an overall lowering of hybridization signals, this decrease is consistent among all samples allowing meaningful comparisons between specimens. We found that a total of 38 genes were differentially expressed among cells derived from different aged individuals. Several different clustering algorithms are currently being used to define a minimal set of genes whose expression patterns can be used to classify stem cell populations. This includes hierarchical, Bayesian, k-mean, two-way, self-organizing maps, and Pearson rank clustering algorithms. Each provides a different means to identify genes with similar expression patterns and has been used to more finely classify several different forms of cancer.

COLLABORATIVE SUBPROJECTS

GENE THERAPY FOR ALZHEIMERS DISEASE (0008)

NPRC UNIT: BRAIN, MIND, & BEHAVIOR

%NPRC $: 5.545%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
GAGE, FRED		A	INSTITUTE OF AGING	SALK INSTITUTE, CA USA
Waines	PHD	C	PSYCHOLOGY	
	DVM	C	PRIMATE CENTER	
	MD, PHD	A		UCSD, CA USA

AXIS I CODES: 1A, 2, 3 **AXIS II CODES:** 30, 55, 63C

ABSTRACT

Alzheimer's disease is the most common neurological degenerative disorder, currently affecting 4 million people in the U.S.. Existing therapies for this disease are few in number and relatively ineffective. Novel therapies are needed.

A promising class of natural biological proteins called nervous system growth factors offers the potential to reduce cell degeneration in the brain in such disorders as Alzheimer's disease. Gene therapy offers a uniquely effective means of delivering these growth factors to the brain.

Work performed under this study has demonstrated the delivery of nerve growth factor (NGF) to the brain using ex vivo gene therapy can prevent cholinergic neuronal death in the brain and ameliorate the effects of aging. A total of eight animals are currently being tested on the CANTAB automated testing apparatus to see if NGF gene therapy will also ameliorate cognitive decline with aging. There are six aged animals with equal numbers of males and females and two young animals, a male and a female. Tasks include paired associate learning, delayed matching to sample, progressive ratio, and intradimensional/extradimensional shift. Once animals are trained on the tasks, the role of the cholinergic system in performance of these tasks is determined by the administration of cholinergic agonists and antagonists.

Following completion of the pilot behavioral testing, ten aged animals will be tested before and after receiving NGF gene delivery to determine effects of the graft on cognition. We have performed testing in the last year and early results are being tabulated. Progress on the study has been very good.

ACTIVITY-DEPENDENT PLASTICITY IN ADULT SENSORY CORTEX (0085)

NPRC UNIT: BRAIN, MIND, & BEHAVIOR

%NPRC $: 0.738%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
JONES, EDWARD G	MD, PHD	A	CTR FOR NEUROSCIENCE	

AXIS I CODES: 1A, 21 **AXIS II CODES:**72, 82

ABSTRACT

This study, which is nearing completion, deals with a potential brainstem and thalamic substrate for the extensive reorganization of somatosensory cortical maps that occurs following chronic, large-scale loss of input from the cutaneous sense organs. We previously showed that transneuronal atrophy occurred in neurons of the dorsal column (DCN) and ventral posterior lateral thalamic (VPL) nuclei in monkeys subjected to cervical and upper thoracic dorsal rhizotomies for 13-21 years and that had shown extensive representational plasticity in somatosensory cortex and thalamus. In the current studies we are exploring the extent to which withdrawal of axons of atrophying cells from higher synaptic stations in the pathway promotes plastic reorganization of the representation in that station. 14 adult monkeys were subjected to unilateral cuneate fasciculotomy at the C1 spinal level. We are currently nearing completion of the second set of experiments in which axonally transported tracers are injected into the ipsilateral cuneate nucleus to label axon terminations in the contralateral VPL thalamic nucleus, in conjunction with electrophysiological; mapping of the representation in VPL or in the somatosensory cortex. To date, 8 monkeys have been subjected to the second round of experiments. The remainder are scheduled for completion in the next few weeks.

ESTROGEN & AGING BRAIN (0006)

NPRC UNIT: BRAIN, MIND, & BEHAVIOR

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
MORRISON, JOHN	PHD	A	NEUROBIOLOGY	MOUNT SINAI SCHOOL OF MEDICINE, NY USA
[illegible]	DVM, MPVM	C	VM:PATH/MICROBIOL/IMMUNO	

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

ABSTRACT

The overall goals of this project are to assess the effects of estrogen replacement on cognitive function and neuroanatomy in an aged non-human primate model of surgical menopause. During the fourth year all of the 16 aged female rhesus macaques have completed behavioral testing to assess cognitive function in aging. Fourteen young female rhesus have been screened and identified as suitable for the young behavioral group and have begun testing. These females are assigned to treatment and control groups and are receiving replacement injections (estrogen or placebo) every three weeks. All of the proposed aged (n=10) and young histology (n=10) animals have been treated and perfused for anatomical study. Four manuscripts are currently in preparation from the results of the behavioral and anatomical studies. Approximately 8,106 urine samples have been analyzed for estrogen and progesterone metabolites for a total of over 16,312 assays performed. In addition, a new assay was developed to directly measure the concentration of estradiol directly in urine samples in addition to measurement of estrogen metabolites. A total of 50 animals have been assigned to the study and two more are pending for assignment.

ENVIRONMENTAL FACTORS IN THE ETIOLOGY OF AUTISM (0333)

NPRC UNIT: BRAIN, MIND, & BEHAVIOR

%NPRC $: 2.096%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
PESSAH, ISAAC N.	PHD	A	UNKNOWN	UNKNOWN, CA USA
C Names 3	PHD	C	MED:PSYCHIATRY	
	PHD	A	UNKNOWN	UNKNOWN, CA USA

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

ABSTRACT

No abstract available.

COGNITIVE FUNCTION IN THE AGED MONKEY (0185)

NPRC UNIT: BRAIN, MIND, & BEHAVIOR

%NPRC $: 0.861%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
RAPP, PETER R	PHD	A	NEUROBIOLOGY AND AGING	MT SINAI SCHOOL OF MEDICINE, NY USA
C name 3	PHD	C	PSYCHOLOGY	

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

ABSTRACT

Significance: The overall goal of this project is develop a nonhuman primate model for defining the relationship between cognitive, neurobiological, and ovarian hormone decline during normal aging.

Objectives: Groups of young and aged rhesus monkeys are tested across a variety of well-established and newly developed neuropsychological testing procedures aimed at characterizing the nature and severity of age-related cognitive decline. Ovarian hormone status is monitored for all females in the project in order to relate these parameters to individual differences in the cognitive outcome of aging.

Results: Cumulative results from the project establish several key concepts about the cognitive consequences of aging in the monkey. First, the significant deficits aged subjects display on standard delayed response and delayed nonmatching-to-sample tasks increase at longer retention intervals, specifically as a function of the demands of testing on memory. Second, the status of recognition memory varies considerably among aged individuals and many at the end of their expected life span continue to score as accurately as young adults. Third, age-related deficits in working and recognition memory are unrelated, suggesting that aging independently influences the integrity of the neural systems that mediate these capacities. These findings comprise a valuable framework for related studies aimed at identifying neurobiological alterations that might contribute to normal cognitive aging. In this regard, investigations completed during the current project period demonstrate that although the cholinergic innervation of the hippocampus is vulnerable to aging, structural comprise in this neurochemical input fails to predict age-related deficits in memory mediated by the medial temporal lobe system.

Future Directions: Experiments currently in progress represent a continuation of the initiatives described above. The research program is expected to advance progress toward defining the interactions between cognitive, endocrine and neurobiological aging in primates.

NEURAL CORRELATES OF AUDITORY AND VISUAL PERCEPTION (0090)

NPRC UNIT: BRAIN, MIND, & BEHAVIOR

%NPRC $: 0.833%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
RECANZONE, GREGG HOWARD	PHD	A	CTR FOR NEUROSCIENCE	
	BS	A	CENTER FOR NEUROSCIENCE	UC DAVIS, CA USA
	BS	A	CENTER FOR NEUROSCIENCE	UC DAVIS, CA USA
		A	CENTER FOR NEUROSCIENCE	UC DAVIS, CA USA

AXIS I CODES: 21 **AXIS II CODES:** 40

ABSTRACT

The auditory system must perform two key functions: to determine "what" a sound is (identification), and to determine "where" the sound came from (localization). While studies on the visual system have provided important clues as to the cortical mechanisms of these fundamental perceptions, very little is understood how the auditory cortex processes these aspects of acoustic stimuli. In order to begin to quantify potential neural correlates of auditory perception, adult macaque monkeys are trained at a variety of sound localization tasks. During performance of these tasks, the activity of single cortical neurons is measured. The activity of these neurons is then correlated with the perceptions of the animal. The results thus far have indicated that the responses of neurons in secondary auditory cortical areas, but not the primary auditory cortex, have responses that are consistent with sound localization performance.

FREQUENCY INTEGRATION IN AUDITORY CORTEX (0161)

NPRC UNIT: BRAIN, MIND, & BEHAVIOR

%NPRC $: 0.666%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
SUTTER, MITCHELL L		A	CENTER FOR NEUROSCIENCE	
c-name: 3		A	CENTER FOR NEUROSCIENCE	

AXIS I CODES: 21, 25A **AXIS II CODES:** 40, 41, 45

ABSTRACT

The goal of this work is to elucidate the relationship between neural activity in auditory cortex and sound perception. The applicant will determine 1) the abilities of humans and nonhuman primates to perceive and integrate spectral and temporal features of sounds, and 2) the relationship of single neuron responses in auditory cortex to psychophysical performance. For Aim 1, human and nonhuman subjects will be trained to discriminate sounds that vary along temporal or spectral dimensions, and for Aim 2, neurons will be recorded in nonhuman primate auditory cortex during behavioral discriminations. Signal detection methods will be used to determine the discriminative capabilities of single neurons, and whether their firing is more closely associated with the physical attributes of sound or the higher level decision to respond to the sound. The data will provide information for understanding the effects of cortical disruptions, as well as basic understanding of temporal acoustic processing. The results are of potential use for treating stroke and dyslexia.

GENE THERAPY FOR TREATMENT OF SPINAL INJURY (0009)

NPRC UNIT: BRAIN, MIND, & BEHAVIOR

%NPRC $: 1.781%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
TUSZYNSKI, MARK H	MD, PHD	A		UCSD, CA USA
Named]	PHD	C	PSYCHOLOGY	
	DVM	C	PRIMATE CENTER	

AXIS I CODES: 1A, 2, 3 **AXIS II CODES:** 55, 63C, 92(TRAUMA)

ABSTRACT

Spinal cord injury (SCI) currently afflicts 200,000 Americans and there exist no effective therapies for promoting recovery of function. New therapies to promote regeneration and recovery after SCI are needed.

This research has established a primate model of limited spinal cord injury that results in weakness in one limb, allowing the testing of regeneration strategies in a species with a spinal cord of size and circuitry that resembles the human system. Lesion in either the thoracic and cervical region are being evaluated for their effect on motor skills and fine motor control. Currently five animals have lesions are being tested on locomotion and behavioral tests. Initial studies demonstrate that lesioned animals demonstrate modest impairment in both areas. Remodeling of axons has been observed in control animals receiving SCI. Functional and neuronal labeling studies are underway to examine mechanisms and extent of this remodeling process.

Axons of the primate spinal cord are sensitive to the delivery of growth factors using gene therapy. Studies to determine the effects of the grafting on function and anatomy are being conducted. Future studies are focused on promoting growth of important motor systems after these limited injuries in primates. In 2001 a total of seven animals have been enrolled on this study.

FUNCTIONAL PROPERTIES OF NEURONAL CIRCUITS FOR VISION (0159)

NPRC UNIT: BRAIN, MIND, & BEHAVIOR

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
USREY, WILLIAM M		A	CENTER FOR NEUROSCIENCE	
ename 3		G	CENTER FOR NEUROSCI	UC DAVIS, CA USA

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

ABSTRACT

The long-term objectives of this proposal are to understand the functional organization of feedforward and feedback pathways between the lateral geniculate nucleus (LGN) and visual cortex. For sensory systems, feedforward projections from thalamic relay cells provide the cortex with information about the external environment The cortex, in turn, sends extensive feedback to thalamic relay cells. The cortex thus functions both to process information supplied by the thalamus as well as to influence dynamically the transmission of thalamic input. The proposed studies involve three sets of experiments.

The first set of experiments deals with the issue of what role magnocellular and parvocellular LGN inputs play in the construction of postsynaptic receptive fields in layer 4C of visual cortex. Recordings will be made from monosynaptically connected neurons in the LGN and layer 4C in order to compare the organization of pre- and postsynaptic receptive fields as well as to assess the dynamics of synaptic transmission. The second set of experiments deals with determining the physiology of corticogeniculate feedback neurons located in layer 6 of visual cortex. Neurons in layer 6 that provide feedback input to the LGN are located in the upper third and lower third of the layer. Neurons in the upper third project exclusively to the parvocellular geniculate layers; neurons in the lower third project primarily to the magnocellular layers. We will examine the physiological properties of these neurons to determine whether they are differentially sensitive to visual stimuli If so, then it seems likely that neurons in the upper and lower regions of layer 6 should be able to differentially modulate activity traveling in the magno- and parvocellular streams. The third set of experiments deals with the functional influence of cortical feedback on geniculate activity. By recording from ensembles of geniculate neurons, we will determine whether cortical feedback selectively influences the activity of neurons in the magno- and parvocellular layers of the LGN. If feedback is found to influence the temporal patterns of LGN activity, then we will examine data from the first set of experiments to determine the efficacy of these patterns in driving cortical responses. Results from this work will not only increase our understanding of how visual information is processed by the nervous system, but will provide a framework for understanding the functional relationship that exists between thalamus and cortex. Only by such a detailed understanding of the normal balance between feedforward and feedback interactions can disorders of this relationship, such as appear in many forms of epilepsy, be understood.

LINKING FUNCTIONAL IMAGING, NEUROPHYSIOLOGY AND ANATOMY (0316)

NPRC UNIT: COLLABORATIVE RES PROGRAM

%NPRC $: 1.413%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
DISBROW, ELIZABETH A.	PHD	A	RADIOLOGY	UC SAN FRANCISCO, CA USA

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

ABSTRACT

Brain imaging methods such as functional magnetic resonance imaging (fMRI), magnetic source imaging (MSI) and diffusion tensor imaging (DTI) are rapidly evolving as essential tools for assaying normal and abnormal brain function. The overall goal of this research is to enhance our understanding of the relationship between the signals measured using these imaging techniques and the underlying neural activity. We propose to conduct a series of experiments in anesthetized macaque monkeys to examine the correlation between functional brain imaging signals, specifically the BOLD signals of fMRI, the modeled current sources of MSI, and the imaging of white-matter tracts with DTI, with "gold standard" single and multi-unit electrophysiological recordings, and neuroanatomical tracing techniques. The specific aims are 1) To measure the stimulus evoked changes in magnitude, location and timing of functional brain imaging signals and relate them to changes in underlying neural activity, 2) To correlate non-invasive anatomic connectivity measures derived from tractography of DTI with connectivity derived using neuroanatomical techniques, and 3) To compare measures of functional connectivity based on the covariance of fMRI and MSI time-series with anatomic connectivity derived from DTI and neuroanatomic studies. These experiments represent a unique collaborative effort to combine several techniques in the same animal to generate a better understanding of the ability of modern imaging techniques to track changes in the nervous system under varying stimulus conditions and to uncover the circuitry necessary for complex sensory abilities. Our efforts are among the first to bridge the gap between imaging, neurophysiology and anatomy, an essential step in relating the wealth of electrophysiological recording data from macaque monkeys to the human cortex, and in understanding complex functions such as the sensory integration necessary for cognitive processes like object recognition and language.

PHARMACOKINETIC STUDIES OF SELECT MILLENNIUM COMPOUNDS IN CYNOMOLGUS MONKEYS (0284)

NPRC UNIT: COLLABORATIVE RES PROGRAM

%NPRC $: 0.034%

INVESTIGATOR	DEGREES STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
GREGORY, CLARE R	A	VET MED SURGERY	

AXIS I CODES: 1A **AXIS II CODES:** 50B

ABSTRACT

No abstract available.

STRUCTURAL BASIS OF AMBLYOPIA & STRABISMUS (0083)

NPRC UNIT: COLLABORATIVE RES PROGRAM

%NPRC $: 1.669%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
HORTON, JONATHON C	MD, PHD	A		UCSF, CA USA

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

ABSTRACT

BACKGROUND: In primate visual cortex, the inputs serving each eye are segregated into separate domains called ocular dominance columns. These columns have been the focus of our research, because they are affected in amblyopia and strabismus, diseases that cause blindness in children.

METHODS: Ocular dominance columns were labeled in squirrel monkeys by removal of one eye. This causes a loss of metabolic activity in the enucleated eye's ocular dominance columns. This change in metabolism can be visualized by processing the flattened cortex for a metabolic enzyme, cytochrome oxidase.

RESULTS: Two major new findings have emerged from our studies during the past year. First, we have found a representation of retinal blood vessels in the primary visual cortex. It appears because the blood vessels that supply the inner retina are located in front of the photoreceptor layer, blocking access to light. Their shadows create a pattern of blindness in the field of vision that corresponds precisely to the location of the largest vessels in the eye. Focal deprivation by blood vessels leads to rewiring of the eye's geniculocortical projections, imprinting an image of the retinal vascular tree onto the primary visual cortex. Second, in a group of 12 normal squirrel monkeys, we have found enormous variability in the expression of ocular dominance columns. They were well-developed in some normal individuals and nearly absent in others.

DISCUSSION: Our studies illustrate vividly that local imbalances in neuronal activity can influence column formation during normal development. The representation of retinal blood vessels in the cortex reflects a local form of amblyopia, induced by deprivation of photoreceptors. This phenomenon reveals that the precision of the cortical map is able to represent shadows only a few cones wide. The inconsistent expression of ocular dominance columns in squirrel monkeys provides a challenge to identify a visual function that can be correlated with their development.

DIAGNOSIS AND THERAPY OF LYME NEUROBORRELIOSIS USING THE MONKEY MODEL (0242)

NPRC UNIT: COLLABORATIVE RES PROGRAM

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
PACHNER, ANDREW R	MD	A	NEUROSCIENCES	UMDNJ-NEW JERSEY MEDICAL SCHOOL, NEWARK, NJ USA
Names	DVM, PHD	A	CENTER FOR COMP MED	UC DAVIS, CA USA
		A	CENTER FOR COMP MED	UC DAVIS, CA USA

AXIS I CODES: 1, 20, 21 **AXIS II CODES:**64, 66

ABSTRACT

The objectives are to gain knowledge about infection of the nervous system with Borrelia burgdorferi in the Rhesus macaque animal model that would aid in the diagnosis and treatment of human Lyme neuroborreliosis (LNB). This includes: (a) optimizing the current experimental model of LNB in non-human primates; (b) learning more about neurotropism and neuropathogenicity in the expression of LNB, as well as the mechanisms involved; and (c) determining whether long-term infection with B. burgdorferi results in damage to the central and/or peripheral nervous system.

INTRAMARROW GENE TRANSFER IN NEONATAL RHESUS MONKEYS (0131)

NPRC UNIT: REPROD & GENETIC SCIENCES

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BUNNELL, BRUCE A.	PHD	A	PHARMACOLOGY	TULANE UNIVERSITY HEALTH SCIENCES CENTER, LA USA
F Names 3	PHD	G	PRIMATE CENTER	
	PHD	C	MED:PEDIATRICS	

AXIS I CODES: 1A, 7B, 17 **AXIS II CODES:** 31, 55, 60, 62

ABSTRACT

The development of gene therapy strategies that target hematopoietic stem cells has been proposed as a long-term treatment for a wide array of lymphohematopoietic genetic and acquired disorders. These studies focus on exploring in vivo vector administration for assessing both the efficiency of gene transfer to hematopoietic stem/progenitor cell populations, and the safety of these gene delivery techniques in infant rhesus monkeys with and without SIV infection. Overall, these investigations have shown safe administration of irradiated vector producer cells and supernatant preparations when injected directly into the bone marrow cavity of infant monkeys; detectable vector sequences in hematopoietic progenitor cells which persist for several months; limited vector biodistribution to other cells and tissues; and healthy infants as evidenced by daily health checks, food intake, monthly hematology and clinical chemistry assessments, and overall growth. These studies highlight that in vivo gene transfer is an effective alternative to ex vivo gene therapy approaches, and that in situ transduction of hematopoietic stem and progenitor cells can be achieved without preconditioning and myeloablation. Studies currently in progress are evaluating new lentiviral vector constructs which are proposed to increase the levels of gene marking that have observed in the studies performed, to date.

MECHANISMS OF LUTEINIZATION IN THE PRIMATE OVARY (0318)

NPRC UNIT: REPROD & GENETIC SCIENCES

%NPRC $: 0.841%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
CHAFFIN, CHARLES L	PHD	A		MED COLLEGE , GA USA
Cj Rannie	PHD	C	MED:OBSTETRICS/GYN ECOLOGY	

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

ABSTRACT

Recent evidence in primates demonstrates that proliferation of granulosa cells is arrested within the first quarter of the periovulatory interval. However, specific markers of cell cycle progression, e.g., cyclin D2, are increased while levels of cell cycle suppressors such as p53 are reduced in concurrence with cell cycle arrest. This application will test the hypothesis that an ovulatory stimulus induces a transient burst of granulosa cell proliferation that is an essential feature of terminal differentiation and luteal formation in the primate. Experiments are planned to examine cell cycle characteristics of granulosa cells at early time points following a luteinizing dose of gonadotropin to granulosa cells in vitro and after an ovulatory stimulus to adult, female rhesus monkeys in vivo (aim 1). The functional consequences of the proliferative burst on terminal differentiation and luteinization of granulosa cells will be determined using in vitro protocols (aim 2). This application will further test the hypothesis that estrogen mediates the proliferative burst via regulation of key cell cycle components, and that early periovulatory estrogen action is essential to the formation of a functional corpus luteum (aim 3). The proposed studies will utilize an in vivo controlled ovarian stimulation model in which the differential effects of gonadotropins and steroids can be determined. Granulosa cells will be obtained from rhesus monkeys undergoing controlled ovarian stimulation prior to an ovulatory stimulus for in vitro experimentation. Levels of mRNA will be determined with real time RT-PCR, and protein levels and activity by western blot, gel shift, and kinase assays. Concentrations of steroid hormones will be measured by RIA. The proposed studies are expected to demonstrate that primate granulosa cells undergo a proliferative burst in response to the ovulatory stimulus that is an essential component of luteinization. It is expected that estrogen plays a heretofore unexpected role in driving the proliferative burst through the regulation of key cell cycle components. These studies will provide insight into the etiologies of ovarian cancer and certain kinds of infertility, as well as provide potential novel avenues for contraceptive agents.

ENDOCRINE DISRUPTION ON ADOLESCENCE METHOXYCHLOR (0011)

NPRC UNIT: REPROD & GENETIC SCIENCES

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
GOLUB, MARI S	PHD	A	PRIMATE CENTER	
E names	PHD	C	VM:POPULAT HLTH&REPRODU	
C	PHD	C	MED:PEDIATRICS	

AXIS I CODES: 1A, 2, 15, 17, 21, 26 **AXIS II CODES:** 54A, 60, 63C, 71, 93

ABSTRACT

The objective of this research project is to determine whether administration of estrogenic agents disrupts the timeline of female adolescent development and leads to long term effects on reproductive, skeletal, immune and nervous system function in a non-human primate. This topic is relevant to current public health concerns about endocrine disruption by environmental pollutants. Oral dosing of the pre-menarchal monkeys extended from May 2000 to May 2001, followed by a one-year recovery period. The agents administered were DES (0.5 mg/kg/day) as a positive control and two doses (25 amd 50 mg/kg/day) of methoxychlor, a pesticide with estrogenic properties. Four papers have resulted from the project, two published in 2002 and 2003, with another in review and the fourth submitted in 2004. A follow-up project was submitted to NIH for funding but was not funded and will be revised in 2004. After completion of the formal evaluations and upon reaching full reproductive maturity, the entire cohort was mated according to standard colony protocols. To date, the estrogen treated animal have demonstrated more menstrual cycles and a higher level of successful mating than controls. Pregnancy outcomes are not yet known.

RENAL ALLOGRAFT SURVIVAL IN A NONHUMAN PRIMATE MODEL (0213)

NPRC UNIT: REPROD & GENETIC SCIENCES

%NPRC $: 0.083%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
GREGORY, CLARE R		A	VET MED SURGERY	
E. Nunez	PHD	C	MED:PEDIATRICS	

AXIS I CODES: 1A, 27 **AXIS II CODES:**88

ABSTRACT

Purpose: The purpose of this study was to compare the survival times of renal allografts in nonhuman primates treated with either ISATX247, a novel calcinurin inhibitor, or cyclosporine (CsA). Methods: Adult, male Cynomolgus monkeys were divided into blood group compatible and mixed lymphocyte stimulation mismatched (2.5X) donor/recipient pairs. Heterotopic renal transplantation and bilateral native nephrectomy were performed on each recipient. The monkeys were then placed into either a CsA or ISATX247 treatment group. Animals in both groups were dosed twice daily to maintain a 12-hr trough concentration of approximately 150 ng/ml. Whole blood concentrations of ISATX247 or CsA and serum chemistry profiles were preformed 3 times a week. Euthanasia was performed if the serum creatinine concentration became 7 mg/dl, or if a serious complication or illness developed. A necropsy was performed with histopathological examination of the allograft, spleen, heart, lung, liver, brain, bowel, testes and lymph nodes. Statistical analysis of survival was performed using the Kaplan Meyer survival curve. Results: The group receiving ISATX247 (N = 8) survived significantly (p =0.0036) longer than the group receiving CsA (N=7). In the ISATX247 group, two monkeys rejected their kidneys at 18 and 19 days (Banff Type II A) ; one monkey was killed at day 4 due to delayed graft function. One monkey died at day 26 due to aspiration pneumonia; two monkeys were killed at days 59 and 66 due to posttranplant lymphoproliferative disorder. Two monkeys are living. In the CsA group, 6 monkeys rejected their kidneys at days 18,8,9,21, 18 and 9 (Banff Type IA, IB, IIA). One monkey was killed at day 3 due to delayed graft function. The mean trough blood concentration of CsA was 159 +/- 87 ng/ml; ISATX247 was 137+/77 ng/ml. The average AUC(0-12) for CsA was 4919+/-823 ng/ml.hr and 6045+/-1679 ng/ml.hr for ISATX247. There was no significant difference in total drug exposure (p= 0.4). The average percent calcinurin inhibition at trough blood concentrations was 48+/-12% for CsA and 80+/-11% for ISATX247. Histopathologic examination of multiple organ systems did not reveal toxicity associated with either agent.

Conclusions: Allografts in the monkeys treated with ISATX247 survived significantly longer than those in the monkeys treated with CsA. Based on survival times and degree of calcinurin inhibition, ISATX247 has demonstrated to be a more potent immunosuppressive agent than CsA at equal exposure levels in this nonhuman primate model of renal allograft transplantation.

BLOCKADE OF VEGF ACTION ON ENDOMETRIAL DEVELOPMENT AND DIFFERENTIATION (0294)

NPRC UNIT: REPROD & GENETIC SCIENCES

%NPRC $: 0.098%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
EASLEY, BILL L	PHD	C	VM:POPULAT HLTH&REPRODU	
[illegible]	PHD	A		STANFORD UNIVERSITY, CA USA

AXIS I CODES: 1A, 15, 23 **AXIS II CODES:** 50, 77, 93

ABSTRACT

The objective of this study is to identify novel genes responsible for P-withdrawal bleeding in the primate endometrium. Clinically, extensive bleeding from the endometrium results in a range of disorders and can significantly affect quality of life for women with these disorders. In this study, 5 females were ovariectomized, then treated with subcutaneous E2 implants for 14 days followed by P implants for an additional 14 days to induce an artificial menstrual cycle. Following the artificial cycle, animals were treated with a vascular endothelial growth factor inhibitor at different timepoints in order to study the effects of the inhibitor on the endometrium. Animals were again induced to cycle artificially by treatment with E2 and P implants for a second cycle. Animals were euthanized after removal of the P implant after the second menstrual cycle. The endometrium was analyzed for genes/factors involved in inducing P-withdrawal bleeding.

EFFECT OF REDUCING FORMULA PROTEIN CONTENT ON METABOLISM (0211)

NPRC UNIT: REPROD & GENETIC SCIENCES

%NPRC $: 0.061%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
LONNERDAL, BO	PHD	A	NUTRITION	
c name 3	BS	A	NUTRITION	

AXIS I CODES: 1, 16D **AXIS II CODES:** 71, 74B, 78

ABSTRACT

Background: The optimal protein concentration to use in infant formula has not yet been well defined. Most cow's milk based formulas contain 15 g protein/L, while some formulas contain as low as 13 g protein/L. A primary consideration when determining the appropriate level of protein to use in formula has been the resultant plasma amino acid pattern. It has been argued that lowering the protein content would lower the concentrations of some amino acids and make them more similar to those of breast-fed infants. On the other hand, lowering the protein level too much may result in specific essential amino acids being lower than in breast-fed infants, which would be inappropriate as it is believed that the protein requirement of infants is close to that provided by breast milk. Methods: In this study 24 infant monkeys (6 infants/group) were breastfed or fed infant formulas containing different protein levels. The formulas contained 15 g protein/L, 11 g protein/L or 11 g protein/L with branched chain amino acids (BCAA) supplemented to the levels found in the 15 g protein/L formula. Weight and length was measured monthly, food intake recorded daily and blood was drawn every 2 weeks for CBC and further analysis. Infants were given a glucose tolerance test (1 g/kg) and blood was collected pre-dose and 30, 60, 90 and 120 min later. Results: Sample analysis has not been completed. However, breastfed infants weighed less and had higher fasting insulin and glucose levels than formula fed infants. Infants fed low protein formula had higher fasting glucose and glucose absorption following a glucose dose. Plasma amino acid profiles remain to be analyzed. Conclusion: These results suggest that lowering infant formula protein levels is safe and results in fasting insulin and glucose levels more closer to those observed in breastfed infants.

EFFECTS OF MANGANESE ON BEHAVIOR AND COGNITIVE FUNCTION (0241)

NPRC UNIT: REPROD & GENETIC SCIENCES

%NPRC $: 0.061%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LONNERDAL, BO	PHD	A	NUTRITION	
	PHD	A	DEPT OF PEDIATRICS	UNIV OF CALIF IRVINE, CA USA
Nanez 3	BS	G	NUTRITION	UC DAVIS, CA USA

AXIS I CODES: 1A, 17, 21 **AXIS II CODES:**36, 41, 71, 78

ABSTRACT

Manganese (Mn) is an essential mineral, but may be neurotoxic at high levels. Breast milk has a very low Mn concentration (~3-10 ug/L). Infant formula based on cow's milk contains higher levels of manganese (~30-50 ug/L), whereas soy formulas contain substantially higher levels of manganese, (~300-500 ug/L). Therefore, infants who are fed formula based on either cow's milk or soy formula have substantially increased exposure to Mn. Whether these elevated levels of Mn intake result in toxicity or neurotoxic consequences are still unknown, although it has been suggested overexposure to Mn results in attention deficit hyperactivity disorder (ADHD) since elevated hair Mn levels have been found in children with ADHD. This may be a direct effect of Mn toxicity on brain function, although it is possible that some effects due to interference of Mn with other trace element, such as iron, which is known to affect psychomotor and cognitive development. The present study proposal was designed to determine the effects of neonatal exposure to elevated levels of dietary Mn on Mn absorption and retention and indices of behavior, using a rhesus monkey model. A secondary aim was to determine whether this increased Mn intake would result in decreased Fe status and absorption.

In this study, male infants were formula fed (varying levels of Mn) from birth until 5 months of age. Blood was drawn monthly for complete blood count (CBC). Whole blood and serum were collected for Mn and Fe status. At 4, 12, and 19 weeks of age, infants were given 54Mn and 59Fe in formula and whole body absorption and retention was measured by whole body counting. Every month, physical exam including crown-rump length, arm and thigh circumferences, and anogenital distance were measured. At 6 and 8 month of age, a battery of tests was conducted. In addition, cerebrospinal fluid was obtained at 4 and 8 mos. for assessment of neurotransmitters. Although our research is still in progress, preliminary data suggest possible differences in behavioral development and neurotransmitter levels. The completion of the study and data analysis is necessary before conclusion and health implications can be made.

EFFECT OF ELEVATED COPPER INTAKE ON INFANT HEALTH (I). (0269)

NPRC UNIT: REPROD & GENETIC SCIENCES

%NPRC $: 0.061%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LONNERDAL, BO	PHD	A	NUTRITION	
E name ?	BS	A	NUTRITION	

AXIS I CODES: 1, 16D **AXIS II CODES:** 71, 74B, 78

ABSTRACT

Background: Copper is an essential nutrient but can also be toxic at high dietary levels. Elevated exposure of copper is of concern in areas where industrial mining is conducted and where copper water pipes are used or where well-water pH is low. However, the range of safe dietary copper intake, particularly for infants and children, as well as the infant's ability to regulate copper absorption to protect itself from copper toxicity, has not been adequately established. Unfortunately, biomarkers for determining elevated copper exposure are inadequate, as circulating copper and copper transport proteins are maintained across a wide range of copper intakes. We hypothesize that neonates have the ability to regulate gastrointestinal copper absorption and that this ability protects infants from copper toxicity. Methods: In this project we determined effects of elevated dietary copper during infancy on liver patho-physiology, circulating liver enzymes and hematological parameters from birth through 5 months of age and at 9 and 12 mo, to determine long term-effects of elevated copper intake during neonatal life. Results: Copper absorption was lower at 6 mo than at 1 mo and was lower in Cu-supplemented animals compared to controls at 8 mo. There was no effect on growth, Fe status, plasma albumin, most liver enzyme activity, plasma Cu or ceruloplasmin. White blood cells populations were significantly affected, plasma Zn was lower and alkaline phosphatase was higher in Cu-supplemented infants until weaning. Histological analysis is on-going. Discussion: Results from this study suggest that infants are able to down-regulate Cu absorption to some extent. However, excess dietary Cu negatively affects liver enzymes, Zn status and white blood cell population suggesting secondary effects of high Cu intake on infant health.

EFFECT OF ELEVATED COPPER INTAKE ON INFANT HEALTH (II) (0270)

NPRC UNIT: REPROD & GENETIC SCIENCES

%NPRC $: 0.061%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
LONNERDAL, BO	PHD	A	NUTRITION	
c name a	BS	A	NUTRITION	

AXIS I CODES: 1, 16D **AXIS II CODES:** 71, 74B, 78

ABSTRACT

Background: Copper is an essential nutrient but can also be toxic at high dietary levels. Elevated exposure of copper is of concern in areas where industrial mining is conducted and where copper water pipes are used or where well-water pH is low. However, the range of safe dietary copper intake, particularly for infants and children, as well as the infant's ability to regulate copper absorption to protect itself from copper toxicity, has not been adequately established. Unfortunately, biomarkers for determining elevated copper exposure are inadequate, as circulating copper and copper transport proteins are maintained across a wide range of copper intakes. We hypothesize that infants have the ability to regulate gastrointestinal copper absorption and that this ability protects infants from copper toxicity. Methods: In this project we determined effects of elevated dietary copper during adolescence on liver patho-physiology, circulating liver enzymes and hematological parameters from 6 to 12 mo. Results: The project is ongoing so no results are available.

FUNCTION OF MACAQUE SPERM PROTEINS IN FERTILIZATION (0018)

NPRC UNIT: REPROD & GENETIC SCIENCES

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
OVERSTREET, JAMES W	MD, PHD	A	MED:OBSTETRICS & GYNEC	
	PHD	A	ENVIR TOX	
	PHD	A	CELL BIO AND HUMAN ANATOMY	

AXIS I CODES: 1D, 23 **AXIS II CODES:**74C

ABSTRACT

To identify sperm-surface components that are highly antigenic and therefore potential targets for contraceptive agents, we immunized female cynomolgus macaques with sperm surface proteins that were released following treatment with phosphatidylinositol-specific phospholipase C (PI-PLC). One of these proteins was shown to be a surface coating protein as demonstrated by displacement of some, but not all of the protein from the sperm surface under conditions of increased osmolarity. Thoroughly washed, acrosome intact, fixed sperm injected into rabbits elicited a potent immune response to this same surface coat glycoprotein. Purification and digestion of the glycoprotein resulted in a number of peptides, four of which were analyzed for amino acid sequence. All four of the sequenced peptides had 100% homology with an epididymal secretory protein, ESP13.2, which has been reported previously to be a small, cationic rich peptide that may be a member of the defensin family. Antibodies developed to purified ESP13.2 recognized a number of protein bands on Western blots of nonreduced PI-PLC-released sperm components and nonreduced whole sperm extracts. After chemical disulfide reduction of PI-PLC-released sperm components and whole sperm extracts, only a single broad band from 31 kDa-35 kDa was recognized on Western blots by anti-ESP13.2 antibodies. Indirect immunofluorescence showed that ESP13.2 is distributed over the entire surface of ejaculated macaque sperm. Fluorescence was reduced somewhat after sperm were washed through 80% Percoll and again after an additional 24 hr of incubation in a capacitating medium. Exposure of the incubated sperm to 1mM cAMP and 1mM caffeine (capacitation activators) resulted in almost complete loss of ESP13.2 from the sperm surface. Electrophoretic analysis of sperm proteins released after introduction of activators revealed that ESP13.2 was the primary component. A potent inhibitor of macaque fertilization in vitro completely blocked the release of ESP13.2 from the sperm surface, even following treatment with activators. These findings suggest that the ß-defensin, ESP13.2, has a function in the capacitation of macaque spermatozoa and may modulate sperm surface receptor presentation at the time of fertilization. This sperm surface coating protein may be a vulnerable target for contraceptive agents.

GENETIC DISEASE, A STRATEGY TO DEVELOP ANIMAL MODELS (0244)

NPRC UNIT: REPROD & GENETIC SCIENCES

%NPRC $: 0.000%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
WINE, JEFFREY J		A	PSYCH, MOL CELL PHYSIO	STANFORD UNIVERSITY, CA USA
[illegible]		A		

AXIS I CODES: 1A, 3, 9, 16, 23, 24 **AXIS II CODES:** 58, 62, 64, 77

ABSTRACT

We have devised a strategy for developing natural animal models of human recessive genetic diseases. The approach uses rapid mutation screening of genomic DNA to detect unaffected carriers of disease genes. Because carrier frequencies of recessive genetic diseases are much higher than the incidence of disease (1/500 carriers for a disease with 1/1,000,000 incidence), the method works even for rare diseases. The strategy is practical with present methods for screening genomic DNA for unknown mutations, and will be increasingly cost-effective as novel, high efficiency methods for mutation detection are perfected. To establish feasibility, we used single strand conformation polymorphism and heteroduplex (SSCP/HD) analysis to screen genomic DNA of ~1,300 non-human primates for mutations in CFTR, the gene responsible for cystic fibrosis. We detected 40 different amino acid changes in the coding region, and considered ~half of these to be candidate missense mutations. Physiological assays indicated that at least 4 of the candidate mutations have reduced function. A selective breeding program is underway to determine if homozygous animals have a distinctive phenotype.

MECHANISMS OF HEMEOSTASIS AND REPAIR IN THE LUNG (0319)

NPRC UNIT: RESPIRATORY DISEASES

%NPRC $: 0.845%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
BEAMAN, BLAIN L	PHD	A	NIEHS	
[illegible]	PHD	C	VM ANAT/PHYSI&CELL B	

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

ABSTRACT

The functions of gamma delta T lymphocytes in pulmonary epithelia are poorly understood. They probably mediate immune responses in the mucosa since they secrete cytokines, chemokines and epithelial growth factors. Our hypothesis is that sequential recruitment of distinct subpopulations of gamma delta T lymphocytes into the lungs at sites of epithelial cell damage is essential in maintaining pulmonary homeostasis and regulating epithelial repair. The following 2 specific aims will test this, and determine the functions of gamma delta T cells. 1. The sequential localization and quantification of subclasses of gamma delta T cells will be determined within normal, damaged and repairing pulmonary epithelia after exposure to either ozone or N. asteroides. 2. The modulation and regulation of gamma delta T lymphocytes will be studied using sequential reconstitution of characterized subpopulations of gamma delta T lymphocytes into the lungs of knockout mice. Two models of pulmonary injury will be used in normal and gamma delta T cell deficient mice to correlate specific attributes of gamma delta T cell function with the mechanisms for maintaining lung mucosal integrity. Comparing and contrasting the roles of gamma delta T cells in each model will help to elucidate the nature of their recognition and regulation of homeostasis and repair. Subsets of gamma delta T cells will be selected and reconstituted into gamma delta T cell deficient mice. These studies will be accomplished by a combination of flow cytometry, laser scanning cytometry, tissue microarrays, cell sorting, and quantitative morphometry. The goal of this research is to reveal those attributes of gamma delta T cell function that contribute to epithelial integrity, and when breached determine the beneficial levels of inflammation and repair.

IMMUNOSTIMULATORY DNA PRIMING OF LUNG INNATE IMMUNITY (0317)

NPRC UNIT: RESPIRATORY DISEASES

%NPRC $: 2.121%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION : STATE, COUNTRY
COFFMAN, ROBERT L.		A		DYNAVAX TECHNOLOGIES CORPORATION, AND UC DAVIS, CA USA
[name]	PHD	C B	VM ANAT/PHYSI&CELL	

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

ABSTRACT

Synthetic oligonucleotides with immunostimulatory sequences (ISS) containing unmethylated CpG dinucleotides mimic the innate recognition of microbial DNA and show great promise as adjuvants and immune modulators in a wide variety of therapeutic settings. In addition to their ability to activate multiple components of innate immunity, ISS have shown the ability to "prime" the innate immune system to give enhanced innate and subsequent adaptive responses to a number of bacterial and viral pathogens (3). This can lead to enhanced resistance to both lethal and sublethal challenges. A single administration of ISS in animal models can provide measurable protection for two to four weeks and increased resistance can be maintained with periodic administration of ISS. Prophylactic vaccination through the innate immune system has significant potential as a first-line defense for populations threatened with exposure to bioterrorism/biowarfare agents or exotic or emerging infectious diseases. This proposal is for the development of an inhaled form of ISS as a prophylaxis for airborne infectious agents. We currently are developing 1018 ISS for treatment of asthma and have completed preclinical development and Phase I safety studies in man. The current studies would provide a set of proof-of-principle studies for its use as an inhaled prophylactic and would generate a set of surrogate assays that would be essential for clinical development for this indication.

PATHOGENICITY OF SIVMAC239 VARIANTS IN NEONATAL MACAQUES (0220)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 1.194% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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[redacted]	PHD	C	VM:PATHOMICROBIOL/IMMUNO	
[redacted]	DVM, PHD	A	PRIMATE CENTER	

AXIS I CODES: 1A, 7B, 17, 19 **AXIS II CODES:** 31, 64, 66, 71, 77, 91

ABSTRACT

SIV and all lentiviruses depend on the viral Rev regulation for the nucleo-cytoplasmic export and expression of the RRE-containing mRNAs. We have generated SIV variants that have the essential viral regulatory mechanism replaced by the export elements of the type D retroviruses, CTE, which utilizes a cellular factor hTAP for its transport. Primary cells infected by these SIV variants produce lower amounts of virus having reduced infectivity. The neonate macaque represents a critical and sensitive model system to evaluate the pathogenicity of potentially attenuated SIV variants. Neonatal macaques were infected with a Rev-independent strain of SIV that expresses all viral genes including nef or an SIV strain the lacks nef and that contains a weaker CTE-related RNA element. All monkeys showed a rapid increase of viral RNA in the plasma reaching 1 to 10 million copies/ml, followed by a rapid decline to levels below the threshold (100 copies SIV RNA per ml). All monkeys developed anti-SIV gag and env antibodies. Hematological values remained normal and none of the animals showed any signs of disease. Some of these data were recently published [von Gegerfelt et al., Journal of Virology 76: 96-104 (2002)]. We are continuing to follow the animal's to evaluate the potential pathogenicity of these viral strains over longer periods of time.

ORAL HIV TRANSMISSION MODE RAPID DISSEMINATION OF SIV AFTER ORAL INOCULATION (0166)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
SODORA, DONALD L	PHD	A		SOUTHWESTERN MED CTR, TX USA
	PHD	C	VM-PATHO/MICROBIO L/IMMUNO	
		A		UNIV TEXAS SOUTHWESTERN MED CTR, TX USA
	DVM	A		NE RPRC, MA USA

Names

AXIS I CODES: 1A, 1D, 7B, 17, 19 **AXIS II CODES:** 31, 64, 66, 77, 83

ABSTRACT

The majority of HIV infections occur via transmission of the virus across a mucosal surface as occurs during oral transmission following both mother-to-child and genital-oral exposure. To assess the sites of infection and rate of spread of SIV following a non-traumatic oral administration of virus, rhesus macaques were orally inoculated with SIVmac251 and euthanized from 1 to 7 days post-inoculation (dpi). The presence of SIV nucleic acid was assessed utilizing in situ hybridization, quantitative real-time PCR and nested PCR techniques. We found evidence that SIV infects oral and esophageal mucosa, as well as tonsils and local and peripheral lymph nodes within 4 days after oral SIV exposure. By 4 dpi hundreds and by 7 dpi more than ten thousand copies of SIV-DNA (per million cell equivalents) were detected in numerous lymph nodes. Identification of SIV nucleic acid within T cells and macrophages implicates these cell types in the viral spread, although dissemination of free virus likely plays a role as well. This rapid viral dissemination after oral SIV exposure suggests that interventions (microbicides, antiviral drugs or vaccines) designed to inhibit HIV spread from the oral cavity would need to be administered within a few hours after oral exposure to HIV.

TRANSMISSION OF H. PYLORI INFECTION IN THE RHESUS MONKEY (0193)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 1.029% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
SOLNICK, JAY V	MD, PHD	A	MED:INTERNAL MED	
	DVM	A	PRIMATE CENTER	
	DVM, MPVM	C	VM:PATHOMICROBIOL/IMMUNO	
	MD	A	INTERNAL MEDICINE	STANFORD UNIVERSITY SCHOOL OF MEDICINE, CA USA

AXIS I CODES: 1A, 7A, 16F **AXIS II CODES:**31, 66, 77

ABSTRACT

Rhesus monkeys are naturally infected with H. pylori that is very similar to strains that infect humans, and this animal model provides a unique opportunity to study experimentally the transmission of H. pylori in a naturally infected host. We hypothesize that acuity of infection, the presence of vomiting and diarrhea, and the CagA pathogenicity island are critical variables in transmission of H. pylori. Furthermore we propose that there may be a cooperativity between transmission of H. pylori and transmission of bacterial enteric diseases. Diarrheal and vomiting diseases may increase H. pylori transmission by increasing the shedding H. pylori in feces and vomitus, and in turn, H. pylori infection may cause increased gastric pH and thereby promote infection with enteric bacteria by reducing the gastric bactericidal barrier. We propose to address four specific aims in this proposal: 1)Determine how H. pylori is shed into the environment during acute and chronic infection; 2) Examine experimentally the effects of vomiting, diarrhea and the CagA pathogenicity island on the natural transmission of H. pylori; 3) Determine the effects of H. pylori infection on the acquisition of Campylobacter jejuni, and 4) Determine the effects of the CagA pathogenicity island on colonization and shedding. Our progress in Year 3 has to date included: (1) Successful cultivation of H. pylori from vomitus and from saliva after vomiting has occurred; (2) Determination that the sensitivity of detection of H. pylori in stool is approximately 10 organisms/ml; (3) Description of the quantitative relationship between colonization of the stomach and shedding of H. pylori in vomitus (4) Successful cultivation of H. pylori from diarrheal but not normal stools of experimentally infected macaques; (5) Demonstration of H. pylori transmission via fomites without direct animal-to-animal contact.

TRANSCRIPTION OF H. PYLORI GENES IN THE RHESUS MONKEY (0194)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
SOLNICK, JAY V	MD, PHD	A	MED:INTERNAL MED	
[illegible]	DVM	A	PRIMATE CENTER	

AXIS I CODES: 1A, 7A, 16F **AXIS II CODES:**31, 59, 66, 74G, 77

ABSTRACT

A full understanding of H. pylori pathogenesis requires an analysis of bacterial gene and host gene expression in vivo in a relevant animal model. The availability of the complete H. pylori genome sequence, together with novel technologies for measurement of gene expression, makes it possible to address this problem in the rhesus monkey model that we have recently developed at the California Regional Primate Research Center (CRPRC). We hypothesize that H. pylori genes important in virulence will be induced by contact with the host gastric epithelium. Quantitative cultures from five inoculated SPF macaques showed that they were infected with between 4 to 7 log10 CFU of H. pylori J166/gram gastric tissue. An additional 6 antral biopsies were obtained for extraction of total DNA and RNA. Real time RT-PCR was performed on DNA and DNase-I-treated RNA using primers to genes on the Cag pathogenicity island. mRNA copies/cell in vivo was calculated by the DCt between DNA and RNA. Mean mRNA copies/cell in vivo ranged over 4 orders of magnitude and were highly reproducible across the five monkeys. Compared to levels for H. pylori J166 grown in culture, some transcripts were induced 2 to 4 fold. Unlike in a previous experiment, no induction of cagA was found. Control experiments using buffer containing Mg+2 (in which DNA polymerase activity of Tth is active but reverse transcriptase is not) confirmed that our in vivo estimates of mRNA copy number are based on RNA and not contaminating DNA. In order to better understand host factors of pathogenesis, we also studied the gastric transcription profile of H. pylori infection of the rhesus macaque using DNA microarrays. Significant changes were found in expression of genes important for innate immunity, chemokines and cytokines, cell growth and differentiation, apoptosis, structural proteins, and signal transduction and transcription factors. This broad transcription profile demonstrated both expected up-regulation of cell structural elements and the host inflammatory and immune response, as well as novel findings such as down-regulation of protease inhibitors and heat shock proteins. These results provide a unique view of acute H. pylori infection in a relevant animal model system and will direct future studies regarding the host response to H. pylori infection.

LONG-TERM SAFETY AND EFFICACY OF PMPA (TENOFOVIR) (0069)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

%NPRC $: 0.169% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
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[name]	PHD	C	VM:PATHO/MICROBIO L/IMMUNO	

AXIS I CODES: 1A, 2, 7B **AXIS II CODES:** 31, 50A, 50B, 64, 66

ABSTRACT

OBJECTIVE: To find better and safer antiviral drugs to treat HIV infection.

RESULTS: Simian immunodeficiency virus infection of newborn and infant macaques is a useful animal model of human AIDS to evaluate novel antiviral drugs. Previously, we initiated studies to evaluate the long-term therapeutic and toxic effects of tenofovir (9-[2-(phosphonomethoxy)-propyl]adenine ; PMPA). Macaques infected with SIV or SHIV were started on tenofovir treatment at different stages after infection. In addition, three uninfected macaques were started on tenofovir shortly after birth.

All infected animals have developed viral mutants with 5-fold reduced susceptibility to tenofovir. Some of these animals, however, have been able to achieve low or undetectable viremia levels after prolonged tenfovir treatment, associated with the development of strong antiviral immune responses. Even animals that have moderate to high levels of viremia have prolonged disease-free survival in comparison to untreated animals. We continue to monitor these animals for long-term efficacy and safety. These animals have now been on daily tenofovir treatment for 2 to 9 years.

The results from our animal experiments suggest that tenofovir has a very promising safety, efficacy and resistance profile for long-term treatment of HIV-infected patients, including children. Because tenofovir has currently been approved for the treatment of HIV-infected adults, while pediatric trials have recently been initiated, the results of our long-term studies are highly relevant.

ENHANCED SAFETY & EFFICACY OF AIDS VACCINES BY IFN (0097)

NPRC UNIT: VIROLOGY & IMMUNO - AIDS

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

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
YILMA, TILAHUN D	DVM, PHD	A	VM INTERNATL LAB MOL	
NONE	PHD	A	VM INTERNATL LAB MOL	
	PHD	A	VM: INTERNATL LAB MOL	CD DAVIS, CA USA

AXIS I CODES: 1A, 1D, 4, 7, 17, 19 **AXIS II CODES:** 31, 39, 64, 66, 83, 91

ABSTRACT

To address the problems of constructing safe and effective AIDS vaccines we took the novel approach of expressing the lymphokine interferon-gamma (IFN-gamma) in place of the nef gene in SIV vectors (SIVHyIFN) and evaluated this vaccine in the SIV-rhesus macaque model. Studies revealed increased safety, partial protection, decreased virus loads, and increased survival time for animals vaccinated with SIVHyIFN compared to SIVDnef. SIVHyIFN-vaccinated juvenile macaques had no clinical manifestation of AIDS before challenge and had significant reduction in post-challenge virus load compared to SIVDnef--vaccinated macaques. In neonatal macaques, complete protection against infection with pathogenic SIVmac251 was achieved in 25-33% animals vaccinated at the time of birth. Vaccination with high oral and low intravenous doses of SIVHyIFN resulted in significantly reduced viral loads and no clinical signs. These experiments were terminated by 6/01 due to a lack of funding.

In the current experiment, two groups of five rhesus macaques were vaccinated orally with SIVHyIFN or an rVV expressing SIV proteins and IFN-gamma (vSIVggen). All macaques became infected with SIVHyIFN but one of the five vSIVgammagen-vaccinated animals was not infected by this route. Monkeys given vSIVgammagen were boosted intramuscularly twice more with vSIVgammagen, then twice with a mixture of baculovirus-expressed SIV Gag, gp160, and IFN-gamma. All vaccinated macaques had positive antibody, proliferative and ELISPOT responses to vaccination by 47 weeks post-vaccination. Despite these responses, all vSIVgammagen-vaccinated macaques became infected with a high dose vaginal challenge of SIVmac251 although the initial viral loads were lower in the vaccinated animals compared to five unvaccinated controls. Animals vaccinated with SIVHyIFN have the lowest viral loads of all three groups and three of the animals appear to have resisted challenge with SIVmac251. The two animals that are positive for SIVmac251 are controlling the infection and have no signs of AIDS. One of the naïve controls was euthanized at 32 weeks post-challenge and two other animals had early signs on AIDS when euthanized. All animals were euthanized by 1/31/03 due to a lack of funding. We have completed analysis of the collected samples and are currently completing manuscripts for publication.

RESEARCH SERVICES

NAME	NON-HOST INSTITUTION: STATE, COUNTRY	# SPECIES: SPECIMEN
	UNIVERSITY OF ARIZONA: AZ	UNKNOWN: TISSUES
	NIH: NATIONAL INSTITUTE ON AGING: MD	UNKNOWN: TISSUES
	NIH: NATIONAL INSTITUTES ON AGING: MD	UNKNOWN: TISSUES
	LDS, INC.: MN	UNKNOWN: TISSUES
	UC DAVIS: DEPT. OF MOLECULAR BIOLOGY SCIENCE: CA	UNKNOWN: TISSUES
	AGENSYS, INC.: CA	UNKNOWN: TISSUES
	UC DAVIS: NEUROPHYS &BEH/DBS: CA	UNKNOWN: TISSUES
	UC DAVIS: ANTIBODY ENGINEERING LAB: CA	UNKNOWN: TISSUES
	RAVEN BIOTECHNOLOGIES: CA	UNKNOWN: TISSUES
	UC DAVIS: POP. HEALTH AND REPRODUCTION: CA	UNKNOWN: TISSUES
	UC DAVIS MEDICAL CENTER: PULMONARY AND CRITICAL MED: CA	UNKNOWN: TISSUES
	UC DAVIS: IMMUNOLOGY: CA	UNKNOWN: TISSUES
	UC DAVIS: CELL BIOLOGY AND HUMAN ANATOMY: CA	UNKNOWN: TISSUES
	UNIVERSITY OF PITTSBURGH: PA	UNKNOWN: TISSUES
	UC DAVIS: INTERNAL MEDICINE/PULMONARY: CA	UNKNOWN: TISSUES
	UNIVERSITY OF UTAH: UT	UNKNOWN: TISSUES
	DIABETES INSTITUTE OF IMMUNOLOGY AND TRANSPLANT: MN	UNKNOWN: TISSUES
	UC DAVIS: REPRODUCTIVE AND GENETIC SCIENCES: CA	UNKNOWN: TISSUES
	WAYNE STATE MEDICAL SCHOOL: MI	UNKNOWN: TISSUES
	UC DAVIS: CENTER FOR NEUROSCIENCE: CA	UNKNOWN: TISSUES
	IMMCO DIAGNOSTICS: NY	UNKNOWN: TISSUES
	UC DAVIS: PSYCHOLOGY AND BEHAVIORAL SCIENCE: CA	UNKNOWN: OTHERS
	UC DAVIS MEDICAL CENTER: RHEUM. AND ALLERGY: CA	UNKNOWN: TISSUES
	CNPRC: POP. HEALTH AND REPRODUCTION: CA	UNKNOWN: TISSUES

CNPRC: RESPIRATORY DISEASES: CA	UNKNOWN: TISSUES
UC DAVIS: ANATOMY,PHYSIO AND CELL BIOLOGY: CA	UNKNOWN: TISSUES
UC DAVIS: PHYSIO., ANATOMY AND CELL BIOLOGY: CA	UNKNOWN: TISSUES
DEPT. OF VETERANS AFFAIRS MEDICAL CENTER: UT	UNKNOWN: TISSUES
UC DAVIS: REPRODUCTIVE BIOLOGY: CA	UNKNOWN: TISSUES
UC SAN DIEGO:DEPT. OF NEUROSCIENCE: CA	UNKNOWN: TISSUES
UC DAVIS: DEPT. OF ENVIRONMENTAL TOXICIOLOGY: CA	UNKNOWN: TISSUES
MEDIUMMUNE INC.: MD	UNKNOWN: TISSUES
VIRGINIA COMMONWEALTH UNIVERSITY: VA	UNKNOWN: TISSUES
VIRAL AND RICKETTISIAL DISEASE LAB: CA	UNKNOWN: TISSUES
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CNPRC: PATHOLOGY: CA	UNKNOWN: TISSUES
UC DAVIS MEDICAL CENTER: OPTHALMOLOGY: CA	UNKNOWN: TISSUES
SAGRES DISCOVERY: CA	UNKNOWN: TISSUES
CNPRC: PATHOLOGY: CA	UNKNOWN: TISSUES
GENENTECH: CA	UNKNOWN: TISSUES
UC DAVIS: INTERNAL MED./ PULMONARY: CA	UNKNOWN: TISSUES
TEXAS A&M UNIVERSITY: TX	UNKNOWN: TISSUES

PUBLISHED: ABSTRACTS, BOOKS & JOURNALS

‡ NPRC Cited *NPRC Personnel

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0011	‡ In press publication
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0083	‡ In press publication
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0004	‡ In press publication
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Unknown [In press publication]

SOURCE OF INVESTIGATORS' SUPPORT

NON-FEDERAL

FOUNDATION

INVESTIGATOR ORGANIZATION	GRANT/CONTRACT	TOTAL FUNDING	SPID
name			
	51050-25-PG	$ 0	
BARRY, PETER A			
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BRITTEN, KENNETH H			
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ESSER, URSULA			
	ID01-D-130	$ 24,240	0268
FELBER, BARBARA K			
	21X5033A	$ 416,378	0220
JONES, EDWARD G			
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LONNERDAL, BO			
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LUCIW, PAUL A			
	51050-25-PG	$ 0	0253
MATSELL, DOUGLAS G			
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MILLER, CHRISTOPHER J			
		$ 95,479	0329
		$ 416,675	0328
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OVERSTREET, JAMES W			
	CIG-00-60	$ 0	
		$ 0	0018
PAPPAGIANIS, DEMOSTHENES			
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TARANTAL, ALICE F			
		$ 0	
VAN-ROMPAY, KOEN K A			
		$ 58,920	0069
ZAHORSKY-REEVES, JOANNE			
		$ 32,692	0339

private source

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	FOUNDATION	$	1,246,450

INDUSTRY

INVESTIGATOR ORGANIZATION	GRANT/CONTRACT		TOTAL FUNDING	SPID
name				
		$	14,668	0279
GREGORY, CLARE R				
		$	11,769	0284
HAVEL, PETER J				
	02-00154V	$	0	
	02-00021V	$	0	
		$	15,817	0307
LONNERDAL, BO				
		$	21,390	0211
MCCHESNEY, MICHAEL B				
	01-00662V	$	0	
	INDUSTRY	$	63,644	

private source

private sources

PVAS

INVESTIGATOR ORGANIZATION	GRANT/CONTRACT		TOTAL FUNDING	SPID
HAVEL, PETER J				
private source		$	0	
	PVAS	$	0	

OTHER NON FEDERAL

INVESTIGATOR ORGANIZATION	GRANT/CONTRACT		TOTAL FUNDING	SPID
ABEL, KRISTINA				
		$	78,379	0315
ESSER, URSULA				
		$	6,276	0268
name				
		$	0	
GREGORY, CLARE R				
	PY1111	$	29,059	0213
HAVEL, PETER J				
		$	60,346	0308
JOAD, JESSE P				
		$	1,173	0324
LONNERDAL, BO				
		$	21,390	0270
		$	21,390	0269

private funding

LU, FABIEN X				
[redacted]		21XS048A		0265
[redacted]			$ 34,356	0294
PINKERTON, KENT E				
[redacted]		6RT-0327	$ 0	0027
		OTHER NON FEDERAL	$ 252,369	

FEDERAL

INVESTIGATOR ORGANIZATION	GRANT/CONTRACT	TOTAL FUNDING	SPID
FEDERAL - NON PHS			
FULLER, CHARLES A			
NASA	NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE	$ 0	0187
GOLUB, MARI S			
EPA	R82740401	$ 0	0011
	FEDERAL - NON PHS	$ 0	
FEDERAL - PHS			
[redacted]			
NIH	2R44HD039087-02	$ 0	
AMARAL, DAVID G			
NIH	2R37MH057502-06	$ 553,903	0002
NIH	5R01NS016980-23	$ 371,250	0003
NIH	5R01MH041479-17	$ 329,889	0001
[redacted]			
NIH	5R01AI040085-07	$ 263,580	
NIH	5R01AI036178-09	$ 344,656	
BARNES, CAROL			
NIH	2R01AG003376-22	$ 211,877	0295
BARRY, PETER A			
NIH	5R01AI049342-03	$ 454,338	0218
NIH	5R03AI053208-02	$ 74,250	0229
[redacted]			
NIH	5R01AI026815-17	$ 334,125	
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	
BEAMAN, BLAIN L			
NIH	5R01HL069426-03	$ 294,640	0319
[redacted]			
NIH	5U42RR016026-03	$ 806,832	
BRITTEN, KENNETH H			
NIH	5R01EY010562-09	$ 0	0272

BUCKPITT, ALAN R				
NIH	5R01ES004311-15	$	305,438	
NIH	5R01ES008408-05	$	0	0273
BUNNELL, BRUCE A.				
NIH	R01AI047693-03	$	0	0131
CAPITANIO, JOHN P				
NIH	5P51RR000169-41	$	125,585	0136
NIH	5R01MH049033-11	$	438,917	0004
CHAFFIN, CHARLES L				
NIH	5R01HD038724-04	$	192,960	
NIH	1R01HD043358-01A1	$	293,278	0318
COFFMAN, ROBERT L.				
NIH	1U01AI056435-01	$	739,815	0317
[name]				
NIH	5R01AI052737-02	$	266,875	
DANDEKAR, SATYA				
NIH	5R01AI043274-06	$	366,884	
NIH	5R01DK061297-02	$	359,707	
NIH	5R01DK043183-11	$	295,176	0271
[name]				
NIH	5R01AI042400-04	$	326,543	
[name]				
NIH	1R01AI43894-01	$	0	
DISBROW, ELIZABETH A.				
NIH	1R01NS044590-01A1	$	492,854	0316
DOUGLAS, GORDON C				
NIH	1R03HD043863-01	$	74,250	0309
NIH	1R01HL068035-01A2	$	360,095	
DUNAIF, ANDREA				
NIH	P50HD044405	$	82,487	0230
[name]				
NIH	5R01RR007849-10	$	288,288	
[name]				
NIH	5R21AI049804-02	$	0	
GAGE, FRED				
NIH	5R03TW006130-02	$	53,072	
NIH	5R01AG021876-02	$	284,550	
NIH	5R01AG020938-02	$	414,020	
NIH	5P01AG010435-13	$	1,931,174	0008
NIH	5R01AG008514-16	$	409,752	
GERSHWIN, LAUREL J				
NIH	5P51RR000169-4205	$	29,668	0285
GERSHWIN, MERRIL E.				
NIH	5R01AT000637-04			0321
GOTHARD, KATI				
NIH	5K01MH001902-06			0306
HAASE, ASHLEY				

NIH	1R01AI056997-01A1	$	510,535	
NIH	5R01AI048484-04	$	782,176	0327
NIH	5R37AI028246-15	$	356,837	
NIH	5T32AI007421-09	$	254,390	
HAGERMAN, PAUL J				
NIH	5R01NS043532-02	$	286,175	
NIH	5R01HD040661-02	$	267,300	0249
HECKER, JAMES G				
NIH	5K08NS001960-06	$	161,406	0237
NIH	1R01NS046591-01	$	351,064	
HORTON, JONATHON C				
NIH	2R01EY010217-11	$	582,306	0083
HYDE, DALLAS M				
NIH	5P51RR000169-4203	$	62,577	0223
NIH	1C06RR017548-01	$	1,948,732	0290
NIH	1G20RR016932-01			0258
NIH	G20RR014532	$	0	0261
NIH	G20RR017053-01	$	0	0260
NIH	G20RR016039-01	$	0	0259
JONES, EDWARD G				
NIH	5P20MH060975-08	$	1,380,586	
NIH	5R01NS039094-05	$	306,454	
NIH	5R01NS021377-19	$	257,417	0085
KAN, Y.W.				
NIH	5P01HL053762-09	$	0	0128
KEARNS-JONKER, MARY				
NIH	5R21AI049922-03			0231
C name 3				
NIH	5F31MH012876-03	$	26,749	
C name 3				
NIH	2S07RR018250-02	$	149,359	
KOEHLER, JANE				
NIH	5R01AI052813-02	$	498,547	0256
KOHN, DONALD B				
NIH	1P01HL073104-01	$	1,731,873	
NIH	5R01AI052798-03			0235
KRUBITZER, LEAH A				
NIH	5R01NS035103-07	$	371,250	0310
C name 3				
NIH	5R01CA039207-20	$	311,099	
LANDAY, ALAN L.				
NIH	5P01AI055793-02	$	1,483,984	0337
NIH	5P01HD040539-03	$	1,061,538	
LASLEY, BILL L				
NIH	5P51RR000169-4201	$	144,575	0221
NIH	5P01ES006198-10	$	849,493	0190,0191,0192,0245,0292,0293
NIH	N01HD-6-3247	$	0	

[name]				
NIH	5D43TW005718-03	$	151,000	
LERCHE, NICHOLAS W				
NIH	5P51RR000169-4202	$	979,207	0222
NIH	5U42RR016023-04	$	756,580	0168
NIH	5U24RR018144-02	$	1,735,872	0275
LOZOFF, BETSY				
NIH	3T37TW000035-07S1	$	189,179	
NIH	5P01HD039386-03	$	1,364,588	0228
NIH	5R01HD033487-07	$	441,571	
NIH	5R37HD031606-10	$	202,068	
LU, FABIEN X				
NIH	R21RR013149-00	$	0	0264
NIH	5U01AI046747-03	$	49,229	0263
[name]				
NIH	5R03AR047104-03	$	73,750	
LUCIW, PAUL A				
NIH	5R03AI054202-02	$	74,250	0298,0299
NIH	5R01AI038532-08			0323
LYONS, LESLIE				
NIH	5R24RR016094-02	$	316,789	
NIH	1R24RR017584-01A1	$	263,943	0305
NIH	1R03DE014965-01	$	71,074	
MARTHAS, MARTA L				
NIH	5R21AI052000-02	$	169,300	0297
NIH	5R01AI046320-05	$	548,955	0163
NIH	5R01AI39109-05	$	0	
[name]				
NIH	5R01AI041952-07	$	580,288	
NIH	5R01AI044596-06	$	629,175	
NIH	5R24RR016986-02	$	602,611	
MATSUMURA, FUMII				
NIH	5P30ES005707-13			0338
MCCHESNEY, MICHAEL B				
NIH	5R03AI051131-03	$	59,650	0198
NIH	5R01AI045827-03	$	238,600	0199
CDC	U50CCU913348-06	$	40,269	0055
[name]				
NIH	5R01HL065937-04	$	240,000	
[name]				
NIH	5R01DC004976-03	$	251,125	
[name]				
NIH	5R37NS020331-20	$	340,875	
NIH	5R37MH046823-13	$	340,875	
MENDOZA, SALLY P				
NIH	5R21MH066756-02	$	148,193	0301
MEYERS, STUART A				
NIH	5R01RR016581-02	$	289,628	0225

NIH	1R21RR017419-01A1	$	142,936	0225
MILLER, CHRISTOPHER J				
NIH	5P51RR000169-4206	$	331,482	0286
NIH	5U19AI051596-02	$	2,433,228	0334
NIH	5R24RR014555-05	$	703,649	
NIH	5R01AI051239-02	$	1,193,789	0335
NIH	5R01AI044480-05			0162
MORRISON, JOHN				
NIH	5P01AG016765-06	$	0	0006
NORTH, THOMAS W				
NIH	R01RR013967-04	$	0	
NIH	R01AI47070-03	$	0	0267
PACHNER, ANDREW R				
NIH	N01AI095358-01	$	0	0242
[name]				
NIH	1F32EY014503-01A1	$	46,420	
[name]				
NIH	1R03CA103492-01	$	78,200	
NIH	5K30HL004130-05	$	200,000	
NIH	5R01DK053689-06	$	263,760	
NIH	5R01CA095946-02	$	117,750	
NIH	5R01AI042801-05	$	617,571	
NIH	5T32AI007502-09	$	309,370	
PEREZ, RICHARD V				
NIH	P51RR000169-42	$	0	0215
[name]				
NIH	5K01ES010959-03	$	118,930	
PESSAH, ISAAC N.				
NIH	5P01ES011269-03	$	731,064	0312,0333
PINKERTON, KENT E				
NIH	5R01ES011634-02	$	281,303	0027
PLOPPER, CHARLES G				
NIH	5P51RR000169-4204	$	158,938	0226
NIH	5P01ES000628-30	$	1,168,676	0123,0124,0183,0184
POLLARD, RICHARD B.				
NIH	5P30AI049366-03	$	732,522	0322
POSTLETHWAIT, EDWARD M				
NIH	5P01ES011617-02			0336
[name]				
NIH	5U54HD029125-13	$	1,251,146	0018
[name]				
NIH	5R01AG017902-04	$	179,155	
RAPP, PETER R				
NIH	5U01MH062448-03	$	334,110	
NIH	5R01AG010606-11	$	300,522	0185
[name]				
NIH	5P01AI040682-07	$	1,377,953	

RECANZONE, GREGG HOWARD				
NIH	5R01EY013458-03	$	290,750	0090,0296
[name]				
NIH	5T35ES007301-09	$	33,035	
NIH	5R01AR027130-20	$	244,578	
NIH	2T32ES007059-26	$	286,614	
[name]				
NIH	1R01HL074704-01	$	437,500	
[name]				
NIH	5R01HL071488-02	$	327,682	
NIH	2R01HL055667-08	$	294,623	
[name]				
NIH	5R01AI046145-04	$	310,935	
SCHELEGLE, EDWARD				
NIH	5R01ES006791-07	$	297,000	0320
[name]				
NIH	1R01AI057020-01	$	145,572	
NIH	5R21NS044796-02	$	213,750	
NIH	1R21AI054235-01	$	40,257	
[name]				
NIH	5K23AG000946-04	$	127,926	
SODORA, DONALD L				
NIH	2R01AI035522-11A1	$	194,802	
NIH	5R01DE012926-05	$	0	0166
SOLNICK, JAY V				
NIH	5R01AI042081-06	$	369,795	
NIH	5R01RR014298-03	$	359,125	0193,0194,0227
SPARGER, ELLEN				
NIH	5R01AI054204-02	$	0	0262
SUTTER, MITCHELL L				
NIH	5R01DC002514-08	$	232,292	0161
TARANTAL, ALICE F				
NIH	5U01HL069748-03	$	562,169	0206
NIH	3U01HL069748-03S1	$	59,650	0313
NIH	1R01HL073220-01	$	323,250	
NIH	1R13HL072168-01	$	20,000	0232
NIH	R21AI046026	$	0	
TUSZYNSKI, MARK H				
NIH	5R01NS042291-03	$	621,426	0009
NIH	5R21NS042038-03	$	194,507	
USREY, WILLIAM M				
NIH	R01EY013588-03	$	0	0159
VANDEVOORT, CATHERINE A				
NIH	5R01RR013439-06	$	551,925	0132
VAN-ROMPAY, KOEN K A				
NIH	1R21AI058056-01			0288
[name]				

NIH	1P51RR00169-39	$	0	
NIH	5K01HL004142-05	$	136,687	
NIH	5K01RR000150-05	$	100,991	
WIEHLE, RONALD				
NIH	5R44HD039087-03	$	225,407	0291
NIH	5T32ES007055-27	$	250,617	
WINE, JEFFREY J				
NIH	5R01DK051817-07	$	317,427	
NIH	5P01AG017164-04	$	788,863	
NIH	5R37AG002224-23	$	297,000	
NIH	5R37HL035635-16	$	310,010	
NIH	5R01ES009701-05	$	244,101	
YILMA, TILAHUN D				
NIH	1R01AI054951-01	$	256,933	0304
NIH	5R21AI053811-02			0303
YOUNG, GLENN M				
NIH	1R21AI056042-01	$	334,125	
ZAHORSKY-REEVES, JOANNE				
NIH	5K01RR016582-03	$	81,243	
ZERN, MARK A.				
NIH	5R01AA006386-20	$	343,120	
NIH	1R01AA014173-01	$	445,500	0332
	FEDERAL - PHS	$	63,150,026	
	FEDERAL	$	63,150,026	

UKN

INVESTIGATOR ORGANIZATION	GRANT/CONTRACT		TOTAL FUNDING	SPID
MILLER, CHRISTOPHER J				
DARPA-DSO		$	66,776	0330
	UKN	$	66,776	

TOTAL FUNDING: **$ 64,779,265**

RESOURCE SUMMARY: SUBPROJECTS

The following only includes information associated with subprojects.

	Mgmt. A	Research B	Pilot C	Collab. D	Total (excludes
Number of Subprojects	7	100	6	32	145
Number of Investigators	7	300	14	57	335
Number In Press	0	10	0	10	20
%AIDS of NPRC Dollars	7.755%	36.240%	0.068%	2.392%	46.455%
%Non-AIDS of NPRC Dollars	0.048%	33.629%	0.000%	19.868%	53.545%
Total Percent of NPRC Funds Awarded	7.803%	69.869%	0.068%	22.260%	100.000%

RESOURCE SUMMARY: ADMINISTRATIVE

PERSONNEL		On Subprojects	Not On Subprojects
Core Personnel			
DOCTORAL LEVEL SCIENTISTS (C)		23	0
	Core Personnel	23	0
Non-Core Personnel			
AFFILIATED (A)		285	78
GRADUATE STUDENT/POST DOCTORAL SCIENTIST (G)		27	17
	Non-Core Personnel	312	95
Personnel Total:		335	95

ACCESS BY NON-NPRC PERSONNEL

GEOGRAPHICAL USAGE BY INVESTIGATORS AT NON-HOST INSTITUTIONS

Foreign Investigators by Country	**20**
AUSTRALIA	1
BRAZIL	1
BRITISH COLUMBIA	1
CANADA	1
CHINA	2
FRANCE	5
JAPAN	3
PUERTO RICO	2
TAIWAN	1
UK	1
UNKNOWN	2
USA Investigators by State	**295**
AL	2
AZ	5
CA	140
CT	2
DC	1
FL	5
GA	11
IA	1
IL	2
KY	1
LA	12
MA	10
MD	20
ME	1
MI	5
MN	3
MT	1
NC	1
NE	4
NJ	7
NM	2
NV	2
NY	9
OH	5
OK	2
OR	4
PA	8
TX	11
UT	1
VA	6
WA	7
WI	4
Total Investigators at Non Host Institutions:	**315**

RESEARCH SERVICES

Scientists Provided with Services	43
Services Provided	

RESEARCH SERVICES BY COUNTRY

Research Services to USA Investigators by State	**43**
AZ	1
CA	30
MD	3
MI	1
MN	2
NY	1
PA	1
TX	1
UT	2
VA	1
Total Research Services:	**43**

INFRASTRUCTURE TABLE

GRANT REPORTED UNITS	**%NPRC USE**
ADMINISTRATIVE	7.180%
AIDS COMPONENT	38.660%
BRAIN, MIND, & BEHAVIOR	3.910%
COLLABORATIVE RES PROGRAM	0.000%
MODERNIZE & IMPROVE - AID	4.240%
MODERNIZE & IMPROVEMENT	4.570%
NIA	1.040%
PILOT STUDY	2.760%
PILOT STUDY - AIDS	1.470%
PRIMATE SERVICES	22.870%
REPROD & GENETIC SCIENCES	2.600%
RESEARCH CORES	6.650%
RESPIRATORY DISEASES	1.410%
VIROLOGY & IMMUNO - AIDS	2.640%
TOTAL NPRC:	**100.00%**

RESEARCH TABLE

UNITS GENERATED BY SUBPROJECTS	**%NPRC USE**
BRAIN, MIND, & BEHAVIOR	23.815%
COLLABORATIVE RES PROGRAM	3.333%
MODERNIZE & IMPROVE - AID	5.586%
MODERNIZE & IMPROVEMENT	0.000%
PILOT STUDY	0.136%
PRIMATE SERVICES	2.169%
REPROD & GENETIC SCIENCES	12.967%
RESEARCH CORES	3.618%
RESPIRATORY DISEASES	10.478%
VIROLOGY & IMMUNO - AIDS	37.898%
TOTAL NPRC:	**100.000%**

RESOURCE SUMMARY: PUBLICATION/SUPPORT

PUBLICATIONS

	Cited	Not Cited	Total
Published			
Journals	28	65	93
In Press			
Abstracts	0	1	1
Books	2	2	4
Journals	34	17	51
Unknown	0	1	1
Total	64	86	150

INVESTIGATOR SUPPORT

NON-FEDERAL		
	$	252,369
FOUNDATION	$	1,246,450
INDUSTRY	$	63,644
PVAS	$	0
UNKNOWN	$	66,776
NON-FEDERAL	**$**	**1,629,239**
FEDERAL		
NON-PHS		
EPA	$	0
NASA	$	0
NON-PHS	**$**	**0**
PHS		
AA	$	788,620
AG	$	4,944,839
AI	$	17,723,834
AR	$	318,328
AT	$	0
CA	$	507,049
CDC	$	40,269
DC	$	483,417
DE	$	71,074
DK	$	1,236,070
ES	$	4,566,271
EY	$	919,476
HD	$	5,456,593
HL	$	5,298,179
MH	$	3,553,222
NS	$	3,968,428

RR		$	12,881,106
TW		$	393,251
	PHS	**$**	**63,150,026**
	TOTAL SUPPORT	**$**	**64,779,265**

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-0
MACACA MULATTA								
Adult Females	553	0	112	0	10	0	92	563
Adult Males	172	0	33	0	7	0	65	133
Infants/Juveniles	750	352	244	0	39	0	452	855
MACACA MULATTA (SPF)								
Adult Females(SPF)	110	0	53	0	3	0	0	160
Adult Males(SPF)	43	0	20	0	2	0	0	61
Infants/Juveniles(SPF)	275	98	107	0	14	0	161	305
	1,903	**450**	**569**	**0**	**75**	**0**	**770**	**2,077**

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 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-0
CALLICEBUS MOLOCH								
Adult Females	12	0	2	0	1	0	2	11
Adult Males	15	0	0	2	0	0	0	13
Infants/Juveniles	9	6	5	0	2	0	5	13
MACACA FASCICULARIS								
Adult Females	241	0	96	45	14	0	35	243
Adult Males	91	0	26	5	3	0	17	92
Infants/Juveniles	83	20	32	3	10	0	46	76
MACACA MULATTA								
Adult Females	668	0	283	5	41	0	257	648
Adult Males	320	0	140	15	19	0	115	311
Infants/Juveniles	406	218	227	60	23	0	382	386
MACACA RADIATA								
Adult Males	0	0	0	0	0	0	0	0
	1,845	**244**	**811**	**135**	**113**	**0**	**859**	**1,793**

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

CNPRC RESEARCH HIGHLIGHTS

SPID(s): 0123, 0124, 0136, 0183, 0185, 0301

The mission of the California National Primate Research Center (CNPRC) is to provide interdisciplinary programs in biomedical research on significant human health_related problems in which nonhuman primates are the models of choice. In 2003-04, a variety of research opportunities were provided to staff and affiliate scientists. These researchers reported 145 projects encompassing many aspects of biology and medicine, including AIDS and other infectious diseases, reproduction, infertility, neourodegenerative diseases such as Alzheimer's, nutrition, cystic fibrosis, asthma, xenotransplantation, and behavior. The following represent the CNPRC's most significant scientific accomplishments of 2003-04.

BRAIN, MIND AND BEHAVIOR

The Brain, Mind and Behavior Unit of CNPRC provides services, training, and consulting and collaborative expertise in the areas of basic neuroscience, stress physiology, psychoneuroimmunology, cognitive neuroscience, and psychosocial processes in nonhuman primates. Particular emphasis is on studying the interrelations of processes at multiple levels of analysis: social, psychological, neuroendocrine, and neurobiological.

In the past year, scientists working in the BMB Unit have made a number of significant discoveries pertaining to human health:

SPID0136: The hypothalamic pituitary adrenal axis is a major stress response system, affecting virtually every other physiological system in the organism. Alterations in the regulation of this system have been associated with a variety of both psychological and physical disorders. Research in Dr. Capitanio's laboratory has focused on developing a biobehavioral assessment program for young infant monkeys that could identify risk factors for later poor health, behavioral, social, and reproductive outcomes, and one important component of this program has been study of the regulation of the HPA axis. Using cluster analysis on data from more than 500 monkeys, three patterns of HPA regulation have been identified, including an abnormal pattern that is characterized by very high cortisol concentrations and a failure in negative feedback control. Preliminary evidence suggests that this pattern is associated with a greater risk of colitis in our colony. This study demonstrates that knowledge of the regulatory characteristics of this stress response system might be a significant predictor of health outcomes that are typically attributed to "stress", and could be an important tool for colony management.

SPID0301: Most primates including humans have a propensity to seek contact and to form strong positive social relationships, and this is exemplified in the extreme by the South American titi monkey. In nature and in the laboratory, these monogamous primates spend up to 90% of their day in physical contact with other members of their family group. A unique aspect of social contact in titi monkeys is tail-twining. Very often all members of a family group (3-5 individuals) sit in a row and combine their tails in a single twine. Collaborative research between Dr. Sally Mendoza and Dr. Leah Krubitzer is investigating the neuroanatomical pathways mediating social contact in titi monkeys. Electrophysiological recordings indicate that somatosensory representation of body parts relevant to social behavior, such as the lateral surface of the body, is magnified in titi monkeys. Moreover, somatosensory pathways have been traced to areas of the frontal lobe that are hypothesized to play a direct role in social expression. This research program demonstrates that species-typical patterns of social affiliation, and in particular physical contact, are reflected in brain organization.

SPID0185: Perhaps the most common psychological consequences of aging is a reduction in memory function. A research program by Dr. Peter Rapp is focused on characterizing the nature and severity of age-related cognitive decline, using animals from the National Institute of Aging

colony of aged monkeys at CNPRC. A number of important results have been demonstrated, not the least of which is that the status of recognition memory varies considerably among aged individuals, with many at the end of their expected life span continuing to score as accurately as young adults. In addition, age-related deficits in working and recognition memory are unrelated, suggesting that aging independently influences the integrity of the neural systems that mediate these capacities. Moreover, although the cholinergic innervation of the hippocampus is vulnerable to aging, structural comprise in this neurochemical input fails to predict age-related deficits in memory mediated by the medial temporal lobe system. Thus, the cognitive and anatomical changes in memory associated with aging are not uniform.

REPRODUCTIVE AND GENETIC SCIENCES

Staff Scientists in the Reproductive Sciences Unit have made substantial contributions to research and service efforts at the CNPRC, and are committed to work in compelling areas of research that will enhance scientific and medical progress, provide essential expertise to the greater research community, and train the next generation of investigators with expertise in the nonhuman primate model. Unit research efforts have focused on reproductive endocrinology and aging, gamete biology, fetal development, and stem cells and gene therapy. In one set of studies, adrenal activity during aging was shown to be gender-specific in both human and nonhuman primates. The increase in adrenal activity observed in older women was not observed in men, and was shown to be specific to ovarian aging and ethnicity. Weak androgen production from the adrenal has also been shown in perimenopausal rhesus monkeys, and found to result in individual differences in circulating sex steroids. Thus, the monkey model will provide key insights into understanding 'healthy aging' and the different responses of women to hormone replacement therapy.

Many compounds that are found in the environment have unsuspected biological properties and a large group are categorized as endocrine disruptors because they interfere with hormone action. Environmental toxins such as dioxin is one of these compounds, and dioxin has been shown to specifically block the estrogen-accelerated mobilization of specific fatty acids which are essential for brain development. Studies in gravid rhesus monkeys indicate that dioxin exposure is associated with defects in neural tube development, an early precursor in the development of the brain. Exposure of mature rhesus macaques to other weak environmental estrogens, even at doses that reveal no acute adverse effects, have been shown to have adverse latent effects days or weeks after the initial exposure; this was demonstrated by alterations of normal menstrual cycles.

Other studies focusing on the ovary include those on in vitro maturation and cryopreservation of rhesus oocytes, which may have a direct application to women. These studies are important because they can evaluate the early development of embryos that are produced from these oocytes. Currently, experiments are being conducted on the role of cumulus cell processes and their survival after freezing. Embryos are also being used for the production of rhesus embryonic stem cell lines without the use of murine products; alternative feeder layers are under assessment for their ability to support stem cell outgrowth from the inner cell mass of rhesus monkey embryos.

The Northwestern University Specialized Center of Research on Sex and Gender Factors Affecting Women's Health is a multidisciplinary NIH-funded program which includes investigators from two National Primate Research Centers (California and Wisconsin), Pennsylvania State University, the University of Chicago, and the Mayo Clinic. This Specialized Center of Research encompasses human and nonhuman primate studies, and uses the monkey model to investigate the ovarian syndrome proposed to be associated with prenatal androgen excess. Initial results from these investigations support the hypothesis that fetal androgen excess reprograms luteinizing hormone secretion and insulin release, and provide the first direct link of fetal events to adult polycystic ovary syndrome traits.

A model of fetalmaternal microchimerism represents a new development in demonstrating that fetal DNA can be detected in the maternal circulation of rhesus monkeys, with gestational changes and postnatal clearance characteristics parallel to those found in humans. In further studies it was shown that fetal cells circulate and persist long-term in the maternal compartment. This model will

be crucial for elucidating a myriad of unanswered questions in humans such as the origin of the cells, the relationship between cellular and cell-free DNA transfer between the fetus and mother, and the role of fetal cells and DNA in maternal health and disease. Using similar PCR-based techniques for the rhesus Y-chromosome, a rapid method for determining the gender of developing rhesus monkeys from maternal blood samples and prior to sexual differentiation was also achieved, thus providing a noninvasive method for routine gender screening.

Gene therapy studies have focused on direct organ-targeting during development, including intrapulmonary and intramyocardial fetal gene delivery techniques. Efficient gene transfer was shown to occur when using these ultrasound-guided methods, with few vector copies found in non-thoracic tissues, and no evidence of germ cell gene transfer. Normal postnatal lung and heart function was also observed indicating that organ-targeted prenatal gene transfer and subsequent transgene expression both prenatally and postnatally does not alter organ structure or function. Current findings suggest that direct in utero organ-targeting approaches may be the best method for obtaining maximum therapeutic effect for the treatment of congenital or acquired diseases of the heart and lung, and highlight the importance of the rhesus monkey model for assessments of gene transfer efficiency and safety prior to human application.

Studies on stem cells include an analysis of the effects of age on the frequency and cell cycle characteristics of hematopoietic stem and progenitor cells in fetal through aged rhesus monkeys. The results of these studies suggest that the greatest quantity of CD34+Lin- hematopoietic cells are found in fetuses, that the frequency of cycling CD34+ cells gradually declines with maturation and aging, and that an age-dependent difference in lineage commitment occurs. New techniques for the growth and analysis of bone marrow-derived rhesus mesenchymal stem cells were also developed. In one study, cells from fetal, newborn, juvenile, and adult rhesus monkeys were isolated, and growth kinetics, cell surface expression, and differentiation capabilities assessed. These investigations showed that fetal cells have greater proliferative capabilities when compared to adults, which was further supported by gene expression profiles where age-related differences were found. The transduction kinetics of lentiviral vectors was also explored, and results indicated that the viral vectors used in these studies can efficiently transduce mesenchymal stem cells without inhibiting growth or differentiation potential.

RESPIRATORY DISEASES

ASTHMA

Respiratory diseases is one of the major categories of debilitating and fatal diseases in the United States. In recent years there has been a large upsurge in the incidence of debilitating respiratory diseases such as asthma among children in major urban centers in the United States. Epidemiologic studies suggest that a primary etiology for this upsurge has been the increase in the amount of environmental pollution associated with these population centers. The Respiratory Diseases Unit represents a component of a larger group of over 30 faculty investigators on the Davis campus who study the respiratory system of non-human primates as a model for human respiratory diseases. Projects cover practical clinical applications as well as cellular and mechanistic studies. Highlighted here are three investigations of the pulmonary effects of environmental oxidant air pollutants, with an emphasis on children. This research program explores the relationship between childhood lung diseases, like asthma, and exposure to the air pollutant ozone. Evidence suggests that early exposure to ozone fundamentally alters lung development, changing the organ's structure, compromising its function and making it hypersensitive to allergens, setting the stage for asthmatic conditions. Young primates - monkeys and humans alike - are particularly vulnerable to air pollution's effects because their lungs undergo critical growth and development in the first months and years following birth.

In most respects, monkeys that were exposed to both dust mites and ozone underwent the most profound changes. One of the most startling changes was in the structure of the lung overall. Airways of normal rhesus monkey lungs have 14-16 branches; the monkeys exposed to ozone and

allergens had an average of 8-10 branches. Our most recent findings indicate that these changes begin very early in life and that removal from exposure conditions for 6 months does not promote recovery. Other impacts of normal growth of the lungs includes accelerated alveolarization and hyperinnervation airway smooth muscle, the effector of airway constriction, is increased in thickness and becomes reoriented in such a way as to promote excessive airway closure. Again, these changes begin very early, and cessation of exposure after 6 months and exposure to filtered air for an additional 6 months does not allow recovery.

In short, exposure to ozone and to allergens - and especially to both - at an early age seems to train the body to give an exaggerated response to later assaults. Our initial observations suggest that the changes in the lung's architecture and function are reversible. In a recent experiment, infant monkeys were exposed to pollution for six months, then allowed to breathe clean air for another six months before the scientists examine them.

POSTNATAL REMODELING IN DIST. AIRWAY OF INFANT MONKEYS EXP. TO OZONE & ALLERGEN

SPID 183
Reporting Period 5/01-4/30/02
Charles Plopper

KEYWORDS: OZONE, OXIDANT AIR POLLUTANTS, ALLERGIC ASTHMA

ABSTRACT: Airway smooth muscle has been implicated in the excessive bronchoconstriction of asthma. The present study addressed the question of whether the episodic nature of urban exposure to oxidant air pollutants contributes to the rise in childhood respiratory diseases by altering postnatal lung development. Left cranial lobes from control infant rhesus monkeys (30, 60, 90, 180 days old plus adults) and from infant monkeys (30 days old) exposed to filtered air (FA), house dust mite allergen (HDMA), ozone (O3), or HDMA+O3 for 11 episodes (5 days 0.5 ppm O3 + 9 days FA) were inflation fixed with paraformaldehyde, dissected to expose the airway tree and incubated with phalloidin, a fluorochrome with a high affinity for actin. Smooth muscle distribution was imaged via confocal microscopy. The smooth muscle is organized in wide bands in both terminal (TB) and respiratory bronchioles (RB) at 30 days old. At 60 days old, there is a clear transition between TB and the filamentous smooth muscle of the RB. This pattern was also found in 180 day old FA monkeys, but in challenged monkeys, the smooth muscle bundles are thicker and more closely packed in areas of alveolar outpocketings. Cessation of exposure and return to FA for 6 months did not allow return of the changes to control conditions. The airways hyperreactivity continues even during an additional six months of exposure to filtered after removal of allergen and ozone. We conclude that the periodic cycles of acute injury and repair associated with the episodic nature of environmental patterns of ozone exposure alters postnatal morphogenesis of smooth muscle in the distal lung of infant primates and that these alterations are not reversible with cessation of exposure.

FUNDING: NIH 5P01ES000628-29

IMMUNE RESP IN NEONATAL HOUSE DUST MITE-SENSITIZED MONKEYS FOL. EXP.TO OZONE

SPID 124
Reporting Period 5/01-4/30/03
Charles Plopper

KEYWORDS: ALLERGIC ASTHMA, HOUSEDUST MITE, INTRAPULMONARY

BRONCHI

ABSTRACT: Indoor allergens such as house dust mite (HDM) are a contributing factor to the development of allergy and asthma in children. There is increasing evidence that air pollutants such as ozone may effect the initiation or severity of atopic diseases. In order to further our understanding of the effects of HDM and ozone on the developing immune system, neonatal Rhesus Monkeys (n=3/group) were exposed for 22 weeks to one of 4 regimens: 1) filtered air (FA), 2) priming doses of HDM + adjuvant parenterally follwed by 3 times weekly aerosolized HMD (HDM), 3) ozone at 0.5 ppm for 8 hrs/day 5 days on and 9 days off (O3, or 4) HDM +O3. Immune cells were identified at specific airway generations by immunohistochemistry and their abundance estimated by their volume per surface of basal lamina on lung sections. HDM-sensitized animals exhibited an increase in abundance of CD1a+dendritic cells, with most pronounced differences in proximal airways. O3 exposure had a modest effect on increasing CD1a+cell abundance within proximal airway interstitium of HDM-sensitized animals. The abundance of CD4+ and CD25+ cells increased in proximal airways of HDMA-sensitized animals, but appeared to decrease with concomitant O3 exposure. Proliferating cells (indicated by BrdU incorporation) increased within both epithelial and interstitial compartments of HDM-sensitized animals as compared to FA or o# groups. Interstitial proliferation of leukocytes peaked in distal airways of HDM-sensitized animals, but appeared to be maximal within proximal airways of HDM+O3 group animals. Post exposure recovery occurs in only a limited number of immunologic parameters. Cumulatively, these data indicate that episodic exposure to

ozone has an immunomodulatory effect on the accumulation of leukocytes and antigen presenting cells throughout the

airways that continues after removal of allergen and ozone.

FUNDING: NIH 5P01ES000628-29

AFFERENT NERVE ACTIV. IN ISOL. TRACHEA OF INF. MONKEYS EXP. TO OZONE & ALLERGEN

SPID 123

Reporting Period 5/01-4/30/03

Charles Plopper

KEYWORDS: PULMONARY FUNCTION, OZONE, HDMA, ALLERGIC ASTHMA

ABSTRACT: Twenty-four infant rhesus monkeys were exposed to 11 episodes (starting at 30 days old) of either filtered air (FA), house dust mite allergen aerosol (HDMA), ozone (O3) or HDMA + O3 (5 days each followed by 9 days of FA). O3 was delivered for 8 hr/day at 0.5 ppm. Twelve monkeys were sensitized to house dust mite allergen (Dermatophagoides farinae) at age 14 and 21 days. HDMA sensitization was confirmed via skin testing. Sensitized monkeys were exposed to HDMA aerosol for 2 hr/day on day 3-5 of either FA (HDMA, n=6) or O3 (HDMA + O3, n=6) exposure. Non-sensitized monkeys were exposed to either FA (FA, n=6) or O3 (O3, n=6). On the eleventh day of the tenth episode the concentration of histamine aerosol required to double breathing frequency (EC200fb) and reduce tidal volume by one half (EC50Vt) was determined. At time of necropsy a 4cm section of distal trachea, along with its vagal innervation, was removed and placed in a partitioned recording chamber in which one side (containing the trachea) was perfused with 35 deg. C Krebs and the other (containing the vagus) was filled with light parrafin oil. Small slips of the vagus were placed on a recording electrode. The luminal surface of the trachea was then gently probed to locate active receptor fields. Conduction velocities were used to characterize nerve fiber type. The EC200fb was 0.368 (FA), 0.396 (HDMA), 0.301 (O3), and 0.205 mg/ml (HDMA+O3). The EC50Vt was 0.316, 0.417, 0.332, and 0.171 respectively. Baseline nerve impulse activity of the A-delta fibers was 5.79 (n=5), 4.82 (n=4), 9.50 (n=15), and 16.61 (n=8) imps/sec respectively. This data indicates that airway A-delta fibers may play an important role in the heightened breathing pattern response to inhaled histamine in infant monkeys sensitized and exposed to HDMA+O3.

FUNDING: NIH 5P01ES000628-29

V&I UNIT RESEARCH PROGRESS HIGHLIGHTS

The V&I unit focuses on understanding the complex relationship between a host and viral pathogen that determines the outcome of viral infections. In particular, all of the Staff Scientists study viral infections in monkeys that are models of human viral infections with the goal of developing interventions (vaccines and therapies) that will prevent or alleviate the human suffering associated with viral infections. A number of the Staff Scientists study viral agents that are zoonotic or could be used in a biodefense setting. The Unit is anxious to develop a program in emerging, zoonotic and bioterror viral agents, however, the lack of BSL_3 and BSL_4 animal and laboratory facilities at the CNPRC have been a major impediment to progress in this regard. Vaccines are the best approach to controlling viral infectious diseases, including bioterror agents and modern vaccine development requires detailed studies of immune response and mechanisms of pathogenesis.

SPID0297: The most important means of eliminating pediatric HIV infection is to prevent women from becoming HIV-infected before or during pregnancy. However, there is little information regarding the efficacy of vaccines to prevent vaginal HIV transmission in pregnant women or HIV transmission from mother to infant. The SIV/cynomolgus macaque model has been recently used to demonstrate that a vaccine consisting of live, recombinant Sabin polio virus vaccine expressing multiple SIV antigens is immunogenic and can elicit protection against vaginal challenge with pathogenic SIV. Dr. Marthas has focused on evaluating the safety and immunogeneicity of an infectious polio_SIV vaccine in pregnancy and infants. Preliminary results indicate that Sabin polio vaccine-based anti-HIV vaccines may be safe to administer to women to prevent genital HIV transmission and to human infants to protect against HIV breast milk transmission.

SPID0055: Across the world, approximately one million children die from measles every year. The live, attenuated measles vaccine that is typically given is very effective, but maternal antibody prevents its administration prior to 6 months of age. Dr. McChesney is investigating the ability of a DNA vaccine encoding the measles viral hemagglutinin, fusion and nucleoprotein to protect newborn infants from measles (disease). New work demonstrates that a measles DNA vaccine protects infant macaques from pathogenic measles virus challenge when the DNA vaccine is adjuvanted with a DNA plasmid expressing an IL_2/IgG heavy chain. This vaccine strategy models a practical approach to vaccinating newborns in developing countries.

SPID0218: There are no licensed vaccines for human cytomegalovirus (HCMV). Limited clinical trials have been conducted with live attenuated and recombinant subunit vaccines. Despite partial success protecting from disease in renal transplant recipients, the goal of developing an HCMV vaccine that elicits protective immunity has not been achieved. Dr. Barry has demonstrated that CMV appears to have evolved strategies that alter lymphoid cell signaling and trafficking. Thus, effective HCMV vaccines must be directed against both structural and immune modulating gene products. For example, in vitro evidence indicates that viral interleukin_10 should profoundly alter the ability of dendritic cells to elicit fully protective immune responses following viral infection. A modified rhesus CMV (RhCMV) variant has been constructed in which the viral interleukin_10 gene has been deleted. This is currently being analyzed in vitro. A successful outcome of this approach will demonstrate that attenuation of the CMV immunomodulatory genes by immunization represents a rational vaccine strategy. This would fundamentally alter the paradigm for vaccine approaches to HCMV.

Publications:

ADMINISTRATIVE INFORMATION

ALLOCATION OF RESOURCE ACCESS

Allocation of CNPRC resources is formally granted by the Director's Office, with the concurrence of the CNPRC Research Advisory Committee. The criteria used for granting access to the Center's resources include the following

* Funding source
* Justification for using primates
* Relevance of the study to the Center Program (fulfillment of the Center's mission)
* Impact on the CNPRC program (ongoing commitments, staff expertise,duration)
* Primate availability (species, age, sex, numbers, housing type)
* Space availability
* Procedures required

All investigators are required to submit a pre-proposal to the CNPRC's Research Advisory Committee (RAC) prior to the development of a grant proposal to assure that the Center is able to provide the necessary resources. This form provides information for
evaluating the above criteria. For the period 5/1/03-4/30/04, 84 pre-proposals were submitted to the RAC committee. Of these pre-proposal submissions, none were denied, three were revised and approved and 81 were approved.

COMMITTEE REPORTS

1. CNPRC Research Advisory Committee – This committee is composed of the Director, the Associate Director for Research, the Associate Director for Primate Services, the Assistant Director for Administration, the Assistant Director for Colony Management and Research Services, Executive Assistant to the Director, and the Unit Leaders. To enhance translational research, [illegible] is an invited member of the committee. The committee meets biweekly to review and discuss proposed research projects and other matters relating to the Center's research needs. All projects are discussed and evaluated in terms of scientific merit, resources available, availability of animals, applicability to use of nonhuman primates, priority, and humane treatment of animals.

Member's include:

D. Hyde, Chair
Ph.D.
Professor,Director
VM:Anatomy, Physio.& Cell Biology

J. Capitanio
Ph.D.
Professor, Assoc. Director for Research
L&S:Psychology

N. Lerche
D.V.M., M.P.V.M.
Adjunct Professor,
Assoc. Director for Primate Services
VM:Population Health and Reproduction

C. Plopper
Ph.D.
Professor
VM:Anatomy, PhysioL & Cell Biology

C. Miller
D.V.M., Ph.D.
Professor
VM:Pathol./

Microbiol./Immunol.

A. Tarantal
Ph.D.
Professor
MED:Pediatrics

S. Mendoza
Ph.D.
Professor
L&S:Psychology

[name]

[name]

[name]

[name]

]

2. UC Davis Organized Research Unit Advisory Committee – This committee, which reports to the Chancellor of the University and the Vice Chancellor for Research, evaluates the effectiveness of the CNPRC on an annual basis, particularly its effectiveness in relation to its interactions with the UC Davis campus.

Member's include:

S. Dandekar, Chair
Ph.D.
Professor
Med:Micro. & Immun.

C. Fuller
Ph.D.
Professor
Neuro./Phys. & Beh.

E. Jones
M.D., Ph.D.
Professor
Med:Psychiatry

[name]

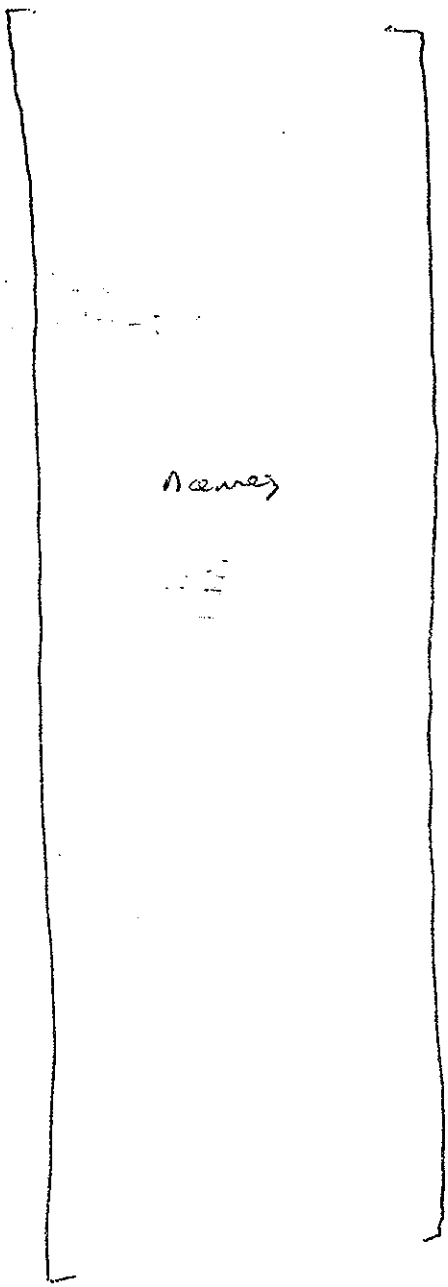
Ph.D.
Professor
L&S:Psychology

C. Miller
D.V.M., Ph.D.
Professor
VM:Pathol./Microbiol./Immun.

C. Plopper
Ph.D.
Professor
VM:Anatomy, Physiol.& Cell Biology

D. Hyde (ex officio)
Ph.D. Professor, Director
VM:Anatomy, Physiol.& Cell Biology

4. CNPRC National Scientific Advisory Board (NSAB) – This committee reviews research and administrative programs annually and provides recommendations to the Principal Investigator and Director. The Director's Office is responsible for implementing appropriate recommendations. Current members are:



5. Director's Management Committee – This committee is composed of the Director, Associate Director for Research, Associate Director for Primate Services, Assistant Director for Administration, Assistant Director for Colony Management and Research Services, Public Information Officer, Facilities Director, and Executive Assistant to the Director. The committee meets weekly to discuss administrative, facility, and colony management topics relating to the Center. This committee also defines and evaluates currently-assigned space, makes recommendations for consolidation in space use, and reviews and makes recommendations regarding renovation plans. Many of the issues (e.g. space) discussed in this committee are brought in a more formal manner to the Research Advisory Committee for further discussion and consensus building. Current members are D. Hyde, J. Capitanio, N. Lerche,

MEMBERS

(Non-Voting)

DISSEMINATION

Dissemination of Information

Our research results are disseminated through publications in scientific journals and presentation of papers, poster sessions and seminars at scientific and professional meetings. In addition, research accomplishments of public concern were distributed to the media.

Enhancing and formalizing the communication efforts of the Center continued to be a high priority this past year. The Center continued to formalize the role of the Research Advisory Committee to assure dissemination of information to collaborative and affiliate scientists. In addition, the web site continues to be enhanced, providing information about the core services at the Center and promoting the Pilot Research Program. Our employee newsletter also continues to be a resource for staff.

The CNPRC also has an Education Outreach Program, the primary goal of which is to introduce K-6 students to nonhuman primates, general science concepts, animals in research, and biomedical research programs and careers. Under the direction of [name] (principal illustrator at the CNPRC) a coloring and puzzle book was developed and is provided to each child during the program. As part of the program, [name] also developed class-specific curricula that meets the California State Standards for Science Content. [name] and volunteer staff from CNPRC present 1-2 programs per month at elementary schools in Davis and the surrounding communities.

This past year the Primate Center continued to co-host, with the Center for Comparative Medicine, a weekly seminar series, inviting speakers from institutions around the country to present seminars on various topics of interest to the primate research community. This series continues to serve as an effective mechanism to increase awareness of our program and services.

PATENTS, LICENSES, INVENTIONS AND COPYRIGHTS

None for this reporting period.

AWARDS, HONORS, SPECIAL RECOGNITIONS

Honors and Awards

David G. Amaral, Ph.D., Staff Scientist and Principal Investigator at the California NPRC, received a Merit Award from the National Institute of Mental Health. Dr. Amaral's award is for his research program involving use of lesion and behavioral techniques to analyze the neural substrates of primate social behavior.

John P. Capitanio, Ph.D., Staff Scientist, Principal Investigator, and Associate Director for Research, California NPRC was made a Fellow of the American Psychological Association in Division 6 (Behavioral Neuroscience and Comparative Psychology).

INFRASTRUCTURE

**INFRASTRUCTURE:
Physical Plant

List of Major Renovation Projects Completed:

Project
Fund Source
Cost

Lab Renov. for Labs 1210, 1214
Base Grant Income
$64,000

Central Supply/Locker2 Building
Base Grant Income
$770,800

Installation of BMB Trailer
Base Grant Income
$176,000

Instal. of Sec. System Ctr-Wide

Base Grant Income
$128,000

Instal. of Emergency Wash Units
Base Grant Income
$16,102

Modular Off. Bldg Compl. Costs
Base Grant Income
$24,119

Stainless Steel Door

Installation/ New An Wing
BaseGrant Income
$50,000

Renovation of Animal Wing for BSL-3 Capability
G-20
$621,113

Construction of Aggregate Base Field Road
Base Grant Income
$49,000

Reception area security improvements
Program Income
$93,000

Renovate Lab [animal lab]
Program Income
$48,000

Renovate Room [animal location]
Program Income
$53,000

Construct 8 new Corn Cribs cages
Base Grant Income
$160,000
Necropsy Improvements
G20
$121,000

[ ] Renovations room number
Program Income
$84,000

Seven [ ] Corrals square footage
Base Grant Income
$1,169,000

[ ] corral covers square footage
Base Grant Income
$270,000

O2 installation

Program income
$48,000

Modular freezer building
G20
$465,000

Modular animal Buildings
G20
$698,990

renovations room number
G20
$700,000

Storm water Improvements
$1,700,000

Corn Cribs pad
Base Grant Income $82,729

List of Major Equipment Items Purchased:

Purchase cage Racks
Base Grant Income $621,000

Purchase Steris Rack washer
Base Grant Income $186,000

Feed Storage Container
Program Income $5,280

Quarantine rack washer
Base Grant Income $64,000

Utility Vehicle
Base Grant Income $7,000

Tractor
Base Grant Income $27,000

Central Supply/Locker Furniture Base
Grant Income $60,000

Modular Off Building Furniture
Base Grant Income $30,000

Animal Cages/ Supplies purchased/
Built in-house
Base Grant Income $60,000

Absorbance Reader
Base Grant Income $5,609

ABX Diagnostics:
Analyzer, Pentra 60C+ UC Davis $41,350

Kendro Sorvall Biofuge
Pico w/ Rotor UC Davis $1,875
ABI Prism Sequence Detector UC Davis $93,122
Edwards Copier UC Davis $2,681
Kendro/ Incubators UC Davis $13,933
FACSAira Cell Sorter UC Davis $208,377
Computers for Research Work UC Davis $58,941
Image Database System &
Document Scanning UD Davis $144,360
Centrifuge, Sorvall Legend RT Program Income $7,369
Pressure Washers (2) Program Income $20,592
Delta Vision Model D-OL Dual
Camera System Program Income $240,905
Aerosol Management System Program Income $13,406

**Colony Management

The heavy demand for animals and need for additional space continues to be a central focus for CNPRC colony management. Efforts towards SPF colony production continue, supported by both the base grant and support from NCRR for production of pedigreed Indian-origin rhesus macaques, as well as Chinese-origin rhesus. The expansion of SPF production is currently limited by a shortage of space for nurseries, SPF indoor housing, and separate hospital housing for both indoor and outdoor animals.
In 2003 the fourth outdoor production caqe of SPF animals was established.
This past year we have continued with the ongoing service in the nursery service to provide 24-hour care for infants in research and colony nurseries. During 2003, approximately 300 infants were nursery-housed for ongoing studies in asthma, autism, gene therapy, including pediatric AIDS treatment and vaccine development.

**Animal Care Unit

The 2003 year brought about changes and enhancements to the Animal Care Unit with some changes in organization. The overall goal was to reduce the overall size of the very large areas, and provide supervisors with the opportunity to have time to cover the areas needing attention. This plan to improve the focus in special areas also helps in the planning for impending growth in each of the unique animal care areas. This year two new Animal Resource Supervisors were hired, adding to the five that were currently in place. The first was in the North colony where the Center's 17 long term breeding cages reside. This was made a distinct area, separate from the South colony. This has allowed the supervisor and new crew members to focus on the area entirely and the outcome has resulted in a new level of excellence in overall husbandry, area maintenance, and research support. In the next year, 7 new field cages will be constructed, and the new supervisor and staff will be prepared as this area of the colony continues to expand. The second new supervisor hired was in the area of Cage Change and Security. With as many as 2100 indoor single cages that are required to be sanitized every 2 weeks, this operation has grown and requires constant scheduling and oversight. The level of security provided to the Center during heightened times of activity, and around the clock has benefited from the direct support and oversight of this new unit.

The other important addition to the Animal Care staff was the new position of the "Training and Education Coordinator". With 85+ staff member in Animal Care continued training and evaluation is essential. The Coordinator interacts with the Animal Resource Supervisors, and the staff members on a daily basis. It provides an excellent program covering the initial orientation and safety training for all Animal Care Staff members. The Coordinator also
conducts weekly classes for staff to prepare for the AALAS technician and technologists certification testing. Classes in laboratory animals laws and regulations is also provided to all staff.

The Animal Care Staff provided husbandry, preventive health care and research support for approximately 4,700 animals. This included approximately 2600 animals housed outdoors (Corn Cribs and 1/2 acre Corrals) and 2100 animals indoors (non-infectious, infectious, nurseries, and quarantine).

The centralized Animal Care Office/ Locker and Central Supply facility (7569 ASF) was constructed. The new facility provides improved locker and shower facilities for animal care personnel as well as a larger more centrally located Storehouse for the Center.

Progress in Core Services Units:

**Primate Services

Primate Services is the centralized research support unit that maintains the animal colony and its database as well as provides service and support to all investigators ranging from initial development of their research protocol, to technical support and final collection of their data. The emphasis in 2002 was on increasing support for specialized needs of Primate Center investigators. The Primate Services Unit is administered by the Associate Director, Primate Services, and by supervisors from each of the support areas in Primate Services. The goal of Primate Services is simple; to facilitate biomedical and behavioral research utilizing the non-human primate model.

**Primate Medicine

The demands on Primate Medicine increase in 2003 with expanding colony numbers, funding of a new SPF grant in addition to the already funded NCRR grant, and a desire from investigators for more direct interaction with members of the veterinary staff. The interest in increased interaction with investigators is driven by a greater need for project consultation and an interest in getting more detailed information regarding spontaneous health problems in the colony. Biweekly meetings with some investigators were initiated to facilitate project management and anticipate problems before they occur. This interaction has improved communication but does have a negative impact on the veterinary workload. Plans are being developed to expand the clinical staff to meet the basic needs of veterinary care for the colony as well as provide the type of research support being requested by investigators. The expansion of SPF rhesus macaque production and housing for infectious disease studies continues to pose challenges for separate hospital space and support facilities.

Veterinary staff and residents conducted clinical studies in several areas. These included clinical evaluation of oral administration of anesthetic agents and a project to look at the epidemiology of aggression in our outdoor housing area. Specialized surgical and technical procedures continued to occupy significant professional time of the veterinary staff. This included procedures for gastrointestinal biopsy, chronic electrophysiology implants, and intra-operative and post-operative support of transplant animals.

There also continues to be demand for veterinary support in imaging procedures including MRI's, CAT scans, endoscopic and laparoscopic procedures.

Primate Medicine Service also continued its focus on teaching, both in the classroom and the clinic. Veterinary staff participated in laboratory animal medicine, pathology, and ultrasound rounds, and weekly seminars in laboratory animal science. In addition there is an expanded coordination of the residency program between the Primate Center and the Center for Laboratory Animal Science on the UC Davis campus. The CRPRC also hosted visiting veterinarians and veterinary students from around the United States and Canada.

**Animal Care and Facilities Management

The Animal Care Staff provided husbandry, preventive health care and research support for approximately 4,700 animals. This included approximately 2600 animals housed outdoors (Corn Cribs and [illegible] Corrals) and 2100 animals indoors (non-infectious, infectious, nurseries, and quarantine).

Training was an area of focus for Animal Care personnel. In coordination with the Office of the Campus Veterinarian, a weekly class on laboratory animal science was conducted at the Primate Center. The class was required for all Assistant Animal Technicians and all levels of Technicians were encouraged to participate. During the summer, a ten-week series of training classes were held for all Primate Services personnel in preparation for the AAALAC site visit in November. The Primate Center program was reviewed favorably in the AAALAC visit.

Two additional Corn Cribs and an outdoor group cages were constructed. The centralized Animal Care Office/ Locker and Central Supply facility (7569 ASF) was constructed. The new facility provides improved locker and shower facilities for animal care personnel as well as a larger more centrally located Storehouse for the Center. Room [illegible] was renovated to accommodate a MicroPET imaging system. Renovations were completed to allow BSL 3 housing in up to five animal rooms. This project included installation of HEPA filters, air balancing, and purchase and installation of a

large pass through autoclave. Laboratories [illegible] were renovated and new laboratory furniture installed. Room [illegible] was converted to laboratory space.

**Research Services:

Research Services continues to experience growth in the number of ongoing projects that this Unit provides daily research support for. Over the past year, studies in transplantation, diabetes, neuroscience, nutrition and infectious disease have been very progressive and have presented unique support needs. Staff Research Associates are now on duty 7 days per week, and supply technical support for overnight projects as needed. The staff continues to provide investigators with project support in the areas of; animal selection and screening based on investigator criteria, daily project technical support, sample collection and processing, and animal monitoring. SRA's routinely transport animals to offsite scanning sites including UCD campus, UCD Medical Center, as well as to the Bay Area.

With the increasing size of the Center's SPF colony, increasing efforts are spent in managing viral testing, harvesting, and overall management of these animals. Currently the Center has 4 full production cages, and is well on its way to stocking a fourth cage by early 2005. Genetic screening of the colony continues to progress. Paternity data is available for all of the Center's outdoor breeding cages, and infants are sampled routinely months after they are born. With project demands for animals very high, harvest activity continues to increase.

**Quality Assurance:

The Quality Assurance Unit (QA) continues to support the regulatory activities for projects at the Center that are conducted under GLP guidelines. In 2003, this included 5 ongoing projects. The QA provides ongoing training to all staff members to standardize data recording and documentation of husbandry and research events. A focus of the QA Unit this year was the continued refinement of the "controlled substances" program. New tracking procedures and documentation records were implemented. Extensive staff training was also completed. QA continues to monitor colony quality functions such as; water quality reports, feed analysis, and environmental monitoring. Quality assurance services have also routinely provided to investigators on the UCD campus, on a fee for service basis.

**Pathology Service:

The Pathology Service provides diagnostic service for the breeding colony and research groups both within and outside the CNPRC through necropsies (738 in 2003) and biopsies (321 in 2003) according to standard operating procedures that are reviewed and revised annually. Histologic processing for light microscopy is performed under contract with the UCD medical school on the UC Davis campus and for electronmicroscopy with the CNPRC Computational Imaging Core. The Pathology Unit also performs special (terminal) procedures on a recharge basis for investigators at the CNPRC, as well as for investigators outside the facility either under contract or as part of the Biospecimen Request Program administered by the Pathology Unit. These procedures include perfusions of specified organs (brain, liver, lung, uterus, etc.) with specific fixatives, sterile collection of specific tissues (blood, CSF, and various organs) at euthanasia/necropsy, collection of tissues for specialized analyses such as immunohistochemistry or electronmicroscopy, GLP necropsies, and antemortem collection of tissues (blood, bone marrow, CSF, lymphoid tissues, and brain) for in vitro studies. Collaborative efforts are ongoing with neuroscientists to study the anatomic correlates of learning, memory, and aging in the central nervous system and with virologists/immunologists in an attempt to understand the pathophysiology of AIDS. In addition, collaborative studies are in progress with investigators at the University of Nebraska to study colonic spirochetosis and with investigators at UCDMC, UC Davis Veterinary School, and Stanford University Medical School to study Helicobacter pylori induced gastritis. The Pathology Unit also handles the collection, organization, storage, and retrieval of wet tissues, tissue blocks, glass slides, kodachrome slides, and electronic images of pathologic lesions, and maintains these as a resource for researchers both here and around the world. The Pathology Unit provides consultation and collaboration to CNPRC and outside investigators in the development of experimental designs, as well as in monitoring and evaluating animals on experimental protocols, and supervises the training of pathology residents, primate medicine residents, veterinary students, staff research associates, and laboratory assistants in the theory and practice of pathology as it applies to non-human primates in colony management and research applications.

	Clinical	Diagnostic	Research	Total
Necropsies	336	402		738
Biopsies	68	192		260

**Data Services:

The Data Services unit continued to provide information and computing services for the center. A number of enhancements were made to existing data systems. We completed numerous ad hoc queries for investigators and research staff. Several new programming projects were completed:

- WebVitals is our new data lookup program for colony data. This version offers many features over its text-based predecessor, such as the web interface, clickable data, export functionality to a spreadsheet, and a custom query tool. As further improvements and additions are made to the Colony database, they will be implemented in the web version of Vitals. In addition it will be a major entry point for the Image database as we start cataloging pathology and surgery images.
- The V&I unit samples database is a web-based interface for the V&I unit to enter, query, edit, and checkout samples stored in their cryotanks/freezers. The software can handle various sample data types, such as Cell, Serum, Virus and others.
- A similar web enabled database has been completed for the RGS unit sample storage. This application has additional capabilities including the ability to enter data on tissue harvesting.
- A database for departmental training records was created and is in final testing stages now. This database will allow our training officer to track all needed aspects of the training records for employees and supervisors. Regular scheduling of training classes, training reviews and documentation are all facilitated by the system.
- We have updated the SNOMED system by creating a hierarchy within each record group for a SNOMED entry. This has made searches and reporting easier and more efficient.
- We have created a new database for the Pathogen Detection Lab; it is in the final stages of testing. Data from their old system, approximately 150,000 records will be moved once the testing is complete. This will greatly improve the data collection and reporting for the lab, and will feed billing information into the center's billing system much more efficiently than the previous system.
- A new pathology report system was created and is going through testing now. This system will streamline the data entry process for pathology, and provide a case list of open reports. It will also tie into the Image database for indexed retrieval of digital images for that animal.
- The Image database hardware and software have been purchased and configured. Initial data and images are being entered into the system while the setup is being completed and tested. The system can store a wide variety of image formats typical for our environment. We can accommodate up to 1.5 terabytes of image data in the current system.
- A document management system was purchased and installed. The system currently supports production scanning, barcode indexing, text based OCR, and web access to electronic files. It currently holds approximately 600 searchable/indexed documents and is steadily growing.

We have maintained our desktop support for both the Macintosh and Intel based PC platforms. We added an additional forty five new PCs and Macintoshes; thirty older PCs were reformatted and redeployed in less demanding applications. Thirty-five older PCs and Macintoshes were retired. Five new printers were installed, and three were retired. Data Services desktop support staff handled approximately one thousand question, repair or upgrade calls. The domain, and file services were updated. A tape backup library system was purchased and installed. This provides backup for our file servers, and the data store for the image and document management systems. We have continued our desktop server maintenance and upgrades. Our new public website was set up this year, and the internal only site is being updated. We have implemented a PC operating system update server to handle the numerous OS and application updates from
Microsoft and others that are continuing to be released.

**APR Training Section

Requirements:

In order to receive training with or from the Primate Center, a University California Davis Employee must have an affiliation with the center either by putting effort on a CNPRC grant or by working at the center itself. CNPRC offers training both on a day to day basis through seminars and classes located at the Center or on the University campus and through an annual training program with special funds allocated for training classes located off of the University Campus. If an employee elects to participate in training at the Center or University then eligibility is determined based upon availability of the classes and workload restrictions. The primate center has also recently begun a training program for individuals who wish to obtain one of the following degrees: Assistant Laboratory Animal Technician (ALAT), Lab Animal Technician (LAT), Laboratory Animal Technologist (LATG). If an employee elects to participate in an off campus training class they must submit an annual application for training funds. Selection for off campus training is made by the CNPRC Research Advisory Council based on: whether an employee has received training off campus previously, how much

funding is available, and the benefit of the training to the Center.

Statistics:

For the year beginning May 2002 and ending April 2003 the Primate Center had $21,254 available for off campus training. This amount was split amongst thirty applicants who applied for various training including educational seminars and symposiums, University Extension Courses, and visits to other research institutes. For the year of May 2003 to April 2004 the Primate Center had $11,102.46 for off campus training. Out of twenty four applicants, ten were selected for full or partial funding. These individuals attended classes varying from informational meetings and seminars to technological courses.

**Clinical Labs:

The clinical laboratories primary function continues to be the diagnostic support for monitoring and defining the health status of the colony. In addition, it continues to provide clinical laboratory technical support to outside investigators on a recharge basis. The key services provided include hematology, parasitology, microbiology, urinalysis, chemistry, cytology, serology, reference serum and buffy coat bank, and flow cytometry. In the year 2003, the laboratory continued to provide flow cytometry expertise. It has validated new antibodies for the identification of tumor cells in non-human primates, investigated intracellular cytokines, and antibodies used for DNA cell-cycling. In addition, the Primate Center has purchased a FACS Aria which enables the lab to perform multicolor flow analysis. Currently we have done up to 9 colors in one tube. The Clinical laboratory oversees the multi-use of this piece of equipment. By broadening the flow cytometry service, the laboratory has continued to meet the ever changing needs of investigators.

The clinical laboratory has supported continuing education for all laboratory personnel. National conferences including American Society of Microbiology (ASM) and American Society of Clinical Pathology (ASCP) have been attended. In-house training has continued mainly in the safety area. Safety seminars were routinely given for all up and coming infectious disease projects to educate staff on the proper handling and processing of clinical laboratory specimens. The clinical laboratory has begun work towards the computerization of the laboratory data. SNOMED entries for microbiology and parasitology are made on a daily basis. We are currently investigating Laboratory Information Systems that will interface with the new hematology analyzer as well as chemistry data we receive from the Veterinary Teaching Hospital. This is a big step towards the computerization of clinical laboratory results.

Samples submitted to Clinical Laboratories in 2003:

Clinical diagnosis: Samples submitted for diagnosis or surveillance of disease.
Research: Samples submitted by investigators for specific experimental projects.

Chemistry:	Clinical Diagnosis	Research	Total
CRPRC	3475	152	3627
Veterinary Medical Teaching Hospital	633	1532	2165
Outside Lab	35	42	77
TOTAL CHEMISTRY	4143	1726	5869

Microbiology:	Clinical Diagnosis	Research	Total
Cultures other than rectal	321	127	448
Rectal Cultures	2511	111	2622
Necropsy Cultures	777	0	777
Environmental Monitoring	23	0	23
TOTAL MICROBIOLOGY	3632	238	3870

Parasitology	Clinical Diagnosis	Research	Total
Direct Exams	974	2	976
Cryptosporidium/GiardiaIFA	290	2	292
Concentration Exams	7	0	7

Quarantine concentrations	110	0	110
TOTAL PARASITOLOGY	1381	4	1385

Hematology	Clinical Diagnosis	Research	Total
Complete Blood Counts	988	6158	7146
Partial Blood Counts	777	825	1602
Urinalysis	177	240	417
Flow Cytometry			
3-Color Panel	5	383	388
4-Color Panel	6	1743	1749
3/4/8	0	748	748
3/4/8/20	2	2263	2265
Crossmatch	0	8	8
TOTAL HEMATOLOGY	1955	12368	14323

CORE SCIENCE:

**Computational Imaging Core:

Our facility provides microscopy, stereology, digital imaging and consultation services for the CNPRC researchers and all campus departments on a recharge basis. Our goal is to assist faculty, staff and students with their research needs for qualitative and quantitative applications. We can assist with the production of publication quality images and offer consultation on experimental approaches for use of our equipment. Instrumentation housed in our facility is available 24 hours per day, 7 days per week for trained users, with consultation, training and support services available from 8-5 Monday through Friday.

Our expanding base of instrumentation offers many possibilities including the creation of 3D images from microscopy specimens; performing quantitative analysis of counts, lengths, areas and/or volumes of cellular and subcellular structures; imaging and co-localization analysis of fluorescence labeled microscopy specimens; and standard brightfield, DIC or epifluorescence microscopy. In addition we can generate publication quality prints, and 35 mm film records of virtually any image. To achieve our service goals, the facility houses the following resources:

- Brightfield, DIC and epifluorescence microscopy with digital image capture
- A 35mm film recorder for creating slides or prints of virtually any image including PhotoShop and PowerPoint presentations
- C.A.S.T. Grid Stereology system for quantifying number, length, area and/or volume of microscopic structures
- PhotoShop, software
- A flatbed scanner for reflective and transparency work
- A color printer to produce publication quality color images
- A variety of microtomes for frozen, paraffin, and plastic sections
- A Delta Vision Restoration Microscopy System for very high resolution fluorescence imaging of live cells or fixed specimens in 2D, 2D time lapse, 3D or 3D time lapse.
- A fully computer controlled research microscope for fluorescence, DIC and/or brightfield imaging with high resolution digital capture and a computer controlled stage. The system is also outfitted with software for stereological analysis of fluorescence, DIC or brightfield images.
- A second fully computerized research microscope with fluorescence, DIC and/or brightfield imaging capabilities is available for the development of stereological techniques that can be applied to fluorescently labeled specimens.
- Equipment additions anticipated for the future include: Confocal microscopy, multiphoton microscopy, slide scanning for virtual histology / telepathology, and hyperspectral imaging.

**Endocrine Core:

In response to NIH/NCRR directives in 1998, an Endocrine Core Laboratory (ECL) was established with the previous competitive renewal. The charge of this Core was to perform endocrine service for all CNPRC faculty and staff. In addition, this facility responds

to outside requests that cannot be performed by any other facility. ECL has several analytical protocols that are unique and commonly applied to human and non-human primate investigations. The ECL also has the ability to respond to contracts that require Good Laboratory Practices and this mode of operation is required for all work that will eventually be reviewed by FDA or USDA and become part of the Federal Register. The ECL has experienced growth from its inception. In the first year, the request for service required the
addition of a 1.0 FTE and it appears an additional FTE will be required in the near future.

Services Offered
The services provided by the Endocrine Core are summarized as follows:

Reproductive Endocrine Core
* Urinary EIC & Hy-Pdg EIA & Chemiluminescent Immunoassays (CLIA)
* Serum LNG EIA
* Urinary total FSH ELISA & CLIA
* Serum mCG ELISA
* Celite RIA
* Non-Celite RIA
* DPC RIA
* Bayer CLIA
Stress Endocrine Core
* ACTH
* Cortisol
* CBG

Users
The primary users of the Reproductive Endocrine Core are Staff Scientists, which accounts for approximately 80% of our activities. The remaining 20% is generated by outside investigators that require our unique services. These investigators represented research facilities that focus on human or nonhuman primate reproduction. A major portion of our response is to requests made for training in our assay technology as well as purchasing of our reagents. This core provides most if not all of the technology and critical reagents for the monitoring of reproductive function in primates using the non-invasive urinary monitoring.

Research & Development:
Our primary research activity in the Reproductive Endocrine Core is the development and validation of new assay systems. During the past year we have produced antisera against the beta mCG peptide in rabbits. Currently, a chemiluminescent immunoassay (CLIA)for serum and urinary mCG is being developed for use in detecting and monitoring early pregnancy in non human primates.

In the past year, we have adapted our microtitered plate based EIC & HyPdG EIAs as well as the FSH ELISA to chemiluminescent immunoassays (CLIAs). By utilizing chemiluminescent technology, we are now able to perform our most popular assays on the Bayer ACS-180 Automated Chemiluminescence System. The automated platform has reduced the turn around time needed for many analytes while also decreasing the chance of human error and thereby increasing the productivity of the Core while reducing the number of assays requiring repeated analyses. In addition, we have also developed an Estriol CLIA for use in serum and urine.

We are beginning to focus on monkey inhibins that currently do not have specific assay systems for their quantification. This activity will be in collaboration with [illegible] (Cambridge, UK) who has a unique collection of antibodies to human inhibins and activins and a superior track record for developing assays for circulating inhibins and activin in the human. Our first step will be to develop assays for urinary inhibin in the human and monkey. This work is being initiated this summer.

Approximately two-dozen peer-reviewed manuscripts have been produced as a result of the development and validation of unique assay systems for use in primate research and medicine. Our urinary assays for sex steroids and FSH are the only assays that are available for primate studies. By use of these assays, we have recently shown that capture and restrain of primates results in perturbations of FSH secretion. This report will undoubtedly encourage more investigators to use non-invasive urinary monitoring when possible. We have also developed and validated an assay for urinary cortisol and are currently assessing the effect of acute physical stress on latent ovarian function. We have also developed new assay methods for monitoring ovarian estrogen production at times when estrogen conjugates do not provide sufficient relibility. This methodology will be critical in future studies of aging and/or estrogen deficiency-replacement.

The Stress Endocrine Core began to develop assays that can be used to evaluate brain function through pharmacological challenge of endocrine systems. Specifically we will use prolactin response to monoaminergic agonists to evaluate strength of monoaminergic pathways. We also intend to develop assays in the coming year to evaluate receptor concentrations for steroid hormones in circulation (lymphocytes) and brain. We have also received a request to assay betamethasone, a synthetic glucocorticoid, in the serum of treated animals. This drug is often used clinically for treatment of problems during pregnancy in humans and monkeys. We are in the process
of developing such an assay for use as a clinical and research tool.

Training:
Training has been provided to staff that desired to establish our systems in their laboratories, graduate students from Pharmacology-Toxicology, Comparative Pathology and Physiology, as well as for technicians from other institutions who need to establish our system in their laboratories. Visiting scientists included [name], a research associate from Stanford University, Dr. Ron Whiele, an investigator from Zonagen, TX. The research associate was allowed to perform the animal phase of his study onsite. The investigator from Zonagen was allowed to conduct portions of the animal phase of his study onsite. Other visiting scientists included [name] from the University of Nebraska, [name], from UC Davis, [name] from UCLA and
[names] from the All India Institute.

Recharge Activities:
The following represents the procedures performed by the Endocrine Core between the date for 5/1/2003 and 4/30/2004.

Colony Management Research Total	
Urinary EIC, Hy-Pdg and Cortisol	
EIA Assays	10536
Urinary Total FSH ELISA Assays	3942
Celite RIA assays	53
DPC RIA	379
Serum mCG	86
Labor	849.33 hrs
Misc Supplies	$13,339.40

Cortisol Assays	3	1,271	1,274
TOTAL ENDOCRINE CORE	3	11,690	11,693

**Simian Retrovirus Laboratory

The SRL is a research support and service laboratory to provide retrovirologic and serodiagnostic services in support of non-human primate resource development and on-going extramurally-funded biomedical research, and to provide training opportunities for students, technical staff and visiting scientists. This Core provides testing for detection of simian retrovirus infections, monitoring of humans with known occupational exposures to non-human primate retroviruses, serves as a designated reference laboratory for simian type D retroviruses, provides expertise in the interpretation of test results and the development of testing strategies, provides virologic and serodiagnostic assays for four exogenous simian retroviruses, and has an Agent Use Authorization for HIV-1 and HIV-2.

**Virology and Immunology

The Immunology Service Core is designed to provide 1) standardized measures of immune response in macaques, 2) advice to outside investigators on experimental design of primate immunology studies, 3) development of new technology for assessing immune responses in this animal model, 4) information on techniques and reagents that are useful for primate immunology, and 5) training of personnel in the use of immunology assays for work with macaques. Because of the large volume of AIDS-related research done by both staff and non-staff scientists at the CNPRC, the emphasis of this core was on antiviral immunity. In addition, assays to nominal test antigens were available for other infectious and non-infectious research at the CNPRC. The Core, which began operation in August 2000, has two services or work areas corresponding to humoral immunity (requires BSL-2 only for initial sample processing) and cellular immunity (requires BSL-2 containment throughout the time of assay). Humoral immune assays include the detection of antibodies to viral antigens by ELISA. In addition, antibody levels to the nominal antigens, tetanus toxoid, cholera toxin and keyhole limpet hemocyanin are measured by ELISA. Cellular assays include the detection of antiviral cytotoxic T lymphocytes (CTL) or natural killer cells (NK) and lymphocyte proliferation to viral and nominal antigens. A mixed lymphocyte reaction is available for genetics and transplantation. Cytokine/chemokine-secreting cells are assayed by ELISPOT and cytokine/chemokine mRNA transcript

levels by real-time PCR.

Services Offered
The services offered by the Immunology Core are summarized as follows:
* Sample Processing
* Total IgG, IgA ELISA assays
* Ag Specific IgG, IgA ELISA assays
* Total IgG, IgA ELISPOT assays
* Ag Specific IgG, IgA ELISPOT assays
* Cytotoxic T Lymphocyte assay
* T-cell Proliferation assay
* Ag Specific IFN-g ELISPOT
* B Cell Transformation
* Mixed Lymphocyte Reaction
* SIV gag PCR
* Nucleic acid extraction
* Natural Killer Cell assay
* Real-time PCR to quantify cytokine/chemokine mRNA

Inhalation Exposure Facility

Overview

The Inhalation Exposure Facility located at the CNPRC is one of the largest in existence on a university campus. It permits unique human health-related pulmonary research opportunities using non-human primates. Capabilities exist for in vivo or in vitro exposure to precisely characterized and controlled atmospheres of gases and aerosols. For health effects of air pollution research, the range of test subjects used for exposure studies can include animals, isolated and perfused lungs, tracheal explants and human or monkey lung cell cultures. This permits an integrated, comparative approach to defining mechanisms of respiratory system injury and repair. A recent addition to the capabilities is a pulmonary function laboratory that offers a comprehensive array of testing for infant through adult non-human primates.

Services Offered
Special Exposures
Ozone Generation and Monitoring
Aerosol Generation and Analysis
NOx Generation and Monitoring
Allergen Generation and Analysis
Filtered Air Exposure
ETS Generation and Analysis
Pulmonary Function Testing Laboratory
Baseline Airway Resistance Testing
Airway Responsiveness Testing
Allergen Responsiveness Testing
Static Lung Mechanics Testing
Physiologic Monitoring - Aerosol Therapy

Users
This facility continued to provide stable, well characterized exposures to air pollutants, allergens, therapeutic agents, aerosols and other test atmospheres as required by the research projects supported. As a core service provider, the facility supported 18 research projects during the reporting period with some 39 major investigators. In addition to UC Davis investigators, core services were provided to scientists at UC San Diego, DyNAvax Technology Corp., University of Alabama at Birmingham, Michigan State University, Pennsylvania State University, Louisiana State University, Chemical Industry Institute of Toxicology, U.S. EPA, Pacific Northwest National Laboratory, Genentech, Inc., UC San Francisco and UC Irvine.

Research and Development
Major emphasis in research activities was directed to further inhalation exposure studies of asthma and air pollution in non-human primates. Inhaled steroid aerosol delivery with plasma concentration measurements was developed for infant non-human

primates. An exposure regimen is in progress that includes groups exposed to house dust-mite allergen aerosol + ozone and filtered air control groups. Animals in each group will be treated with the inhaled steroid, budesonide, or a placebo aerosol. Aerosol therapy studies with inhaled immunostimulatory sequence DNA aerosols continued with improved inhaled dose estimates for adult non-human primates. Other non-human primate projects included metabolic measurements using indirect calorimetry and prenatal and postnatal exposure to aged and diluted cigarette smoke.

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VIROLOGY & IMMUNO - AIDS

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