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

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5P51RR000168-42
# NEW ENGLAND PRIMATE RESEARCH CENTER

Final

## NEW ENGLAND PRIMATE RESEARCH CENTER

HARVARD MEDICAL SCHOOL

## ANNUAL PROGRESS REPORT

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

70.389% AIDS Related

Ronald C. Desrosiers 4-8-04
Signature Date

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# TABLE OF CONTENTS

RESEARCH SUBPROJECTS

COMPARATIVE PATHOLOGY



IMMUNOLOGY

# PERSONNEL ROSTER

## Core Doctoral Scientists

| Name, Degree | Department | Non-Host Institution: State, Country |
|---|---|---|
| BRAUN, STEPHEN, PHD | IMMUNOLOGY | |
| BURRILL, THOMAS F., BS | ENGINEERING AND MAINTENANCE | |
| [illegible] | PRIMATE RESOURCES | |
| CHAREST, GREGORY P, BS | ADMINISTRATION | |
| CHOI, JOONG-KOOK, PHD | TUMOR VIROLOGY | |
| COHEN, GEORGE, PHD | IMMUNOLOGY | |
| DESROSIERS, RONALD C, PHD | MICROBIOLOGY | |
| DEWS, PETER, PHD | EMERITUS | |
| ELLIOTT, MICHELLE W, DVM | COMPARATIVE PATHOLOGY | |
| [illegible] | ADMINISTRATION | |
| EVANS, DAVID T., PHD | MICROBIOLOGY | |
| FAHEY, MICHELLE A, DVM | PRIMATE RESOURCES | |
| [illegible] | CENTRAL SUPPLY PRIMATE SURGERY | |
| FINGOLD, SYDNEY, BS | ADMINISTRATION | |
| GAUDUIN, MARIE-CLAIRE, PHD | IMMUNOLOGY | |
| HUNT, RONALD, DVM | EMERITUS | |
| JOHNSON, R PAUL, MD | IMMUNOLOGY | |
| JOHNSON, WELKIN E, PHD | MICROBIOLOGY | |
| JUNG, JAE U, PHD | TUMOR VIROLOGY | |
| KAUR, AMITINDER, MD | IMMUNOLOGY | |
| KLUMPP, SHERRY A, DVM | COMPARATIVE PATHOLOGY | |
| LANG, SABINE, PHD | MICROBIOLOGY | |
| LUDLAGE, ELISABETH, DVM | PRIMATE RESOURCES | |
| MADRAS, BERTHA K, PHD | NEUROCHEMISTRY | |
| MANSFIELD, KEITH G, DVM | PRIMATE RESOURCES | |
| MARTIN, JOSEPH B, MD, PHD | NEUROBIOLOGY | HARVARD MEDICAL SCHOOL: MA, USA |
| MEANS, ROBERT E., PHD | TUMOR VIROLOGY | |
| MILLER, GREGORY M, PHD | NEUROCHEMISTRY | |
| [illegible] | ANIMAL CARE | |
| O'NEIL, SHAWN P, DVM, PHD | COMPARATIVE PATHOLOGY | |
| PLATT, DONNA M, PHD | BEHAVIORAL BIOLOGY | |
| ROSENZWEIG, MICHAEL, BVSC, PHD | IMMUNOLOGY | |
| ROWLETT, JAMES K, PHD | BEHAVIORAL BIOLOGY | |
| SEHGAL, PRABHAT K, BVSC | PRIMATE RESOURCES | |
| SPEALMAN, ROGER D, PHD | BEHAVIORAL BIOLOGY | |
| [illegible] | BEHAVIORAL BIOLOGY | |
| WESTMORELAND, SUSAN V, VMD | COMPARATIVE PATHOLOGY | |
| WORTHAM, JAMES T., MA | ADMINISTRATION | |

## Affiliated

## Affiliated

| Name, Degree | Department | Non-Host Institution: State, Country |
|---|---|---|
| | SURGERY | MASSACHUSETTS GENERAL HOSPITAL: MA, USA |
| | WASHINGTON NAT'L PRIMATE RES C | UNIVERSITY OF WASHINGTON: WA, USA |
| | | UC DAVIS: CA, USA |
| ALDOVINI, ANNA, MD | PEDIATRICS | CHILDREN'S HOSPITAL: MA, USA |
| | EPIDEMIOLOGY & PUBLIC HEALTH | YALE MEDICAL SCHOOL: CT, USA |
| | NUCLEAR MEDICINE | MASS GENERAL HOSPITAL, BOSTON: MA, USA |
| | MICROBIOLOGY AND IMMUNOLOGY | EMORY VACCINE CENTER - YERKES: GA, USA |
| | | TULANE NATL PRIMATE RESEARCH CENTER: LA, USA |
| | | YERKES PRIMATE RESEARCH CENTER: GA, USA |
| | | YERKES PRIMATE RESEARCH CENTER: GA, USA |
| | | WYETH-AYERST LABORATORIES: NJ, USA |
| | | UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL: MA, USA |
| | | JEWISH GENERAL HOSPITAL, MONTREAL, CANADA |
| | AIDS VACCINE PROGRAM | NCI FREDERICK CAN RES & DEV CTR: MD, USA |
| | NEUROBIOLOGY | HARVARD MEDICAL SCHOOL: MA, USA |
| | PATHOLOGY | BRIGHAM AND WOMEN'S HOSPITAL: MA, USA |
| | | JOHNS HOPKINS SINGAPORE, SINGAPORE |
| | PRIMATE MEDICINE | OREGON NATIONAL PRIMATE RESEARCH CENTER: OR, USA |
| | INFECTIOUS DISEASE MICROBIOLOG | UNIVERSITY OF PITTSBURGH: PA, USA |
| | BIOLOGY | CLAFLIN UNIVERSITY: SC, USA |
| | BIOLOGY | UNIVERSITY OF NORTH CAROLINA: NC, USA |
| | MEDICINE | BRIGHAM AND WOMEN'S HOSPITAL: MA, USA |
| BARBAS, HELEN, PHD | HEALTH SCIENCES | BOSTON U: MA, USA |
| | MEDICINE | BETH ISRAEL DEACONESS MEDICAL CENTER: MA, USA |
| | | UC DAVIS: CA, USA |
| | | SAIC, FREDERICK: MD, USA |
| | INFECTIOUS DISEASE RESEARCH DE | SOUTHERN RESEARCH INSTITUTE: MD, USA |

## Affiliated

| Name, Degree | Department | Non-Host Institution: State, Country |
|---|---|---|
| | | INSTITUT COCHIN DE GENETIQUE MOLECULAIRE, FRANCE |
| | SURGERY | MASSACHUSETTS GENERAL HOSPITAL: MA, USA |
| | MEDICAL SCIENCES | OREGON STATE UNIVERSITY: OR, USA |
| | | TRUDEAU INSTITUTE: NY, USA |
| | | ORGANIX, INC., WOBURN: MA, USA |
| | PHYSIOLOGY, SOM | UNIVERSITY OF MARYLAND: MD, USA |
| | NUCLEAR MEDICINE | MASS GENERAL HOSPITAL, BOSTON: MA, USA |
| | | TULANE NATIONAL PRIMATE RESEARCH CTR: LA, USA |
| | CHEMISTRY | SYRACUSE UNIVERSITY: NY, USA |
| | NEUROBIOLOGY | HARVARD MED SCH: MA, USA |
| | BASIC SCIENCES | NATIONAL CANCER INSTITUTE: MD, USA |
| | | MAYO CLINIC: MN, USA |
| | MEDICINE | MASSACHUSETTS GENERAL HOSPITAL: MA, USA |
| | | QUALITY BIOLOGICAL, INC.: MD, USA |
| | RADIOLOGY | MASSACHUSETTS GENERAL HOSPITAL: MA, USA |
| | NUCLEIC ACID BIOCHEMISTRY | INDIANA UNIVERSITY: IN, USA |
| | | PAIN THERAPEUTICS, INC: CA, USA |
| | IMMUNOLOGY | THE SCRIPPS RESEARCH INSTITUTE: CA, USA |
| | | CALIFORNIA NATIONAL PRIMATE RESEARCH CTR: CA, USA |
| | | ALBANY MEDICAL COLLEGE: NY, USA |
| | WEILL MEDICAL COLLEGE | CORNELL UNIVERSITY: NY, USA |
| | | SENTION, INC.: RI, USA |
| | MEDICINE | BETH ISRAEL DEACONESS MEDICAL CENTER: MA, USA |
| | WEILL MEDICAL COLLEGE | CORNELL UNIVERSITY: NY, USA |
| | | UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL: MA, USA |
| | PATHOLOGY | BRIGHAM & WOMEN'S HOSPITAL: MA, USA |

## Affiliated

| Name, Degree | Department | Non-Host Institution: State, Country |
|---|---|---|
| | | BROOKHAVEN NATIONAL LABORATORY: NY, USA |
| | MICRO IMMUNO & MEDICINE | UCLA AIDS INSTITUTE: CA, USA |
| | MICROBIAL PATHOGENESIS | YALE SCHOOL OF MEDICINE: CT, USA |
| | MEDICINE | BETH ISRAEL DEACONESS MEDICAL CENTER: MA, USA |
| CHIOCCA, ENNIO ANTONIO, MD, PHD | SURGERY | MASSACHUSETTS GENERAL HOSPITAL: MA, USA |
| | | KAIST, KOREA |
| | HOWARD HUGHES MED INSTITUTE | UNIVERSITY OF PENNSLVANIA: PA, USA |
| | MOLECULAR GENETICS AND MICRO | UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL: MA, USA |
| | VIRAL VECTOR CORE FACILITY | COLUMBUS CHILDREN'S RESEARCH INSTITUTE: OH, USA |
| | MOLECULAR BIOLOGY AND BIOLOGY | TUFTS MEDICAL SCHOOL: MA, USA |
| | | GEORGIA INSTITUTE OF TECHNOLOGY: GA, USA |
| | CHEMISTRY | UNIVERSITY OF WISCONSIN: WI, USA |
| | | ROSKAMP INSTITUTE: FL, USA |
| | CENTRE FOR VIRUS RESEARCH | WESTMEAD MILLENNIUM INSTITUTE, AUSTRALIA |
| | | CHIRON, EMERYVILLE: CA, USA |
| | DIVISION OF INFECTIOUS DISEASE | UNIVERSITY OF CALIFORNIA, DAVIS: CA, USA |
| | PSYCHOLOGY | UNIVERSITY OF MASSACHUSETTS, AMHERST: MA, USA |
| | PATHOLOGY | UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL, WORCESTER: MA, USA |
| | | MERCK, SHARP, DOHME, UK |
| | | ALBERT EINSTEIN COLLEGE OF MEDICINE: NY, USA |
| | | IMPERIAL COLLEGE OF LONDON, UK |
| | | WISCONSIN NAT'L PRC: WI, USA |
| | | GEORGIA INSTITUTE OF TECHNOLOGY: GA, USA |
| | MICROBIOLOGY AND IMMUNOLOGY | UNIVERSITY OF ROCHESTER: NY, USA |
| | NIAID | NIH: MD, USA |
| | | V A MEDICAL CENTER: MI, USA |

## Affiliated

| Name, Degree | Department | Non-Host Institution: State, Country |
|---|---|---|
| | MICROBIOLOGY & IMMUNOLOGY | UNIVERSITY OF OKLAHOMA HEALTH SCIENCE CTR: OK, USA |
| | PSYCHIATRY | MASSACHUSETTS GENERAL HOSPITAL: MA, USA |
| DOGON, I LEON, DMD | RST DENT & BIOMATERIALS | HARVARD SCHOOL OF DENTAL MEDICINE: MA, USA |
| | DEPT. OF PATHOLOGY & LAB. MEDI | UNIVERSITY OF PENNSYLVANIA: PA, USA |
| | | EMORY UNIVERSITY: GA, USA |
| | VETERINARY & BIOMED SCIENCES | UNIVERSITY OF NEBRASKA - LINCOLN: NE, USA |
| | | PFIZER, INC: CT, USA |
| | PSYCHIATRY | MASSACHUSETTS GENERAL HOSPITAL: MA, USA |
| | BIOCHEMISTRY AND BIOPHYSICS | HOWARD HUGHES MEDICAL INSTITUTE: PA, USA |
| | | VIRXSYS, GAITHERSBURG: MD, USA |
| | NEUROBIOLOGY | HARVARD MEDICAL SCHOOL: MA, USA |
| | INST. FUR KLINISCHE & MOL VIRO | UNIVERSITAT ERLANGEN-NURNBERG, GERMANY |
| | MEDICAL SCIENCE | IRISICAIXA FOUNDATION, SPAIN |
| | VACCINE RESEARCH CENTER | EMORY UNIVERSITY: GA, USA |
| | | ABL-BASIC RESEARCH PROGRAM, FREDERICK: MD, USA |
| | PSYCHIATRY | UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL: MA, USA |
| | RADIOLOGY | MASSACHUSETTS GENERAL HOSPITAL, BOSTON: MA, USA |
| | MEDICINE | MASSACHUSETTS GENERAL HOSPITAL: MA, USA |
| | INST. FUR KLINISCHE & MOLE VIR | UNIVERSITAT ERLANGEN-NURNBERG, GERMANY |
| | MOLECULAR & CELL PHYSIOLOGY | UNIVERSITY OF COLORADO HEALTH SCIENCES CENTER: CO, USA |
| | MEDICINE | BRIGHAM & WOMEN'S HOSPITAL: MA, USA |
| | NEUROPHARMACOLOGY | THE SCRIPPS RESEARCH INSTITUTE: CA, USA |
| | COMPARATIVE MEDICINE | MASS INSTITUTE OF TECHNOLOGY: MA, USA |
| | CLINICAL SCIENCES | TUFTS U SCH MED: MA, USA |

## Affiliated

| Name, Degree | Department | Non-Host Institution: State, Country |
|---|---|---|
| | PATHOBIOLOGY | UNIVERSITY OF CONNECTICUT: CT, USA |
| | HUMAN RETROVIROLOGY | DANA FARBER CANCER INSTITUTE: MA, USA |
| | MICROBIOL PATHOGENESIS | YALE UNIVERSITY SCHOOL OF MEDICINE: CT, USA |
| | | SCRIPPS RESEARCH INSTITUTE: CA, USA |
| | DEPARTMENT OF MICROBIOLOGY | HOWARD HUGHES MEDICAL INSTITUTE: CA, USA |
| | RHEUMATOLOGY UNIT | INSTITUTE OF CHILD HEALTH, UK |
| | | UNIVERISTY OF TX HEALTH SCIENCE CTR, SAN ANTONIO: TX, USA |
| | | BIORECLAMATION, INC: NY, USA |
| | ENDOCRINOLOGY & MET | UNIVERSITY OF TORONTO, CANADA |
| | MEDICINE | HARVARD MEDICAL SCHOOL: MA, USA |
| | ANTHROPOLOGY | UNIVERSITY OF MASSACHUSETTS, AMHERST: MA, USA |
| | MEDICINE | BRIGHAM AND WOMEN'S HOSPITAL: MA, USA |
| | FAM MED AND COMM HLTH | TUFTS UNIVERSITY SCHOOL OF MEDICINE: MA, USA |
| | | GENETICS INSTITUTE: MA, USA |
| | PATHOBIOLOGY | UNIVERSITY OF PENNSYLVANIA: PA, USA |
| GONZALEZ, R. GILBERTO, MD, PHD | RADIOLOGY | MASSACHUSETTS GENERAL HOSPITAL: MA, USA |
| | NEUROLOGY | UNIV. OF PENNSYLVANIA MEDICAL CENTER: PA, USA |
| GORBACH, SHERWOOD L, MD | FAM MED & COM HLTH | TUFTS U SCH MED: MA, USA |
| | | UNIVERSITY OF CONNECTICUT HEALTH SCICNE CENTER: CT, USA |
| | | REPLIGEN CORPORATION: MA, USA |
| | | MASSACHUSETTS COLLEGE OF PHARMACY AND ALLIED HEALTH: MA, USA |
| | BRAIN AND COG SCI | MASSACHUSETTS INSTITUTE OF TECHNOLOGY: MA, USA |
| | | SANOFI-SYNTHELABO: NY, USA |
| | | INOVA THERAPEUTICS: VA, USA |
| | | NIH/NIDCR: MD, USA |

## Affiliated

| Name, Degree | Department | Non-Host Institution: State, Country |
|---|---|---|
| [names] | MEDICINE | BRIGHAM AND WOMEN'S HOSPITAL: MA, USA |
| | CELL BIOLOGY | HARVARD MEDICAL SCHOOL: MA, USA |
| HANSEN, BARBARA C, PHD | PHYSIOLOGY, SOM | UNIVERSITY OF MARYLAND: MD, USA |
| [names] | GENETICS INSTRUCTION & RESEARC | WASHINGTON UNIVERSITY: MO, USA |
| | PATHOLOGY | MASSACHUSETTS GENERAL HOSPITAL: MA, USA |
| [names] | BIO CHEM & MOL PHAMACOL | HARVARD MEDICAL SCHOOL: MA, USA |
| | | BRIGHAM & WOMEN'S HOSPITAL: MA, USA |
| HAUSER, MARC D, PHD | PSYCHOLOGY | HARVARD MEDICAL SCHOOL: MA, USA |
| [names] | PHARMA & MOLECULAR SCIENCE | JOHNS HOPKINS UNIVERSITY: MD, USA |
| | | CENTERS FOR DISEASE CONTROL AND PREVENTION: GA, USA |
| | MOLECULAR BIOLOGY AND GENETICS | CORNELL UNIVERSITY: NY, USA |
| | INFECTIOUS DISEASE UNIT | MASS GENERAL HOSPITAL: MA, USA |
| | LMM, NIAID | NIH: MD, USA |
| | | AARON DIAMOND AIDS RESEARCH CENTER: NY, USA |
| | NEROSURGERY | MASSACHUSETTS GENERAL HOSPITAL: MA, USA |
| | SURGERY | MASSACHUSETTS GENERAL HOSPITAL: MA, USA |
| | PHARMACOLOGY | EMORY U SCHOOL OF MEDICINE: GA, USA |
| | DERMATOLOGY | MASSACHUSETTS GENERAL HOSPITAL: MA, USA |
| [names] | IMMUNOBIOLOGY | HOWARD HUGHES MED./YALE UNIVERSITY: CT, USA |
| | | UNIVERSITY OF PENNSYLVANIA: PA, USA |
| | DAVIS CANCER CENTER | UC DAVIS: CA, USA |
| IACOMINI, JOHN J, PHD | SURGERY | ORGANIX, INC: MA, USA<br>MASSACHUSETTS GENERAL: MA, USA |
| [names] | | UNIVERSITY OF NEBRASKA MEDICAL CENTER: NE, USA |
| [names] | | MOUNT SINAI HOSPITAL, CANADA |
| ISACSON, OLE, PHD, DMSC | NEUROLOGY | MCLEAN HOSP: MA, USA |

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| Name, Degree | Department | Non-Host Institution: State, Country |
|---|---|---|
| | GENE THERAPY CENTER | TULANE HEALTH SCIENCE CENTER: LA, USA |
| | | KOBE UNIVERSITY, GRADUATE SCHOOL OF MEDICINE, JAPAN |
| IWASAKI, AKIKO, PHD | EPIDEMIOLOGY & PUBLIC HEALTH | YALE UNIVERSITY: CT, USA |
| | PSYCHIATRY & BEHAVIORAL SCIENC | UNIVERSITY OF MIAMI SCHOOL OF MEDICINE: FL, USA |
| JACOBS, JAMES R, PHD | | CORNELL UNIVERSITY: NY, USA |
| | RADIATION ONCOLOGY | MASSACHUSETTS GENERAL HOSPITAL: MA, USA |
| | | ICGEB, INDIA |
| | | VA MEDICAL CENTER: MI, USA |
| | | SEPRACOR, INC.: MA, USA |
| | MICRO & MOLECULAR GENETICS | HARVARD MEDICAL SCHOOL: MA, USA |
| | CHILDREN'S HOSPITAL | OHIO STATE UNIVERSITY: OH, USA |
| | | MILLENNIUM PHARMACEUTICALS: MA, USA |
| KASPER, DENNIS L, MD | MEDICINE | BRIGHAM AND WOMEN'S HOSPITAL: MA, USA |
| | BRAIN IMAGINING CENTER | MCLEAN HOSPITAL: MA, USA |
| | MEDICINE | BRIGHAM & WOMENS HOSP: MA, USA |
| | CELL BIOLOGY | CHILDRENS HOSPITAL: MA, USA |
| | MEDICINE | UNIVERSITY OF NEW SOUTH WALES, AUSTRALIA |
| | INFECTIOUS DISEASES | TUFTS UNIVERSITY SCHOOL OF VETERINARY MEDICINE: MA, USA |
| | | MCARDLE LABORATORY FOR CANCER RESEARCH: WI, USA |
| | | QUEENSLAND INSTITUTE OF MEDICAL RESEARCH, AUSTRALIA |
| | CLINICAL MEDICAL VIROLOGY CTR | UNIVERSITY OF QUEENSLAND, AUSTRALIA |
| | MEDICINE | BRIGHAM & WOMENS HOSP: MA, USA |
| | MEDICINE/ONCOLOGY | UNIVERSITY OF WASHINGTON: WA, USA |
| | MICRO & IMMUNOLOGY M & D | UNIVERSITY OF ROCHESTER MEDICAL CTR: NY, USA |
| | | NCI: MD, USA |
| | | UNIVERSITY OF HAWAII, MANOA: HI, USA |

## Affiliated

| Name, Degree | Department | Non-Host Institution: State, Country |
|---|---|---|
| | | ABTEILUNG VIROLOGIE - UNIVERSITÄTSKLINIKUM, GERMANY |
| | | JEWISH GENERAL HOSPITAL, CANADA |
| | AIDS RES CTR | MASS GENERAL HOSPITAL: MA, USA |
| | MEDICINE | BOSTON UNIVERSITY: MA, USA |
| KLEPPER-KILGORE, NANCY, PHD | VETERINARY TECHNOLOGY | MOUNT IDA COLLEGE: MA, USA |
| KNIPE, DAVID, PHD | MICROBIO & MOLECULAR GENETICS | HARVARD MED SCH: MA, USA |
| | NEUROLOGY | BRIGHAM & WOMEN'S HOSPITAL: MA, USA |
| | NEUROLOGY | MASSACHUSETTS GENERAL HOSPITAL: MA, USA |
| | IMMUNOLOGY LABORATORY | VACCINE RESEARCH CENTER NIAID/NIH: MD, USA |
| | | ASTRAZENECA PHARMACEUTICALS: DE, USA |
| | PEDIATRICS | CHILDREN'S HOSPITAL, BOSTON: MA, USA |
| | | U PUERTO RICO MEDICAL CENTER, PUERTO RICO |
| | PEDIATRIC INFECTIOUS DISEASE | UNIVERSITY OF CALIFORNIA: CA, USA |
| | AUTOIMMUNITY | IMMCO DIAGNOSTICS: NY, USA |
| | BIOLOGICAL CHEMISTRY | UC DAVIS CANCER CENTER: CA, USA |
| KURODA, MARCELO J., PHD, MD | MEDICINE, VIRAL PATHOGENEIS | BETH ISRAEL DEACONESS MEDICAL CENTER: MA, USA |
| | | TULANE NATL PRIMATE RESEARCH CENTER: LA, USA |
| | BIOCHEMISTRY | GEORGE WASHINGTON UNIVERSITY MEDICAL SCHOOL: MD, USA |
| | COMPARATIVE MEDICINE | HARVARD MEDICAL SCHOOL: MA, USA |
| | | CENTERS FOR DISEASE CONTROL: GA, USA |
| | | POHANG UNIVERSITY OF SCIENCE AND TECHNOLOGY, KOREA |
| | CNS RESEARCH | BRISTOL MYERS SQUIBB, WALLINGFORD: CT, USA |
| LEMERE, CYNTHIA A, PHD | NEUROLOGY | BRIGHAM AND WOMEN'S HOSPTIAL: MA, USA |
| | RADIOLOGY | MASSACHUSETTS GENERAL HOSPITAL: MA, USA |
| LETVIN, NORMAN L, MD | MEDICINE, VIRAL PATHOGENESIS | BETH ISRAEL DEACONESS MEDICAL CENTER: MA, USA |

## Affiliated

| Name, Degree | Department | Non-Host Institution: State, Country |
|---|---|---|
| | MEDICINE/VIRAL PATHOLGENESIS | BETH ISRAEL DEACONESS MEDICAL CENTER: MA, USA |
| | HEMATOLOGY/ONCOLOGY | UNIVERSITY OF CALIFORNIA, SAN FRANCISCO: CA, USA |
| | | BIOQUAL, INC: MD, USA |
| | RADIOLOGY | UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL: MA, USA |
| | GENE EXPRESSION AND REGULATION | WISTAR INSTITUTE: PA, USA |
| | AIDS VACCINE PROGRAM | NCI/FREDERICK: MD, USA |
| | | RESEARCH INST. FOR GENETIC & HUMAN THERAPY, WASHINGTON: DC, USA |
| LIVINGSTONE, MARGARET S, PHD | NEUROBIOLOGY | HARVARD MEDICAL SCHOOL: MA, USA |
| | RADIOLOGY | MASS GENERAL HOSPITAL, BOSTON: MA, USA |
| | | NORTHWESTERN UNIVERISTY SCHOOL OF MEDICINE: IL, USA |
| | | UC DAVIS: CA, USA |
| | PATHOLOGY | MASSACHUSETTS GENERAL HOSPITAL: MA, USA |
| | PATHOLOGY, MICROBIOLOGY & IMMU | UNIVERISTY OF CALIFORNIA, DAVIS: CO, USA |
| LU, SHAN, PHD | MEDICINE | UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL: MA, USA |
| | INFECTIOUS DISEASE UNIT | MASS GENERAL HOSPITAL: MA, USA |
| | | INST FUR KLINISCH UND MOLEKULARE VIROLOGIE, GERMANY |
| | BIODEFENSE & MEDICAL VIROLOG | KUMAMOTO UNIVERSITY SCHOOL OF MEDICINE, JAPAN |
| MAKI, TAKASHI, MD, PHD | SURGERY | BETH ISRAEL DEACONESS MEDICAL CENTER: MA, USA |
| MARASCO, WAYNE A., MD, PHD | CANCER IMMUNOLOGY AND AIDS | DANA FARBER CANCER INSTITUTE: MA, USA |
| | MOL & CELL PHYSIOLOGY | UNIVERSITY OF COLORADO HEALTH SCIENCES CENTER: CO, USA |
| | | CORNELL UNIVERSITY: NY, USA |
| | MRC LAB MOLE CELL BIOL | UNIVERSITY COLLEGE LONDON, UK |
| | MOLECULAR MICROBIOLOGY | NIH: MD, USA |
| | | AARON DIAMOND AIDS RESEARCH CENTER: NY, USA |

## Affiliated

| Name, Degree | Department | Non-Host Institution: State, Country |
|---|---|---|
| | NMR CENTER | MASS GENERAL HOSPITAL: MA, USA |
| | GENE FUNCTION AND EXPRESSION | UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL: MA, USA |
| | | THERION BILOGICS CORP: MA, USA |
| | MICROBIOLOGY AND IMMUNOLOGY | EMORY UNIVERSITY YERKES NATL PRC: GA, USA |
| | | MERCK RESEARCH LABORATORIES: NJ, USA |
| | | ORGANIX, INC., WOBURN: MA, USA |
| | VETERINARY MEDICINE | UNIVERSITY OF FLORIDA: FL, USA |
| | PSYCHOLOGY | UNIVERSITY OF MASSACHUSETTS, AMHERST: MA, USA |
| | BEHAVIORAL BIOLOGY | TUFTS UNIVERSITY: MA, USA |
| | ORAL MEDICINE SECTION | UNIVERSITY OF KENTUCKY, COLLEGE OF DENTISTRY: KY, USA |
| | SURGERY | BETH ISRAEL DEACONESS MEDICAL CENTER: MA, USA |
| | SURGERY | DUKE MEDICAL CENTER: NC, USA |
| | | UNIVERSITY OF MARYLAND BIOTECHNOLOGY INSTITUTE: MD, USA |
| | MOLECULAR GENETICS & BIOCHEM | UNIVERSITY OF PITTSBURGH: PA, USA |
| | MICRO & IMMUNOL | WEILL MEDICAL COLLEGE, CORNELL UNIVERSITY: NY, USA |
| | AIDS RESEARCH CENTER | TSUKUBA PRIMATE CENTER, JAPAN |
| | MICROBIOLOGY | UNIVERSITY OF ALABAMA: AL, USA |
| | | HARVARD MEDICAL SCHOOL: MA, USA |
| | | UNIVERSITY OF ROCHESTER: NY, USA |
| | | EPIMMUNE: CA, USA |
| | MEDICINE | MASSACHUSETTS GENERAL HOSPITAL: MA, USA |
| | | ROSKAMP INSTITUTE: FL, USA |
| | GENETICS | CHILDREN'S HOSPITAL: MA, USA |
| | CANCER IMMUNOLOGY & AIDS | DANA-FARBER CANCER INSTITUTE: MA, USA |
| | TUMOR VIROLOGY | |

## Affiliated

| Name, Degree | Department | Non-Host Institution: State, Country |
|---|---|---|
| | | KYOTO UNIVERSITY OF PATHOLOGY, KOREA |
| | MICRO, MOL GEN & IMMUNOL | UNIVERSITY OF KANSAS MEDICAL CENTER: KS, USA |
| | NIAID | NIH: MD, USA |
| | INST. FUR KLINISCHE & MOLE VIR | UNIVERSITAT ERLANGEN-NURNBERG, GERMANY |
| | REHABILITATION MEDICINE | BOSTON UNIVERSITY: MA, USA |
| NEUTRA, MARIAN R, PHD | PEDIATRICS | CHILDREN'S HOSPITAL, BOSTON: MA, USA |
| NOVAK, MELINDA A, PHD | PSYCHOLOGY | UNIVERSITY OF MASSACHUSETTS, AMHERST: MA, USA |
| | RESEARCH RESOURCES | EMORY UNIVERSITY, YERKES NATL PRC: GA, USA |
| | BIOLOGICAL SCIENCE | UNIVERSITY OF MONTANA: MT, USA |
| | PHARMACOLOGY | UNIVERSITY OF TORONTO, CANADA |
| | SURGERY | BETH ISRAEL DEACONESS MEDICAL CENTER: MA, USA |
| | | POHANG UNIVERSITY, KOREA |
| | PATHOLOGY | GEORGE WASHINGTON MEDICAL CENTER: DC, USA |
| | MOLEC GROWTH | NIH: MD, USA |
| | PHARMACOLOGY | UNIVERSITY OF CONNECTICUT HEALTH SCIENCES CENTER: CT, USA |
| | | ADVANCED BIOSCIENCE LABORATORIES, INC: CA, USA |
| | | MEDAREX PHARMACEUTICAL: NJ, USA |
| | | UNIVERSITY OF NEW MEXICO: NM, USA |
| | | THERION BIOLOGICS CORPORATION: MA, USA |
| | | IRCCS POLICLINICO SAN MATTEO, ITALY |
| | | PFIZER, INC: CT, USA |
| | GENE THERAPY LABORATORY | LOUISIANA STATE UNIVERSITY HEALTH SCIENCES CENTER: LA, USA |
| | | KAIST, KOREA |
| | PEDIATRIC INFECTIOUS DISEASE | MASSACHUSETTS GENERAL HOSPITAL: MA, USA |
| | MICROBIOLOGY | UNIVERSITY OF PENNSYLVANIA: PA, USA |

## Affiliated

| Name, Degree | Department | Non-Host Institution: State, Country |
|---|---|---|
| | | UNIVERSITY OF WISCONSIN-MADISON: WI, USA |
| | HUMAN RETROVIRUS SECTION | NCI: MD, USA |
| | | INSTITUTE OF MEDICAL &VETERINARY SCIENCE, AUSTRALIA |
| | | MERCK RESEARCH LABORATORIES: NJ, USA |
| | | ALTON OCHSNER HOSPITAL: LA, USA |
| | | LOS ALAMOS NATIONAL LABORATORY: NM, USA |
| | | UNIVERSITY OF PUERTO RICO, PUERTO RICO |
| | | VIROLOGIC, INC: CA, USA |
| PHINNEY, DONALD G, PHD | GENE THERAPY CENTER | TULANE HEALTH SCIENCE CENTER: LA, USA |
| | SAIC | NCI FREDERICK: MD, USA |
| | PATHOLOGY | OREGON HEALTH AND SCIENCE UNIVERSITY: OR, USA |
| | RADIOLOGY | MASSACHUSETTS GENERAL HOSPITAL: MA, USA |
| | PATHOLOGY | HARVARD MEDICAL SCHOOL: MA, USA |
| | CTR FOR BIOMEDICAL RES | UNIVERSITY ERLANGEN-NUERNBERG, GERMANY |
| | MICROBIOLOGY/IMMUNOLOGY | CENTER FOR BIOMEDICAL RESEARCH POPULATION COUNCIL: NY, USA |
| | | ST. LUKE'S-ROOSEVELT HOSPITAL CENER: NY, USA |
| | MICRO, IMMUNOL, BIOCHEMISTRY | MOREHOUSE SCHOOL OF MEDICINE: GA, USA |
| | MICROBIOLOGY AND IMMUNOLOGY | ALBERT EINSTEIN COLLEGE OF MEDICINE: NY, USA |
| | VIROLOGY | LERNER RESEARCH INSTITUTE: OH, USA |
| | IMMUNOLOGY | WISCONSIN NAT'L PRIMATE RES CTR: WI, USA |
| | BIOCHEM & MOLECULAR PHARMACOL | UNIVERSITY OF MASSACHUSETTS MEDICAL CENTER: MA, USA |
| | NEUROLOGY | BRIGHAM & WOMEN'S HOSPITAL: MA, USA |
| | | NICHD: MD, USA |
| RASO, VICTOR, PHD | | BOSTON BIOMEDICAL RESEARCH INSTITUTE: MA, USA |

## Affiliated

| Name, Degree | Department | Non-Host Institution: State, Country |
|---|---|---|
| | RADIOLOGY | MASSACHUSETTS GENERAL HOSPITAL: MA, USA |
| RAVIOLA, ELIO, MD | NEUROBIOLOGY | HARVARD MEDICAL SCHOOL: MA, USA |
| | NEUROBIOLOGY | HARVARD MEDICAL SCHOOL: MA, USA |
| REIMANN, KEITH A, DVM | MEDICINE, VIRAL PATHOGENESIS | BETH ISRAEL-DEACONESS MEDICAL CENTER: MA, USA |
| | INFECTIOUS DISEASES/MICRO | UNIVERSITY OF PITTSBURGH: PA, USA |
| | BASIC SCIENCE | THE INSTITUTE OF HUMAN VIROLOGY: MD, USA |
| | | UNIVERSITY OF OXFORD, UK |
| | | UNIVERSITY OF PITTSBURGH: PA, USA |
| | | BRIGHAM AND WOMEN'S HOSPITAL: MA, USA |
| | | NCI/NIH: MD, USA |
| | | UNIVERSITY OF PENNSYLVANIA SCHOOL OF MEDICINE: PA, USA |
| | YERKES PRIMATE CENTER | EMORY UNIVERSITY: GA, USA |
| | PEDIATRICS | TULANE UNIVERSITY MEDICAL CENTER: LA, USA |
| | | UNIVERSITY OF MICHIGAN MEDICAL SCHOOL: MI, USA |
| | | US ARMY/MRICD: MD, USA |
| | | UNIVERSITY OF IOWA: IA, USA |
| | GENETICS | SOUTHWEST FOUNDATION FOR BIOMEDICAL RESEARCH: TX, USA |
| | | BOSTON UNIVERSITY: MA, USA |
| | | EAST CAROLINA UNIVERSITY: NC, USA |
| | | CITY OF HOPE, DUARTE: CA, USA |
| | PSYCHIATRY | CASE WESTERN RESERVE UNIVERSITY: OH, USA |
| | MEDICINE | DANA-FARBER CANCER INSTITUTE: MA, USA |
| | | YESHIVA UNIVERSITY: NY, USA |
| | SURGERY | MASS GENERAL HOSPITAL: MA, USA |
| | NEUROSCIENCE | UNIVERSITY OF WASHINGTON, SEATTLE: WA, USA |
| | DERMATOLOGY | HARVARD MEDICAL SCHOOL: MA, USA |
| | BRAIN AND COG SCI | MASSACHUSETTS INSTITUTE OF TECHNOLOGY: MA, USA |

## Affiliated

| Name, Degree | Department | Non-Host Institution: State, Country |
|---|---|---|
| | PSYCHIATRY | MCLEAN HOSPITAL: MA, USA |
| | | MILLENNIUM PHARMACEUTICALS, INC: MA, USA |
| | | UNIVERSITY OF POMPEU FABRA, SPAIN |
| | MEDICINE | MASSACHUSETTS GENERAL HOSPITAL: MA, USA |
| | CHEM ENGR | UNIVERSITY OF CALIFORNIA, BERKELEY: CA, USA |
| | PATHOLOGY | ANGELL MEMORIAL HOSPITAL: MA, USA |
| | CHEMISTRY | BROOKHAVEN NATIONAL LABORATORIES: NY, USA |
| | | EMORY UNIVERSITY: GA, USA |
| | | MERCK AND COMPANY: NJ, USA |
| SCHLOSSMACHER, MICHAEL G, MD | NEUROLOGY | BRIGHAM AND WOMEN'S HOSPITAL: MA, USA |
| | MEDICINE, VIRAL PATHOGENESIS | BETH ISRAEL DEACONESS MEDICAL CENTER: MA, USA |
| | | HANNOVER UNIVERSITY, GERMANY |
| | PHYSICAL BIOSCIENCES | LAWRENCE BERKLEY NATIONAL LABORATORIES: CA, USA |
| | | MERCER UNIVERSITY SCHOOL OF MEDICINE: GA, USA |
| | NEUROLOGY | BRIGHAM & WOMEN'S HOSPITAL: MA, USA |
| | | EPIMMUNE, SAN DIEGO: CA, USA |
| SHANNON, RICHARD P, MD | MEDICINE | ALLEGHENY GENERAL HOSPITAL, PITTSBURGH: PA, USA |
| | | KOREA ADV INSTITUTE FOR SCIENCE AND TECHNOLOGY, KOREA |
| | NEUROLOGY | BRIGHAM & WOMEN'S HOSPITAL: MA, USA |
| | | EPIMMUNE, INC, SAN DIEGO: CA, USA |
| | MOL BIO & GENETICS | HOWARD HUGHES MEDICAL INSTITUTE: MD, USA |
| | | EMORY VACCINE CENTER: GA, USA |
| | | CHARLES RIVER LABORATORY, WILMINGTON: MA, USA |

## Affiliated

| Name, Degree | Department | Non-Host Institution: State, Country |
|---|---|---|
| | BIOMEDICAL SCIENCES | TUFTS U SCHOOL OF VETERINARY MEDICINE: MA, USA |
| | | COLD SPRING HARBOR LABORATORIES: NY, USA |
| | | UNIVERSITY OF CALIFORNIA: CA, USA |
| | | SOUTHWEST FOUNDATION FOR BIOMEDICAL RESEARCH: TX, USA |
| | IMMUNOLOGY | UNIVERSITY OF TENNESSEE SCHOOL OF MEDICINE: TN, USA |
| | IMMUNOLOGY AND MICROBIOLOGY | RUSH UNIVERSITY MEDICAL CENTER: IL, USA |
| | | UNIVERSITY HOSPITAL OF ZURICH, SWITZERLAND |
| | YERKES NAT'L PRIMATE RES CT | EMORY UNIVERSITY: GA, USA |
| | PSYCHIATRY | MASSACHUSETTS GENERAL HOSPITAL: MA, USA |
| | PEDIATRICS | CHILDREN'S HOSPITAL: MA, USA |
| | | EMORY UNIVERSITY,: GA, USA |
| | MOLECULAR BIOLOGY & BIOCHEM | YALE UNIVERSITY: CT, USA |
| | MOLECULAR MEDICINE | U MASS MED CTR: MA, USA |
| | | BOEHRINGER INGELHEIM, GERMANY |
| | PATHOLOGY AND MEDICINE | JEFFERSON MED COL: PA, USA |
| | NIAID | NIH: MD, USA |
| | DEVELOPMENTAL BIOLOGY | MSKCC: NY, USA |
| | PROGRAM IN MOLECULAR MEDICINE | U. MASS MEDICAL SCHOOL: MA, USA |
| | | FRIEDRICH MIESCHER INSTSITUTE, SWITZERLAND |
| | | NICHD: MD, USA |
| | | IMPERIAL COLLEGE OF LONDON, UK |
| | AIDS, STD AND TB LAB RESEARCH | CENTER FOR DISEASE CONTROL: GA, USA |
| SYKES, MEGAN, MD | SURGERY | MASS GENERAL HOSPITAL: MA, USA |
| | PATHOLOGY | MASSACHUSETTS GENERAL HOSPITAL: MA, USA |
| | LABORATORY OF IMMUNOLOGY | NATIONAL INSTITUTE ON AGING: MD, USA |
| | ANTHROPOLOGY | DUKE UNIVERSITY MED CTR: NC, USA |
| | RHEUMATOLOGY | VANDERBILT UNIVERSITY: TN, USA |

## Affiliated

| Name, Degree | Department | Non-Host Institution: State, Country |
|---|---|---|
| [illegible] | SURGERY | MASSACHUSETTS GENERAL HOSPITAL: MA, USA |
| [illegible] | GASTROENTEROLOGY | VAMC, WAYNE STATE U: MI, USA |
| [illegible] | MOLECULAR ANTHROPOLOGY | NEW YORK UNIVERSITY: NY, USA |
| [illegible] | GRAD SCHOOL OF BIOMED SCIENCES | UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL, WORCESTER: MA, USA |
| [illegible] | CENTRE HOSPITALIER | UNIVERSITAIRE DE QUEBEC, CANADA |
| TROILO, DAVID, PHD | BIOLOGICAL SCIENCES | NEW ENGLAND COLLEGE OF OPTOMETRY: MA, USA |
| TZIPORI, SAUL, DSC, DVM, PHD | BIOMEDICAL SCIENCES | TUFTS U SCHOOL OF VETERINARY MEDICINE: MA, USA |
| [illegible] | | VANDERBILT UNIVERSITY SCHOOL OF MEDICINE: TN, USA |
| [illegible] | SURGERY | BRIGHAM & WOMEN'S HOSPITAL: MA, USA |
| [illegible] | VIROLOGY | UNIVERSITY OF STELLENBOSCH, SOUTH AFRICA |
| [illegible] | MICRO, PATH AND IMMUNOL | COLORADO STATE UNIVERSITY: CO, USA |
| [illegible] | | UNIVERSITY OF COLORADO HEALTH SCIENCE CENTER: CO, USA |
| [illegible] | PATHOLOGY | TULANE NATIONAL PRIMATE RESEARCH CENTER: LA, USA |
| [illegible] | | UNIVERSITY OF PENNSYLVANIA: PA, USA |
| [illegible] | NEUROCHMISTRY | EMORY UNIVERSITY: GA, USA |
| [illegible] | PSYCHIATRY | MCCLEAN HOSPITAL: MA, USA |
| [illegible] | ANTHROPOLOGY | DUKE UNIVERSITY MEDICAL CENTER: NC, USA |
| [illegible] | PATH, IMMUNO, & MOLE MICROBIOL | WASHINGTON UNIVERSITY SCHOOL OF MEDICINE: MO, USA |
| [illegible] | | NCI: MD, USA |
| [illegible] | MEDICINE | MASS GENERAL HOSPITAL: MA, USA |
| WANG, FREDERICK C, MD | MEDICINE | BRIGHAM & WOMENS HOSP: MA, USA |
| [illegible] | ANTHROPOLOGY | UNIVERSITY OF MISSOURI: MO, USA |
| [illegible] | ANATOMY | NE OHIO UNIVERSITY COLLEGE OF MEDICINE: OH, USA |
| [illegible] | PATHOLOGY | HARVARD SCHOOL OF PUBLIC HEALTH: MA, USA |

## Affiliated

| Name, Degree | Department | Non-Host Institution: State, Country |
|---|---|---|
| | PATHOLOGY & LAB MEDICINE | WISCONSIN NATL PRC: WI, USA |
| | PATHOLOGY | UNIVERSITY OF PENNSYLVANIA: PA, USA |
| | | UNIVERSITY OF MASSACHUSETTS, AMHERST: MA, USA |
| | | CORNELL UNIVERSITY: NY, USA |
| | MEDICINE | BETH ISRAEL DEACONESS MEDICAL CENTER: MA, USA |
| WOLF, DONALD P, PHD | REPRO SCIENCES | OREGON NATIONAL PRIMATE RESEARCH CENTER: OR, USA |
| | | UC SD SCHOOL OF MEDICINE: CA, USA |
| | PSYCHIATRY | MCLEAN HOSPITAL: MA, USA |
| | SCHOOL OF BIOLOGICAL SCIENCE | UNIVERSITY OF NEBRASKA: NE, USA |
| | FAMILY MED & COM HLTH | TUFTS U SCHOOL OF MED: MA, USA |
| | MEDICINE | UC SD: CA, USA |
| | | LAMPIRE BIOLOGICAL LABORATORIES: PA, USA |
| | | THERION: MA, USA |
| | SURGERY | NORTHWESTERN UNIVERSITY FIENBERG SCHOOL OF MEDICINE: IL, USA |
| | | THERION BIOLOGICS CORP., CAMBRIDGE: MA, USA |
| | SURGERY | MASSACHUSETTS GENERAL HOSPITAL: MA, USA |
| | | ORGANIX, INC: MA, USA |
| | REPRO SCIENCES | OREGON NATIONAL PRIMATE RESEARCH CENTER: OR, USA |
| | VET PATHOL, MICRO & IMMUNOL | UC DAVIS: CA, USA |
| | MICRO & INFECT DISEASE PEDIA | UNIVERSITY OF CALGARY MEDICAL SCHOOL, CANADA |
| | SCHOOL OF DENTAL MEDICINE | UNIVERSITY OF PENNSYLVANIA: PA, USA |
| | | UC DAVIS CANCER CENTER: CA, USA |
| | VIROLOGY | BECKMAN RESEARCH INSTITUTE: CA, USA |
| | | NCI/NIH: MD, USA |
| | CANCER IMMUNOLOGY AND AIDS | DANA FARBER CANCER INSTITUTE: MA, USA |
| | | UNIVERSITY OF NEBRASKA MEDICAL CENTER: NE, USA |

## Affiliated

| Name, Degree | Department | Non-Host Institution: State, Country |
|---|---|---|
| [illegible] | BIOMEDICAL SCIENCES | TUFTS U SCHOOL OF VETERINARY MEDICINE: MA, USA |
| | MOLECULAR VIROLOGY | ST. LOUIS UNIVERSITY SCHOOL OF MEDICINE: MO, USA |
| | | BIOGEN: MA, USA |
| | | ORGANIX, INC.: MA, USA |

## Graduate Student/Postdoctoral Scientists

| Name, Degree | Department | Non-Host Institution: State, Country |
|---|---|---|
| [illegible] | IMMUNOLOGY | |
| | MICROBIOLOGY | |
| | MICROBIOLOGY | |
| | TUMOR VIROLOGY | |
| | TUMOR VIROLOGY | |
| | TUMOR VIROLOGY | |
| | BEHAVIORAL BIOLOGY | |
| | TUMOR VIROLOGY | |
| | TUMOR VIROLOGY | |
| | TUMOR VIROLOGY | |
| | COMPARATIVE PATHOLOGY | |
| | NEUROCHEMISTRY | |
| | COMPARATIVE PATHOLOGY | |
| | TUMOR VIROLOGY | |
| | BEHAVIORAL BIOLOGY | |
| | TUMOR VIROLOGY | |
| | TUMOR VIROLOGY | |
| | BEHAVIORAL BIOLOGY | |
| | COMPARATIVE PATHOLOGY | |
| | BEHAVIORAL BIOLOGY | |
| MACCHIA, IOLE, PHD | IMMUNOLOGY | |
| [illegible] | COMPARATIVE PATHOLOGY | |
| | COMPARATIVE PATHOLOGY | |
| | MICROBIOLOGY | |
| | TUMOR VIROLOGY | |
| | BEHAVIORAL BIOLOGY | |
| | IMMUNOLOGY | |
| | IMMUNOLOGY | |
| | IMMUNOLOGY | |
| | RESEARCH FELLOW IN PSYCHIATRY | NEUROCHEMISTRY: MA, USA |
| | COMPARATIVE PATHOLOGY | |
| | MICROBIOLOGY | |

## SUBPROJECT DESCRIPTIONS

# NPRC MANAGEMENT SUBPROJECTS

## ENGINEERING AND MAINTENANCE (0136)

**NPRC UNIT:** ADMINISTRATIVE

**%NPRC $:** 1.350%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| BURRILL, THOMAS F. | BS | C | ENGINEERING AND MAINTENANCE | |

**AXIS I CODES:** 11 **AXIS II CODES:**92(ENGINEERING & MAINTENANCE)


**ABSTRACT**

General:

Engineering and Maintenance continued its supportive role to the Center's scientific divisions. During the year 2,240 work requisitions were completed along with many projects, mainly renovations to laboratories, animal housing, offices, building and grounds.

The following mile stones were achieved:

All campus drinking water wells were deepened an additional 500 feet and new pumps were installed to help provide a higher yield from our sources.

Replacement of Research Building 1's HVAC system phase I was completed. All air handling units (supply and exhaust) were replaced with state of the machines, controls systems, and a new steam absorption unit, to provide air conditioning, was also installed. This major renovation provides better air quality and temperature control for the building.

Fit out of shell space in Research Building 5 was completed to house the Behavior Biology Department (office, support and laboratory space) and to provide additional animal housing.

Construction of Research Building 6 is underway. It will be a new [ ]+ square foot state of the art laboratory research facility with a 106 seat seminar center.

Future Programs:

Replacement of Research Building 1's 2nd steam absorption unit to provide an additional reliable source of tempered air for the cooling season. Complete renovation of the old operating room and prep area, to provide laboratory space for Dr. Keith Mansfield. Continued renovation of Research Building 1 [ animal location level, from animal holding to research laboratory and support office spaces. General modernization programs are being developed and will be place in operation. These include the replacement of old equipment, updating existing laboratory spaces and animal holding areas in all 6 research buildings.

## INFORMATION TECHNOLOGY 2002 (0285)

**NPRC UNIT:** ADMINISTRATIVE

**%NPRC $:** 1.350%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| CHAREST, GREGORY P | BS | C | ADMINISTRATION | |

**AXIS I CODES:** 28(INFRASTRUCTURE) **AXIS II CODES:**92(INFORMATION TECHNOLOGY 2002)

**ABSTRACT**

The IT Department provides local and wide area network connectivity, file and print services, database and information security support, Internet and Intranet web site development and maintenance, training and end-user assistance to approximately 200 Center staff.

In the past year, the IT Department was expanded and reorganized to better support research and administrative needs. An Information Technology manager was hired and the existing Graphics Services function was moved into the IT Department, bringing the IT staffing level to a total of four. An Information Technology Steering Committee was formed to identify and articulate long range IT priorities and to provide input on IT policies.

The IT Department made significant upgrades to the Center's overall networking and server support capabilities. Three additional servers were brought on-line, shared user disk space was moved to a central network attached storage device and the existing tape backup system was upgraded. The construction of a new research building required the addition of 96 additional network ports, bringing the total to 720. An upgrade from a T1 to T3 data connection to the Harvard Medical School router is scheduled for May, 2004 and a wireless network pilot project is currently underway for Research Building 5.

In addition to maintaining the Center's public Internet site, IT staff developed an Intranet web site to distribute news and information to Center staff and as a platform for common applications. Web based applications are being developed to support common administrative and research needs.

A review of existing Center animal and research databases was carried out by the IT Steering Committee and a project initiated to develop centralized database for all animal census, housing, health, research protocol, billing and pathology data. A needs assessment and requirements analysis was conducted and a RFP for system development services is expected to be distributed in April, 2004.

Graphics Services continues to provide specialized in-house photographic and electronic imaging support to core staff and collaborative and visiting scientists. The shift from 35mm slides to digital imaging and presentations continued and a corresponding increase in user technical support has been required. In addition, the Graphics Specialist provides Intranet web site development and audiovisual support to the Center.

## LIBRARY (0204)

**NPRC UNIT:** ADMINISTRATIVE

**%NPRC $:** 1.350%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| FINGOLD, SYDNEY | BS | C | ADMINISTRATION | |

**AXIS I CODES:** 28(INFRASTRUCTURE) **AXIS II CODES:**92(LIBRARY)

**ABSTRACT**

We continue to welcome the challenge of providing the most current technology and resources in meeting the information needs of the Center. The addition of PDF capability this past year has greatly enhanced our document delivery service, both in turn around time and copy clarity. Even though there has been a major increase in the number of electronic journals our staff are able to access themselves, our document delivery statistics remain the same indicating the strong need for the literature and our services. Out of a total of 1174 interlibrary loan transactions for the year, we remain net borrowers, filling 415 loans while requesting 759.

As in the past, the library continues its collaboration with area consortia, the Medical School and the University through the Science Libraries Council. We remain in a close working relationship with the other Primate Centers under the NCRR Primate Research Centers Program. The library is staffed by one [ ] and one [ ] assistant. The librarian participates in conferences, workshops and takes essential technical training whenever possible to remain current. In April the librarian was chosen as the recipient of this year's professional achievement award and was inducted in the Massachusetts Health Sciences Library Network (MAHSLIN) "Hall of Fame".

percentage of effort

## EDUCATION AND TRAINING (0144)

**NPRC UNIT:** ADMINISTRATIVE

**%NPRC $:** 1.350%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| JUNG, JAE U | PHD | C | TUMOR VIROLOGY | |

**AXIS I CODES:** 28(28 (EDUCATION)) **AXIS II CODES:**51


**ABSTRACT**

The multiple scientific disciplines represented by the faculty and research laboratories of the Primate Research Center provides an intellectually and rewarding environment for the education and training of students and scientists at all levels of academic development. These activities are coordinated by the Education and Training Unit of the Center under the supervision of Dr. Jae U. Jung, Chair of the Division of Tumor Virology. Virtually all of the Center's faculty are involved in pre- and post-doctoral level research training conducted in conjunction with their ongoing research programs and service responsibilities. In addition, several of the faculty at the Center are also actively involved in teaching courses that are a part of the Harvard medical School curriculum.

Training programs include: Post-doctoral training in Biological Sciences and Veterinary and Comparative Pathology; Graduate Research Training; Summer Fellowship Program for Students of medicine and Veterinary medicine; and Pre-Baccalaureate Summer Program.

FUNDING: Funding for individuals participating in various training programs at the Center comes from a variety of sources including: individual ROI research grants, individual and institutional training grants, special fellowship grants and the Primate Center base grant, all funded by the National Institutes of Health, as well as from fellowship grants from foreign governments and private agencies or foundations.

## CENTER OPERATIONS (0203)

**NPRC UNIT:** ADMINISTRATIVE

**%NPRC $:** 1.350%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| WORTHAM, JAMES T. | MA | C | ADMINISTRATION | |
| | MD | C | IMMUNOLOGY | |
| | MD, PHD | C | NEUROBIOLOGY | HARVARD MEDICAL SCHOOL, MA USA |
| | PHD | C | BEHAVIORAL BIOLOGY | |

**AXIS I CODES:** 28(INFRASTRUCTURE) **AXIS II CODES:**92(CENTER OPERATIONS)


**ABSTRACT**

A major priority again this year was improvement to the Center's infrastructure. Two significant milestones were accomplished that represent the most drastic improvements in 40 years to the Center's facilities. The first of these milestones was the opening of a new Neuroscience facility in September 2003 (C06 funded). This facility provides a square foot laboratory, animal holding, and Administrative space for both core and collaborative scientists. The second milestone occurred in May 2003 with the ground breaking of a square foot new research building and auditorium (Harvard funded). This new building (RSB #6) will provide wet lab space for five PI's and their research programs. A formal dedication is planned in May 2004 when the building is scheduled for completion.

pending support

Recruiting is underway for new faculty to occupy RSB #6 with six individual search committees currently in progress.

Three Scientific Reviews are scheduled for the spring of 2004, one for the Comparative Pathology Division, one for Primate Resources and one for the Immunology Division.

The Center successfully recruited a new Chief of Information Technology (Greg Charest) from a list of over 200 applicants. His priority has been the establishment of a new data base to be utilized throughout the Center.

The Center's grant portfolio again remained strong in 2003 with approximately 65 grants being administered at the Center.

A successful USDA inspection was completed at the Center in November 2003.

# RESEARCH SUBPROJECTS

## ALTERED HPA AXIS FUNCTION IN RHESUS SELF-INJURIOS MONKEYS (0369)

**NPRC UNIT:** BEHAVIORAL BIOLOGY

**%NPRC $:** 0.170%


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| NOVAK, MELINDA A | PHD | A | PSYCHOLOGY | UNIVERSITY OF MASSACHUSETTS, AMHERST, MA USA |
| | PHD | A | PSYCHOLOGY | UNIVERSITY OF MASSACHUSETTS, AMHERST, MA USA |
| | PHD | G | BEHAVIORAL BIOLOGY | |


**AXIS I CODES:** 1A, 2, 15 **AXIS II CODES:**36, 74E


### ABSTRACT

Individually housed rhesus monkeys sometimes spontaneously develop self-injurious behavior (SIB) in the form of self-directed biting that, on occasion, results in severe tissue damage and mutilation. We previously demonstrated lower levels of plasma cortisol in rhesus monkeys with a history of self-wounding (SW) when compared to non-wounders (NW). Furthermore, cortisol levels were negatively correlated with rates of self-directed biting. The present study was designed to further characterize the relationships between hypothalamic-pituitary-adrenocortical (HPA) activity, self-wounding, and self-directed biting. Basal 24-h urinary free cortisol excretion, the urinary free cortisol response to a low dose of dexamethasone, and the plasma cortisol response to ACTH were examined in 24 individually housed rhesus monkeys, based on wounding history, i.e. the presence/absence of a veterinary record of self-wounding, and current rates of self-directed biting, i.e. the median split of self-directed biting frequency (independent of wounding status). There were no reliable group differences on any of the physiological measures when analyzed by wounding history. However, the plasma cortisol response 30 min post-ACTH stimulation was significantly correlated with wounding recency such that lower responsivity was associated with more recent wounding episodes. When the results were analyzed on the basis of biting frequency, high frequency biters (HFB) compared to low frequency biters (LFB) showed decreased HPA negative feedback sensitivity to dexamethasone and a trend towards an attenuated plasma cortisol response to ACTH stimulation. These findings suggest that SIB in socially reared monkeys is associated with complex changes in HPA axis function that are related to the expression of the pathology, i.e. self-directed biting, and to the recency of a wounding episode. It remains to be determined whether humans who exhibit SIB show similar alterations in HPA function.

## SHORT AND LONG-TERM EFFECTS OF CHANGE IN CAGE SIZE ON BEHAVIOR IN RHESUS MONKEYS (0371)

**NPRC UNIT:** BEHAVIORAL BIOLOGY

**%NPRC $:** 0.170%


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
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**AXIS I CODES:** 1A **AXIS II CODES:**36


**ABSTRACT**

We investigated the effects of a 6-fold increase in cage size on the behavior of individually housed male rhesus monkeys. Limitations of previous studies included the magnitude of change in cage size, the length of the observation period, and the potential confounds of relocation. Prior to this study, eight male monkeys were individually housed in pens ( cubic meters) for varying lengths of time before moving to baboon cages ( cubic meters) located within their pens. After two years in baboon cages, monkeys were returned to their pen environment ( cubic meters). Monkeys were observed for forty 5-min observation periods representing four phases: short (1st four months) and long-term (after 23 months) exposure to the baboon cage followed by short (1st month) and long-term (after 8 months) exposure to the pen environment. Contrary to expectations, general activity decreased and abnormal behavior remained unchanged when the monkeys were returned to their pens.

# FENFLURAMINE CHALLENGE, SELF-INJURIOUS BEHAVIOR AND AGGRESSION IN RHESUS MONKEYS (0374)

**NPRC UNIT:** BEHAVIORAL BIOLOGY

**%NPRC $:** 0.170%


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
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| | PHD | G | BEHAVIORAL BIOLOGY | |


**AXIS I CODES:** 1A, 2, 15 **AXIS II CODES:** 36, 50B, 74E, 77


## ABSTRACT

Self-injurious behavior (SIB) and aggression have been linked to reduced serotonergic (5-HT) functioning in both humans and nonhuman primates. The present study examined serum prolactin and cortisol responses to the 5-HT releasing agent d,l-fenfluramine (FEN) in 24 individually housed rhesus monkeys (Macaca mulatta), 15 of which carried a veterinary record of self-wounding (SW). Subjects received two doses of FEN, 4 and 2 mg/kg, separated by an interval of at least 2 months. For control purposes, monkeys were given an i.m. saline injection 1 week prior to each FEN challenge. The relationship between the hormonal responses to FEN, wounding history, the rates of self-directed biting and aggression were determined for each animal based on 100 5-min observations conducted over a period of 12 months surrounding the challenge procedures. Prolactin and cortisol responses to FEN were unrelated either to wounding history or to rates of self-directed biting. However, there were significant inverse correlations between levels of aggression and the prolactin response to both doses of FEN. The present findings provide no evidence for reduced 5-HT system function in rhesus monkeys with SIB under the present challenge conditions. However, the results are consistent with a previously reported inverse relationship between serotonergic activity and aggression. Moreover, a dose-dependent response to FEN was observed only for prolactin, suggesting that this variable is more appropriate than cortisol as an endpoint for FEN challenge in monkeys.

## ENDOGENOUS OPIOID ACTIVITY IN NONHUMAN PRIMATES (0431)

**NPRC UNIT:** BEHAVIORAL BIOLOGY

**%NPRC $:** 0.170%


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
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**AXIS I CODES:** 1A, 2, 15 **AXIS II CODES:**36, 74E, 77


**ABSTRACT**

Altered opioid activity has been proposed to play a role in the expression of self-injurious behavior (SIB) in humans. A low but persistent percentage of individually housed rhesus monkeys also develop SIB, which usually takes the form of self-directed biting that on occasion results in severe tissue damage and mutilation. The present study examined basal morning levels of plasma beta-endorphin-like immunoreactivity (IR) in 24 individually housed rhesus monkeys, 15 of which carried a veterinary record of self-inflicted wounding. The relationships between beta-endorphin-like IR, self-directed biting (as an index of current severity of the syndrome), and stereotypy were examined. Levels of beta-endorphin-like IR were unrelated to current rates of self-directed biting but were significantly associated with stereotypy and the age at which monkeys were first individually caged (one of the major risk factors for the development of SIB in monkeys). The present findings are consistent with previous reports of reduced plasma opioid activity in humans with SIB and raise the possibility that SIB may function to stimulate endogenous opioid peptide release.

## ENDOGENOUS OPIOID INVOLVEMENT IN SELF-INJURIOUS BEHAVIOR IN RHESUS MONKEYS (0432)

**NPRC UNIT:** BEHAVIORAL BIOLOGY

**%NPRC $:** 0.170%


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
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| | PHD | G | BEHAVIORAL BIOLOGY | |


**AXIS I CODES:** 1A, 2, 15 **AXIS II CODES:**36, 77


### ABSTRACT

A small but persistent percentage of captive nonhuman primates spontaneously develop self-injurious behavior (SIB). In rhesus monkeys this pathology usually takes the form of self-directed biting that on occasion can result in severe tissue damage and mutilation. We previously demonstrated that self-directed biting in monkeys is preferentially directed towards body areas associated with acupuncture/acupressure analgesia. The present study examined the association between central opioid activity and the expression of SIB. Basal levels of the opioid peptide met-enkephalin were measured in the cerebrospinal fluid (CSF) of 26 individually housed adult male rhesus monkeys (Macaca mulatta), 17 of which carried a veterinary record of self-inflicted wounding. Rates of self-directed biting and stereotypic behavior were determined based on 100 5-min modified frequency observations. As indicated by one-way analysis of variance, monkeys with a history of self-inflicted wounding showed attenuated levels of enkephalin when compared to monkeys without a wounding history. Although CSF enkephalin levels were not related to overall rates of either self-directed biting or stereotypic behavior, they were positively correlated with the proportion of bites directed towards acupressure sites. These findings suggest a possible role for the endogenous opioid system in the expression and maintenance of SIB in rhesus monkeys.

## EXTINCTION DEFICITS IN MALE MONKEYS WITH A HISTORY OF SELF-INJURIOUS BEHAVIOR (0433)

**NPRC UNIT:** BEHAVIORAL BIOLOGY

**%NPRC $:** 0.170%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
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**AXIS I CODES:** 1A, 15

**AXIS II CODES:** 36, 41, 72, 74E


### ABSTRACT

Self-injurious behavior (SIB) is known to occur in captive macaque populations. This harmful behavior may be associated with an inability to inhibit certain responses. We utilized a lever-pressing task to further explore response inhibition and predicted that monkeys with SIB would show extinction deficits. Subjects were 15 individually-housed adult male rhesus macaques, 10 with a record of self-injury. They were initially trained to lever-press for food rewards to a criterion of 400 total responses. We then conducted 30-minute test sessions divided into six 5-minute cycles on each of 5 consecutive days. Day 1 consisted of continuous reinforcement. Days 2-4 consisted of alternating reinforced/unreinforced cycles. Day 5 consisted of no reinforcement. A buzzer cued reinforced cycles. Number of lever presses and behavioral data were recorded during each cycle. Saliva samples were collected before and after test sessions on days 1, 2, and 5 for cortisol analyses. Repeated measures ANOVA results indicated that SIB subjects lever-pressed more than controls during nonreinforced cycles on days 2-4. Frequency of stereotypies increased during these cycles. Frequency of scratching and yawning in all subjects increased when reinforcement was inconsistent (days 2-4) or absent (day 5). Changes in salivary cortisol were unrelated to this effect. The presence of extinction deficits suggest that SIB may persist in monkeys because they have trouble inhibiting this behavior.

## "LAST SEEN" AND "GRAVITY BIAS" STRATEGIES AND PROBLEM SOLVING IN RHESUS MONKEYS (0434)

NPRC UNIT: BEHAVIORAL BIOLOGY

%NPRC $: 0.170%


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION : STATE, COUNTRY |
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AXIS I CODES: 1A AXIS II CODES:41


### ABSTRACT

On ramp tasks, monkeys select a door that is consistent with a "last seen" strategy rather than a gravity strategy (the lowest door). However, in one published study, monkeys exposed to a vertical task appeared to follow a gravity strategy rather than a "last seen" strategy. This discrepancy might result from the different motor requirements involved in vertical vs. horizontal reaches. A vertically oriented tube was used to assess various response strategies by three individually housed adult male rhesus monkeys at the UMass Primate Lab and by six monkeys at NEPRC. Treats were invisibly dropped onto an obstacle within the tube at one of three door locations. In the initial experiment, monkeys appeared to follow a "last seen" strategy of selecting the top door rather than the expected gravity strategy of selecting the bottom door. Four additional experiments were conducted using different configurations in which one door was made inaccessible and instead became a window through which the monkey could observe the trajectory of the treat. Under these conditions, monkeys only did better than chance when the two available doors were separated by a window. These experiments provide additional support for the view that monkeys use a last seen strategy to track the movement of hidden objects rather than a gravity bias.

# GABA-A/ALPHA1 RECEPTOR INVOLVEMENT IN THE HYPERPHAGIC EFFECT OF BENZODIAZEPINES (0373)

**NPRC UNIT:** BEHAVIORAL BIOLOGY

**%NPRC $:** 0.170%

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

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


## ABSTRACT

Although benzodiazepines are useful for treating anxiety disorders, their clinical utility is constrained by side effects such as abuse potential, sedation, and hyperphagia. Benzodiazepines act via subtypes of the GABA-A receptor. The development of subtype specific ligands creates the possibility of clinically effective benzodiazepine-type drugs with reduced side effects. The present study investigated the potential role of GABA-A receptors containing the alpha1 subunit in the hyperphagic effect of benzodiazepine agonists using subtype selective ligands. Non-food deprived squirrel monkeys were administered a benzodiazepine agonist or vehicle and given access to sucrose pellets for ten minutes. The nonselective benzodiazepines triazolam and alprazolam increased feeding by 200% of baseline food intake, while the GABA-A/alpha1-preferring agonists zolpidem and zaleplon produced a 300% and 480% increase, respectively. For the GABA-A/alpha1-preferring drugs, the hyperphagic effect emerged at doses lower than those producing sedation, whereas these behavioral effects occurred at similar doses for the nonselective benzodiazepines. The hyperphagic effects of triazolam and zolpidem were re-evaluated in the presence of beta-CCT, a GABA-A/alpha1-preferring antagonist. Beta-CCT antagonized the hyperphagic effects of triazolam and zolpidem in a surmountable fashion. Taken together, these results suggest GABA-A/alpha1 receptors play a prominent role in mediating the hyperphagic effect of benzodiazepines.

# BEHAVIORAL EFFECTS OF THE FUNCTIONALLY SELECTIVE GABA-A AGONIST SL651498 (0427)

**NPRC UNIT:** BEHAVIORAL BIOLOGY

**%NPRC $:** 0.170%


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
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| | PHD | C | BEHAVIORAL BIOLOGY | |


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


## ABSTRACT

Benzodiazepines (BZs) are prescribed for a wide variety of disorders including those involving anxiety and sleep. In addition to therapeutic effects, BZs also have unwanted side effects such as ataxia and abuse potential that limit their use. Recent research has aimed to elucidate the receptor mechanisms underlying the behavioral effects of BZs in order to determine which GABA-A receptor subtypes mediate particular effects of the drugs, with the hope of developing new anxiolytic drugs having both maximum clinical benefit and minimum adverse side effects. One such compound that has recently been developed is SL651498, a novel pyridoindole derivative that is a full agonist at GABA-A receptors containing the alpha2 and alpha3 subunits and a partial agonist at alpha1 and alpha5 subunit containing receptors. The present studies assessed the ability of SL651498 to engender anxiolytic, subjective, and motor effects characteristic of BZ-type drugs in non-human primates. Anxiolytic-like activity was assessed with a conflict procedure in rhesus monkeys, whereas the subjective effects of SL651498 were assessed in squirrel monkeys trained to discriminate the non-selective BZ triazolam from saline. Motor effects were evaluated in squirrel monkeys using observational techniques. These studies indicated that SL651498 has anti-conflict effects similar to the commonly prescribed anxiolytic, alprazolam. In contrast, SL651498 partially substituted for triazolam in the drug discrimination studies. This compound induced pronounced muscle relaxation, but unlike conventional BZs, engendered minimal ataxia. Together, these studies suggest that compounds such as SL651498 that have high intrinsic efficacy at alpha2 and/or alpha3 GABA-A receptors may have clinical potential as non-sedating anxiolytics and muscle relaxants. Moreover, a compound with reduced efficacy at alpha1 and/or alpha5 GABA-A receptors may lack some of the subjective effects associated with conventional BZs.

## ABUSE-RELATED EFFECTS OF BENZODIAZEPINE-TYPE HYPNOTICS (0430)

**NPRC UNIT:** BEHAVIORAL BIOLOGY

**%NPRC $:** 0.170%


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
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**AXIS I CODES:** 1A, 2, 21 **AXIS II CODES:**36, 50B


### ABSTRACT

Drugs used to treat sleep disorders are some of the most commonly prescribed medications worldwide, but their use is constrained by the potential for abuse and dependence. These drugs characteristically have relatively short durations of action, as well as unique interactions with the benzodiazepine site on the GABA-A receptor. The extent to which these factors contribute to the abuse-related effects of hypnotics are not well understood; therefore, the present study examined the discriminative stimulus and reinforcing effects of three commonly prescribed hypnotics with differing activity at GABA-A receptors but similar pharmacokinetic profiles. Squirrel monkeys were trained to discriminate triazolam (hypnotic with unusually high intrinsic efficacy at GABA-A receptor subtypes) from vehicle and were tested with zolpidem (GABA-A/alpha-1 subtype preferring agonist) and zopiclone (hypnotic that may bind to a unique site associated with GABA-A receptors). All three compounds engendered triazolam-like levels of responding (i.e., greater than 80% drug-lever responding) at doses that did not impair rates of responding, suggesting that these drugs share similar subjective effects. In rhesus monkeys responding under a progressive-ratio schedule of i.v. drug delivery, the three hypnotics maintained levels of self-administration reliably above those maintained by vehicle availability. However, zolpidem maintained significantly higher levels of self-administration than either triazolam or zopiclone. These findings suggest that although the three hypnotics shared discriminative stimulus effects, preferential binding to alpha-1 subunit-containing GABA-A receptors may confer enhanced reinforcing effects compared to other benzodiazepine-type hypnotics.

## SUPPRESSION OF COCAINE- MAINTAINED BEHAVIOR BY D2 RECEPTOR LIGANDS (0163)

**NPRC UNIT:** BEHAVIORAL BIOLOGY

**%NPRC $:** 0.170%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
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| | PHD | C | BEHAVIORAL BIOLOGY | |

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

**ABSTRACT**

The D2-like receptor partial agonist terguride has a profile of behavioral effects in rats that suggests potential benefit as a pharmacotherapy for cocaine addiction. The present study investigated the effects of terguride on cocaine- and food-maintained behavior in squirrel monkeys. Squirrel monkeys were trained to respond on a second-order schedule (FI 10 min, FR 10 or 30:S) of either i.v. cocaine injection or food pellet delivery. Additional monkeys were studied using quantitative observational techniques to construct side effect profiles. Under each procedure, the effects of terguride were compared with those of the reference D2-like receptor antagonist nemonapride and the D2-like receptor full agonist quinpirole. Terguride and nemonapride, but not quinpirole, dose-dependently reduced cocaine-maintained behavior. In animals self-administering food, terguride decreased response rates at doses lower than those required to suppress cocaine-maintained behavior. Effective doses of terguride had no systematic effect on motor activity or muscle rigidity, whereas effective doses of nemonapride virtually eliminated motor activity and induced severe catalepsy. The primary observable effects of terguride were a modest increase in self-directed behavior (a D2 receptor agonist-like effect) at intermediate doses and a small increase in static posture (a D2 receptor antagonist-like effect) at the highest dose tested. The results suggest that terguride has advantages over conventional D2-like receptor antagonists and agonists as a candidate pharmacotherapy for cocaine abuse; however, terguride significantly reduces food-maintained behavior at lower doses than those needed to decrease cocaine-maintained behavior suggesting limitations on the utility of terguride as a medication for cocaine addiction.

## OPIOID PARTIAL AGONIST EFFECTS OF 3-O-METHYLNALTREXONE (0166)

**NPRC UNIT:** BEHAVIORAL BIOLOGY

**%NPRC $:** 0.170%

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

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


### ABSTRACT

3-O-methylnaltrexone (3-MNTX ), a putative antagonist of morphine-6-beta-D-glucuronide(M6G) receptors, has been reported to block the behavioral effects of heroin at doses that do not block those of morphine, suggesting that M6G receptors may play a unique role in the addictive properties of heroin. This study investigated the effects of 3-MNTX in monkeys trained to discriminate i.v. heroin from vehicle or to self-administer i.v. heroin under a progressive-ratio schedule. Additional in vitro studies determined the effects of 3-MNTX and reference drugs on adenylyl cyclase activity in caudate-putamen membranes of monkeys and rats. In drug discrimination experiments, heroin, morphine, and M6G substituted for heroin in all subjects, whereas 3-MNTX substituted for heroin in half the monkeys tested. In these latter monkeys, the effects of 3-MNTX were antagonized by naltrexone, and pretreatment with 3-MNTX enhanced the effects of heroin, M6G and morphine, indicative of mu agonist activity. In monkeys showing no substitution of 3-MNTX for heroin, 3-MNTX antagonized the effects of heroin, M6G and morphine. In self-administration experiments, heroin and 3-MNTX maintained injections/session significantly above those maintained by vehicle when the initial response requirement (IRR) was low; only heroin maintained significant self-administration when the IRR was high. In vitro, 3-MNTX inhibited adenylyl cyclase activity in both monkey and rat brain membranes. The degree of inhibition produced by 3-MNTX was less that that produced by the full agonist DAMGO. The results suggest that 3-MNTX functions primarily as a partial agonist at mu receptors in monkeys and do not support a singular role for M6G receptors in the abuse-related effects of heroin.

# BLOCKADE OF ALPHA2-ADRENOCEPTORS INDUCES REINSTATEMENT OF COCAINE SEEKING (0364)

**NPRC UNIT:** BEHAVIORAL BIOLOGY

**%NPRC $:** 0.170%


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
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| | PHD | G | BEHAVIORAL BIOLOGY | |


names

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


## ABSTRACT

Converging evidence suggests a role for noradrenergic mechanisms in stress-induced reinstatement of cocaine seeking in animals. Yohimbine, an alpha2 adrenoceptor antagonist, is known to be anxiogenic and induce stress-related responses in humans and animals. Here, we tested the ability of yohimbine to reinstate cocaine-seeking behavior and induce behavioral and physiological signs characteristic of stress in squirrel monkeys. Drug seeking subsequently was extinguished by substituting saline for cocaine injections and omitting the cocaine-paired stimulus. The ability of yohimbine and the structurally distinct alpha2-adrenoceptor antagonist RS-79948 to reinstate cocaine-seeking behavior was assessed by administering priming injections immediately before test sessions in which the cocaine-paired stimulus was either present or absent. Priming injections of yohimbine or RS-79948 induced dose-related reinstatement of cocaine-seeking behavior. The magnitude of yohimbine-induced reinstatement was similar regardless of the presence or absence of the cocaine-paired stimulus. Yohimbine also significantly increased salivary cortisol levels. In drug interaction experiments, pretreatment with the alpha2 adrenoceptor agonist clonidine dose-dependently inhibited yohimbine-induced reinstatement of cocaine seeking. In contrast, pretreatment with the dopamine receptor antagonist flupenthixol failed to inhibit yohimbine-induced reinstatement of cocaine seeking. The results show that pharmacological blockade of alpha2-adrenoceptors can induce reinstatement of cocaine-seeking behavior and characteristic stress responses in squirrel monkeys, providing a potentially useful model of stress-induced relapse to drug seeking.

## GABA-A RECEPTOR MECHANISMS IN THE SUBJECTIVE EFFECTS OF ETHANOL (0375)

**NPRC UNIT:** BEHAVIORAL BIOLOGY

**%NPRC $:** 0.170%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
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| [illegible] | PHD | C | BEHAVIORAL BIOLOGY | |

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

**ABSTRACT**

Ethanol's ability to enhance gamma-aminobutyric acid (GABA) neurotransmission via GABA-A receptors has been implicated as an important mechanism underlying its discriminative stimulus (DS) effects in animals and subjective effects in humans. The GABA-A receptor is a pentamer consisting of subunits from at least five different families including alpha, beta, and gamma subunits. At least six isoforms of the alpha subunit exist, and recent findings in rodents implicate both GABA-A/alpha1 and GABA-A/alpha5 receptor mechanisms in the effects of ethanol related to its abuse. The present study assessed potential reduction of the DS effects of alcohol by selective GABA-A/alpha1 and GABA-A/alpha5 antagonists. Squirrel monkeys were trained to discriminate ethanol (1.0 g/kg, i.v.) from saline under a 10-response fixed-ratio schedule of food delivery. Under test conditions, ethanol engendered a dose-dependent increase in drug-lever responding, reaching an average maximum of greater than 80%. When combined with ethanol, the GABA-A/alpha1 antagonist BCCT failed to attenuate the DS effects of ethanol. BCCT also did not alter appreciably the ethanol-like DS effects of the selective GABA-A/alpha1 agonists, zolpidem and zaleplon. In contrast, pretreatment with the GABA-A/alpha5 inverse agonist L-655,708 dose-dependently attenuated the DS effects of ethanol as well as the ethanol-like DS effects of the selective GABA-A/alpha5 agonist QH-ii-066. Antagonism of both ethanol and QH-ii-066 by L-655,708 occurred at doses that did not alter response rate suggesting that this blockade was pharmacologically specific and not the result of a nonspecific disruption of behavior. These findings suggest a key role for GABA-A/alpha5, but not GABA-A/alpha1, receptor mechanisms in the DS effects of ethanol and the ethanol-like DS effects of benzodiazepine agonists.

# KAPPA AGONIST MODULATION OF COCAINE PRIMING-INDUCED REINSTATEMENT (0378)

**NPRC UNIT:** BEHAVIORAL BIOLOGY

**%NPRC $:** 0.170%


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
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| [illegible] | PHD | C | BEHAVIORAL BIOLOGY | |


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


## ABSTRACT

Kappa opioid agonists attenuate the reinstatement of cocaine-seeking behavior induced by cocaine priming. As of yet, the mechanisms underlying this effect of kappa agonists are not fully characterized. In addition to stimulating kappa opioid receptors, kappa agonists increase extracellular levels of the neurotransmitter serotonin (5HT). This study investigated the role of kappa opioid receptor and 5HT mechanisms in kappa agonist modulation of cocaine priming in squirrel monkeys. Subjects were trained to self-administer cocaine under a second-order schedule in which drug seeking was maintained jointly by cocaine injections and a cocaine-paired visual stimulus. In subsequent extinction sessions, saline was substituted for cocaine and the cocaine-paired stimulus was omitted. During test sessions in which only saline was available for self-administration and response-contingent presentations of the cocaine-paired stimulus were restored, priming injections of cocaine induced robust reinstatement of drug seeking, reaching levels of responding similar to those maintained by active cocaine self-administration. Pretreatment with the kappa agonists enadoline and spiradoline attenuated the priming effects of cocaine, shifting the cocaine dose-response function rightward and downward. Inhibition of cocaine-induced reinstatement by kappa agonists could be reversed by the kappa antagonist nor-binaltorphimine. The 5HT transport blockers fluoxetine and citalopram also inhibited cocaine-induced reinstatement. Moreover, the ability of both fluoxetine and spiradoline to attenuate cocaine-induced reinstatement could be reversed with the 5HT-1A agonist, 8-OHDPAT. These results suggest that the ability of kappa agonists to increase extracellular 5HT levels may underlie kappa agonist-modulation of cocaine-seeking behavior.

## SECOND-ORDER SCHEDULE OF COCAINE SELF-ADMINISTRATION: ANALYSIS OF DRUG SEEKING (0428)

**NPRC UNIT:** BEHAVIORAL BIOLOGY

**%NPRC $:** 0.170%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| SPEALMAN, ROGER D | PHD | C | BEHAVIORAL BIOLOGY | |
| [illegible] | PHD | G | BEHAVIORAL BIOLOGY | |

**AXIS I CODES:** 1A, 2, 21 **AXIS II CODES:**35, 50B, 87

**ABSTRACT**

Second-order schedules of i.v. drug injection have been proposed as useful animal models of drug seeking, because lever pressing before the first drug injection reflects drug seeking in the absence of other pharmacological effects of the self-administered drug. Specifically, drugs of abuse have been reported to have rate-altering and reinstating effects, which can significantly affect lever pressing during drug self-administration experiments. We studied cocaine self-administration under a second-order schedule fixed interval (FI) 10 min, fixed ratio (FR) 10 in squirrel monkeys. Daily sessions consisted of five cycles of the schedule. The dose of cocaine was systemically varied from 0.1 to 0.56 mg/kg/injection, a range that is similar to that used in human clinical studies. Each dose of cocaine was available for 15 sessions followed by 10 sessions of saline self-administration. All doses of cocaine maintained high response rates compared to those observed during saline self-administration. The response rate in the first cycle of the daily session (i.e. before the first cocaine injection) was an increasing asymptotic function of dose in all subjects, whereas response rates in subsequent cycles showed marked inter-subject variability as the dose of cocaine was changed. The consistent monotonic dose-response function observed in the initial cycle of the second-order schedule suggests that drug seeking before the first injection may be particularly useful index of the reinforcing effects of cocaine in the absence of cocaine's priming and rate-altering effects.

## SALIVARY CORTISOL SAMPLING IN UNRESTRAINED SQUIRREL MONKEYS (0435)

**NPRC UNIT:** BEHAVIORAL BIOLOGY

**%NPRC $:** 0.170%


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| SPEALMAN, ROGER D | PHD | C | BEHAVIORAL BIOLOGY | |
| | PHD | G | BEHAVIORAL BIOLOGY | |
| | PHD | A | PSYCHOLOGY | UNIVERSITY OF MASSACHUSETTS, AMHERST, MA USA |
| | PHD | G | BEHAVIORAL BIOLOGY | |


**AXIS I CODES:** 1A, 9, 15 **AXIS II CODES:**74E


### ABSTRACT

The use of noninvasive measures of hypothalamic-pituitary-adrenal (HPA) axis function is of growing interest among preclinical and clinical investigators. This report describes a method for the repeated assessment of salivary free cortisol in awake, unrestrained squirrel monkeys (Saimiri sciureus) based on a saliva sampling technique previously developed for rhesus monkeys. Individually housed adult male squirrel monkeys were trained to chew on dental rope attached to a pole, from which saliva was extracted by centrifugation and analyzed for cortisol by radioimmunoassay (RIA). Eight of nine monkeys readily acquired the task, reliably providing adequate saliva samples for the assay. Salivary free cortisol levels were examined in these subjects under basal conditions and in response to two types of neuroendocrine challenge. Levels of salivary free cortisol showed relatively low intra- and inter-individual variability with individual morning levels ranging between 17.1 and 37.9 microgram/dl. Squirrel monkeys demonstrated a consistent daily rhythm in salivary free cortisol ranging from a high of 27.4 ± 5.2 microgram/dl (mean ± SEM) at 12 PM to a low of 7.5 ± 1.6 microgram/dl at 6 PM. Intravenous (IV) challenges with 1 microgram/kg ACTH, or 10 and 50 microgram/kg CRF resulted in significant increases in salivary free cortisol. The described sampling technique provides a reliable and sensitive means for repeated measurement of HPA activity in unrestrained, awake squirrel monkeys. In addition, our findings illustrate several features of HPA system rhythmicity and reactivity using salivary cortisol instead of blood plasma or serum.

## ATTENUATION OF COCAINE AND FOOD SELF-ADMINISTRATION BY AN MGLUR5 ANTAGONIST (0429)

**NPRC UNIT:** BEHAVIORAL BIOLOGY

**%NPRC $:** 0.170%


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| SPEALMAN, ROGER D | PHD | C | BEHAVIORAL BIOLOGY | |
| | PHD | C | BEHAVIORAL BIOLOGY | |
| | PHD | C | BEHAVIORAL BIOLOGY | |


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


**ABSTRACT**

The metabotropic glutamate subtype 5 receptor (mGluR5) antagonist MPEP has been shown to attenuate cocaine self-administration in rodents and nonhuman primates. This study investigated the ability of MPEP to modify the dose-response function for i.v. cocaine self-administration in squirrel monkeys and compared the ability of MPEP to reduce self-administration of cocaine and a non-drug reinforcer (food). Four adult male squirrel monkeys were trained to self-administer cocaine under a 10-response fixed-ratio (FR) schedule of i.v. cocaine delivery. Evaluation of a range of cocaine doses revealed that the number of injections/session were bitonic functions of dose. MPEP reduced self-administration of cocaine at doses lower than those required to reduce self-administration of food. At the higher dose of cocaine, however, similar doses of MPEP suppressed both cocaine and food self-administration. The results suggest that mGluR5 blockade attenuates the reinforcing effects of cocaine, and that this attenuation is most pronounced at relatively low unit doses of cocaine.

## VIRAL LOCALIZATION BY IN SITU HYBRIDIZATION (0228)

**NPRC UNIT:** COMPARATIVE PATHOLOGY

**%NPRC $:** 1.420% **AIDS RELATED RESEARCH**


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| ELLIOTT, MICHELLE W | DVM | C | COMPARATIVE PATHOLOGY | |
| | DVM | C | COMPARATIVE PATHOLOGY | |
| | DVM, PHD | C | COMPARATIVE PATHOLOGY | |
| | VMD | C | COMPARATIVE PATHOLOGY | |


**AXIS I CODES:** 1D, 7B, 16F, 21 **AXIS II CODES:**31, 66


**ABSTRACT**

The infection of rhesus macaque monkeys with simian immunodeficiency virus (SIV) and SIV/HIV chimeric viruses (SHIVs) serves as an important animal model for studying the pathogenesis of HIV infection and AIDS. In addition, this model provides a challenge system for evaluating the efficacy of vaccines and antiretroviral agents designed to prevent infection or AIDS in humans. We have designed several molecular probes for localizing viral RNA in tissues of monkeys infected with various isolates and clones of SIV and SHIV. These probes are used to measure the quantity and distribution of infected cells in the tissues of infected monkeys. We also have probes that hybridize with target RNA or DNA sequences of several other viral pathogens, including SRV-1, CMV, SV40, EBV, Herpes saimiri, and parvovirus.

## IMMUNOHISTOCHEMICAL ID, LEUKOCYTE MARKERS, INTERMEDIATE FILAMENT & INFECT AGENTS (0230)

**NPRC UNIT:** COMPARATIVE PATHOLOGY

**%NPRC $:** 1.420% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| ELLIOTT, MICHELLE W | DVM | C | COMPARATIVE PATHOLOGY | |
| | DVM | C | COMPARATIVE PATHOLOGY | |
| | DVM, PHD | C | COMPARATIVE PATHOLOGY | |
| | VMD | C | COMPARATIVE PATHOLOGY | |

**AXIS I CODES:** 1D, 16, 21, 22, 27 **AXIS II CODES:** 31, 64, 66, 77

**ABSTRACT**

In order to improve our diagnostic pathology capabilities, we are systematically evaluating commercially available antibodies directed against human cells/tissues and infectious agents for application in the nonhuman primate species housed at the NEPRC. Antibodies are selected for potential applications in diagnostic and/or experimental pathology, and for reactivity in either snap-frozen or formalin-fixed, paraffin-embedded tissues. In one study we were able to identify 21 of 21 antigens in 4 macaque species and 17 of 21 in New World monkeys.

## RESEARCH TRAINING IN EXPERIMENTAL PATHOLOGY (0238)

**NPRC UNIT:** COMPARATIVE PATHOLOGY

**%NPRC $:** 1.420% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| O'NEIL, SHAWN P | DVM, PHD | C | COMPARATIVE PATHOLOGY | |
| | PHD | C | MICROBIOLOGY | |
| | DVM | C | COMPARATIVE PATHOLOGY | |
| | DVM, PHD | A | PATHOBIOLOGY | UNIVERSITY OF CONNECTICUT, CT USA |
| | DVM | G | COMPARATIVE PATHOLOGY | |
| | MD | C | IMMUNOLOGY | |
| | DVM | C | COMPARATIVE PATHOLOGY | |
| | DVM | G | COMPARATIVE PATHOLOGY | |
| | DVM | G | COMPARATIVE PATHOLOGY | |
| | DVM | C | PRIMATE RESOURCES | |
| | DVM, PHD | G | COMPARATIVE PATHOLOGY | |
| | DVM | G | COMPARATIVE PATHOLOGY | |
| | VMD | C | COMPARATIVE PATHOLOGY | |
| | DVM | G | COMPARATIVE PATHOLOGY | |

**AXIS I CODES:** 1A, 7, 16, 19 **AXIS II CODES:**31, 51, 64, 66

**ABSTRACT**

The Division of Comparative Pathology has primary responsibility for the training of postdoctoral fellows in both diagnostic and experimental pathology. During the past year, the Division mentored 6 fellows in training. The fellows rotate through the necropsy and biopsy service while concurrently engaged in specific research projects. Research project training is individualized according to each fellow's prior experience, but includes individual meetings with senior core professional staff both within the Division of Comparative Pathology and other Center Divisions, as well as weekly departmental research meetings and seminars. Each fellow is encouraged to present experimental findings at these meetings and to publish in peer-reviewed journals.

## DIAGNOSTIC AND CLINICAL PATHOLOGY (0304)

**NPRC UNIT:** COMPARATIVE PATHOLOGY

**%NPRC $:** 1.420% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| O'NEIL, SHAWN P | DVM, PHD | C | COMPARATIVE PATHOLOGY | |
| | DVM | C | COMPARATIVE PATHOLOGY | |
| | DVM | G | COMPARATIVE PATHOLOGY | |
| | DVM | C | COMPARATIVE PATHOLOGY | |
| | DVM | G | COMPARATIVE PATHOLOGY | |
| | DVM | G | COMPARATIVE PATHOLOGY | |
| | DVM | C | PRIMATE RESOURCES | |
| | DVM, PHD | G | COMPARATIVE PATHOLOGY | |
| | DVM | G | COMPARATIVE PATHOLOGY | |
| | VMD | C | COMPARATIVE PATHOLOGY | |
| | DVM | G | COMPARATIVE PATHOLOGY | |

**AXIS I CODES:** 1A, 1D, 7, 17, 19, 21 **AXIS II CODES:**31, 64, 65, 66, 76


### ABSTRACT

The Division of Comparative Pathology provides anatomic and clinical pathology services to the various Divisions of the Center, affiliated scientists, collaborative scientists, and other scientific investigators from the USA who utilize the resources of this center.

The number of requisitions for these services can be categorized as follows:

a. number of post-mortem examinations performed: 475
b. number of biopsy specimens processed and examined: 264
c. number of complete blood counts (CBCs): 4,043
d. number of other clinical pathology requisitions(including fecal examinations, chemistry analyses, urinalyses, cytological examinations, and fluid analyses): 1,184
e. number of specimens collected for outside investigators: 273

Complete postmortem and histopathologic examinations were performed on all nonhuman primates that died at the Center, including abortuses and stillbirths from the numerous breeding colonies, animals dying of spontaneous disease while not involved in research projects, and those animals that died or were sacrificed while on specific studies. The data generated from examination of those tissues is used to monitor outbreaks of infectious diseases in our colony, to provide ancillary support for ongoing research studies, and to provide diagnostic support to our clinical veterinary staff.

The diagnostic laboratory plays a critical role in the recognition of certain natural diseases of captive nonhuman primates that may be developed into animal models for various diseases of humans. Examples of nonhuman primate models for human diseases that have been developed at the Center include simian AIDS, colitis and colonic carcinoma, and glomerulonephritis. AIDS pathogenesis studies,

using the SIV/rhesus macaque model, remain a major focus of the research conducted in the Division of Comparative Pathology. More recently described conditions of nonhuman primates that are currently being investigated for model development include SV40-induced oncogenesis, arteriopathy in SIV-infected rhesus, cryptosporidial infection in rhesus, and the pathogenesis of Mycobacterium avium infection in SIV-infected rhesus.

## CNS AS A VIRAL RESERVOIR IN SIV INFECTED MACAQUES (0357)

**NPRC UNIT:** COMPARATIVE PATHOLOGY

**%NPRC $:** 1.420% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| O'NEIL, SHAWN P | DVM, PHD | C | COMPARATIVE PATHOLOGY | |

**AXIS I CODES:** 1A, 2, 7B, 17, 19, 21 **AXIS II CODES:**31, 64, 66

**ABSTRACT**

Like lymphoid organs, the central nervous system (CNS) is an important tissue reservoir for HIV. Most antiretroviral agents do not cross the blood-brain barrier (BBB) efficiently, thus it is unknown whether these agents will be able to inhibit virus replication in the brain. We have developed a nonhuman primate model of HIV encephalitis that uses an isolate of SIV (SIVsmmFGb) that is highly neuropathogenic in pig-tailed macaques. In preliminary studies, 12 of 12 rapid progressor (RP; less than 30 weeks survival) and 3 of 5 slow progressor (SP; greater than 30 weeks survival) SIVsmmFGb-infected macaques developed SIV encephalitis (SIVE). To determine whether viral load in cerebrospinal fluid (CSF) was predictive of brain virus burden in the SIVsmmFGb model, we measured virion-associated RNA in CSF and brain specimens from 12 macaques necropsied at 10-13 weeks after inoculation. Viral load was positively correlated between brain and CSF ($R = 0.94$; $p < 0.01$). To test the effect of antiretroviral therapy on brain virus burden, we treated 2 of 4 RP macaques with the reverse transcriptase inhibitor PMPA for 4 weeks beginning 9 weeks after inoculation. One of the two PMPA-treated RP macaques was euthanatized due to rapid disease progression after only 8 days of PMPA therapy, and had high brain virus burden. Brain virus burden was also very high in untreated RP macaques; however, viral RNA could not be detected in the RP macaque that received the full complement of 4 weeks of PMPA therapy. This is the only SIVsmmFGb-infected RP pig-tailed macaque that has not developed SIVE (1 of 16). These results suggest that antiretroviral therapy during the early post-acute phase of lentivirus infection may be associated with suppressing brain virus burden. We are currently developing a quantitative real time assay to measure provirus load in brain tissue, to evaluate the impact of treatment on latent CNS infection.

## ORAL TRANSMISSION OF SIV IN NEONATAL AND ADULT MACAQUES (0358)

**NPRC UNIT:** COMPARATIVE PATHOLOGY

**%NPRC $:** 1.420% **AIDS RELATED RESEARCH**

| INVESTIGATOR | | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|---|
| O'NEIL, SHAWN P | | DVM, PHD | C | COMPARATIVE PATHOLOGY | |
| | 3 | DVM | A | MICROBIOLOGY AND IMMUNOLOGY | EMORY UNIVERSITY YERKES NATL PRC, GA USA |
| | 2 | DVM | A | RESEARCH RESOURCES | EMORY UNIVERSITY, YERKES NATL PRC, GA USA |

**AXIS I CODES:** 1A, 7B, 16C, 16F, 19, 22 **AXIS II CODES:**31, 66, 71


### ABSTRACT

Ingestion of HIV contaminated breast milk is a major route of pediatric HIV infection; however, the portals of viral entry, patterns of virus dissemination, and early target cells following oral exposure to HIV have not been identified. We are using the simian immunodeficiency virus (SIV) model to investigate the mechanism of lentivirus transmission across the mucosa of the alimentary tract in neonatal and adult monkeys. During the past year we have compared DC-SIGN (dendritic cell-specific ICAM-3 grabbing nonintegrin) expression in the alimentary mucosa between Asian macaques and African mangabeys. DC-SIGN is a C-type lectin that is expressed on the surface of mucosal dendritic cells. DC-SIGN is known to bind to the gp120 envelope glycoprotein of both HIV and SIV, and is thought to transport virions from mucosal surfaces to downstream lymphoid tissues. DC-SIGN expression in the lymphoid tissues of SIV-negative mangabeys resembles that in uninfected Asian macaques. However, whereas DC-SIGN expression was markedly reduced in spleens from chronically-infected macaques with AIDS, spleens from mangabeys had normal levels of DC-SIGN expression, even after 10 or more years of apathogenic SIV infection. We are currently using confocal microscopy to co-localize DC-SIGN with other dendritic cell and antigen presenting cell proteins (e.g. CD83, p55 (fascin), CD68, and HLA-DR) to definitively identify the phenotype of DC-SIGN positive cells in the spleens of macaques and mangabeys before and after SIV infection. In other studies, we are investigating the patterns of DC-SIGN expression throughout the alimentary tracts of newborn, infant and adult macaques to evaluate the putative role of this molecule in mucosal transmission. DC-SIGN-positive cells are commonly observed immediately beneath the columnar epithelium of the gastrointestinal tract, which suggests that DC-SIGN-expressing cells may play a role in mucosal transmission and dissemination of virions across the lower alimentary tract after oral exposure.

# CHEMOKINE RECEPTOR-MEDIATED NEURONAL INJURY IN SIV-INFECTED MACAQUE MODEL (0301)

**NPRC UNIT:** COMPARATIVE PATHOLOGY

**%NPRC $:** 1.420% **AIDS RELATED RESEARCH**


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| WESTMORELAND, SUSAN V | VMD | C | COMPARATIVE PATHOLOGY | |


**AXIS I CODES:** 1A, 7B, 9, 21 **AXIS II CODES:**31, 60, 63I, 64, 66


## ABSTRACT

Chemokine receptor activation of neurons involves the downstream activation of multiple signaling pathways including MAPK, ERK-1/2, IP3, cAMP, SHP/syk, and PI3/Akt. These pathways likely result in alterations in the expression of various unidentified genes important in neuronal injury or repair. We have begun to screen for differences in gene expression in brain tissue from adult SIV-infected rhesus macaques with and without encephalitis compared to uninfected age-matched controls by microarray gene analysis. Total RNA was isolated from snap-frozen frontal gray matter and hippocampus from SIVmac251-infected adult rhesus and age-matched uninfected controls. A cDNA probe was generated from total RNA labeled with [alpha-33P]-dCTP. The probe was hybridized overnight to Superarray or Clontech human gene microarray nylon membranes, which contained 25 to 250 human stress, apoptosis, and neuroregulatory genes in duplicate, as well as puc18 DNA as an internal negative control, and betta-actin and GAPDH as experimental controls. A phosphoimager was used to directly quantify the intensity of the signals. Data derived from SIV-infected rhesus frontal gray matter and hippocampus were normalized to brain from uninfected, age-matched control animals. Expression of neuroregulatory genes tended to be decreased, while expression of survival and repair genes was generally increased. Several genes of interest involved in neuronal function that have decreased expression in SIVE include neurogranin, neuropeptide Y, calcitractin, and calcium channel 4. Different genes involved in neurosurvival and repair that have increased expression in SIV infection include clusterin, heat shock protein (hsp) 27, Bcl-2-binding protein (bag-1), GNB-1, myelin oligodendrocyte basic protein (MOBP), GAP-43, EGFR, HGF, and ubiquitin. These data depict a complex series of events resulting in altered expression of genes that function in the regulation, survival, repair, and apoptosis of neurons in response to SIV infection. The results support a complex multifactorial pathogenesis culminating in neuronal injury and death, and verify the relevance of studying the mediators of these pathways in an in vivo model.

## STEM CELL TRANSDUCTION BY LENTIVIRAL VECTORS (0222)

**NPRC UNIT:** IMMUNOLOGY

**%NPRC $:** 1.600% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| BRAUN, STEPHEN | PHD | C | IMMUNOLOGY | |
| C | MD | C | IMMUNOLOGY | |
| | PHD | A | | UC DAVIS, CA USA |
| name | PHD | A | GENETICS | CHILDREN'S HOSPITAL, MA USA |
| J | PHD | A | MEDICINE | UC SD, CA USA |

**AXIS I CODES:** 1D, 7B, 17, 19 **AXIS II CODES:**31, 55, 64, 66

**ABSTRACT**

Genetic modification of hematopoietic stem cells (HSC) offers the potential of reconstituting immune function in HIV-infected individuals with a lifelong source of hematopoietic cells resistant to HIV infection. Construction of retroviral vectors based on lentiviruses has resulted in efficient transduction of hematopoietic stem cells. However, the optimal position within lentiviral vectors for expression of small RNA inhibitors has not been determined. We examined expression of the tRNAval Pol III promoter/SIV-specific ribozyme 9456 cassette in a series of a self-inactivating HIV-1 based vectors with the inhibitor in both the sense and antisense orientations. Expression of the ribozyme 9456 was highest in the sense orientation. Overall levels of ribozyme expression delivered by lentiviral vectors were not always predictive of the efficacy of inhibition, suggesting that localization of inhibitory genes may also play a role in mediating the degree of inhibition.

## STEM CELL GENE THERAPY FOR AIDS USING AN ANTI-ENVELOPE ANTISENSE MOLECULE (0323)

**NPRC UNIT:** IMMUNOLOGY

**%NPRC $:** 1.600% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| BRAUN, STEPHEN | PHD | C | IMMUNOLOGY | |
| | PHD | A | | VIRXSYS, GAITHERSBURG, MD USA |
| | MD | C | IMMUNOLOGY | |

**AXIS I CODES:** 1D, 7B, 17, 19 **AXIS II CODES:**31, 55, 64, 66

**ABSTRACT**

The introduction of inhibitory genes into hematopoietic stem cells offers the potential for long-lived immune reconstitution with progeny cells resistant to HIV-1 replication. However, successful development of stem cell gene therapy for AIDS is likely to require preclinical testing in the rhesus macaque model. We examined the ability of a HIV-1-based lentiviral vector (VRX494) encoding a 937 bp antisense HIV-1 envelope sequence to inhibit viral replication. Because HIV-1 does not replicate in rhesus macaques, chimeric SIV/HIV-1 viruses with the HIV-1 envelope were used to determine the efficacy of VRX494. Challenge of VRX494-transduced CEMx174 cells resulted in potent inhibition of HIV-1 and several SHIV strains. To evaluate the efficacy of the VRX494 in CD4+ T cells derived from transduced CD34+ cells, rhesus CD34+ bone marrow cells were transduced with VRX494 and then cultured on rhesus fetal thymus stromal cells to induce T cell differentiation. Transduction conditions for CD34+ cells were optimized so as to yield relatively high levels of transduction efficiency (greater than 50%), with minimal effective multiplicity of infection. Purified CD4+GFP+ T cells derived from VRX494-transduced cells strongly inhibited SHIV HXBc2P 3.2 and SHIV 89.6P replication compared to controls. Southern blot analysis of T cell clones derived from transduced CD34+ cells revealed a subset of cells with multiple proviral copies per cell highlighting the importance of optimizing transduction conditions to minimize the possibility of multiple integration events per cell. These results indicate that a lentiviral vector expressing an HIV-1 antisense sequence strongly inhibits HIV-1 and SHIV replication and that the SHIV macaque model should serve as a useful preclinical model to evaluate stem cell gene therapy for AIDS.

## OPTIMIZATION OF ONCORETROVIRAL VECTORS ENCODING RNA DECOYS (0346)

NPRC UNIT: IMMUNOLOGY

%NPRC $: 1.600% AIDS RELATED RESEARCH

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| BRAUN, STEPHEN | PHD | C | IMMUNOLOGY | |
| [illegible] | MD | C | IMMUNOLOGY | |

AXIS I CODES: 1D, 7B, 17, 19 AXIS II CODES:31, 55, 64, 66


### ABSTRACT

RNA decoys have a number of advantages for the inhibition of HIV replication, including their lack of immunogenicity and their ability to target conserved genes essential for viral replication. However, optimal inhibition of viral replication by RNA decoys has generally been obtained with multimeric RNA decoys, which significantly increase the risk of transgene instability when delivered using retroviral vectors. We therefore examined a number of parameters affecting the ability of oncoretroviral vectors to stably deliver HIV-1 RNA decoys and inhibit viral replication. To facilitate subsequent evaluation of an optimized construct in a primate model, we examined the ability of these constructs to inhibit simian immunodeficiency virus (SIV) replication. For the retroviral backbone, we chose the oncoretroviral vector MMP, which does not contain a selectable marker gene, and generated a series of vectors with and without intact splice donor and splice acceptor signals, and with the oncoretroviral LTR or an internal HIV-1 LTR transcriptionally regulating the polymeric TAR and RRE RNA decoys. By decreasing the number of TAR decoys, vector stability was increased, resulting in more efficient inhibition of viral replication in transduced cells. Inclusion of an internal HIV promoter within the retroviral vector provided more consistent viral inhibition. The efficiency of these different vectors has been evaluated in multiple T cell clones derived from transduced cells and stable high titer producer cell lines generated. These optimized vectors will facilitate analysis of the efficacy of RNA decoys for stem cell gene for AIDS in a nonhuman primate model.

## EVALUATION OF INHIBITION OF SHIV REPLICATION BY SIRNA VECTORS (0348)

**NPRC UNIT:** IMMUNOLOGY

**%NPRC $:** 1.600% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| BRAUN, STEPHEN | PHD | C | IMMUNOLOGY | |
| | MD | C | IMMUNOLOGY | |
| | PHD | A | | CITY OF HOPE, DUARTE, CA USA |

**AXIS I CODES:** 1D, 7B, 17, 19 **AXIS II CODES:**31, 55, 64, 66


### ABSTRACT

Introduction of genes able to inhibit HIV replication into hematopoietic stem cells offers the potential for long-lived immune reconstitution. However, multiple ethical and practical considerations significantly constrain the ability to address basic questions regarding stem cell gene therapy for AIDS in human clinical trials. Experiments in nonhuman primates therefore offer the opportunity to rigorously address these issues in an in vivo experimental model. A number of recent reports have highlighted the potential utility of small interfering RNA (siRNA) molecules to inhibit viral replication. In collaboration with J. Rossi, we initiated inhibition studies of various SHIV strains with siRNA targeting Tat and Rev. We obtained two siRNA (one targeting both Tat and Rev and the other targeting only Rev) and a control sequence, each transcriptionally regulated by the polymerase III promoter U6. Using transient transfection both si(I) and si(II) strongly inhibited HIV-1 (as previously shown), SHIV 89.6p and SHIV Hxbc2 3.2P (viruses with homologous envelopes). Using a second generation construct expressing the site I and site II interfering RNAs as a hairpin sequence (shRNA) has demonstrated even more potent inhibition of SHIV replication by over 1000-fold. These encouraging results support further studies of the utility of siRNA to inhibit SHIV replication in vivo in the macaque model.

## MUCOSAL PRIMING SIV-SPECIFIC CTL RESPONSES BY SALMONELLA (0425)

**NPRC UNIT:** IMMUNOLOGY

**%NPRC $:** 1.600% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| EVANS, DAVID T. | PHD | C | MICROBIOLOGY | |
| | PHD | A | MICROBIAL PATHOGENESIS | YALE SCHOOL OF MEDICINE, CT USA |
| | PHD | C | MICROBIOLOGY | |
| | PHD | A | VETERINARY & BIOMED SCIENCES | UNIVERSITY OF NEBRASKA - LINCOLN, NE USA |
| | DVM, PHD | A | MICROBIOL PATHOGENESIS | YALE UNIVERSITY SCHOOL OF MEDICINE, CT USA |
| | MD | C | IMMUNOLOGY | |
| | MD | A | AIDS VACCINE PROGRAM | NCI/FREDERICK, MD USA |
| | DVM | C | PRIMATE RESOURCES | |
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**AXIS I CODES:** 1A, 7B, 19 **AXIS II CODES:** 31, 64, 66, 91


### ABSTRACT

Nearly all HIV infections are acquired mucosally and the gut-associated lymphoid tissues are important sites for early virus replication. Thus, vaccine strategies designed to prime virus-specific CTL responses that home to mucosal compartments may be particularly effective at preventing or containing HIV infection. The Salmonella type III secretion system has been shown to be an effective approach for stimulating mucosal CTL responses in mice. We therefore tested DphoP-phoQ-attenuated strains of Salmonella typhimurium and S. typhi expressing fragments of the SIV Gag protein fused to the type III-secreted bacterial SopE protein for the ability to sensitize rhesus macaque cells for CTL recognition in vitro. Rhesus cell lines infected with these Salmonella recombinants were efficiently lysed by Gag-specific CTLs derived from SIV-infected animals. To further explore the potential of these recombinants to induce CTL responses in primates, Mamu-A*01+ macaques were inoculated with three oral doses of recombinant Salmonella followed by a peripheral boost with modified-vaccinia Ankara expressing SIV Gag (MVA Gag). Transient low level CTL responses to the Mamu-A*01 Gag181-189 epitope were detected following each dose of Salmonella. After boosting with MVA Gag, strong Gag-specific CTL responses were consistently detected and tetramer staining revealed the expansion of Gag181-189-specific CD8+ T cell responses in peripheral blood. A significant percentage of the Gag181-189-specific T cell population in each animal also expressed the intestinal homing receptor alpha4betta7. Additionally, Gag-specific CD8+ T cells were detected in lymphocytes isolated from the colon indicating that these cells were homing to the gastrointestinal mucosa. These findings demonstrate the potential of mucosal priming by the Salmonella type III secretion system to direct cellular immune responses to the gastrointestinal mucosa of immunized macaques.

## IDENTIFICATION OF SIV-SPECIFIC T HELPER EPITOPES AND THEIR RESTRICTING ALLELES (0218)

**NPRC UNIT:** IMMUNOLOGY

**%NPRC $:** 1.600% **AIDS RELATED RESEARCH**


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| GAUDUIN, MARIE-CLAIRE | PHD | C | IMMUNOLOGY | |
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| | PHD | A | PATHOLOGY & LAB MEDICINE | WISCONSIN NATL PRC, WI USA |


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


### ABSTRACT

We have focused on identification of epitopes using ELISPOT assays in which purified CD4+ T cells are incubated with pools of SIV Gag peptides. SIV-specific CD4+ T cell response in the majority of animals infected with attenuated SIV strains recognize 4 to 6 Gag peptide pools. The diversity of this response is reinforced by the fact that 13 of the 15 pools have been found to be recognized by CD4+ T cells from at least one animal. CD4+ T cell responses have been identified to at least 20 of 50 individual peptides to date. Ten macaques have been characterized in detail with regard to their MHC class II alleles and restricting class II alleles for individual epitopes are being identified. Recent studies have focused on identification of the MHC class II molecule responsible for presentation of an immunodominant epitope in Gag using a panel of cell lines expressing single DP or DR alleles. These results suggest that the CD4+ T cell response in animals infected with attenuated SIV strains is broadly directed against multiple epitopes. The identification of T helper epitopes in SIV should prove useful in the design and evaluation of candidate AIDS vaccines and in the preparation of MHC tetramers to identify SIV-specific CD4+ cells.

# CD8-DEPLETION OF EARLY TREATED SIV-INFECTED MACAQUES RESULTS IN REBOUND VIREMIA (0418)

**NPRC UNIT:** IMMUNOLOGY

**%NPRC $:** 1.600% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| GAUDUIN, MARIE-CLAIRE | PHD | C | IMMUNOLOGY | |
| | BVSC | C | PRIMATE RESOURCES | |
| | MD | C | IMMUNOLOGY | |
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**AXIS I CODES:** 1A, 7B, 19 **AXIS II CODES:**31, 64, 66, 91


## ABSTRACT

We examined the effects of CD8+ lymphocyte depletion in macaques that had undetectable plasma viremia following discontinuation of early antiretroviral therapy. Three Mamu-A01 positive rhesus macaques were infected with pathogenic SIVmac239 and treated with antiretroviral therapy early after infection. After 40 weeks, treatment was stopped and viral load rebounded transiently in all three animals but was rapidly controlled, associated with generation of broad SIV-specific CD8+ and CD4+ T cell responses. Depletion of CD8+ lymphocytes yielded a dramatic rise in plasma viremia (peak levels of 100,000 to 10,000,000 copies eq/ml) by day 10 in all animals, which rapidly declined to undetectable levels by day 20. The dramatic fall in viremia coincided with the recovery of CD8+ T lymphocytes in peripheral blood and significant increase of SIV-specific CD8+ T cells in lymph nodes of all animals. In addition, a significant expansion of the level of Mamu-A01 positive Gag181-189 tetramer-binding cells (mean values of 35 to 40 percent) was detected in lymph nodes at day 14. IFN-gamma ELISPOT assays confirmed the expansion of SIV Gag-specific CD8+ T cell responses in the lymph nodes. These findings provide direct evidence for the role of CD8+ T lymphocytes in controlling viremia in the setting of early retroviral therapy followed by treatment interruption.

## SIV-SPECIFIC CD4+ AND CD8+ T CELL RESPONSES DURING ACUTE SIV INFECTION (0419)

**NPRC UNIT:** IMMUNOLOGY

**%NPRC $:** 1.600% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| GAUDUIN, MARIE-CLAIRE | PHD | C | IMMUNOLOGY | |
| C | PHD | A | MICROBIOLOGY AND IMMUNOLOGY | EMORY VACCINE CENTER - YERKES, GA USA |
| Name | MD | C | IMMUNOLOGY | |
| | MD | A | AIDS VACCINE PROGRAM | NCI/FREDERICK, MD USA |
| 3 | PHD | A | SAIC | NCI FREDERICK, MD USA |
| C | MD | G | IMMUNOLOGY | |

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

**ABSTRACT**

HIV-specific CD8+ T cells are thought to play a major role in control of viremia during primary HIV infection, however, little is known about the development of virus-specific CD4+ T cell responses or the ability of CD8+ T cells to control viral replication during acute infection. We addressed these questions in eight macaques, six of which were Mamu-A01+ infected either with attenuated SIVmac239delta/nef or pathogenic SIVmac239. Peak plasma viremia occurred at day 10 in SIV239-infected macaques with mean values of 7.2 log copies/mL and mean plateau viremia of 6.4 log copies/mL. In contrast, animals infected with delta-nef had significantly lower viremia with a 3-4 log decrease in peak viral load and a steady decline to undetectable viral load by week 6 to 10. IFN-gamma ELISPOT assays revealed SIV Gag, Env, and Tat-specific T cell responses in both wild-type and delta/nef-infected animals. Using intracellular cytokine staining, Gag-specific T cell responses were detected as early as 1 week post-infection in delta/nef-infected animals, with frequencies from 0.65 to 2.14 percent of CD4+ T cells and from 1.79 to 6 percent for CD8+ T cells. Gag-specific T cell responses were also detected in wild type infected animals, with peak CD4+ responses ranging from 0.32 percent to 1.30 percent at week 2 and peak CD8+ responses ranging from 1.22 to 3.94 percent at week 2 to 4. These early responses may be important in determining the in vivo viral set-point and ultimate progression to simian AIDS.

**OPTIMIZATION OF ICS FOR QUANTITATION OF SPECIFIC CD4+ RESPONSES IN MACAQUES (0420)**

**NPRC UNIT:** IMMUNOLOGY

**%NPRC $:** 1.600% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| GAUDUIN, MARIE-CLAIRE | PHD | C | IMMUNOLOGY | |
| | DVM, PHD | A | | UC DAVIS, CA USA |
| | MD | C | IMMUNOLOGY | |
| | MD | C | IMMUNOLOGY | |
| | MD | A | AIDS VACCINE PROGRAM | NCI/FREDERICK, MD USA |
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names 3

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

**ABSTRACT**

Standard proliferation assays used for analysis of CD4+ T cell function have significant shortcomings, including limited sensitivity, lack of truly quantitative readouts and significant variability. We have optimized an intracellular cytokine staining (ICS) assay in rhesus macaques which allows us to identify virus-specific CD4+ T cells at the single-cell level with high sensitivity while reducing background staining to a minimum. Central to our optimized protocol was the addition of cross-linked costimulatory anti-CD28 and anti-CD49d Mabs, a modification, which resulted in up to three-fold enhancement of the frequency of TNF-alpha-secreting CD4+ T cells following superantigen or antigen-specific stimulation. The ICS protocol was also optimized with respect to antigen concentration and duration of antigenic stimulation. These modifications resulted in a convenient and highly reproducible assay with intra- and inter-assay variability of less than 10%. Although cryopreservation of PBMC generally led to a 40% to 80% decrease in the frequency of antigen-specific CD4+ T cells detected by ICS using stimulation with viral proteins, the use of overlapping peptide pools minimized the effects of cryopreservation on ICS responses. The use of more sensitive techniques such as ICS permits delineation of antigen-specific cells at the single cell level and should provide new insights into pathogen-specific immune responses in the rhesus macaque model.

## INHIBITION OF SHIV REPLICATION BY HIV-SPECIFIC APTAMERS (0417)

**NPRC UNIT:** IMMUNOLOGY

**%NPRC $:** 1.600% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| JOHNSON, R PAUL | MD | C | IMMUNOLOGY | |
| | PHD | C | IMMUNOLOGY | |
| Name ⊃ | PHD | A | MICROBIOLOGY AND IMMUNOLOGY | ALBERT EINSTEIN COLLEGE OF MEDICINE, NY USA |

**AXIS I CODES:** 1A, 1D, 7B, 17, 19 **AXIS II CODES:**31, 55, 64, 66

**ABSTRACT**

Despite the dramatic success of highly active antiretroviral therapy (HAART) in inhibiting viral replication in HIV-infected subjects, it is increasingly clear that there is a compelling rationale for the development of complementary therapies, most notably genetic therapies for HIV disease. Recent experiments have demonstrated quite potent inhibition of HIV-1 and RT-SHIV replication by RT-specific aptamers. Aptamers have a number of distinctive advantages as a modality to inhibit HIV replication, including the ability to target multiple elements of the retroviral life cycle, their relative resistance to the emergence of escape viruses, and their observed potency in inhibiting HIV replication. Following transduction of cell lines with retroviral vectors expressing aptamers specific for HIV-1, we observed significant inhibition of SHIV RT replication. These studies should yield important information regarding the efficacy and safety of aptamer-based stem cell gene therapy for AIDS and ultimately facilitate the development of similar trials in HIV-infected people.

## GENE THERAPY FOR BRAIN TUMORS (0423)

**NPRC UNIT:** IMMUNOLOGY

**%NPRC $:** 1.600%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| JOHNSON, R PAUL | MD | C | IMMUNOLOGY | |
| | PHD | A | NEROSURGERY | MASSACHUSETTS GENERAL HOSPITAL, MA USA |
| | MD | A | MICRO & MOLECULAR GENETICS | HARVARD MEDICAL SCHOOL, MA USA |
| | MD | C | IMMUNOLOGY | |
| | PHD | A | MICROBIO & MOLECULAR GENETICS | HARVARD MED SCH, MA USA |
| | MD | A | PATHOLOGY | MASSACHUSETTS GENERAL HOSPITAL, MA USA |
| | MD | A | PEDIATRIC INFECTIOUS DISEASE | MASSACHUSETTS GENERAL HOSPITAL, MA USA |

**AXIS I CODES:** 1A, 7B, 9, 21 **AXIS II CODES:** 55, 64, 66, 76

### ABSTRACT

Malignant gliomas constitute one of the brain tumors that are most refractory to treatment. Herpes simplex virus (HSV) vectors are being tested for selective delivery of drug-enhancing genes to tumor cells. The goal of this project is to investigate the contribution of immune mechanisms to HSV-mediated oncolysis. Immune responses to HSV vectors and their effect on tumor regression are being evaluated in common marmoset monkeys. It is hypothesized that cytolytic T lymphocytes to HSV vectors selectively targeting tumor cells will enhance virus-induced oncolysis.

# CELLULAR IMMUNE RESPONSES INDUCED BY ATTENUATED SIV CONTRIBUTE TO PROTECTION (0426)

**NPRC UNIT:** IMMUNOLOGY

**%NPRC $:** 1.600% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| JOHNSON, R PAUL | MD | C | IMMUNOLOGY | |
| | PHD | C | MICROBIOLOGY | |
| | MD | A | MEDICINE, VIRAL PATHOGENESIS | BETH ISRAEL DEACONESS MEDICAL CENTER, MA USA |
| | MD | A | AIDS VACCINE PROGRAM | NCI/FREDERICK, MD USA |
| | DVM | A | MICROBIOLOGY AND IMMUNOLOGY | EMORY UNIVERSITY YERKES NATL PRC, GA USA |
| | PHD | A | SURGERY | DUKE MEDICAL CENTER, NC USA |
| | DVM | A | MEDICINE, VIRAL PATHOGENESIS | BETH ISRAEL DEACONESS MEDICAL CENTER, MA USA |
| | MD, PHD | A | MEDICINE | DANA-FARBER CANCER INSTITUTE, MA USA |
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**AXIS I CODES:** 1A, 7B, 19 **AXIS II CODES:** 31, 64, 66, 91


## ABSTRACT

Although live, attenuated vaccines can provide potent protection against heterologous SIV and SHIV challenge, the specific immune responses that confer this protection have not been determined. To test whether cellular immune responses mediated by CD8+ lymphocytes contribute to this vaccine-induced protection, we depleted vaccinated rhesus macaques of CD8+ lymphocytes, then challenged them SIVmac251 by the IV route. The study included 6 SIVmac239delta3 vaccinated macaques treated with control monoclonal antibody, 4 unvaccinated control animals that received no antibody and 7 SIVmac239delta3 vaccinated animals that received anti-CD8 mAb. While vaccination with SIVmac239delta3 did not block infection with challenge virus, the post-challenge levels of plasma virus in control antibody-treated animals were significantly lower than in unvaccinated animals. Depletion of CD8+ lymphocytes at the time of challenge resulted in intermediate median plasma virus levels that were between the vaccinated and unvaccinated controls suggesting the cell-mediated immune responses contributed to, but were not solely responsible for, protection. Interestingly, at the time of challenge, animals expressing Mamu A*01 showed significantly higher frequencies of SIV-specific CD8+ T cell responses and lower neutralizing antibody titers than Mamu A*01- animals. Consistent with this finding, depletion of CD8+ lymphocytes abrogated vaccine-induced protection to a greater extent in Mamu A*01+ than in Mamu A*01- animals. These results indicate that live-attenuated SIV vaccines can provide protection by inducing both humoral and cellular immune responses and the relative contribution of each of these responses to protection is genetically determined.

## PATHOGENESIS OF EBV INFECTION IN THE RHESUS MACAQUE (0217)

**NPRC UNIT:** IMMUNOLOGY

**%NPRC $:** 1.600% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| KAUR, AMITINDER | MD | C | IMMUNOLOGY | |
| | PHD | A | MEDICINE | MASSACHUSETTS GENERAL HOSPITAL, MA USA |
| | PHD | A | MEDICINE | BRIGHAM & WOMEN'S HOSPITAL, MA USA |
| | MD | A | MEDICINE | MASSACHUSETTS GENERAL HOSPITAL, MA USA |
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**AXIS I CODES:** 1A, 7B **AXIS II CODES:** 31, 64, 66


### ABSTRACT

Although inhibition of MHC class I antigen presentation of the EBV EBNA1 protein mediated by its internal Glycine-Alanine repeat (GAr) domain has been shown to protect EBNA1-expressing cells from CD8+ cytotoxic T lymphocytes (CTL), it is not known whether this immune evasion mechanism is essential for maintenance of life-long latent EBV infection. Rhesus lymphocryptovirus (RhLCV) is genetically similar to EBV, and results in persistent latent infection in rhesus macaques. However, the GAr domain of RhLCV EBNA1 is condensed and does not inhibit antigen processing. In order to determine the CTL repertoire in RhLCV infected rhesus macaques, we measured the frequency of interferon-g-secreting peripheral blood mononuclear cells responding to stimulation with vaccinia recombinants expressing the RhLCV EBNA1, 2, 3A, 3B, 3C, LP and portions of LMP1 and 2 proteins by ELISPOT assays. Surprisingly, and in contrast to humans, EBNA1 was the predominant and most frequently recognized latent protein in naturally and experimentally LCV-infected macaques. These data suggest that an immune response to the EBNA1 protein does not prevent latency and that the EBV GAr may not be an important immune evasion mechanism, allowing viral persistence.

## CYTOMEGALOVIRUS REACTIVATION FOLLOW SIV INFECTION (0226)

**NPRC UNIT:** IMMUNOLOGY

**%NPRC $:** 1.600% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
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| | MD | C | IMMUNOLOGY | |
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**AXIS I CODES:** 1A, 7B, 19 **AXIS II CODES:**31, 64, 66


### ABSTRACT

Although opportunistic infections like cytomegalovirus (CMV) are a common sequelae of end-stage AIDS, the immune events leading to CMV reactivation in HIV-infected individuals are not well-defined. The role of cellular and humoral CMV-specific immune responses in immune control of latent CMV infection was evaluated prospectively in a cohort of eleven simian immunodeficiency virus (SIV)-infected CMV-seropositive rhesus macaques, 6 of whom had histologic evidence of CMV disease at death. Macaques with CMV disease differed from macaques without CMV disease in having significantly higher levels of plasma SIV RNA and CMV DNA, and significantly lower titers of anti-CMV binding antibodies (Abs) at the time of death. A significant decline in anti-CMV Abs and CMV-specific CD4+ and CD8+ T lymphocytes over time was observed in the macaques with CMV disease, but not in the macaques without CMV disease. Reduction in CMV-specific CD8+ T lymphocytes and anti-CMV neutralizing Abs was significantly correlated with a decline in CMV-specific CD4+ T lymphocytes. Although declines in CMV-specific T lymphocytes alone were sufficient for reactivation of low-level CMV viremia, high-level viremia (greater than 1000 copies/ml plasma CMV DNA) was observed when anti-CMV neutralizing and binding Abs had also declined. Thus, the occurrence of CMV reactivation-associated disease in AIDS is associated with suppression of both cellular and humoral CMV-specific immune responses. The underlying mechanism may be a dysfunction of memory B and CD8+ T lymphocytes associated with SIV-induced impairment of CMV-specific CD4+ T cell help. Ongoing studies are investigating the role of CD4+ T helper dysfunction in contributing to impairmanets of CMV-specific CD8+ T lymphocytes.

## SEQUENCING OF THE RHESUS CYTOMEGALOVIRUS GENOME (0324)

**NPRC UNIT:** IMMUNOLOGY

**%NPRC $:** 1.600% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| KAUR, AMITINDER | MD | C | IMMUNOLOGY | |
| E | MD | C | IMMUNOLOGY | |
| names | PHD | A | | BRIGHAM AND WOMEN'S HOSPITAL, MA USA |
| ] | MD | A | MEDICINE | BRIGHAM & WOMENS HOSP, MA USA |

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


### ABSTRACT

Cytomegalovirus (CMV) infection produces life-threatening disease in immunosuppressed individuals and is a frequent opportunistic pathogen in AIDS. However, mechanisms underlying CMV reactivation, factors that establish latency and persistent infection in immunocompetent hosts, and the natural history of CMV infection are not well characterized. Some of these questions are better addressed in animal models and we have established the rhesus macaque model of SIV infection to study the biology of CMV infection in AIDS. The goal of this project is to sequence the genome of a clinical isolate of rhesus CMV that was isolated from a macaque that died of AIDS. A library of overlapping cosmid clones of the rhesus CMV genome has been generated, and greater than 90% of the genome has been sequenced. Gene annotation carried out thus far reveals a high degree of sequence homology between the clinical isolate of rhCMV (180-92) and the ATCC strain of rhCMV (68-1) published previously. However, there are significant differences in a 22kb region (UL115-U56) which are being characterized. This project lays the foundation for future studies that precisely define the molecular pathogenesis of CMV infection in the rhesus macaque animal model of AIDS.

## MAPPING OF IMMUNODOMINANT CD8+ AND CD4+ T LYMPHOCYTE EPITOPES IN RHESUS CMV (0325)

**NPRC UNIT:** IMMUNOLOGY

**%NPRC $:** 1.600% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| KAUR, AMITINDER | MD | C | IMMUNOLOGY | |
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| | PHD | A | | UC DAVIS, CA USA |
| | PHD | A | | EPIMMUNE, SAN DIEGO, CA USA |
| | PHD | A | | EPIMMUNE, INC, SAN DIEGO, CA USA |
| | PHD | A | | THERION BIOLOGICS CORP., CAMBRIDGE, MA USA |

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

**ABSTRACT**

In order to conduct a comprehensive evaluation of CMV-specific cellular immunity in rhesus macaques, immunodominant CD8+ and CD4+ T lymphocyte epitopes in rhesus CMV are being mapped using a variety of techniques including interferon-gamma ELISPOT assays, intracellular cytokine staining assay and tetramers. Four Mamu-A*01 restricted epitopes have been identified and their tetramers synthesized. In addition vaccinia recombinants expressing the rhesus CMV immediate early 1 and 2 proteins, pp65 protein and IL-10 protein have been constructed, and 15 aa overlapping 11 peptides spanning these rhesus CMV proteins have been synthesized. Results to date show that naturally CMV-infected breeder rhesus macaques have high frequencies of circulating CD8+ T lymphocytes (as high as 6%) targeting epitopes in the rhesus CMV immediate early proteins. Mapping of immunodominant epitopes using overlapping peptides has revealed several new CMV epitopes in the immediate early and pp65 genes. The MHC Class I restriction of these epitopes is being determined. These studies will enable more precise assessment of the protective correlates of CMV-specific cellular immunity and help in the design of appropriate vaccine strategies for prevention of CMV disease.

## A NONHUMAN PRIMATE MODEL FOR CYTOMEGALOVIRUS VACCINES (0350)

**NPRC UNIT:** IMMUNOLOGY

**%NPRC $:** 1.600%


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| KAUR, AMITINDER | MD | C | IMMUNOLOGY | |
| [illegible] | PHD | A | | UC DAVIS, CA-USA |


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


### ABSTRACT

The main goal of this project is to investigate the role of immunomodulatory proteins encoded by rhesus CMV in establishing persistent CMV infection. CMV-seronegative rhesus macaques immunized with plasmids encoding the rhCMV IL-10, pp65 and gB genes developed humoral and cellular immune responses to the CMV immunogens. Following challenge with rhesus CMV, all vaccinated animals were infected. However, the peak CMV viremia was 10 to 100-fold lower and appeared to be delayed in vaccinated as compared to unvaccinated animals. So far, no differences have been observed between vaccinated macaques that did or did not receive vIL-10 immunization. Construction of rhCMV variants with deletion of viral immunomodulatory genes likes IL-10 and US28 are under way. These studies should facilitate elucidation of the immunological determinants of CMV persistence.

## CMV REACTIVATION IN XENOTRANSPLANTATION (0351)

**NPRC UNIT:** IMMUNOLOGY

**%NPRC $:** 1.600%


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| KAUR, AMITINDER | MD | C | IMMUNOLOGY | |
| [illegible] | MD | A | MEDICINE | MASSACHUSETTS GENERAL HOSPITAL, MA USA |
| [illegible] | MD | A | MEDICINE | MASSACHUSETTS GENERAL HOSPITAL, MA USA |


**AXIS I CODES:** 1A, 2, 7B **AXIS II CODES:** 66, 88


**ABSTRACT**

The xenotransplantation of porcine organs carries the potential risk of transmission of viruses between species as well as the reactivation of latent virus in donor and recipient tissues. We have investigated the species-specificity of baboon CMV (BCMV) and porcine CMV (PCMV) in a highly-immunosupressed pig-to-primate model of xenotransplantation. Tissues originating from a series of six swine-to-baboon composite thymokidney xenotransplants were investigated. Four baboons died (survival range 7 – 27 days) with the graft in situ while under immunosuppression. BCMV was activated in three (75%) of these baboons and was thought to be responsible for pneumonitis and death of one of the animals. Consumptive coagulopathy resulted in graftectomy (post-operative day 15 and 18) and discontinuing of immunosuppression in two baboons (survival greater than 200 days). PCMV was upregulated in five xenografts (83%) at time of death or graftectomy. PCMV infection was associated with ureteric necrosis in one xenograft. Although significantly upregulated in normal host tissue, low levels of BCMV and PCMV were also detected in the tissues of the other species. The cross-species presence of CMV did not appear to cause clinical or histological signs of active infection. Thus, viral infections presenting as clinical disease were restricted to tissues of the native host species. Due to the intensive immune suppression currently required for xenotransplantation, a significant risk of reactivation of latent infections by BCMV and PCMV is associated with this procedure. Whether viral DNA detected across species' lines represents cellular microchimerism, viral infection, or uptake of free virus by host tissues is under investigation. The observation of graft injury due to PCMV suggests that CMV will remain an important pathogen in immunosuppressed xenograft recipients. Strategies must be developed to exclude CMV from porcine donors.

## CELLULAR IMMUNE RESPONSES IN SIV-INFECTED SOOTY MANGABEYS (0352)

**NPRC UNIT:** IMMUNOLOGY

**%NPRC $:** 1.600% **AIDS RELATED RESEARCH**


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| KAUR, AMITINDER | MD | C | IMMUNOLOGY | |
| | DVM | A | MICROBIOLOGY AND IMMUNOLOGY | EMORY UNIVERSITY YERKES NATL PRC, GA USA |
| | MD | A | | EMORY UNIVERSITY,, GA USA |
| | PHD | G | IMMUNOLOGY | |


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


### ABSTRACT

The role of SIV-specific cellular immune responses in maintaining nonpathogenic SIV infection in sooty mangabeys is being investigated using Elispot and intracellular cytokine staining assays as well as by in vivo CD8+ T lymphocyte depletion studies. In vivo CD8 depletion using the mouse-human chimeric anti-CD8 mAB cM-T807 resulted in a two-log or greater increase in SIV viremia in 5/6 mangabeys. Return of SIV viremia levels to baseline values was coincident with recovery of peripheral CD8+ T lymphocytes. These data suggest that CD8+ T lymphocytes do inhibit SIV replication in vivo in SIV-infected sooty mangabeys. In a cross-sectional analysis, positive SIV-specific interferon-gamma Elispot responses ranging between 510-5244 spot forming cells per million PBMC were observed in 25/25 SIV-infected mangabeys and were comparable to that observed in four rhesus macaques infected for more than one year with SIVmac251. In the majority of sooty mangabeys, the interferon-gamma responses to SIV Gag and/or Env proteins accounted for at least two-thirds of the total SIV-specific response. In 9 mangabeys examined, the interferon-gamma responses to Gag and Env were predominantly mediated by high avidity CD8+ T lymphocytes. Naturally SIV-infected sooty mangabeys mount a substantial SIV-specific cellular immune response, suggesting that immune tolerance is neither a feature nor a requirement for maintenance of nonpathogenic infection in this natural host of SIV infection.

## T CELL DYNAMICS IN SIV-INFECTED SOOTY MANGABEYS (0421)

**NPRC UNIT:** IMMUNOLOGY

**%NPRC $:** 1.600% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| KAUR, AMITINDER | MD | C | IMMUNOLOGY | |
| | PHD | A | NIAID | NIH, MD USA |
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| | DVM | A | MICROBIOLOGY AND IMMUNOLOGY | EMORY UNIVERSITY YERKES NATL PRC, GA USA |
| | PHD | A | | LOS ALAMOS NATIONAL LABORATORY, NM USA |
| | PHD | A | | UNIVERSITY OF OXFORD, UK |

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

**ABSTRACT**

Sooty mangabeys are natural hosts of the simian immunodeficiency virus (SIV) that do not progress to AIDS despite sustained high viral loads. Understanding the dynamics of T-lymphocyte turnover in these animals may shed light on the mechanisms of CD4+ T cell depletion in HIV-infected humans and SIV-infected rhesus macaques. 6 SIV-infected and 5 uninfected sooty mangabeys were given daily BrdU i.p. for 2 weeks. BrdU incorporation in T-cells was measured frequently during the labeling (first 2 weeks) and the follow-up de-labeling phase (median 10 weeks). The percentage of BrdU labeled T-cells vs time was fitted using a model of T-cell dynamics, from which we estimated the average death rate of the T-cell population. The mean death rate for both uninfected and infected CD4+ T-cells was 0.01 day-1, and for CD8+ T-cells it was 0.008 day-1 and 0.009 day-1, respectively. Using the Mann-Whitney U-test, there was no statistically significant difference in the average death rates of uninfected and infected monkeys, either in the CD4+ ($p=0.53$) or the CD8+ ($p=0.41$) T cell subsets. In contrast to hosts with pathogenic sequelae of lentiviral infection, CD4+ and CD8+ T-cell turnover as measured by BrdU incorporation is not increased in SIV-infected sooty mangabeys. This suggests that the natural host and virus have co-evolved so that viral infection does not increase average CD4+ T cell death rates despite ongoing viral replication. Understanding how this equilibrium is achieved may be relevant for HIV infection.

## HERPESVIRUS VECTORS AS AN AIDS VACCINE (0422)

**NPRC UNIT:** IMMUNOLOGY

**%NPRC $:** 1.600% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| KAUR, AMITINDER | MD | C | IMMUNOLOGY | |
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| | PHD | A | MICROBIO & MOLECULAR GENETICS | HARVARD MED SCH; MA USA |
| | PHD | C | MICROBIOLOGY | |
| | MD | A | HUMAN RETROVIRUS SECTION | NCI, MD USA |

Names

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

**ABSTRACT**

We are testing the ability of herpes simplex virus (HSV) recombinants to serve as AIDS vaccine vectors. We previously showed that macaques vaccinated with HSV-1 vectors were partially protected against SIV challenge. Our current work aims to generate improved vaccine vector candidates by using a multiple IE-gene deleted HSV recombinant, HSV-1 d106, which does not express 4 immediate early proteins, some of which are implicated in host immune modulation and evasion. One group of rhesus macaques was immunized with HSV d106 recombinants expressing SIV env, SIV gag, or an SIV rev-tat-nef fusion protein, and a second group was immunized twice with plasmid vectors and then twice with the d106 viral vectors. CD8+ T cell responses were measured by Gag p11c tetramer responses and by interferon-gamma ELISPOT responses of unfractionated PBMC against SIVmac239 peptide pools. HSV-1 vector immunized animals showed low level cellular responses specific for gag and env with limited increases with multiple boosts. More importantly, DNA-primed animals showed low level cellular responses that were strongly boosted by immunization with the HSV vectors. Tetramer responses were 1-2% of the CD8+ T cells after one HSV vector boost, and ELISPOT responses were 400 -3000 spot forming cells per million PBMC for gag and env peptide pools. The HSV-1 d106 vaccine vector strongly boosted T cell responses induced by plasmid vectors in rhesus macaques. Therefore, this novel viral vector has the potential to serve as a new component in prime-boost protocols to further enhance T cell responses for immunization against HIV.

**PHENOTYPIC & FUNCTIONAL CHARACTERIZATION CD4+/CD8+ DP T LYMPHOCYTES IN MONKEYS (0424)**

**NPRC UNIT:** IMMUNOLOGY

**%NPRC $:** 1.600% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| MACCHIA, IOLE | PHD | G | IMMUNOLOGY | |
| | PHD | C | IMMUNOLOGY | |
| Named | MD | C | IMMUNOLOGY | |
| | MD | C | IMMUNOLOGY | |

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

**ABSTRACT**

Circulating T lymphocytes co-expressing CD4+ and CD8+ have been described in the peripheral blood of humans and several animal species. In healthy humans, CD4+/CD8+ DP T cells represent a minor subset of T cells (1-2 percent), while non-human primates possess a larger pool of this cell population. The origin and functional properties of DP T cells remain poorly understood. In the present study, we evaluated the frequency, phenotype and function of peripheral DP T cells in rhesus macaques, either uninfected or infected with wild-type or attenuated (SIVmac239 delta nef or SIVmac239 delta 3) strains of SIV. Two distinct populations of DP T cells were identified: the dominant one is CD4hiCD8low and expresses the CD8-alpha alpha homodimer, while the minor population is CD4lowCD8hi and expresses the CD8 alpha beta heterodimer. The percentage of CD4hiCD8low T cells was lower in wild-type SIV-infected animals compared to uninfected controls, an observation borne out by prospective studies of SIV-infected animals. Phenotypic analysis, using different combinations of naïve/memory and activation markers, indicated that CD4hiCD8low T cells exhibited an effector memory phenotype and were proliferating at a higher rate than single positive CD4+ T cells. Furthermore, they expressed relatively low levels of CD7, one of the earliest markers for T-cells, and relatively high levels of granzyme B. Data obtained by intracellular cytokine staining indicated that DP cells produced cytokines in response to stimulation with CMV virions and that the frequency of CMV-specific cells was enriched in CD4hiCD8low cells compared with CD4hiCD8– cells. Finally, using a real-time PCR assay to quantitate the TCR-rearrangement excisional DNA circles (TRECs), a marker for recent thymic emigrants, we observed that the number of TRECs in CD4hiCD8low cells was lower than in naïve CD4+ T cells. Taken together, these data suggest that CD4hiCD8low T cells represent an effector memory subset of CD4+ T cells and that this cell population is depleted during the course of SIV infection.

# XENOGENEIC THYMIC TRANSPLANTATION AS AN ADJUNCT TO THE TREATMENT OF AIDS (0210)

**NPRC UNIT:** IMMUNOLOGY

**%NPRC $:** 1.600% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| ROSENZWEIG, MICHAEL | BVSC, PHD | C | IMMUNOLOGY | |
| [illegible] | MD | C | IMMUNOLOGY | |
| [illegible] named | MD | A | SURGERY | MASS GENERAL HOSPITAL, MA USA |
| [illegible] 3 | MD | A | SURGERY | MASS GENERAL HOSPITAL, MA USA |
| | MD | A | SURGERY | MASSACHUSETTS GENERAL HOSPITAL, MA USA |

**AXIS I CODES:** 1D, 7B, 19 **AXIS II CODES:** 31, 64, 88


## ABSTRACT

The goal of this project is to determine the feasibility of xenogeneic pig thymus to engraft in SIV-infected macaques, and to determine if this has any impact on T cell reconstitution. Our data demonstrate poor to absent xeno and allo- responses in macaques with advanced SIV disease, as well as 1-2 log reduction in the proliferation response to lectin. In vivo experiments examining the engraftment of pig thymic tissue has demonstrated failure of engraftment. Experiments over the past year have focused on the use of vascular thymic transplants and have demonstrated short term graft survival though grafts were eventually lost due to vascular problems not rejection. There experiments demonstrate that the immunologic barriers to xenotransplantation are quite significant and should ultimately help determine if xenotransplantation of pig thymic tissue is a useful strategy to reconstitute immune function in HIV-infected people.

## SINGLE CYCLE SIV (0322)

**NPRC UNIT:** MICROBIOLOGY

**%NPRC $:** 0.628% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| DESROSIERS, RONALD C | PHD | C | MICROBIOLOGY | |
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**AXIS I CODES:** 1D, 7B, 19 **AXIS II CODES:**31, 64, 66, 91


### ABSTRACT

We have devised a novel approach for producing SIV, and potentially HIV-1, strains that are limited to a single cycle of infection. Unlike previous lentiviral vectors, our single-cycle SIV is capable of expressing eight of the nine viral gene products and infected cells release immature virus particles that are unable to complete subsequent rounds of infection. Single-cycle SIV (scSIV) was produced using a two-plasmid system specifically designed to minimize the chances of generating replication-competent virus by recombination or nucleotide substitutions in the gag-pol-frameshift site to inactivate Pol expression. To ensure inactivation of Pol and to prevent the recovery of wild-type virus by nucleotide reversion, deletions were also introduced into the viral pol gene. In order to provide Gag-Pol in trans, a Gag-Pol complementing plasmid was constructed that included a single nucleotide insertion to permanently place gag and pol in the same reading frame. We also mutated the frameshift site of this Gag-Pol expression construct so that any recombinants between the two plasmids would remain defective for replication. Co-transfection of both plasmids into 293T cells resulted in the release of Gag-Pol-complemented virus that was capable of one round of infection and one round of viral gene expression, but was unable to propagate a spreading infection. The infectivity of scSIV was limited by the amount of Gag-Pol provided in trans and was dependent on the presence of a functional integrase provided by the Gag-Pol complementing plasmid. Single-cycle SIV produced by this approach will be useful for addressing questions relating to viral dynamics and viral pathogenesis and for evaluation as an experimental AIDS vaccine in rhesus macaques.

## MODULATION OF ENV CONTENT IN VIRIONS OF SIV (0406)

**NPRC UNIT:** MICROBIOLOGY

**%NPRC $:** 0.628% **AIDS RELATED RESEARCH**


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| DESROSIERS, RONALD C | PHD | C | MICROBIOLOGY | |
| [illegible] | MD, PHD | A | DEPT. OF PATHOLOGY & LAB. MEDI | UNIVERSITY OF PENNSYLVANIA, PA USA |
| [illegible] | PHD | G | MICROBIOLOGY | |


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


### ABSTRACT

Specific mutations were created in the cytoplasmic domain of the gp41 transmembrane protein of simian immunodeficiency virus strain 239 (SIV239). The resultant strains included a mutant in which Env residue 767 was changed to a stop codon, a double mutant in which positons 738 and 739 were changed to stop codons, another in which a prominent endocytosis motif was changed from YRPV to GRPV by the substitution of Tyrosine 721 and a final combination mutant bearing the Q738stop, Q739stop and Y721G mutations. The effects of these mutations on cell surface expression, on Env incorporation into virions, and on viral infectivity were examined. The molar ratio of Gag to gp120 of 54:1 that we report here for SIV239 virions agrees very well with the ratio of 60:1 reported previously by Chertova et al. (Chertova, E., Bess, Jr. J. W., Crise, J., Sowder II, R. C., Schaden, T. M., Hilburn, J. M., Hoxie, J. A., Benveniste, R. E. Lifson, J.D., Henderson, L. E., Arthur, L. O. J. Virol. 76: 5315-5325, 2002) using very different methodologies. Assuming 1,200 to 2,500 Gag molecules per virion, this corresponds to 7 to 16 Env trimers per SIV239 virion particle. Although all of the mutations increased Env levels in virions, E767stop had the most dramatic effect, increasing Env content per virion by 25-50 fold. Increased levels of Env content in virions correlated strictly with higher levels of Env expression on the cell surface. Increased Env content with E767stop also correlated with increased infectivity, but the degree of change was not proportional; the 25-50 fold increase in Env content only increased infectivity 2-3 fold. All of the mutants replicated efficiently in CEMX174 and Rh221-89 cell lines. Although some of these findings have been reported previously, our findings show that effects of the cytoplasmic domain of gp41 on Env content in virions can be dramatic, that Env content in virions correlates strictly with the levels of cell surface expression and that Env content in virions can determine infectivity; furthermore, our results define a particular change with the most dramatic effects.

## LIVE ATTENUATED VACCINE APPROACHES FOR AIDS (0407)

**NPRC UNIT:** MICROBIOLOGY

**%NPRC $:** 0.628% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| DESROSIERS, RONALD C | PHD | C | MICROBIOLOGY | |
| | MD | C | IMMUNOLOGY | |
| | PHD | C | MICROBIOLOGY | |
| | MD | C | IMMUNOLOGY | |
| | DVM | C | PRIMATE RESOURCES | |

**AXIS I CODES:** 1A, 7B, 9 **AXIS II CODES:**31, 39, 66, 91

**ABSTRACT**

Continued study of live attenuated vaccine approaches for AIDS using SIV in rhesus monkeys is justified on two grounds: i) for what such studies may teach us about what is needed for protective immunity; ii) to generate a state of preparedness regarding the identification of strains and regimens with optimal safety/efficacy profiles in the event that science and society elect to take this route in the future. Previous studies from our group have utilized single and combination deletions involving nef and other auxiliary genes; these studies have not identified any strain with a safety/efficacy profile that would warrant intensive investigation from a vaccine perspective. Ongoing studies are focusing on two strains with much more promising properties in this regard. SIVdeltaV1-V2 is missing 100 amino acids that encompass the entire V1-V2 loops of Envelope. SIVdeltaV1-V2 has appeared safe in the 22 monkeys examined so far and was highly effective in the single vaccine/challenge experiment performed with it to date. SIVdeltavif is missing the vif gene. SIVdeltavif is very highly attenuated and has elicited both humoral and cellular anti-SIV immune responses. Results of challenge of SIVdeltaV1-V2 –vaccinated monkeys indicate that high-level immune responses mesureable in the peripheral blood by standard assays are not necessary to achieve strong protection, even against strains such as SIV239.

# STRATEGIES OF IMMUNE EVASION IN AIDS: RESISTANCE TO NEUTRALIZING ANTIBODIES (0408)

**NPRC UNIT:** MICROBIOLOGY

**%NPRC $:** 0.628% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| DESROSIERS, RONALD C | PHD | C | MICROBIOLOGY | |
| | PHD | A | IMMUNOLOGY | THE SCRIPPS RESEARCH INSTITUTE, CA USA |
| | MD | A | | UNIVERSITY OF PENNSYLVANIA, PA USA |
| | PHD | C | MICROBIOLOGY | |
| | MD | A | PEDIATRICS | TULANE UNIVERSITY MEDICAL CENTER, LA USA |

**AXIS I CODES:** 1D, 7B, 19 **AXIS II CODES:** 31; 64, 66, 74, 91


## ABSTRACT

Simian immunodeficiency virus (SIV) of macaques isolate SIVmac239 is highly resistant to neutralization by polyclonal antisera or monoclonal antibodies, a property that it shares with most primary isolates of human immunodeficiency virus type 1 (HIV-1). This resistance is important for the ability of the virus to persist at high levels in vivo. To explore the physical features of the viral envelope complex that contribute to the neutralization-resistant phenotype, we examined a panel of SIVmac239 derivatives for sensitivity to neutralization by a large collection of monoclonal antibodies (MAbs). These MAbs recognize both linear and conformational epitopes throughout the viral envelope proteins. The variant viruses included three derivatives of SIVmac239 with substitutions in specific N-linked glycosylation sites of gp120 and a fourth variant that lacked the100 amino acids that encompass the V1 and V2 loops. Also included in this study was SIVmac316, a variant of SIVmac239 with distributed mutations in env that confer significantly increased replicative capacity in tissue macrophages. These viruses were chosen to represent a broad range of neutralization sensitivities based on susceptibility to pooled, SIV-positive plasma. All three of these very different kinds of mutations (amino acid substitutions, elimination of N-glycan attachment sites, and a 100-amino-acid deletion spanning variable loops V1 and V2) dramatically increased sensitivity to neutralization by MAbs from multiple competition groups. Thus, the mutations did not simply expose localized epitopes but rather conferred global increases in neutralization sensitivity. The removal of specific N-glycan attachment sites from V1 and V2 led to increased sensitivity to neutralization by antibodies recognizing epitopes from both within and outside of the V1-V2 sequence. Surprisingly, while most of the mutations that gave rise to increased sensitivity were located in the N-terminal half of gp120 (surface subunit [SU]), the greatest increases in sensitivity were to MAbs recognizing the C-terminal half of gp120 or the ectodomain of gp41 (transmembrane subunit [TM]). This reagent set and information should now be useful for defining the physical, structural, thermodynamic, and kinetic factors that influence relative sensitivity to antibody-mediated neutralization.

## COCAINE-INDUCED BEHAVIORS IN SQUIRREL MONKEYS (0188)

**NPRC UNIT:** NEUROCHEMISTRY

**%NPRC $:** 0.212%


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| MADRAS, BERTHA K | PHD | C | NEUROCHEMISTRY | |
| C | PHD | A | BRAIN AND COG SCI | MASSACHUSETTS INSTITUTE OF TECHNOLOGY, MA USA |
| Nancy | PHD | A | BRAIN AND COG SCI | MASSACHUSETTS INSTITUTE OF TECHNOLOGY, MA USA |


**AXIS I CODES:** 1A, 1D, 2, 21 **AXIS II CODES:**36, 50B, 72, 74H, 77, 87


### ABSTRACT

Repeated intermittent administration of cocaine to rodents results in progressive increases in locomotor activity and extracellular dopamine levels in the dopamine-rich basal ganglia, even after periods of abstinence. The heightened functional response to cocaine in rodents, termed sensitization, is thought to reflect the transition from casual to compulsive drug-seeking behavior in humans. In nonhuman primates, repeated cocaine exposure reportedly produces a gradual increase in extracellular dopamine levels, but locomotor sensitization has not been consistently reported. These results indicate that behavioral sensitization to a relatively high dose of cocaine in squirrel monkeys is reflected by a progression of qualitative behavioral changes, rather than by increased locomotor activity, observed in rodents. Research to clarify the neurochemical correlates of these changes is ongoing. Extrapolation from animal to human responses to cocaine should be viewed in light of species differences in behavioral responses to psychostimulants.

## TROPANE ANALOGS OF DOPAMINE (0189)

**NPRC UNIT:** NEUROCHEMISTRY

**%NPRC $:** 0.212%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| MADRAS, BERTHA K | PHD | C | NEUROCHEMISTRY | |
| [name] | PHD | C | NEUROCHEMISTRY | |

**AXIS I CODES:** 1D, 2, 21 **AXIS II CODES:**36, 50B, 72, 87


### ABSTRACT

Cocaine is an effective inhibitor of the dopamine transporter. Accumulating evidence indicates that cocaine-induced increases of dopamine levels contribute to the stimulant effects and abuse liability of cocaine. Accordingly, tropane analogues of cocaine, targeted to the dopamine transporter (DAT), are a major focus of drug design for the development of medications to treat cocaine addiction. We created tropane analogs of dopamine to investigate whether they could serve as partial antagonists of cocaine. The introduction of the dihydroxyl functionality in "cocadopa" led to reduced binding potency at monoamine transporters compared with tropane progenitors, but increased potency relative to dopamine. It is likely that the binding domain for these compounds on the dopamine transporter is not the same as that for dopamine. Notwithstanding the moderate potency of the free catechols (greater than 100 nM), the dihydroxy analog stimulated locomotor activity in rodents with a duration of effect that exceeded 4 h. To further investigate the therapeutic potential of this series of compounds, we created a diacetoxy prodrug of "cocadopa" which substituted fully for cocaine in a rat drug-discrimination paradigm. These hybrid molecules are demonstrating promise in preclinical evaluation as potential medications for cocaine abuse.

**NOVEL TECHNETIUM LABELED PROBE TO MONITOR DOPAMINE TRANSPORTER DENSITY IN LIVI (0199)**

**NPRC UNIT:** NEUROCHEMISTRY

**%NPRC $:** 0.212%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| MADRAS, BERTHA K | PHD | C | NEUROCHEMISTRY | |
| | PHD | A | | ORGANIX, INC., WOBURN, MA USA |
| | PHD | A | NUCLEAR MEDICINE | MASS GENERAL HOSPITAL, BOSTON, MA USA |
| | MD, PHD | A | RADIOLOGY | MASSACHUSETTS GENERAL HOSPITAL, BOSTON, MA USA |
| | PHD | A | | ORGANIX, INC, MA USA |
| | PHD | A | RADIOLOGY | MASS GENERAL HOSPITAL, BOSTON, MA USA |
| | PHD | A | | ORGANIX, INC., WOBURN, MA USA |
| | PHD | A | | ORGANIX, INC, MA USA |
| | PHD | A | | ORGANIX, INC., MA USA |

**AXIS I CODES:** 1A, 1D, 12B, 21 **AXIS II CODES:** 46, 60, 63F, 72, 77, 80

**ABSTRACT**

The dopamine transporter (DAT), located presynaptically and exclusively on dopamine neurons, provides a marker for Parkinson's disease and possibly in attention deficit hyperactivity disorder (ADHD). In ADHD, DAT density levels are elevated, while in Pd these levels are depleted. The depletion of DAT levels also corresponds with the loss of dopamine. We designed, synthesized, assessed in vitro and in vivo by SPECT imaging of nonhuman primate brain, a second-generation 99m technetium-based tropane ligands. We improved selectivity by placing the aromatic ring on the C-3 alpha- rather than the C-3 beta position, and improved biological stability by replacing the ester link in the C-2 position with a ketone. With this new structure ((N-[(2-((3'-N'-propyl-(1' 'R)-3' 'alpha -(4-fluorophenyl)tropane-2' 'b-1-propanoyl)(2-mercaptoethyl)amino)acetyl)-2-aminoethanethiolato]technetium(V) oxide), sufficient levels of fluoratec entered the brain and labeled the DAT in vivo. With this lead compound, we succeeded in quantifying DAT density in nonhuman primate brain. Fluoratec, a DAT imaging agent that has emerged from these studies and is now in phase 1 clinical trials.

## NON-AMINE DOPAMINE TRANSPORT INHIBITORS RETAIN PROPERTIES OF AMINES (0201)

**NPRC UNIT:** NEUROCHEMISTRY

**%NPRC $:** 0.212%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| MADRAS, BERTHA K | PHD | C | NEUROCHEMISTRY | |
| | PHD | A | NUCLEAR MEDICINE | MASS GENERAL HOSPITAL, BOSTON, MA USA |
| | PHD | A | | ALBERT EINSTEIN COLLEGE OF MEDICINE, NY USA |
| | DVM | C | PRIMATE RESOURCES | |
| | MD, PHD | A | RADIOLOGY | MASSACHUSETTS GENERAL HOSPITAL, BOSTON, MA USA |
| | MD | A | ENDOCRINOLOGY & MET | UNIVERSITY OF TORONTO, CANADA |
| | PHD | A | | REPLIGEN CORPORATION, MA USA |
| | PHD | A | RADIOLOGY | MASS GENERAL HOSPITAL, BOSTON, MA USA |
| | PHD | A | | ORGANIX, INC., WOBURN, MA USA |
| | PHD | C | NEUROCHEMISTRY | |
| | PHD | A | PHARMACOLOGY | UNIVERSITY OF TORONTO, CANADA |
| | PHD | C | BEHAVIORAL BIOLOGY | |

**AXIS I CODES:** 1A, 1D, 2, 4, 21 **AXIS II CODES:** 36, 46, 50B, 63E, 72, 80, 87


### ABSTRACT

Without exception, therapeutic and addictive drugs that produce their primary effects by blocking monoamine transporters in brain contain an amine nitrogen in their structure. This fundamental canon of drug design was based on a prevailing premise that an amine nitrogen is required to mimic the structures of monoamine neurotransmitters and other natural products. Non-amines, a novel class of compounds that contain no amine nitrogen, block monoamine transporters in the nM range and display markedly high selectivity for monoamine transporters, but not for receptors. Non-amines retain a spectrum of biochemical and pharmacological properties characteristic of amine-bearing counterparts. Selective non-amines bind to and block the dopamine transporter with high affinity, distribute in living brain or post-mortem tissue to dopamine-rich brain regions, increase extracellular dopamine levels, and produce cocaine-like subjective effects in a drug discrimination paradigm. We produced other non-amines that displayed selectivity for the serotonin transporter. These novel drugs compel a revision of current concepts of drug-monoamine transporter complex formation and open avenues for discovery of a new generation of therapeutic drugs targeted to monoamine transporters. Inhibitors of monoamine transporters are used therapeutically to treat attention deficit hyperactivity disorder, depression, narcolepsy, Parkinson's disease, nicotine addiction, and others.

## A TRACE AMINE RECEPTOR (TAR1) IS A NOVEL AMPHETAMINE RECEPTOR IN PRIMATE BRAIN (0382)

**NPRC UNIT:** NEUROCHEMISTRY

**%NPRC $:** 0.212%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| MADRAS, BERTHA K | PHD | C | NEUROCHEMISTRY | |
| [redacted] | PHD | C | NEUROCHEMISTRY | |

**AXIS I CODES:** 1D, 2, 4, 21 **AXIS II CODES:** 50A, 50B, 59, 72, 87


### ABSTRACT

The "trace" amines (TAs) tyramine, tryptamine and beta-phenylethylamine are hypothesized to be neuromodulators, as they are dynamically and spatially regulated, packaged and released with other monoamines and altered in various brain disorders. Recently, Borowsky et al (PNAS 98:16;2001) identified a family of intronless G-protein-coupled trace amine receptors (TARs; 4 subtypes in human, 14 subtypes in rat). As human TAR1 shares only 78% amino acid similarity with rodents, and as the number of TAR subtypes between the two species differ, rodents may not serve as optimal models for TAR-mediated drug response. Genetically similar to humans, rhesus monkeys (m) are widely used to model psychostimulant drug effects and medications development. Based on an assumption that mTARs may share a greater structural similarity with human TARs, we cloned mTAR receptor subtypes from rhesus monkeys. mTAR subtypes 1 and 4 were greater than 96% homologous to human TAR1 and TAR4. Using a newly developed CRE-Luc reporter assay for this system, we demonstrate that amphetamine, MDMA (ecstasy) as well as tyramine and beta-phenylethylamine, are potent stimulators of cAMP in mTAR1 but not mTAR4-expressing HEK-293 cells. Like human but unlike mouse, we found that mTAR1 mRNA was expressed in amygdala. Our findings support the use of monkeys for clarifying a novel mechanism of action of amphetamines in the brain.

## THE TROJAN HORSE STRATEGY FOR DEVELOPING COCAINE ANTAGONISTS (0414)

**NPRC UNIT:** NEUROCHEMISTRY

**%NPRC $:** 0.212%


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| MADRAS, BERTHA K | PHD | C | NEUROCHEMISTRY | |
| | PHD | A | NUCLEAR MEDICINE | MASS GENERAL HOSPITAL, BOSTON, MA USA |
| | MD, PHD | A | RADIOLOGY | MASSACHUSETTS GENERAL HOSPITAL, BOSTON, MA USA |
| | PHD | G | NEUROCHEMISTRY | |
| | PHD | A | RADIOLOGY | MASS GENERAL HOSPITAL, BOSTON, MA USA |
| | PHD | A | | ORGANIX, INC., WOBURN, MA USA |
| | PHD | C | NEUROCHEMISTRY | |


**AXIS I CODES:** 1A, 2, 4, 21 **AXIS II CODES:** 50B, 63E, 72, 74H, 80, 87


### ABSTRACT

Inhibitors of the dopamine transporter (DAT) are candidate compounds to treat cocaine addiction. The "trojan horse", based on suicide inhibitors, is designed to function as a partial cocaine antagonist by reacting covalently with cysteine residues on the DAT. Several novel compounds partially blocked cocaine occupancy of the DAT while permitting dopamine transport. To investigate 'trojan horse' mechanisms and their therapeutic potential, in vitro assays with a mutant form of the DAT and in vivo Positron Emission Tomography (PET) were performed. To determine whether a putative cocaine antagonist reacts with a cysteine residue on the DAT, we are developing cell lines in which select cysteine residues are mutated to alanine. To monitor whether the compounds enter the brain and occupy cocaine binding sites on the DAT, PET imaging was conducted with 11C CFT to label the DAT. In pilot studies, the affinity of a candidate compound for one of the cys/ala DAT mutants was not affected acutely suggesting that other cysteine residues other mechanisms may be involved. In PET imaging, O-2729, a partial inhibitor of dopamine transport but an effective inhibitor of cocaine binding on the DAT, occupied more than 80 percent of DAT sites following pretreatment at 1 hr. DAT mutants may clarify "Trojan horse" mechanisms and PET imaging efficiently identifies compounds that merit further investigation in behavioral paradigms. The relationship between drug potencies necessary to occupy the DAT with potencies for attenuating the subjective effects of cocaine may provide guidelines for achieving an appropriate level of transporter occupancy for partial cocaine antagonist therapy. Ongoing molecular, microdialysis and behavioral studies will clarify "Trojan horse" mechanisms.

## THE TRACE AMINE RECEPTOR: A NOVEL INDIRECT TARGET OF COCAINE (0415)

**NPRC UNIT:** NEUROCHEMISTRY

**%NPRC $:** 0.212%


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| MADRAS, BERTHA K | PHD | C | NEUROCHEMISTRY | |
| = Marcus | PHD | C | NEUROCHEMISTRY | |
| | PHD | A | NEUROCHMISTRY | |


**AXIS I CODES:** 1D, 2, 4, 21 **AXIS II CODES:**36, 50B, 72, 74H, 87


### ABSTRACT

The newly reported trace amine receptors (TARs) are potential targets for drugs of abuse, including amphetamine and MDMA. We cloned full-length TAR1 and TAR4 from rhesus monkey (rh) and found each to be 96% homologous with human TAR1 and TAR4. (In contrast, the structural homology of rodent and human TAR1 is less than 80%.) The trace amines tyramine and B-phenylethylamine, and the psychostimulant drugs amphetamine and MDMA, stimulated cAMP accumulation in rhTAR1- but not rhTAR4-expressing cell lines, as measured by a CRE-luciferase assay. The functional responses of rhTAR1 support the hypothesis that this receptor is a direct target of drugs of abuse in the primate. Cocaine did not activate the TAR1 receptor. To investigate whether cocaine may indirectly activate trace amine receptors via blockade of monoamine transporters, we used a radiolabeled form the of trace amine B-Phenethylamine ([3H]B-phenylethylamine ([3H]-B-PEA) and HEK-293 cell lines expressing the human dopamine transporter (hDAT). We report for the first time that [3H]B-PEA is actively transported by the dopamine transporter. Transport of [3H]B-PEA was dose-, transporter- and temperature-dependent. Surprisingly, at equimolar concentrations of [3H]dopamine and [3H]B-PEA, the potency of (-)-cocaine for inhibiting [3H-B-PEA transport was more than 4 times higher than its potency to inhibit dopamine transport, even though the affinity (Km) of dopamine and B-PEA as substrates did not differ significantly. These findings suggest that cocaine may be an indirect target of trace amine receptors in brain, and implicate trace amines/trace amine receptors as potential contributors to the behavioral effects of cocaine. If confirmed in brain tissue, trace amine receptors may offer novel targets to develop medications to treat cocaine addiction.

# A NEW CLASS OF MONOAMINE TRANSPORT INHIBITORS: THIA ANALOGS OF TROPANES (0416)

**NPRC UNIT:** NEUROCHEMISTRY

**%NPRC $:** 0.212%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| MADRAS, BERTHA K | PHD | C | NEUROCHEMISTRY | |
| [name] | PHD | A | | ORGANIX, INC., WOBURN, MA USA |

**AXIS I CODES:** 2, 4, 21 **AXIS II CODES:** 50B, 72, 77, 87


## ABSTRACT

Diverse tropane analogs of cocaine have been widely explored as potential medications to treat cocaine addiction. We and others have reported the feasibility of designing tropane analogs with varied selectivity and potency for the dopamine (DAT), serotonin (SERT) and norepinephrine (NET) transporters. A small number of these analogs are currently undergoing advanced pharmacological evaluation. One is in a final Phase III clinical study as a diagnostic agent for assessment of the DAT. We have previously reported that the nitrogen atom present in the 3-aryltropanes is, contrary to prior expectation, not essential for the ability of 8-azabicyclo[3.2.1]octanes to bind to monoamine transporters and block transport. Replacement of the amine (8-N) for an ether (8-O) and a carba (8-CH2), retains potency and selectivity for transporters. We concluded that the molecular topology of the compounds was more important than functional groups for binding to transporter proteins. We now report further evidence in support of the importance of topology versus functionality. A new class of compounds, in which the amine nitrogen is replaced by a sulfur atom (8-thia-3-arylbicyclo[3.2.1]octanes) were synthesized and their affinities assessed in cell lines transfected with the DAT, NET SERT. Select thia compounds exhibited nanomolar potency at the DAT and 1,000-10,000-fold selectivity for DAT:SERT. Affinity for the NET varied, but several displayed high affinity for this transporter. As observed for the 8-oxa and 8-aza-tropanes, selectivity is strongly influenced by the orientation of the aryl ring at C3- of the bicyclooctane skeleton. Compounds in which the amine nitrogen is replaced by a thia can be designed to range from equipotency at DAT and SERT to substantial selectivity for the DAT. This novel class of compounds offers new opportunities for developing therapeutic agents and for modeling monoamine transporter binding domains.

## IN VITRO PATHOGENESIS OF MYCOBACTERIUM AVIUM COMPLEX (0401)

**NPRC UNIT:** PRIMATE RESOURCES

**%NPRC $:** 0.125% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| MANSFIELD, KEITH G | DVM | C | PRIMATE RESOURCES | |
| | BVSC | C | PRIMATE RESOURCES | |
| | DVM | G | COMPARATIVE PATHOLOGY | |

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

**ABSTRACT**

Mycobacterium avium complex (MAC) is the most common disseminated bacterial infection in humans infected with the human immunodeficiency virus (HIV) and has been an interest of the Division of Primate Resources for several years. Recent work in the Division has focused on the investigating the role of viral determinants in promoting mycobacterial disease. Sequencing of env clones from animals with spontaneous disseminated MAC revealed consistent changes in the predicted amino acid sequence at key positions. Recombinant viruses were constructed using these clones revealing a shift to macrophage tropism, as compared to the T-lymphocyte tropic parental strain SIVmac239, and resulting in disseminated mycobacterial disease in co-inoculation studies in macaques. Similar to animals infected with SIVmac251, cells infected with the recombinant viruses developed progressive mycobacterial infection. Intracellular cytokine staining cells indicated a decreased expression of the proinflammatory cytokines, IFN-gamma and TNF-alpha and increased expression of the Th-2-type IL-4. Marked increases in supernatant MCP-1 were detected following experimental inoculation with MAC. These findings suggest that viral determinants within env have a role in the development of progressive disseminated MAC disease during SIV infection.

## PATHOGENESIS OF GB VIRUS B (0402)

**NPRC UNIT:** PRIMATE RESOURCES

**%NPRC $:** 0.125%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| MANSFIELD, KEITH G | DVM | C | PRIMATE RESOURCES | |

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


### ABSTRACT

GB virus B is a newly recognized infectious agent and member of the flaviviridae family related to hepatitis C (30). Hepatitis C virus (HCV) is the most common blood borne pathogen recognized in the United States and the incidence and health impact of this agent is expected to increase dramatically in the next decade. HCV causes a persistent viral infection leading to chronic hepatitis and hepatocellular carcinoma. The only current animal model of HCV utilizes the chimpanzee. However, this model is faced with a number of drawbacks including ethical issues, availability and cost of housing such animals.

The GB agents are a group of closely related viruses initially recognized by investigators attempting to identify other infectious causes of non A-E hepatitis in man. GB virus A, another member of the flaviviridae family, may be found as a common asymptomatic infection of many species of New World primates. GB virus B is a hepatotropic virus that results in acute hepatitis when inoculated into new world primates. Unlike GB virus A the natural host of GB virus B is unknown. GB virus B shares overall genomic organization with HCV and 25-30% homology with the HCV polyprotein. The putative envelop proteins E1 and E2 share structural motifs with HCV and similar function and specificity have been demonstrated for the NS3 serine protease in cleaving the viral polyprotein. GB virus B inoculation of several species of New World primates results in the development of acute hepatitis and shows promise as a novel surrogate animal model of HCV infection of man.

Recently we have developed an in vitro primary hepatocyte culture system that supports the growth of GB virus B. This coupled with the availability of infectious molecular clones of the virus and the ability to infect several species of New World primates promises to foster the development of a useful animal model with which to study the pathogenesis of chronic hepatic infections caused by this group of agents. The potential to create chimeric GB virus B-HCV molecular clones may allow examination of viral determinants of virulence and persistence in a small nonhuman primate model.

## SPECIFIC PATHOGEN FREE MACAQUE BREEDING AND RESEARCH PROGRAM (0344)

**NPRC UNIT:** PRIMATE RESOURCES

**%NPRC $:** 0.125% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| SEHGAL, PRABHAT K. | BVSC | C | PRIMATE RESOURCES | |
| | PHD | C | MICROBIOLOGY | |
| C Name 7 | DVM | C | PRIMATE RESOURCES | |

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


### ABSTRACT

The NERPRC SPF program is very productive and has remained specific pathogen-free for the past nine years. All of the animals in the groups stayed pathogen free. There are currently 330 adult females and 34 adult males in the breeding harem groups. The breeding groups consist of a maximum of 10 females and 1 adult male. The breeding program at the NERPRC consists of specific pathogen free animals with Herpes B antibody negative animals only.

Regular screening of all animals both adults and juveniles for the target retroviruses is a key to maintaining and deriving SPF breeding group. Established groups are screened at least semi-annually unless more frequent testing is warranted by an unexpected clinical illness in the colony.

During 2003, approximately 1,800 individual serologic tests were performed for the presence of viral agents. Specific tests for the presence of antibodies included herpes simplex virus/herpes Be virus (HBV), simian retrovirus type D (SRV-D), STLV-1, SIV. Only antibody testing is done at the NERPRC following well established techniques. Whenever confirmatory retrovirus testing is required, we use indirect immunoflourence testing or send samples out for commercial western blot testing. Serum samples from the SPF colony are always saved and stored at -70 degrees C for future reference.

All of the SPF animals from the exterior housing have been moved to a new macaque breeding facility consisting of [ ] sq. ft. at the Southborough Campus. It was completed in June of 1999, replacing the exterior housing. The heating, ventilation and air conditioning system is controlled by a state of the art building maintenance system (BMS) that adjusts to the outside environmental conditions year round. Approximately five hundred macaques are housed in pens and individual cages, supporting harem and timed-mating practices. Pens are constructed of epoxy painted concrete block, stainless steel wire and epoxy resin floors. The animal housing areas are sanitized at 180 degrees F, by three stationary natural gas fired high pressure systems that are piped throughout the facility. Four procedure rooms and four isolation rooms support the veterinary requirements of the breeding colony on a daily basis.

## DISTINCT ROLES OF LCK AND P80 IN HERPESVIRUS SAIMIRI TIP FUNCTION (0310)

**NPRC UNIT:** TUMOR VIROLOGY

**%NPRC $:** 1.157% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| JUNG, JAE U | PHD | C | TUMOR VIROLOGY | |
| | PHD | G | TUMOR VIROLOGY | |
| | PHD | A | | KAIST, KOREA |
| | PHD | C | TUMOR VIROLOGY | |
| | PHD | G | TUMOR VIROLOGY | |
| | PHD | A | | KAIST, KOREA |

**AXIS I CODES:** 4, 7, 17 **AXIS II CODES:** 31, 60, 64, 66, 76

**ABSTRACT**

Lipid rafts are proposed to function as platforms for both receptor signaling and trafficking. Following interaction with antigenic peptides, the T cell receptor (TCR) rapidly translocates to lipid rafts, where it transmits signals and subsequently undergoes endocytosis. The Tip protein of Herpesvirus saimiri (HVS), which is a T lymphotropic tumor virus, interacts with cellular Lck tyrosine kinase and p80, a WD domain-containing endosomal protein. Interaction of Tip with p80 induces enlarged vesicles and recruits Lck and TCR complex into these vesicles for trafficking. We report here that Tip is constitutively present in lipid rafts, and that Tip interaction with p80, but not with Lck, is necessary for its efficient localization in lipid rafts. The Tip/Lck interaction was required for the recruitment of TCR complex to lipid rafts, and the Tip/p80 interaction was critical for the aggregation and internalization of lipid rafts. These results suggest the potential mechanism for Tip-mediated TCR downregulation: Tip interacts with Lck to recruit TCR complex to lipid rafts, and it subsequently interacts with p80 to initiate the aggregation and internalization of the lipid raft domain and thereby, downregulate the TCR complex. Thus, the signaling and targeting functions of HVS Tip rely on two functionally and genetically separable mechanisms.

## STRUCTURAL ANALYSIS OF THE KSHV K1 PROTEIN (0353)

**NPRC UNIT:** TUMOR VIROLOGY

**%NPRC $:** 1.157% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| JUNG, JAE U | PHD | C | TUMOR VIROLOGY | |
| | MD | A | PATHOLOGY | MASSACHUSETTS GENERAL HOSPITAL, MA USA |
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| | MD | A | PATHOLOGY | MASSACHUSETTS GENERAL HOSPITAL, MA USA |

**AXIS I CODES:** 4, 7, 17 **AXIS II CODES:** 31, 60, 64, 66, 76


### ABSTRACT

The K1 protein of Kaposi's-Sarcoma-Associated Herpesvirus (KSHV) efficiently transduces extracellular signals to elicit cellular activation events through its cytoplasmic immunoreceptor tyrosine-based activation motif (ITAM). In addition, the extracellular domain of K1 demonstrates regional homology with the immunoglobulin (Ig) family, and contains conserved regions (C1 and C2) and variable regions (V1 and V2). To generate mouse monoclonal antibodies directed against the KSHV K1 protein, BALB/c mice were primed and given boosters with K1 protein purified from mammalian cells. Twenty-eight hybridomas were tested for reactivity with K1 protein by ELISA, immunofluorescence, flow cytometry, immunohistochemistry, and immunoblotting. Deletion mutants of the K1 extracellular domain were used to map the epitope of each antibody. All antibodies were directed to the Ig, C1, and C2 regions of K1. Furthermore, antibody recognition of a short sequence (amino acids 92-125) of the C2 region overlapping with the Ig region of K1 efficiently induced intracellular free calcium mobilization; antibody recognition of the other regions of K1 did not. The efficient signal transduction of K1 induced by antibody stimulation required both the ITAM sequence of the cytoplasmic domain and also the normal structure of the extracellular domain. Finally, immunological assays showed that K1 was expressed during the early lytic cycle of viral replication in primary effusion lymphoma cells. K1 was readily detected in Multicentric Castleman's disease tissues, whereas it was not detected in Kaposi's sarcoma lesions, suggesting that K1 is preferentially expressed in lymphoid cells. Thus, these results indicate that the conserved regions, particularly the Ig and C2 regions, of the K1 extracellular domain are exposed on the outer surface and play an important role in K1 structure and signal transduction, whereas the variable regions of K1 appear to be away from the surface.

## KSHV K7 CONTROLS PROTEIN DEGRADATION (0354)

**NPRC UNIT:** TUMOR VIROLOGY

**%NPRC $:** 1.157% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| JUNG, JAE U | PHD | C | TUMOR VIROLOGY | |
| | PHD | G | TUMOR VIROLOGY | |
| | PHD | G | TUMOR VIROLOGY | |
| | PHD | G | TUMOR VIROLOGY | |
| | PHD | A | | UNIVERSITY OF MARYLAND BIOTECHNOLOGY INSTITUTE, MD USA |
| | MD, PHD | A | TUMOR VIROLOGY | |

**AXIS I CODES:** 4, 7, 17 **AXIS II CODES:** 31, 60, 64, 66, 76


### ABSTRACT

Pathogens exploit host machinery to establish an environment that favors their propagation. Due to their pivotal roles in cellular physiology, protein degradation pathways are common targets for viral proteins. Protein linking integrin-associated protein and cytoskeleton 1 (PLIC1), also called ubiquilin, contains an amino-terminal ubiquitin-like (UBL) domain and a carboxy-terminal ubiquitin-associated (UBA) domain. PLIC1 is proposed to function as a regulator of the ubiquitination complex and proteasome machinery. Kaposi's sarcoma-associated herpesvirus (KSHV) contains a small membrane protein, K7, that protects cells from apoptosis induced by various stimuli. We report here that cellular PLIC1 is a K7-interacting protein and that the central hydrophobic region of K7 and the carboxy-terminal UBA domain of PLIC1 are responsible for their interaction. Cellular PLIC1 formed a dimer and efficiently bound to polyubiquitinated proteins through its carboxy-terminal UBA domain, and this activity correlated with its ability to stabilize cellular IkappaB protein. In contrast, K7 interaction prevented PLIC1 from forming a dimer and binding to polyubiquitinated proteins, consequently leading to the rapid degradation of IkappaB. Furthermore, K7 expression promoted efficient degradation of the p53 tumor suppressor, resulting in inhibition of p53-mediated apoptosis. These results indicate that KSHV K7 targets a regulator of the ubiquitin/proteasome-mediated degradation machinery to deregulate cellular protein turnover, which potentially provides a favorable environment for viral reproduction.

## PARP-1 AND HKFC ACT AS REPRESSORS FOR GAMMA-2 HERPESVIRUS REPLICATION (0356)

**NPRC UNIT:** TUMOR VIROLOGY

**%NPRC $:** 1.157% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| JUNG, JAE U | PHD | C | TUMOR VIROLOGY | |
| | PHD | G | TUMOR VIROLOGY | |
| | PHD | A | CELL BIOLOGY | HARVARD MEDICAL SCHOOL, MA USA |
| | PHD | A | BIOLOGICAL CHEMISTRY | UC DAVIS CANCER CENTER, CA USA |
| | PHD | G | TUMOR VIROLOGY | |
| | MD, PHD | A | TUMOR VIROLOGY | |
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**AXIS I CODES:** 4, 7, 17 **AXIS II CODES:**31, 60, 64, 66, 76

**ABSTRACT**

The replication and transcription activator (RTA) of gamma-2 herpesvirus is sufficient to drive the entire viral lytic cycle. Hence, the control of RTA activity could be critical in maintaining viral latency. We found that cellular poly(ADP-ribose) polymerase-1 (PARP-1) and Ste20-like kinase hKFC interacted with the serine/threonine-rich region of gamma-2 herpesvirus RTA, and that these interactions efficiently transferred ADP-ribose and phosphate units to RTA. These modifications strongly repressed RTA-mediated transcriptional activation by inhibiting RTA recruitment onto the promoters of viral lytic genes. Conversely, the genetic ablation of RTA interactions with PARP-1 and hKFC or the knockout of PARP-1 activity significantly enhanced gamma-2 herpesviral lytic replication. This is the first demonstration that cellular PARP-1 and hKFC act as molecular sensors to regulate RTA activity and thereby, herpesviral latency.

**ACTIVATION - STAT3 TRANSCRIPTION FACTOR BY HERPESVIRUS SAIMIRI STP-A ONCOPROTEIN (0404)**

**NPRC UNIT:** TUMOR VIROLOGY

**%NPRC $:** 1.157% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| JUNG, JAE U | PHD | C | TUMOR VIROLOGY | |
| | PHD | G | TUMOR VIROLOGY | |
| | PHD | G | TUMOR VIROLOGY | |
| | PHD | G | TUMOR VIROLOGY | |
| | BS | G | TUMOR VIROLOGY | |
| | PHD | G | TUMOR VIROLOGY | |

**AXIS I CODES:** 4, 7, 17 **AXIS II CODES:** 31, 60, 64, 66, 76

**ABSTRACT**

The saimiri transforming protein (STP) oncogene of Herpesvirus saimiri subgroup A stain 11 (STP-A11) is not required for viral replication, but is required for lymphoid cell immortalization in culture and lymphoma induction in primates. We previously showed that STP-A11 interacts with cellular Src kinase through its SH2 binding motif, and that this interaction elicits Src signal transduction. Here, we demonstrate that STP-A11 interacts with signal transducer and activator of transcription 3 (Stat3) independent of Src association, and that the amino terminal short proline-rich motif of STP-A11 and the central linker region of Stat3 are necessary for their interaction. STP-A11 formed a triple complex with Src kinase and Stat3 where Src kinase phosphorylated Stat3, resulting in the nuclear localization and transcriptional activation of Stat3. Consequently, the constitutively active Stat3 induced by STP-A11 elicited cellular signal transduction, which ultimately induced cell survival and proliferation upon serum deprivation. Furthermore, this activity was strongly correlated with the induction of Fos, cyclin D1, and Bcl-XL expression. These results demonstrate that STP-A11 independently targets two important cellular signaling molecules, Src and Stat3, and both of these proteins efficiently cooperate to induce STP-A11-mediated transformation.

## MODULATION OF TCR PATHWAY BY HERPESVIRAL SIGNALING ADAPTOR (0405)

**NPRC UNIT:** TUMOR VIROLOGY

**%NPRC $:** 1.157% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| JUNG, JAE U | PHD | C | TUMOR VIROLOGY | |
| | PHD | G | TUMOR VIROLOGY | |
| | PHD | G | TUMOR VIROLOGY | |
| | PHD | G | TUMOR VIROLOGY | |
| | PHD | G | TUMOR VIROLOGY | |
| | PHD | G | TUMOR VIROLOGY | |

**AXIS I CODES:** 4, 7, 17 **AXIS II CODES:**31, 66, 76

**ABSTRACT**

Because of its central regulatory role, T cell receptor (TCR) signal transduction is a common target of viruses. We report here the identification of a small signaling protein, ORF5, of T lymphotropic tumor virus Herpesvirus saimiri (HVS). ORF5 is predicted to contain 89-91 amino acids with an amino-terminal myristoylation site and six SH2 binding motifs, showing structural similarity to cellular LAT (linker for activation of T cells). Sequence analysis showed that, despite extensive sequence variation, the myristoylation site and SH2 binding motifs were completely conserved among 13 different ORF5 isolates. Upon TCR stimulation, ORF5 was efficiently tyrosine phosphorylated and subsequently interacted with cellular SH2-containing signaling proteins Lck, Fyn, SLP-76, and p85 through its tyrosine residues. ORF5 expression resulted in the marked augmentation of TCR signal transduction activity, evidenced by increased cellular tyrosine phosphorylation, intracellular calcium mobilization, CD69 surface expression, IL-2 production, and the activation of NF-AT, NF-?B, and AP-1 transcription factors. Despite its structural similarity to cellular LAT, however, ORF5 could only partially substitute for LAT function in TCR signal transduction. These results demonstrate that HVS utilizes a novel signaling protein, ORF5, to activate TCR signal transduction. This activation probably facilitates viral gene expression and thereby, persistent infection.

# PILOT SUBPROJECTS

# ASSOCIATION OF SIMIAN VIRUS 40 AND LYMPHOMA IN SIV INFECTED RHESUS MACAQUES (0436)

**NPRC UNIT:** COMPARATIVE PATHOLOGY

**%NPRC $:** 1.420% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| KLUMPP, SHERRY A | DVM | C | COMPARATIVE PATHOLOGY | |
| | DVM | G | COMPARATIVE PATHOLOGY | |
| | DVM, PHD | C | COMPARATIVE PATHOLOGY | |
| | VMD | C | COMPARATIVE PATHOLOGY | |

**AXIS I CODES:** 1D, 7B, 19 **AXIS II CODES:** 31, 66, 76B


## ABSTRACT

Polio vaccine in the late 1950's was contaminated with simian virus 40 (SV40). Reports of SV40 infections and the occurrence of rare tumors as a result of the SV40 contaminated vaccine have been controversial. However, the evidence for a role of SV40 in the developments of these tumors in human beings is mounting. In macaques, the natural host of SV40, progressive multifocal leukoencephalomalacia (PML) and tubulointerstitial nephritis can occur due to SV40 infection. In SIV infected macaques, SV40 can also cause meningoencephalitis. Recently, SV40 has been detected by PCR in B cell lymphomas in human beings. B cell lymphomas also occur in SIV-infected macaques and the role of SV40 in the occurrence of these neoplasms is being investigated. The purpose of this study is to develop an animal model to investigate the putative role of SV40 in rare forms of human cancer. The results of this study will elucidate the oncogenic potential of SV40 in its natural host. To determine whether there is a relationship between SV40 and lymphomas in macaques, polymerase chain reaction (PCR), in situ hybridization, and immunohistochemistry will be used for detection of SV40 in lymphomas of SIV positive macaques. All procedures detect SV40's distinctive large T-antigen, or its coding genetic material, which is thought to inhibit cells' natural p53 and pRb tumor suppressor proteins. For all procedures, brain and kidney, known to be infected with SV40, and lymphomas are being tested. Preliminary data from PCR amplification for SV40 from lymphomas are negative, suggesting that SV40 does not have a role in the induction of B cell lymphomas in rhesus macaques. However, additional primers for amplification of SV40 from DNA extracted from paraffin-embedded lymphomas, and brain and kidney, known to be infected with SV40, are currently being tested.

## DO MDMA SELECTIVE EFFECTS ON TRANSPORTERS ACCOUNT FOR SELECTIVE NEUROTOXICITY? (0409)

**NPRC UNIT:** NEUROCHEMISTRY

**%NPRC $:** 0.212%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| MADRAS, BERTHA K | PHD | C | NEUROCHEMISTRY | |
| Nanda | PHD | C | NEUROCHEMISTRY | |
| | PHD | A | NEUROCHMISTRY | |

**AXIS I CODES:** 2, 4, 21 **AXIS II CODES:**36, 46, 50A, 72, 87


### ABSTRACT

3, 4-methylenedioxymethamphetamine (MDMA, ecstasy) is neurotoxic to serotonin neurons in primate brain, but effects on other monoaminergic neurons (dopamine, norepinephrine) are largely undocumented. The illicit drug also produces psychological deficits after long term use, with mechanisms poorly understood. We investigated the hypothesis that dopamine neurons are resistant to MDMA-induced toxicity because of MDMA's limited access to the intracellular milieu of dopamine neurons. As the dopamine (DAT), serotonin (SERT), and norepinephrine (NET) transporters are the conduit of entry of substrates into neurons, we examined MDMA effects in HEK-293 cell lines stably transfected with the DAT, SERT and NET, using [3H]dopamine, [3H]serotonin and [3H]norepinephrine and subsequently, with newly synthesized [3H]MDMA. Results: MDMA inhibited the transport of all three monoamines in the 100–600 nM range. The rank order of potencies, SERT (IC50: 151 nM), NET (IC50: 382 nM), DAT (IC50: 608 nM), suggested that differential toxicity of MDMA for serotonin neurons was not convincingly accounted for by this conventional method. In contrast, the affinity of [3H]MDMA as a substrate for the DAT (4341 nM) was considerably lower than its affinity for the NET (436 nM) and SERT (183 nM). The affinity of [3H]MDMA as a substrate for the DAT, NET and SERT is a more sensitive indicator of MDMA access to the cell interior via transporters than MDMA inhibition of monoamine transport. The 20-fold higher substrate affinity for the SERT compared with the DAT, may account for MDMA's selective neurotoxicity of serotonin neurons, compared with dopaminergic neurotoxicity. Based on the similar substrate affinities of MDMA for the NET and SERT, MDMA may also be neurotoxic to noradrenergic neurons in primate brain, with associated psychological sequelae bearing a noradrenergic component.

# EPHRINS, IMPLICATED IN NEURODEVELOPMENT, ARE EXPRESSED IN ADULT MONKEY BRAIN (0410)

**NPRC UNIT:** NEUROCHEMISTRY

**%NPRC $:** 0.212%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| MADRAS, BERTHA K | PHD | C | NEUROCHEMISTRY | |
| E. Nemeroff | PHD | C | NEUROCHEMISTRY | |
| | PHD | G | RESEARCH FELLOW IN PSYCHIATRY | NEUROCHEMISTRY, MA USA |

**AXIS I CODES:** 1A, 2, 21 **AXIS II CODES:** 50B, 59, 72, 74G, 80


## ABSTRACT

An ongoing goal in the Division is to investigate drug-induced neuroadaptation in brain, with a view to clarifying molecular events that correlate with progression to addiction and to reversibility of these processes. This pilot study focuses on ephrins, a family of tyrosine kinase receptors and ligands. In the developing brain, ephrins are implicated in dopamine neuron pathway development; in the adult brain, they are postulated to contribute to neuronal plasticity involved in learning, memory and to cocaine-induced neuroadaptation in rodent brain. To clarify the role of ephrins in neuroadaptative processes in adult primate brain, we initially investigated whether ephrin receptors and their ligands are expressed. In various nuclei of primate brain, we detected mRNA expression of ephrin genes ephrin-B2 (modulated by dopaminergic projection systems) and EphA4, the only receptor that cross talks with other Eph family members. EphA4 and ephrin-B2 were expressed robustly in medial and orbitofrontal cortices, hippocampus, amygdala, nucleus accumbens, thalamus, caudate/putamen, and cerebellum, and to a lesser extent in globus pallidus. EphB1 was found only in cerebellum and its ligand, ephrin-B1, was not detected in adult monkey brain. To develop an in vitro model system for detailed study of ephrin regulation, we explored ephrin family expression in a neuroblastoma cell line, SK-N-MC which endogenously expresses the D1 dopamine receptor. EphA4 was detected in this cell line, but not ephrin-B2, EphB2 and EphB1. The discovery that ephrins and their receptors are expressed in monkey brain indicates the feasibility of investigating cocaine-mediated modulation of ephrin family members. Based on the discovery of EphA4 receptor mRNA (and others) in adult monkey brain and in SK-N-MC cell lines, we are exploring dopamine and cocaine-induced modulation of ephrins in primates.

## MOLECULAR TARGETS OF THE ANTI-NARCOLEPTIC DRUG MODAFINIL (0411)

**NPRC UNIT:** NEUROCHEMISTRY

**%NPRC $:** 0.212%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| MADRAS, BERTHA K | PHD | C | NEUROCHEMISTRY | |
| | PHD | A | NUCLEAR MEDICINE | MASS GENERAL HOSPITAL, BOSTON, MA USA |
| Name? | MD, PHD | A | RADIOLOGY | MASSACHUSETTS GENERAL HOSPITAL, BOSTON, MA USA |
| | PHD | A | RADIOLOGY | MASS GENERAL HOSPITAL, BOSTON, MA USA |
| | MD, PHD | A | PSYCHIATRY | CASE WESTERN RESERVE UNIVERSITY, OH USA |

**AXIS I CODES:** 1A, 2, 4, 21 **AXIS II CODES:** 36, 50B, 63E, 72, 80, 87


### ABSTRACT

The novel stimulant medication modafinil enhances vigilance and wakefulness. It is widely used to treat narcolepsy and has been tested as adjunct therapy for depression and chronic fatigue syndrome. This psychostimulant profile implicates dopamine, glutamate, and orexin systems in the brain, but in human drug discrimination studies, modafinil does not generalize to the psychostimulant cocaine, and in rodents, modafinil-induced locomotor activity is not antagonized by dopamine receptor antagonists. In the absence of definitive evidence for the mechanisms of action of modafinil, we investigated pre-synaptic dopamine systems as potential targets of modafinil. Our preliminary conclusion is that modafinil does not produce stimulation by targeting the dopamine transporter. A ongoing receptor screen of modafinil may reveal novel targets. In contrast to amphetamine stimulants, the intriguing pharmacological profile of modafinil suggests the feasibility of producing drugs that enhance alertness and wakefulness, but with reduced abuse liability.

# AN OPIOID RECEPTOR SNP: RELEVANCE TO STRESS RESPONSE AND AGGRESSION IN MONKEYS (0412)

**NPRC UNIT:** NEUROCHEMISTRY

**%NPRC $:** 0.212%


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| MADRAS, BERTHA K | PHD | C | NEUROCHEMISTRY | |
| | PHD | C | NEUROCHEMISTRY | |
| | PHD | A | PSYCHOLOGY | UNIVERSITY OF MASSACHUSETTS, AMHERST, MA USA |
| | PHD | G | BEHAVIORAL BIOLOGY | |


**AXIS I CODES:** 1A, 1D, 2, 4, 21 **AXIS II CODES:** 36, 58, 59, 72, 74E, 74H, 77, 87


## ABSTRACT

Variations in the human mu-opioid receptor gene are implicated in biochemical, physiological and pathological conditions. We investigated the presence of variations in the nonhuman primate mu-opioid receptor gene to determine whether nonhuman primates can model genotype/phenotype associations of relevance to humans. Similar to the A118G single nucleotide polymorphism (SNP) in the human mu-opioid receptor gene, a SNP discovered in the rhesus monkey mu-opioid receptor gene (C77G) alters an amino acid in the N-terminal arm of the receptor (arginine for proline at position 26). To determine the function of the SNP, we isolated two mu-opioid receptor coding regions from rhesus monkey brain with different SNPs, expressed and characterized them in HEK-293 cells. In parallel with a report of increased beta-endorphin affinity by the A118G SNP in the human (Bond et al, Proc Natl Acad Sci U S A 95:9608-13, 1998), the rhesus monkey mu-opioid receptor protein from a G77-containing allele demonstrated a 3.5-fold greater affinity for beta-endorphin than the receptor derived from the C77-containing allele. The incidence of the C77G SNP in a behaviorally and physiologically characterized cohort of rhesus monkeys (n=32) was 44% homozygous for C77-containing alleles, 50% heterozygous, and 6% homozygous for G77-containing alleles. The presence of G77-containing alleles was associated with significantly lower basal and ACTH-stimulated plasma cortisol levels (p less than 0.03-0.05 and p less than0.02, respectively) and a significantly higher aggressive threat score (p less than 0.05) in vivo. In twenty monkeys, a trend towards an inverse correlation between aggressive threat and plasma cortisol levels was observed. Discussion: The mu-opioid receptor haplotypes in monkeys may contribute to individual variability in stress response and related aggression. The data support the use of nonhuman primates to investigate mu-opioid receptor genotype/phenotype relationships of relevance to humans.

# COLLABORATIVE SUBPROJECTS

## SIV DNA VACCINES AND MUCOSAL IMMUNITY (0240)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505% **AIDS RELATED RESEARCH**


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| ALDOVINI, ANNA | MD | A | PEDIATRICS | CHILDREN'S HOSPITAL , MA USA |


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


**ABSTRACT**

Transmission of HIV infection occurs predominately via mucosal routes. The ability of vaccines to induce mucosal immunity may be required for protection against HIV infection or AIDS. We have investigated the immunostimulatory properties of a DNA vaccine that produces genetically inactivated SHIV particles, similar to the wild type virus in protein content but not infectious because a total of 22 mutations in three different proteins (NC, RT, IN). To evaluate the induction of SHIV specific immunity, 5 groups of Rhesus macaques were vaccinated with the SHIV DNA at time 0, 2 and 6 months with the SHIV construct at the rectal mucosa, or nasally. Two groups of animals vaccinated nasally also received at the same site DNA expressing IL-2 or IL12. MVA expressing Gag, Pol and Env was administered rectally (one group) or nasally (all groups) 2 months after the last DNA vaccination. SHIV specific immune responses were evaluated during the vaccination protocol. SHIV-specific IgA were detected sporadically in secretions after DNA alone vaccination. When viral DNA was administered together with IL-2 or IL-12 DNA, SHIV-specific IgA were detected earlier and more consistently among animals. SHIV specific IgG responses were present systemically in some of the groups and were boosted by the mucosal administration of rMVA. Cell mediated immune responses were found both at mucosal sites and systemically, in particular when the vaccination was boosted by MVA or occurred at the nasal mucosa. The nasal route of vaccination stimulated surprisingly strong Env-specific cellular responses. These responses were present systemically and were higher than the Gag responses, which were of the same order of magnitude of those observed by others with a DNA-adenovirus vaccination regime. After rectal challenge with cloned SHIV89.6P, all animals became infected but significant control of viremia was observed in the animals in which systemic cellular responses had been detected. The data indicate that mucosal administration of a DNA vaccine can significantly stimulate both mucosal and systemic humoral and cell-mediated responses, in particular when administered nasally. However, the efficacy of the mucosal responses cannot be evaluated in these animal trials because of the extremely high amounts of virus used for the challenge and needs to be evaluated after natural virus exposure, when the virus inoculum is relatively small.

## PREFRONTAL ANATOMIC PATHWAYS IN EXECUTIVE CONTROL (0242)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| BARBAS, HELEN | PHD | A | HEALTH SCIENCES | BOSTON U, MA USA |

**AXIS I CODES:** 1A, 21 **AXIS II CODES:**41, 63C, 72, 86

**ABSTRACT**

The goal of our research project is to investigate the organization and synaptology of efferent pathways from prefrontal cortices to superior temporal auditory association areas. Our working hypothesis is that functionally distinct prefrontal areas exert varied excitatory and inhibitory effects through distinct patterns of termination on pyramidal neurons and inhibitory interneurons in temporal cortices. Our plan is to analyze the pattern of termination of axons from prefrontal cortices in distinct superior temporal cortices, to study their relationship to local inhibitory interneurons at the light microscopic level, and their synaptology at the electron microscopic (EM) level.

One of our goals during the past year was to determine if functionally distinct prefrontal cortices terminate in different layers of temporal cortices, and if a given prefrontal area has a different pattern of termination in distinct temporal cortices. We addressed this issue by investigating the extent and pattern of termination of projections from the functionally distinct areas 32 and 10 within specific superior temporal cortices.

Area 32 is part of the limbic component of the medial prefrontal cortex, associated with emotional communication and emotional expression (Barbas et al, 2003). Area 10, on the other hand, is involved in specific aspects of working memory (for review see Barbas et al, 2002). Our findings showed that these functionally distinct prefrontal areas have some overlapping projections on auditory association areas, but also show important differences suggesting functional divergence in these circuits. Projections from area 10 terminated in posterior sectors of auditory association cortex, targeting predominantly layer I, suggesting a predominant mode in feedback communication. The specific projections from area 10 may have a role in the selection of information to guide behavior in specific working memory tasks. In contrast, area 32 appears to influence anterior temporal areas, through "feedforward" projections targeting the deep layers. The specific projection to the deep layers of the temporal pole may have a role in emotional communication associated with these interconnected areas. The involvement of area 32 in emotions was further demonstrated by its robust descending projections and synaptic interactions with hypothalamic autonomic centers, which have a role in emotional expression.

In another study we addressed the more global on pathways associated with emotional processing. Experiencing emotions engages high order orbitofrontal and medial prefrontal areas, and expressing emotions involves low level autonomic structures and peripheral organs. How is information from the cortex transmitted to the periphery? We used two parallel approaches to map simultaneously multiple pathways to determine if hypothalamic autonomic centers are a key link for orbitofrontal areas and medial prefrontal areas, which have been associated with emotional processes, as well as low level spinal and brainstem autonomic structures. The latter innervate peripheral autonomic organs (such as the lungs and the heart), whose activity is markedly increased during emotional arousal. We first determined if pathways linking the orbitofrontal cortex with the hypothalamus overlapped with projection neurons directed to the intermediolateral column of the spinal cord, with the aid of bidirectional tracers injected in these disparate structures. We found that axons from orbitofrontal and medial prefrontal cortices converged in the hypothalamus with neurons projecting to brainstem and spinal autonomic centers, linking the highest with the lowest levels of the neuraxis. Using a parallel approach, we injected bidirectional tracers in the lateral hypothalamic area, an autonomic center, to label simultaneously cortical pathways leading to the hypothalamus, as well as hypothalamic axons projecting to low level brainstem and spinal autonomic centers. We found densely distributed projection neurons in medial prefrontal and orbitofrontal cortices leading to the hypothalamus, as well as hypothalamic axonal terminations in several brainstem structures and the intermediolateral column of the spinal cord, all of

## ORGANIZATION OF PREFRONTAL FEEDBACK CIRCUITS (0244)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505%


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| BARBAS, HELEN | PHD | A | HEALTH SCIENCES | BOSTON U, MA USA |


**AXIS I CODES:** 1A, 21 **AXIS II CODES:** 41, 63C, 72, 86


**ABSTRACT**

The goal of our research project is to investigate feedback connections issued from functionally distinct limbic and eulaminate prefrontal cortices to specific thalamic and amygdaloid nuclei. Our overarching hypothesis is that pathways linking these structures have specific roles in memory, emotion and cognition.

We continued our investigation on the organization of input and output zones linking prefrontal cortices with the amygdala. The strongest connections of the amygdala were with caudal medial and caudal orbitofrontal cortices. Overall, all prefrontal areas received projections from the amygdala, whereas reciprocal projections originated mainly from caudal medial and caudal orbitofrontal cortices. Prefrontal input and output zones connected with the amygdala were partially separate in the prefrontal cortices both by area and layers. Thus, projection neurons directed to the amygdala originated mainly from layer 5 in all areas, and to a lesser extent from layers 2 and 3, the latter noted specifically in medial areas 24, 25 and orbitofrontal area OPro. In the reciprocal direction, axons from the amygdala terminated in all layers of the prefrontal cortex, but their density within layers varied widely. The most common pattern of axonal terminations was bilaminar, innervating most heavily layers 1- 2 and 5-6. Quantitative analysis using stereologic procedures revealed that in areas with the densest innervation, such as the caudal orbitofrontal and caudal medial prefrontal areas, axonal terminations assumed a columnar pattern, including substantial innervation of the middle layers.

Cognitive functions associated with lateral prefrontal cortices likely are influenced by input from the amygdala, as noted in our study. Our findings also suggest that lateral prefrontal areas issue limited, if any, feedback projections to the amygdala. In contrast, medial and orbitofrontal cortices, which seem to serve as monitors and integrators of affective, reward, and conflict in the environment, interact with the amygdala in a bidirectional manner, issuing and receiving both feedforward and feedback projections. Bidirectional pathways, may prolong activity until appropriate cognitive responses can be abstracted and relayed for expression.

which innervate peripheral autonomic organs. We then provided direct evidence that axons from medial prefrontal cortex synapse with hypothalamic neurons, terminating as large boutons, comparable in size to the highly efficient thalamocortical system. The direct pathway from medial area 32 avoided inhibitory interneurons, and formed asymmetric, and presumed excitatory synapses, targeting preferentially spines in the hypothalamus, which are enriched on dendrites of excitatory neurons. The interlinked orbitofrontal, medial prefrontal areas, and hypothalamic autonomic centers were also connected with the amygdala. These pathways provide the means for speedy influence of the prefrontal cortex on the autonomic system, in processes underlying appreciation and expression of emotions (Barbas et al, 2003).

## PRECLINICAL EVALUATION OF INTRA-ARTERIAL ONCOLYTIC VIRUS IN PRIMATES (0385)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| CHIOCCA, ENNIO ANTONIO | MD, PHD | A | SURGERY | MASSACHUSETTS GENERAL HOSPITAL, MA USA |
| Name | MD | A | SURGERY | MASSACHUSETTS GENERAL HOSPITAL, MA USA |
| | MD | A | SURGERY | MASSACHUSETTS GENERAL HOSPITAL, MA USA |

**AXIS I CODES:** 1A, 1D, 7B, 21 **AXIS II CODES:**39, 55, 64, 76B, 77, 86

### ABSTRACT

Background: In this project, a preclinical study of intra-arterial injection of G207, a tumor-specific HSV1 mutant, with or without immunosuppression by cyclophosphamide is being carried out. Evidence for clinical and histologic toxicity is being sought. Tissues form euthanized animals and body fluids are being collected.

Results from the study will be submitted to the FDA in preparation for a phase I clinical trial of intra-arterial injection of G207 in patients suffering from intractable, recurrent malignant glioma.

# A HISTOLOGICAL EVALUATION OF A NEW ADHESIVE/COMPOSITE RESTORATIVE SYSTEM (0250)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505%


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| DOGON, I LEON | DMD | A | RST DENT & BIOMATERIALS | HARVARD SCHOOL OF DENTAL MEDICINE, MA USA |


**AXIS I CODES:** 1A, 2, 22 **AXIS II CODES:**50, 86


## ABSTRACT

Polymerization shrinkage and microleakage are among the major factors for composite material failures in the oral environment. Materials which remain dimensionally stable on polymerization, coupled with an advanced bonding to the enamel and dentin will markedly enhance the stability of the restoration under functional stress. OBJECTIVES: The purpose of this investigation is to evaluate the biological response of an experimental material ) exhibiting reduced polymerization shrinkage used with a compatible adhesive METHODS: Class V cavities were prepared in M. fascicularis. The experimental system was compared to the Single Bond/Z100 Restorative System The materials were randomly placed in the teeth and the outcome observed so that the dwell time of the materials was 7 and 63 days. The teeth were histologically prepared by recognized methods and examined in a double-blind study. RESULTS: Significant pathology was seen only in the specimen that exhibited pulp exposure during placement. A total of 5 exposures were observed. The range of thickness of the dentin in the remaining 49 teeth which was measured along the dentinal tubules to the deepest portion of the pulp was 0.12mm's to 1.79mm's. Twelve specimen of the experimental material at 7 days exhibited no pulpal reaction and 4 a slight reaction. All 8 specimen of SB/Z100 demonstrated no reaction. At 63 days 10 of the 13 specimen with the experimental material showed no reaction and 3 a slight reaction. The control material exhibited 5 no reaction specimen and 7 with a slight reaction. CONCLUSIONS: No significant differences were observed between the two restorative material systems.


$ = Private Funding

# MR SPECTROSCOPY OF BRAIN IN THE SIV INFECTED MACAQUE (0252)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.852% **AIDS RELATED RESEARCH**


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| GONZALEZ, R. GILBERTO | MD, PHD | A | RADIOLOGY | MASSACHUSETTS GENERAL HOSPITAL, MA-USA |
| | PHD | A | RADIOLOGY | MASSACHUSETTS GENERAL HOSPITAL, MA USA |
| | PHD | A | RADIOLOGY | MASSACHUSETTS GENERAL HOSPITAL, MA USA |
| | PHD | A | RADIOLOGY | MASSACHUSETTS GENERAL HOSPITAL, MA USA |
| | BVSC | C | PRIMATE RESOURCES | |
| | VMD | C | COMPARATIVE PATHOLOGY | |


**AXIS I CODES:** 1A, 21 **AXIS II CODES:** 31, 63C, 63D, 63F


## ABSTRACT

Our goals are to elucidate the pathways that lead to cerebral injury by HIV infection, and to develop a rapid model for testing therapies. Neuroinvasion occurs soon after infection and 30-40% of those infected with HIV develop AIDS dementia complex (ADC). There is evidence of more pronounced neuronal injury in brains with HIVE than in HIV infected individuals without encephalitis. Utilizing Magnetic Resonance Spectroscopy we study neurochemical changes in vivo before and after infection in the SIV model.

Macaques with SIVE have less NAA (a spectroscopic neuronal marker) than macaques without encephalitis and controls. Last year after infecting 4 macaques with SIVmac251, depleted them of CD8+ lymphocytes, we found they rapidly developed SIVE and had profound decreases in NAA/Cr in frontal cortex. This year four monkeys were also infected with SIV, CD8+ depleted, but at 4 weeks post infection HAART therapy was begun. By 4 weeks post infection NAA/Cr ratios decreased with a mean decline of 10% (Holm's t-test, $p=0.007$) from those of pre-infection. MR spectroscopy revealed reversal of the NAA/Cr decline in all animals after initiation of HAART. After 4 weeks of daily HAART, NAA/Cr ratios increased with a mean of 8% (Holm's t-test, p less than 0.03). Pathology confirmed no signs of SIVE existed in these macaques. A significant relationship was observed between NAA/Cr and plasma viral load during disease progression for all macaques. HPLC analysis for the HAART (RCV & PMPA) metabolites in plasma and CSF before and during treatment failed to detect RCV metabolites in the CSF. This data indicates control of the virus in the periphery has a direct and almost immediate effect on the health of the neurons in the CNS.

We have validated the use of the CD8+ depletion model as a rapid means of evaluating drug therapies proposed for the neurocognitive abnormalities produced by HIV infection. In the future we intend to study other suspected neuroprotective reagents.

## IMPACT OF MICRONUTRIENTS OF PROGRESSION OF SIV (0254)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505% **AIDS RELATED RESEARCH**


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| GORBACH, SHERWOOD L | MD | A | FAM MED & COM HLTH | TUFTS U SCH MED, MA USA |
| | DVM, PHD | A | CLINICAL SCIENCES | TUFTS U SCH MED, MA USA |
| | PHD | A | FAM MED AND COMM HLTH | TUFTS UNIVERSITY SCHOOL OF MEDICINE, MA USA |
| | DVM | C | PRIMATE RESOURCES | |
| | DSC | A | FAMILY MED & COM HLTH | TUFTS U SCHOOL OF MED, MA USA |


**AXIS I CODES:** 1A, 2, 7C, 15 **AXIS II CODES:** 31, 60, 66, 74A, 74F, 78


### ABSTRACT

Studies in patients with HIV have revealed that serum micronutrient levels are often below normal levels, particularly for vitamins A, B12 and E and selenium. Some studies have correlated low micronutrient levels with more rapid progression of HIV-related diseases. Intervention trials with micronutrients are difficult to carry out in humans for many reasons, both practical and ethical. Other studies have documented the effects of antiretroviral treatments on changes in body composition, glucose metabolism and lipid metabolism. The Simian Immunodeficiency Virus (SIV) produces an infection in rhesus macaques that is remarkably similar to that caused by HIV in humans and provides an ideal model to examine the potential benefit of micronutrient supplementation and antiretroviral intervention. The current study is designed to examine the effects of supplementation with micronutrients on the progression of SIV infection by measuring changes in body composition using somatometrics, abdominal ultrasound and DEXA, serum micronutrients, viral load, CD4 cell counts and by monitoring the development of opportunistic infections. In addition, data are also being collected on a group of animals currently maintained on a Western diet that will be treated with antiretrovirals and followed for changes in fat and glucose metabolism. These animals will undergo glucose tolerance tests before and after antiretroviral administration. Data from these tests are pending. Thus far, supplementation with micronutrients has had no significant impact on viral load, CD4 counts or body composition. Three phases of alterations in body composition were observed in all animals after SIV infection: an acute phase during which there was loss of body weight primarily from fat, a compensation period during which animals grew at a reduced rate and a terminal phase during which there was wasting of all tissues. Further study is required to determine whether changes in diet will affect the changes in body composition observed in the first round of observations.

## OBESITY, DIABETES, AND AGING ANIMAL RESOURCE (0328)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| HANSEN, BARBARA C | PHD | A | PHYSIOLOGY, SOM | UNIVERSITY OF MARYLAND, MD USA |
| C name | PHD | A | PHYSIOLOGY, SOM | UNIVERSITY OF MARYLAND, MD USA |

**AXIS I CODES:** 1A, 2 **AXIS II CODES:** 49, 78

**ABSTRACT**

The Obesity, Diabetes and Aging Animal Resource at the University of Maryland, Baltimore, has been established by the National Institute on Aging for the purpose of providing broad access to an invaluable aging primate model of spontaneous obesity and diabetes. Virtually all aspects of aging, obesity, and Type 2 diabetes in adult rhesus monkeys have been found to be similar to these disorders in humans.

Our aim is to examine the pathophysiology of obesity, Type 2 diabetes mellitus, and aging and to gain insight into the natural history, mechanisms of development and effective therapy of these disorders. Related disorders including hyperinsulinemia, insulin resistance, hypertension, dyslipidemia, glucose intolerance, and clusters of these disorders including metabolic syndrome X and renal and eye disease are also under intense study. A unique advantage of the primates in the ODAAR colony is our large and detailed database, which has been compiled over the lifespan of these aging monkeys. Therefore, these primates provide an invaluable opportunity to study these metabolic conditions and to focus on those scientific questions which cannot be readily asked in humans.

Our current studies in these unique primates include interventional protocols such calorie restriction, weight reduction, and the application of newly developed pharmaceutical compounds showing promise of therapeutic benefit. We utilize molecular, biochemical, and metabolic/physiological approaches in order to achieve a greater understanding of the related disease mechanisms. Our primary goal is to combine the highest level of primate care and husbandry with excellence in research and science.

## CONCEPTUAL KNOWLEDGE AND PERCEPTION IN TAMARINS AND MARMOSETS (0448)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| HAUSER, MARC D | PHD | A | PSYCHOLOGY | HARVARD MEDICAL SCHOOL, MA USA |

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

**ABSTRACT**

Our work over the last two years has focused on the nature of conceptual representation and acoustic perception in tamarins, and more recently marmosets. We use non-invasive behavioral techniques to understand such problems as: 1) the nature and format of number representation and quantification, 2) the conceptual representations underlying tool use, 3) the acoustic morphology of their vocal repertoires and the features used in call perception, 4) the mechanisms underlying language processing and the extent to which they are shared with humans and other species. In addition, this year we plan on extending our work to look at brain function, using non-invasive neuroimaging techniques. This work will be done in collaboration with researchers at MIT.

# INDUCTION OF TOLERANCE IN MACAQUES W/GENETICALLY ALTERED AUTOLOGOUS BONE MARROW (0437)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505%


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| IACOMINI, JOHN J | PHD | A | SURGERY | MASSACHUSETTS GENERAL, MA USA |
| C | | A | SURGERY | MASSACHUSETTS GENERAL HOSPITAL, MA USA |
| Names | MD | A | SURGERY | MASS GENERAL HOSPITAL, MA USA |
| J. | MD | A | SURGERY | MASSACHUSETTS GENERAL HOSPITAL, MA USA |


**AXIS I CODES:** 1A, 1D **AXIS II CODES:** 55, 88

## ABSTRACT


Humoral rejection mediated by xenoreactive natural antibodies (XNA) that bind the carbohydrate epitope Galalpha1-3Galbeta1-4GlcNAc-R (alphaGal) (1-3) remains the major immunological barrier to pig to human xenotransplantation. While there has been remarkable progress in modifying pig tissues through trangenesis and modifying the host to temporarily remove XNA, the major obstacle to discordant xenotransplantation remains DXR mediated by alphaGal XNA. The induction of specific tolerance to alphaGal is the most promising way to overcome humoral rejection of xenotransplants mediated by XNA, without the need for immunosuppression. Somatic transfer of a functional gene encoding the glucosyltranferase UDP galactose: beta-D-galactosyl-1,4-N-acetyl-D-glucosaminide alpha(1-3)galactosyltranferase (E.C. 2.4.1.151, hereafter referred to as alphaGT) into autologous BM using retroviral transduction represents a new approach to the induction of such specific tolerance. This approach involves introducing a functional alphaGT gene by retroviral gene transfer into autologous BM hematopoietic progenitors to establish molecular rather than cellular chimerism. The retrovirally transduced alphaGT gene synthesizes alphaGal epitopes that are expressed on the surface of the BM derived cells or secreted proteins that in turn can tolerize B cells that produce alphaGal reactive antibodies. Using the alphaGT knockout mouse model, we have shown that expression of a retrovirally transduced alphaGT gene in BM derived cells induces stable long-term tolerance to the alphaGal epitope in host that are otherwise immunocompetent. The focus of this proposal is to examine whether a similar approach could be used to tolerize B cells producing alphaGal XNA in primates.

**BRAIN REPAIR STUDIES OF PD MODELS BY NEUROSURGICAL, PET AND MRI/MRS METHODS (0260)**

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| ISACSON, OLE | DMSC, PHD | A | NEUROLOGY | MCLEAN HOSP, MA USA |
| [illegible] | PHD | A | RADIOLOGY | MASSACHUSETTS GENERAL HOSPITAL, MA USA |
| Namba | MD, PHD | A | PSYCHIATRY | MCLEAN HOSPITAL, MA USA |
| [illegible] | MD, PHD | A | SURGERY | BRIGHAM & WOMEN'S HOSPITAL, MA USA |

**AXIS I CODES:** 1A, 2, 9, 21 **AXIS II CODES:** 36, 46, 50B, 63A, 63C, 63E

**ABSTRACT**

We propose to develop new functional diagnostics and treatments for Parkinson's disease (PD) from pre-clinical experiments in rat and primate models of neurotoxically induced PD. Given that (1) dopamine (DA) neurons die and a stable PD-like behavioral syndrome appears in primates after chronic administration of a neurotoxin: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), (2) loss of dopaminergic axon can be diagnostically detected by positron emission tomography (PET) and ligands to label striatal DA reuptake sites, (3) neural transplantation may replace neurotoxically eliminated neurons and reverse PD-like symptoms and drug induced side effects, we will now determine how implanted fetal porcine neural DA and control non-DA cells can repair neural systems and reverse behavioral deficits. Pallidotomy is tested as a parallel therapeutic method. We will measure DA receptors and cerebral oxidative glucose metabolism by PET and neuroanatomy, hemodynamics, levels and profiles of brain tissue neurochemicals by MRI/MRS in rodent and primate animal models. The data-sets from PET and MRI/MRS are correlated with behavioral and post-mortem studies. This project develops 1) objective in vivo measurements of brain damage associated with neurotoxins and 2) therapies for neurotoxically induced PD.

## TRANSGENIC XENOGRAFTS FOR HUNTINGTON'S DISEASE (0261)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505%


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| ISACSON, OLE | DMSC, PHD | A | NEUROLOGY | MCLEAN HOSP, MA USA |
| | MD, PHD | A | PSYCHIATRY | MCLEAN HOSPITAL, MA USA |
| Name | MD, PHD | A | SURGERY | BRIGHAM & WOMEN'S HOSPITAL, MA USA |
| | MD, PHD | A | PSYCHIATRY | MCCLEAN HOSPITAL, MA USA |


**AXIS I CODES:** 1A, 2, 9, 21 **AXIS II CODES:** 36, 46, 50B, 63A, 63C, 63E


**ABSTRACT**

Brain cell transplantation research has shown that structural and functional repair of the adult brain is possible. We are testing the functional hypothesis that embryonic striatal neurons can replace neurons lost in adult primate striatum and improve signs of Huntington's disease (HD). The lack of an optimal human donor cell source in a clinical scenario has led us to utilize xenogeneic (here transgenic pig) embryonic donor cells. Our preliminary in vivo data show that successful xenograft survival in the primate brain requires immunosuppression by cyclosporine, azathioprine, methylprednisolone and complement inhibition (CD59 transgenic donor tissue and monoclonal antibodies against complement C5).

To test the functional hypothesis, we propose the following experiments:

We will transplant CD59 complement aggregation inhibitor expressing transgenic porcine fetal striatal (E35 LGE) cells to the caudate-putamen of a non-human primate (Macaca mulatta) with neuronal loss similar to that seen in HD. To determine how functional recovery depends on survival and growth of porcine striatal transplants, we will collect physiological in vivo data by PET/MRI/MRS and behavioral data by examining motor and cognitive function. The physiological analysis of LGE graft function by in vivo imaging and behavioral assays is followed by detailed morphological studies. Combined, these studies will provide essential data on the relationship between structural and functional integration of embryonic neuronal xenografts in a HD primate model. These experiments will improve our knowledge of basal ganglia function and plasticity, as well as determine parameters for optimal cell transplantation in patients with neurological disease

## NOVEL THERAPEUTIC APPROACHES FOR PD (0263)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| ISACSON, OLE | DMSC, PHD | A | NEUROLOGY | MCLEAN HOSP, MA USA |
| C | MD, PHD | A | PSYCHIATRY | MCLEAN HOSPITAL, MA USA |
| Nanlo | MD, PHD | A | SURGERY | BRIGHAM & WOMEN'S HOSPITAL, MA USA |
| J | MD, PHD | A | PSYCHIATRY | MCCLEAN HOSPITAL, MA USA |

**AXIS I CODES:** 1A, 2, 9; 21 **AXIS II CODES:**36, 46, 50B, 63A, 63C, 63E


### ABSTRACT

There are compelling research opportunities for Parkinson's disease PD) therapies. While L-dopa provides an initial relief, there is a need for alternative strategies to deal with the continued loss of dopaminergic (DA) neurons, axons and terminals. We have a functional collaborative scientific group centered at McLean Hospital, Harvard Primate Center and Massachusetts General Hospital that can investigate neuroprotective, neuromodulatory and neural transplantation approaches for PD. We will use animal models, including MPTP-treated primates with loss of dopamine cells, synapses and function. This work is synergistically linked in four projects: Project 1. A neurophilin ligand induced prevention of dopaminergic degeneration induced by MPTP in the primate. Two paradigms are tested; a) neuroprotection by a neurophilin ligand to reduce the loss of dopamine terminals and b) a regeneration paradigm with post neurophilin ligand treatment to regenerate remaining DA terminals. Project 2. We will test neuronal replacement by fetal dopamine cells into the striatum, the subthalamic nucleus and the substantia nigra in a primate model of PD. We hypothesize that a full reinnervation with novel dopaminergic fibers in these regions will fully restore the dysfunctional circuitry responsible for PD. Project 3. By generating dopaminergic neurons from blastula stage stem cells, we can obtain renewable cells to be transplanted for functional tests into animal models of parkinsonism. These stem cell derived dopaminergic neurons will be compared in function to those derived from phenotypically normal embryonic fetal cells. These projects are supported by 2 Cores that further integrate these projects; namely, an Administrative Core that supports the research teams involved, and the Imaging Core involving functional MRI and PET scans and analysis.

In summary, we feel this compelling research collaboration on novel realistic approaches to PD treatment is of exceptional value. The allocation of these resources will test major scientific hypotheses in protecting, repairing or replacing the dopaminergic system responsible for the signs of PD.

## NOVEL ANTI-INFLAMMATORY THERAPIES FOR PD (0264)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| ISACSON, OLE | DMSC, PHD | A | NEUROLOGY | MCLEAN HOSP, MA USA |
| | PHD | A | RADIOLOGY | MASSACHUSETTS GENERAL HOSPITAL, MA USA |
| | MD | A | HUMAN RETROVIRUS SECTION | NCI, MD USA |
| | MD, PHD | A | PSYCHIATRY | MCLEAN HOSPITAL, MA USA |
| | MD, PHD | A | PSYCHIATRY | MCCLEAN HOSPITAL, MA USA |

**AXIS I CODES:** 1A, 2, 9, 21 **AXIS II CODES:** 36, 46, 50B, 63A, 63C, 63E


### ABSTRACT

A recent large Parkinson's disease (PD) twin study indicates that environmental and toxic factors play major roles in causing typical PD (Tanner et al. JAMA, 1999). Interestingly, neuroinflammation seen in the caudate-putamen is a part of the pathophysiology (Brooks, 1999). The progressive decline of dopamine (DA) terminals seen in idiopathic PD can be closely modeled in Macaca fascicularis by low-dose exposure to the mitochondrial toxin, MPTP, over nine to fourteen months. We demonstrated by PET imaging of DA terminal and MRS that such primates provide a physiological chart of degeneration and appearance of PD signs (Brownell et al., Nat. Med., 1998). This data profile enables the design of an experimental paradigm for realistically determining toxicity, neuroinflammation and neuroprotection in idiopathic PD.

In this project using the PD primate model, we now propose to examine neuroprotection of the dopaminergic system by anti-inflammatory agents. Based on several studies, we hypothesize that a cyclooxygenase (COX) 1 and 2 inhibitor (indomethecin [1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1-H-indole-3-acetic acid]) can decrease inflammatory reactions caused by MPP+ toxicity and also reduce chronic neurodegenerative processes. In the non-human primate, a slow progressive lesion of the nigro-striatal dopaminergic system follows repeated MPTP treatment. Using PET scanning with a receptor ligand for the peripheral benzodiazepine receptor site (11C-PK11195), our preliminary experiments indicate that we can visualize the neuroinflammatory reactions during CNS DA degeneration (as determined by 11C-CFT). These measurements will be combined with MRI and MRS studies of lactate and choline as in vivo biomarkers for the glial inflammatory and toxic responses of the nigrostriatal system. As a therapy, during and after neurotoxic exposure to MPTP, we will treat the PD primates with a COX 1 and 2 inhibitor to evaluate anti-inflammatory prevention of onset and continued degeneration. Protection of the dopaminergic system by anti-inflammatory agents would be of tremendous therapeutic value for Parkinson disease.

## THE USE OF EMBRYONIC PRIMATE STEM CELLS IN PARKINSON'S DISEASE MODELS (0438)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| ISACSON, OLE | DMSC, PHD | A | NEUROLOGY | MCLEAN HOSP, MA USA |
| | MD, PHD | A | PSYCHIATRY | MCLEAN HOSPITAL, MA USA |
| | PHD | C | BEHAVIORAL BIOLOGY | |
| | MD, PHD | A | DEVELOPMENTAL BIOLOGY | MSKCC, NY USA |
| | MD, PHD | A | PSYCHIATRY | MCCLEAN HOSPITAL, MA USA |

**AXIS I CODES:** 1A, 2, 9, 21 **AXIS II CODES:** 36, 46, 50B, 63A, 63C, 63E


### ABSTRACT

Parthenogenetic stem cells might become a valid alternative to fetal tissue for transplantation in human patients if appropriate neuronal differentiation and integration are shown in vivo. In this study we will investigate the efficacy of parthenogenetic primate stem cells (Cyno-1, Cibelli et al 2002) to restore motor function in animal models of PD. Cyno-1 cells can be maintained and expanded for long periods of time and using appropriate protocols 80% differentiate into neurons in vitro. Twenty-five percent of these neurons express tyrosine hydroxylase (TH) and release dopamine (DA) in response to KCl depolarization (Cibelli et al, 2002). In this study we will investigate the potential of these cells to differentiate in vivo into DA neurons and restore motor function in animal models of PD. Initial studies will be performed in the 6-OHDA-lesioned rat model to optimize the in vivo conditions. We have already obtained successful DA differentiation using mice stem cells in this model (Bjokrlund et al, 2002). Primate studies are critical to evaluate the functional efficacy of stem cell derived DA neurons. In this study donor and host are from the same species, which minimizes immunological problems but in order to identify grafted cells we will use GFP expressing Cyno-1 cells. GFP expression did not alter mouse ES cells differentiation into DA neurons in the mouse. Moreover, we will transplant into male host so we will use in situ hybridization (FISH) for the Y chromosome to differentiate TH neurons derived from Cyno-1 (parthenogenetic) from host derived TH-intrinsic striatal neurons. We will combine behavioral and functional neuroimaging techniques (Brownell et al., 1998) to determine recovery of motor signs in correlation with graft maturation and integration, which we assess in vivo using positron emission tomography (PET) and specific ligands for pre and postsynaptic DA markers. We feel that our experience in primate studies, the availability of neuroimaging techniques and the expertise in the stem cell field within our group and collaborators provides a solid framework to successfully develop this project.

## RECTAL AND VAGINAL DENDRITIC CELLS (0330)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505% **AIDS RELATED RESEARCH**


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| IWASAKI, AKIKO | PHD | A | EPIDEMIOLOGY & PUBLIC HEALTH | YALE UNIVERSITY, CT USA |


**AXIS I CODES:** 1A, 7B, 16C, 23 **AXIS II CODES:**31, 64, 83, 93


**ABSTRACT**

The vaginal and rectal mucosal surfaces represent the first site of entry for HIV in sexual transmission. Dendritic cells (DCs) have been proposed to play an important role in the entry of HIV by transporting the virus to the sites of replication. Recently, we have identified unique populations of DCs that express the virus adhesion molecule DC-SIGN in the Peyer's patches and the appendices of both humans and rhesus macaques. We also determined that the DCs in the vaginal epithelium changes dramatically during the estrous cycle in female mice. Here, we propose to "track" the cells infected with SIV expressing green-fluorescence protein, introduced to both the rectal and the vaginal mucosal surfaces of rhesus macaques. We will perform multiple immunofluorescence staining of the exposed sites to determine which cell types are infected and which cell types adhere to the SIV. The expression of co-receptors (CD4, CCR5, CXCR4) and virus adhesion receptors (DC-SIGN and DC-SIGNR) on these cells will be analyzed. Finally, DCs will be isolated from the infected animals to determine their phenotypic and functional changes as a result of SIV infection. Comparing the role of mucosal DCs in viral entry via the rectal and the vaginal routes is essential for designing effective preventative interventions for sexual transmission of HIV-1.

In a separate project, we determined the expression of poliovirus entry receptor in archived tissue, CD155 in collaboration with [ name ]. We determined that the Peyer's patches of rhesus macaques express low levels of CD155 compared to those of humans, and that this may explain the lack of pathogenesis of oral poliovirus infection in rhesus macaques. Based on these data (see publication), we have submitted grant applications to study the in vivo entry mechanism of poliovirus in cynomolgous macaques.

## GBV CELL CULTURE MODEL FOR HEPATITIS C (HCV) (0439)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505%


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| JACOBS, JAMES R | PHD | A | | CORNELL UNIVERSITY, NY USA |


**AXIS I CODES:** 1D, 7B, 16D **AXIS II CODES:**50B, 66, 77


**ABSTRACT**

We proposed the development of GBV-B infected marmoset hepatocytes as a surrogate culture model to screen novel synthetic and natural antiviral compounds for HCV. The advantages of using the GBV-marmoset model lie in the close phylogenetic relationship between HCV/GBV (both members of Flaviviridae), which exhibit greater than 25% homology at the amino acid level. The use of primate liver allows the study of targeted antiviral therapies in a relevant animal model, bringing us a step closer to clinical trials. Primary hepatocytes were isolated by procedures that maintain viable long-term (greater than 3 months) cultures. Ribavirin and IFNalpha, the only two drugs approved by the FDA for use against HCV were effective against GBV-B. By analogy, other compounds tested in this system that exhibit similar or greater antiviral activity may also inhibit HCV. One chemical constituent of the Mulberry plant, deoxynojirimycin (1-DNJ), has been chemically synthesized and used as an anti-hyperglycemic in non-insulin dependent diabetes and synthetic derivatives of 1-DNJ demonstrate antiviral effects in vitro. Natural 1-DNJ is concentrated in the foregut of silkworms feeding on Mulberry leaves and this extract demonstrates anti-hyperglycemic effects in humans. 1-DNJ purified from the silkworm extract also demonstrated antiviral activity in vitro against GBV-B and related flaviviruses. Based upon the similar mechanisms of action for the natural derived and synthetic 1-DNJ, we propose to evaluate the efficacy of the silkworm extract as an antiviral therapy. In response to NIH/NCCAM PA-02-124, "Basic & Preclinical Research on Complementary & Alternative Medicine," we have submitted an R01 entitled, "Mulberry Plant Extract as a Therapy for Viral Hepatitis." The specific aims of the proposal are designed to provide a pre-clinical assessment of this therapy in surrogate animal models for viral hepatitis prior to Phase 1 clinical trials in humans.

# STRUCTURE OF BACTERIAL POLYSACCHARIDES AND THE DEGREE OF IGG SWITCH ASSOCIATION (0440)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505%


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| KASPER, DENNIS L | MD | A | MEDICINE | BRIGHAM AND WOMEN'S HOSPITAL, MA USA |
| | MD, PHD | A | MEDICINE | BRIGHAM AND WOMEN'S HOSPITAL, MA USA |
| | MD | A | MEDICINE | BOSTON UNIVERSITY , MA USA |
| | DVM | C | PRIMATE RESOURCES | |


**AXIS I CODES:** 1A, 2

**AXIS II CODES:** 64, 66, 71, 77, 91, 94


## ABSTRACT

Group B Streptococcus (GBS) is a major cause of serious infections in newborns and young infants. The capsular polysaccharide (PS) of GBS defines its serotype and is both an important virulence factor and a protective antigen. In rodent models of GBS infection, glycoconjugate vaccines (PS coupled to tetanus toxoid, TT) against all GBS serotypes induce a substantial amount of IgM antibodies (Abs) with increasing levels of isotype switched IgG Abs after boosting. In humans, immunization with GBS type III glycoconjugate vaccine (III-TT) results in protective PS-specific IgG Abs with little IgM response. In contrast, GBS type V-TT glycoconjuagte vaccine induces a substantial amount of IgM in humans, even after boosting. There are important structural differences between these two GBS PSs. They are both made up of repeat units of three sugar backbones but the type III has only a single side chain while type V contains two. We sought to determine whether a relationship existed between capsular PS structure, immunodominant carbohydrate epitope(s) and isotype switching and if a non-human primate model might better serve as a predictor of human immune responses. We injected three rhesus macaques (Macaca mulatta) twice with either III-TT or V-TT and determined the Ab responses, epitope recognition and functional activity of the induced Abs. We observed substantial differences in the degree of IgG switching after immunization with III-TT compared to V-TT. This pattern of immunoglobulin switching in macaques, in contrast to rodents, was similar to what we observed in humans. Competitive binding experiments revealed a dominant epitope on the backbone of the VPS including one of the side chains in both human and macaque sera, while the other type V side chain was the dominant epitope in mouse sera. For type IIIPS the dominant epitope was the same in all species. Both the IgG and IgM fractions of the vaccine-induced Abs in humans and macaques promote opsonophagocytic killing of live bacteria. In conclusion, our results suggest that the structure of the PS antigen affect the degree of IgG switch in humans. Furthermore, macaques may be a valuable animal model to understand the basis for differences in the immune response to clinically relevant PSs in humans compared to the mouse.

## EFFECTS OF INFANT MONKEYS ON BEHAVIOR OF ADULT MEMBERS OF RHESUS MONKEY HAREMS (0441)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| KLEPPER-KILGORE, NANCY | PHD | A | VETERINARY TECHNOLOGY | MOUNT IDA COLLEGE, MA USA |

**AXIS I CODES:** 28(NONE) **AXIS II CODES:**36, 92(OBSERVATION ONLY)

**ABSTRACT**

The spontaneous behavior of group-housed adult monkeys is observed to discover whether changes in activity and social behavior are associated with the presence and subsequent removal of infants from rhesus monkey breeding groups. Data analysis will compare rates of affiliative behavior, aggressive behavior, stereotypic behavior, and overall activity of adult monkeys when infants are present and after infants have been removed. Scan samples of each group and focal samples (Altmann, 1974) of each individual constitute the major types of data collected. Data is collected by live observation using a personal digital assistant (PDA) and software produced by Noldus Information Technology. This software enables continuous recording of the sequence and durations of specified behaviors of individual subjects (focal samples), as well as recording of physical contact and proximity of each individual in a group at specified intervals (scan samples). It is hypothesized that mothers with infants and infants themselves may be the objects of more affiliative behavior than those without infants. It is anticipated that this study will document positive aspects of association with infants for both mothers and nonmothers.

## HERPESVIRUSES AS VACCINE VEHICLES FOR AIDS (0331)

NPRC UNIT: COLLABORATIVE RES PROGRAM

%NPRC $: 0.505% AIDS RELATED RESEARCH

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| KNIPE, DAVID | PHD | A | MICROBIO & MOLECULAR GENETICS | HARVARD MED SCH, MA USA |
| C name 1 | PHD | C | MICROBIOLOGY | |
| name 2 | MD | C | IMMUNOLOGY | |
| | MD | C | IMMUNOLOGY | |
| | PHD | C | MICROBIOLOGY | |
| name 3 | MD | A | HUMAN RETROVIRUS SECTION | NCI, MD USA |

AXIS I CODES: 1A, 1D, 7B, 19, 21 AXIS II CODES: 31, 66, 91


### ABSTRACT

We are using recombinant herpes simplex virus as an experimental, persisting, AIDS vaccine in monkeys. Recombinant DNA priming was used with the hope of focusing strong immune response to SIV antigens as has been demonstrated by a number of other groups in different systems. DNA of clinical-grade quality was provided by C name 3 Five different constructs were present in the DNA inoculation: i) one that expresses a secreted fusion protein of p39Gag with the chemokine MCP-3; ii) one that expresses a fusion protein of SIVmac239 Env wit the chemokine MCP-3; iii) one that expresses intracellular degraded Gag; iv) one that expresses intracellular degraded Env; v) one that expresses intracellular degraded Pol-Nef-Tat-Vif fusion protein. Each animal received 1 mg into 2 to 3 sites intramuscularly for each administration. Some of the cellular and humoral immune response measurements have been completed. Preliminary result suggest impressive cellular immune responses, particularly in the DNA prime recombinant HSV boost animals. Antibody responses against SIV and HSV were also measured in all six monkeys. Neutralizing antibody responses against lab-adapted SIV251 were detected in all six animals. Preliminary results suggest a statistically-significant level of protection in the vaccinated monkeys.

## DEFINITION OF MAMU DR* W201 HELPER EPITOPES (0332)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| KURODA, MARCELO J. | MD, PHD | A | MEDICINE, VIRAL PATHOGENEIS | BETH ISRAEL DEACONESS MEDICAL CENTER, MA USA |

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

**ABSTRACT**

The central importance of virus-specific CD4+ T lymphocytes in containing HIV-1 replication has recently been appreciated. Studies have shown that control of viral replication in vivo is associated with vigorous HIV-1-specific CD4+ T lymphocyte proliferative responses. It will be important to characterize of these lymphocytes in greater depth to determine how they contribute to containing HIV-1 replication. However, our ability to study these lymphocyte populations has been limited by the technologies available to carry out such analyses.

The application of the tetramer technology to the study of CD4+ T lymphocyte responses should increase our ability to evaluate the role of these cells in disease pathogenesis. Specifically, we are currently performming CD4+ T lymphocyte epitope mapping in this SHIV-infected rhesus monkey using overlap peptide of the gag protein. Once the epitopes are defined, we will construct novel Mamu-DR*W201/peptide tetramers.

## MUCOSAL ABETA VACCINATION; MODULATING THE IMMUNE RESPONSE (0442)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505%


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| LEMERE, CYNTHIA A | PHD | A | NEUROLOGY | BRIGHAM AND WOMEN'S HOSPTIAL, MA USA |


**AXIS I CODES:** 1A, 2, 21 **AXIS II CODES:**30, 41, 50, 64, 91


### ABSTRACT

Abeta immunotherapy has potential for preventing and possibly treating Alzheimer 's disease (AD) in humans. Studies in genetically-engineered AD mouse models have consistently demonstrated efficacy of the Abeta vaccine both in lowering CNS Abeta and improving cognition. However, the first human clinical trial was halted due to meningoencephalitis in approximately 6% of patients; recognition of the full-length Abeta immunogen as a self-protein may have attributed to these adverse events. In collaboration with The Behavioral Science Foundation in St. Kitts, Eastern Caribbean, we conducted an Abeta immunization study in 10 aged vervets for 10 months (in St Kitts) to determine if we could modulate Abeta levels in brain, CSF and plasma. Non-human primates have the same amyloid precursor protein (APP) and Abeta as humans, and often have age-related cerebral plaque deposition. Thus, they may serve as a better model than mice for studying Abeta clearance and immune response to Abeta vaccination. We found significant decreases in Abeta levels in brain and CSF and increased Abeta levels in plasma. The NEPRC provided support for immunologic studies.

# PATHOGENICITY OF SIV VARIANTS THAT ESCAPE CTL RESPONSES IN RHESUS MONKEYS (0443)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505% **AIDS RELATED RESEARCH**


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| LETVIN, NORMAN L | MD | A | MEDICINE, VIRAL PATHOGENESIS | BETH ISRAEL DEACONESS MEDICAL CENTER, MA USA |


**AXIS I CODES:** 1A, 2, 7B **AXIS II CODES:**31, 66, 77, 91


## ABSTRACT

We have demonstrated that viral escape from dominant epitope-specific CTL may prove a limitation of current CTL-based AIDS vaccines. In this study, we assessed the pathogenicity and viral sequence stability of SIV variants with mutations in dominant CTL epitopes when transferred to naïve rhesus monkeys. We infected 4 Mamu-A*01-positive and 5 Mamu-A*01-negative rhesus monkeys with plasma from animals in our previous study containing SIVsmE660 variants with mutations in the Mamu-A*01-restricted Gag p11C epitope. Both Mamu-A*01-positive and Mamu-A*01-negative monkeys generated broad and potent virus-specific ELISPOT responses. These data contrast with the highly focused responses directed primarily against the p11C epitope that are typically observed in Mamu-A*01-positive monkeys infected with wildtype SIV. The SIV variants replicated to high levels that were comparable to those observed with wildtype SIVsmE660 in our previous study, suggesting that SIV variants with mutations in dominant CTL epitopes were highly pathogenic when transferred to naïve monkeys. We have also sequenced viral clones from each of these animals at multiple points in time. The analysis to date demonstrates that reversions to wildtype sequences occur in vivo. These studies demonstrate that SIV that escapes from epitope-specific CTL responses remains highly pathogenic, but that there is a fitness cost associated with maintaining these mutations.

## RECORDING IN ALERT ANIMALS (0400)

NPRC UNIT: COLLABORATIVE RES PROGRAM

%NPRC $: 0.505%


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| LIVINGSTONE, MARGARET S | PHD | A | NEUROBIOLOGY | HARVARD MEDICAL SCHOOL, MA USA |
| [redacted] | PHD | A | NEUROBIOLOGY | HARVARD MEDICAL SCHOOL, MA USA |


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


### ABSTRACT

The first specific aim of the previous proposal was to use 1-dimensional reverse-correlation mapping (Jones and Palmer, 1987) to map the organization of excitatory and inhibitory ON and OFF inputs to direction-selective cells in alert macaque V1 (and later in V2). This has been accomplished for V1 (Conway and Livingstone, 2003), and, as described below, further explorations of direction processing were in MT rather than in V2. Sparse noise reverse correlation (Emerson et al., 1987; Jones and Palmer, 1987; Ohzawa et al., 1990) was used to map the receptive-field organization and interactions between pairs of stimuli not only for directional cells (Conway and Livingstone, 2003), but also for disparity-tuned (Tsao et al, 2003) and color-selective neurons (Conway, 2001; Conway et al., 2002) in alert macaque V1. In addition the technique was used to map subunit structure of direction and disparity interactions in alert macaque MT (Livingstone et al., 2001; Pack et al., 2003a,b).

The second specific aim was to look at 2-bar interactions in directional cells, using the same data from which spatiotemporal maps were obtained. This was accomplished (Conway and Livingstone, 2003). This part of the study showed that both simple and complex cells showed directional interactions (nonlinearities) to pairs of flashed bars (a 2-bar apparent motion stimulus). The data showed that directional mechanisms comprise both preferred-direction facilitation and null-direction suppression. Both simple and complex cells showed reversed directional interactions for inverting-contrast stimulus sequences—a neural correlate of reverse phi (Anstis, 1970). The space-time slant of the simple cells correlated with the optimum deltaX/deltaT (velocity) of the paired-bar interactions. Some complex cells also showed a space-time slant, and the direction of the slant correlated with the preferred direction.

The third specific aim of the previous proposal was to ask how different models fit the results. This was done, and has been submitted for publication, but not yet accepted. Directional interactions in simple cells were mapped at very high spatial resolution. The interaction patterns reflected contrast-sign-dependent nonlinearities within and between individual ON and OFF subregions. The interaction patterns fit neither the Reichardt model nor the Energy model, but were best explained by a modification of the Energy model (Heeger, 1993) consisting of contrast-selective combination of responses, followed by a rectification and a facilitatory nonlinearity.

## IMMUNOGENICITY OF GB VIRUS-B DNA VACCINES IN COMMON MARMOSETS (0444)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505%


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| LU, SHAN | PHD | A | MEDICINE | UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL, MA USA |


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


### ABSTRACT

There is a growing need for an affordable yet relevant animal model that can be used to study the pathogenesis and vaccine development of Hepatitis C virus (HCV). Recently, GB virus-B was shown to be phylogenetically most closely related to HCV and has been proposed as a potential surrogate model for HCV. The objective of our study is to test the immunogenicity of GBV-B DNA vaccines in marmosets. We expect that the information learnt from this study will not only guide us to develop a potential HCV vaccine but will also offer useful tools, reagents and unique systems for further basic and translational research in our understanding of pathogenesis and immune protection related to hepatitis infection.

The genes coding for the viral envelope glycoproteins (E1 and E2) were amplified from a plasmid DNA encoding a full length GBV-B infectious clone and cloned in a eukaryotic expression vector. These DNA vaccine constructs either encoded a C-terminal deleted form of E2 (tPA dE2) or a C-terminal deleted form of E1 in frame with full length E2 (tPA dE1E2). Two marmosets were immunized by gene gun with approximately 25 ug of tPA dE2 DNA vaccine, two with tPA dE1E2 DNA vaccine and the other two were left unimmunized. Immunization was carried out four times at an interval of four weeks.

From ELISA and Western blot analysis of the animal sera it was evident that DNA immunization with tPA dE2 generated high levels of anti-E2 antibodies in both the animals. Marmosets immunized with tPA dE1E2 did not generate detectable levels of antibodies post immunization, however, anti-E2 antibodies could be detected in these animals post challenge indicating the priming of their immune system as a result of DNA immunization. Viral load analysis by RT-PCR of the post challenge plasma samples indicated a transient infection of the animals which peaked around 2-4 weeks post infection and spontaneously cleared by 12 weeks. Unexpectedly, the viral titer in the immunized animals was found to be 2-3 log values higher than the naïve animals.

From the results obtained thus far, we can speculate that this phenomenon might be the result of antibody-mediated infection. At this point, we are trying to validate our speculation by establishing an in-vitro cell culture model system with marmoset hepatocytes.

## INDUCTION OF TOLERANCE IN NON-HUMAN PRIMATES (0335)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505%


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| MAKI, TAKASHI | MD, PHD | A | SURGERY | BETH ISRAEL DEACONESS MEDICAL CENTER, MA USA |
| [illegible] | MD | A | SURGERY | BETH ISRAEL DEACONESS MEDICAL CENTER, MA USA |
| [illegible] | MD | A | SURGERY | BETH ISRAEL DEACONESS MEDICAL CENTER, MA USA |


**AXIS I CODES:** 1A, 1D, 17, 27 **AXIS II CODES:** 64, 66, 88


### ABSTRACT

Chronic renal failure is an important clinical condition of aging human beings. Chronic immunosuppression is associated with complications and failure to control rejection. Induction of tolerance is a goal of clinical transplantation. We investigated the effectiveness of the antilymphocyte serum, rapamycin and donor bone marrow (BM) infusion protocol, which produced robust tolerance in mice, to induce tolerance in cynomolgus monkeys. The results indicate that the regimen consisting of Thymoglobulin, rapamycin and donor bone marrow infusion is effective in prolonging allograft survival.

## ANTI-HIV-1 TAT HUMAN SFV INTRABODY GENE THERAPY AGAINST SHIV IN RHESUS MACAQUES (0270)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION : STATE, COUNTRY |
|---|---|---|---|---|
| MARASCO, WAYNE A. | MD, PHD | A | CANCER IMMUNOLOGY AND AIDS | DANA FARBER CANCER INSTITUTE, MA USA |
| | MD | C | IMMUNOLOGY | |
| | BS | A | CANCER IMMUNOLOGY & AIDS | DANA-FARBER CANCER INSTITUTE, MA USA |
| | MD, PHD | A | CANCER IMMUNOLOGY AND AIDS | DANA FARBER CANCER INSTITUTE, MA USA |

**AXIS I CODES:** 1D **AXIS II CODES:**31, 55


### ABSTRACT

The rhesus macaque model is a very useful experimental system to evaluate effects of T cell autotransfusion and gene therapies for HIV-1 infection and AIDS prior to a clinical trial. Over the last twelve months, we have completed testing of 23 human anti-tat intrabodies for their antiviral activity against HIVHXBC2. Based on these results, we have chosen two anti-tat intrabodies, termed huTat2 and E46 for further in vivo evaluation in the SHIV/macaque model. We are currently completing the characterization of six phoenix packaging cell lines that produce MuLV vectors encoding huTat2, E46 and an irrelevant control intrabody A3H5 with and without immunoglobulin leader sequences. These two designs are based on our unexpected results that the intrabodies with leader often have more potent anti-viral activity compared to intrabodies that are translated and expressed in the cytosol. Our current hypothesis is that the presence of the leader sequence allows a greater amount of the intrabody to be properly folded and when combined with efficient retrograde transport from the ER into the cytoplasm results in more efficient anti-viral activity. We are planning on transducing CEMx174 cells with the retroviral supernatants of these six cell lines and then challenge the cell lines with pathogenic SHIVs that encode the HIV tat gene with an epitope that is recognized by the anti-tat intrabody.

## MUCOSAL IMMUNIZATION WITH LIVE ATTENUATED SIV (0386)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| NEUTRA, MARIAN R | PHD | A | PEDIATRICS | CHILDREN'S HOSPITAL, BOSTON, MA USA |
| [illegible] | PHD | A | PEDIATRICS | CHILDREN'S HOSPITAL, BOSTON, MA USA |

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

**ABSTRACT**

The goal of this study is to develop immunization protocols using a live, highly-attenuated SIV vaccine candidate to protect against mucosal transmission. Prime/boost immunization protocols using attenuated SIV able to undergo a single cycle of replication (scSIV), and aldrithiol-2 inactivated SIV particles (AT-2 SIV) were tested for induction of humoral and cell-mediated immune responses. The data suggest that a prime/boost strategy using highly attenuated SIV boosted with nonliving antigens, delivered via intradermal and intranasal routes, is worth further investigation.

# SAFETY OF MESENCHYMAL STEM CELL ADMINISTRATION TO THE CNS OF RHESUS MACAQUES (0445)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| PHINNEY, DONALD G | PHD | A | GENE THERAPY CENTER | TULANE HEALTH SCIENCE CENTER, LA USA |
| [redacted] | PHD | A | GENE THERAPY CENTER | TULANE HEALTH SCIENCE CENTER, LA USA |

**AXIS I CODES:** 1A, 21 **AXIS II CODES:** 46, 81


## ABSTRACT

Lysosomal storage diseases are a heterogeneous group of disorders caused by the deficiency of a specific acid hydrolase, resulting in the accumulation of glycosaminoglycans, glycoproteins or sphingolipids in organs throughout the body. Deficiencies in different enzymes results in distinct patterns of substrate accumulation in organs, producing a wide spectrum of clinical symptoms. Bone marrow transplantation is a common treatment for these diseases. However, because only a small percentage of bone marrow cells cross the blood-brain barrier it is ineffective at reversing neurodegeneration within the central nervous system (CNS), which is common to many forms of storage disease. The overall aim of this proposal is to evaluate the therapeutic potential of mesenchymal stem cells (MSCs) as cellular vectors for treating neurodegenerative disease by first establishing their safety and toxicity when administered directly to the CNS of Rhesus macaques. Once the risk assessment of MSCs is complete, their efficacy as therapeutic agents will be tested in macaques afflicted with Krabe's disease, a lysosomal storage disease that causes neurodegeneration in the central and peripheral nervous system. These studies are a necessary step toward the development of MSCs as cellular vectors to clinically treat CNS neurodegeneration in humans afflicted with lysosomal storage disease.

## ALZHEIMER'S DISEASE VACCINE (0273)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505%


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| RASO, VICTOR | PHD | A | | BOSTON BIOMEDICAL RESEARCH INSTITUTE, MA USA |


**AXIS I CODES:** 1A, 2, 3, 9, 17, 19, 21 **AXIS II CODES:** 30, 46, 50B, 62, 64, 91


### ABSTRACT

The beta-amyloid peptide and the cerebral plaques that it forms are the likely cause of Alzheimer's disease. We are designing vaccines that will elicit specific antibodies against beta-amyloid and serve as a therapeutic intervention that could prevent or reverse Alzheimer's disease. As we surmised, this beta-amyloid vaccine approach can prevent plaque formation in young mice and dissipate preestablished plaques in older mice.

Those preclinical experiments used synthetic beta-amyloid peptides emulsified in complete Freund's adjuvant. However vaccine preparations formulated in that adjuvant are not appropriate for use in humans. Therefore we focused on producing and testing in non-human primates several alternative adjuvant and antigen formulations that are compatible with clinical standards. In addition to our synthetic peptides we have produced several new genetically engineered beta-amyloid fusion vaccines. These expressly designed beta-amyloid antigens and adjuvants form the basis for our treatment of Alzheimer's disease using highly specific beta-amyloid vaccines.

## EXPERIMENTAL MYOPIA IN PRIMATES (0338)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| RAVIOLA, ELIO | MD | A | NEUROBIOLOGY | HARVARD MEDICAL SCHOOL, MA USA |

**AXIS I CODES:** 21, 25B **AXIS II CODES:**92(REFRACTIVE ERRORS, BLINDNESS)

**ABSTRACT**

The objective of this study is to clarify the mechanisms responsible for the genesis of myopia, which is the seventh most frequent cause of legal blindness in this country, and to develop procedures to prevent this condition. Fusion of the lids of one eye in primates induces an axial myopia that is very similar to intermediate myopia in humans. The fused lids act by degrading the visual experience to the perception of formless shadows. In rhesus macaques and African green monkeys, elongation of the eye is caused by disruption of the retinal control of postnatal eye growth. The objective of this proposal is to identify the molecule(s) released by the retina that cause axial elongation upon lid fusion.

## RESOURCE FOR NONHUMAN PRIMATE CELL-DEPLETING ANTIBODIES (0446)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505%


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| REIMANN, KEITH A | DVM | A | MEDICINE, VIRAL PATHOGENESIS | BETH ISRAEL DEACONESS MEDICAL CENTER, MA USA |
| E name 3 | BVSC | C | PRIMATE RESOURCES | |


**AXIS I CODES:** 1A, 9, 17 **AXIS II CODES:**77


**ABSTRACT**

The in vivo administration of monoclonal antibodies that bind to cell-surface molecules can block the actions mediated by those molecules, deliver stimulatory signals through the bound molecules, or result in depletion of the targeted cell population. This approach has been extremely useful to study immunopathogenic events in rodent models. To enhance the usefulness of existing nonhuman primate models of disease, we have performed in vivo evaluation of antibodies or antisera targeting CD4+ T cells, CD8b+ T cells and natural killer (NK) cells. The ability of these candidate research reagents to deplete the targeted lymphocyte subpopulation was assessed.

## SIV CARDIOMYOPATHY IN NON-HUMAN PRIMATES (0277)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION : STATE, COUNTRY |
|---|---|---|---|---|
| SHANNON, RICHARD P | MD | A | MEDICINE | ALLEGHENY GENERAL HOSPITAL, PITTSBURGH, PA USA |
| | BVSC | C | PRIMATE RESOURCES | |
| Namba | BVSC | C | PRIMATE RESOURCES | |

**AXIS I CODES:** 1, 13 **AXIS II CODES:**31


### ABSTRACT

HIV associated cardiac pathology is being recognized increasingly as patients with chronic HIV infection survive to live productive lives. HIV associated cardiomyopathy is among the most common cardiac specific manifestation of chronic HIV infection and was observed in between 6-12% of patients that succumb to AIDS. However, cardiovascular involvement has emerged as more than a pathologic curiosity, but rather as a significant cause of morbidity as individuals live longer, more productive lives with HIV. Increased use of HAART therapy has served to unmask HIV associated predispositions to cardiac involvement. Despite the increased recognition, the risks factors for, the pathogenesis of, and the specific treatments required in HIV associated cardiac disease remain unknown.

The nonhuman primate model of SIV infection in rhesus macaques affords an unparalleled opportunity to study these critical features. Prior work from our laboratory has characterized the time course, the role of CD4 counts, and the pleomoprhic cardiac manifestations in simian AIDS. The work has demonstrated the need to consider both viral and host factors in identifying those at increased risk and to create a consistent, reproducible model of cardiac involvement for further investigation. We have determined that macrophage-tropic strains of SIV are most commonly associated with lymphocytic myocarditis. SIV is localized to the myocardium in approximately one third of cases of cardiac involvement, and when present, always co-localizes to cells of the macrophage lineage, either tissue macrophages or cardiac dendritic cells. TNFalpha, produced by activated macrophages, mediates both upregulation of NOS2 in cardiac myocytes and the expression of Fas (CD95) receptors leading to cardiac myocyte apoptosis. As such, we have shown that cytokines play a central mechanistic role in both reversible LV dysfunction (increased NF-kappa B NOS2 expression) and irreversible myocardial injury (Fas-FasL mediated apoptosis). In addition, lymphocytic infiltrates are frequently perivascular and associated with coronary vascular lesions characterized by endothelial activation, smooth muscle proliferation, and thrombotic occlusions, leading to acute ischemic injury. These pathological features are mirrored in the lung where lymphocytic interstitial pneumonia and pulmonary vasculopathy are observed and contribute to increased right ventricular dysfunction. We plan to explore both host and viral factors that lead to SIV transmission into the myocardium (SIV cardiotropism) and SIV mediated injury (cardiovirulence). The identified mechanisms will serve as a prerequisite for exploring specific strategies to prevent cardiac involvement in chronic SIV infection.

## XENOGENEIC STEM CELL AND THYMIC REPLACEMENT IN AIDS (0447)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| SYKES, MEGAN | MD | A | SURGERY | MASS GENERAL HOSPITAL, MA USA |
| Named | MD | C | IMMUNOLOGY | |
| | BVSC, PHD | C | IMMUNOLOGY | |

**AXIS I CODES:** 1A, 4, 19 **AXIS II CODES:** 31, 64, 66, 88


### ABSTRACT

This IPCP proposal is a continuation of an NCDDG Program Project grant that has been funded since April 1996. The overall goal of our Program is to explore the potential of xenogeneic (porcine) thymic transplantation to augment immune reconstitution in HIV-1-infected people showing incomplete reconstitution in the presence of HAART. We have demonstrated that porcine thymic xenografts can support human thymopoiesis and protect human thymocytes from HIV-1-induced destruction in immunodeficient mice. In conditioned normal mice, murine T cells emerging from porcine thymus grafts mediate effective recipient-restricted responses and clear opportunistic pathogens. Primate studies indicate that host conditioning is required to avoid rejection of xenogeneic thymus grafts, even in the presence of advanced SIV disease. Porcine thymic engraftment and function have been demonstrated in large animals, and partial reconstitution of naïve CD4 cells has been achieved in conditioned primates receiving porcine thymus grafts. In the IPCP application, Project 1 will further examine the immune function and HIV resistance of human T cells developing in porcine thymic grafts in immunodeficient mice. Project 2 will investigate the optimal host conditioning, thymic transplantation site, and age of porcine thymic donors, for achievement of optimal immune restoration in normal primates. Project 3 will adapt this information in SIV-infected primates. These two projects are closely interrelated, and build on information on the thymic donor age, host conditioning, effects of natural antibodies and of adding porcine hematopoietic cells, obtained in all Projects in the NCDDG grant. Project 4 is new, and consists initially of a clinical trial in patients with AIDS lymphoma of a novel non-myeloablative allogeneic bone marrow transplantation protocol developed by the investigators for the treatment of advanced, refractory lymphomas. When milestones in Projects 2, 3, and 4 and Core B have been met, information on the effects of this non-myeloablative conditioning protocol on host toxicity, viral load and immune reconstitution in HIV-infected persons will be applied in a trial of porcine thymic transplantation in patients showing incomplete T cell reconstitution on HAART. The administrative Core (A) will coordinate the Program Project. Core B is new, and includes breeding of porcine thymic donors and the analysis of specimens from all Projects for the possible transmission of porcine pathogens to human and non-human primate cells. These Projects and Cores constitute a highly integrated pre-clinical and clinical program aimed at thymic xenotransplantation as an approach to achieving immune reconstitution in the treatment of HIV-infected people.

## ACCOMMODATION, THE CONTROL OF EYE GROWTH AND THE DEVELOPMENT OF MYOPIA (0280)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| TROILO, DAVID | PHD | A | BIOLOGICAL SCIENCES | NEW ENGLAND COLLEGE OF OPTOMETRY, MA USA |

**AXIS I CODES:** 1A, 21, 25B **AXIS II CODES:** 77, 86

**ABSTRACT**

This work has potential value for the treatment of human myopia. Myopia is a leading cause of blindness. Its control is an old and controversial subject. Our work helps establish the importance of visual experience, accommodation, and possible mechanisms in the refractive development of the eye. The work in our laboratory will help provide answers to clinically relevant questions about the development of myopia in children. The work may ultimately be related to both the prediction of risk factors and the development of effective treatments.

Our relationship with the New England Regional Primate Research Center is an important factor in the success of this project. We rely on the center for breeding stock and their expertise in primate care.

## CONTRIBUTION OF OIS TO INTESTINAL DYSFUNCTION AND WASTING (0281)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505% **AIDS RELATED RESEARCH**


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| TZIPORI, SAUL | DSC, DVM, PHD | A | BIOMEDICAL SCIENCES | TUFTS U SCHOOL OF VETERINARY MEDICINE, MA USA |
| L [illegible] | DVM, PHD | A | BIOMEDICAL SCIENCES | TUFTS U SCHOOL OF VETERINARY MEDICINE, MA USA |
| E [illegible] | DVM | A | BIOMEDICAL SCIENCES | TUFTS U SCHOOL OF VETERINARY MEDICINE, MA USA |


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


### ABSTRACT

A significant loss of CD4+ T cells may be responsible for the development of chronic cryptosporidiosis and microsporidiosis in AIDS patients. SIV-infected macaques were used to investigate this relationship. Fecal samples were collected and analyzed for the presence of intestinal pathogens. SIV-infected macaques are being tested for the occurrence of C. parvum and E. bieneusi by PCR. Majority of the SIV-infected macaques were tested positive for E. bieneusi but not for C. parvum, especially when their CD4+ counts were less than 500 cell/ul of blood. There is a possible association between a rapid decrease of CD4 counts after SIV-infection and increase of E. bieneusi loads in the feces. Significance: Study on cohort group of macaques showed that spontaneous acquisition of E. bieneusi infection in SIV-infected macaques occurred when their CD4+ counts drops less than 500 cell/ul of blood, establishing a relationship between E. bieneusi infection and the immune status of SIV-infected macaques.

## PATHOGENESIS OF EPSTEIN-BARR VIRUS INFECTION (0282)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| WANG, FREDERICK C | MD | A | MEDICINE | BRIGHAM & WOMENS HOSP, MA USA |

**AXIS I CODES:** 7B **AXIS II CODES:**31, 64, 66, 76

**ABSTRACT**

Primary EBV infection is the most common cause of infectious mononucleosis in humans. Acute EBV infection is controlled by the development of EBV specific immune responses, but the virus is able to persist for life in infected hosts. Persistent EBV infection is usually asymptomatic, but immunosuppression and other tumorigenic insults may result in the emergence of EBV associated malignancies such as lymphoproliferative disease, Burkitt's Lymphoma, nasopharyngeal carcinoma, and Hodgkin's disease. Considerable progress has been made in the molecular and cell biology of EBV infection, but better understanding of viral pathogenesis has been limited by the lack of a suitable animal model.

We have recently demonstrated that experimental infection of rhesus monkeys with a rhesus herpesvirus in the same lymphocryptovirus (LCV) subgroup as EBV reproduces many important aspects of acute and persistent EBV infection in humans. We have also made substantial progress in cloning the rhesus LCV genome, characterizing the similarities and differences between rhesus LCV and EBV, and manipulating the rhesus LCV genome in order to generate recombinant viruses. The overall goals of these experiments are to:

1. Study the molecular pathogenesis of various LCV genes which are suspected to be important for acute and persistent infection in vivo, eg, EBNA-3B, LMP2A, vIL-10, EBERs.
2. To develop a model for LCV induced tumorigenesis and to study the effects of LCV and SIV/SHIV coinfection.

## NEW WORLD ONCOGENIC LYMPHOCRYPTOVIRUSES (0392)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| WANG, FREDERICK C | MD | A | MEDICINE | BRIGHAM & WOMENS HOSP, MA USA |

**AXIS I CODES:** 7B **AXIS II CODES:** 31, 64, 66, 76


### ABSTRACT

We have also recently isolated a new herpesvirus, CalHV-3 (Callithrix herpesvirus 3), from spontaneous B cell lymphomas arising in common marmosets (Callithrix jacchus), a New World primate. Like EBV, this virus can immortalize B cells in tissue culture. Sequence analysis of a 35 kb cosmid clone indicates that the virus is most appropriately categorized as a LCV, but is more distant from EBV than other LCV found in Old World primates. A viral oncogene with structural and functional similarities, but little sequence homology, to the EBV LMP1 is positionally conserved as in other gamma herpesviruses. Persistent CalHV-3 infection is present in healthy animals from two independent domestic colonies indicating that it is a naturally occurring infectious disease. A similar LCV can be identified in squirrel monkeys (Saimiri scireus) providing further evidence that the classic paradigm for LCV evolution only in Old World primates needs to be redefined.

The specific aims of these studies are as follows:

Specific aim #1. To clone and sequence the complete CalHV-3 genome.

Specific aim #2. To identify latent infection, transformation associated viral genes expressed in CalHV-3 infected, immortalized B cells.

Specific aim #3. To identify the spectrum of New World primates naturally infected with LCV and to identify possible disease associations.

Specific Aim #4. To experimentally infect animals with CalHV-3.

These studies will redefine our understanding for the evolution of oncogenic gamma herpesviruses. This model is particularly interesting since virus associated malignant disease occurs spontaneously in the natural host without overt immunosuppression. These viruses provide an important model of how LCV can cause persistent infection and contribute to malignant disease.

## ORAL PATHOGENESIS OF GAMMAHERPESVIRUS INFECTIONS (0393)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| WANG, FREDERICK C | MD | A | MEDICINE | BRIGHAM & WOMENS HOSP, MA USA |

**AXIS I CODES:** 7B **AXIS II CODES:** 31, 64, 66, 76


### ABSTRACT

Epstein-Barr virus (EBV) and Kaposi's sarcoma herpesvirus (KSHV) are related human gammaherpesviruses and important pathogens in immunocompetent and immunosuppressed hosts. Oral transmission is the primary mechanism for EBV infection, and oral EBV infection is associated with nasopharyngeal carcinoma and oral hairy leukoplakia. The importance of oral transmission for KSHV infection remains to be determined, but persistent oral infection and oral virus shedding are common features for EBV and KSHV infections. However, in both instances oral viral infection is poorly understood including the cell types infected in the oral cavity, the viral genes important for oral transmission, primary infection and viral persistence, the role of oral epithelial cell versus lymphocyte infection, and the mucosal immune responses important for controlling oral infection.

This program will combine virology, immunology, and pathology expertise to address fundamental issues in the oral biology of gammaherpesvirus infections in immunocompetent and immunosuppressed hosts. The recent discovery, cloning and sequencing of two gammaherpesviruses closely related to EBV and KSHV and naturally infecting rhesus macaques provide new experimental animal models and will serve as a starting point to define the biology of oral gammaherpesvirus infection and to experimentally test the role of specific viral genes in vivo. Advances in defining KSHV-specific immune responses, mucosal immune responses to other viral antigens, and immune responses in the macaque animal model will be applied to better understand the immunology of oral gammaherpesvirus infections. An antibody core will develop new antibody reagents for these studies, and a pathology core will coordinate, develop, and apply innovative pathologic methods to study and detect oral viral infections. Translation of results from animal models to human studies is an important and intrinsic component of the program. This program will combine the comparative powers of studying closely related gammaherpesviruses with the synergy of clinicians, virologists, pathologists, and immunologists to better understand the oral pathogenesis of gammaherpesvirus infections in immunocompetent and immunosuppressed hosts.

# PROPAGATION OF MONKEY MODELS OF HUMAN DISEASE (0342)

**NPRC UNIT:** COLLABORATIVE RES PROGRAM

**%NPRC $:** 0.505% **AIDS RELATED RESEARCH**


| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| WOLF, DONALD P | PHD | A | REPRO SCIENCES | OREGON NATIONAL PRIMATE RESEARCH CENTER, OR USA |
| Names | DVM | C | PRIMATE RESOURCES | |
| | BVSC | C | PRIMATE RESOURCES | |
| | PHD | A | REPRO SCIENCES | OREGON NATIONAL PRIMATE RESEARCH CENTER, OR USA |


**AXIS I CODES:** 1A, 9, 23, 28(ASSISTED REPRODUCTIVE TECHNOLOGIES) **AXIS II CODES:**31, 39, 60


**ABSTRACT**

There is currently a significant need for populations of animals with specified genotypes which can't be satisfied by the importation of animals from the wild or by the identification and propagation of valuable founder animals by selective breeding. Indian-origin, rhesus macaques carrying the MHC class I allele, A*01, are particularly needed for vaccine development research. The objective of this application, is to demonstrate that the assisted reproductive technologies (ARTs) can be applied to the rapid, efficient propagation of a valuable founder animal and to the production of identical twins using existing technology, thereby establishing an effective approach to satisfying animal requirements of the biomedical research community. The rationale for focusing on a homozygous, founder male is simple, all offspring produced by this animal will be Mamu-A*01 positive. Moreover, if heterozygous carriers of the A*01 allele are used as oocyte donors, 50% of the offspring will be homozygous for the allele, creating additional founder animals. Three specific aims are proposed. 1: Produce Mamu-A*01 positive animals using sperm from the NERPRC, homozygous Mamu-A*01 positive donor. This aim will establish the paradigm and create new populations of heterozygous and homozygous animals without impacting the natural reproduction of either the sperm or oocyte donors. 2: Induce spermatogenesis in candidate, homozygous Mamu-A*01 positive, infant males.

## NONHUMAN PRIMATE TISSUE DISTRIBUTION (0396)

**NPRC UNIT:** COMPARATIVE PATHOLOGY

**%NPRC $:** 1.420% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| O'NEIL, SHAWN P | DVM, PHD | C | COMPARATIVE PATHOLOGY | |
| | DVM | A | | TULANE NATIONAL PRIMATE RESEARCH CTR, LA USA |
| | UNK | A | | PAIN THERAPEUTICS, INC, CA USA |
| | PHD | C | MICROBIOLOGY | |
| | PHD | A | ANTHROPOLOGY | UNIVERSITY OF MASSACHUSETTS, AMHERST, MA USA |
| | PHD | A | EPIDEMIOLOGY & PUBLIC HEALTH | YALE UNIVERSITY, CT USA |
| | PHD | A | PSYCHIATRY & BEHAVIORAL SCIENC | UNIVERSITY OF MIAMI SCHOOL OF MEDICINE, FL USA |
| | MD | C | IMMUNOLOGY | |
| | MD | A | CELL BIOLOGY | CHILDRENS HOSPITAL, MA USA |
| | PHD | A | INFECTIOUS DISEASES | TUFTS UNIVERSITY SCHOOL OF VETERINARY MEDICINE, MA USA |
| | PHD | A | AUTOIMMUNITY | IMMCO DIAGNOSTICS, NY USA |
| | PHD | A | NEUROLOGY | BRIGHAM AND WOMEN'S HOSPTIAL, MA USA |
| | MD | A | MEDICINE, VIRAL PATHOGENESIS | BETH ISRAEL DEACONESS MEDICAL CENTER, MA USA |
| | PHD | A | NEUROBIOLOGY | HARVARD MEDICAL SCHOOL, MA USA |
| | DVM | C | PRIMATE RESOURCES | |
| | UNK | A | GENE FUNCTION AND EXPRESSION | UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL, MA USA |
| | MD | A | NEUROBIOLOGY | HARVARD MEDICAL SCHOOL, MA USA |
| | UNK | A | IMMUNOLOGY | UNIVERSITY OF TENNESSEE SCHOOL OF MEDICINE, TN USA |
| | PHD | A | PEDIATRICS | CHILDREN'S HOSPITAL, MA USA |
| | PHD | A | ANTHROPOLOGY | DUKE UNIVERSITY MED CTR, NC USA |
| | MD | A | GASTROENTEROLOGY | VAMC, WAYNE STATE U, MI USA |
| | PHD | A | ANTHROPOLOGY | DUKE UNIVERSITY MEDICAL CENTER, NC USA |
| | MD | A | MEDICINE | BRIGHAM & WOMENS HOSP, MA USA |
| | PHD | A | ANTHROPOLOGY | UNIVERSITY OF MISSOURI, MO USA |
| | PHD | A | ANATOMY | NE OHIO UNIVERSITY COLLEGE OF MEDICINE, OH USA |

**AXIS I CODES:** 1A, 1D, 15, 16, 17, 21 **AXIS II CODES:** 31, 34, 64, 66, 76, 86

**ABSTRACT**

The procurement, processing, and distribution of tissues from various species of Old and New World nonhuman primates is an important mission of the Division of Comparative Pathology. The Center receives requests from many investigators, both regionally and nationally, for tissue or organ specimens from nonhuman primates at death, and the Division of Comparative Pathology attempts to accommodate all possible requests. In 2003, the Division collected and dispersed 273 specimens to investigators outside the Center, including fresh brains and a variety of organs. In satisfying this mission, the Division of Comparative Pathology helps optimize the unique resources of this Center.

## IMMUNOLOGICAL REAGENT AND SAMPLE DISTRIBUTION (0399)

**NPRC UNIT:** IMMUNOLOGY

**%NPRC $:** 4.940% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| JOHNSON, R PAUL | MD | C | IMMUNOLOGY | |
| | UNK | A | MICRO IMMUNO & MEDICINE | UCLA AIDS INSTITUTE, CA USA |
| | PHD | A | | VIRXSYS, GAITHERSBURG, MD USA |
| | UNK | A | | GENETICS INSTITUTE, MA USA |
| | UNK | A | MEDICINE/ONCOLOGY | UNIVERSITY OF WASHINGTON, WA USA |
| | PHD | A | MOLECULAR MICROBIOLOGY | NIH, MD USA |
| | PHD | A | | AARON DIAMOND AIDS RESEARCH CENTER, NY USA |
| | UNK | A | | EPIMMUNE, CA USA |
| | PHD | A | | UNIVERSITY OF WISCONSIN-MADISON, WI USA |
| | PHD | A | | UNIVERSITY OF PITTSBURGH, PA USA |
| | MD | A | MEDICINE | MASSACHUSETTS GENERAL HOSPITAL, MA USA |

**AXIS I CODES:** 3 **AXIS II CODES:**31

**ABSTRACT**

The Division of Immunology provides a broad array of immunological and virological reagents to investigators involved in AIDS, gene therapy and hematopoeisis research. Examples of reagents provided by the Division of Immunology include samples of rhesus macaque bone marrow, lymphocytes and thymocytes, cryopreserved rhesus thymic stroma, monoclonal antibodies specific for macaque T cells, peptides used for immunological assays of cell-mediated immune responses, the S594 cell line (a producer cell line for herpesvirus papio, which is routinely used for the transformation of macaque B cell lines) and retroviral vectors and packaging lines. Provision of rhesus thymic stroma to outside investigators represents a particularly unique resource; this reagent supports the in vitro T cell differentiation of both monkey and human CD34+ progenitor cells, a process that has traditionally required in vivo studies.

## HERPESVIRUSES AS VACCINE VEHICLES FOR AIDS (0145)

**NPRC UNIT:** MICROBIOLOGY

**%NPRC $:** 0.628% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| DESROSIERS, RONALD C | PHD | C | MICROBIOLOGY | |
| F | MD | C | IMMUNOLOGY | |
| name | MD | C | IMMUNOLOGY | |
| | PHD | A | MICROBIO & MOLECULAR GENETICS | HARVARD MED SCH, MA USA |
| | PHD | C | MICROBIOLOGY | |
| 3 | MD | A | HUMAN RETROVIRUS SECTION | NCI, MD USA |

**AXIS I CODES:** 1A, 1D, 7B, 19, 21 **AXIS II CODES:** 31, 66, 91


### ABSTRACT

We are using persisting, recombinant herpesviruses as a vectored vaccine approach for AIDS. We are using recombinant herpes simplex virus (HSV) and are doing the preliminary experiments to use recombinant rhesus monkey rhinovirus (RRV).

In a new round of experiments begun in 2003, one group of three monkeys received recHSV recHSV recHSV recHSV at weeks 0, 4, 12, and 20. The other group of three monkeys received DNA DNA recHSV recHSV at weeks 0, 4, 12, and 20. Each recHSV administration contained an equal mixture of strains expressing SIVgag, env and tat-rev-nef in the new HSV vector d106. Recombinant DNA priming was used with the hope of focusing strong immune response to SIV antigens as has been demonstrated by a number of other groups in different systems. DNA of clinical-grade quality was provided by C. name

3 Five different constructs were present in the DNA inoculation: i) one that expresses a secreted fusion protein of p39Gag with the chemokine MCP-3; ii) one that expresses a fusion protein of SIVmac239 Env wit the chemokine MCP-3; iii) one that expresses intracellular degraded Gag; iv) one that expresses intracellular degraded Env; v) one that expresses intracellular degraded Pol-Nef-Tat-Vif fusion protein. Each animal received 1 mg into 2 to 3 sites intramuscularly for each administration. Some of the cellular and humoral immune response measurements have been completed. Preliminary result suggest impressive cellular immune responses, particularly in the DNA prime recombinant HSV boost animals. Antibody responses against SIV and HSV were also measured in all six monkeys. Neutralizing antibody responses against lab-adapted SIV251 were detected in all six animals. SIV challenge was performed on Oct 21, 2003. Preliminary results suggest a statistically-significant level of protection in the vaccinated monkeys.

Overlapping cosmid clones have been derived that span the entire RRV genome. Experiments are in progress to develop a genetic system that will allow expression of SIV antigens by RRV.

## MICROBIOLOGICAL REAGENT AND SAMPLE DISTRIBUTION (0395)

**NPRC UNIT:** MICROBIOLOGY

**%NPRC $:** 0.628% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| DESROSIERS, RONALD C | PHD | C | MICROBIOLOGY | |
| | UNK | A | WASHINGTON NAT'L PRIMATE RES C | UNIVERSITY OF WASHINGTON, WA USA |
| | PHD | A | EPIDEMIOLOGY & PUBLIC HEALTH | YALE MEDICAL SCHOOL, CT USA |
| | UNK | A | | JOHNS HOPKINS SINGAPORE, SINGAPORE |
| | UNK | A | INFECTIOUS DISEASE MICROBIOLOG | UNIVERSITY OF PITTSBURGH, PA USA |
| | UNK | A | BIOLOGY | CLAFLIN UNIVERSITY, SC USA |
| | UNK | A | BIOLOGY | UNIVERSITY OF NORTH CAROLINA, NC USA |
| | DVM, PHD | A | INFECTIOUS DISEASE RESEARCH DE | SOUTHERN RESEARCH INSTITUTE, MD USA |
| | UNK | A | | INSTITUT COCHIN DE GENETIQUE MOLECULAIRE, FRANCE |
| | UNK | A | CHEMISTRY | SYRACUSE UNIVERSITY, NY USA |
| | PHD | A | BASIC SCIENCES | NATIONAL CANCER INSTITUTE, MD USA |
| | UNK | A | | QUALITY BIOLOGICAL, INC., MD USA |
| | PHD | A | NUCLEIC ACID BIOCHEMISTRY | INDIANA UNIVERSITY, IN USA |
| | PHD | A | IMMUNOLOGY | THE SCRIPPS RESEARCH INSTITUTE, CA USA |
| | UNK | A | | ALBANY MEDICAL COLLEGE, NY USA |
| | PHD | A | VIRAL VECTOR CORE FACILITY | COLUMBUS CHILDREN'S RESEARCH INSTITUTE, OH USA |
| | UNK | A | CENTRE FOR VIRUS RESEARCH | WESTMEAD MILLENNIUM INSTITUTE, AUSTRALIA |
| | PHD | A | MICROBIOLOGY AND IMMUNOLOGY | UNIVERSITY OF ROCHESTER, NY USA |
| | PHD | A | BIOCHEMISTRY AND BIOPHYSICS | HOWARD HUGHES MEDICAL INSTITUTE, PA USA |
| | PHD | A | MEDICAL SCIENCE | IRISICAIXA FOUNDATION, SPAIN |
| | MD, PHD | A | VACCINE RESEARCH CENTER | EMORY UNIVERSITY, GA USA |
| | MD, PHD | A | NEUROPHARMACOLOGY | THE SCRIPPS RESEARCH INSTITUTE, CA USA |
| | UNK | A | | SCRIPPS RESEARCH INSTITUTE, CA USA |
| | PHD | A | RHEUMATOLOGY UNIT | INSTITUTE OF CHILD HEALTH, UK |
| | PHD | A | MEDICINE | HARVARD MEDICAL SCHOOL, MA USA |

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|---|---|---|---|---|
| | MD | A | MEDICINE | BRIGHAM AND WOMEN'S HOSPITAL, MA USA |
| | PHD | A | BIO CHEM & MOL PHAMACOL | HARVARD MEDICAL SCHOOL, MA USA |
| | UNK | A | | CENTERS FOR DISEASE CONTROL AND PREVENTION, GA USA |
| | MD | A | | AARON DIAMOND AIDS RESEARCH CENTER, NY USA |
| | DVM, PHD | | COLLEGE OF VETERINARY MEDICINE AND BIOMEDICAL SCIENCE | COLORADO STATE COLLEGE, CO USA |
| | MD | A | | UNIVERSITY OF PENNSYLVANIA, PA USA |
| | UNK | A | | UNIVERSITY OF NEBRASKA MEDICAL CENTER, NE USA |
| | DVM | A | | ICGEB, INDIA |
| | MD | A | CHILDREN'S HOSPITAL | OHIO STATE UNIVERSITY, OH USA |
| | PHD | A | MEDICINE | UNIVERSITY OF NEW SOUTH WALES, AUSTRALIA |
| | UNK | A | CLINICAL MEDICAL VIROLOGY CTR | UNIVERSITY OF QUEENSLAND, AUSTRALIA |
| | UNK | A | MICRO & IMMUNOLOGY M & D | UNIVERSITY OF ROCHESTER MEDICAL CTR, NY USA |
| | UNK | A | | UNIVERSITY OF HAWAII, MANOA, HI USA |
| | PHD | A | | ABTEILUNG VIROLOGIE - UNIVERSITÄTSKLINIKUM, GERMANY |
| | UNK | A | | JEWISH GENERAL HOSPITAL, CANADA |
| | UNK | A | | CENTERS FOR DISEASE CONTROL, GA USA |
| | MD | A | HEMATOLOGY/ONCOLOGY | UNIVERSITY OF CALIFORNIA, SAN FRANCISCO, CA USA |
| | PHD | A | | BIOQUAL, INC, MD USA |
| | PHD | A | | UC DAVIS, CA USA |
| | UNK | A | BIODEFENSE & MEDICAL VIROLOG | KUMAMOTO UNIVERSITY SCHOOL OF MEDICINE, JAPAN |
| | UNK | A | | CORNELL UNIVERSITY, NY USA |
| | PHD | A | MRC LAB MOLE CELL BIOL | UNIVERSITY COLLEGE LONDON, UK |
| | UNK | A | | MERCK RESEARCH LABORATORIES, NJ USA |
| | UNK | A | VETERINARY MEDICINE | UNIVERSITY OF FLORIDA, FL USA |
| | PHD | A | MICRO & IMMUNOL | WEILL MEDICAL COLLEGE, CORNELL UNIVERSITY, NY USA |
| | PHD | A | MICROBIOLOGY | UNIVERSITY OF ALABAMA, AL USA |
| | DVM, PHD | A | MICRO, MOL GEN & IMMUNOL | UNIVERSITY OF KANSAS MEDICAL CENTER, KS USA |

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|---|---|---|---|
| UNK | A | NIAID | NIH, MD USA |
| UNK | A | BIOLOGICAL SCIENCE | UNIVERSITY OF MONTANA, MT USA |
| UNK | A | | IRCCS POLICLINICO SAN MATTEO, ITALY |
| PHD | A | GENE THERAPY LABORATORY | LOUISIANA STATE UNIVERSITY HEALTH SCIENCES CENTER, LA USA |
| PHD | A | MICROBIOLOGY | UNIVERSITY OF PENNSYLVANIA, PA USA |
| UNK | A | | INSTITUTE OF MEDICAL &VETERINARY SCIENCE, AUSTRALIA |
| UNK | A | | VIROLOGIC, INC, CA USA |
| UNK | A | CTR FOR BIOMEDICAL RES | UNIVERSITY ERLANGEN-NUERNBERG, GERMANY |
| PHD | A | MICROBIOLOGY/IMM UNOLOGY | CENTER FOR BIOMEDICAL RESEARCH POPULATION COUNCIL, NY USA |
| UNK | A | | ST. LUKE'S-ROOSEVELT HOSPITAL CENER, NY USA |
| PHD | A | MICRO, IMMUNOL, BIOCHEMISTRY | MOREHOUSE SCHOOL OF MEDICINE, GA USA |
| PHD | A | VIROLOGY | LERNER RESEARCH INSTITUTE, OH USA |
| UNK | A | IMMUNOLOGY | WISCONSIN NAT'L PRIMATE RES CTR, WI USA |
| PHD | A | BIOCHEM & MOLECULAR PHARMACOL | UNIVERSITY OF MASSACHUSETTS MEDICAL CENTER, MA USA |
| PHD | A | BASIC SCIENCE | THE INSTITUTE OF HUMAN VIROLOGY, MD USA |
| UNK | A | | EAST CAROLINA UNIVERSITY, NC USA |
| MD, PHD | A | MEDICINE | DANA-FARBER CANCER INSTITUTE, MA USA |
| UNK | A | | UNIVERSITY OF POMPEU FABRA, SPAIN |
| UNK | A | CHEM ENGR | UNIVERSITY OF CALIFORNIA, BERKELEY, CA USA |
| MD | A | MOL BIO & GENETICS | HOWARD HUGHES MEDICAL INSTITUTE, MD USA |
| MD, PHD | A | | COLD SPRING HARBOR LABORATORIES, NY USA |
| PHD | A | IMMUNOLOGY AND MICROBIOLOGY | RUSH UNIVERSITY MEDICAL CENTER, IL USA |
| PHD | A | MOLECULAR MEDICINE | U MASS MED CTR, MA USA |
| PHD | A | NIAID | NIH, MD USA |
| PHD | A | LABORATORY OF IMMUNOLOGY | NATIONAL INSTITUTE ON AGING, MD USA |

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|---|---|---|---|---|
| [redacted] | UNK | A | VIROLOGY | UNIVERSITY OF STELLENBOSCH, SOUTH AFRICA |
| [redacted] | UNK | A | MICRO, PATH AND IMMUNOL | COLORADO STATE UNIVERSITY, CO USA |
| [redacted] | DVM, PHD | A | PATHOLOGY | TULANE NATIONAL PRIMATE RESEARCH CENTER, LA USA |
| [redacted] | UNK | A | PATHOLOGY | UNIVERSITY OF PENNSYLVANIA, PA USA |
| [redacted] | UNK | A | | UC SD SCHOOL OF MEDICINE, CA USA |
| [redacted] | MD | A | VIROLOGY | BECKMAN RESEARCH INSTITUTE, CA USA |
| [redacted] | PHD | A | MOLECULAR VIROLOGY | ST. LOUIS UNIVERSITY SCHOOL OF MEDICINE, MO USA |

**AXIS I CODES:** 2, 3, 6, 7A, 7B **AXIS II CODES:**31, 39, 66, 74G, 76

**ABSTRACT**

The Division of Microbiology is a major source of SIV reagents to the AIDS research community throughout the world. Reagents include recombinant plasmid clones containing SIV sequences, mutant clones, virus stocks, animal-titered virus stocks, and sera. Reagents are distributed via the NIH AIDS Repository and directly from the stores of the Microbiology Division. The Desrosiers laboratory has been one of the most significant contributors to the NIH AIDS Repository; twenty one individual reagents have been deposited and are distributed by the NIH Repository. The Division of Microbiology also continues to be a major source of other reagents, including stocks of herpesvirus saimiri and rhesus monkey rhadinovirus, assorted herpesvirus cloned DNAs, early passage rhesus monkey fibroblast cell lines, the 221 cell line, SEAP reporter cell lines and assorted other reagents.

## O-GLYCOSYLATION OF ALPHA-SYNUCLEIN IN PRIMATE BRAIN AND PARKIN BINDING (0413)

**NPRC UNIT:** NEUROCHEMISTRY

**%NPRC $:** 0.212%

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| SCHLOSSMACHER, MICHAEL G | MD | A | NEUROLOGY | BRIGHAM AND WOMEN'S HOSPITAL, MA USA |
| | PHD | A | PATHOLOGY | BRIGHAM & WOMEN'S HOSPITAL, MA USA |
| | UNK | A | | IMPERIAL COLLEGE OF LONDON, UK |
| | MD | A | NEUROLOGY | BRIGHAM & WOMEN'S HOSPITAL, MA USA |
| | PHD | C | NEUROCHEMISTRY | |
| | PHD | A | NEUROLOGY | BRIGHAM & WOMEN'S HOSPITAL, MA USA |
| | MD | A | NEUROLOGY | BRIGHAM & WOMEN'S HOSPITAL, MA USA |
| | MD | A | NEUROLOGY | BRIGHAM & WOMEN'S HOSPITAL, MA USA |
| | UNK | A | | IMPERIAL COLLEGE OF LONDON, UK |

**AXIS I CODES:** 1D, 2, 4, 21 **AXIS II CODES:**46, 74H

**ABSTRACT**

Introduction: We previously reported a link between alpha-synuclein and (A-S) and parkin, each of which is associated with Parkinson's disease (PD). We have now extended this work to show that glycosylated A-S is detectable in human and monkey brains, occurring as 20-22 kDa isoforms. cDNAs generated from cynomolgus and small squirrel monkey brain revealed 100% aa sequence identity with human A-S, in contrast to the 8 aa difference in mouse and rat, which have no detectable A-S(glyc) (even in human A-S transgenic mice). In human cortex, A-Sp22 (glyc) accounted for less than 1% of monomeric A-S detectable by Western blotting. Although human midbrain contained approximately 70% less unglycosylated A-Sp16 than did cortex, the relative amount of A-Sp22 (glyc) was approximately 5-fold higher in Substania nigra than cortex. Cortex from subjects with Pd, dementia and Lewy bodies and multiple system atrophy also contained Aa-Sp22 (glyc). Lectin-binding assays and glycosidase treatments revealed a mucin-type glycosylation of A-S: an O-linked disaccharide, N-acetylgalactosamine-alpha-1,4-galactosamine, with terminal sialic acid modification. Mass spectrometry of A-Sp22 (glyc) purified to homogeneity from human cortex identified 134 of the 140 aa, suggesting that the O-glycosylation occurs at the hydroxyl groups of Ser9 and/or Thr22. Importantly, only glycosylated A-S (but not human A-Sp16) interacted with parkin in vitro. Discussion: Our data suggest that a small fraction of primate brain A-S can undergo O-glycosylation, perhaps via passage through the secretory pathway, representing a rare but obligatory modification for subsequent recognition of A-Sp22 (glyc) by parkin. This post transitional modification of A-S may play a role in the pathogenesis of PD.

## BIOLOGICAL MATERIAL SAMPLE DISTRIBUTION (0397)

**NPRC UNIT:** PRIMATE RESOURCES

**%NPRC $:** 0.125% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| MANSFIELD, KEITH G | DVM | C | PRIMATE RESOURCES | |
| | MD | A | PEDIATRICS | CHILDREN'S HOSPITAL , MA USA |
| | PHD | A | EPIDEMIOLOGY & PUBLIC HEALTH | YALE MEDICAL SCHOOL, CT USA |
| | UNK | A | | JEWISH GENERAL HOSPITAL, MONTREAL, CANADA |
| | PHD | A | NEUROBIOLOGY | HARVARD MEDICAL SCHOOL, MA USA |
| | MD, PHD | A | MEDICINE | BRIGHAM AND WOMEN'S HOSPITAL, MA USA |
| | PHD | A | HEALTH SCIENCES | BOSTON U, MA USA |
| | MD | A | MEDICINE | BETH ISRAEL DEACONESS MEDICAL CENTER, MA USA |
| | PHD | A | | UC DAVIS, CA USA |
| | UNK | A | | SAIC, FREDERICK, MD USA |
| | DVM, PHD | A | INFECTIOUS DISEASE RESEARCH DE | SOUTHERN RESEARCH INSTITUTE, MD USA |
| | DVM | A | | TULANE NATIONAL PRIMATE RESEARCH CTR, LA USA |
| | MD | A | NEUROBIOLOGY | HARVARD MED SCH, MA USA |
| | UNK | A | | PAIN THERAPEUTICS, INC, CA USA |
| | UNK | A | WEILL MEDICAL COLLEGE | CORNELL UNIVERSITY, NY USA |
| | PHD | A | MEDICINE | BETH ISRAEL DEACONESS MEDICAL CENTER, MA USA |
| | UNK | A | WEILL MEDICAL COLLEGE | CORNELL UNIVERSITY, NY USA |
| | MD, PHD | A | SURGERY | MASSACHUSETTS GENERAL HOSPITAL, MA USA |
| | UNK | A | | ROSKAMP INSTITUTE, FL USA |
| | UNK | A | PATHOLOGY | UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL, WORCESTER, MA USA |
| | UNK | A | | WISCONSIN NAT'L PRC, WI USA |
| | UNK | A | | V A MEDICAL CENTER, MI USA |
| | PHD | A | MICROBIOLOGY & IMMUNOLOGY | UNIVERSITY OF OKLAHOMA HEALTH SCIENCE CTR, OK USA |
| | DMD | A | RST DENT & BIOMATERIALS | HARVARD SCHOOL OF DENTAL MEDICINE, MA USA |
| | UNK | A | | PFIZER, INC, CT USA |
| | PHD | A | BIOCHEMISTRY AND BIOPHYSICS | HOWARD HUGHES MEDICAL INSTITUTE, PA USA |
| | PHD | A | | VIRXSYS, GAITHERSBURG, MD USA |
| | PHD | A | | ABL-BASIC RESEARCH PROGRAM, FREDERICK, MD USA |

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|---|---|---|---|---|
| | PHD | A | PSYCHIATRY | UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL, MA USA |
| | MD, PHD | A | RADIOLOGY | MASSACHUSETTS GENERAL HOSPITAL, BOSTON, MA USA |
| | DVM, PHD | A | COMPARATIVE MEDICINE | MASS INSTITUTE OF TECHNOLOGY, MA USA |
| | DVM, PHD | A | MICROBIOL PATHOGENESIS | YALE UNIVERSITY SCHOOL OF MEDICINE, CT USA |
| | MD | A | DEPARTMENT OF MICROBIOLOGY | HOWARD HUGHES MEDICAL INSTITUTE, CA USA |
| | UNK | A | | BIORECLAMATION, INC, NY USA |
| | MD | A | ENDOCRINOLOGY & MET | UNIVERSITY OF TORONTO, CANADA |
| | PHD | A | MEDICINE | HARVARD MEDICAL SCHOOL, MA USA |
| | PHD | A | ANTHROPOLOGY | UNIVERSITY OF MASSACHUSETTS, AMHERST, MA USA |
| | BVMS | A | PATHOBIOLOGY | UNIVERSITY OF PENNSYLVANIA, PA USA |
| | MD, PHD | A | RADIOLOGY | MASSACHUSETTS GENERAL HOSPITAL, MA USA |
| | MD | A | FAM MED & COM HLTH | TUFTS U SCH MED, MA USA |
| | PHD | A | | MASSACHUSETTS COLLEGE OF PHARMACY AND ALLIED HEALTH, MA USA |
| | PHD | A | BRAIN AND COG SCI | MASSACHUSETTS INSTITUTE OF TECHNOLOGY, MA USA |
| | UNK | A | | INOVA THERAPEUTICS, VA USA |
| | PHD | A | PHYSIOLOGY, SOM | UNIVERSITY OF MARYLAND, MD USA |
| | UNK | A | GENETICS INSTRUCTION & RESEARC | WASHINGTON UNIVERSITY, MO USA |
| | PHD | A | PSYCHOLOGY | HARVARD MEDICAL SCHOOL, MA USA |
| | UNK | A | PHARMA & MOLECULAR SCIENCE | JOHNS HOPKINS UNIVERSITY, MD USA |
| | PHD | A | MOLECULAR BIOLOGY AND GENETICS | CORNELL UNIVERSITY, NY USA |
| | PHD | A | DERMATOLOGY | MASSACHUSETTS GENERAL HOSPITAL, MA USA |
| | UNK | A | IMMUNOBIOLOGY | HOWARD HUGHES MED./YALE UNIVERSITY, CT USA |
| | MD | A | | UNIVERSITY OF PENNSYLVANIA, PA USA |
| | PHD | A | SURGERY | MASSACHUSETTS GENERAL, MA USA |
| | UNK | A | | MOUNT SINAI HOSPITAL, CANADA |
| | DMSC, PHD | A | NEUROLOGY | MCLEAN HOSP, MA USA |

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|---|---|---|---|---|
| PHD | A | EPIDEMIOLOGY & PUBLIC HEALTH | YALE UNIVERSITY, CT USA |
| PHD | A | PSYCHIATRY & BEHAVIORAL SCIENC | UNIVERSITY OF MIAMI SCHOOL OF MEDICINE, FL USA |
| PHD | A | | CORNELL UNIVERSITY, NY USA |
| MD, PHD | A | | VA MEDICAL CENTER, MI USA |
| UNK | A | | MILLENNIUM PHARMACEUTICALS, MA USA |
| MD | A | MEDICINE | BRIGHAM AND WOMEN'S HOSPITAL, MA USA |
| PHD | A | INFECTIOUS DISEASES | TUFTS UNIVERSITY SCHOOL OF VETERINARY MEDICINE, MA USA |
| UNK | A | | MCARDLE LABORATORY FOR CANCER RESEARCH, WI USA |
| UNK | A | MEDICINE/ONCOLOGY | UNIVERSITY OF WASHINGTON, WA USA |
| UNK | A | | NCI, MD USA |
| PHD | A | MICROBIO & MOLECULAR GENETICS | HARVARD MED SCH, MA USA |
| MD, PHD | A | NEUROLOGY | MASSACHUSETTS GENERAL HOSPITAL, MA USA |
| PHD | A | AUTOIMMUNITY | IMMCO DIAGNOSTICS, NY USA |
| PHD | A | BIOCHEMISTRY | GEORGE WASHINGTON UNIVERSITY MEDICAL SCHOOL, MD USA |
| UNK | A | | POHANG UNIVERSITY OF SCIENCE AND TECHNOLOGY, KOREA |
| PHD | A | NEUROLOGY | BRIGHAM AND WOMEN'S HOSPTIAL, MA USA |
| MD | A | MEDICINE, VIRAL PATHOGENESIS | BETH ISRAEL DEACONESS MEDICAL CENTER, MA USA |
| PHD | A | | BIOQUAL, INC, MD USA |
| PHD | A | GENE EXPRESSION AND REGULATION | WISTAR INSTITUTE, PA USA |
| MD | A | AIDS VACCINE PROGRAM | NCI/FREDERICK, MD USA |
| PHD | A | NEUROBIOLOGY | HARVARD MEDICAL SCHOOL, MA USA |
| PHD | A | RADIOLOGY | MASS GENERAL HOSPITAL, BOSTON, MA USA |
| MD, PHD | A | SURGERY | BETH ISRAEL DEACONESS MEDICAL CENTER, MA USA |
| MD, PHD | A | CANCER IMMUNOLOGY AND AIDS | DANA FARBER CANCER INSTITUTE, MA USA |
| UNK | A | | CORNELL UNIVERSITY, NY USA |
| PHD | A | MOLECULAR MICROBIOLOGY | NIH, MD USA |
| PHD | A | | AARON DIAMOND AIDS RESEARCH CENTER, NY USA |

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|---|---|---|---|---|
| | UNK | A | GENE FUNCTION AND EXPRESSION | UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL, MA USA |
| | UNK | A | | MERCK RESEARCH LABORATORIES, NJ USA |
| | UNK | A | VETERINARY MEDICINE | UNIVERSITY OF FLORIDA, FL USA |
| | DMD | A | ORAL MEDICINE SECTION | UNIVERSITY OF KENTUCKY, COLLEGE OF DENTISTRY, KY USA |
| | UNK | A | | UNIVERSITY OF ROCHESTER, NY USA |
| | UNK | A | | EPIMMUNE, CA USA |
| | DVM, PHD | A | MICRO, MOL GEN & IMMUNOL | UNIVERSITY OF KANSAS MEDICAL CENTER, KS USA |
| | MD | A | REHABILITATION MEDICINE | BOSTON UNIVERSITY, MA USA |
| | PHD | A | PEDIATRICS | CHILDREN'S HOSPITAL, BOSTON, MA USA |
| | PHD | A | | POHANG UNIVERSITY, KOREA |
| | UNK | A | | PFIZER, INC, CT USA |
| | PHD | A | | UNIVERSITY OF WISCONSIN-MADISON, WI USA |
| | UNK | A | | MERCK RESEARCH LABORATORIES, NJ USA |
| | UNK | A | | ALTON OCHSNER HOSPITAL, LA USA |
| | UNK | A | | VIROLOGIC, INC, CA USA |
| | PHD | A | GENE THERAPY CENTER | TULANE HEALTH SCIENCE CENTER, LA USA |
| | MD | A | PATHOLOGY | OREGON HEALTH AND SCIENCE UNIVERSITY, OR USA |
| | UNK | A | CTR FOR BIOMEDICAL RES | UNIVERSITY ERLANGEN-NUERNBERG, GERMANY |
| | PHD | A | MICROBIOLOGY/IMMUNOLOGY | CENTER FOR BIOMEDICAL RESEARCH POPULATION COUNCIL, NY USA |
| | PHD | A | MICROBIOLOGY AND IMMUNOLOGY | ALBERT EINSTEIN COLLEGE OF MEDICINE, NY USA |
| | PHD | A | VIROLOGY | LERNER RESEARCH INSTITUTE, OH USA |
| | UNK | A | IMMUNOLOGY | WISCONSIN NAT'L PRIMATE RES CTR, WI USA |
| | MD | A | NEUROBIOLOGY | HARVARD MEDICAL SCHOOL, MA USA |
| | MD, PHD | A | NEUROBIOLOGY | HARVARD MEDICAL SCHOOL, MA USA |
| | DVM | A | MEDICINE, VIRAL PATHOGENESIS | BETH ISRAEL DEACONESS MEDICAL CENTER, MA USA |
| | UNK | A | INFECTIOUS DISEASES/MICRO | UNIVERSITY OF PITTSBURGH, PA USA |
| | PHD | A | | UNIVERSITY OF PITTSBURGH, PA USA |

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|---|---|---|---|---|
| | PHD | A | | UNIVERSITY OF PENNSYLVANIA SCHOOL OF MEDICINE, PA USA |
| | MD | A | PEDIATRICS | TULANE UNIVERSITY MEDICAL CENTER, LA USA |
| | MD, PHD | A | DERMATOLOGY | HARVARD MEDICAL SCHOOL, MA USA |
| | DVM, PHD | A | | MILLENNIUM PHARMACEUTICALS, INC, MA USA |
| | MD | A | MEDICINE | MASSACHUSETTS GENERAL HOSPITAL, MA USA |
| | PHD | A | CHEMISTRY | BROOKHAVEN NATIONAL LABORATORIES, NY USA |
| | UNK | A | | MERCK AND COMPANY, NJ USA |
| | MD | A | NEUROLOGY | BRIGHAM AND WOMEN'S HOSPITAL, MA USA |
| Name | UNK | A | PHYSICAL BIOSCIENCES | LAWRENCE BERKLEY NATIONAL LABORATORIES, CA USA |
| | UNK | A | | KOREA ADV INSTITUTE FOR SCIENCE AND TECHNOLOGY, KOREA |
| | MD, PHD | A | | COLD SPRING HARBOR LABORATORIES, NY USA |
| | UNK | A | | UNIVERSITY OF CALIFORNIA, CA USA |
| | UNK | A | IMMUNOLOGY | UNIVERSITY OF TENNESSEE SCHOOL OF MEDICINE, TN USA |
| Name | PHD | A | PEDIATRICS | CHILDREN'S HOSPITAL, MA USA |
| | PHD | A | MOLECULAR MEDICINE | U MASS MED CTR, MA USA |
| | UNK | A | | FRIEDRICH MIESCHER INSTSITUTE, SWITZERLAND |
| | BS, MPH | A | AIDS, STD AND TB LAB RESEARCH | CENTER FOR DISEASE CONTROL, GA USA |
| | MD | A | SURGERY | MASS GENERAL HOSPITAL, MA USA |
| | PHD | A | ANTHROPOLOGY | DUKE UNIVERSITY MED CTR, NC USA |
| | UNK | A | RHEUMATOLOGY | VANDERBILT UNIVERSITY, TN USA |
| | MD | A | GASTROENTEROLOGY | VAMC, WAYNE STATE U, MI USA |
| Name | UNK | A | MOLECULAR ANTHROPOLOGY | NEW YORK UNIVERSITY, NY USA |
| | UNK | A | GRAD SCHOOL OF BIOMED SCIENCES | UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL, WORCESTER, MA USA |
| | PHD | A | BIOLOGICAL SCIENCES | NEW ENGLAND COLLEGE OF OPTOMETRY, MA USA |
| | UNK | A | | VANDERBILT UNIVERSITY SCHOOL OF MEDICINE, TN USA |
| | UNK | A | | UNIVERSITY OF COLORADO HEALTH SCIENCE CENTER, CO USA |
| | UNK | A | | UNIVERSITY OF PENNSYLVANIA, PA USA |

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|---|---|---|---|---|
| | PHD | A | ANTHROPOLOGY | DUKE UNIVERSITY MEDICAL CENTER, NC USA |
| | MD, PHD | A | PATH, IMMUNO, & MOLE MICROBIOL | WASHINGTON UNIVERSITY SCHOOL OF MEDICINE, MO USA |
| | UNK | A | | NCI, MD USA |
| | MD | A | MEDICINE | BRIGHAM & WOMENS HOSP, MA USA |
| | PHD | A | ANATOMY | NE OHIO UNIVERSITY COLLEGE OF MEDICINE, OH USA |
| | PHD | A | PATHOLOGY & LAB MEDICINE | WISCONSIN NATL PRC, WI USA |
| | UNK | A | | CORNELL UNIVERSITY, NY USA |
| Names | PHD | A | MEDICINE | BETH ISRAEL DEACONESS MEDICAL CENTER, MA USA |
| | PHD | A | REPRO SCIENCES | OREGON NATIONAL PRIMATE RESEARCH CENTER, OR USA |
| | UNK | A | SCHOOL OF BIOLOGICAL SCIENCE | UNIVERSITY OF NEBRASKA, NE USA |
| | DSC | A | FAMILY MED & COM HLTH | TUFTS U SCHOOL OF MED, MA USA |
| | UNK | A | | LAMPIRE BIOLOGICAL LABORATORIES, PA USA |
| | MD, PHD | A | SURGERY | NORTHWESTERN UNIVERSITY FIENBERG SCHOOL OF MEDICINE, IL USA |
| | DMD | A | SCHOOL OF DENTAL MEDICINE | UNIVERSITY OF PENNSYLVANIA, PA USA |
| | PHD | A | | NCI/NIH, MD USA |
| names | PHD | A | | UNIVERSITY OF NEBRASKA MEDICAL CENTER, NE USA |
| | UNK | A | | BIOGEN, MA USA |

**AXIS I CODES:** 1A, 1D, 13, 16, 17 **AXIS II CODES:**31, 49, 64, 66, 72, 77

**ABSTRACT**

The Division of Primate Resources provides clinical support in the distribution of biological materials and provision of well defined research animals to both core and collaborative scientists. The NERPRC currently houses five major nonhuman colonies: 1) Rhesus macaque (Macaca mulatta) colony, 2) Long tail macaque (Macaca fascicularis) colony, 3) Common marmoset (Callithrix jacchus) colony, 4) Cotton top tamarin (Saguinus oedipus) colony and 5) Squirrel monkey (Saimiri sciureus) colony. Provision of biological samples is an essential core function that enhances access and allows a number of investigators to achieve their research objectives.

## TUMOR VIROLOGY SAMPLE DISTRIBUTION (0398)

**NPRC UNIT:** TUMOR VIROLOGY

**%NPRC $:** 1.157% **AIDS RELATED RESEARCH**

| INVESTIGATOR | DEGREES | STAFF CODE | DEPARTMENT | NON-HOST INSTITUTION: STATE, COUNTRY |
|---|---|---|---|---|
| JUNG, JAE U | PHD | C | TUMOR VIROLOGY | |
| | UNK | A | | SAIC, FREDERICK, MD USA |
| | UNK | A | WEILL MEDICAL COLLEGE | CORNELL UNIVERSITY, NY USA |
| | UNK | A | WEILL MEDICAL COLLEGE | CORNELL UNIVERSITY, NY USA |
| | PHD | A | MICROBIOLOGY & IMMUNOLOGY | UNIVERSITY OF OKLAHOMA HEALTH SCIENCE CTR, OK USA |
| | MD | A | DEPARTMENT OF MICROBIOLOGY | HOWARD HUGHES MEDICAL INSTITUTE, CA USA |
| | UNK | A | PHARMA & MOLECULAR SCIENCE | JOHNS HOPKINS UNIVERSITY, MD USA |
| | PHD | A | DERMATOLOGY | MASSACHUSETTS GENERAL HOSPITAL, MA USA |
| | UNK | A | | MOUNT SINAI HOSPITAL, CANADA |
| | PHD | A | BIOCHEMISTRY | GEORGE WASHINGTON UNIVERSITY MEDICAL SCHOOL, MD USA |
| | PHD | A | GENE EXPRESSION AND REGULATION | WISTAR INSTITUTE, PA USA |
| | DMD | A | ORAL MEDICINE SECTION | UNIVERSITY OF KENTUCKY, COLLEGE OF DENTISTRY, KY USA |
| | MD, PHD | A | TUMOR VIROLOGY | |
| | PHD | A | | POHANG UNIVERSITY, KOREA |
| | PHD | A | | UNIVERSITY OF PENNSYLVANIA SCHOOL OF MEDICINE, PA USA |
| | UNK | A | | FRIEDRICH MIESCHER INSTSITUTE, SWITZERLAND |
| | UNK | A | | UNIVERSITY OF PENNSYLVANIA, PA USA |
| | MD, PHD | A | PATH, IMMUNO, & MOLE MICROBIOL | WASHINGTON UNIVERSITY SCHOOL OF MEDICINE, MO USA |
| | UNK | A | SCHOOL OF BIOLOGICAL SCIENCE | UNIVERSITY OF NEBRASKA, NE USA |
| | DMD | A | SCHOOL OF DENTAL MEDICINE | UNIVERSITY OF PENNSYLVANIA, PA USA |
| | PHD | A | | UNIVERSITY OF NEBRASKA MEDICAL CENTER, NE USA |

**AXIS I CODES:** 1D, 2, 3, 4, 7A, 7B **AXIS II CODES:**31, 64, 66, 74G, 76, 83

**ABSTRACT**

The Division of Tumor Virology serves as a national and international resource for a variety of reagents of herpesvirus research community throughout the world. These reagents include recombinant DNAs, purified proteins, virus stocks, antibodies, cell lines, and techniques.

# RESEARCH SERVICES

| NAME | NON-HOST INSTITUTION: STATE, COUNTRY | # SPECIES: SPECIMEN |
|---|---|---|
| | CHILDREN'S HOSPITAL: MA | 5 MACACA MULATTA: WHOLE |
| | YALE UNIVERSITY MEDICAL SCHOOL: CT | 2 MACACA MULATTA: WHOLE |
| | YALE UNIVERSITY MEDICAL SCHOOL: CT | UNKNOWN: GENETIC MATERIAL |
| | JEWISH GENERAL HOSPITAL | UNKNOWN: CELLS |
| | HARVARD MEDICAL SCHOOL: MA | 4 MACACA MULATTA: WHOLE |
| | BRIGHAM AND WOMEN'S HOSPITAL: MA | UNKNOWN: CELLS |
| | BOSTON UNIVERSITY: MA | 1 MACACA MULATTA: WHOLE |
| | UNIVERSITY OF CALIFORNIA, DAVIS: CA | UNKNOWN: OTHERS |
| | NCI: MD | UNKNOWN: CELLS |
| | SOUTHEREN RESEARCH INSTITUTE: MD | UNKNOWN: OTHER SUB-CELLULAR |
| | TULANE NATIONAL PRIMATE RESEARCH CENTER: LA | UNKNOWN: TISSUES |
| | HARVARD MEDICAL SCHOOL: MA | 4 MACACA MULATTA: WHOLE |
| | PAIN THERAPEUTICS, INC: CA | UNKNOWN: TISSUES |
| | WEILL MEDICAL COLLEGE OF CORNELL UNIVERSITY: NY | UNKNOWN: GENETIC MATERIAL |
| | BETH ISRAEL DEACONESS HOSPITAL: MA | UNKNOWN: TISSUES |
| | WEILL MEDICAL COLLEGE OF CORNELL UNIVERSITY: NY | UNKNOWN: OTHER SUB-CELLULAR |
| | MASSACHUSETTS GENERAL HOSPITAL: MA | 4 CALLITHRIX JACCHUS: WHOLE |
| | HARVARD MEDICAL SCHOOL: MA | 2 MACACA MULATTA: WHOLE |
| | ROSKAMP INSTITUTE: FL | UNKNOWN: TISSUES |
| | UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL: MA | UNKNOWN: CELLS |
| | WISCONSIN NATIONAL PRIMATE RESEARCH CENTER: WI | UNKNOWN: OTHERS |
| | VA MEDICAL CENTER: MI | UNKNOWN: TISSUES |
| | UNIVERSITY OF OKLAHOMA HEALTH SCIENCE CTR: OK | UNKNOWN: GENETIC MATERIAL |
| | HARVARD SCHOOL OF DENTAL MEDICINE: MA | 2 MACACA FASCICULARIS: WHOLE |
| | PFIZER, INC: CT | MACACA MULATTA: CELLS |
| | HOWARD HUGHES MEDICAL INSTITUTE: P | UNKNOWN: GENETIC MATERIAL |

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|---|---|
| VIRXSYS, INC: MD | UNKNOWN: GENETIC MATERIAL |
| NCI, SAID: MD | MACACA MULATTA: CELLS |
| UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL: MA | 42 CALLITHRIX JACCHUS: WHOLE |
| MASSACHUSETTS GENERAL HOSPITAL: MA | UNKNOWN: OTHERS |
| HOWARD HUGHES MEDICAL INSTITUTE: CA | UNKNOWN: OTHERS |
| BIORECLAMATION, INC: NY | CALLITHRIX JACCHUS: CELLS |
| UNIVERSITY OF TORONTO | UNKNOWN: OTHERS |
| HARVARD MEDICAL SCHOOL: MA | UNKNOWN: OTHER SUB-CELLULAR |
| UNIVERSITY OF MASSACHUSETTS, AMHERST: MA | UNKNOWN: TISSUES |
| GENETICS INSTITUTE: MA | UNKNOWN: CELLS |
| UNIVERSITY OF PENNSYLVANIA: PA | UNKNOWN: TISSUES |
| MASSACHUSETTS GENERAL HOSPITAL: MA | 2 MACACA MULATTA: WHOLE |
| TUFTS UNIVERSITY SCHOOL OF MEDICINE: MA | 18 MACACA MULATTA: WHOLE |
| MASSACHUSETTS COLLEGE OF PHARMACY: MA | UNKNOWN: CELLS |
| MASSACHUSETTS INSTITUTE OF TECHNOLOGY: MA | 14 SAIMIRI SCIUREUS: WHOLE |
| INOVA THERAPEUTICS | UNKNOWN: TISSUES |
| UNIVERSITY OF MARYLAND, BALTIMORE: MD | 6 MACACA MULATTA: WHOLE |
| WASHINGTON UNIVERSITY: MO | UNKNOWN: OTHERS |
| HARVARD MEDICAL SCHOOL: MA | 5 CALLITHRIX JACCHUS: WHOLE |
| JOHNS HOPKINS UNIVERSITY: MD | UNKNOWN: CELLS |
| CORNELL UNIVERSITY: NY | UNKNOWN: CELLS |
| HOWARD HUGHES MEDICAL/YALE UNIVERSITY: CT | UNKNOWN: CELLS |
| MASSACHUSETTS GENERAL HOSPITAL: MA | UNKNOWN: GENETIC MATERIAL |
| UNIVERSITY OF PENNSYLVANIA: PA | UNKNOWN: OTHER SUB-CELLULAR |
| MASSACHUSETTS GENERAL HOSPITAL: MA | 6 MACACA MULATTA: WHOLE |
| MT. SINAI HOSPITAL | UNKNOWN: GENETIC MATERIAL |
| MCLEAN HOSPITAL: MA | 7 MACACA FASCICULARIS: WHOLE |
| YALE UNIVERSITY: CT | UNKNOWN: TISSUES |
| UNIVERSITY OF MIAMI SCHOOL OF MEDICINE: FL | UNKNOWN: TISSUES |
| VA MEDICAL CENTER: WI | UNKNOWN: OTHERS |

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|---|---|
| MILLENIUM PHARMACEUTICALS: MA | CALLITHRIX JACCHUS: CELLS |
| MILLENIUM PHARMACEUTICALS: MA | MACACA MULATTA: CELLS |
| MILLENIUM PHARMACEUTICLAS: MA | MACACA FASCICULARIS: CELLS |
| HARVARD MEDICAL SCHOOL: MA | 9 MACACA MULATTA: WHOLE |
| TUFTS UNIVERSITY SCHOOL OF VETERINARY MEDICINE: MA | UNKNOWN: TISSUES |
| MCARDLE LABORATORY FOR CANCER RESEARCH: WI | UNKNOWN: CELLS |
| UNIVERSITY OF WASHINGTON: WA | UNKNOWN: CELLS |
| NCI: MD | UNKNOWN: CELLS |
| HARVARD MEDICAL SCHOOL: MA | 6 MACACA MULATTA: WHOLE |
| MASSACHUSETTS GENERAL HOSPITAL: MA | UNKNOWN: OTHERS |
| IMMCO DIAGNOSTICS: NY | UNKNOWN: TISSUES |
| GEROGE WASHINGTON UNIVERSITY MEDICAL SCHOOL: MD | UNKNOWN: GENETIC MATERIAL |
| POHANG UNIVERSITY OF SCIENCE AND TECHNOLOGY | UNKNOWN: CELLS |
| BRIGHAM AND WOMEN'S HOSPITAL: MA | 11 CHLOROCEBUS AETHIOPS: WHOLE |
| BETH ISRAEL DEACONESS MEDICAL CENTER: MA | MACACA MULATTA: TISSUES |
| BETH ISRAEL DEACONESS MEDICAL CENTER: MA | 2 MACACA MULATTA: WHOLE |
| BIOQUAL, INC: MD | UNKNOWN: OTHER SUB-CELLULAR |
| WISTAR INSTITUTE: PA | UNKNOWN: CELLS |
| SAIC NCI: MD | UNKNOWN: OTHERS |
| HARVARD MEDICAL SCHOOL: MA | MACACA MULATTA: TISSUES |
| HARVARD MEDICAL SCHOOL: MA | 3 MACACA MULATTA: WHOLE |
| MASSACHUSETTS GENERAL HOSPITAL: MA | 3 MACACA MULATTA: WHOLE |
| BETH ISRAEL DEACONESS MEDICAL CENTER: MA | 12 MACACA FASCICULARIS: WHOLE |
| DANA-FARBER CANCER INSTITUTE: MA | UNKNOWN: CELLS |
| CORNELL UNIVERSITY: NY | UNKNOWN: CELLS |
| NIH: MD | UNKNOWN: OTHERS |
| AARON DIAMOND AIDS RESEARCH CENTER: NY | UNKNOWN: CELLS |
| MERCK RESEARCH LABORATORIES: NJ | UNKNOWN: OTHER SUB-CELLULAR |
| UNIVERISTY OF FLORIDA: FL | UNKNOWN: CELLS |
| UNIVERSITY OF KENTUCKY SCHOOL OF DENTISTRY: KY | UNKNOWN: CELLS |

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|---|---|
| VANDERBILT UNIVERSITY SCHOOL OF MEDICINE: TN | UNKNOWN: CELLS |
| UNIVERISITY OF COLORADO HEALTH SCIENCE CENTER: CO | UNKNOWN: CELLS |
| UNIVERSITY OF PENNSYLVANIA: PA | UNKNOWN: CELLS |
| DUKE UNIVERSITY MEDICAL CENTER: NC | UNKNOWN: TISSUES |
| WASHINGTON UNIVERSITY SCHOOL OF MEDICINE: MO | UNKNOWN: GENETIC MATERIAL |
| NCI: MD | UNKNOWN: CELLS |
| BRIGHAM AND WOMEN'S HOSPITAL: MA | UNKNOWN: OTHERS |
| NE OHIO UNIVERSITY COLLEGE OF MEDICINE: OH | UNKNOWN: TISSUES |
| WISCONSIN NATIONAL PRIMATE RESEARCH CENTER: WI | UNKNOWN: GENETIC MATERIAL |
| WISCONSIN NATIONAL PRIMATE RESEARCH CENTER: WI | UNKNOWN: CELLS |
| CORNELL UNIVERSITY: NY | UNKNOWN: CELLS |
| BETH ISRAEL DEACONESS MEDICAL CENTER: MA | UNKNOWN: TISSUES |
| OREGON NATIONAL PRIMATE RESEARCH CENTER: OR | UNKNOWN: CELLS |
| UNIVERSITY OF NEBRASKA: NE | UNKNOWN: CELLS |
| LAMPIRE BIOLOGICAL LABORATORIES: PA | CALLITHRIX JACCHUS: CELLS |
| NORTHWESTERN UNIVERSITY MEDICAL SCHOOL: IL | CALLITHRIX JACCHUS: CELLS |
| UNIVERSITY OF PENNSYLVANIA: PA | UNKNOWN: GENETIC MATERIAL |
| NCI, NIH: MD | HOMO SAPIEN: CELLS |
| UNIVERSITY OF NEBRASKA MEDICAL CENTER: NE | UNKNOWN: GENETIC MATERIAL |
| BIOGEN: MA | UNKNOWN: CELLS |

# PUBLISHED: ABSTRACTS, BOOKS & JOURNALS

‡ NPRC Cited *NPRC Personnel

| SPIDs | | Reference |
|---|---|---|
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| 0218 | ‡ | ABDEL-MOTAL, UM, JOHNSON, RP. Identification of SIV-specific T helper epitopes and their restricting alleles. 11th Conference on Retroviruses and Opportunistic Infections, February 8-11, 2004. San Francisco, CA |
| 0352 | ‡ | APETREI, C, KAUR, A, KOHLER, J, METZGER, M, STAPRANS, S, MCCLURE, HM, MARX, PA. SIVsm diversity in primate centers in the United States and its potential consequences for monitoring and psthogenesis. Oral Presentation - 21st Annual Symposium on Nonhuman Primate Models for AIDS. October 22-25, 2003. Seattle, Washington |
| 0244, 0242 | | BARBAS, H; HILGETAG, CC. Rules of cortical patterns of connections derived from quantitative anatomic data. IBRO, July, 2003 |
| | ‡ | CROMWELL M, ALVAREZ X, ALTMANN J, WESTMORELAND S, KLUMPP S, LUSTER A, LACKNER A, JOHNSON RP. Expression of lymphocyte homing receptors by SIV-specific CD8+ T-cells in the female reproductive tract of rhesus macaques. Conference on Retroviruses and Opportunistic Infections, February 10-14, 2003, Boston, MA |
| 0244, 0242 | | DERMON, CR; IOAKIMIDIS, J; MOSS, M; BARBAS, H. Altered expression of alpha 2 and beta adrenoceptors in prefrontal cortices of hypertensive rhesus monkeys. IBRO, July, 2003 |
| | ‡ | EVANS, D.T., BRICKER, J.E., SANFORD, H., LANG, S., JOHNSON, P.R., MANSFIELD, K.G., PIATEK, M., Jr., LIFSON, J.D., DESROSIERS, R.C. Immunization with Single-cycle SIV Stimulates Broad Virus-specific Immune Responses and Reduces Acute Plasma Viral Loads in Macaques after an Intravenous Challenge with SIVmac239. 21st Annual Symposium on Nonhuman Primate Models for AIDS. Seattle, Washington, October 22-25, 2003 |
| 0217 | ‡ | FOGG, MH, CHO, YG, KAUR, A, WANG, F. The rhesus LCV EBNA1 protein recognized by CTLS in the peripheral blood of rhesus macaques. Oral Presentation - 28th International Herpesvirus Workshop, July 26-31, 2003. Madison, WI |
| | ‡ | GAUDUIN M-C, BLANCOU P, YU Y, PIERCE J, O'CONNOR D, DODDS E, LIFSON JD, DESROSIERS R, WATKINS DI, JOHNSON RP. Evidence for functional SIV-specific CD8+ T cell responses in SIV-infected newborn macaques. Keystone Symposia; HIV Vaccine Development: Immunological & Biological Challenges. March 29 - April 4, 2003. Banff, Alberta, Canada |
| | ‡ | GAUDUIN M-C, O'CONNOR D, LIFSON JD, WATKINS DI, JOHNSON RP. Tat-specific cytotoxic T lymphocytes select for SIV escape in acutely infected rhesus newborns. Conference on Retroviruses and Opportunistic Infections, February 10-14, 2003, Boston, MA |
| 0419 | ‡ | GAUDUIN, M-C, WALSH, SR, BARABASZ, A, YU, Y, LIU, C, PIATAK, M, LIFSON, JD, ALTMAN, J, JOHNSON, RP. SIV-specific CD4+ and CD8+ T cell responses during the acute phase of SIV infection in rhesus macaques. 21st Annual Symposium on Nonhuman Primate Models for AIDS, Oct. 22-25, 2003, Seattle, WA |
| 0418 | ‡ | GAUDUIN, M-C, YU, Y, CARVILLE, A, PIATAK, M, CONNOLE, M, LIFSON, JD, JOHNSON, RP. Depletion of CD8+ lymphocytes results in rebound viremia in SIV-infected macaques with undetectable viral replication following early antiretroviral therapy. Keystone Symposium, HIV Vaccine & Pathogenesis, April 12-18, 2004, Whistler, BC |
| 0440 | ‡ | GUTTORMSEN, H-K, MANSFIELD, KG, KASPER, DL. Association between the structure of bacterial capsular polysaccharides and the degree of IGG isotype switching in humans. Abstract submitted to 12th International Congress of Immunology and 4th Annual Conference of FOCIS, 2003 |
| 0280 | | HARB, EN, THORN, F, TROILO, D. Accommodation during sustained near reading. Invest Ophthalmol Vis Sci (ARVO Suppl), 44(12), E-Abstract 2732, 2003 |
| 0448 | | HAUSER, MD, CHEN, K, CHEN, F, CHUANG, E. Give unto others: genetically unrelated cotton-top tamarin monkeys preferentially give food to those who give food back. Proceedings of the Royal Society, London, B 270:2363-2370, 2003 |

0448 HAUSER, MD, TSAO, F, GARCIA, P, SPELKE, ES. Evolutionary foundations of number: spontaneous representations of numerical magnitudes by cotton-top tamarins. Proceedings of the Royal Society, London, B 270: 1441-1446, 2003.

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‡ JOHNSON, W.E., SCHWALL, L., PARREN, P.W.H.I., BURTON, D.R., ROBINSON, J.E., LIFSON, J., DESROSIERS, R.C. Defined Genetic Changes in SIV that Result in Global Increases in Neutralization Sensitivity Also Increase Antibody Binding to Envelope Spikes on Virions. Cold Spring Harbor, N.Y., May 19-25, 2003.

0226 ‡ KAUR A, KASSIS N, HALE CL, SIMON M, ELLIOTT M, GOMEZ-YAFAL A, LIFSON JD, DESROSIERS, RC, WANG, F, BARRY, P, MACH, M, JOHNSON, RP. Direct relationship between suppression of virus-specific immunity and emergence of cytomegalovirus disease in simian AIDS. Oral Presentation - 9th International Cytomegalovirus Workshop. May 20-25, 2003. Maastvicht, The Netherlands

0226 ‡ KAUR A, KASSIS N, HALE CL, SIMON M, ELLIOTT M, GOMEZ-YAFAL A, LIFSON JD, DESROSIERS, RC, WANG, F, BARRY, P, MACH, M, JOHNSON, RP. Direct relationship between suppression of virus-specific immunity and emergence of cytomegalovirus disease in simian AIDS. Poster Presentation - Keystone Symposia on HIV Vaccine Development: Immunologic and Biological Challenges. March 29-April 4, 2003, Banff, Alberta, Canada

0434 ‡ KLITZING, PA, KAUFMAN, BM, POULIOT, AL, NOVAK, MA. Captive rhesus macaque (Macaca mulatta) search behavior on a vertical invisible displacement task. Am J Primatol 60:48-9, 2003.

0422 ‡ KNIPE, D, KAUR, A, WATANABE, D, BROCKMAN, M, MATHEWS, L, NDUNG'U, T, PAVLAKIS, G, DELUCA, N, DESROSIERS, R. Herpes simplex virus AIDS vaccine vectors show strong boosting of DNA-primed T cell responses. National Institutes of Health AIDS Vaccine Meeting. New York, NY. September 18-21, 2003

‡ LANG, S.M., ASTER, J.C., WANG, F., DESROSIERS, R.C. Establishment of persistently RRV infected Rhesus B celllines as a model to study viral latency and reactivation. Sixth International Workshop on KSHV/HHV8 and Related Rhadinoviruses, Glen Cove, New York, July 18-22, 2003

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| 0406 | ‡ | In press publication |

# SOURCE OF INVESTIGATORS' SUPPORT

## NON-FEDERAL

### FOUNDATION

| INVESTIGATOR ORGANIZATION | GRANT/CONTRACT | | TOTAL FUNDING | SPID |
|---|---|---|---|---|
| CHIOCCA, ENNIO ANTONIO | | | | |
| [ ] | [ private funding ] | $ | 74,000 | 0385 |
| DESROSIERS, RONALD C | | | | |
| [ ] | | $ | 73,472 | |
| [ name ] | | | | |
| [ private funding ] | 5128-04 | $ | 37,500 | 0310,0354,0404,0405 |
| IWASAKI, AKIKO | | | | |
| [ ] | | $ | 0 | 0330 |
| JOHNSON, R PAUL | | | | |
| [ private funding ] | | $ | 130,000 | 0418 |
| JOHNSON, WELKIN E | | | | |
| [ private funding ] | | $ | 36,000 | |
| JUNG, JAE U | | | | |
| [ private funding ] | 1583-01 | $ | 95,000 | 0310,0353,0354,0356,0404,0405 |
| LEMERE, CYNTHIA A | | | | |
| [ private funding ] | | | | 0442 |
| PHINNEY, DONALD G | | | | |
| [ private funding ] | 541720K1 | $ | 121,209 | 0445 |
| RAVIOLA, ELIO | | | | |
| [ ] — private funding | | $ | 26,900 | 0338 |
| [ name ] | | | | |
| [ ] private funding | | $ | 0 | |
| | **FOUNDATION** | $ | 594,081 | |

private funding

### INDUSTRY

| INVESTIGATOR ORGANIZATION | GRANT/CONTRACT | | TOTAL FUNDING | SPID |
|---|---|---|---|---|
| DOGON, I LEON | | | | |
| [ ] | GRANT | $ | 0 | 0250 |
| MADRAS, BERTHA K | | | | |
| [ ] | | $ | 20,915 | |
| ROWLETT, JAMES K | | | | |

private funding

[ ] private funding

| | | |
|---|---|---|
| CONTRACT | $ | 52,648 |
| INDUSTRY | $ | 73,563 |

## OTHER NON FEDERAL

| INVESTIGATOR ORGANIZATION | GRANT/CONTRACT | TOTAL FUNDING | SPID |
|---|---|---|---|
| ISACSON, OLE | 403142 | $ 102,378 | 0438 |
| [ ] - private funding KLEPPER-KILGORE, NANCY | | | 0441 |
| [ name ] [ private funding ] | | $ 0 | |
| | OTHER NON FEDERAL | $ 102,378 | |

## FEDERAL

| INVESTIGATOR ORGANIZATION | GRANT/CONTRACT | TOTAL FUNDING | SPID |
|---|---|---|---|
| **FEDERAL - PHS** | | | |
| ALDOVINI, ANNA | | | |
| NIH | 5R01AI041365-07 | $ 634,388 | 0240 |
| NIH | 1R21AI055291-01 | $ 242,250 | |
| [ name ] | | | |
| NIH | 5R21AI053488-02 | $ 160,000 | |
| NIH | 5R01AI057029-02 | $ 629,365 | |
| [ name ] | | | |
| NIH | 5R01NS041000-04 | $ 430,000 | |
| [ name ] | | | |
| NIH | 2R01CA082308-05 | $ 406,342 | |
| [ name ] | | | |
| NIH | 5U24RR018107-02 | $ 1,316,833 | |
| NIH | 5U42RR016025-04 | $ 1,097,716 | |
| [ name ] | | | |
| NIH | 3R01AI050463-02S1 | $ 48,000 | |
| NIH | 5R01AI050463-02 | $ 296,066 | |
| [ name ] | | | |
| NIH | 1P20CA096426-01A1 | $ 221,468 | |
| [ name ] | | | |
| NIH | 2R01AI035098-11 | $ 327,132 | |
| NIH | 2R01CA075080-06A1 | $ 307,504 | |
| NIH | 5T32CA009688-12 | $ 109,021 | |
| NIH | 1R21AI053900-01A1 | $ 254,132 | |
| NIH | 1R21DK065203-01 | $ 146,000 | |
| NIH | 5R01AI035098-10 | $ 256,255 | |
| [ name ] | | | |
| NIH | 5R01CA087986-04 | $ 31,500 | |
| NIH | 1R01CA099900-01 | $ 107,500 | |
| NIH | 1R01CA099163-01 | $ 243,565 | |
| BARBAS, HELEN | | | |
| NIH | 5R01NS024760-15 | $ 407,500 | 0242 |

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|---|---|---|---|---|
| NIH | 5R01MH057414-05 | $ | 179,830 | 0244 |
| C name 3 | | | | |
| NIH | 5R01AI049342-03 | $ | 454,338 | 0350 |
| NIH | 5R03AI053208-02 | $ | 74,250 | |
| C name 3 | | | | |
| NIH | 5R01AI047010-05 | $ | 325,809 | |
| C name 3 | | | | |
| NIH | 5R01AI051602-02 | $ | 389,250 | |
| NIH | 5R01AI038349-07 | $ | 346,000 | |
| NIH | 1R03AG022175-01 | $ | 86,500 | |
| C name 3 | | | | |
| NIH | 3R01GM032691-14A2 S1 | $ | 6,878 | |
| NIH | 1R41GM068413-01 | $ | 100,000 | |
| NIH | 2R01GM032691-14A2 | $ | 272,543 | |
| C name 3 | | | | |
| NIH | 5R01EY011379-08 | $ | 344,000 | |
| C name 3 | | | | |
| NIH | 5R01AI052057-02 | $ | 774,821 | |
| NIH | 5U01AI048494-04 | $ | 368,686 | |
| NIH | 5R01AI048053-04 | $ | 310,275 | |
| NIH | 5R37AI033292-12 | $ | 498,748 | |
| NIH | 1R01AI055332-01 | $ | 771,584 | |
| C name 3 | | | | |
| NIH | 5R01NS040666-04 | $ | 276,500 | |
| C name 3 | | | | |
| NIH | 5K08AI053971-02 | $ | 114,480 | |
| CARVILLE, ANGELA | | | | |
| NIH | 5R01CA089712-03 | $ | 9,745 | |
| NIH | 5R01RR013537-04 | $ | 64,350 | |
| NIH | 5R01AI044476-05 | $ | 0 | |
| C name 3 | | | | |
| NIH | 5R01CA068939-08 | $ | 276,073 | |
| C name 3 | | | | |
| NIH | 1K24DA016170-01 | $ | 142,438 | |
| C name 3 | | | | |
| NIH | 5R01HL064560-05 | $ | 609,000 | |
| C name 3 | | | | |
| NIH | 5R01MH064408-03 | $ | 318,000 | |
| C name 3 | | | | |
| NIH | 5R01CA089441-04 | $ | 601,407 | |
| NIH | 5R01CA092192-03 | $ | 396,250 | |
| C name 3 | | | | |
| NIH | 5R01MH046851-13 | $ | 322,731 | 0373,0375 |
| C name 3 | | | | |
| NIH | 3R01DK043183-11S1 | $ | 55,599 | |
| NIH | 5R01AI043274-06 | $ | 366,884 | |
| NIH | 5R01DK061297-02 | $ | 359,707 | |

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|---|---|---|---|---|
| NIH | 5R01DK043183-11 | $ | 295,176 | |
| DESROSIERS, RONALD C | | | | |
| NIH | 5P01AI035365-09 | $ | 851,420 | 0322,0406,0408 |
| NIH | 5R01AI050421-03 | $ | 382,500 | 0406 |
| NIH | 5R37AI025328-16 | $ | 430,205 | |
| NIH | 5P01DE014388-03 | $ | 168,133 | |
| NIH | 1P01AI46006-01 | $ | 250,000 | 0145 |
| C name | | | | |
| NIH | 5R01DA011541-05 | $ | 293,680 | |
| C name | | | | |
| NIH | 3R01DE014194-03S1 | $ | 49,597 | |
| NIH | 5R01DE014194-03 | $ | 303,050 | |
| NIH | 5R01NS040315-04 | $ | 279,125 | |
| NIH | 5R25GM064133-02 | $ | 348,277 | |
| NIH | 5T32AI049815-03 | $ | 165,596 | |
| C name | | | | |
| NIH | 5R01AI046942-04 | $ | 272,425 | |
| NIH | 5R01AI050469-03 | $ | 396,250 | |
| NIH | 5R01AI040880-07 | $ | 391,152 | |
| NIH | 5T32AI007632-04 | $ | 314,975 | |
| NIH | 1T32AI055400-01 | $ | 228,826 | |
| C name | | | | |
| NIH | 1R21AI052448-01A1 | $ | 289,116 | |
| EVANS, DAVID T. | | | | |
| NIH | 1K22AI052751-01 | $ | 162,000 | |
| C name | | | | |
| NIH | 5R01AI049155-03 | $ | 808,621 | |
| NIH | 5P01AI046007-05 | $ | 1,832,252 | |
| C name | | | | |
| NIH | 5R42DA013867-03 | $ | 250,000 | |
| NIH | 5R01DA013517-03 | $ | 401,392 | |
| NIH | 3R01DA013517-02S1 | $ | 24,726 | |
| NIH | 5R01MH052280-09 | $ | 241,385 | |
| NIH | 2R42DA013867-02 | $ | 250,000 | |
| C name | | | | |
| NIH | 1R01NS045534-01A1 | $ | 445,788 | |
| NIH | 5R01NS037567-05 | $ | 394,430 | |
| NIH | 5P30MH062261-04 | $ | 2,088,295 | |
| NIH | 5R01MH061224-05 | $ | 292,034 | |
| NIH | 5R01MH059468-05 | $ | 425,045 | |
| NIH | 5R21AA013836-02 | $ | 185,200 | |
| C name | | | | |
| NIH | 5R01CA067529-09 | $ | 323,306 | |
| NIH | 5R01AI050952-02 | $ | 331,000 | |
| NIH | 5R01AI037750-08 | $ | 331,000 | |
| NIH | 2T32RR007036-16 | $ | 420,599 | |
| C name | | | | |
| NIH | 5R01DA016549-02 | $ | 405,652 | |
| NIH | 5R01NS037277-06 | $ | 416,845 | |

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|---|---|---|---|---|
| NIH | 5R01NS035734-07 | $ | 340,448 | |
| NIH | 1R01DA016549-01 | $ | 394,129 | |
| E name 3 | | | | |
| NIH | 3R37AI030492-14S1 | $ | 28,917 | |
| NIH | 5R01AI046953-04 | $ | 400,780 | |
| NIH | 5R37AI030492-15 | $ | 424,615 | |
| NIH | 5T32AI007640-04 | $ | 173,491 | |
| NIH | 9R01AI055472-10 | $ | 523,200 | |
| E name 3 | | | | |
| NIH | 5R01AI046958-03 | $ | 310,275 | |
| NIH | 1R01AI054196-01A1 | $ | 375,400 | |
| E name 3 | | | | |
| NIH | 5R01CA096491-02 | $ | 336,717 | |
| NIH | 5R01CA073506-08 | $ | 275,456 | |
| E name 3 | | | | |
| NIH | 5R01CA096512-02 | $ | 323,526 | |
| E name 3 | | | | |
| NIH | 5R01HL059838-07 | $ | 568,249 | |
| NIH | 3R01GM056492-04S1 | $ | 112,247 | |
| GONZALEZ, R. GILBERTO | | | | |
| NIH | R01NS034626 | $ | 0 | 0252 |
| NIH | 5R01RR013213-03 | $ | 0 | 0252 |
| E name 3 | | | | |
| NIH | 5P01NS027405-15 | $ | 1,192,392 | |
| NIH | 5R01MH067734-02 | $ | 482,127 | |
| NIH | 5R01NS035743-08 | $ | 278,700 | |
| NIH | 2T35HL007789-11 | $ | 183,177 | |
| NIH | 2T32NS007180-22 | $ | 209,006 | |
| GORBACH, SHERWOOD L | | | | |
| NIH | 5R01RR013843-05 | $ | 469,080 | 0254 |
| NIH | 5P01DK045734-10 | $ | 1,443,538 | |
| NIH | 5P30DA013868-02 | $ | 978,519 | |
| NIH | 5T32AI007389-13 | $ | 275,358 | |
| E name 3 | | | | |
| NIH | 5R01NS025529-16 | $ | 383,696 | |
| NIH | 5R01MH060379-04 | $ | 243,575 | |
| NIH | 5R01HD028341-11 | $ | 337,477 | |
| NIH | 5R01EY012848-04 | $ | 366,702 | |
| E name 3 | | | | |
| NIH | 5K22HG000041-05 | $ | 267,360 | |
| NIH | 1R01GM067945-01 | $ | 472,728 | |
| E name 3 | | | | |
| NIH | 5R01AI042793-05 | $ | 301,765 | |
| NIH | 5R01AI019687-20 | $ | 344,250 | |
| E name 3 | | | | |
| NIH | 5R01AI049980-03 | $ | 197,500 | |
| NIH | 2R37CA013202-32 | $ | 363,563 | |
| E name 3 | | | | |
| NIH | 5R01HL056252-08 | $ | 329,303 | |

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|---|---|---|---|---|
| HAUSER, MARC D | | | | |
| NIH | 1R01DC005863-01A1 | $ | 259,578 | 0448 |
| NIH | 5R01AI024576-17 | $ | 327,000 | |
| NIH | 5R01CA081422-05 | $ | 292,994 | |
| NIH | 2R01AI024576-16A1 | $ | 303,157 | |
| NIH | 2R01GM004842-46A1 | $ | 305,689 | |
| NIH | 5R01NS008527-32 | $ | 392,500 | |
| NIH | 5T32AI007387-14 | $ | 273,393 | |
| NIH | 5R01AI049414-33 | $ | 389,250 | |
| NIH | 3U01CA062406-09S1 | $ | 134,083 | |
| NIH | 5P01CA069246-08 | $ | 2,177,781 | 0423 |
| NIH | 5R01DA014122-02 | $ | 306,603 | |
| NIH | 5K05DA000008-29 | $ | 119,264 | |
| NIH | 5R01AI049784-03 | $ | 758,178 | |
| NIH | 5R01AI045378-05 | $ | 466,665 | |
| NIH | 5P30AI045008-05 | $ | 1,425,153 | |
| IACOMINI, JOHN J | | | | |
| NIH | 5R01AI053666-02 | $ | 327,750 | |
| NIH | 5R01AI044268-05 | $ | 262,850 | |
| NIH | 1R01AI050602-01A2 | $ | 486,000 | |
| NIH | 5R01AI050894-03 | $ | 147,000 | |
| ISACSON, OLE | | | | |
| NIH | 5P50NS039793-05 | $ | 1,341,350 | 0263 |
| NIH | 5R01NS041263-04 | $ | 510,208 | 0264 |
| NIH | R01NS030064 | $ | 225,000 | 0261 |
| NIH | USAMRMC DAMD17-98-1-8618 | $ | 180,476 | 0260 |
| IWASAKI, AKIKO | | | | |
| NIH | 5R01AI039485-05 | $ | 0 | 0330 |
| NIH | 1R01AI054359-01A1 | $ | 282,048 | |
| NIH | 5R21DA013936-03 | $ | 189,375 | |
| NIH | 1R01DA015119-01A2 | $ | 189,375 | |
| NIH | 5R01DA011960-00 | $ | 131,745 | 0166 |
| NIH | 3P01CA080124-03S1 | $ | 418,679 | |
| NIH | 2T32CA073479-06 | $ | 225,925 | |
| NIH | 1P01AI056354-01 | $ | 776,021 | |
| JOHNSON, R PAUL | | | | |
| NIH | 5P01AI056356-02 | $ | 56,917 | |
| NIH | 5P01CA069246-08 | $ | 88,146 | 0423 |

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|---|---|---|---|---|
| NIH | 5R01AI045314-04 | $ | 228,840 | 0218,0419,0420 |
| NIH | 1R21AI055384-01A1 | $ | 294,219 | |
| NIH | 5R01CA073473-06 | $ | 340,425 | 0323,0346,0348,0417 |
| NIH | P01AI45992-04 | $ | 0 | 0222 |
| NIH | 5R01RR14447-03 | $ | 89,422 | 0270 |
| NIH | 5P01AI35365-09 | $ | 424,316 | 0425,0426 |
| NIH | 5R01AI39755 | $ | 108,400 | 0210 |
| NIH | 5P01AI48244-03 | $ | 0 | |
| JOHNSON, WELKIN E | | | | |
| NIH | 5R01AI057039-02 | $ | 295,750 | |
| JUNG, JAE U | | | | |
| NIH | 5R01CA091819-03 | $ | 306,478 | 0354,0356 |
| NIH | 5R01CA086841-04 | $ | 275,400 | 0405 |
| NIH | 5R01CA031363-20 | $ | 325,394 | 0310,0353,0404 |
| NIH | 2R01CA082057-05 | $ | 357,435 | 0353,0354,0356 |
| NIH | 1P01AI46006-04 | $ | 146,000 | |
| KASPER, DENNIS L | | | | |
| NIH | 5R01AI039576-07 | $ | 385,600 | |
| NIH | 1U54AI057159-01 | $ | 4,152,399 | |
| NIH | 2R01AI039576-06A2 | $ | 192,800 | |
| NIH | 2T32AI007061-26 | $ | 437,779 | |
| E name | | | | |
| NIH | 5R01DA014674-02 | $ | 368,204 | |
| KAUR, AMITINDER | | | | |
| NIH | 7P30AI042851 | $ | 5,000 | 0324 |
| NIH | 5R01AI043890-06 | $ | 422,500 | 0226,0324,0325,0421,0424 |
| NIH | 5R01AI049809-03 | $ | 294,690 | 0352 |
| NIH | 5R01AI049342-02 | $ | 55,288 | |
| NIH | 5P01DE14388-03 | $ | 83,151 | 0217 |
| E name | | | | |
| NIH | 5R01CA082036-05 | $ | 346,658 | |
| E name | | | | |
| NIH | 5R01HL046401-14 | $ | 343,963 | |
| E name | | | | |
| NIH | 5R01CA085180-04 | $ | 705,115 | |
| NIH | 5R01CA047006-16 | $ | 657,708 | |
| NIH | 5T32CA009031-28 | $ | 291,902 | |
| E name | | | | |
| NIH | 1R01HL074162-01 | $ | 432,500 | |
| NIH | 1R21DK063324-01 | $ | 173,000 | |
| E name | | | | |
| NIH | 5R01AI049781-02 | $ | 275,625 | |
| E name | | | | |
| NIH | 1K02NS045607-01 | $ | 176,418 | |
| E name | | | | |

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|---|---|---|---|---|
| NIH | 1UC6AI058618-01 | $ | 128,021,180 | |
| NIH | 5R21AI053376-02 | $ | 216,368 | |
| NIH | 5R01AI037241-08 | $ | 402,500 | |
| KLUMPP, SHERRY A | | | | |
| NIH | 5T32RR007000-28 | $ | 233,160 | |
| NIH | 5P01DE014388-03 | $ | 5,535 | |
| KNIPE, DAVID | | | | |
| NIH | 5P01AI046006-05 | $ | 984,549 | 0331,0422 |
| NIH | 5R01AI020530-18 | $ | 380,218 | |
| NIH | 2T32AI007245-21 | $ | 451,970 | |
| name | | | | |
| NIH | 1R21NS045327-01 | $ | 205,438 | |
| name | | | | |
| NIH | 5R01DA008648-08 | $ | 495,528 | |
| name | | | | |
| NIH | 1R21AI060463-01 | $ | 191,458 | |
| NIH | 5R01AI051996-02 | $ | 700,144 | |
| NIH | 1R01AI051996-01A1 | $ | 718,554 | |
| name | | | | |
| NIH | 5R01CA039207-20 | $ | 311,099 | |
| KURODA, MARCELO J. | | | | |
| NIH | 5R01AI048400-03 | $ | 464,530 | 0332 |
| name | | | | |
| NIH | 5R01NS030769-13 | $ | 365,152 | |
| NIH | 1C06RR017563-01A1 | $ | 2,499,064 | |
| NIH | 5R01MH061192-06 | $ | 293,022 | |
| NIH | 5R01DK050550-10 | $ | 480,651 | |
| NIH | 1G20RR018397-01 | $ | 697,400 | |
| LEMERE, CYNTHIA A | | | | |
| NIH | 5R01AG020159-03 | $ | 420,400 | |
| LETVIN, NORMAN L | | | | |
| NIH | 2R01AI020729-21 | $ | 663,778 | 0443 |
| name | | | | |
| NIH | 5R01AI056992-02 | $ | 621,203 | |
| NIH | 5U01AI041531-06 | $ | 1,850,423 | |
| NIH | 1R01AI056992-01 | $ | 302,155 | |
| NIH | 5T32AI007395-14 | $ | 123,282 | |
| name | | | | |
| NIH | 5R01GM054687-07 | $ | 304,642 | |
| NIH | 5R01CA093606-02 | $ | 303,788 | |
| NIH | 5R01CA085678-03 | $ | 261,601 | |
| LIVINGSTONE, MARGARET S | | | | |
| NIH | 5R01EY013135-04 | $ | 339,800 | |
| name | | | | |
| NIH | 5T32CA009216-23 | $ | 113,374 | |
| NIH | 2R01CA057683-11 | $ | 312,600 | |
| NIH | 5R01CA057683-10 | $ | 292,637 | |
| LU, SHAN | | | | |
| NIH | 5R21AI044338-02 | $ | 0 | |

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|---|---|---|---|---|
| NIH | 1U01AI056536-01 | $ | 550,179 | |
| [ name ] | | | | |
| NIH | 5R01AI050892-02 | $ | 404,263 | |
| NIH | 5R01CA069212-08 | $ | 423,996 | |
| NIH | 5R01AI046999-04 | $ | 419,829 | |
| NIH | 5R01AI040618-07 | $ | 413,374 | |
| NIH | 2T32AR007258-26 | $ | 229,364 | |
| MADRAS, BERTHA K | | | | |
| NIH | 5K05DA015305-02 | $ | 116,251 | 0188,0189,0201,0409,0410,0411,0412,0414,0415 |
| NIH | 5R01DA011558-07 | $ | 374,943 | 0188,0189,0199,0201,0382,0411,0415,0416 |
| NIH | 4R37DA006303-14 | $ | 380,250 | 0188,0189,0199,0201,0382,0409,0410,0411,0412,0414,0415,0416 |
| MAKI, TAKASHI | | | | |
| NIH | 5R01DK060721-03 | $ | 282,625 | |
| MANSFIELD, KEITH G | | | | |
| NIH | 5U42RR016020-04 | $ | 85,169 | 0344 |
| NIH | 5R01AI041365-07 | $ | 166,851 | |
| NIH | 5P01DK055510-03 | $ | 759,067 | 0401 |
| NIH | 1R01RR13843-04 | $ | 123,447 | |
| NIH | 5P01AI35365-09 | $ | 293,134 | |
| MARASCO, WAYNE A. | | | | |
| NIH | 5R01AI052829-02 | $ | 425,370 | |
| NIH | 5R21AI053822-02 | $ | 256,500 | |
| NIH | 5R01AI048436-03 | $ | 309,713 | |
| NIH | 1R21AI054268-01 | $ | 254,370 | |
| MARTIN, JOSEPH B | | | | |
| NIH | 1G20RR018322-01 | $ | 616,349 | |
| [ name ] | | | | |
| NIH | 5R01HL065937-04 | $ | 240,000 | |
| MEANS, ROBERT E. | | | | |
| NIH | 1R21CA102535-01 | $ | 100,000 | |
| [ name ] | | | | |
| NIH | 2R01AI039126-09 | $ | 108,750 | |
| NIH | 5R01AI051166-02 | $ | 253,750 | |
| [ name ] | | | | |
| NIH | 3R01DA002632-24S1 | $ | 63,000 | |
| NIH | 1R01AA013983-01A1 | $ | 487,904 | |
| [ name ] | | | | |
| NIH | 5R01DE014142-03 | $ | 266,159 | |
| [ name ] | | | | |
| NIH | 5U01AI051694-02 | $ | 437,083 | 0335 |

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|---|---|---|---|---|
| NIH | 5R01AI014551-25 | $ | 297,500 | |
| name | | | | |
| NIH | 5R01AG016839-05 | $ | 263,344 | |
| NIH | 1R01GM066287-01A1 | $ | 294,030 | |
| name | | | | |
| NIH | 2R01AI025850-16 | $ | 309,211 | |
| NIH | 5R01CA049296-13 | $ | 293,781 | |
| NIH | 5T32AI049820-03 | $ | 279,338 | |
| NIH | 5R01AI047758-04 | $ | 266,817 | |
| name | | | | |
| NIH | 5P01AI052048-03 | $ | 1,364,201 | |
| NIH | 5R01AI045463-06 | $ | 486,773 | |
| NIH | 5R01AI041420-08 | $ | 423,750 | |
| NIH | 1R21AI054159-01 | $ | 291,740 | |
| NIH | 4R37AI036082-11 | $ | 404,985 | |
| name | | | | |
| NIH | 1R21DE015535-01 | $ | 217,500 | |
| NIH | 5R01NS044508-02 | $ | 344,375 | |
| NIH | 5R37AI034749-10 | $ | 249,051 | |
| NIH | 1R01MH067736-01 | $ | 290,000 | |
| NIH | 1R21NS045346-01 | $ | 172,188 | |
| name | | | | |
| NIH | 5P20RR016443-03 | $ | 2,123,599 | |
| NIH | 5R01AI051220-02 | $ | 712,734 | |
| NIH | 5R01RR006753-13 | $ | 690,390 | |
| NIH | 5R01NS040238-05 | $ | 600,247 | |
| NEUTRA, MARIAN R | | | | |
| NIH | 5P30DK034854-20 | $ | 934,759 | |
| NIH | 5R01HD017557-21 | $ | 283,264 | |
| NIH | 2P01AI035365-09 | $ | 0 | 0386 |
| NOVAK, MELINDA A | | | | |
| NIH | 5R01RR011122-07 | $ | 250,000 | 0369,0371,03<br>74,0431,0432<br>,0433,0434 |
| name | | | | |
| NIH | 1R01MH067769-01 | $ | 511,887 | |
| name | | | | |
| NIH | 1R21AI054266-01A1 | $ | 210,000 | |
| NIH | 1R03AI054388-01 | $ | 70,000 | |
| O'NEIL, SHAWN P | | | | |
| NIH | 5R01DE012936-04 | $ | 285,941 | |
| NIH | 5P01DK055510-04 | $ | 128,642 | |
| NIH | 7R01MH061232-05 | $ | 378,020 | 0357 |
| name | | | | |
| NIH | 5U01CA086739-04 | $ | 86,179 | |
| name | | | | |
| NIH | 5R01MH054718-07 | $ | 253,750 | |
| name | | | | |
| NIH | 3P01AI026507-14S1 | $ | 1,126,760 | |

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|---|---|---|---|---|
| [ name ] | | | | |
| NIH | 1R21DK062920-01 | $ | 142,000 | |
| [ name ] | | | | |
| NIH | 3R01CA069632-07S1 | $ | 72,910 | |
| NIH | 5R01CA069632-07 | $ | 322,548 | |
| NIH | 5T32CA009140-29 | $ | 649,568 | |
| [ name ] | | | | |
| NIH | 3R01RR006555-12S1 | $ | 33,150 | |
| NIH | 5R01RR006555-12 | $ | 232,050 | |
| NIH | 5R37AI028433-12 | $ | 217,086 | |
| PHINNEY, DONALD G | | | | |
| NIH | 5R01NS039033-03 | $ | 259,875 | |
| [ name ] | | | | |
| NIH | 1R01AI054292-01 | $ | 692,773 | |
| [ name ] | | | | |
| NIH | 5K08AI051158-02 | $ | 109,620 | |
| [ name ] | | | | |
| NIH | 5R01AI038577-10 | $ | 301,000 | |
| NIH | 1R01AI057182-01 | $ | 336,000 | |
| NIH | 5R01GM062502-03 | $ | 301,860 | |
| NIH | 5T32CA086878-04 | $ | 240,400 | |
| NIH | 5T32AI007498-09 | $ | 133,517 | |
| NIH | 5R01AI034893-11 | $ | 424,833 | |
| NIH | 4R37AI033456-12 | $ | 566,621 | |
| [ name ] | | | | |
| NIH | 5R01NS044513-02 | $ | 298,300 | |
| NIH | 5R01NS041864-04 | $ | 318,000 | |
| NIH | 5R21AA013849-02 | $ | 157,000 | |
| [ name ] | | | | |
| NIH | 1R01DE015512-01 | $ | 520,051 | |
| NIH | 5R01AI040877-07 | $ | 751,768 | |
| [ name ] | | | | |
| NIH | 5R01NS043110-02 | $ | 358,633 | |
| NIH | 5R01NS039191-05 | $ | 294,156 | |
| [ name ] | | | | |
| NIH | 5D43TW001403-04 | $ | 254,553 | |
| NIH | 5R01AI030861-09 | $ | 482,132 | |
| NIH | 5T32AI007501-09 | $ | 244,409 | |
| [ name ] | | | | |
| NIH | 5K23AI001780-05 | $ | 122,256 | |
| [ name ] | | | | |
| NIH | 5R01AI043198-08 | $ | 357,750 | |
| NIH | 5R21AI054181-02 | $ | 238,500 | |
| NIH | 5R01AI041404-08 | $ | 397,500 | |
| NIH | 2R01AI043198-07 | $ | 178,875 | |
| RASO, VICTOR | | | | |
| NIH | 3R44AG015746-03S1 | $ | 133,750 | 0273 |
| NIH | 1R44AG023461-01 | $ | 100,000 | |
| NIH | 5R01AG017658-04 | $ | 420,400 | 0273 |

| | | | | |
|---|---|---|---|---|
| NIH | 1R01CA105218-01 | $ | 272,340 | |
| NIH | 5R01CA063417-07 | $ | 334,737 | |
| NIH | 1R21AI055383-01 | $ | 229,500 | |
| RAVIOLA, ELIO | | | | |
| NIH | 5R01EY001344-28 | $ | 619,238 | |
| NIH | 3R01EY010115-12S1 | $ | 43,707 | |
| NIH | 5R01EY012815-04 | $ | 333,271 | |
| NIH | 5R01EY010115-12 | $ | 430,000 | |
| NIH | 2P30EY012196-06 | $ | 624,023 | |
| REIMANN, KEITH A | | | | |
| NIH | 5R24RR016001-04 | $ | 693,540 | 0446 |
| NIH | 5R01MH061205-05 | $ | 311,737 | |
| NIH | 1R01CA099905-01A1 | $ | 297,371 | |
| NIH | 3R01DA009448-09S1 | $ | 176,718 | |
| NIH | 5K24DA015116-02 | $ | 121,270 | |
| NIH | 5R01DA014178-03 | $ | 690,786 | |
| NIH | 5R01DA009448-09 | $ | 521,329 | |
| NIH | 3P01AI043045-05S1 | $ | 1,119,409 | |
| NIH | 5P01AI049364-03 | $ | 3,892,120 | |
| NIH | 5R01AI046275-05 | $ | 241,067 | |
| NIH | 5R01AI024030-16 | $ | 297,000 | |
| NIH | 1R21AI052844-01A1 | $ | 222,750 | |
| NIH | 5R24RR015383-04 | $ | 317,120 | |
| NIH | 5R01RR008781-10 | $ | 308,000 | |
| NIH | 5R01MH065462-02 | $ | 396,000 | |
| NIH | 2R37AI040357-08 | $ | 163,500 | |
| NIH | 2R01AI045510-05 | $ | 637,975 | |
| NIH | 5P01AG000001-28 | $ | 2,032,301 | |
| ROSENZWEIG, MICHAEL | | | | |
| NIH | 1R43AI056508-01 | $ | 181,532 | |
| NIH | 5R21AI051213-02 | $ | 1 | |
| NIH | 1R01HL074704-01 | $ | 437,500 | |
| NIH | 5R01AI042552-07 | $ | 306,250 | |
| NIH | 5R37AI029329-15 | $ | 485,121 | |
| NIH | 5R01MH057635-10 | $ | 349,839 | |

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|---|---|---|---|---|
| NIH | 3R01MH057635-09S1 | $ | 45,977 | |
| NIH | 1R01DA017204-01 | $ | 356,000 | |
| NIH | 5R01MH061887-04 | $ | 229,500 | |
| NIH | 5K02MH001366-08 | $ | 118,584 | |
| ROWLETT, JAMES K | | | | |
| NIH | 5R01DA013591-02 | $ | 50,000 | 0427 |
| NIH | 5R01DA011792-05 | $ | 161,027 | 0373,0375,04 27,0430 |
| [illegible] | | | | |
| NIH | 5R37AI034266-09 | $ | 689,455 | |
| NIH | 5P01AI048240-04 | $ | 1,966,903 | |
| NIH | 5R01RR014180-05 | $ | 739,280 | |
| NIH | 5R01DE012937-05 | $ | 386,329 | |
| NIH | 1R21AI054183-01 | $ | 497,060 | |
| [illegible] | | | | |
| NIH | 5R01MH064647-02 | $ | 357,194 | |
| [illegible] | | | | |
| NIH | 5R01HL060528-07 | $ | 432,500 | |
| NIH | 5R01CA084156-04 | $ | 344,966 | |
| NIH | 1R01HL073714-01 | $ | 605,500 | |
| [illegible] | | | | |
| NIH | 5R01HL044851-13 | $ | 432,500 | |
| NIH | 3R01DK050234-09S1 | $ | 193,308 | |
| NIH | 5R01HL065909-03 | $ | 408,290 | |
| NIH | 5R01DK050234-09 | $ | 341,374 | |
| NIH | 5U01CA071375-09 | $ | 418,282 | |
| [illegible] | | | | |
| NIH | 5F31DA015874-02 | $ | 44,722 | |
| [illegible] | | | | |
| NIH | 5R37AI041980-07 | $ | 195,507 | |
| [illegible] | | | | |
| NIH | 5R01AI048394-03 | $ | 496,777 | |
| SEHGAL, PRABHAT K | | | | |
| NIH | 1U01AI051694-02 | $ | 177,113 | |
| NIH | 5R01RR016030-02 | $ | 53,944 | |
| NIH | 1R21AI044338-02 | $ | 0 | |
| [illegible] | | | | |
| NIH | 5R37AG006173-17 | $ | 410,875 | |
| NIH | 2P01AG015379-06 | $ | 2,961,344 | |
| NIH | 2R01AG012749-08 | $ | 366,418 | |
| [illegible] | | | | |
| NIH | 5R01AI056268-02 | $ | 845,827 | |
| SHANNON, RICHARD P | | | | |
| NIH | 1R01HL075836-01 | $ | 580,859 | |
| NIH | R01HL59070 | $ | 0 | 0277 |
| [illegible] | | | | |
| NIH | 5R37GM034277-19 | $ | 432,759 | |
| NIH | 5P01CA042063-18 | $ | 1,594,788 | |
| [illegible] | | | | |

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|---|---|---|---|---|
| NIH | 5T32GM007309-29 | $ | 2,108,272 | |
| NIH | 5R01AI051178-02 | $ | 363,951 | |
| [name] | | | | |
| NIH | 1R21AI054234-01A1 | $ | 331,100 | |
| NIH | 1R01AI052755-01A1 | $ | 400,000 | |
| [name] | | | | |
| NIH | 2R01AI042561-06 | $ | 622,495 | |
| [name] | | | | |
| NIH | 2R01AI035522-11A1 | $ | 194,802 | |
| NIH | 5R01DE012926-05 | $ | 290,579 | |
| [name] | | | | |
| NIH | 5R01AI049099-02 | $ | 342,000 | |
| NIH | 5R01AI041851-07 | $ | 427,500 | |
| NIH | 5R01AI040895-07 | $ | 562,349 | |
| NIH | 5R01AI039420-08 | $ | 331,974 | |
| NIH | 5R01AI033832-11 | $ | 520,059 | |
| NIH | 5P30AI028691-15 | $ | 1,619,026 | |
| NIH | 5R37AI024755-17 | $ | 603,316 | |
| NIH | 2R01AI031783-13 | $ | 415,829 | |
| [name] | | | | |
| NIH | 5R01CA010056-37 | $ | 414,048 | |
| SPEALMAN, ROGER D | | | | |
| NIH | 5R01DA011054-06 | $ | 382,500 | 0364,0378,0428,0435 |
| NIH | 5R01DA000499-29 | $ | 336,785 | 0163,0364,0428,0429,0435 |
| NIH | 2R01DA011928-06 | $ | 338,000 | 0166,0378 |
| NIH | 1R21AA013850-01 | $ | 153,000 | 0375 |
| NIH | 5R01DA011541-04 | $ | 22,874 | |
| [name] | | | | |
| NIH | 1R01AI058057-01 | $ | 338,000 | |
| NIH | 1R01CA095318-01A2 | $ | 320,400 | |
| NIH | 2R01CA052004-15 | $ | 338,400 | |
| NIH | 5R01CA087650-04 | $ | 324,000 | |
| NIH | 5R01CA058524-10 | $ | 265,501 | |
| NIH | 5R01CA043143-17 | $ | 284,800 | |
| [name] | | | | |
| NIH | 1R01MH064019-01A2 | $ | 570,674 | |
| [name] | | | | |
| NIH | 1R01HL075766-01 | $ | 759,317 | |
| NIH | 1R21AI054260-01 | $ | 400,000 | |
| [name] | | | | |
| NIH | 2R01GM026154-33 | $ | 266,203 | |
| [name] | | | | |
| NIH | 3R01AI038996-07S1 | $ | 87,502 | |
| NIH | 5R01AI048833-05 | $ | 318,000 | |
| NIH | 5R01AI038996-07 | $ | 238,500 | |
| [name] | | | | |
| NIH | 5R01AI032890-12 | $ | 312,000 | |
| NIH | 5R01RR011589-09 | $ | 439,417 | |

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|---|---|---|---|---|
| NIH | 5R01MH064411-08 | $ | 318,000 | |
| NIH | 5R01AI049152-03 | $ | 318,000 | |
| NIH | 5P30AI042845-06 | $ | 678,632 | |
| NIH | 5R37AI037475-10 | $ | 351,000 | |
| [name] | | | | |
| NIH | 1R21MH069122-01 | $ | 157,000 | |
| NIH | 1U01AI056456-01 | $ | 270,950 | |
| NIH | 5P01AI048244-04 | $ | 865,618 | |
| NIH | 5R01AI041399-06 | $ | 504,472 | |
| [name] | | | | |
| NIH | 5R01NS044819-11 | $ | 412,791 | |
| NIH | 5R21NS044231-02 | $ | 188,219 | |
| [name] | | | | |
| NIH | 2S07RR018165-02 | $ | 149,916 | |
| NIH | 5P01AI049320-03 | $ | 1,036,550 | |
| [name] | | | | |
| NIH | 5P30AI050410-06 | $ | 1,587,705 | |
| NIH | 5R01AI050485-02 | $ | 326,074 | |
| NIH | 2T32AI007419-11 | $ | 187,605 | |
| NIH | 1R01MH067751-01 | $ | 493,195 | |
| SYKES, MEGAN | | | | |
| NIH | 5R01HL063474-05 | $ | 303,522 | |
| NIH | 5R01HL049915-11 | $ | 324,100 | |
| NIH | 5R01CA079989-04 | $ | 221,230 | |
| NIH | 5P01AI039755-07 | $ | 935,446 | 0210,0447 |
| NIH | 1R01AI055581-01 | $ | 104,206 | |
| [name] | | | | |
| NIH | 3R01AR046732-05S1 | $ | 52,232 | |
| NIH | 5R01AR046732-05 | $ | 232,073 | |
| NIH | 1R01AI051448-01A2 | $ | 110,733 | |
| NIH | 1R21AI051448-01A1 | $ | 138,282 | |
| [name] | | | | |
| NIH | 5R01AI052417-02 | $ | 296,625 | |
| TROILO, DAVID | | | | |
| NIH | 5R01EY011228-08 | $ | 330,650 | 0280 |
| NIH | 1R24EY014817-01 | $ | 274,500 | |
| TZIPORI, SAUL | | | | |
| NIH | 5R01AI050471-02 | $ | 396,250 | |
| NIH | 5R01DK058993-04 | $ | 334,000 | |
| NIH | 5R21AI052792-02 | $ | 231,900 | |
| NIH | 2R01AI041326-06A2 | $ | 178,313 | |
| [name] | | | | |
| NIH | 5R01AI049131-03 | $ | 302,000 | |
| NIH | 1R21AI055349-01 | $ | 226,500 | |
| [name] | | | | |
| NIH | 5R01AI052055-02 | $ | 317,500 | |
| [name] | | | | |
| NIH | 5R01AI049080-03 | $ | 355,049 | |
| NIH | 5R01AA013563-02 | $ | 554,215 | |

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|---|---|---|---|---|
| NIH | 1R01HL075833-01 | $ | 649,987 | |
| NIH | 5R24RR016988-02 | $ | 304,000 | |
| NIH | 2R01CA074730-06A1 | $ | 359,550 | |
| NIH | 5R01HL060090-06 | $ | 382,500 | |
| NIH | 5R01CA096511-02 | $ | 267,665 | |
| NIH | 5R01AI049286-04 | $ | 294,500 | |
| NIH | 5R01AI045019-04 | $ | 346,500 | |
| NIH | 1R01AI054483-01 | $ | 344,250 | |
| NIH | 5P30AI042851-05 | $ | 1,507,853 | |
| NIH | 5R37AI028568-15 | $ | 424,863 | |
| NIH | 5R21AI053911-02 | $ | 219,350 | |
| NIH | 5U01AI052403-02 | $ | 2,170,255 | |
| NIH | 5R01AI044656-05 | $ | 360,195 | |
| NIH | 5R01AI031563-11 | $ | 346,000 | |
| NIH | 5R01AI030914-10 | $ | 389,250 | |
| WANG, FREDERICK C | | | | |
| NIH | 5P01DE014388-03 | $ | 1,263,718 | 0282,0392,0393 |
| NIH | 5R01CA089172-03 | $ | 276,274 | 0282,0392,0393 |
| NIH | 5R01CA068051-09 | $ | 406,170 | 0282,0392,0393 |
| NIH | 5R24RR016038-03 | $ | 490,135 | |
| NIH | 5R24RR015371-04 | $ | 551,851 | |
| NIH | 5R01AI049120-03 | $ | 931,391 | |
| NIH | 5R01AI046366-05 | $ | 440,507 | |
| NIH | 1R01AI052056-01A1 | $ | 661,445 | |
| NIH | 5P01AI048241-03 | $ | 1,549,799 | |
| NIH | 1U01AI054988-01 | $ | 471,262 | |
| WESTMORELAND, SUSAN V | | | | |
| NIH | 5K01RR000150-05 | $ | 100,991 | 0301 |
| NIH | 5R01NS034626-03 | $ | 49,723 | |
| NIH | 2R01NS037654-06A1 | $ | 386,866 | |
| NIH | 5R01NS040237-05 | $ | 315,970 | |
| WOLF, DONALD P | | | | |
| NIH | 1R01-RR16030-01 | $ | 0 | 0342 |
| NIH | 2R01CA075903-06A1 | $ | 516,026 | |
| NIH | 5P20RR015635-04 | $ | 2,152,219 | |
| NIH | 3D43TW001429-04S1 | $ | 100,000 | |
| NIH | 3P20RR015635-04S1 | $ | 471,772 | |
| NIH | 5D43TW001429-04 | $ | 300,000 | |
| NIH | 5R01HD039620-03 | $ | 317,250 | |

| | | | |
|---|---|---|---|
| NIH | 5R01DK063619-02 | $ | 277,375 |
| [illegible] | | | |
| NIH | 1R01AI054951-01 | $ | 256,933 |
| [illegible] | | | |
| NIH | 5R01GM034365-20 | $ | 427,500 |
| NIH | 1R01AI055021-01 | $ | 780,970 |
| NIH | 1R01HG002668-01 | $ | 1,671,399 |
| [illegible] | | | |
| NIH | 3R01DA013918-04S1 | $ | 90,195 |
| NIH | 1R01DA016540-01A1 | $ | 634,171 |
| NIH | 5R01DA013918-04 | $ | 652,167 |
| NIH | 5R01DA012326-05 | $ | 313,820 |
| [illegible] | | | |
| NIH | 5R01CA086839-04 | $ | 285,300 |
| NIH | 5R01AI052789-02 | $ | 317,000 |
| [illegible] | | | |
| NIH | 5R01AI036554-09 | $ | 381,250 |
| NIH | 4R37AI036059-10 | $ | 381,250 |
| [illegible] | | | |
| NIH | 5R01AI047682-04 | $ | 287,000 |
| NIH | 1R21AI054254-01A1 | $ | 247,635 |
| | **FEDERAL - PHS** | $ | 342,979,869 |
| | **FEDERAL** | $ | 342,979,869 |
| **TOTAL FUNDING:** | | **$** | **343,749,891** |

# RESOURCE SUMMARY: SUBPROJECTS

The following only includes information associated with subprojects.

| | Mgmt. A | Research B | Pilot C | Collab. D | Total (excludes |
|---|---|---|---|---|---|
| Number of Subprojects | 5 | 69 | 5 | 47 | 126 |
| Number of Investigators | 8 | 134 | 14 | 278 | 381 |
| Number of Published | 0 | 36 | 4 | 40 | 78 |
| Number In Press | 0 | 25 | 2 | 12 | 37 |
| %AIDS of NPRC Dollars | 0.000% | 51.644% | 1.420% | 17.325% | 70.389% |
| %Non-AIDS of NPRC Dollars | 6.750% | 9.681% | 0.848% | 12.332% | 29.611% |
| Total Percent of NPRC Funds Awarded | 6.750% | 61.325% | 2.268% | 29.657% | 100.000% |

# RESOURCE SUMMARY: ADMINISTRATIVE

| PERSONNEL | On Subprojects | Not On Subprojects |
|---|---|---|
| **Core Personnel** | | |
| DOCTORAL LEVEL SCIENTISTS (C) | 30 | 8 |
| **Core Personnel** | 30 | 8 |
| **Non-Core Personnel** | | |
| AFFILIATED (A) | 325 | 111 |
| GRADUATE STUDENT/POST DOCTORAL SCIENTIST (G) | 25 | 7 |
| **Non-Core Personnel** | 350 | 118 |
| **Personnel Total:** | 380 | 126 |

**ACCESS BY NON-NPRC PERSONNEL**

**GEOGRAPHICAL USAGE BY INVESTIGATORS AT NON-HOST INSTITUTIONS**

| | |
|---|---|
| **Foreign Investigators by Country** | **46** |
| AUSTRALIA | 5 |
| CANADA | 7 |
| FRANCE | 1 |
| GERMANY | 8 |
| INDIA | 1 |
| ITALY | 1 |
| JAPAN | 3 |
| KOREA | 6 |
| PUERTO RICO | 2 |
| SINGAPORE | 1 |
| SOUTH AFRICA | 1 |
| SPAIN | 2 |
| SWITZERLAND | 2 |
| UK | 6 |
| **USA Investigators by State** | **390** |
| AL | 1 |
| CA | 30 |
| CO | 5 |
| CT | 13 |
| DC | 2 |
| DE | 1 |
| FL | 4 |
| GA | 21 |
| HI | 1 |
| IA | 1 |
| IL | 3 |
| IN | 1 |
| KS | 1 |
| KY | 1 |
| LA | 9 |
| MA | 160 |
| MD | 34 |
| MI | 4 |
| MN | 1 |
| MO | 4 |
| MT | 1 |
| NC | 5 |
| NE | 4 |
| NJ | 5 |
| NM | 2 |
| NY | 28 |
| OH | 5 |
| OK | 1 |
| OR | 5 |
| PA | 19 |
| RI | 1 |
| SC | 1 |
| TN | 3 |
| TX | 3 |
| VA | 1 |
| WA | 3 |
| WI | 6 |
| **Total Investigators at Non Host Institutions:** | **436** |

**RESEARCH SERVICES**

| | |
|---|---|
| Scientists Provided with Services | 147 |
| Services Provided | 216 |

**RESEARCH SERVICES BY COUNTRY**

| | |
|---|---|
| **Research Services to Foreign Investigators by Country** | **8** |
| CANADA | 3 |
| GERMANY | 1 |
| KOREA | 3 |
| SWITZERLAN | 1 |
| **Research Services to USA Investigators by State** | **138** |
| CA | 7 |
| CO | 1 |
| CT | 5 |
| FL | 3 |
| GA | 1 |
| IL | 1 |
| KS | 1 |
| KY | 1 |
| LA | 4 |
| MA | 50 |
| MD | 13 |
| MI | 1 |
| MO | 2 |
| NC | 2 |
| NE | 2 |
| NJ | 3 |
| NY | 14 |
| OH | 3 |
| OK | 1 |
| OR | 2 |
| PA | 10 |
| TN | 3 |
| WA | 1 |
| WI | 7 |
| **Research Services to Unknown Locations** | **1** |
| **Total Research Services:** | **147** |

**INFRASTRUCTURE TABLE**

| **GRANT REPORTED UNITS** | **%NPRC USE** |
|---|---|
| ADMINISTRATIVE | 42.483% |
| AIDS COMPONENT | 0.000% |
| BEHAVIORAL BIOLOGY | 2.818% |
| COLLABORATIVE RES PROGRAM | 1.791% |
| COMPARATIVE PATHOLOGY | 7.287% |
| IMMUNOLOGY | 5.609% |
| MICROBIOLOGY | 5.229% |
| NEUROCHEMISTRY | 2.539% |
| PRIMATE RESOURCES | 29.474% |
| TUMOR VIROLOGY | 2.770% |
| **TOTAL NPRC:** | **100.00%** |

**RESEARCH TABLE**

| UNITS GENERATED BY SUBPROJECTS | %NPRC USE |
|---|---|
| ADMINISTRATIVE | 6.750% |
| BEHAVIORAL BIOLOGY | 3.060% |
| COLLABORATIVE RES PROGRAM | 20.547% |
| COMPARATIVE PATHOLOGY | 12.780% |
| IMMUNOLOGY | 41.740% |
| MICROBIOLOGY | 3.768% |
| NEUROCHEMISTRY | 2.756% |
| PRIMATE RESOURCES | 0.500% |
| TUMOR VIROLOGY | 8.099% |
| **TOTAL NPRC:** | **100.000%** |

# RESOURCE SUMMARY: PUBLICATION/SUPPORT

## PUBLICATIONS

| | Cited | Not Cited | Total |
|---|---|---|---|
| **Published** | | | |
| Abstracts | 37 | 10 | 47 |
| Books | 1 | 2 | 3 |
| Journals | 44 | 89 | 133 |
| **In Press** | | | |
| Abstracts | 32 | 6 | 38 |
| Books | 1 | | 1 |
| Journals | 20 | 7 | 27 |
| **Total** | 135 | 114 | 249 |

## INVESTIGATOR SUPPORT

### NON-FEDERAL

| | |
|---|---|
| | $ 102,378 |
| FOUNDATION | $ 594,081 |
| INDUSTRY | $ 73,563 |
| **NON-FEDERAL** | **$ 770,022** |

### FEDERAL

**PHS**

| | |
|---|---|
| AA | $ 1,537,319 |
| AG | $ 7,195,332 |
| AI | $ 228,971,306 |
| AR | $ 513,669 |
| CA | $ 22,603,395 |
| DA | $ 10,767,438 |
| DC | $ 259,578 |
| DE | $ 3,839,743 |
| DK | $ 6,346,821 |
| EY | $ 3,705,891 |
| GM | $ 5,753,628 |
| HD | $ 937,991 |
| HG | $ 1,938,759 |
| HL | $ 8,022,767 |
| MH | $ 9,667,401 |
| MR | $ 180,476 |
| NS | $ 12,269,839 |
| -R | $ 0 |
| RR | $ 17,813,963 |
| TW | $ 654,553 |
| **PHS** | **$ 342,979,869** |

| | | |
|---|---|---|
| **TOTAL SUPPORT** | **$** | **343,749,891** |

# 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 |
|---|---|---|---|---|---|---|---|---|
| **CALLITHRIX JACCHUS** | | | | | | | | |
| Adult Males | 340 | 63 | 0 | 0 | 83 | 18 | 15 | 287 |
| **MACACA CYCLOPIS** | | | | | | | | |
| Adult Males | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| **MACACA FASCICULARIS** | | | | | | | | |
| Adult Males | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **MACACA MULATTA** | | | | | | | | |
| Adult Males | 510 | 136 | 222 | 0 | 13 | 7 | 112 | 736 |
| **MACACA MULATTA (SPF)** | | | | | | | | |
| Adult Males(SPF) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **MACACA NEMESTRINA** | | | | | | | | |
| Adult Males | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **SAGUINUS OEDIPUS** | | | | | | | | |
| Adult Males | 183 | 19 | 0 | 0 | 28 | 0 | 0 | 174 |
| **SAIMIRI SCIUREUS** | | | | | | | | |
| Adult Males | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | **1,034** | **218** | **222** | **0** | **124** | **25** | **127** | **1,198** |

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

## Non-Primate Colony Only

*Note: These animals are not supported by NCRR Comparative Medicine.*

| 1Genus Species | May-03 | 2Live Births | 3Other Additions | Exper. Use | 4Other Reduct. | 5Sold or Trans. | 6Trans. in Center | Apr-0 |
|---|---|---|---|---|---|---|---|---|
| **CANINE** | | | | | | | | |
| Adult Males | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **LAGOMORPH** | | | | | | | | |
| Adult Males | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **MUS MUSCULUS** | | | | | | | | |
| Adult Males | 12 | 88 | 32 | 59 | 0 | 0 | 0 | 73 |
| **PORCINE** | | | | | | | | |
| Adult Males | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **RATTUS NORVEGICUS** | | | | | | | | |
| Adult Males | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | **12** | **88** | **32** | **59** | **0** | **0** | **0** | **73** |

## 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 |
|---|---|---|---|---|---|---|---|---|
| **AOTUS TRIVIRGATUS** | | | | | | | | |
| Adult Males | 7 | 0 | 0 | 0 | 0 | 0 | 0 | 7 |
| **CALLITHRIX JACCHUS** | | | | | | | | |
| Adult Males | 16 | 0 | 15 | 7 | 0 | 0 | 0 | 24 |
| **CHLOROCEBUS AETHIOPS** | | | | | | | | |
| Adult Females | 0 | 0 | 11 | 0 | 0 | 0 | 0 | 11 |
| **MACACA FASCICULARIS** | | | | | | | | |
| Adult Males | 71 | 0 | 12 | 24 | 5 | 0 | 0 | 54 |
| **MACACA MULATTA** | | | | | | | | |
| Adult Males | 493 | 0 | 94 | 112 | 0 | 2 | 152 | 321 |
| **MACACA MULATTA (SPF)** | | | | | | | | |
| Adult Males(SPF) | 53 | 0 | 20 | 6 | 0 | 0 | 12 | 55 |
| **MACACA NEMESTRINA** | | | | | | | | |
| Adult Males | 18 | 0 | 0 | 0 | 0 | 0 | 0 | 18 |
| **PAPIO ANUBIS** | | | | | | | | |
| Adult Males | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **SAGUINUS OEDIPUS** | | | | | | | | |
| Adult Males | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **SAIMIRI SCIUREUS** | | | | | | | | |
| Adult Males | 57 | 0 | 13 | 14 | 0 | 0 | 0 | 56 |
| | **715** | **0** | **165** | **163** | **5** | **2** | **164** | **546** |

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

## HERPESVIRUS PATHOGENESIS

SPID(s): 0310, 0353, 0354, 0356, 0404

The replication and transcription activator (RTA) of gamma-2 herpesvirus is sufficient to drive the entire viral lytic cycle. Hence, the control of RTA activity could be critical in maintaining viral latency. We found that cellular poly(ADP-ribose) polymerase-1 (PARP-1) and Ste20-like kinase hKFC interacted with the serine/threonine-rich region of gamma-2 herpesvirus RTA, and that these interactions efficiently transferred ADP-ribose and phosphate units to RTA. These modifications strongly repressed RTA-mediated transcriptional activation by inhibiting RTA recruitment onto the promoters of viral lytic genes. Conversely, the genetic ablation of RTA interactions with PARP-1 and hKFC or the knockout of PARP-1 activity significantly enhanced gamma-2 herpesviral lytic replication. This is the first demonstration that cellular PARP-1 and hKFC act as molecular sensors to regulate RTA activity and thereby, herpesviral latency.

The K1 protein of KSHV efficiently transduces extracellular signals to elicit cellular activation events through its cytoplasmic immunoreceptor tyrosine-based activation motif (ITAM). In addition, the extracellular domain of K1 demonstrates regional homology with the immunoglobulin (Ig) family, and contains conserved regions (C1 and C2) and variable regions (V1 and V2). To generate mouse monoclonal antibodies directed against the KSHV K1 protein, BALB/c mice were primed and given boosters with K1 protein purified from mammalian cells. Twenty-eight hybridomas were tested for reactivity with K1 protein by ELISA, immunofluorescence, flow cytometry, immunohistochemistry, and immunoblotting. Deletion mutants of the K1 extracellular domain were used to map the epitope of each antibody. All antibodies were directed to the Ig, C1, and C2 regions of K1. Furthermore, antibody recognition of a short sequence (amino acids 92-125) of the C2 region overlapping with the Ig region of K1 efficiently induced intracellular free calcium mobilization; antibody recognition of the other regions of K1 did not. The efficient signal transduction of K1 induced by antibody stimulation required both the ITAM sequence of the cytoplasmic domain and also the normal structure of the extracellular domain. Finally, immunological assays showed that K1 was expressed during the early lytic cycle of viral replication in primary effusion lymphoma cells. K1 was readily detected in Multicentric Castleman's disease tissues, whereas it was not detected in Kaposi's sarcoma lesions, suggesting that K1 is preferentially expressed in lymphoid cells. Thus, these results indicate that the conserved regions, particularly the Ig and C2 regions, of the K1 extracellular domain are exposed on the outer surface and play an important role in K1 structure and signal transduction, whereas the variable regions of K1 appear to be away from the surface.

Lipid rafts are proposed to function as platforms for both receptor signaling and trafficking. Following interaction with antigenic peptides, the T cell receptor (TCR) rapidly translocates to lipid rafts, where it transmits signals and subsequently undergoes endocytosis. The Tip protein of Herpesvirus saimiri (HVS), which is a T lymphotropic tumor virus, interacts with cellular Lck tyrosine kinase and p80, a WD domain-containing endosomal protein. Interaction of Tip with p80 induces enlarged vesicles and recruits Lck and TCR complex into these vesicles for trafficking. We demonstrate that Tip is constitutively present in lipid rafts, and that Tip interaction with p80, but not with Lck, is necessary for its efficient localization in lipid rafts. The Tip/Lck interaction was required for the recruitment of TCR complex to lipid rafts, and the Tip/p80 interaction was critical for the aggregation and internalization of lipid rafts. These results suggest the potential mechanism for Tip-mediated TCR downregulation: Tip interacts with Lck to recruit TCR complex to lipid rafts, and it subsequently interacts with p80 to initiate the aggregation and internalization of the lipid raft domain and thereby, downregulate the TCR complex. Thus, the signaling and targeting functions of HVS Tip rely on two functionally and genetically separable mechanisms that independently target cellular Lck tyrosine kinase and p80 endosomal protein.

The saimiri transforming protein (STP) oncogene of Herpesvirus saimiri subgroup A stain 11 (STP-A11) is not required for viral replication, but is required for lymphoid cell immortalization in culture and lymphoma induction in primates. We previously showed

that STP-A11 interacts with cellular Src kinase through its SH2 binding motif, and that this interaction elicits Src signal transduction. We demonstrate that STP-A11 interacts with signal transducer and activator of transcription 3 (Stat3) independent of Src association, and that the amino terminal short proline-rich motif of STP-A11 and the central linker region of Stat3 are necessary for their interaction. STP-A11 formed a triple complex with Src kinase and Stat3 where Src kinase phosphorylated Stat3, resulting in the nuclear localization and transcriptional activation of Stat3. Consequently, the constitutively active Stat3 induced by STP-A11 elicited cellular signal transduction, which ultimately induced cell survival and proliferation upon serum deprivation. Furthermore, this activity was strongly correlated with the induction of Fos, cyclin D1, and Bcl-XL expression. These results demonstrate that STP-A11 independently targets two important cellular signaling molecules, Src and Stat3, and both of these proteins efficiently cooperate to induce STP-A11-mediated transformation.

Protein linking integrin-associated protein and cytoskeleton 1 (PLIC1), also called ubiquilin, contains an amino-terminal ubiquitin-like (UBL) domain and a carboxy-terminal ubiquitin-associated (UBA) domain. PLIC1 is proposed to function as a regulator of the ubiquitination complex and proteasome machinery. KSHV contains a small membrane protein, K7, that protects cells from apoptosis induced by various stimuli. Yeast two-hybrid screen has shown that cellular PLIC1 is a K7-interacting protein and that the central hydrophobic region of K7 and the carboxy-terminal UBA domain of PLIC1 are responsible for their interaction. Cellular PLIC1 formed a dimer and efficiently bound to polyubiquitinated proteins through its carboxy-terminal UBA domain, and this activity correlated with its ability to stabilize cellular IkB protein. In contrast, K7 interaction prevented PLIC1 from forming a dimer and binding to polyubiquitinated proteins, consequently leading to the rapid degradation of IkB. Furthermore, K7 expression promoted efficient degradation of the p53 tumor suppressor, resulting in inhibition of p53-mediated apoptosis. These results indicate that KSHV K7 targets a regulator of the ubiquitin/proteasome-mediated degradation machinery to deregulate cellular protein turnover, which potentially provides a favorable environment for viral reproduction.

**Publications:**

[ In press publication ]

[ In press publication ]

[ In press publication ]

GWACK, Y., BAEK, JH., NAKAMURA H, LEE SH, MEISTERERNST, M., ROEDER, RG., AND JUNG, JU. Principal role of TRAP/Mediator and SWI/SNF complexes in Kaposi's sarcoma associated herpesvirus RTA-mediated lytic reactivation. Molecular and Cellular Biology 23: 2055-2067, 2003.

GWACK, YOUSANG;NAKAMURA, HIROYUKI;LEE, SUN HWA;SOUVLIS, JOHN;YUSTEIN, JASON T;GYGI, STEVE;KUNG, HSING-JIEN;JUNG, JAE U* Poly(ADP-ribose) polymerase 1 and Ste20-like kinase hKFC act astranscriptional repressors for gamma-2 herpesvirus lytic replication. Mol Cell Biol 23 8282-94 2003

LEE SH, JUNG JU, AND MEANS R. "Complementing" viral infection: mechanism for evading innate immunity. Trends in Microbiology 11: 449-451, 2003

LEE, BOK-SOO*;CONNOLE, MICHELLE;TANG, ZUOQUIN;HARRIS, NANCY L;JUNG, JAE U Structural analysis of the Kaposi's sarcoma-associated herpesvirus K1protein. J Virol 77 8072-86 2003

[ In press publication ]

NAKAMURA, H., LU M., GWACK, Y., SOUVLIS, J., ZEICHNER, S., AND JUNG, JU. Global changes in Kaposi's sarcoma-associated herpesvirus gene expression patterns following expression of a tetracycline-inducible Rta transactivator. Journal of Virology 77: 4205-4220, 2003

PARK, JUNSOO;CHO, NAM-HYUK;CHOI, JOONG-KOOK;FENG, PINGHUI*;CHOE, JOONHO;JUNG, JAE U Distinct roles of cellular Lck and p80 proteins in herpesvirus saimiri Tipfunction on lipid rafts. J Virol 77 9041-51 2003

## STRESS AND RELAPSE TO COCAINE ADDICTION

SPID(s): 0364

Drug addiction is a chronic disorder characterized by recurring episodes of persistent drug use, abstinence, and relapse. Increased appreciation of the cyclic nature of addiction has led to the emergence of relapse prevention as a major goal for long-term management of compulsive drug use.

Stress has been widely implicated as a risk factor in drug addiction and may be a leading trigger of relapse amoung cocaine abusers. The brain's norepinephrine (NE) system is a key component of the chemical messenger complex mediating the physiological and behavioral responses to stress. Stress causes release of NE from neuronal cells under the regulation of a specific type of receptor called the alpha-2 adrenoceptor. Blockade of the alpha-2 adrenoceptor stimulates NE release and induces stress-related physiological and psychological changes in humans and nonhuman primates.

Research in the Division of Behavioral Biology has focused on understanding the link between the NE system, stress, and relapse to cocaine addiction using a novel nonhuman primate model of cocaine relapse. This model utilizes intravenous drug self-administration techniques to investigate the extent to which stress and other putative triggers of relapse reinstate cocaine-seeking behavior after a period of imposed abstinence. Monkeys were surgically implanted with chronic venous catheters and given daily access to intravenous cocaine, which they could administer to themselves by pressing a lever to activate an infusion pump. After an extended history of cocaine self-administration, placebo was substituted for cocaine until active drug seeking was no longer apparent.

In the test phase of the study, two drugs that selectively block the alpha-2 adrenoceptor (yohimbine and the experimental compound RS 79948) were tested for their ability to reinstate cocaine-seeking behavior. The stress hormone, cortisol, was monitored as a physiological marker of stress. Clonidine, a drug that opposes the effects of alpha-2 adrenoceptor blockade, and flupenthixol, a drug that blocks dopamine receptors, were tested for their ability to reverse the effects of yohimbine.

The results show that pharmacological blockade of the alpha-2 adrenoceptor causes a pronounced stress response, as measured by the hormonal marker cortisol, and induces significant relapse, as measured by robust reinstatement of cocaine-seeking behavior. Furthermore, clonidine but not flupenthixol reversed yohimbine-induced reinstatement of cocaine seeking. The results provide direct pharmacological evidence linking the NE system to stress-induced relapse and identify the alpha-2 adrenoceptor as a potential target for development of medications to promote cocaine abstinence

**Publications:**

[In press publication]

**DIRECT RELATIONSHIP BETWEEN SUPPRESSION OF VIRUS-SPECIFIC IMMUNITY AND EMERGENCE OF CYTOMEGALOVIRUS DISEASE IN SIMIAN AIDS**

SPID(s): 0226

Although opportunistic infections like cytomegalovirus (CMV) are common sequelae of end-stage AIDS, the immune events leading to CMV reactivation in human immunodeficiency virus (HIV)-infected individuals are not well defined. The role of cellular and humoral CMV-specific immune responses in immune control of latent CMV infection was evaluated in simian immunodeficiency virus (SIV) rhesus macaques. Macaques with CMV disease differed from macaques without CMV disease in having significantly higher levels of plasma SIV RNA and CMV DNA and significantly lower titers of anti-CMV binding antibodies. A significant decline in anti-CMV antibodies and CMV-specific CD4+ and CD8+ T lymphocytes over time was observed in the macaques with CMV disease, but not in the macaques without CMV disease. Reduction in CMV-specific CD8+ T lymphocytes and anti-CMV neutralizing antibodies was significantly correlated with a decline in CMV-specific CD4+ T lymphocytes. Although declines in CMV-specific T lymphocytes alone were sufficient for reactivation of low-level CMV viremia, high-level viremia was observed when anti-CMV neutralizing and binding antibodies had also declined. Thus, the occurrence of CMV reactivation-associated disease in AIDS is associated with suppression of both cellular and humoral CMV specific immune responses. The underlying mechanism may be a dysfunction of memory B and CD8+ T lymphocytes associated with SIV-induced impairment of CMV-specific CD4+T-cell help. Identification of specific immunologic mechanisms associated with reactivation of opportunisitic pathogens will help in the design of immunotherapeutic strategies to reduce the incidence of opportunistic infections in patients with HIV/AIDS.

**Publications:**

KAUR, AMITINDER;KASSIS, NADINE;HALE, CORRINA L;SIMON, MEREDITH;ELLIOTT, MICHELLE;GOMEZ-YAFAL, ALICIA;LIFSON, JEFFREY D;DESROSIERS, RONALD C;WANG, FRED;BARRY, PETER;MACH, MICHAEL;JOHNSON, R PAUL* Direct relationship between suppression of virus-specific immunity andemergence of cytomegalovirus disease in simian AIDS. J Virol 77 5749-58 2003

## COMMITTEE MEMBERS

### ANIMAL ALLOCATION COMMITTEE MEMBERS

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PRIMATE RESOURCES

[ name ]
CENTRAL SUPPLY PRIMATE SURGERY

ROWLETT, JAMES K
BEHAVIORAL BIOLOGY

WORTHAM, JAMES T.
ADMINISTRATION

### PILOT RESEARCH REVIEW COMMITTEE MEMBERS

# ADMINISTRATIVE INFORMATION

## ALLOCATION OF RESOURCE ACCESS

To ensure the equitable distribution of available resources the NERPRC maintains an Animal Allocation Committee. This Committee is charged with equitably allocating animalrelated resources at NERPRC among core, collaborating, and affiliated scientists. The committee is appointed by the director of NERPRC. The committee consists of two core staff members, two non-core staff members, and the chair of the Primate Resources Division as coordinator. The director of NERPRC retains oversight responsibility but is not a member of the committee. An annual report is prepared for Dr. Dennis Kasper, Executive Dean for Academic Programs, Harvard Medical School.

The committee meets once monthly to consider animal related resource requests and all animal requests must receive approval prior to assignment and sale to individual investigators. A principal investigator requesting animals must submit an animal request form under an approved Harvard Medical School IACUC animal protocol. The committee considers a number of criteria in the allocation process: 1) equitable distribution of resources among core and collaborating scientists, 2) availability of requested species, 3) animal disposition following completion of experimental procedures, 4) compatibility with existing programs, and 5) quality and importance of proposed scientific work.

## DISSEMINATION

Activities that help disseminate technological developments and promote awareness to the scientific community of the Center's resources include variety of mechanisms e.g.: international and national scientific conferences, computer web sites, regional medical school newspapers, newsletters, National Scientific Journals, NIH grant announcements, and word of mouth among scientists, and brochure mailings.

## AWARDS, HONORS, SPECIAL RECOGNITIONS

Sydney Ann Fingold, Library Director, New England Primate Research Center was chosen by The Massachusetts Health Sciences Library Network (MAHSLIN) as a recipient of the April 2003 professional achievement award and induction into the MAHSLIN "Hall of Fame". This award is in recognition of Sydney's outstanding performance in her field and the leadership she has offered the members of the health sciences library community.

## INFRASTRUCTURE

See attached beginning on page 219

## Others

UNITED STATES PATENTS

#6,525,206
Issued: February 25, 2003
Title: Compounds with high monoamine transporter affinity.
Inventors: Meltzer; PC Blundell; P, Wang; P; Madras; BK

#6,548,041
Issued: April 15, 2003
Title: Dopamine transporter imaging agents.
Inventors: Meltzer; PC, Blundell; P, Madras; BK, Fischman; AJ, Jones; AG., Mahmood; A.

#6,670,375
Issued: December 30, 2003
Title: Tropane analogs and methods for inhibition of monoamine transport
Inventors: Meltzer, PC, Madras, BK, Blundell, P, Chen, Z.

#6,677,338.
Issued: January 13 2004
Title: Serotonin transport inhibitors
Inventors: Madras BK and Meltzer, PC.

## PILOT RESEARCH REVIEW COMMITTEE MEMBERS

Name

Name

Name

Name

## SCIENTIFIC ADVISORY COMMITTEE MEMBERS

Names

## C. INFRASTRUCTURE

### 1. Physical Plant

2003 was another year of ongoing initiatives to improve the physical plant through renovations and construction projects. Major projects completed or initiated in 2004 include the following:

- Room [ ] was completely renovated with modern wet lab capability for the Neurochemistry Division.
- Room [ ] underwent renovation to provide additional laboratory expansion for the Pathology Division.
- The final stages of a complete HVAC upgrade to RSB #1 was initiated and will be completed in April 2004. This project involves the replacement of Absorber #2 which will enhance air conditioning.
- A new Neuroscience Facility was completed and occupied in September 2004. This project provided [ ] square feet of new laboratory, animal holding capability, and administrative space in RSB #5. This construction was a result of a CO6 application headed by Dr. Roger Spealman.
- A Harvard funded [ ] square foot new research building with adjoining auditorium was completed in March 2004. This new building will provide laboratory space for five Principal Investigators as well as their support staff. The new auditorium will seat 106 individuals and was a much needed facility for the Center.
- A [ ] square foot renovation of room [ ] in RSB #1 is underway to provide laboratory space for Dr. Keith Mansfield's research program. This project will be completed in April 2004.
- [ ] pending support [ ]

Listed below are major equipment purchases and source(s) of funding:

Proposed for Year 43

This coming year's focus will be to complete the flow cytometry facility, HVAC upgrade and occupy to the fullest extent the new research building (RSB #6).

**Equipment Purchases over $5000.00 for period May 2003 to Present**

| Division | Item Description | Cost | Grant |
|---|---|---|---|
| Administration | Computer Network | 71,210 | CRA |
| | Refrig. Centrifuge & Rotors | 24,598 | MOD |
| | 6 ea. -80 Freezers | 48,582 | MOD |
| | Refrig. Centrifuge & Rotors | 15,691 | MOD |
| | 2 ea. Milli-Q Water Systems | 10,028 | MOD |
| | Hot Pack Oven | 11,484 | MOD |
| | 6 ea. Tissue Culture Hoods | 31,794 | MOD |
| | 24K Cryostorage System | 14,774 | MOD |
| | Getinge Disinfecting Washer | 40,786 | MOD |
| | Getinge 533 Gravity Sterilizer | 43,342 | MOD |
| | Getinge 733 Gravity Sterilizer | 74,112 | MOD |
| Animal Care | 107 Primate Housing Units | 378,116 | G20 |
| Engineering | Steam Generator | 6,732 | MOD |
| | HVAC Absorber Unit | 341,405 | MOD |
| | HVAC Condensor Unit | 13,500 | MOD |
| | Diesel Generator | 58,790 | MOD |

| | | | |
|---|---|---|---|
| Immunology | -80 Freezer | 8,117 | 383559 |
| Microbiology | Refrig. Centrifuge & Rotor | 10,518 | Base |
| | -80 Freezer | 6,909 | Base |
| | 2 ea. CO2 Incubators | 16,020 | Base |
| | MultiLable Reader System | 48,472 | 383586 |
| | BioSafety Cabinet | 6,373 | 383553 |
| | Thermal Cycler | 17,220 | 383578 |
| Neurochemistry | Refrig. Microcentrifuge | 5,680 | DA06303 |
| | -80 Freezer | 7,058 | 746152 |
| | Scintillation Counter | 22,995 | Base |
| Pathology | 2 ea. -80 Freezers | 19,654 | CRA |
| | Environmental Monitoring System | 89,268 | CRA |
| | Leica Microtome | 27,802 | MOD |
| Primate Medicine | -80 Freezer | 7,150 | Base |
| | Color Ultrasound System | 38,250 | G20 |
| | Ultrasound Transducer | 11,970 | MOD |
| | 2 ea. Anesthesia Monitoring Systems | 15,514 | G20 |
| Tumor Virology | Refrig. Ultracentrifuge & Rotors | 52,102 | MOD |
| | Refrig. Centrifuge & Rotors | 12,559 | MOD |
| | Total: | $1,608,575 | |

**2. Colony Management**

Animal populations managed by the Division of Primate Resources have changed in the last year. While the Center no longer houses dogs or swine, nonhuman primate colony size changed from 1773 to 1743.

The relative demand for SPF macaques has shifted in conjunction with recent occupational health and safety concerns over *Herpes B virus* (BV) transmission to laboratory workers. Many of the regional facilities that rely upon the Center to supply experimental animals are now demanding SPF, BV-free animals. Combined with increased demand for these animals by Core Staff investigators, this situation has resulted in the inability of the SPF breeding colony to meet current experimental demands. The SPF breeding colony will have to be expanded to approximately 450 animals. To accommodate these increased needs and housing space, the primate center has recently completed construction of [ ]square feet SPF macaque breeding facility. Funding has recently been secured to expand this colony and a number of new breeding groups have been formed in 2002 and 2003. The last remaining conventional groups have been phased out.

**Breeding:** The Division of Primate Resources maintains breeding colonies of rhesus monkeys, common marmosets and cotton-top tamarins. All breeding colonies supply animals for approved research, and allow us to provide well-defined subjects for experimental use. We have worked with the Division of Microbiology to establish and maintain a specific-pathogen-free rhesus monkey colony for AIDS research.
We maintain detailed genealogical records on all colony-born animals to facilitate identification of genetically linked traits and maintain genetic diversity. Breeding colony managers use the genetic management software PEDSYS to assure that potential matings do not result in unintended inbreeding, a process that formerly required extensive searching of manual records. We have also used PEDSYS to determine whether certain disease conditions may have a genetic component. A summary of breeding colony statistics for 2003 is appended to this report.

**Primate Resources Services Unit**

The resources of the Primate Medicine Unit are devoted to preventive medicine and quarantine, clinical medicine, breeding, and clinical research projects. The veterinarians and technicians conduct daily rounds of all animal colonies

to facilitate recognition of colony health problems and meet weekly for a discussion of current issues related to individual animal or colony health. A wide variety of research support services is also provided including daily monitoring, drug administration, special procedures, and pre- and post- operative care. Primate Medicine also performs various clinical procedures in support of the Division of Collaborative Research.

**Quarantine:** Any animal originating outside of the Primate Center is quarantined on arrival for a minimum of 45 days. Macaques and New World species are housed in our CDC approved quarantine facility in the Research Building 2.

New animals are tranquilized, weighed and examined following a conditioning period of 7-10 days. Each animal must have three negative tuberculosis tests at least two weeks apart before release. The minimum database on every arrival includes complete blood count, serum chemistry profile, fecal culture for enteric pathogens, and fecal examination for ova and parasites. Viral serology for simian retrovirus type D (D/SRV-D), *B virus* (BV), and simian T-lymphotropic virus (STLV-1) is performed in the case of macaque species. Serum is stored on all animals for future reference, and all species receive attenuated live measles vaccine. Sick or injured animals are treated as necessary. A medical record, which consists of observations and treatments, diagnostic tests and laboratory results, and housing history, is initiated on each animal upon arrival in quarantine. Computerization of this record-keeping system was begun in 1998.

**Preventive Medicine:** Preventive medicine and colony health surveillance are major responsibilities of the Unit of Primate Medicine. For each species, the veterinarians have devised written protocols regarding health surveillance, immunization and animal husbandry. All monkeys are weighed and examined quarterly and squirrel monkeys are examined on a daily basis by investigators who report disease problems to the veterinarians. Old World monkeys are TB tested quarterly, and New World monkeys are TB tested annually. All nonhuman primates are vaccinated for measles using an attenuated live virus vaccine. Newborns are vaccinated after weaning.

Miscellaneous procedures such as pregnancy palpation, vitamin injections, immunizations, tattooing and annual serum banking are performed when the animals are weighed. Sick or injured animals are identified and treated as necessary. Serum banking is used to facilitate epidemiological studies in the event of a disease outbreak as described in the Unit of Clinical Research and Laboratories description below.

**Clinical Medicine:** Sick animals are identified by the clinical veterinarians during daily rounds, during routine physical examinations in conjunction with preventive medicine procedures and by animal care workers. The clinical veterinarians provide formal and informal instruction to animal care workers on recognition of signs of clinical illness in primates.

Treatment of ill or injured animals is provided in the main clinic. Treatment is provided by the clinical veterinarians or by trained veterinary technicians under a veterinarian's supervision. Minor injuries are frequent among group-housed primates. In contrast, serious injury associated with fighting is rare. Detailed diagnostic work-up of animals is performed when indicated in order to improve individual and colony health and allow identification and description of previously unrecognized diseases. These procedures include short-term intravenous infusions, dentistry, skin biopsies, colon biopsies, gastroscopy, bronchoscopy, bronchoalveolar lavage, ultrasonography, bone marrow aspirates, and cerebrospinal fluid collection.

A full range of diagnostic services is available. Clinical pathology, hematology, microbiology, and virology services are provided in-house. Daily courier service by Tufts Veterinary Diagnostic Laboratory provides rapid access to serum biochemistry profiles and other laboratory services. The Center recently purchased two portable istat serum chemistry analyzers (Heska Corp.) to aid in the management of acutely ill patients. Endoscopy and other sonography equipment was upgraded in 1999. The division purchased an HP Imagepoint Color
doppler ultrasound for cardiology and abdominal ultrasound.

The radiography and darkroom facilities are heavily utilized. The darkroom facilities are maintained by the Division of Primate Resources and are used by the Unit of Primate Medicine for the development of radiographs and by the Divisions of Microbiology and Immunology for the development of autoradiographs. Approximately 175 radiographs were taken by the Unit of Primate Medicine in 2003.

As evidenced here, the quantity of clinical services delivered by this unit to Core Staff and Affiliated scientists has increased by over 12% in the last year and even more substantially since 1995. The addition of a fifth veterinarian to

the Division has helped to solidify all divisional activities, but it will be necessary to recruit additional technical staff in support of Primate Medicine and Surgery if this growth in service demand continues.

**PRIMATE SURGERY**

This unit provides technical services and support to the Center staff, collaborative and affiliated scientists. It is also responsible for Central Supply, operating room services, collaborative research and perinatology.

**Central Supply and Operating Room Services**: A registered nurse and two technical support personnel head the Central Supply staff. Its main function includes providing decontamination of glassware and instruments for all core staff, collaborative, and affiliated scientists, as well as monitoring of the functioning of the virus room autoclave. During the calendar year 2003, the Central Supply cleaned and decontaminated approximately 500,000 pieces of glassware and instruments.

There are two surgical suites at the Center. All major surgical procedures are performed in one of the operating rooms by the veterinarians or individual investigator. The registered nurse and a senior research assistant, who are trained and familiar with operating room procedures, assist in surgery. A Primate Surgery veterinarian is available to collaborative investigators on request or if a problem arises. In the calendar year of 2003 a total of 158 surgeries were performed.

**Biocontainment Facilities:** The Center operates two biocontainment facilities for the conduct of infectious disease studies in animals. The Animal Biohazard Level 3 facility is located on the [ ] floor of the main building. Access to it is permitted only to authorized personnel. There are three [ ] animal care personnel responsible for providing daily care and maintenance to the animals five days a week and one [ ] technician responsible for the area on weekends and holidays. In the year 1998, the ABL3 facility had a total capacity to house 60 animals in individual enclosed cages. In 2001 renovation and expansion of Research Building 2 was completed. This has increased housing capacity to 300 animals. Renovations included installation of new cage wash, refinishing of floors, removal of incinerator and construction of two new animal rooms. Renovation and expansion of the existing ABL-3 facility was completed in 1999. This new facility expands animal housing to 154 animals and provides a dedicated cage wash, clinical procedure room, necropsy, surgery and ICU.

These biocontainment facilities are supervised by a Primate Resources staff veterinarian who is also responsible for development and implementation of the guidelines under the rules and regulations of the Harvard Environmental Health and Safety department. There are two [ ] technicians who work during weekdays and one [ ] technician for weekend and holidays. The veterinarian is responsible for clinical procedures and is assisted by two [ ] research assistants, one of which is assigned to ABL3 and the other to the ABL2 facility. The technicians are responsible for implementation of research protocols in coordination with the veterinarian in charge and have other duties in Primate Medicine. The Unit of Primate Surgery performs all inoculations, venipunctures and surgical procedures for all the animals housed in biocontainment facilities.

**3. Progress In Core**

The Division of Behavioral Biology conducts biannual behavioral assessments of individually housed macaques and squirrel monkeys to identify animals that exhibit behavioral abnormalities requiring enrichment or other treatment interventions. Behavioral assessments consist of direct observations by trained observers of each of approximately 300-400 individually-housed macaques and 50 squirrel monkeys in the Center's colony. Animals exhibiting self-biting or at least three other types of less severe abnormal behaviors (excluding pacing) are referred to the Enrichment Coordinator in the Division of Primate Resources. The behavioral assessment data are also cross-referenced with colony records to identify potential risk factors for specific behavioral categories. In the case of new behavioral problems identified by investigators or animal care personnel, a problem report is issued to the Behavioral Assessment staff, which evaluates the behavior of the identified animal and reports its analysis and recommendations to the Enrichment Coordinator.

**Table 1**

**Summary of Behavioral Assessments**

| Date of Assessment | Species | # of Animals Observed | % Exhibiting Self-Biting | % Exhibiting ≥ 3 Other Behavioral Categories | % Referred to Enrichment Coordinator |
|---|---|---|---|---|---|
| January 2003 | M. mulatta | 300 | 10.0% | 2.0% | 12.0% |
| | M. fascicularis | 27 | 0% | 7.4% | 7.4% |
| | S. sciureus | 50 | 0% | 0% | 0% |
| June 2003 | M. mulatta | 360 | 0.3% | 0.8% | 11.1% |
| | M. fascicularis | 46 | 4.3% | 2.2% | 6.5% |
| | S. sciureus | 50 | 0% | 0% | 0% |

**Pathology Services**

The Division of Comparative Pathology has a significant service commitment to the Center, and these service functions can be divided into five major areas: 1) necropsy and biopsy service, 2) electron microscopy, 3) confocal microscopy and image analysis, 4) clinical pathology and 5) tissue procurement and consultation.

Pathology service support is provided to the clinical veterinary staff at the Center as part of our colony surveillance program. The Division of Comparative Pathology furnishes support in each of these five areas to staff scientists within other divisions at the Center, affiliated and collaborating scientists using the resources of the Center, and regional, national, and international scientists, who request assistance in interpretation of nonhuman primate specimens.

Over the last several years the facilities and equipment available to fulfill the service functions of Pathology have been significantly upgraded increasing our capabilities. During this same time the demand for these services has increased. Unfortunately, the financial support provided by the base grant has not kept pace. Thus far we have been able to find other sources of support to maintain our current level of service but this is not a viable long-term solution.

**Necropsy and Biopsy Service**

The necropsy and biopsy service is the core of the Division's service functions. Drs. Sherry Klumpp and Michelle Elliott oversee day-to-day operation of this service. The necropsy and biopsy service provides investigators and collaborators at the Center with gross and histopathologic evaluations of organs and tissues for the purpose of understanding pathologic changes in relation to experimental protocol. In addition, the service assists the clinical veterinarians with colony health and management.

Moreover, through the ongoing identification and investigation of disease syndromes of nonhuman primates, the necropsy and biopsy service serves as a primary mechanism by which the Center is able to monitor colony health. These investigations serve not only to provide further understanding of disease processes in general, but also have the potential to identify new nonhuman primate models for the study of human disease. Our models of human AIDS, colitis, colonic carcinoma, *Enterocytozoon bieneusi* and rhesus rhadinovirus and rhesus Epstein-Barr virus infections and recognition of a novel CNS lesion associated with SV40 infection arose in this manner.

Over the last year the Division of Comparative Pathology processed and examined 264 biopsy specimens and performed 475 postmortem examinations. Of the postmortem examinations, 449 were performed on Center nonhuman primates, 19 were nonhuman primates from other institutions, and 7 were other experimental animals including rodents. These 475 postmortem examinations were performed for Center investigators within other Divisions of the Center, as part of research programs within the Division of Comparative Pathology, or in collaboration with investigators outside the Center.

In **Table 2**, nonhuman primates necropsied at the Center during the past year are categorized according to species and cause of death. Experimental deaths are defined as those animals assigned to a specific research protocol. The death may or may not have been related to the experimental protocol(s).

**Table 2**
**Necropsies of NEPRC nonhuman primates-2003**

| Species | Experimental | Neonatal/ abortion less than 8 days | Spontaneous disease | Total |
|---|---|---|---|---|
| Macaca mulatta | 127 | 15 | 25 | **167** |
| Macaca fascicularis | 18 | 0 | 0 | **18** |
| Cercopithecus aethiops | 0 | 3 | 0 | **3** |
| Saguinus oedipus | 0 | 52 | 33 | **85** |
| Callithrix jacchus | 18 | 80 | 83 | **181** |
| Saimiri sciureus | 14 | 0 | 0 | **14** |
| **Total** | **177** | **150** | **141** | **468** |

**Electron Microscopy (EM)**

The EM laboratory provides support for diagnostic services as well as research projects within the Center. EM laboratory service for the past year is categorized in **Table 3** [redacted], our resident EM research associate, is responsible for processing and sectioning all EM specimens. As an accomplished electron microscopist, [redacted] is also responsible for ultrastructural examination of each grid produced in the laboratory.

The EM laboratory continues to be an integral component of the research activities of the Center. Examples of procedures routinely performed in the EM laboratory include the identification of viruses in infected cell cultures, identification and localization of pathogens in tissues, characterization of ultrastructural alterations in cells and tissues, and identification of specific proteins at the ultrastructural level through the use of immunoelectronmicroscopy (IEM).

**Table 3 - 2003**
**Electron Microscopy**

| Dept: | Primate Medicine | Microbiology | Pathology | Neuro-chem | Immunology | Tumor Virology | Outside Invest. | Total |
|---|---|---|---|---|---|---|---|---|
| Specimens | 12 | 23 | 76 | | | | 12 | 123 |
| Samples Processed | 21 | 21 | 283 | | | | 9 | 334 |
| Thick sections | 32 | 8 | 70 | | | | 4 | 114 |
| Thin sections | 103 | 72 | 142 | | | | 8 | 325 |
| Photo Negatives | 52 | 104 | 163 | | | | 42 | 361 |
| IEM Runs | | | | | | | | 0 |
| Frozen sections | | | | | | | | 0 |
| Cytospins | 11 | 10 | | | | | | 21 |
| Grids negatively stained | | 21 | | | | | 25 | 46 |

### Confocal microscopy and image analysis

In 1998 the center acquired a Leica TCS SP confocal microscope system equipped with three lasers capable of simultaneously collecting information in four channels. Together with our Olympus Vanox research microscope and Leica Quantimet image analysis system, this instrument allows us to perform multilabel analyses (up to 4 fluorochromes plus differential interference contrast) as well as quantitative analyses of tissue markers. Senior Research Assistant [name 3] is responsible for maintaining the confocal microscope and other imaging equipment in the Image Analysis Laboratory, and assisting investigators with proper specimen preparation, instrument operation, and analysis of the results. The confocal microscope and image analysis facility has been used extensively for a variety of purposes including: identifying the phenotype of DC-SIGN-expressing cells in the alimentary tracts of macaques and mangabeys, identifying the phenotype of MCP-1-expressing cells in the CNS, and identifying the subpopulation of macrophages in the brain that are infected with SIV in cases of SIV encephalitis. During the past year, 21 different investigators used the confocal microscope, including 20 Center investigators and 1 outside collaborator.

### Clinical Pathology

The clinical pathology laboratory operates under the supervision of Senior Research Assistant [name 3], a medical technologist. This laboratory provides bioanalytical data for animals involved in specific research projects as well as for colony animals. The procedures performed by the clinical pathology laboratory include hematology, serum chemistry, fecal analysis, fluid analysis, urinalysis, and cytology, as well as serum storage on all Center animals.

The clinical pathology laboratory submissions for 2003 are summarized in **Table 4**. A total of 4,043 complete blood counts were processed. In addition, 870 serum chemistry specimens were received and 314 requisitions were submitted to the laboratory for cytology, fluid analysis, urine/fecal analysis or other tests (serology, hormone levels, etc.).

**Table 4**
**2003 Clinical Pathology**

| Specimens | Type | Number of Requisitions |
|---|---|---|
| Hematology | experimental<br>clinical | |
| | **Total** | 4,043 |
| Serum Chemistries | experimental<br>clinical | |
| | **Total** | 870 |
| Urinalyses | | 21 |
| Fecals | | 280 |
| Cytologies | | 8 |
| Miscellaneous | | 5 |
| **TOTAL** | | 5,227 |

### Tissue Procurement and consultation

The Center receives requests from many investigators, both regionally and nationally, for tissue or organ specimens from nonhuman primates at death. The Division of Comparative Pathology is responsible for collection and distribution

of these specimens and tries to accommodate all requests. In 2003, the Division collected and dispersed 273 specimens to investigators outside the Center. These specimens included fresh brains and a variety of organs.

The Division also serves as an information resource for the Center staff and for outside investigators, providing information concerning nonhuman primate histopathology, histologic techniques, specimen collection and processing, and the use of nonhuman primates in experimental protocols involving infectious diseases and inflammation.

**Graphic Services**

Graphic Services is staffed by one Graphics Specialist, The service provides a high quality, specialized, in-house source of photographic and electronic imaging needs to Core Staff, Collaborative scientists and Visiting scientists. The geographic isolation of the Center, specialized needs, and short turn around times required by investigators is not readily available from independent photographic laboratories.

There has been an enormous shift in presentation media from 35mm slides to electronic presentations. While the production of 35-mm slides has reduced, the time preparing images and files for electronic media using the computer and digital imaging equipment has dramatically increased. The need for graphics software technical support has also increased. This has led to in-house software training for employees. The department also maintains a web-based intranet for the Center employees.

In addition, the department serves as a centralized supply and purchasing agent for all photographic materials and audiovisual equipment needed for the Center.

**DNA Sequencing Facility**

The Microbiology Division operates a core laboratory for the analysis of DNA sequences for both the NEPRC personnel, as well as its collaborative investigators. The facility uses a Beckman-Coulter CEQ 8000 capillary sequencer. In 2003, the facility ran and analyzed approximately 11,000 sequences.

**Reagents and Testing for Antiviral Antibodies**

The Microbiology Division operates a core laboratory for the detection of antiviral antibodies in monkeys. This core laboratory supports testing for our SPF rhesus monkey colony (free of 4 viruses: Type D retrovirus, herpes B virus, SIV, STLV1) and our superclean SPF group (free of 9 viruses: the four above plus rhesus monkey rhadinovirus, rhesus CMV, SV40, rhesus EBV and foamy virus). Seven of the nine tests are done in house; tests for rhesus EBV and foamy virus are currently sent out. Of the seven done in house, six of the seven utilize viruses purified at moderate scale by the core within the Microbiology Division. ELISA plates are prepared and quality controlled prior to use for antibody testing. HTLV-1 plates for testing for STLV-1 antibodies are purchased from a commercial source. Herpes simplex virus is used for testing for antibodies to herpes B. Control testing has shown high reliability with use of the heterologous but highly cross-reactive sources of antigen. Approximately 560 ELISA samples were tested in the last year.

The Microbiology Division has also developed sensitive, reliable tests for measuring neutralizing activity against SIV. Currently, standardized tests are in place for 12 different strains. Testing is performed as a core service for NEPRC and collaborative investigators. Approximately 833 assays for neutralizing titer have been performed in the last 12 months.

**SIV Reagent Repository**

The NEPRC Microbiology Division is a major source of SIV reagents to the AIDS research community around the world. Reagents include plasmid clones containing SIV sequences, mutant clones, virus stocks, animal-titered virus stocks, and sera. Reagents are distributed via the NIH AIDS Repository and directly from the stores of the Microbiology Division. Twenty-one individual reagents have been deposited and are distributed by the NIH AIDS Repository. In fact, the Desrosiers laboratory is probably the largest single contributor to the NIH AIDS Repository. Over the last 12 months, approximately 146 reagent distributions to 71 different investigators have been made by the

repository and approximately 31 reagent distributions to 17 different investigators were made directly from the Microbiology Division.

**Gene Expression Array Technology**

| | |
|---|---|
| Immunology: | **8 arrays**<br>2 human PBMC samples (human 1.2K gene arrays)<br>2 rhesus PBMC samples (human 1.2K gene arrays)<br>1 rhesus PBMC sample (cytokine array)<br>2 rhesus PBMC samples (human trial array)<br>1 human PBMC sample (human trial array) |
| Tumor Virology: | **25 arrays**<br>9 Jurkat cell samples (NFkB array)<br>6 BJAB cell samples (cytokine array)<br>4 NIH3T3 cell samples (mouse cancer array)<br>4 NIH3T3 cell samples (super array)<br>2 A20 cell line samples (mouse cancer array) |
| Total: | **33 arrays** |

**Flow Cytometry**

The Division of Immunology provides flow cytometry services to other divisions at NEPRC with regards to AIDS-related and other research projects carried out in the Divisions of Microbiology, Tumor Virology, Pathology and Primate Medicine. Supported by a supplemental grant from the Office of AIDS Research, NIAID, the facility was renovated in 1994 to include a Becton Dickinson FACScan, which provides routine three-color immunophenotyping, and a Becton Dickinson Vantage, which can perform four and five-color analysis and cell sorting. Subsequently, two FACS Caliburs, both with dual laser capacity were acquired. These have increased throughput of four color samples significantly. In the last year the FACS Vantage has undergone significant upgrades to include high speed turbo-sorting capability and installation of a DiVa option. The DiVa upgrade has allowed transition from two-way sorting to four-way sorting capability. Further, the option of digital real-time compensation now allows us to expand our flourochrome panel from four-color to six-color flow cytometry. In addition to routine immunophenotyping performed on SIV-infected animals, projects outside the Division of Immunology supported by the Flow Cytometry Facility include:

1. Acute infection with rhesus EBV (F. Wang, Brigham and Women's Hospital)
2. Detection of SIV infection using reporter genes (Microbiology)
3. Routine CD4+ T cell level determinations (NEPRC- Microbiology, Pathology, Immunology)
4. Detecting viral envelope expression (Microbiology)
5. Effects of M. avium infection of surface antigen expression in rhesus monocytes (Primate Medicine).
6. The functional role of KSHV proteins in B and T cells (Tumor Virology).
7. The consequences of various H. saimirii proteins on T cell function (Tumor Virology).
8. Immune evasion strategies of Kaposi's sarcoma associated herpesvirus (Tumor Virology)
9. Development of stable drug target receptor gene-expressing cell line (Neurochemistry)
10. Neutralization of viruses (Microbiology)
11. Immunity to cryptosporidiosis in SIV-infected macaques (S. Tzipori, Tufts University)
12. Impact of micronutrients on progression of SIV (S. Gorbach, Tufts University)
13. Testing of live attenuated strains of M. tuberculosis (B. Bloom, Harvard School of Public Health)
14. Peripheral sequestration of amyloid-beta protein by gelsolin in a nonhuman primate model (C. Lemere, Harvard Institute of Medicine)
15. HIV and SIV SNA vaccines and mucosal immunity (A. Aldovini, Children's Hospital)
16. Immunization with live attenuated SIV and inactivated SIV particles (M. Neutra, Children's Hospital)

Over 24,000 samples were processed on the two FACS Caliburs in the preceding 12 months. In addition, an average of 4-8 sorts/month and 4-6 calcium flux studies/month have been carried out on the FACS Vantage in the past year. If we compare our costs to an outside lab, this translates to a savings over $300,000. In addition, we have produced a number of antibodies in house, using the Cellco culture system. With an expenditure of $24,648 we have generated

a stock of both conjugated and unconjugated antibodies that translates to a commercial value of $271,292. We continue to use these antibodies as well as supply them to other investigators. This will obviously provide a substantial savings on reagents over the next 5 years. In addition, we have made "in house" reagents available for routine CD4 immunophenotyping at NEPRC; as well as to other departments for use in studies requiring FACS analysis. Unique reagents (anti-CD3) have been made freely available.

We have also provided reagents to:

In addition, our laboratory responds to numerous questions regarding the immunophenotyping of rhesus macaque blood and bone marrow.

Publications resulting from work performed by the NEPRC Flow Core Services over the past year include:

1. Johnson WE, Lipson JD, Lang SM, Johnson UP, Desrosiers RC. Importance of B-cell responses for immunological control of variant strains of simian immunodeficiency virus. J. Viol. 2003; 77:375-381

2. Evans DT, Chen L-M, Gilles J, Lin K-C, Party B, Mazara GP, Denis RO, Mansfield KG, Lipson JD, Desrosiers RC, Gala JE, Johnson UP. Mucosa priming of SIV-specific C.L. responses in rhesus macaques by the Salmonella type III secretion antigen delivery system. J. Viol. 2003; 77:2400-9

3. Karur A, Assis N, Hale CL, Simon M, Elliott M, Gomez-AFL A, Lipson JD, Desrosiers RC, Wang F, Barry P, Mach M, Johnson UP. Direct relationship between suppression of virus-specific immunity and emergence of cytomegalovirus disease in simian AIDS. J. Viol. 2003; 77:5749-58

4. Sestak K, Ave PP, Buckholt M, Mansfield KG, Lackner AA, Tzipori S. Quantitative evaluation of Entercytozoon bieneusi infection in simian immunodeficiency virus-infected rhesus monkeys. J. Med. Primatol. 2003; 32:74-81

5. Permar SR, Klumpp SA, Mansfield KG, Kim WK, Gorgone DA, Lifton MA, Williams KC, Schmitz JE, Reimann KA, Axthelm MK, Polack FP. Role of CD8(+) lymphocytes in control and clearance of measles virus infection of rhesus monkeys. J. Viol. 2003; 77:4396-400

6. Park J, Cho NH, Choi JK, Geng P, Choe J, Jung JU. Distinct roles of cellular Lck and p80 proteins in herpesvirus saimiri Tip function on lipid rafts. J. Viol. 2003; 77:9041-51.

7. Lee BS, Connole M, Tang Z, Harris NL, Jung JU. Structural analysis of the Kaposi's sarcoma-associated herpesvirus K1 protein. J. Viol. 2003; 77:8072-86.

8. Gwack Y, Baek JH, Nakamura H, Lee SH, Meisterernst M, Roeder RG, Jung JU. Principal role of TRAP/Mediator and SWI/SNF complexes in Kaposi's sarcoma associated herpesvirus RTA-mediated lytic reactivation. Molecular and Cellular Biology 2003; 23:2055-2067.

9. Gwack Y, Nakamura H, Lee SH, Souvlis J, Yustein JT, Gygi S, Kung HJ, Jung JU. PARP-1 and Ste-20-like kinase hKFC act as repressors for gamma-2 herpesviral lytic replication. Molecular and Cellular Biology 2003; 23:8283-8294.

10. [ In press publication ]

11. [ In press publication ]

**Major histocompatibility complex class I and class II typing of rhesus macaques**

The class I and class II major histocompatibility (MHC) molecules play a key role in determining the host response to infectious agents. Accurate characterization of MHC class I and class II molecules is important to better understand the variable course of infectious diseases such as AIDS in nonhuman primates. In addition, accurate MHC typing plays an important role in colony management and assignment of animals to research studies. However, only limited techniques and reagents for MHC typing are available. Based on research initially carried out by [ Name ] laboratory at the Wisconsin Regional Primate Research Center, our laboratory has established sequence-specific polymerase chain reaction (SSP PCR) primers for the typing of 8 common MHC class I alleles, including Mamu-A*01. Over the past year over 150 animals from our colony and 100 animals from other centers (primarily the Oregon Regional Primate Research Center) have been typed for the Mamu-A*01 allele and approximately 20 animals have been typed for all 8 alleles in our class I panel. Typing of MHC class II alleles is carried out by plasmid cloning of PCR amplified MHC class II alleles followed by sequencing of the exon II of approximately 60 to 80 clones per animal. Over the past year over 200 class II clones from 4 animals have been sequenced. This detailed genetic information should improve the design of research experiments and colony management.

**Rhesus Thymic Stromal Cultures**

Efforts to study T cell differentiation in vitro have been significantly limited by the fact that T cell differentiation normally occurs only in the unique three-dimensional environment of the thymus. We have recently described an in vitro system employing cultures of fetal rhesus thymic stroma that is able to support T cell differentiation of both human and rhesus CD34+ hematopoietic progenitor cells (Rosenzweig, Blood 87, 1996: 4040-4048). This culture system provides a unique capability to support in vitro T lymphopoiesis that has found widespread application in the fields of hematopoiesis, gene therapy and lymphocyte biology, including:

- Examination of T cell ontogeny
- Effects of SIV/HIV on T progenitors in the thymus
- Evaluation of the effects of cytokines on T progenitors.
- Determination of the role of notch during T cell ontogeny
- Effects of various gene therapy protocols on T cell progenitors
- Xenogeneic T cell differentiation
- The role of NFKB binding sites in SIV replication in thymocytes
- Differentiation of transduced T cell progenitors into CD4+ and CD8+ T cells
- Establishment of limiting dilution assay of T cell progenitor activity

We have supplied this reagent to multiple collaborators, including:

[ reagent users ]

**CLINICAL RESEARCH AND LABORATORIES**

**Clinical diagnostic bacteriology**

In previous years the primary function of the bacteriology laboratory was to provide clinical diagnostic support to members of Primate Medicine, Comparative Pathology and individual investigators. Bacterial pathogens are arguably the major cause of morbidity and mortality in nonhuman primate colonies. Important pathogens include *Shigella flexneri, Klebsiella pneumoniae, Campylobacter jejuni, Yersinia pseudotuberculosis, Mycobacterium tuberculosis* and

enteropathogenic *E. coli.* Despite this fact, advances in understanding the epidemiology and pathogenesis of spontaneous bacterial diseases in nonhuman primates has lagged behind other areas of investigative primatology. The significance of many bacterial pathogens to colony health and their effect on experimental research are poorly understood. Bacteriologic services are provided by a medical technologist with 13 years of experience working with nonhuman primate bacterial isolates. Continued in house bacteriologic testing is essential to providing timely, cost efficient and consistent results which directly impact animal welfare and experimental work. Expansion and modernization of bacteriologic services at NEPRC are an ongoing effort.

Clinical specimens are submitted by members of the divisions of Primate Medicine, Comparative Pathology, Immunology, and Microbiology. Common sources include feces, blood, tissues obtained at necropsy, bronchoalveolar lavage, and urine. Samples are examined for aerobes (MacConkey agar, blood agar, phenyl ethyl alcohol agar, Campylobacter agar), anaerobes (Brucella agar), *Mycobacteria sp.* (7H10 agar), and fungi (Potato flake agar) as dictated by clinical history and findings. For most routine *Enterobacteriaceae, micrococci, Staphylococci* and nonfermenting gram-negative bacteria commercially available miniaturized rapid substrate systems are utilized for bacterial identification (API Rapid 20E and API Staph-IDENT, bioMerieux Vitek). This methodology uses a set of substrates carefully selected to allow a positive- and negative-reaction pattern to emerge creating a metabolic profile which can then be compared with an established database profile. In addition to these techniques, conventional procedures which include reactions in tube media, observation of physical characteristics such as colony morphology and results of Gram stains, agglutination tests and susceptibility patterns. Isolates of *Mycobacterium avium* are sent to the Massachusetts Department of Public Health State Laboratory Institute for identification by DNA probe analysis (Gen-Probe).

All clinical accessions are entered in a computerized data bank which is cross referenced with animal number, signalment and clinical history. Specimen accessions for the year 2003 are outlined in tables 5 and 6 by animal source and bacterial identification respectively. Specimens were submitted from 7 nonhuman primate species 1719 isolates were identified from samples.

**Table 5**
**2003 SAMPLES SUBMITTED FOR BACTERIOLOGIC ANALYSIS**

| SPECIES | NUMBER |
|---|---|
| *Aotus trivirigatus* | 2 |
| *Cercopithecus aethiops* | 14 |
| *Callithrix jacchus* | 134 |
| *Macaca cyclopis* | 0 |
| *Macaca fascicularis* | 23 |
| *Macaca mulatta* | 593 |
| *Macaca nemestrina* | 17 |
| *Saguinus oedipus* | 62 |
| *Saimiri sciureus* | 28 |
| Homo sapiens | 0 |
| Feline | 0 |
| Canine | 3 |
| **Total** | **876** |

When clinically indicated, antimicrobial susceptibility testing is performed. We currently use a disk diffusion method that allows categorization of bacterial isolates as susceptible, resistant or intermediate to a variety of antimicrobial agents. To perform the test, paper disks impregnated with a specified amount of antimicrobial drug (Sensi-disc, BBL) are applied to the surface of Mueller-Hinton agar that has been inoculated with the test organism. Plates are examined 18 to 24 hours after inoculation and the zone of inhibition measured. Gram negative isolates are examined for resistance against enrofloxacin, gentamycin, chloramphenicol, amikacin, cefoxotin, tetracycline, tircacillin, sulfamethoxazole/trimethoprim, ampicillin, cephalothin and tobromycin. Gram positive isolates are examined for resistance against oxacillin, erythromycin, penicillin, amoxicillin, ampicillin, cephalothin, chloramphenicol, clindamycin, sulfamethoxazole/trimethoprim and tetracycline. Susceptibility patterns are not obtained on all isolates and choice of antimicrobial agents is often made on an empirical basis by the clinical staff. Indications for antimicrobial susceptibility testing are: 1) isolation of an unusual organism for which susceptibility pattern at NEPRC is not well established, 2)

unusual clinical presentation, 3) poor response to antimicrobial therapy, 4) presence of life threatening infection, and 5) bacterial infection in study animals which may affect experimental outcome.

**Table 6**
**2003 BACTERIAL AND FUNGAL ISOLATES**

| ORGANISM | NUMBER | PERCENT |
|---|---|---|
| Acinetobacter species | 10 | 0.58 |
| Acinetobacter lwoffi | 3 | 0.17 |
| Aeromonas salmonicide | 1 | 0.06 |
| Bacillus species | 16 | 0.93 |
| Bacillus species (Beta hemolytic) | 1 | 0.06 |
| Bacteriodes fragilis | 2 | 0.12 |
| Bordatella bronchisepta | 3 | 0.17 |
| Campylobater jejuni | 33 | 1.92 |
| Citrobacter species | 1 | 0.06 |
| Citrobacter freundii | 3 | 0.17 |
| Diptheroids | 100 | 5.82 |
| Enterobacter cloacae | 6 | 0.35 |
| Enterobacter species | 5 | 0.29 |
| Enterococcus species | 1 | 0.06 |
| EPEC (total swabs submitted for) | 415 | 24.14 |
| Escherichia coli | 375 | 21.82 |
| Escherichia coli (Beta hemolytic) | 15 | 0.87 |
| Fungi (yeast) | 6 | 0.35 |
| Klebsiella pneumoniae | 118 | 6.86 |
| Neisseria species | 2 | 0.12 |
| Proteus species | 24 | 1.4 |
| Proteus mirabilis | 34 | 1.97 |
| Proteus vulgaris | 1 | 0.06 |
| Pseudomonas aeruginosa | 3 | 0.17 |
| Pseudomonas cepacia | 1 | 0.06 |
| Pseudomonas fluorescens | 6 | 0.35 |
| Pseudomonas stutter | 2 | 0.12 |
| Shigella flexneri | 2 | 0.12 |
| Staphylococcus aureus | 85 | 4.94 |
| Staphylococcus BH coal. neg. | 4 | 0.23 |
| Staphylococcus (non-hemolytic) | 128 | 7.45 |
| Streptococcus (Alpha hemolytic) | 293 | 17.04 |
| Streptococcus (Beta hemolytic) | 1 | 0.06 |
| Streptococcus (non-hemolytic) | 19 | 1.11 |
| Total | 1719 total | 100 percent |

Specialized techniques are available to identify bacterial pathogens when clinically indicated. For example we have recognized *C. difficult* as a major cause of antibiotic-associated diarrhea and pseudo membranous colitis in macaques treated with betalactam antibiotics and clindamycin for extended periods. To aid in the diagnosis of *C. difficult* associated disease, we use a combination of direct examination of feces, culture and isolation, and latex agglutination assays for cytotoxins A and B. Ideally a minimum of 5.0 gm or 5 ml of watery stool is obtained and cultured within 2 hours of collection on anaerobe blood agar or phenylethyl alcohol blood agar under anaerobic conditions. Bacterial

identification (ANA II System) and toxin detection (Techlab, Blacksburg, VA) on fecal filtrates are made with commercially available reagents.

This laboratory is responsible for monitoring tissue culture lines for the presence of *Mycoplasma sp.* and other possible contaminants. In addition to conventional techniques, PCR has been used to identify *Mycoplasma* sp. in cell culture lines. Quality control for sterility of autoclaved surgical packs, tissue culture media, monkey diets and formulae and environmental sampling of animal facilities for presence of other pathogens is routinely performed.

**Molecular techniques in clinical diagnosis and epidemiological analysis**

As noted above bacterial pathogens represent a significant source of morbidity and mortality in nonhuman primate colonies. Expansion and modernization of bacteriologic services at NEPRC would benefit colony health through expediting clinical diagnosis, tracking and treatment of bacterial diseases. We have begun to integrate molecular techniques into our clinical laboratory to accomplish these goals. Polymerase chain reaction is a versatile technique that has revolutionized the field of molecular biology. While initially used as tool in the basic sciences, its utilization in clinical diagnosis has increased dramatically. In a clinical setting, PCR may have several uses including: 1) recognition and identification of pathogens that are difficult to isolate, 2) identification of virulence factors and antimicrobial susceptibility and 3) molecular epidemiologic analysis.

The department has recently purchased several PCR thermocyclers. Guidelines against PCR contamination are followed as previously described and include use of appropriate positive and negative controls and physical separation of DNA preparation, PCR preparation and post PCR manipulations. We are currently using PCR based techniques for molecular epidemiologic analysis of spontaneous *Mycobacterium avium* complex infection and to delineate isolates of pathogenic *E. coli* obtained from colony housed animals. We hypothesize that pathogenic *E. coli* may play a major role in both acute and persistent diarrhea in our macaque colony. Unfortunately the role these agents play in the spontaneous disease of nonhuman primates is poorly understood. We are currently investigating the use of several PCR primer combinations directed against the ipaH gene of enteroinvasive *E coli*, heat-labile enterotoxin gene of enterotoxigenic *E. coli* and verocytotoxin genes of enterotoxigenic and verotoxigenic *E. coli.* Multiplex PCR performed on DNA from *E. coli* isolated in cases of clinical diarrhea would allow determination of virulence factors associated with its occurrence.

**Archive of clinically relevant bacterial isolates from nonhuman primates**

The establishment of an archive of clinically relevant bacterial isolates from nonhuman primates would aid in the investigation of spontaneous disease by helping to elucidate the epidemiology and factors associated with bacterial virulence. To accomplish this goal multiple subcultures of original isolates are dispersed in 50% glycerol and frozen at -70C for future use. Accessions are cataloged in a computerized database cross referenced with clinical history, animal number, species, sex, and location. This program was initiated in 1996 and has currently acquired 321 accessions from four species of nonhuman primates. The archive includes clinical isolates of *M. avium, Shigella flexneri,* enteroaggregative and enteropathogenic *E. coli, Campylobacter jejuni, Klebsiella pneumoniae* and *Citrobacter freundii.* As outlined below, this archive has been used to investigate the epidemiology of *M. avium* and *S. flexneri* in rhesus macaques and to identify pathogenic *E. coli* in *Callithrix jacchus.*

**Serologic testing**

During 2003, 3,333 individual serologic tests were performed for the presence of viral agents. Specific tests for the presence of antibodies included the following viruses: herpes simplex virus/herpes B virus (HBV), simian retrovirus type D (SRV-D), STLV-1, SIV, Herpes saimiri virus (HSV), rhesus Kaposi's sarcoma-related herpesvirus (rhKSHV), simian virus 40 (SV40), rhesus cytomegalovirus (RhCMV) and simian foamy virus (SFV).

Most of the testing involves ELISA protocols develop in the Division of Microbiology. Protocols for virus purification, coating of ELISA plates and performance of ELISAs were developed in conjunction with the division of microbiologyand follow well established techniques. For SRV-D, SIVmac, SIVagm and STLV-1 we grow and purify 1.5 liter amounts of virus. The isolates used were originally obtained by the division of microbiology. These include SRV-D (strain 395), SIVmac251, SIVmac239, SIVagm385, and STLV-1. Since the human herpes simplex virus is very closely related to herpes B virus, we use purified herpes simplex virus as test antigen for biosafety reasons. Our previous control experiments showed 100% agreement when herpes simplex virus is used as the test antigen. We also purchase commercially available HTLV-1 plates. When confirmatory testing is needed, we use indirect

immunofluorescence tests or send samples out for commercial western blot testing. Confirmatory retrovirus testing when indicated is performed at the Simian Retrovirus Reference Laboratory at the University of California, Davis; BV testing is performed at the National B Virus Reference Laboratory. SRV-D isolation is performed by the division of Microbiology through cocultivation of PBMCs with Raji cells. Cell cultures are monitored for the appearance of CPE and SRV-D specific immunoreactivity. Under some circumstances cultures may be examined by electron microscopy for viral particles or by PCR for SRV-D DNA.

The vast majority of testing is performed for placement of animals into the specific pathogen free macaque colony and for twice yearly verification that animals in the SPF colony retain their virus free status. The SPF breeding colony currently numbers 450 animals and is free of SRV-D, STLV-1, HBV and SIV; a subset is also free of simian foamy virus. Our procedure has been to examine each animal by ELISA before entry and conservatively select only those animals with ELISA values less than 0.15 to viruses for candidacy. Candidate animals are tested again after 3-6 months of segregation and only those animals with values less than 0.15 on repeat tests are entered into the colony. We have been very successful with this approach in maintaining negative animals for 12 years. The majority of animals from the SPF colony are used by core and collaborating investigators in infectious disease research.

**Maintenance of colony wide serum bank**

The unit maintains an extensive serum bank from colony animals with samples from 9 species of nonhuman primates dating from 1985 to the present. Samples are currently obtained biannually during routine preventative health care, during periods of illness and at death. Serum is collected and stored at -70C for future use. Accessions are numbered sequentially and entered in a computerized database which is cross referenced with species, sex, animal number, date of birth and location.

In 2003 there were 4,373 accessions from 6 nonhuman primate species. The presence of the center wide serum bank, which now contains 34,414 samples, has been an invaluable resource to the investigation of spontaneous disease in nonhuman primates. It is currently used by members of the divisions of Primate Medicine, Comparative Pathology, Microbiology and Immunology, as well as a number of collaborating scientists. Its existence has made possible the investigation of the epidemiology of spontaneous retroviral diseases in *Macaca mulatta*, and the identification of a rhesus macaque Kaposi's sarcoma herpesvirus. More recently we have used sera to identify and investigate two new flavivurses in *S. oedipus* and *C. jacchus*.

**4. Changes in Operation and Committees**

The Animal Allocation Committee which is now in its fourth year of existence continues to serve its goal in equitably allocating available resources to core and collaborative researchers.

**5. Staff Member Training**

All trainings are performed under the direction and with the cooperation of Environmental Health and Safety and meet the various regulations promulgated by Federal and State Law and Agencies. Environmental Health and Safety has produced yearly refresher trainings on the Harvard Web site to facilitate continued training and ensure documentation. NEPRC's participation in these programs in the year 2003 included: Confined Space, OSHA Bloodborne Pathogen, EPA Hazardous Waste training. In support of the Center, EH&S provided respiratory trainings and fit testing for the staff members whose jobs require their use.

Additional training programs at the Center are provided to insure that site specific procedures and policies of work place safety and regulatory compliance are achieved. Training for Bloodborne Pathogens is required of all those working with infectious materials and those entering the Biocontainment animal areas. Staff working within the BL2 laboratory areas were offered the required Hepatitis B vaccinations. CPR/First Aid is provided for all Laboratory Safety Officers as part of the Chemical Hygiene Plan and confine space requirements of the University.

The Center routinely conducts an Orientation Program that provides Zoonotic information, laboratory, and injury treatment procedures to all new staff. The virus Herpes B, which maybe shed by macaque species of primates is of particular concern and ALL STAFF are provided in depth information on it's source, mode of transmission, injury treatment, and documentation. Staff are provided additional material contained in the Zoonoses Packet. Again, outside researchers are provided the same Zoonotic information.

The animal care unit provides training in primate husbandry and laboratory animal science for the animal care technicians and research staff. Following orientation and training by area supervisors, new technicians work with an experienced staff member to ensure that proper skills are learned. We encourage all animal care staff to pursue certification by the American Association for Laboratory Animal Science (AALAS). In 2003, 14 animal care technicians completed a certification course taught by the Facilities Manager and will take appropriate certification exams. One animal care supervisor completed ILAM (Institute for Laboratory Animal Management) in May 2003. In-service training is also provided for veterinary and animal care technicians on a quarterly basis. Topics of these presentations this year included: Post-exposure SIV Prophylaxis, Zoonotic diseases in nonhuman primates, Bacterial diseases of nonhuman primates, B virus, Biocontainment animal housing, NHPs in neuroscience research, and Normal and Abnormal Behavior in Laboratory Primates.
Virus,

Post-exposure SIV Prophylaxis, Zoonotic diseases in nonhuman primates, Bacterial diseases of nonhuman primates, B virus, Biocontainment animal housing, NHPs in neuroscience research, and Normal and Abnormal Behavior in Laboratory Primates.

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