18th SNIP Scientific Conference

Hawaii Prince Hotel Waikiki, HI
April 24-28, 2012

SNIP Administrative Meetings

Tuesday, April 24, 2012

1:00 PM	Opening of Conference Office (*Boardroom*)
3:00 – 4:30 PM	SNIP Executive Committee Meeting (*President's Suite*)
5:00 – 6:30 PM	SNIP Meetings Committee Meeting (*Boardroom*)
7:00 – 9:30 PM	SNIP Council Dinner

Wednesday, April 25, 2012

(All Committee and Council meetings held in the "*Boardroom*")

8:00 – 8:30 AM	Society Awards Committee Meeting
8:30 – 9:15 AM	Young Investigator Committee Meeting
9:15 – 10:00 AM	Communications Committee Meeting
10:00 – 10:45 AM	Membership Committee Meeting
10:45 – 11:30 AM	Finance and Audit Committee Meeting
11:30 – 12:00 PM	Elections and Nominating Committee Meeting
12:00 – 1:00 PM	Lunch – on your own
1:00 – 3:00 PM	Council Meeting and Committee Reports

Scientific Sessions

*All main sessions held in the **Mauna Kea Ballroom** unless otherwise stated*

Wednesday, April 25, 2012

3:00 PM **Registration Opens** (*Mauna Kea Foyer and Boardroom*)

5:00 – 8:00 PM **POSTER SESSION I – Young Investigator Session** (*Mauna Kea Foyer*)

*Please have **ALL** posters mounted on poster boards before 5:00 PM.*

*"**A**" Posters (1A, 2A, etc.) to be presented from **5–6 PM***

*"**B**" Posters (1B, 2B, etc.) to be presented from **6–7 PM***

*"**C**" Posters (1C, 2C, etc.) to be presented from **7–8 PM***

Please remove all posters after the session

5:30 – 7:30 PM **Opening Reception during Poster Session I** (*Mauna Kea Foyer*)

Please come and enjoy some appetizers, refreshments, discussion and networking while attending the Young Investigator Poster Session!

Poster Titles listed by assigned Poster Board Numbers
(see *Journal of Neuroimmune Pharmacology* for complete abstracts)

1A. **THE INTERACTIVE ROLE OF HISTONE DEACETYLASES AND CANNABINOID GENES IN ALCOHOL ABUSERS.** Agudelo M[1], Yndart A[1], Morrison M[1], Napuri J[1], Khatavkar P[1], Nair MPN[1]; [1]Department of Immunology, Institute of Neuro-Immune Pharmacology, Herbert Wertheim College of Medicine, Florida International University, Miami, FL 33199.

1B. **ROLE OF CYP2A6 IN NICOTINE METABOLISM MEDIATED OXIDATIVE STRESS AND HIV-1 REPLICATION.** Ande A[1], Jin M[1], McArthur C[2], Kumar A[1], Kumar S[1]; [1]Division of Pharmacology & Toxicology, University of Missouri-Kansas City School of Pharmacy, Kansas City, MO 64108; [2]Department of Oral Biology, University of Missouri-Kansas City School of Dentistry, Kansas City, MO 64108.

1C. **L-DOPA INCREASES TYROSINE HYDROXYLASE EXPRESSION ON GABAERGIC NEURONS FOLLOWING 1-METHYL-4-PHENYL-1,2,3,6-TETRAHYDROPYRIDINE-INTOXICATION.** Anderson KM[1], Kuenstling MV[1], Szlachetka AM[1], Hutter-Saunders JLA[1], Mosley RL[1]; [1]Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198.

2A. **TIMP-1 ATTENUATES STAUROSPORINE- AND HIV-1-INDUCED APOPTOSIS IN HUMAN NEURONS THROUGH MODULATION OF BCL-2 FAMILY AND MITOCHONDRIAL MEMBRANE PERMEABILITY.** Ashutosh F[1], Chao C[1], Tang L[1], Borgmann K[1], Ghorpade A[1]; [1]Department of Cell Biology and Anatomy, University of North Texas Health Science Center, Fort Worth, TX 76107.

2B. **DIFFERENTIAL EFFECTS OF HIV-1B AND HIV-1C INFECTION ON SYNAPTIC PLASTICITY GENES: IMPLICATION IN HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS.** Atluri, VSR[1], Pilakka-Kanthikeel S[1], Nair MPN[1]; [1]Department of Immunology, Institute of Neuro-Immune Pharmacology, Herbert Wertheim College of Medicine, Florida International University, Miami, FL 33199.

2C. **ETHANOL INCREASES THE SURFACE EXPRESSION OF AMPA RECEPTORS BY MECHANISMS THAT INVOLVE ALTERATIONS IN THE BIOPHYSICAL PROPERTIES OF**

NEURONAL MEMBRANES. Bae M[1], Tovar-Y-Romo LB[1], Bandaru VVR[1], Haughey NJ[1]; [1]Department of Neurology, Johns Hopkins Medical Institutions, Baltimore, MD 21287.

3A. PDGF-BB INDUCTION OF MCP-1: IMPLICATIONS FOR HAND. Bethel-Brown C[1], Yao H[1], Yang L[1], Buch S[1]; [1]Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198.

3B. CATECHOLAMINE PRODUCTION BY VAGINAL EPITHELIAL CELLS: A NON-NEURONAL IMMUNOMODULATORY MECHANISM? Brosnahan AJ[1], Jones BJ[1], Vulchanova-Hart L[1], Brown DR[1]; [1]Department of Veterinary and Biomedical Sciences, College of Veterinary Medicine, University of Minnesota, Saint Paul, MN 55108.

3C. STABLE EXPRESSION OF ANTI-HIV TAT SINGLE CHAIN VARIABLE FRAGMENT INTRABODY IN HUMAN NEURONAL CELLS AS A POTENTIAL THERAPY FOR NEUROAIDS. Byron MM[1], Lu Y[1]; [1]Office of Public Health Sciences, University of Hawaii at Manoa, Honolulu, HI 96822.

4A. LIPOPOLYSACCHARIDE ALTERS THE INTRACELLULAR CONCENTRATION OF SAQUINAVIR IN MACROPHAGES THROUGH ALTERED EXPRESSION LEVELS OF MRP-1 AND MDR1. Cao L[1], Silverstein PS[1], Earla R[1], Kumar A[1]; [1]Division of Pharmacology and Toxicology, School of Pharmacy, University of Missouri-Kansas City, Kansas City, MO 64108.

4B. BUPRENORPHINE DECREASE THE INFLAMMATORY RESPONSE OF MONOCYTES IN THE CONTEXT OF NEUROAIDS. Carvallo L[1], Lopez L[1], Che FY[1], Lim J[1], Eugenin E[1], Nieves E[2], Madrid-Aliste C[3], Fiser A[3], Weiss L[1], Angeletti RH[2], Berman JW[1]; [1]Department of Pathology, Albert Einstein College of Medicine, Bronx, NY 10461; [2]Department of Developmental and Molecular Biology, Albert Einstein College of Medicine, Bronx, NY 10461; [3]Department of Systems and Computational Biology & Department of Biochemistry, Albert Einstein College of Medicine, Bronx, NY 10461.

4C. INTRACELLULAR CB2 RECEPTOR AND RECEPTOR TRAFFICKING IN HUMAN IMMUNE CELLS. Castaneda JT[1], Kiertscher SM[2], Harui A[2], Roth MD[2]; [1]Molecular Toxicology, University of California Los Angeles, Los Angeles, CA 90095; [2]Pulmonary & Critical Care Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095.

5A. EXERCISE ALTERS THE ABUNDANCE AND COMPOSITION OF GUT MICROFLORA AND ATTENUATES PCB-INDUCED CHANGES IN GUT MICROBIOME. Choi JJ[1], Toborek M[1]; [1]Department of Biochemistry and Molecular Biology, University of Miami, Miami, FL 33136.

5B. TRANSFORMING GROWTH FACTOR β-1 BLOCKER RESCUES HIV-1 NEF MEDIATED SPATIAL LEARNING IMPAIRMENT IN SPRAGUE DAWLEY RATS. Chompre G[1], Loucil R[1], Rivera-Amil V[3], Porter JT[2], Noel Jr R[1]; [1]Biochemistry Department, Ponce School of Medicine and Health Sciences, Ponce, 00732; [2]Pharmacology Department, Ponce School of Medicine and Health Sciences, Ponce, 00732; [3]Microbiology Department, Ponce School of Medicine and Health Sciences, Ponce, 00732.

5C. ASTROCYTE TRACE AMINE ASSOCIATED RECEPTOR-1-INDUCED CAMP REGULATES EXCITOTOXICITY: A MECHANISTIC COMMONALITY OF METH AND HIV-1-INDUCED NEUROTOXICITY. Cisneros I[1], Borgmann K[1], Ghorpade A[1]; [1]Cell Biology and Anatomy, University of North Texas Health Science Center, Fort Worth, TX 76107.

6A. HIV X4 AND X4R5 VIRUSES EXHIBIT DECREASED TOTAL ANTI-OXIDANT CAPACITY IN A PUERTO RICAN COHORT OF HIV-INFECTED WOMEN. Colon K[1], Zenon F[1], Delgado G[3], Rivera-Amill V[4], Noel R[4], Wojna V[2], Melendez LM[1]. [1]Departments of Microbiology and [2]Neurology, University of Puerto Rico Medical Sciences, San Juan, 00936; [3]Department of Biology, University of Puerto Rico Rio Piedras, San Juan, 00936; [4]Department of Microbiology, Ponce School of Medicine, Ponce, 00730.

6B. NICOTINE SUPPRESSES TLR3-MEDIATED INFLAMMATION THROUGH A CALCIUM SIGNALING MECHANISM. Cui WY[1], Chang SL[2], Polanowska-Grabowska R[3], Saucerman JJ[3], Li MD[1]; [1]Department of Psychiatry and Neurobehavioral Sciences, University of Virginia, Charlottesville, VA 22911; [2]Institute of NeuroImmune Pharmacology and Department of Biology, Seton Hall University, South Orange, NJ 07079; [3]Department of Biomedical Engineering, University of Virginia, Charlottesville, VA 22903.

6C. EFFICACY AND SAFETY TESTS OF LONG-ACTING NANOFORMULATED ANTI-RETROVIRAL DRUGS IN HIV-1 INFECTED HUMANIZED MICE. Dash PK[1], Gorantla S[1], Roy U[1], Knibbe J[1], Balkundi S[1], McMillan J[1], Gelbard HA[2], Poluektova LY[1], Gendelman HE[1]; [1]Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198; [2]Center for Neural Development and Disease, University of Rochester School of Medicine and Dentistry, New York, NY 14642.

7A. EXCESS SOLUBLE CD40L CONTRIBUTES TO BLOOD BRAIN BARRIER PERMEABILITY IN A MOUSE MODEL OF HIV-ASSOCIATED NEUROCOGNITIVE DISORDER (HAND). Davidson DC[1], Hirschman MP[1], Sun A[1], Kasischke KA[1], Schifitto G[2], Maggirwar SB[1]; [1]Department of Microbiology and Immunology, University of Rochester School of Medicine and Dentistry, Rochester, NY 14642; [2]Department of Neurology, University of Rochester School of Medicine and Dentistry, Rochester, NY 14642.

7B. THE ANTI-INFLAMMATORY α7 NICOTINIC ACETYLCHOLINE RECEPTOR IS UPREGULATED IN IMMUNE CELLS FROM HIV-INFECTED SUBJECTS: POTENTIAL IMPLICATIONS TO THE TREATMENT OF HIV-RELATED CHRONIC INFLAMMATION. Delgado-Velez M[1], Baez-Pagan C[1], Gerena-Lopez Y[6], Quesada O[2], Santiago-Perez L[1], Wojna V[5], Melendez L[4], Silva W[3], Lasalde-Dominicci J[1]; [1]Department of Biology, University of Puerto Rico, Río Piedras Campus, San Juan, PR 00931; [2]Department of Physical Sciences, University of Puerto Rico, Río Piedras Campus, San Juan, 00931; [3]Department of Physiology, University of Puerto Rico, Medical Sciences Campus, San Juan, 00936; [4]Department of Microbiology and Medical Zoology, University of Puerto Rico, Medical Sciences Campus, San Juan, 00936; [5]Internal Medicine, Neurology Division, University of Puerto Rico, Medical Sciences Campus, San Juan, 00936; [6]School of Pharmaceutical Sciences, School of Pharmacy, Medical Sciences Campus, San Juan, 00936.

7C. CANNABINOID MODULATES HIV TAT-ENGENDERED PROTEOME PROFILE OF MICROGLIAL-LIKE CELLS. Ferreira GA[1], Jamerson M[1], Cabral GA[1]; [1]Department of Microbiology and Immunology, Virginia Commonwealth University/School of Medicine, Richmond, VA 23298-0678.

8A. C/EBPβ REGULATES MULTIPLE IL-1β-INDUCED HUMAN ASTROCYTE INFLAMMATORY GENES VIA A P38 DEPENDENT PATHWAY. Fields JA[1], Ghorpade A[1]; [1]Cell Biology and Anatomy, University of North Texas Health Science Center, Fort Worth, TX 76107.

8B. MORPHINE EXACERBATED RESPONSE TO HIV-1 TAT-DEPENDENT SYNAPTODENDRITIC INJURY IS MEDIATED BY [CA2+]I STORES AND ATP DEPLETION. Fitting S[1], Zou S[2], Knapp PE[2], Hauser KF[1]; [1]Department of Pharmacology & Toxicology, Virginia Commonwealth University, Richmond, VA 23298; [2]Department of Anatomy & Neurobiology, Virginia Commonwealth University, Richmond, VA 23298.

8C. HIV-1 VIRAL PROTEIN R (VPR) MEDIATED INDUCTION OF PRO-INFLAMMATORY CYTOKINES IL-6, IL -8 AND RANTES IN THE ASTROCYTES VIA P38 MAPK AND NF-κB PATHWAY. Gangwani MR[1], Kumar A[1]; [1]Department of Pharmacology and Toxicology, University of Missouri-Kansas City, Kansas City, MO 64108.

9A. ALCOHOL MODULATES P2X RECEPTORS IN EMBYRONIC STEM CELL DERIVED MICROGLIA: POTENTIAL ROLE IN MICROGLIA IMMUNE REGULATION. Gofman L[1], Cenna J[1], Potula R[1]; [1]Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140.

9B. ALTERED BRAIN MICROSTRUCTURE IS ASSOCIATED WITH HIGHER CORTISOL LEVELS IN CHRONIC MARIJUANA USERS. Gonzales RMK[1], King GR[1], Sadino J[1], Ernst T[1], Chang L[1]; [1]Department of Medicine, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI 96813.

9C. METHAMPHETAMINE INDUCES TAAR1 RECEPTOR EXPRESSION IN NAÏVE T LYMPHOCYTES: ROLE IN IMMUNOMODULATION. Haldar B[1], Cenna J[1], Fan S[1], Potula R[1]; [1]Departments of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140.

10A. MECHANISMS BY WHICH A CB2-SELECTIVE CANNABINOID INHIBITS T-CELL FUNCTION. Hartzell RR[2], Meissler JJ[1], Adler MW[1], Eisenstein TK[1]; [1]Center for Substance Abuse Research,

Temple University School of Medicine, Philadelphia, PA 19140; [2]Department of Microbiology and Immunology, Temple University School of Medicine, Philadelphia, PA 19140.

10B. HIV TAT MEDIATES DOWN REGULATION OF β-CATENIN SIGNALING IN ASTROCYTES THROUGH ITS INTACT CYSTEINE-RICH REGION AND LOSS OF β-CATENIN LEADS TO SIGNIFICANT IMPAIRMENT OF EXCITATORY AMINO ACID TRANSPORTER 2. Henderson LJ[1], Narasipura SD[1], Min S[1], Al-Harthi L[1]; [1]Department of Immunology and Microbiology, Rush University Medical Center, Chicago, IL 60612.

10C. ALTERED RELATIONSHIP BETWEEN BRAIN GLUTAMATE/GLUTAMINE LEVEL AND BLOOD-OXYGENATION LEVEL DEPENDENT (BOLD) RESPONSE IN HIV-INFECTED INDIVIDUALS. Holt JL[1], Ernst T[1], Jiang CS[1], Chang L[1]; [1]Department of Medicine, John A. Burns School of Medicine, University of Hawaii at Manoa, Honolulu, HI 96813.

11A. MORPHINE-INDUCED CONDITIONED PLACE PREFERENCE AND REINSTATEMENT AFTER EXTINCTION IN HIV-1 TRANSGENIC RATS. Homji NF[1], Vigorito MV[1], Liu CL[1], Chang SL[1]; [1]Institute of NeuroImmune Pharmacology, Seton Hall University, South Orange, NJ 07079; [2]Department of Biological Science, Seton Hall University, South Orange, NJ 07079.

11B. CD40 LIGAND INDUCES BRAIN PERICYTE CELL DEATH: IMPLICATIONS FOR HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS (HAND). Jackson JW[1], Davidson DC[1], Maggirwar SB[1]; [1]Department of Microbiology and Immunology, University of Rochester Medical Center, Rochester, NY 14642.

11C. CYP2E1-MEDIATED ALCOHOL METABOLISM INDUCES EXPRESSIONS OF CYP2A6 AND CYP2E1 THROUGH OXIDATIVE STRESS-INDUCED PKC SIGNALING CASCADES IN MONOCYTES AND ASTROCYTES. Jin M[1], Kumar A[1], Kumar S[1]; [1]Division of Pharmacology and Toxicology, School of Pharmacy, University of Missouri-Kansas City, Kansas City, MO 64108.

12A. PSYCHOLOGICAL DISTRESS AND DEPRESSED MOOD IN HIV PATIENTS AND METHAMPHETAMINE USERS. Katayama N[1], Munsaka SM[1], Jiang C[1], Nakama H[1], Chang L[1]; [1]Department of Medicine, MRI Research Program, John A. Burns School of Medicine, University of Hawaii at Manoa, Honolulu, HI 96822.

12B. METHAMPHETAMINE AND HAART AFFECT NEUROTOXICITY OF HIV GP120 IN A CONCENTRATION- AND CONTEXT-DEPENDENT FASHION. Kaul M[1], Sanchez AB[1], Kinomoto M[1], Maung R[1], Catalan I[1], Cox C[1], Sejbuk NE[1], Hoefer M[1]; [1]Infectious and Inflammatory Disease Center, Sanford-Burnham Medical Research Institute, La Jolla, CA 92037.

12C. EFFECTS OF ANTIRETROVIRAL DRUGS ON HUMAN MACROPHAGES ACTIVATION. King J[1], Akay C[1], Jordan-Sciutto K[1]; [1]Department of Pathology School of Dental Medicine, University of Pennsylvania, Philadelphia, PA 19104.

13A. MOTOR SLOWING IN HIV-INFECTED METHAMPHETAMINE USERS. Kraft-Terry SD[1], Nakama H[1], Jiang C[1], Chang L[1]; [1]Division of Neurology, Department of Medicine, John A. Burns School of Medicine, University of Hawaii at Manoa, Honolulu, HI 96813.

13B. CYCLOOXYGENASE (COX) ENZYMES AND PROSTAGLANDIN E2 (PGE2) MODULATE WEST NILE VIRUS (WNV)-INDUCED NEUROINFLAMMATION, AND REGULATE THE PRODUCTION OF NEUROINFLAMMATORY MOLECULES INCLUDING MATRIX METALLOPROTEINASES (MMPS). Kumar M[1], Verma S[1], Nerurkar VR[1]; [1]Department of Tropical Medicine, Medical Microbiology and Pharmacology, John A. Burns School of Medicine/University of Hawaii, Honolulu, HI 96813.

13C. MORPHINE ALTERS GLOMERULAR FILTRATION BARRIER BY COMPROMISING PODOCYTE INTEGRITY. Lan X[1], Kumar D[1], Malhatra A[1], Singhal PC[1]; [1]The Feinstein Institute for Medical Research, North Shore LIJ Health System, Great Neck, NY 11021.

14A. HUMAN BRAIN ENDOTHELIAL CELLS SUPPRESS HIV REPLICATION IN MACROPHAGES. Li J[1], Wang Y[1], Ye L[1], Wang X[1], Gofman L[1], Persidsky Y[1], Ho W-Z[1]; [1]Department of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140.

14B. EFFECT OF METHAMPHETAMINE ON LPS-INDUCED PRO-INFLAMMATORY CYTOKINE PRODUCTION IS MEDIATED BY MAPK AND NF-κB PATHWAYS. Liu X[1], Silverstein PS[1],

Kumar A[1]; [1]Division of Pharmacology and Toxicology, University of Missouri-Kansas City, Kansas City, MO 64108.

14C. HIV-1 NEF EXPRESSION IN RAT HIPPOCAMPUS INDUCES SYSTEMIC INFLAMMATION AND CHANGES IN THE GASTROINTESTINAL TRACT. Loucil R[1], Chompré G[1], Cruz M[2], Hernández S[2], Ramírez A[2], Appleyard CB[2], Noel RJ[1]; [1]Department of Biochemistry, Ponce School of Medicine and Health Sciences, Ponce, 00732; [2]Department of Physiology and Pharmacology, Ponce School of Medicine and Health Sciences, Ponce, 00732.

15A. CHRONIC MORPHINE INHIBITS WOUND HEALING BY MODULATING TLR4 SIGNALING. Ma J[1], Roy S[2]; [1]Department of Surgery, University of Minnesota, Minneapolis, MN 55455; [2]Departments of Surgery and Pharmacology, University of Minnesota, Minneapolis, MN 55455.

15B. MODULATION OF HUMAN NEURAL PRECURSOR CELL PROLIFERATION AND DIFFERENTIATION BY HIV-1 TRANSACTIVATING PROTEIN, TAT AND DRUGS OF ABUSE. Malik S[1], Saha R, Seth P[1]; [1]Department of Cellular & Molecular Neuroscience, National Brain Research Centre, Manesar, Gurgaon, 122050, India.

15C. COCAINE ACCENTUATES HIV DISEASE PROGRESSION BY DOWN REGULATING ANTI-HIV MIRNA "MIR-125B" IN CD4+ T CELLS. Mantri C[1], Pandhare J[1], Dash C[1]; [1]Laboratory of Retrovirology and Epigenetics, Center for AIDS Health Disparities Research, Vanderbilt Meharry Center For AIDS Research, Meharry Medical College, Nashville, TN 37221.

16A. PROTEOMIC PROFILING OF MONOCYTE DERIVED MACROPHAGES DURING NANOART TREATMENT. Martinez-Skinner A[1], Veerubhotla R[1], Balkundi S[1], Liu H[1], Xiong H[1], McMillan J[1], Gendelman HE[1]; [1]Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68105.

16B. MORPHINE INCREASES INFLAMMATORY ACTIVITY IN THE INTESTINES BY INHIBITING MIR155 AND MIRNA146A. Meng J[1], Yu H[2], Banerjee S[1], Roy S[1]; [1]Department of Pharmacology, University of Minnesota, Minneapolis, MN 55455; [2]Department of Surgery, University of Minnesota, Minneapolis, MN 55455.

16C. ENHANCED COCAINE SENSITIZATION IN ADULT FEMALE HIV-1 TRANSGENIC RATS. Moran LM[1], Booze RM[1], Webb KM[1], Mactutus CF[1]; [1]Department of Psychology, University of South Carolina, Columbia, SC 29208.

17A. MARIJUANA USE MAY INCREASE SUSCEPTIBILITY TO HIV INFECTION AND NEUROINFLAMMATION. Munsaka SM[1], Feger U[1], Nerurkar V[2], Chang L[1]; [1]University of Hawaii, John A. Burns School of Medicine, Department of Medicine, Honolulu, HI 96813; [2]University of Hawaii, John A. Burns School of Medicine, Department of Tropical Medicine, Medical Microbiology and Pharmacology, Honolulu, HI 96813.

17B. MORPHINE SUPPRESSES MIR-155 AND FACILITATES HIV-1 INFECTIVITY IN MONOCYTE DERIVED DENDRITIC CELLS. Napuri J[1], Sudheesh PK[1], Nair MPN[1]; [1]Department of Immunology, Institute of NeuroImmune Pharmacology, Herbert Wertheim College of Medicine, Florida International University, Miami, FL 33199.

17C. CHRONIC MORPHINE TREATMENT DIFFERENTIALLY MODULATES MACROPHAGE PHAGOCYTIC AND BACTERICIDAL MECHANISMS FOLLOWING TLR2 AND TLR4 ACTIVATION. Ninkovic J[1], Roy S[1]; [1]Department of Surgery, Division of Basic and Translational Research, School of Medicine, University of Minnesota, Minneapolis, MN 55455.

18A. ALTERED ANTIOXIDANT AND OXIDATIVE STRESS STATUS IN RAT THALAMUS CAUSED BY HIV-1 TRANSGENESIS AND METHAMPHETAMINE TREATMENT. Pang X[1], Panee J[1], Liu X[2], Berry MJ[1], Chang SL[2], Chang L[3]; [1]Department of Cell and Molecular Biology, John A. Burns School of Medicine, University of Hawaii at Manoa, 651 Ilalo Street BSB 222, Honolulu HI 96813; [2]Institute of NeuroImmune Pharmacology, Seton Hall University, South Orange, NJ 07079; [3]Department of Medicine, John A. Burns School of Medicine, The Queen's Medical Center, Honolulu HI 96813.

18B. SINGLE NUCLEOTIDE POLYMORPHISMS WITHIN THE HIV-1 LTR CORRELATE WITH USE OF DRUGS OF ABUSE IN THE DREXELMED HIV/AIDS GENETIC ANALYSIS COHORT. Parikh N[1], Williams J[1], Wojno A[1], Pirrone V[1], Nonnemacher MR[1], Aiamkitsumrit B[1], Passic S[1], Blakey B[1], Ku J[4], Moldover B[2], Feng R[3], Servance L[4], Downie D[4], Lewis S[4], Jacobson JM[4],

Wigdahl B[1]; [1]Department of Microbiology and Immunology and Institute for Molecular Medicine and Infectious Disease, Drexel University College of Medicine, Philadelphia, PA 19102; [2]Private Company , B-Tech Consulting, Ltd, Philadelphia, PA 19130; [3]Department of Biostatistics and Epidemiology, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, PA 19104; [4]Department of Medicine, Division of Infectious Diseases and HIV Medicine, Drexel University College of Medicine, Philadelphia, PA 19102.

18C. DIFFERENTIAL EFFECTS OF HIV-1 CLADE B AND CLADE C ON THE EXPRESSION OF SILENT INFORMATION REGULATOR2 HOMOLG-1 (SIRT1). Pichili VB[1], Nair MPN[1]; [1]Department of Immunology, Institute of NeuroImmune Pharmacology, Herbert Wertheim College of Medicine, Florida International University, Miami, FL 33199.

19A. COCAINE DOWN REGULATES MICRORNA-146A WITH A RECIPROCAL UPREGULATION OF CXCR-4: IMPLICATIONS IN HIV IMMUNOPATHOGENESIS. Pilakka-Kanthikeel S[1], Napuri J[1], Nair MPN[1]; [1]Department of Immunology, Institute of NeuroImmune Pharmacology, Herbert Wertheim College of Medicine, Florida International University, Miami, FL 33172.

19B. INVOLVEMENT OF GLIAL CCR5 IN MORPHINE AND TAT-MEDIATED NEURODEGENERATION. Podhaizer EM[1], Zhang Y[2], Knapp PE[3], Hauser KF[1]; [1]Pharmacology & Toxicology, Virginia Commonwealth University, Richmond, VA 23298; [2]Medicinal Chemistry, Virginia Commonwealth University, Richmond, VA 23298; [3]Anatomy & Neurobiology, Virginia Commonwealth University, Richmond, VA 23298.

19C. N-FORMYL-METHIONINE-LEUCINE-PHENYLALANINE (FMLP) COATED NANOART. Puligujja P[1], Meyer J[1], McMillan J[1], Gendelman HE[1], Liu X[1]; [1]Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68128.

20A. CANNABINOIDS INHIBIT HIV TAT-ENHANCED ADHESION OF HUMAN U937 MACROPHAGE-LIKE CELLS TO THE EXTRACELLULAR MATRIX. Raborn ES[1], Jamerson M[1], Marciano-Cabral F[1], Cabral GA[1]; [1]Department of Microbiology and Immunology, School of Medicine/Virginia Commonwealth University, Richmond, VA 23298-0678.

20B. DETERMINING THE ROLE OF A UNIQUE POPULATION OF ACTIVATED CD8+ T CELLS IN THE BRAIN AFTER HIV INFECTION. Richards MH[1], Poluektova L[2], Al-Harthi L[1]; [1]Department of Immunology and Microbiology, Rush University Medical Center, Chicago, IL 60612; [2]Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198.

20C. CYSTATIN B INHIBITS THE IFN-β RESPONSE BY PREVENTING STAT-1 TRANSLOCATION AND DECREASING LEVELS OF STAT-1PY: IMPLICATION OF HIV REPLICATION IN MACROPHAGES. Rivera-Rivera L[1], Colón K[1], Meléndez LM[1]; [1]Department of Microbiology and NeuroAIDS Program, University of Puerto Rico-Medical Sciences Campus, San Juan, 00935.

21A. DEPRESSION MANAGEMENT RESULTS IN INCREASED TREATMENT ADHERENCE AND IMPROVED IMMUNE SYSTEM FUNCTION IN HIV-1 INFECTED PUERTO RICANS. Rivera-Rivera Y[1], Toro V[1], Cappas-Ortiz N[1], Rivera-Amill V[1]; [1]Microbiology Department, Ponce School of Medicine & Health Sciences, Ponce, 00717.

21B. THE ANTIRETROVIRAL DRUGS EFAVIRENZ AND LOPINAVIR ALTER MITOCHONDRIAL MEMBRANE POTENTIAL AND CAUSE NEURONAL DAMAGE IN PRIMARY NEURONS IN VITRO. Rivera-Vergara RM[1], Akay C[1], Jordan-Sciutto KL[1]; [1]Department of Pathology, School of Dental Medicine, University of Pennsylvania, Philadelphia, PA 19104.

21C. IN VIVO WEST NILE VIRUS INFECTION MODULATES THE MARKERS OF BLOOD-BRAIN BARRIER INTEGRITY. Roe K[1], Kumar M[1], Lum S[1], Orillo B[1], Nerurkar VR[1], Verma S[1]; [1]Department of Tropical Medicine, Medical Microbiology and Pharmacology, University of Hawaii at Manoa, Honolulu, HI 96813.

22A. GLYCOGEN SYNTHASE KINASE 3β (GSK3β) INHIBITION PREVENTS MONOCYTE (MO) MIGRATION ACROSS BLOOD BRAIN BARRIER (BBB) VIA SUPPRESSION OF RAC1-GTPASE AND FUNCTIONAL ACTIVATION OF β-INTEGRIN. Rom S[1], Reichenbach NL[1], Fan S[1], Dykstra H[1], Ramirez S[1], Persidsky Y[1]; [1]Department of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140.

22B. IMAGING DENDRITIC CELL TRAFFICKING INTO THE CENTRAL NERVOUS SYSTEM DURING STEADY-STATE AND UNDER NEUROINFLAMMATION. Sagar D[1], Lamontagne A[1], Foss C[2], Khan Z[1], Pomper M[2], Jain P[1]; [1]Department of Microbiology and Immunology, PA Biotech Center, Drexel University College of Medicine, Doylestown, PA 18902; [2]Department of Radiology, Johns Hopkins University, Baltimore, MD 21231.

22C. AGE AND ETHANOL CONCENTRATION-DEPENDENT EFFECTS OF ACUTE BINGE DRINKING IN THE HIV-1 TRANSGENIC RAT. Sarkar S[1], Mao X[1], Liu C[1], Chang SL[1]; [1]Institute of NeuroImmune Pharmacology, Seton Hall University, South Orange, NJ 07079.

23A. MODULATION OF EXPERIMENTAL HERPES ENCEPHALITIS-ASSOCIATED NEUROTOXICITY THROUGH SULFORAPHANE TREATMENT. Schachtele SJ[1], Hu S[1], Lokensgard JR[1]; [1]Center for Infectious Disease & Microbiology Translational Research, University of Minnesota, Minneapolis, MN 55455.

23B. SIGNALING MECHANISMS INVOLVED IN METHAMPHETAMINE-MEDIATED INCREASE IN THE EXPRESSIONS OF IL-6/IL-8 IN ASTROCYTES. Shah A[1], Kumar A[1]; [1]Pharmacology & Toxicology, University of Missouri-Kansas City, Kansas City, MO 64108.

23C. EVALUATION OF IMMUNOMODULATORY EFFECTS OF MORPHINE IN A MURINE HIV MODEL. Sharma U[1], Banerjee S[1], Volsky DJ[2], Roy S[1]; [1]Department of Surgery, University of Minnesota, Minneapolis, MN 55455; Molecular Virology Division , St. Luke's-Roosevelt Hospital Center, New York, NY 10019.

24A. MORPHINE AND HIV-1 TAT AS COMORBIDITIES ADDITIVELY REDUCE GUT BARRIER FUNCTION. Sindberg G[1], Meng J[2], Molitor T[1], Roy S[3]; [1]Veterinary Population Medicine, College of Veterinary Medicine, University of Minnesota, Saint Paul, MN 55108; [2]Department of Pharmacology/Medical School, University of Minnesota, Minneapolis, MN 55455; [3]Basic and Translational Research Division/Department of Surgery/Medical School, University of Minnesota, Minneapolis, MN 55455.

24B. DETECTION OF CIRCULATING PLATELET-MONOCYTE COMPLEXES IN HUMAN IMMUNODEFICIENCY VIRUS TYPE-1 INFECTED INDIVIDUALS. Singh MV[1], Davidson DC[1], Kiebala M[1], Maggirwar SB[1]; [1]Department of Microbiology and Immunology, University of Rochester Medical Center, Rochester, NY 14642.

24C. FUNCTIONAL PROPERTIES OF AN IN VITRO MODEL OF THE BLOOD-BRAIN BARRIER FOLLOWING CHRONIC MORPHINE EXPOSURE. Strazza M[1], Pirrone V[1], Wigdahl B[1], Nonnemacher MR[1]; [1]Department of Microbiology and Immunology and Institute for Molecular Medicine and Infectious Disease, Drexel University College of Medicine, Philadelphia, PA 19102.

25A. NEUROINFLAMMATION AND DEPRESSIVE SYMPTOMS IN HIV PATIENTS AND METHAMPHETAMINE USERS. Tanizaki N[1], Munsaka S[2], Nerurkar V[2], Jiang C[3], Chang L[3]; [1]Biomedical Science (Clinical Research), John A. Burns School of Medicine, University of Hawaii, Honolulu, HI 96813; [2]Department of Tropical Medicine, Microbiology and Pharmacology, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI 96813; [3]Department of Medicine, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI 96813.

25B. GENERATION OF INDUCED NEURAL PROGENITOR CELLS (INPCS) BY DIRECT REPROGRAMMING AND THEIR POTENTIAL THERAPEUTIC IMPACTS IN HIV-1 ASSOCIATED DEMENTIA (HAD). Tian CH[1], Ambroz RJ[1], Sun LJ[1], Wang YX[1], Ma KM[1], Chen Q[1], Zhu B[1], Zheng JL[1]; [1]Laboratory of Neuroimmunology and Regenerative Therapy, Department of Pharmacology & Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198-5930.

25C. LONGITUDINAL ANALYSIS OF INTRA-HOST HIV-1 ENVELOPE SPECIES DURING THE COURSE OF HAND. Vazquez-Santiago FJ[1], Melendez LM[2], Plaud-Valentin M[2], Noel RJ[1], Wojna V[2], Rivera-Amill V[1]; [1]Microbiology Department, Ponce School of Medicine and Health Sciences, Ponce, 00730; [2]Medical Sciences Campus, University of Puerto Rico, San Juan, 00936.

26A. RIG-I SENSES HIV-1 INFECTION AND MEDIATES TYPE I INTERFERON RESPONSE IN HUMAN MACROPHAGES: RELEVANT TO HIV-1-ASSOCIATED NEUROCOGNITIVE DISORDERS. Wang M[2], Huang Y[1], Huang J[3], Zheng JL[1]; [1]University of Nebraska Medical Center, Department of Pharmacology and Experimental Neuroscience, Omaha, NE 68198-5930;

[2]Shanghai Jiaotong University, School of Medicine, Shanghai, 200025; [3]Chinese Academy of Sciences, Graduate University, Beijing, 100049.

26B. FOXO3A IS INVOLVED IN THE PROPER GENERATION OF INDUCED PLURIPOTENT STEM CELL (IPSC). Wang YX[1], Tian CH[1], Zheng JL[1]; [1]University of Nebraska Medical Center, Department of Pharmacology and Experimental Neuroscience, Omaha, NE 68198-5930.

26C. HUMAN HEPATIC STELLATE CELLS SUPPRESS HEPATITIS C VIRUS REPLICATION IN HUMAN HEPATOCYTES. Wang YZ[1], Ye L[1], Wang X[1], Li JL[1], Song L[1], Ho WZ[1]; [1]Department of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140.

27A. THE EFFECTS OF DOPAMINE ON LEUKOCYTE TRANSMIGRATION ACROSS THE HUMAN BLOOD BRAIN BARRIER AND ITS ROLE IN THE PATHOGENESIS OF NEUROAIDS. Williams DW[1], Calderon TM[1], Coley JS[1], Gaskill PJ[1], Carvallo L[1], Eugenin EA[1], Berman JW[1]; [1]Pathology, Albert Einstein College of Medicine, Bronx, NY 10461.

27B. SELENOGLYCOPROTEINS ATTENUATE TUMOR CELL ADHESION AND MIGRATION THROUGH HUMAN BRAIN ENDOTHELIUM. Wrobel J[1], Choi JJ[1], Xiao R[2], Kwiatkowski S[2], Power R[2], Toborek M[1]; [1]Department of Biochemistry and Molecular Biology, University of Miami School of Medicine, Miami, FL 33136; [2]Nutrigenomics Research Centre, Alltech, Nicholasville, KY 40356.

27C. CONSTRUCTION AND CHARACTERIZATION OF LENTIVIRAL VECTOR-MEDIATED EXPRESSION OF TNFR AS A POTENTIAL PROTECTIVE MOLECULE IN HUMAN NEURONAL CELLS. Wu C[1], Cao S[1], Maggirwar S[2], Dewhurst S[2], Lu Y[1]; [1]Department of Public Health Sciences, University of Hawaii at Manoa, Honolulu, HI 96822; [2]Department of Microbiology & Immunology, University of Rochester, Rochester, NY 14642.

28A. COCAINE-MEDIATED UPREGULATION OF GLIAL FIBRILLARY ACIDIC PROTEIN: IMPLICATION FOR ASTROCYTE ACTIVATION IN HAND. Yang L[1], Yao H[1], Bethel-Brown C[1], Buch S[1]; [1]Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198.

28B. TLR3 ACTIVATION EFFICIENCY BY LOW AND HIGH MOLECULAR WEIGHT POLY I:C. Zhou Y[1], Wang X[1], Li JL[1], Wang YZ[1], Ye L[2], Guo M[2], Song L[1], Ho WZ[1]; [1]Department of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140; [2]State Key Laboratory of Virology, the Center for Animal Experiment/Animal Biosafety Level III Laboratory, Wuhan University, Wuhan, 430070.

Please remember to take down all posters immediately after the session

Thursday, April 26, 2012

*All main sessions held in the **Mauna Kea Ballroom** unless otherwise stated*

7:00 – 8:00 AM **Continental Breakfast** (*Mauna Kea Ballroom*)

Reminder - Put up Posters for Poster Session II during the lunch break

8:00 – 8:15 AM **INTRODUCTION TO THE MEETING**

Welcome from the Society on NeuroImmune Pharmacology

8:00 – 8:10 AM **Guy A. Cabral, Ph.D.** - **SNIP President**
(Virginia Commonwealth University School of Medicine, Richmond, VA)

8:10 – 8:15 AM **Sulie L. Chang, Ph.D.** - **Chair, SNIP Meetings Committee**
(Seton Hall University, South Orange, NJ)

8:15 – 9:05 AM **PLENARY LECTURE I: Ming D. Li, Ph.D.**
– University of Virginia, Charlottesville, VA

8:15 – 8:20 AM Introduction by **Guy A. Cabral, Ph.D.** – SNIP President

8:20 – 9:05 AM **Lecture:** *"Genetics and Pharmacogenetics of Addiction and Their Implications for Personalized Medicine"*

9:10 – 11:30 AM **SYMPOSIUM I**: **HIV Latency and HIV Reservoirs in the Post-HAART Era**

Session Co-Chairs: **Albert Avila, Ph.D.** – National Institute on Drug Abuse, Bethesda, MD
Guy A. Cabral, Ph.D. – Virginia Commonwealth University School of Medicine, Richmond, VA

9:10 – 9:15 **Introductory Remark: Albert Avila, Ph.D. –** National Institute on Drug Abuse, Bethesda, MD

9:15 – 9:45 **Symposium Lecture: Jonathan Karn, Ph.D. –** Case Western Reserve University, School of Medicine, Cleveland, OH
"Distinct Epigenetic Control Mechanisms Regulating HIV Silencing in T-Cells and Microglial Cells"

9:50 – 10:10 AM **Coffee Break** (Ballroom Foyer)

10:10 – 10:30 **Lecture 1: Shweta Hakre, Ph.D.** – University of California, San Francisco, CA
"Molecular Characterization and Regulation of HIV Latency at the Epigenetic Level"

10:35 – 10:55 **Lecture 2: David Margolis, Ph.D.** – University of North Carolina, Chapel Hill, NC
"Chemokines as Neuromodulators"

11:00 – 11:20 **Lecture 3: Patricia Molina, M.D., Ph.D.** – Louisiana State University, New Orleans, LA
"Systems Approach to Unraveling Mechanisms of Chronic Δ-9-THC Modulation of Simian Immunodeficiency Virus Infection"

11:25 – 11:30 **Conclusions: Guy A. Cabral, Ph.D.** – Virginia Commonwealth University School of Medicine, Richmond, VA

LUNCH ON YOUR OWN

– or –

11:30 – 12:50 PM **Meet the Mentors Luncheon** (*Mauna Kea Ballroom*)
Hosted by the Young Investigator Committee

*For Young Investigators who are presenting their work at the Conference and who have **Confirmed their Reservation** with the Young Investigator Committee*

1:00 – 2:00 PM **SNIP Annual Business Meeting** (*Mauna Kea Ballroom*)

All Society Members are requested to attend and all attendees welcome

2:00 – 4:00 PM **POSTER SESSION II – General Poster Session** (*Ballroom Foyer*)
(see next page for list of poster titles and authors)

*Please have **ALL** posters mounted on poster boards by 2:00 PM.*

Odd numbered posters (G1, G3, etc.) to be presented from 2:00 – 3:00 PM
Even numbered posters (G2, G4, etc.) to be presented from 3:00 – 4:00 PM

2:45 – 3:15 PM **Coffee Break during the Poster Session**

4:00 – 6:35 PM **SYMPOSIUM II**: **Alcohol and NeuroAIDS**

Session Co-Chairs: **Changhai Cui, Ph.D.** – National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD

Yuri Persidsky, Ph.D. – Temple University School of Medicine, Philadelphia, PA

4:00 – 4:10 **Introductory Remarks: Abraham P. Bautista, Ph.D.** – National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD

4:10 – 4:40 **Symposium Lecture: Adolf Pfefferbaum, M.D.** – SRI International, Menlo Park, CA

"Neuroimaging in HIV Infection and Alcoholism Comorbidity"

4:45 – 5:05 **Lecture 1: Jon Levine, M.D., Ph.D.** – University of California, San Francisco, CA

"Alcohol and the Pain of AIDS"

5:10 – 5:30 **Lecture 2: Norman Haughey, Ph.D.** – Johns Hopkins University School of Medicine, Baltimore, MD

"Fluid Movements: Neural Membranes and Receptor Trafficking in Alcohol and HIV"

5:35 – 5:55 **Lecture 3: Maria Jose Miguez, M.D., Ph.D.** – Florida International University School of Integrated Science and Health, Miami, FL

"The Impact of Alcohol Use on Markers of Inflammation, and Cognitive Functioning on Antiretroviral Treated Individuals"

6:00 – 6:20 **Lecture 4: James Haorah, Ph.D.** – University of Nebraska Medical Center, Omaha, NE

"Oxidative Injury and Bio-fuel Imbalance as Unifying Mechanisms for Neurological Disorders in Alcohol and NeuroAIDS"

6:25 – 6:35 **Conclusion: Changhai Cui, Ph.D.** – National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD

Yuri Persidsky, Ph.D. – Temple University School of Medicine, Philadelphia, PA

General Poster Session titles listed by assigned Poster Board Numbers
(see *Journal of Neuroimmune Pharmacology* for complete abstracts)

Please remember to take down all posters immediately after the session

G1. **BRAIN IMMUNOPHILIN IN HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS.** Achim CL[1], Vinters HV[2], Tatro ET[1], Moore DJ[1], Soontornniyomkij B[1], Gospodarev V[1], Gouaux B[1], Masliah E[1], Grant I[1], Soontornniyomkij V[1]; [1]HIV Neurobehavioral Research Program, School of Medicine, University of California San Diego, San Diego, CA 92093; [2]Neuropathology and Neurology, Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA 90095.

G2. **THE ROLE OF EARLY ENDOSOMAL SIGNALING IN HIV-1 INDUCED AMYLOID BETA ACCUMULATION IN BRAIN ENDOTHELIAL CELLS.** Andras IE[1], Toborek M[1]; [1]Biochemistry and Molecular Biology, University of Miami School of Medicine, Miami, FL 33136.

G3. **MOLECULAR MECHANISM OF HIV-1 TAT INDUCED NEURONAL DYSFUNCTION.** Bagashev, A[1], Sawaya, BE[1]; [1]Neurology Department, Temple University, Philadelphia, PA 19140.

G4. **PATHOGENS, TLRS, IL-17 SIGNALING AND THEIR CROSSTALK IN BRONCHIAL MUCOSA.** Banerjee S[1], Ninkovic J[1], Ma J[1], Meng J[2], Roy S[1]; [1]Surgery, University of Minnesota, Minneapolis, MN 55455; [2]Pharmacology, University of Minnesota, Minneapolis, MN 55455.

G5. **REGULATION OF MIR-146A BY IL-1β IN ASTROCYTES.** Banerjee S[1]; Dejos M[1]; Datta PK[1]; [1]Neuroscience/Center for Neurovirology, Temple University, Philadelphia, PA 19140.

G6. **METHAMPHETAMINE REDUCES GLUTATHIONE PEROXIDASE LEVELS.** Barayuga SM[1], Raman AV[1], Rueli RH[1], Andres MA[2], Panee J[1], Berry MJ[1], Bellinger FP[1]; [1]Cell and Molecular Biology, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI 96813; [2]Bekesy Laboratory of Neurobiology, Pacific Biosciences Research Center, University of Hawaii, Honolulu, HI 96822.

G7. **PLATELET-DERIVED GROWTH FACTOR RESTORES HIV TAT AND COCAINE-MEDIATED IMPAIRMENT OF NEUROGENESIS: ROLE OF TRPC 1 CHANNELS.** Buch S[1], Yao HH[1]; [1]Pharmacology, University of Nebraska Medical Center, Omaha, NE 689198.

G8. **DOPAMINE INCREASES CXCL12-MEDIATED T CELL TRANSMIGRATION ACROSS THE BLOOD BRAIN BARRIER.** Calderon TM[1], Gaskill PJ[1], Lopez L[1], Eugenin EA[1], Berman JW[2]; [1]Department of Pathology, Albert Einstein College of Medicine, Bronx, NY 10461; [2]Departments of Pathology and Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, NY 10461.

G9. **MINOCYCLINE PROTECTS MICE AGAINST WEST NILE VIRUS (WNV)-ASSOCIATED SEVERE DISEASE.** Chapagain ML[1], O'Connell M[1], Lazaga NB[1], Kumar M[1], Volper EA[1], Verma S[1], Nerurkar VR[1]; [1]Department of Tropical Medicine, Medical Microbiology and Pharmacology, John A. Burns School of Medicine, Honolulu, HI 96817.

G10. **INFECTION OF CHINESE MACAQUES BY A NEUROTROPIC SIVMAC251/CNS WITHOUT AND WITH TETRAHYDROCANNABINOL (THC).** Chen Z[1], Qiang W[2], Cong Z[2], Liu L[1], Qin C[2], Molina P[3]; [1]AIDS Institute of Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China; [2]Institute of Laboratory Animal Science, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [3]Department of Physiology, Louisiana State University Health Sciences Center, New Orleans, LA 70119.

G11. **DANGER SIGNAL HMGB1 MEDIATES ETHANOL-INDUCED NEUROINFLAMMATION THROUGH TLR AND RAGE RECEPTORS.** Crews FT[1], Vetreno R[1]; [1]Bowles Center for Alcohol Studies, University of North Carolina, Chapel Hill, NC 27599.

G12. **EPIGENETIC MECHANISMS INVOLVED IN THE INDUCTION OF THE COMPLEMENT C3 GENE IN ASTROCYTIC CELLS IN RESPONSE TO IL-1β.** Datta PK[1]; Rappaport J[1]; [1]Neuroscience, Temple University, Philadelphia, PA 19140.

G13. **ENHANCED PULMONARY VASCULAR REMODELING IN MORPHINE TREATED SIV-INFECTED MACAQUES: IMPLICATION IN HIV-ASSOCIATED PULMONARY ARTERIAL**

HYPERTENSION. Dhillon N[1], Cheney P[2], Tawfik O[3], O'Brien-Ladner A[1]; [1]Department of Medicine, Division of Pulmonary and Critical Care Medicine, University of Kanas Medical Center, Kansas City, KS 66160; [2]Department of Molecular and Integrative Physiology, University of Kanas Medical Center, Kansas City, KS 66160; [3]Department of Pathology, University of Kansas Medical Center, Kansas City, KS 66160.

G14. MORPHINE TREATMENT IN THE CONTEXT OF OPPORTUNISTIC INFECTION INDUCES DIFFERENTIAL IMMUNE CELL TRAFFICKING INTO THE CNS BY MODULATING TLR AND CHEMOKINE RECEPTOR EXPRESSION. Dutta R[1], Yu H[1], Charboneau R[2], Barke R[2], Roy S[1,2]; [1]Department of Surgery, University of Minnesota, Minneapolis, MN 55455; [2]Department of Surgery, Veterans Affairs Medical Center, Minneapolis, MN 55417.

G15. METHAMPHETAMINE ALTERS BLOOD BRAIN BARRIER FUNCTIONS FACILITATING CENTRAL NERVOUS SYSTEM INFECTION. Eugenin EA[1], Nosanchuk JD[2,3], Martinez LR[3,4]; [1]Departments of Pathology, Albert Einstein College of Medicine, Bronx, NY 10461; [2]Department of Medicine (Division of Infectious Diseases), Albert Einstein College of Medicine, Bronx, NY 10461; [3]Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, NY 10461; [4]Department of Biomedical Sciences, Long Island University, C. W. Post Campus, Brookville, NY 11548.

G16. IDENTIFICATION OF INTRACELLULAR TOXIC SIGNALS REQUIRED FOR BYSTANDER KILLING THROUGH GAP JUNCTIONS FROM HIV INFECTED ASTROCYTES TO UNINFECTED ASTROCYTES. Eugenin EA[1], Berman JW[1,2]; [1]Departments of Pathology, Albert Einstein College of Medicine, Bronx, NY 10461; [2]Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, NY 10461.

G17. MOTOR FUNCTION AND NEUROMETABOLITES IN CHILDREN WITH PRENATAL METHAMPHETAMINE OR NICOTINE EXPOSURE. Fukaya E[1], Chang L[1], Loehaugen G[2,3], Skranes J[2,3], Alicata D[1], Cunningham E[1], Jiang C[1], Ernst T[1]; [1]Department of Medicine, John A. Burns School of Medicine, University of Hawaii Manoa, Honolulu, HI 96813; [2]Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, Trondheim, Norway; [3]Department of Pediatrics, Sorlandet Hospital, Arendal, Norway.

G18. DOPAMINE MEDIATED INCREASES IN HIV REPLICATION IN MACROPHAGES ARE DUE IN PART TO INCREASED VIRAL ENTRY. Gaskill PJ[1], Berman JW[1]; [1]Department of Pathology, Einstein, Bronx, NY 105302; Department of Microbiology and Immunology, Einstein, Bronx, NY 10530.

G19. HUMANIZED MICE TO ASSESS THE HIV-1 CLADE-SPECIFIC DIFFERENCES: APROPOS OF VIRAL VIRULENCE AND NEUROPATHOLOGY. Gorantla S[1], Makarov E[1], Akther S[1], Wood C[2], Gendelman HE[1], Poluektova L[1]; [1]Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198; [2]Nebraska Center for Virology, University of Nebraska at Lincoln, Lincoln, NE 68588.

G20. PURINERGIC RECEPTORS ARE REQUIRED FOR HIV-1 INFECTION OF PRIMARY HUMAN MACROPHAGES. Hazleton JE[1], Berman JW[1,2], Eugenin EA[1]; [1]Departments of Pathology, Albert Einstein College of Medicine, Bronx, NY 10461; [2]Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, NY 10461.

G21. TCF4 BINDS DIRECTLY TO THE HIV LTR AND ASSOCIATES WITH NUCLEAR MATRIX PROTEIN SMAR1 TO REPRESS HIV TRANSCRIPTION IN ASTROCYTES. Henderson LJ[1], Narasipura SD[1], Adarichev V[2], Kashanchi F[3], Al-Harthi L[1]; [1]Department of Immunology and Microbiology, Rush University Medical Center, Chicago, IL 60612; [2]Department of Medicine, Division of Rheumatology, and Department of Microbiology & Immunology, Albert Einstein College of Medicine, New York City, NY 10461; [3]National Center for Biodefense and Infectious Diseases, George Mason University, Manassas, VA 20110.

G22. EXECUTIVE FUNCTIONING AND CORTISOL RESPONSES IN YOUNG CHILDREN WITH PRENATAL STIMULANT EXPOSURE. Hernandez AB[1], Cloak CC[1], Dowland S[1], Carlson S[2], Ernst TM[1], Chang L[1]; [1]Department of Medicine, University of Hawaii, Manoa , John A. Burns School of Medicine, Honolulu, HI 96813; [2]Institute of Child Development, University of Minnesota, Minneapolis, MN 55455.

G23. PERSISTENT HUMORAL IMMUNE RESPONSES IN THE CNS LIMIT RECOVERY OF REACTIVATED MURINE CYTOMEGALOVIRUS. Hu S[1], Mutnal MB[1], Lokensgard JR[1]; [1]Center for Infectious Diseases and Microbiology Translational Research, University of Minnesota Medical School, Minneapolis, MN 55455.

G24. FOXO3A REGULATES INFLAMMATORY MONONUCLEAR PHAGOCYTE ACTIVATION IN HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS. Huang Y[1], Zheng J[1]; [1]Department of Phamacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198 5930.

G25. PHAGOCYTIC UPTAKE OF HIV-1-INFECTED APOPTOTIC T CELL BODIES FACILITATES HIV-1 ENTRY INTO RENAL TUBULAR CELLS. Husain M[1], Lan X[1], Goel H[1], Singh P[1], Malhotra A[1], Singhal PC[1]; [1]Department of Medicine/Nephrology, Hofstra North Shore-LIJ School of Medicine, Great Neck, NY 11021.

G26. ANTIRETROVIRAL ACTIVITY AND BRAIN PENETRANCE OF FOLATE-COATED NANOFORMULATED ANTIRETROVIRAL DRUGS. Kanmogne GD[1], Roy U[1], Liu Z[1], McMillan J[1], Gorantla S[1], Balkundi S[1], Smith N[1], Alnouti Y[2], Gautam N[2], Poluektova L[1], Kabanov A[2], Bronich T[2], Gendelman HE[1]; [1]Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE, 68198-5215; [2]Department of Pharmaceutical Sciences, University of Nebraska Medical Center, Omaha, NE, 68198-6025.

G27. MONONUCLEAR PHAGOCYTE INTERCELLULAR CROSSTALK FACILITATES TRANSMISSION OF CELL TARGETED NANOFORMULATED ANTIRETROVIRAL DRUGS TO HUMAN BRAIN ENDOTHELIAL CELLS. Kanmogne GD[1], Liu X[1], McMillan J[1], Balkundi S[1], Zhou Y[2], Gendelman HE[1], Singh S[1]; [1]Departments of Pharmacology and Experimental Neuroscience , University of Nebraska Medical Center, Omaha, NE 68198-5215; [2]Center for Biotechnology, University of Nebraska-Lincoln, Lincoln, NE 68588.

G28. POTENTIATING DENDRITIC CELLS TO TARGET HYPOXIC ENVIRONMENT OF BRAIN TUMOR. Khan ZK[1], Masih S[1], Karatas E[1], Sagar D[1], Jain P[1]; [1]Department of Microbiology and Immunology, Drexel University College of Medicine, Doylestown, PA 18902.

G29. MCP-1 EXHIBITS PROFOUND EFFECT ON THE TRAFFICKING OF DENDRITIC CELLS INTO THE CENTRAL NERVOUS SYSTEM. Khan ZK[1], Sagar D[1], Rahman S[1], Manuel S[1], Jain P[1]; [1]Department of Microbiology and Immunology, Drexel University College of Medicine, Doylestown, PA 18902.

G30. NEUROIMMUNE INTERACTION IN THE ADRENAL GLAND OF HUMANIZED MICE: A POSSIBLE ROLE DURING HIV-1 INFECTION. Knibbe J[1], Makarov E[1], Gutti T[1], Dash PK[1], Gorantla S[1], Poluektova L[1]; [1]Pharmacology Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68168.

G31. ACCELERATED CAUDATE ATROPHY IN HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART)-TREATED HIV SUBJECTS OVER THREE YEARS. Kogachi S[1], Chang L[1], Sadino J[1], Jiang CS[1], Ernst TM[1]; [1]Department of Medicine, John A. Burns School of Medicine, University of Hawaii at Manoa, Honolulu, HI 96813.

G32. CENTRAL ROLE OF CYTOCHROMES P450 (CYP) IN ALCOHOL-MEDIATED OXIDATIVE STRESS AND ALCOHOL-ANTIRETROVIRAL THERAPY (ART) INTERACTIONS. Kumar S[1], Jin M[1]; [1]University of Missouri-Kansas City, School of Pharmacy, Kansas City, MO 64108.

G33. IMPULSIVENESS AND RISKY BEHAVIOR IN HIV-INFECTED AND NICOTINE SMOKING INDIVIDUALS. Lau EK[1], Chang L[1], Holt J[1], Jiang CS[1], Lum M[1]; [1]Department of Medicine, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI 96813.

G34. FUNCTIONAL ROLE OF MICRORNAS IN HIV-ASSOCIATED NEPHROPATHY. Malhotra A[1], Rai P[1], Singhal PC[1]; [1]Feinstein Institute for Medical Research, Hofstra North Shore-LIJ School of Medicine, Great Neck, NY 11021.

G35. HIV-1 LTR SINGLE NUCLEOTIDE POLYMORPHISMS (SNPS) CORRELATE WITH DISEASE PARAMETERS. Nonnemacher MR[1], Pirrone V[1], Aiamkitsumrit B[1], Shah S[1], Wojno A[1], Passic S[1], Blakey B[1], Zhong W[1], Moldover B[3], Feng R[4], Randazzo C[4], Downie D[2], Lewis S[2], Jacobson J[2], Wigdahl B[1]; [1]Department of Microbiology and Immunology, Institute for Molecular Medicine and Infectious Disease, Drexel University College of Medicine, Philadelphia, PA 19102; [2]Department

of Medicine, Division of Infectious Diseases and HIV Medicine, Drexel University College of Medicine, Philadelphia, PA 19102; [3]B-Tech Consulting, Ltd, N/A, Philadelphia, PA 19130; [4]Department of Biostatistics and Epidemiology, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, PA 19104.

G36. PANNEXIN1 HEMICHANNELS ARE CRITICAL FOR HIV INFECTION OF HUMAN PRIMARY CD4+ T LYMPHOCYTES. Orellana JA[1], Williams DW[2], Sáez JC[3], Berman JW[2,4]; Eugenin EA[2]. [1]Departamento de Neurología, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile; [1]Departments of Pathology, Albert Einstein College of Medicine, Bronx, NY 10461; [3]Departamento de Fisiología, Pontificia Universidad Católica de Chile, Santiago, Chile. [4]Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, NY 10461.

G37. CEREBROSPINAL FLUID MIRNA PROFILE IN HIV-ASSOCIATED NEUROLOGICAL DISORDERS. Pacifici M[1], Delbue S[4], Ferrante P[2], Jeansonne D[1], Kadri F[1], Nelson S[3], Peruzzi F[1]; [1]Lousianna State University Health Sciences Center, Neurological Cancer Center and Stanley Scott Cancer Center, School of Medicine, New Orleans, LA 70112; [2]Department of Public Health and Microbiology-Virology, University of Milan, Milan, 20123; [31]Lousianna State University Health Sciences Center and Alcohol Research Center, School of Medicine, New Orleans, LA 70112; [4]Ettore Sansavini Health Science Foundation, University of Milan, Milan, 20123.

G38. COCAINE INDUCED ALTERATIONS IN THE METABOLIC SIGNATURES OF CD4+ T CELLS: IMPLICATIONS IN HIV/AIDS AND DRUG ABUSE BIOLOGY. Pandhare J[1], Mantri C[1], Dash C[1]; [1]Laboratory of Retrovirology and Epigenetics, Center For AIDS Health Disparities Research, Vanderbilt-Meharry Center for AIDS Research (CFAR), Meharry Medical College School of Medicine, Nashville, TN 37221.

G39. BLOOD BRAIN BARRIER DISRUPTION BY METHAMPHETAMINE IS REGULATED BY CAVEOLAE-DEPENDENT ENDOCYTOSIS AND ACTIN CYTOSKELETON REARRANGEMENT. Park M[1], Lim B[2], Wylegala A[1], Toborek M[1]; [1]Department of Biochemistry and Molecular Biology, University of Miami School of Medicine, Miami, FL 33136; [2]Department of Biology, Centre College, Danville, KY 40422.

G40. MICRORNA-124 DEACTIVATES HUMAN HIV-1-INFECTED AND CLASSICALLY ACTIVATED MACROPHAGES/MICROGLIA: IMPLICATION FOR NEUROGENESIS. Peng H[1], Jia B[1], Zhu B[1], Chen Q[1], Wang M[1], Yunlong H[1], Zheng J ; [1]Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68105.

G41. POLY(ADP-RIBOSE) POLYMERASE (PARP) INHIBITION IN BRAIN ENDOTHELIUM PROTECTS THE BLOOD BRAIN BARRIER (BBB) UNDER PHYSIOLOGIC AND NEURO-INFLAMMATORY CONDITIONS. Persidsky Y[1], Rom S[1], Fan S[1], Reichenbach N[1], Dykstra H[1], Ramirez SH[1]; [1]Department of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140.

G42. ACTIVATION OF CANNABIOID RECEPTOR 2 (CB2) ATTENUATES LEUKOCYTE-ENDOTHELIAL INTERACTIONS AND BLOOD-BRAIN BARRIER (BBB) DYSFUNCTION UNDER INFLAMMATORY CONDITIONS. Persidsky Y[1], Haskó J[2], Skuba A[3], Fan S[1], Dykstra H[1], Rechenbach N[1], Krizbai I[2], Zhang M[1], Tuma R[4], Son Y[3], Ramirez SH[1]; [1]Department of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140; [2]Institute of Biophysics, Biological Research Center, Szeged, Hungary; [3]Shriners Hospitals Pediatric Research Center and Department of Anatomy and Cell Biology, Temple University School of Medicine, Philadelphia, PA 19140; [4]Department of Physiology, Temple University School of Medicine, Philadelphia, PA 19140.

G43. NEUROCHEMICAL COMPOSITION CORRELATED WITH VARIANCE IN ATTENTION AND HYPERACTIVITY/IMPULSIVITY SCORES: A MULTIVOXEL SPECTROSCOPY STUDY. Pritchett A[1], Chang L[1], Saito A[1], Keating B[1], Alicata D[1], Jiang CS[1], Cloak C[1], Lohaugen G[3], Skranes J[2], Ernst T[1]; [1]Department of Medicine, University of Hawaii John A. Burns School of Medicine, Honolulu, HI 96813; [2]Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, Trondheim, Norway; [3]Department of Pediatrics, Sorlandet Hospital, Arendal, Norway.

G44. EFFECTS OF APOE-EPSILON4 ALLELE AND HIV ON CORTICAL BRAIN STRUCTURES. Sadino J[1], Chang L.[1], Andres MA[2], Ernst TM[1]; [1]Department of Medicine, John A. Burns School of Medicine, University of Hawaii at Manoa, Honolulu, HI 96826; [2]Pacific Biosciences Research Center, University of Hawaii at Manoa, Honolulu, HI 96826.

G45. A COMBINED OPIATE AGONIST AND ANTAGONIST TRETMENT REDUCES ALCOHOL INHIBITORY EFFECTS ON OPIATE RECEPTOR DIMERIZATION AND CYTOLYTIC FUNCTIONS OF NK CELLS AND REDUCES MAMMARY TUMOR GROWTH. Sarkar DK[1], Sengupta A[1], Zhang C[1], Boyadjieva N[1]; [1]Endocrine Program, Rutgers University, New Brunswick, NJ 08901.

G46. CANNABINOID RECEPTOR EXPRESSION IN HUMAN FETAL NEURAL PRECURSOR CELLS. Sheng WS[1], Hu S[1], Rock RB[1]; [1]The Center for Infectious Diseases & Microbiology Translational Research, University of Minnesota Medical School, Minneapolis, MN 55455.

G47. CORTICAL AND WHITE MATTER DEVIATIONS RELATE TO COGNITIVE DEFICITS IN VERY-LOW-BIRTH-WEIGHT (VLBW) YOUNG ADULTS. Skranes J[1], Loehaugen GCC[2], Eikenes L[3], Bjuland KJ[1], Haberg A[4], Brubakk A-M[1]; [1]Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, 7489 Trondheim; [2]Department of Pediatrics, Sorlandet Hospital, Arendal, Norway; [3]Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway; [4]Department of Neuroscience, Norwegian University of Science and Technology, Trondheim, Norway.

G48. WNT SIGNALING IN NEUROAIDS. Tang S-J[1], Gelman B[1], Shi Y[1], Li B[1]; [1]Department of Neuroscience and Cell Biology, University of Texas Medical Branch, Galveston, TX 77555.

G49. NEUROPATHOGENIC MECHANISMS BY HIV-1 CLADE B AND C: ROLE OF LIPID RAFTS. Thangavel S[1], Santiago EM[1], Nair MPN[1]; [1]Institute of NeuroImmune Pharmacology (NIP), College of Medicine, Florida International University, Miami, FL 33199.

G50. EFFECTS OF COCAINE ON HIV INFECTION OF QUIESCENT T CELLS. Vatakis DN[1], Kim SG[1], Zhuo J[1], Baldwin GC[1], Zack JA[1]; [1]Department of Medicine, Division of Hematology and Oncology, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095.

G51. ALCOHOL INHIBITS INTRACELLULAR HIV RESTRICTION FACTORS AND ENHANCES HIV INFECTION OF CORD BLOOD MONOCYTE-DERIVED MACROPHAGES (CBMDM). Wang X[1], Mastrogiannis DS[2], Dai M[1], Ye L[1], Li JL[1], Wang YZ[1], Song L[1], Sakarcan S[1], Ho WZ[1]; [1]Department of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140; [2]Department of Obstetrics, Gynecology and Reproductive Sciences, Temple University School of Medicine, Philadelphia, PA 19140.

G52. POTENTIATION OF NMDA RECEPTOR-MEDIATED EPSCS BY D-SERINE: IMPLICATIONS FOR HIV-1-ASSOCIATED NEUROTOXICITY. Xia JX[1], Xiong H[1]; [1]Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198.

G53. NONMUSCLE MYOSIN LIGHT-CHAIN KINASE MEDIATES MICROGLIAL MIGRATION INDUCED BY HIV TAT: INVOLVEMENT OF B1 INTEGRINS. Yao HH[1], Buch S[1]; [1]Department of Pharmacology, University of Nebraska Medical Center, Omaha, NE 68198.

G54. DIFFERENTIAL REGULATION OF IL-33 BY HIV-1 B AND C CLADE INFECTION IN HUMAN ASTROCYTES (HA): ROLE IN NEUROPATHOGENESIS. Yndart A[1], Agudelo M[1], Nair MPN[1]; [1]Department of Immunology, Institute of Neuro-Immune Pharmacology, Herbert Wertheim College of Medicine, Florida International University, Miami, FL 33199.

G55. ADENOSINE DEAMINASES AS DRUG CANDIDATES FOR THE TREATMENT OF HIV INFECTION. Zavialov A[1], Lu Y[1]; [1]Department of Public Health, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI 96822.

Please remember to take down all posters immediately after the session

Friday, April 27, 2012

7:00 – 8:00 AM **Continental Breakfast**

8:00 – 10:10 AM **SYMPOSIUM III**: **Rodent Models of the Interaction of Substances of Abuse and HIV-associated Neurocognitive Disorders**

Session Co-Chairs: **Abraham P. Bautista, Ph.D.** – National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD

Pooja Jain, Ph.D. – Drexel University College of Medicine, Philadelphia, PA

8:00 – 8:30 **Symposium Lecture: Rosemarie Booze, Ph.D.** – University of South Carolina, Columbia, SC

"Translational Rodent Models of HIV-Associated Neurocognitive Disorders and Psychostimulants"

8:35 – 8:55 **Lecture 1: Michael Vigorito, Ph.D.** – Seton Hall University, South Orange, NJ

"Experience- and Substance-Induced Behavioral Plasticity in the HIV-1 Transgenic Rat"

9:00 – 9:20 **Lecture 2: David Volsky, Ph.D.** – Columbia University, New York, NY

"Molecular Markers of Neurocognitive Deficits in People with HAND and Mice Infected with Chimeric HIV"

9:25 – 9:45 **Lecture 3: Johnny He, Ph.D.** – University of North Texas, Fort Worth, TX

"HIV-1 Tat and HIV/NeuroAIDS: From Mechanistic Studies to Biomarker Discovery"

9:50 – 10:10 **Lecture 4: Jianuo Liu, M.D., Ph.D**. – University of Nebraska Medical Center, Omaha, NE

"Co-morbid Effects of HIV-1gp120 and Meth on Neuronal Physiology and Animal Behavior: Role of Voltage-gated K Channels"

10:15 – 10:30 AM **Coffee Break** (*Ballroom Foyer*)

10:30 – 12:40 AM **SYMPOSIUM IV: Neuroimmunity and Neurodegenerative Diseases**

Session Co-Chairs: **Phil Peterson, M.D.** – University of Minnesota School of Medicine, Saint Paul, MN

Michal Toborek, M.D., Ph.D. – University of Miami School of Medicine, Miami, FL

10:30 – 11:00 **Symposium Lecture: Howard Gendelman, M.D.** – University of Nebraska Medical Center, Omaha, NE

"Cell-Based Targeted Brain Delivery of Therapeutic Nanoparticles"

11:05 – 11:25 **Lecture 1: Xiaoxia Li, Ph.D. –** Lerner Research Institute, Cleveland, OH

"IL-17-Induced ACT1-Mediated Signaling is Critical for Cuprizone-Induced Demyelination."

11:30 – 11:50 **Lecture 2: R. Lee Mosley, Ph.D.** – University of Nebraska Medical Center, Omaha, NE

"T Cell-Mediated Immunity in Neurodegeneration and Parkinson's Disease"

11:55 – 12:15 **Lecture 3: Kalipada Pahan, Ph.D.** –Rush University Medical Center, Chicago, IL

"*Switching Glia from Neuroinflammatory to Neurotrophic in the Nigrostriatum of Hemiparkinsonian Monkeys"*

12:20 – 12:40 **Lecture 4: Jenny S. Henkel, Ph.D.** – Methodist Neurological Institute, Houston, TX

"T Cells Manage the Game in Lou Gehrig's Disease"

12:45 – 1:00 PM **PICK-UP LUNCHES FOR NIH WORKSHOP** (*Ballroom Foyer*)

1:00 – 2:00 PM **NIH WORKSHOP:**

Session Co-Chairs: **David Shurtleff, Ph.D.** – Acting Deputy Director (NIDA/NIH)

Abraham P. Bautista, Ph.D. – Director, Office of Extramural Activities (NIAAA/NIH)

Jeymohan Joseph, Ph.D. – Chief, HIV Pathogenesis, Neuropsychiatry, and Treatment Branch/Division of AIDS Research (NIMH/NIH)

Invited Participants

***David Shurtleff, Ph.D.**, Acting Deputy Director (NIDA/NIH)*

***Jag Khalsa, Ph.D.**, Chief, Medical Consequences Branch, Division of Pharmacotherapies and Medical Consequences of Drug Abuse (NIDA/NIH)*

***Albert Avila, Ph.D.**, Program Director, Division of Basic Neuroscience and Behavioral Research (NIDA/NIH)*

***Woody Lin, M.D., Ph.D.**, Health Scientist Administrator, Div. of Clinical Neuroscience and Behavioral Research (NIDA/NIH)*

***Abraham P. Bautista, Ph.D.**, Director, Office of Extramural Activities (NIAAA/NIH)*

***Ranga Srinivas, Ph.D.**, Chief, Extramural Project Review Branch, OEA (NIAAA/NIH)*

***Changhai Cui, Ph.D.**, Program Director, Div. of Neuroscience and Behavior (NIAAA/NIH)*

***Jeymohan Joseph, Ph.D.**, Chief, HIV Pathogenesis, Neuropsychiatry, and Treatment Branch/Div. of AIDS Research (NIMH/NIH)*

***Eduardo A. Montalvo, Ph.D.**, Scientific Review Officer, AIDS Initial Review Group, Center for Scientific Review (NIH)*

2:00 – 3:30 PM **YOUNG INVESTIGATOR'S SYMPOSIUM**

Session Co-Chairs: **Sylvia M. Kiertscher, Ph.D.** – David Geffen School of Medicine at UCLA, Los Angeles, CA

Ranga Srinivas, Ph.D. – National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD

Pre-Doctoral Presentations:

2:00 – 2:10 **Donna C. Davidson** – Dept. of Microbiology and Immunology, University of Rochester School of Medicine and Dentistry, Rochester, NY

"Excess Soluble CD40L Contributes to Blood Brain Barrier Permeability in a Mouse Model of HIV-Associated Neurocognitive Disorder (HAND)"

2:15 – 2:25 **Jerel A. Fields** – Dept. of Cell Biology and Anatomy, University of North Texas Health Science Center, Forth Worth, TX

"C/EBPβ Regulates Multiple IL-1β-induced Human Astrocyte Inflammatory Genes via a P38 Dependent Pathway"

2:30 – 2:40 **Divya Sagar** – Dept. of Microbiology and Immunology, Drexel University College of Medicine, Philadelphia, PA

"Imaging Dendritic Cell Trafficking into the Central Nervous System during Steady-State and under Neuroinflammation"

Post-Doctoral Presentations:

2:45 – 2:55 **Sylvia Fitting, Ph.D.** – Dept. of Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, VA

"Morphine Exacerbated Responses to HIV-1 TAT-Dependent Synaptodendritic Injury is Mediated by [CA2+]i Stores and ATP Depletion"

3:00 – 3:10 **Jana Ninkovic, Ph.D.** – Dept. of Surgery, Division of Basic and Translational Research, University of Minnesota School of Medicine, Minneapolis, MN

"Chronic Morphine Treatment Differentially Modulates Macrophage Phagocytic and Bactericidal Mechanisms Following TLR2 and TLR4 Activation"

3:15 – 3:25 **Prasanta K. Dash, Ph.D.** – Dept. of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE

"Efficacy and Safety Tests of Long-Acting Nanoformulated Anti-Retroviral Drugs in HIV-1 Infected Humanized Mice"

3:30 PM **FREE TIME –**

YES! – THE AFTERNOON AND EVENING ARE FREE

7:30 – 9:30 PM **Journal of Neuroimmune Pharmacology Editorial Board Meeting**

Saturday, April 28, 2012

7:00 – 8:00 AM **Continental Breakfast**

8:00 – 8:50 AM **PLENARY LECTURE II: Jeffrey Samet, M.D.** – Boston University, Boston, MA

8:00 – 8:05 Introduction of speaker by **Sulie L. Chang, Ph.D.** – Chair, SNIP Meetings Committee

8:05 – 8:50 **Lecture: "***The Impact of Alcohol and Substance Use on the Prevention and Treatment of HIV/AIDS*"

8:55 – 10:45 AM **SYMPOSIUM V: AIDS and Substances of Abuse - A Global Scenario**

Session Co-Chairs: **Mahendra Kumar, Ph.D.** – Miller School of Medicine, Miami, FL

Pankaj Seth, Ph.D. – National Brain Research Centre, Manesar, India

8:55 – 9:15 **Lecture 1: Elinore F. McCance-Katz M.D. Ph.D** – San Francisco General Hospital, San Francisco, CA

"Blood Alcohol Concentrations in HIV: Effect of Antiretroviral Treatment"

9:20 – 9:40 **Lecture 2: Madhavan P. N. Nair, Ph.D.** – Florida International University, Miami, FL

"Drug Abuse and NeuroAIDS in HIV Clades"

9:45 – 10:00 AM **Coffee Break** (*Ballroom Foyer*)

10:00 – 10:20 **Lecture 3: Brian Wigdahl, Ph.D.** – Drexel University College of Medicine, Philadelphia, PA

"HIV-1 Molecular Complexity and Subtype B and C Infection"

10:25 – 10:45 **Lecture 4: Victor Valcour, M.D.** – University of California San Francisco, San Francisco, CA

"Defining the Earliest CNS Events of HIV Infection Through International Collaborations"

10:50 – 11:40 Noon **Opendra "Bill" Narayan Lecture:**

10:50 – 11:00 Introduction of speaker by **Howard Gendelman, M.D.** – Chief Editor of JNIP

11:00 – 11:40 **Lecture: Tony Wyss-Coray, Ph.D** – Stanford University Medical Center, Stanford, CA

"*Can Young Blood Make Brains Younger?"*

11:45 – 12:45 PM **Lunch on your own**

12:50 – 2:15 PM **SYMPOSIUM VI: NeuroImmune Pharmacology Research in Hawaii**

Session Co-Chairs: **Linda Chang, M.D.** – JABSOM, University of Hawaii, Honolulu, HI

Woody (Yu) Lin, Ph.D. – National Institute on Drug Abuse, Bethesda, MD

12:50 – 1:00 **Lecture 1: Bruce Shiramizu, M.D**. – JABSOM, University of Hawaii, Honolulu, HI
"Exploiting Unique Monocyte Phenotypes for Treatment Strategies for HIV-Associated Neurocognitive Disorders"

1:00 – 1:10 **Lecture 2: Marilou Andres, Ph.D.** – JABSOM, University of Hawaii, Honolulu, HI
"Methamphetamine Inhibits L-type Calcium Channels in SH-SY5Y Cells"

1:10 – 1:20 **Lecture 3: Christine Cloak, Ph.D.** – JABSOM, University of Hawaii, Honolulu, HI
"What is happening in the Brains of Adolescent Marijuana Users?"

1:20 – 1:30 **Lecture 4: Yuanan Lu, Ph.D.** – JABSOM, University of Hawaii, Honolulu, HI
"Cell Mediated Novel Gene Therapy for NeuroAIDS"

1:30 – 1:40 **Lecture 5: George King, M.D.** – JABSOM, University of Hawaii, Honolulu, HI
"Cortisol and Behavioral Regulation in Chronic Active Cannabis Users"

1:40 – 1:50 **Lecture 6: Kazuma Nakagawa, M.D. –** JABSOM, University of Hawaii & the Queen's Medical Center, Honolulu, HI
" Racial Disparities Among Native Hawaiians and Other Pacific Islanders With Intracerebral Hemorrhage: Effect of Methamphetamine and Untreated Hypertension"

1:50 – 2:00 **Lecture 7: Vivek Nerurkar, Ph.D. –** JABSOM, University of Hawaii, Honolulu, HI
"Immunobiology of WNV-Induced Neuroinflammation"

2:00 – 2:15 **Discussion**

2:15 – 2:35 PM **Coffee Break** (*Ballroom Foyer*)

2:35 – 4:40 PM **SYMPOSIUM VII: Spice and Bath Salts – An Emerging Health Risk in the United States**

Session Co-Chairs: **Zhiwei Chen, Ph.D., DVM** – The University of Hong Kong LKS Faculty of Medicine, Pokfulan, Hong Kong
Alexandros Makriyannis, Ph.D. – Northeastern University, Boston, MA

2:35 – 2:40 **Introductory remark: Alexandros Makriyannis, Ph.D.** – Northeastern University, Boston, MA

2:40 – 3:10 **Lecture 1: Aron Lichtman, Ph.D.** – Virginia Commonwealth University School of Medicine, Richmond, VA
"Synthetic Marijuana: Pharmacology and Toxicology"

3:15 – 3:35 **Lecture 2: Anu Mahadevan, Ph.D.** – Organix, Inc, Boston, MA
"Synthetic Cannabinoids as Designer Drugs: A Structural Overview "

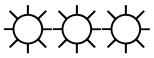
3:40 – 4:00 **Lecture 3: Brian Thomas, Ph.D.** – Research Triangle International, Research Triangle Park, NC
"The Surveillance and Detection of Designer Drugs: A New Challenge in Substance Abuse and Forensic Sciences"

4:05 – 4:25 **Lecture 4: Mahmoud ElSohly**, **Ph.D.** – University of Mississippi, Oxford, MS
"Methylhexylamine, a Stimulant Additive in Some Dietary Supplements: Is It Really a Component of Pelargonium oil?"

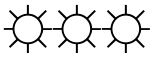
4:30 – 4:40 **Summary, Discussion and Future Considerations**
Alexandros Makriyannis, **Ph.D.** – Northeastern University, Boston, MA

6:45 – 10:00 PM **EVENING BANQUET AND AWARDS CEREMONY** (Mauna Kea Ballroom)
Hosted by **Sabita Roy, Ph.D.** – incoming SNIP President
Special Dinner Presentation: **Bryan Yamamoto, Ph.D.,** University of Toledo School of Medicine, Toledo, OH
"Breaking the Ice: Beyond Biogenic Amines"

Meeting Adjourned!



Sunday, April 29, 2012 – Departure Day



Join us for the 19th SNIP Scientific Conference currently planned for: San Juan, Puerto Rico April, 2013

(Details to be announced)

SPEAKER ABSTRACTS

Plenary Lecture I

GENETICS AND PHARMACOGENETICS OF ADDICTIONS AND THEIR IMPLICATIONS FOR PERSONALIZED MEDICINE. Li, MD[1]; [1]Department of Psychiatry and Neurobehavioral Sciences, University of Virginia, Charlottesville, VA 22911.

With the rapid development of high-throughout genomics techniques, significant progress has been made in identifying susceptibility genes and variants for various addictive behaviors. Unfortunately, except for a few variants with clearly defined biological functions, most of the genetic variants discovered are non-functional. Moreover, applying these genetics findings in the clinic has been a challenge. In this talk, I will first provide an overview of what we have learned from our past 10 years of searches for susceptibility genes for addictions, especially nicotine and alcohol dependence. I then will present a successful example to illustrate how we applied some of our genetic findings in a clinical trial. Although pharmacogenetics and personalized medicine are still in the very early research stage, their potential impact on future medicine and health care is tremendous and significant more research is thus greatly needed.

Symposium I: HIV Latency and HIV Reservoirs in the Post-HAART Era

DISTINCT EPIGENETIC CONTROL MECHANISMS REGULATING HIV SILENCING IN T-CELLS AND MICROGLIAL CELLS. Karn, J[1], Alvarez, D[1], Dobrowolski, C[1], Das, B[1], Harvey, BK[2]; [1]Department of Molecular Biology and Microbiology, Case Western Reserve University School of Medicine, Cleveland, OH 44106; [2]Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health, Baltimore, MD 21224.

Establishment of proviral latency is a complex process that involves blocks to transcription elongation, the reduction of transcription factor levels and the establishment of repressive chromatin structures. Our recent data has shown that the polycomb repressive complex-2 (PRC2) plays an essential role in maintaining HIV latency in T-cells. A recent unbiased shRNA library screen for latency fac tors revealed that of the 10 subunits known to form the PRC2, 6 were found in the top 10% of the hits, while the remaining 4 subunits were represented in the top 25% of all the hits. Additionally, the screen identified the NURD and SIN3 silencing complexes as important participants in HIV silencing. Recently we have developed a model of HIV-latently infected microglial cells (CHME-5/HIV). In contrast to T-cells we found that a distinct set of silencing factors mediate HIV repression. For example, BIX01294, an inhibitor of G9a histone lysine methyl transferase, which is a member of the CoREST repression complex, efficiently reactivated HIV provirus in CHME-5/HIV cells but is unable to do so T-cells. We also found that LPS-mediated reactivation of HIV was severely impaired. ChIP experiments have shown that the recently described Nurr1/CoREST transrepression pathway, which limits over-activation of NF-κB-dependent pro-inflammatory genes, plays a role in limiting HIV over-rea ctivation in infected microglial cells. Finally, using the microglial cells model we have found that methamphetamine and other drugs of abuse are able to potently reactivate latent proviruses. Supported by NIDA DP1 DA028869.

HIV LATENCY, PERSISTENCE, AND RESERVOIRS: MAKING PROGRESS TOWARDS AN ART-LESS FUTURE. Margolis, DM[1]; [1]Department of Medicine,

University of North Carolina Chapel Hill, Chapel Hill, NC 27599.

Despite antiretroviral therapy, proviral latency of human immunodeficiency virus type 1 (HIV-1) remains a principal obstacle to curing the infection. Disrupting latency via the induction HIV-1 expression in latently infected resting CD4+ T cells is a potential strategy to facilitate the clearance of this reservoir. In vitro, histone deacetylase (HDAC) inhibitors such as suberoylanilide hydroxamic acid (vorinostat, VOR) might disrupt HIV-1 latency, and ongoing studies may soon prove that this in vivo. However, this is only the first step down an uncertain path towards viable eradication therapies that must be employed around the world. Careful studies will be required to determine which regimens are safe and result in sustained disruption of HIV latency. The threshold required to fully disrupt purge persistent genomes without exceeding the capability of ART to contain spreading infection must be determined. Single agents for eradication of HIV infection must be developed and validated, and then if necessary, combinations tested. Reagents that disrupt latency may not be sufficient to clear replication-competent HIV, and strategies to augment the immune response or induce the death of infected cells may need to be developed and employed. Low levels of productive infection in other reservoirs such as myeloid or astroglial cells may remain, requiring novel approaches. These clinical challenges highlight the need for the development of larger and more complex substrate for eradication studies than offered by in vitro models currently in use. Supported by NIAID U19-AI096113, NIMH RO1-MH085597, NIDA RO1-DA030156.

TBA

SYSTEMS APPROACH TO UNRAVELING MECHANISMS OF CHRONIC Δ-9-THC MODULATION OF SIMIAN IMMUNODEFICIENCY VIRUS INFECTION. Molina, PE[1], Winsauer, P[1], Amedee, A[1], LeCapitaine, N[1], Zavaleta, J[1]; [1]Physiology, Louisiana State University Health Sciences Center, New Orleans, LA 70112.

Cannabinoids, the principal chemical constituents of marijuana, exert neurobehavioral effects and in addition have the potential of affecting the immune system. Our studies demonstrate that chronic i.m. administration of the major psychoactive cannabinoid in marijuana (Δ-9-tetrahydrocannabinol; Δ-9-THC) prior to and during simian immunodeficiency virus (SIV) infection, ameliorates disease progression and attenuates viral load and tissue inflammation, and significantly reduces morbidity and mortality of SIV-infected macaques. SIV, like HIV is a multisystemic disease affecting multiple organ systems including the CNS, spleen, and gut. Viral entry, integration and replication, and cell injury involve numerous cellular signaling and effector mechanisms determining the overall systemic response to the infection. Investigation of the Δ-9-THC-mediated modulation of disease progression requires recognition of the different cannabinoid receptor subtypes, their widespread distribution, the tissue-specific viral kinetics, and the multiplicity of cellular and molecular mechanisms involved in both control of viral replication as well as immunological dysfunction and cell injury. The multiplicity and interconnectedness of factors cannot be effectively reconciled using isolated organ, cellular, or molecular approaches. Using an integrated systems biology analysis our recent studies have identified salient cellular and molecular signatures prevailing during the infection and their modulation by Δ-9-THC in the SIV-infected rhesus macaque. Our findin gs suggest that chronic Δ-9-THC administration differentially modulates key interconnected and tissue-specific mechanisms responsible for control of disease progression. These processes are clustered in 5 main categories including barrier function, neuroendocrine cell signaling, apoptosis, inflammatory/oxidative stress, and cell cycle/differentiation that interact to suppress viral replication, morbidity, and mortality in SIV-infected non-human primates.

Furthermore, our recent studies clearly suggest that the overall mechanisms mediating the protective effects of cannabinoids involve novel epigenomic regulatory factors/mechanisms underlying changes in the transcriptome in need of systematic investigation. Supported by NIDA-020419 and NIDA030053.

Symposium II: Alcohol and NeuroAIDS

NEUROIMAGING IN HIV INFECTION AND ALCOHOLISM COMORBIDITY. Pfefferbaum, A[1,2] , Sullivan, EV[2]; [1]Neuroscience Program, Center for Health Sciences, SRI International, Menlo Park, CA 94025; [2]Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305-5723.

Alcoholism comorbidity is a common concomitant of HIV infection and can exacerbate HIV infection by acting as an immunosuppressant and interfering with positive effects of antiretroviral therapy. Each condition can also directly compromise brain structure and function and are amenable to study with multiple modalities of in vivo brain imaging. Our controlled neuroimaging studies together with neuropsychological testing are aimed at identifying differential patterns of brain insult in men and women with HIV infection alone, alcoh olism alone, and HIV infection and alcoholism combined. Profound effects have been observed in patients comorbid for HIV infection and alcoholism, especially those who have experienced an AIDS-defining event. The substantial effect of the alcoholism-AIDS interaction on ventricular volumes and the size and mictrostructural integrity of the corpus callosum, in the context of the modest changes observed in non-AIDS, non-alcohol abusing HIV infected individuals, highlights the need to consider alcohol use disorders as a major risk factor for neuropathology among HIV infected persons. MR spectroscopic studies found only the comorbid HIV+alcoholism group to be affected, exhibiting a deficit in N-acetyl aspartate, a marker of the integrity of living neurons. Although neither HIV infection nor alcoholism alone resulted in such abnormalities in these study groups, each disease carried a liability that put affected individuals at heightened risk of neuronal compromise when the disease s were compounded. The high prevalence of alcoholism in HIV-infected individuals and the interfering effect of alcohol on HIV pharmacological response and therapy compliance, plus the observed brain insults, underscore the need to recognize the independent and synergistic contributions of each condition to brain structure and function integrity. Supported by National Institute on Alcohol Abuse and Alcoholism (AA017347, AA012999, AA012388).

Jon Levine

FLUID MOVEMENTS. NEURAL MEMBRANES AND RECEPTOR TRAFFICKING IN ALCOHOL AND HIV. Haughey, NJ[1], Patel, N[1], Bae, M[1]; [1]Neurology, Johns Hopkins University School of Medicine, Baltimore, MD 21287.

Excessive alcohol intake is associated with worse cognitive function in HIV-infected individuals. Although the effects of alcohol on CNS functions are known, mechanistic explanations for these effects have been elusive. Biological membranes contain microdomains that exhibit decreased lateral mobility due to a high focal packing density of saturated lipid species. Rapid and transient alterations in the lipid content of these membrane microdomains regulate the insertion and lateral movements of excitatory amino acid receptors. Alcohol disrupts the structure of membrane microdomains and increases the surface localization of AMPA receptors by alt ering phosphorylation of the GluR1 C-terminal. These surface-located AMPA receptors are calcium permeable and

cluster to ganglioside-rich portions of dendrites. AMPA-evoked calcium flux at these sites is enhanced, and the receptors are resistant to agonist-induced internalization. The effects of alcohol on membrane biophysics and receptor trafficking are more complicated in the setting of HIV-infection where viral proteins, and inflammatory mediators can also perturb the function of membrane microdomains. Thus, alcohol and HIV-associated modifications in brain lipid content disrupts the trafficking of excitatory amino acid receptors that are critical substrates of memory. Supported by AA0017408; MH077542; MH075673.

THE IMPACT OF ALCOHOL USE ON MARKERS OF INFLAMMATION, AND COGNITIVE FUNCTIONING ON ANTIRETROVIRAL TREATED INDIVIDUALS. Miguez, MJ[1], Burbano, X[1], Lewis, J[2], Asthana, D[2], Michelle, T[1], Quiroz, C[1]; [1]School of Integrated Science and Health, Florida International University, Miami, FL 33139; [2]Psychiatry, University of Miami, Miami, FL 33136.

Despite advances in antiretroviral therapy, HIV associated neurological disorders (HAND) affect up to 60% people living with HIV (PLWH). Unfortunately, the underlying mechanisms need to be further elucidated for an effective intervention to occur. Given the high prevalence of hazardous alcohol use (HAU) among PLWH, HAU may contribute to HAND either directly (neurotoxicity) or by sustaining a pro-inflammatory response. Using a longitudinal study in South Florida, the data has been gathered on 300 hazardous and non-hazardous alcohol users receiving medical care. Questionnaires and in-depth neuropsychological assessments were used to ascertain alcohol use and participants' neuropsychological status. Blood was drawn to determine viroimmune status, particularly to assess TNF-α a highly pleiotropic cytokine that plays a key role on viral replication and neuronal apoptosis. According to the collected data, hazardous drinkers, particularly consumers of liquor or beer exhibited higher TNF-α levels. The implications of these findings are far-reaching given that TNFα levels were significantly associated with poor viroimmune responses and cognitive impairment. Cognitive analysis demonstrated that higher TNF-α levels were associated with deficiencies in multiple cognitive domains (Trail Making Test 1 and 2, $p = 0.02$; verbal fluency, learned fewer words, remembered less words after a short period of delay, and possessed less visual search activity). In summary, HAU of liquor or beer significantly affects TNF-α levels, and this pro-inflammatory response was associated with HAND. Supported by NIAAA 5R01AA-018095-03.

OXIDATIVE INJURY AND BIO-FUEL IMBALANCE AS UNIFYING MECHANISMS FOR NEUROLOGICAL DISORDERS IN ALCOHOL AND NEUROAIDS. Haorah, J[1], Schutz, H[1], PM Abdul, M[1], Szlachetka, A[1]; [1]Neurovascular Oxidative Injury Laboratory, Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198.

ABSTRACT: Both alcohol abuse and HIV-infection cause neurovascular injury, neuroinflammation, neurotoxicity and neurological dementia. Combined effect of the two promotes neurological disease progression and short life span. There are multi-facet mechanisms of these co-morbid effects. Here we present energy wasting under oxidative stress as one of the unifying mechanisms for shortening human lives in alcohol abuse with HIV-infection. Alcohol-induced oxidative damage of the neurovascular units leads to inflammatory process, where ethanol metabolite (acetaldehyde) acts as the inducer of oxidative stress. The site of oxidative injury at the blood-brain barrier is also the site of immune cells (HIV-1 infected cells) adhesion and migration into the brain. Ethanol inhibits the uptake/transport of glucose at this site of BBB injury, thereby

restricting the entry of glucose into the brain. Under this limited supply of glucose, the infected astroglial cells amass the limited substrate for progression of HIV-infection in alcoholics. Such a high consumption of energy by these infected cells causes energy wasting to enhance oxidative stress, secretion of toxic viral proteins and accelerate neurotoxicity. Thus, suppression of oxidative stress and stabilization of energy supply by therapeutic agent can prevent alcohol-induced oxidative brain injury and ameliorate HIV-1 infection. But without killing the virus, we cannot cure the HIV-1-mediated neurological disorders and HIV-1/AIDS disease. Our newly discovered neurotoxin drug that easily traverses the blood-brain barrier has a potential to eradicate HIV-1 in the CNS and in the peripheral. Supported by NIH/NIAAA: RO1 AA017398; R21 AA020370-01A1.

Symposium III: Rodent Models of Interaction of Substances of Abuse and HIV-associated Neurocognitive Disorders

TRANSLATIONAL RODENT MODELS OF HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS AND PSYCHOSTIMULANTS. Booze, RM[1], Moran, LM[1], Mactutus, CF[1]; [1]Department of Psychology, University of South Carolina, Columbia, SC 29208.

HIV-1 infected patients have been characterized by suboptimal cognitive performance, despite effective antiretroviral therapy. Such impairments comprise HIV-associated neurocognitive disorders, or HAND. Neuropsychological testing of HAND patients has identified a number of impaired cognitive domains, as well as alterations in specific brain structures through neuroimaging techniques. However, identification of the mechanisms producing specific neurocognitive performance patterns in HAND will be greatly facilitated with the use of preclinical studies. Additionally, putative therapeutic approaches are most effecti vely testing using rodent models that are capable of selectively measuring performance for each cognitive domain implicated in HAND. We will 1) discuss a number of tasks used in rodent models of cognitive function that can be employed in preclinical studies of HAND, given our current understanding of the clinical manifestations of HAND, and 2) identify structural and neurochemical alterations in specific rodent brain areas which correlate with, and may underlie, alterations in HAND. We will present data from a rodent HAND model in which methamphetamine produces behavioral and neurochemical alterations similar to those seen in the human HIV-1+ drug abusing population. The translational relevance of rodent models of cognitive function to cognitive deficits in HAND needs to be addressed in order to have significant predictive utility regarding effective pharmacotherapies for this neurocognitive disorder. Supported by NIH-NIDA R01DA013137.

EXPERIENCE- AND SUBSTANCE-INDUCED BEHAVIORAL PLASTICITY IN THE HIV-1 TRANSGENIC RAT. Vigorito, M[1,2], Chang, SL[2,3]; [1]Department of Psychology, Seton Hall University, South Orange, NJ 07079; [2]Institute of NeuroImmune Pharmacology, Seton Hall University, South Orange, NJ 07079; [3]Department of Biological Sciences, Seton Hall University, South Orange, NJ 07079.

A growing body of evidence suggests that substance-induced behavioral plasticity occurs when substances of abuse commandeer the normal learning and memory systems of the brain. Thus, aberrant neurobiological changes in the neural circuitry mediating experience-induced behavioral plasticity can result in disorders of learning and memory as well as modified sensitivities to substances of abuse and altered vulnerability to addiction. Chronic exposure to viral proteins in humans infected with human immunodeficiency virus (HIV) and under highly active antiretroviral therapy can cause changes to neural circuits as indicated by the high prevalence of neurocognitive

impairment in HIV patients and by accelerated neurological impairments in HIV positive substance abusers. Accordingly, an animal model of HIV-induced neurocognitive dysfunction would be expected to show both experience- and substance-induced alterations in behavioral plasticity. Experiments with the HIV-1 transgenic rat using a water maze task, fear conditioning procedures, and other behavioral measures suggest that the chronic presence of viral proteins can alter experience-induced behavioral plasticity. Experiments with methamphetamine and morphine treatment have also yielded evidence of altered substance-induced behavioral plasticity in HIV-1 transgenic rats. Collectively, these and other experiments demonstrate the utility of the HIV-1 transgenic rat as a model for generating testable hypotheses to better understand the impact of HIV-1 viral proteins on HIV-induced neurocognitive dysfunction. Supported by R01 DA07058, R01 DA026356, RC2 AA019415, K02 DA016149 and R21 DA019836.

David Volsky

HIV-1 TAT AND HIV/NEUROAIDS: FROM MECHANISTIC STUDIES TO BIOMARKER DISCOVERY. He, JJ[1], Fan, Y[1], Zou, W[1], Zhou, B[1], Kim, BO[1]; [1]University of North Texas Health Science Center, Department of Cell Biology and Anatomy, Fort Worth, TX 76107.

HIV-1 gains access to the central nervous system (CNS) soon after the peripheral infection. Even in the era of antiviral therapy, more than 50% HIV-infected individuals experience HIV-associated neurological disorders (HAND), pathologically characterized by astrocytosis and loss of neuronal integrity. The apparent paradox between HIV-infected microglia/macrophages and astrocytes and HIV-affected neurons has led to a variety of hypotheses for HAND over the past two decades, these include improper immune activation, astrocyte dysfunction and host or viral solub le factors. Studies from our group and several others have established that HIV-1 Tat is a major neuropathogenic factor for HAND. In addition, our group has shown that Tat directly up-regulates glial fibrillary acidic protein (GFAP) expression or astrocytosis, the most consistent hallmark of the CNS HIV-1 infection and that GFAP is directly involved in Tat-mediated neurotoxicity. However, the underlying molecular mechanisms are not understood. Our recent studies showed that Tat not only up-regulated GFAP expression but also induced GFAP aggregation in astrocytes and as a result, activated unfolded protein response (UPR) in these cells. Moreover, we showed that GFAP aggregation activated three classic UPR pathways: PERK, IRE1, ATF6 as well as an astrocytes-specific UPR pathway, the old astrocyte specifically induced substance (OASIS) both in vitro and in HIV-infected brain. Importantly, we showed that activation of these UPR pathways in the endoplasmic reticulum (ER) of astrocytes was well correlated with Tat neurotoxicity. Taking together, these findings show for the first time that HIV-1 infection of the CNS induced ER stress response in astrocytes, which in turn adversely affected neuron function and survival. These findings also raise the possibility for the first time that GFAP activation- or astrocytosis-induced ER stress response in astrocytes may likely contribute to neuronal demise in other neurodegenerative diseases. Supported by NIH/NIMH.

CO-MORBID EFFECTS OF HIV-1GP120 AND METH ON NEURONAL PHYSIOLOGY AND ANIMAL BEHAVIOR: ROLE OF VOLTAGE-GATED K CHANNELS. Liu, J[1], Wang, J[1], Chen, LN[1], Reiner, BC[1], Xiong, H[1]; [1]Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198-5880.

HIV-1 brain infection and methamphetamine (Meth) abuse induce neuronal apoptosis leading to cognitive impairment. The underlying mechanisms are, however, not fully understood. We hypothesize HIV-1 infection and Meth abuse exert a co-morbid effect on

neurons by enhancing neuronal outward K+ current (Iko) since activation of voltage-gated K+ (Kv) channels has been considered as an essential pathway for apoptotic cell death. To test this hypothesis, we studied effects of HIV-1gp120 (gp120) and Meth on Iko recorded in rat hippocampal neurons and on animal behavior in SCID mice with HIV encephalitis (HIVE). Our results showed gp120 and Meth enhanced neuronal Iko when applied alone, and exhibited a synergic effect when applied in combination. The gp120- and/or Meth-induced enhancement of neuronal Iko was attenuated by 4-amonopyridine (4-AP), an A-type K+ current blocker (IA), but not by tetraethylammonium (TEA), a delayed rectifier Iko blocker, suggesting gp120 and Meth increase neuronal IA. The enhancement of neuronal IA was associated with neuronal apoptosis mediated by gp120 and/or Meth because such neuronal apoptosis was blocked by 4-AP. The involvement of Kv channels in HIV-1-associated cognitive impairment was demonstrated by experimental results showing that SCID mice with HIVE exhibited an impaired spatial memory detected in a radial-armed water maze test and systemic administration of 4-AP significantly improved animal spatial memory. Our results indicate HIV-1 and Meth alter neuronal physiology and animal behavior via activation of Kv channels. Supported by NIH grant R01 NS041862, R01 NS063878.

Symposium IV: Neuroimmunity and Neurodegenerative Diseases

CELL BASED TARGETED BRAIN DELIVERY OF THERAPEUTIC NANOPARTICLES. Gendelman, HE[1]; [1]Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198-5880.

Nanoformulations of antiretrovirals and immune modulatory molecules were developed to improve clinical outcomes of infectious and neurodegenerative disorders. The chemical, biological, immune, virological, and toxicological properties of the drug-laden nanoparticles were researched to improve drug delivery and pharmacodynamics. Efficacy was realized in laboratory and animal model systems of human disease based on particle coatings, improved circulating drug half-lives, and reduced toxicities. These proved successful in experimental treatments of viral and neurodegenerative disorders. Proposed clinical applications for antimicrobial therapy and targeted d elivery to sites of disease included the central nervous system. The need to reduce cell and immune side effects of the nanoparticles necessitated the development of novel methods for formulation manufacture. To fully realize the potential of nanomedicine, from the bench to bedside, we developed cell-based carriage of drug nanoparticles and optimized particle uptake and intracellular trafficking. The past decade has seen our utilization of cells of mononuclear phagocyte lineage, including dendritic cells, monocytes, and macrophages, as Trojan horses for cell carriage of nanoformulated drugs to target disease sites and positively influence disease outcomes. Supported by National Institutes on Drug Abuse, of Neurological Disorders and Stroke and of Mental Health.

IL-17-INDUCED ACT1-MEDIATED SIGNALING IS CRITICAL FOR CUPRIZONE-INDUCED DEMYELINATION. Li, XX[1], Kang, Z[1], Liu, LP[1]; [1]Immunology, Cleveland Clinic, Cleveland, OH 44195.

Cuprizone inhibits mitochondrial function and induces demyelination in the corpus callosum which resembles pattern III lesions in multiple sclerosis (MS) patients. However, the molecular and cellular mechanism by which cuprizone induces demyelination remains unclear. Interleukin-17 (IL-17) secreted by T helper 17 (Th17) cells and γδT cells are essential in the development of experimental autoimmune encephalomyelitis (EAE). In this study, we examined the importance of IL-17 signaling in cuprizone-induced demyelination. We found that mice deficient in IL-17A, IL-17RC and

adaptor protein Act1 (of IL-17R) all had reduced demyelin ation accompanied by lessened microglial and polydendrocyte cellular reactivity compared to that in wild-type mice in response to cuprizone feeding, demonstrating the essential role of IL-17-induced Act1-mediated signaling in cuprizone-induced demyelination. These results establish that IL-17 exerts neurotoxic effects even in the absence of an adaptive-immune Th17-mediated process. In cuprizone-fed mice IL-17 was produced by CNS γδ T cells and cuprizone-induced demyelination and gliosis were much reduced in Tcrδ-deficient mice compared to that in wild-type mice. Importantly, specific deletion of Act1 in astrocytes reduced the severity of tissue injury in this model, indicating the critical role of CNS resident cells in the pathogenesis of cuprizone-induced demyelination. Supported by National Institutes of Health grants R01NS071996 (XL).

Carol Colton

SWITCHING GLIA FROM NEUROINFLAMMATORY TO NEUROTROPHIC IN THE NIGROSTRIATUM OF HEMIPARKINSONIAN MONKEYS. Pahan, K[1]; [1]Department of Neurological Sciences, Rush University Medical Center, Chicago, IL 60612.

Mechanisms by which activated glial cells could be switched from neuroinflammatory to neurotrophic mode are still elusive. Because the primate model is considered to be one of the best available models for Parkinson's disease (PD), we have evaluated the ability of a peptide corresponding to the NF-kB essential modifier (NEMO)-binding domain (NBD) of IkB kinase (IKK)a or IKKb to switch activated glial cells and protect dopaminergic neurons in hemiparkinsonian monkeys. First, we found that NF-kB was activated within the substantia nigra pars compacta of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-intoxicated hemiparkinsonian monkeys. However, intramuscular injection of wild type NBD (wtNBD) peptide reduced nigral activation of NF-kB, protected the nigrostriatum and improved motor functions. In contrast to previous mouse results, wtNBD peptide did not inhibit nigral glial activation as number, shape and size of activated microglia and astroglia were unchanged. Interestingly, activated glia in the nigra of untreated hemiparkinsonian monkeys expressed proinflammatory molecules, but not neurotrophic factors. Conversely, activated glia in the nigra of wtNBD-treated hemiparkinsonian monkeys expressed neurotrophic factors, but not proinflammatory molecules. Therefore, the novelty of our work lies in the fact that selective inhibition of NF-kB activation by NBD peptide treatment switches glial activation from neuroinflammatory to neurotrophic mode in the nigrostriatum of hemiparkinsonian monkeys. These results may help in the translation of NF-kB-based therapy to PD clinics. Supported by Michael J. Fox Foundation & NIH (NS64564).

T CELLS MANAGE THE GAME IN LOU GEHRIG'S DISEASE. Henkel, JS[1], Appel, SH[1], Beers, DR[1], Zhao, W[1]; [1]Neurology, Methodist Neurological Institute, The Methodist Hospital Research Institute, Houston, TX 77030.

In amyotrophic lateral sclerosis (ALS) mice, CD4+ regulatory T lymphocytes (Tregs) have a documented neuroprotective role slowing disease progression. To address whether Tregs similarly influence progression rates of ALS patients, T lymphocytes from peripheral blood of patients were assessed and compared with their current and future progression rates. Flow cytometry revealed CD4+CD25High Tregs were reduced in rapidly progressing ALS patients compared with controls or slowly progressing patients, and inversely correlated with progression rates. qRT-PCR indicated that mRNA levels for FoxP3, CD25, TGFβ, I L4, and Gata3, a Th2 transcription factor, were reduced in rapidly progressing patients and inversely correlated with progression rates. No differences in Tbx21, a Th1 transcription factor, or IFNγ expression were found between

slow and rapid patients. A 3.5 year prospective cohort study with a second larger group revealed early FoxP3 levels were indicative of progression rates at time of collection: high FoxP3 levels were indicative of slow rates, while low FoxP3 mRNA levels were indicative of rapid rates. Early low FoxP3 mRNA levels were also predictive of a rapidly progressing disease and attenuated survival at the end of the 3.5 year evaluation period. Collectively, these data suggest that Tregs and Th2 lymphocytes influence disease progression rates. Importantly, low FoxP3 mRNA levels were predictive of a rapidly progressing disease and an attenuated survival. Enhancing the numbers or immunosuppressive functions of Tregs could offer potential therapies for ALS patients. Supported by NIH, MDA.

Young Investigator's Symposium

EXCESS SOLUBLE CD40L CONTRIBUTES TO BLOOD BRAIN BARRIER PERMEABILITY IN A MOUSE MODEL OF HIV-ASSOCIATED NEUROCOGNITIVE DISORDER (HAND). Davidson, DC[1], Hirschman, MP[1], Sun, A[1], Kasischke, KA[1], Schifitto, G[2], Maggirwar, SB[1]; [1]Department of Microbiology and Immunology, University of Rochester School of Medicine and Dentistry, Rochester, NY 14642; [2]Department of Neurology, University of Rochester School of Medicine and Dentistry, Rochester, NY 14642.

Despite the use of antiretroviral therapies, a majority of HIV infected individuals still develop HAND, indicating that host inflammatory mediators, in addition to viral proteins, may be contributing to these disorders. Consistently, we have previously shown that levels of the inflammatory mediator soluble CD40 ligand (sCD40L) are elevated in the circulation of HIV infected, cognitively impaired individuals. Here we demonstrate that the non-nucleoside reverse transcriptase inhibitor efavirenz induces the release of sCD40L in HIV infected individuals, thus further contributing to excess plasma concentrations of this mediator. Recent studies from our lab implicate a role for the CD40/CD40L dyad in blood brain barrier (BBB) permeability and interestingly, sCD40L is thought to regulate BBB permeability in other inflammatory disorders of the CNS. Using complementary multiphoton microscopy and quantitative analyses in wild type and CD40L knockout mice, we now reveal that the HIV transactivator of transcription (Tat) can induce BBB permeability in a CD40L dependent manner. This permeability is limited to the BBB and was found to be a result of aberrant platelet activation induced by Tat. Furthermore, Tat treatment led to an increase in Gr1 positive monocytes, indicating an expansion of the inflammatory subset of cells in these mice. Exploring the mechanisms by which the BBB becomes compromised during HIV infection has the potential to reveal novel targets, thereby aiding in the development of adjunct therapies for the management of HAND, which are currently lacking. Supported by National Institutes of Health grants RO1 NS054578 and RO1 NS066801.

C/EBPβ REGULATES MULTIPLE IL-1β-INDUCED HUMAN ASTROCYTE INFLAMMATORY GENES VIA A P38 DEPENDENT PATHWAY. Fields, JA[1], Ghorpade, A[1]; [1]Cell Biology and Anatomy, University of North Texas Health Science Center, Fort Worth, TX 76107.

C/EBPβ regulates gene expression in multiple organ systems and cell types, including the CNS and astrocytes. C/EBPβ is detectable in brains of HIV–associated dementia (HAD) patients and astrocytes increase C/EBPβ expression in response to IL-1β, TNF-α, HIV-1 and LPS. Despite its prevalence in the CNS, little is known about how C/EBPβ contributes to astrocyte gene expression during neuroinflammation. Here, we

sought to define a role for C/EBPβ in regulating the human astrocyte inflammatory response, using IL-1β as the inflammatory stimulus. C/EBPβ knockdown in human astrocytes affected expression of 60% of IL-1β-regulated genes; both increasing and decreasing mRNA levels. C/EBPβ knockdown blocked IL-1β-mediated COX2 expression and a p38-selective small molecule inhibitor blocked increases in C/EBPβ and COX2 mRNA expression. C/EBPβ knockdown enhanced IL-1β-mediated BDKRB2 expression while an ERK1/2-selective small molecule inhibitor blocked IL-1β-mediated BDKRB2 mRNA expression. Interestingly, the ERK1/2-selective small molecule inhibitor increased IL-1β-mediated C/EBPβ expression. A p38-selective small molecule inhibitor blocked IL-1β-mediated C/EBPβ translocation to the nuclei and COX2 expression, whereas the ERK1/2-selective small molecule inhibitor enhanced C/EBPβ translocation to nuclei and COX2 expression. These data suggest that C/EBPβ is part of a transcriptional complex that directs the IL-1β-mediated inflammatory response. Delineating C/EBPβ activity during the astrocyte inflammatory response may lead to effective therapies for HAD and other CNS pathologies. Supported by NINDS/NIH-1F31NS072006-01.

IMAGING DENDRITIC CELL TRAFFICKING INTO THE CENTRAL NERVOUS SYSTEM DURING STEADY-STATE AND UNDER NEUROINFLAMMATION. Sagar, D[1], Lamontagne, A[1], Foss, C[2], Khan, Z[1], Pomper, M[2], Jain, P[1]; [1]Department of Microbiology and Immunology/ PA Biotech Center, Drexel University College of Medicine, Doylestown, PA 18902; [2]Department of Radiology, Johns Hopkins University, Baltimore, MD 21231.

In healthy individuals, infiltration of dendritic cells (DCs) and other lymphocytes into the central nervous system (CNS) is tightly controlled by the highly specialized blood-brain barrier (BBB). Our interest lies in elucidating the path that DCs take while transmigrating across the BBB into an inflammed CNS. We detected the migration of DCs and other leukocytes by non-invasive in vivo imaging (Near Infra-Red, SPECT-CT, and bioluminescence) in mice with experimental autoimmune encephalomyelitis and glioblastoma multiforme. Moreover, histology confirmed MCP-1 presence in brain EAE lesions colocalizing with DCs emerging from perivascular spaces. To further characterize mechanism of DC trafficking, we utilized an in vitro BBB model consisting of human brain microvascular endothelial cells (HBMECs). In these studies, both non-activated and activated DCs exhibited a more efficient transmigration pattern during steady-state as well as under the influence of MCP-1. Extensive in vitro imaging of DCs along with HBMECs in transwells confirmed our observations and suggested an early breach of BBB permeability by MCP-1 supported by its colocalization with CCR2 receptor on HBMECs. Overall, these one of-a-kind comprehensive studies are first to demonstrate that MCP-1 is important in chemoattraction of DCs to the BBB, making these cells more responsive to neuroinflammation. Our results also suggest that MCP-1-mediated breach of the BBB permeability allows an easy passage to all types of leukocytes; however, chemoattraction itself could be influenced by cell type and cellular activation.

MORPHINE EXACERBATED RESPONSE TO HIV-1 TAT-DEPENDENT SYNAPTODENDRITIC INJURY IS MEDIATED BY [CA2+]I STORES AND ATP DEPLETION. Fitting, S[1], Zou, S[2], Knapp, PE[2], Hauser, KF[1]; [1]Dept. Pharmacol. & Toxicol., Virginia Commonwealth University, Richmond, VA 23298; [2]Dept. Anat. & Neurobiol., Virginia Commonwealth University, Richmond, VA 23298.

Synaptodendritic organization and spine density are disrupted by Tat and/or morphine in vivo (as assessed in Golgi-impregnations and by electron microscopy); with combined opioid and Tat induction causing synergistic dendritic pathology at 7-10 days

following continuous exposure to both (Fitting et al., Am J Pathol, 2010). Parallel in vitro studies (primary striatal neuron culture) that showed nearly identical dendritic swellings as seen in vivo, examined the mechanisms underlying synaptodendritic injury. Within a 10 min time window Tat caused significant focal increases in [Na+]i and [Ca2+]i along the dendrites within the first 2 min, which were partially attenuated by NMDA and AMPA receptor antagonists MK801 and CNQX. In contrast, Tat ± morphine treatment caused significant sustained increases in [Na+]i and [Ca2+]i, as well as corresponding increases in focal dendritic swellings. Importantly, Tat ± morphine-induced initial losses in ion homeostasis and increased [Ca2+]i production were attenuated by RyR and IP3 inhibitors as well as Pyruvate, indicating the importance of [Ca2+]i stores and ATP. The Tat and morphine-driven excitotoxic, glutamatergic dysregulation of [Ca2+]i homeostasis appears to be an important event in opioid-HIV-1 Tat synergistic interactions, and is likely to be critical in underlying the loss of synaptic connectivity. The studies outlined herein will contribute to better therapeutic approaches toward allaying the CNS consequences of opioid abuse-HIV-1 comorbidity. Supported by NIDA DA018633, DA027374.

CHRONIC MORPHINE TREATMENT DIFFERENTIALLY MODULATES MACROPHAGE PHAGOCYTIC AND BACTERICIDAL MECHANISMS FOLLOWING TLR2 AND TLR4 ACTIVATION. Ninkovic, J[1], Roy, S[1]; [1]Department of Surgery, Division of Basic and Translational Research, School of Medicine, University of Minnesota, Minneapolis, MN 55455.

The most frequent community acquired opportunistic infection in opioid abusers is infection with Gram-positive (G+) Streptococcus pneumoniae. To our knowledge, no studies have investigated if morphine treatment differentially modulates clearance of (G+) vs (G-) bacteria by macrophages. Upon infection, bacterial clearance is initiated by phagocytosis followed by bactericidal mechanisms. In this study, we show that chronic morphine treatment leads to greater intracellular bacterial growth of (G+), when compared to (G-) bacteria which selectively activate TLR2 and TLR4 respectively. We first investigated if morphine modulates TLR expression and if TLR activation contributes to the differential effects of morphine on phagocytosis of (G+) and (G-) pathogens. Our results show that chronic morphine treatment upregulates TLR2 and TLR4 expression. Interestingly, activation of TLR2 alone led to decreased, while activation of TLR4 led to increased bacterial phagocytosis in both vehicle and morphine treated cells. These differential effects of TLR activation on phagocytosis are abolished in macrophages isolated from TLR2KO and TLR4KO mice. Additionally, bactericidal mechanisms such as ROS release and phagosomal maturation were more significantly suppressed in chronic morphine treated macrophages following internalization of (G+) when compared to (G-) bacteria. Based on these observations we conclude that morphine induced-increase in TLR2 expression and activation by (G+) bacteria leads to decreased phagocytosis and bacterial killing, thereby increasing susceptibility to (G+) infection. Supported by F31 DA026264-01A1 (to J.N.) and RO1 DA12104, RO1 DA12104, RO1 DA022935, KO2 DA015349, P50 DA11806 (to S.R.).

EFFICACY AND SAFETY TESTS OF LONG-ACTING NANOFORMULATED ANTI-RETROVIRAL DRUGS IN HIV-1 INFECTED HUMANIZED MICE. Dash, PK[1], Gorantla, S[1], Roy, U[1], Knibbe, J[1], Balkundi, S[1], McMillan, J[1], Gelbard , HA[2], Poluektova, LY[1], Gendelman, HE[1]; [1]Department of Pharmacology and Expt. Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198; [2]Center for Neural Development and Disease, University of Rochester School of Medicine and Dentistry, New York, NY 14642.

Background: Compliance, escape from immune surveillance and cumulative toxicities underlie treatment failures for antiretroviral therapies (ART) for HIV disease. To this end our laboratories developed atazanvir (ATV) and ritonavir (RTV) nanoformulations (referred to as nanoART). Methods: Newborn NOD/SCID-IL-2γcnull mice were transplanted with human CD34+ hematopoietic stem cells and infected at 22 weeks of age with HIV-1ADA. After eight weeks of infection five mice were injected subcutaneously (sc) at weekly intervals with nanoART at 250mg/kg at 1:1 ATV/RTV concentration for six dosages, and six animals remain as untreated control. Additional 5 uninfected animals were treated by similar schedule for evaluation of the drug safety profile. Animals were sacrificed 17 weeks after infection for analysis of tissue drug levels, viral loads and histopathology. Results: All HIV-1 infected and treated animals survived study and retained human hematopoiesis. Eight weeks after viral infection all animals showed sustained viral load with a median value of 1.63 x 105 HIV-1 RNA copies/ml. After 4 weekly drug injections the viral loads were below the levels of detection and three weeks after the final nanoART treatment viral replication rebounded to levels observed in untreated animals. NanoART treatment preserved damage of human lymphoid tissue by HIV-1 and prevented reduction of CD4+ T cells. Conclusion: The development of long-acting nanoART is now realized and enabling efficient control of HIV-1 replication in humanized mice. Future works in monkeys and in human are being planned.

Plenary Lecture II

THE IMPACT OF ALCOHOL AND SUBSTANCE USE ON THE PREVENTION AND TREATMENT OF HIV/AIDS. Samet, JH[1]; [1]Clinical Addiction Research and Education (CARE) Unit, Section of General Internal Medicine, Department of Medicine, Boston University School of Medicine and Public Health, Boston, MA 02118.

Alcohol and other drug use have played a critical role in the risk, progression and treatment of HIV infection. In 2009, injection drug users (IDUs) accounted for 13% of new HIV infections in the United States and it remains a global problem. Risky alcohol use is more common in HIV-infected than non-infected, a behavior often reported in more than 25%. In this presentation, I will review the multidimensional effects of alcohol and drug use on a number of facets of HIV disease: epidemiology, sex risk behaviors, HIV disease progression, and mental health, specifically depression. In addition, I will review the effects on the liver of alcohol and drug use in the setting of HIV infection, both in the presence and absence of hepatitis. Finally, HIV treatment in the context of alcohol and drug use and addiction treatment in the context of HIV infection will be considered. Strategies and interventions to promote recovery, longevity, and prevention will be presented. Supported by K24-AA015674; R01-AA016059; U24-AA020778; U01-AA020780; R01-DA032082.

Symposium V: Neuroimmunity and Neurodegenerative Diseases

BLOOD ALCOHOL CONCENTRATIONS IN HIV: EFFECT OF ANTIRETROVIRAL TREATMENT. McCance-Katz, EF[1], Lum, P[1], Beatty, G[1], Gruber, VA[1], Peters, M[1], Rainey, PM[2]; [1]Departments of Psychiatry and Internal Medicine, University of California San Francisco, San Francisco, CA 94110; [2]Department of Laboratory Medicine, University of Washington, Seattle, WA 98195.

Alcohol abuse has been associated with HIV progression, but to date the effect of

HIV on alcohol exposure has not been characterized. We studied the effect of untreated HIV infection on blood alcohol concentrations (BAC) and following antiretroviral therapy (ART). In a double-blind, randomized, placebo-controlled human laboratory study, individuals with untreated HIV infection and without alcohol dependence (n=15) were enrolled in a study in which they received one drink containing alcohol (1 g/kg with target peak BAC of 100 mg/dL) or a drink with an alcohol placebo on separate days. Participants were followed with baseline and serial sampling for BAC, physiological, subjective, and cognitive responses. HIV treatment was initiated with directly observed therapy and following 2-3 weeks of treatment, the alcohol studies were repeated. Alcohol area under the time/concentration curve (AUC) was greater in untreated HIV disease ($p=0.011$) with significantly higher maximum BAC ($p=0.015$) and minimum BAC ($p=0.05$). Pharmacokinetics analysis showed that the rate of alcohol elimination was not different between pre- and post-ART conditions. Significant differences in subjective and cognitive effects were not observed. Those with untreated HIV infection may be at greater risk for alcohol-associated toxicities. This study underscores the importance of identifying and providing treatment for alcohol use disorders as well as for HIV infection in those with co-occurring disorders. Supported by NIAAA/NIH.

DRUG ABUSE AND NEUROAIDS IN HIV CLADES. Nair, M[1]; [1]Institute of NeuroImmune Pharmacology, College of Medicine, Florida International University, Miami, FL 33199.

Previous studies have demonstrated that infections with HIV-1 clades differentially contribute to the genesis of HIV-associated neurocognitive disorder (HAND). Recreational drugs such as cocaine and methamphetamine (METH) are also known to exacerbate HIV induced neuronal impairments. The main neuro-immune mediators that play a significant role in these complex regulatory dysfunctions mediated by HIV infection and drug abuse are inflammatory cytokines, chemokines, amino acid metabolites, neurotoxins etc.; leading to dysregulation in synaptic plasticity genes contributing to HAND. Our studies using primary CNS cells, blood brain barrier, infection models and patients demonstrate that HIV-1 B clade significantly potentiates immune and neuronal dysfunctions compared to HIV-1 C clade and these effects were significantly exacerbated with cocaine and/or METH. This suggests a differential effect of HIV-1 B clade leading to increased neuropathogenesis and associated HAND. Supported by National Institute of Health: MH085259, DA021537, DA027049, DA025576.

Brian Wigdahl

DEFINING THE EARLIEST CNS EVENTS OF HIV INFECTION THROUGH INTERNATIONAL COLLABORATIONS. Valcour, V[1], Sailasuta, N[2], Ananworinich, J[3]; [1]Memory and Aging Center/ Neurology, University of California San Francisco, San Francisco, CA 94143; [2]Huntington Medical Research Institute, Pasadena, CA 91105; [3]SEARCH-Thailand, Bangkok; [4]Faculty of Medicine, Chulalongkorn University, Bangkok; [5]HIV-NAT, The Thai Red Cross AIDS Research Centre, Bangkok.

The earliest CNS events associated with HIV infection are incompletely defined in humans owing to challenges associated with identifying individuals in the earliest stages of infection. Consequently, most of our knowledge of acute infection (earlier than primary infection, when antibody response is minimal) is based on animal models. Information about the earliest CNS events in humans may identify factors that inform long-term cognitive outcomes. Feasibility work completed at the Thai Red Cross AIDS Research Centre's Anonymous Clinic identified an estimated a 2.7% HIV incidence per 100 person-years, calculated from the pooled, antibody-negative samples (Ananworanich

2007). Further feasibility work established a research magnetic resonance spectroscopy (MRS) protocol, obtained normative 4-voxel MRS data on 10 HIV-negative Thai healthy controls and established normative neuropsychological testing among over 500 HIV-negative healthy Thai controls. Subsequent enrollment of an acute HIV cohort ensued and included neurological examination, neuropsychological testing, evaluation of cerebrospinal fluid, MRS, and extensive systemic characterization. As of December 2011, 64 subjects were enrolled with all cases in the earliest stage of infection (Fiebig V disease or earlier, typically < 4 weeks after exposure and when little to no HIV antibody response can be detected). Virus has been identified in CSF as early as 9 days post exposure (Valcour, in press) and an inflammatory signature noted on MRS. Data from this cohort will inform the earliest CNS events of HIV in humans. Supported by R21 MH086341, R01 MH095613, R01 NS061696.

Opendra "Bill" Narayan Lecture

CAN YOUNG BLOOD MAKE BRAINS YOUNGER? Wyss-Coray, T[1]; [1]Neurology & Neurological Sciences, VA Palo Alto Health Care System and Stanford University School of Medicine, Palo Alto, CA 94305-5489.

Growing evidence links neurodegeneration with altered immune responses not only in the brain but in the periphery as well. In addition, age is the main risk factor for sporadic forms of neurodegenerative diseases, and aging of peripheral organs may affect brain function. How the systemic environment affects brain health is largely unknown and while some of these interactions may involve cells entering the nervous tissue it is likely that others are mediated by soluble signaling molecules. We use a combination of physiological methods to manipulate systemic aging and proteomic methods to try to identify factors that age or potentially rejuvenate the brain. Our findings point to systemic changes in immune responses and cellular signaling factors with aging and may be relevant for our understanding of age-related neurodegeneration.

Symposium VI: NeuroImmune Pharmacology Research in Hawaii

EXPLOITING UNIQUE MONOCYTE PHENOTYPES FOR TREATMENT STRATEGIES FOR HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS. Shiramizu, B[1]; [1]Hawaii Center for AIDS, University of Hawaii John A. Burns School of Medicine, Honolulu, HI 96813.

In HIV-associated neurocognitive disorders (HAND), activated monocytes (CD14+/16+) are hypothesized to traffic HIV into the CNS and initiate inflammation. Current antiretrovial therapy for HIV effectively suppresses HIV RNA however HIV DNA in activated monocytes persists and may be potential treatment targets as a strategy to treat HAND. Longitudinal activated monocytes were assayed for HIV DNA and were shown to have high HIV DNA copy numbers in patients with compromised HAND diagnoses in the Hawaii HIV with Aging Cohort. As a potential target, activated monocytes could preferentially be affected by polyamine analogs which could target the HIV-infected activated cells. The activated monocytes are known to traffic to the central nervous system by crossing the blood-brain-barrier. Specific polyamine analogs that target HIV-infected activated monocyes could potentially be used to prevent CNS inflammation by minimizing trafficking HIV-infected monocytes. This treatment paradigm could be a new strategy targeting an activated monocyte phenotype to prevent or treat HAND. Supported by AI081450; NS053345.

TBD

WHAT IS HAPPENING IN THE BRAINS OF ADOLESCENT MARIJUANA USERS?
Cloak, CC[1], Chang, L[1], Ernst, TM[1]; [1]Department of Medicine, John A. Burns School of Medicine, University of Hawaii, Manoa, Honolulu, HI 96813.

Marijuana (MJ) use often starts during adolescence and has been affiliated with some psychiatric disorders. We used MRI-based techniques to investigate the effects of MJ on brain development, specifically brain metabolites (1HMRS) and white matter integrity (DTI). Cortisol levels and psychiatric measures (SCL90) were also obtained in this study of adolescents (14-23 years) with and without regular MJ use. All subjects were healthy, with little or no other illicit drug use. The 59 MJ users (34 male) were 19.2±0.3 years old. On average, they began using at 14 years of age, smoked 2g/day, 5 days/week, for 4 years, for a lifetime use of 2046±460 joints. The 50 controls (CON, 27 male) were 18.8±0.4 years old. Some used nicotine or alcohol, but none were alcohol dependent. MJ users had elevated mid-day cortisol levels ($p=0.05$) and more psychiatric symptoms ($p<0.05$ on 6 of 12 measures) than CON. In MJ users, we observed lower white matter diffusion in 6 regions ($p<0.05$). Three of these regions had age by MJ interactions; diffusion in CON subjects decreased with age but increased with age in MJ users. While there were no main effects of MJ on brain metabolites, some showed interactions between MJ, sex and age, as well as correlations with psychiatric symptoms. We observed elevated cortisol, more psychiatric symptoms, normal and aberrant age-related changes in brain metabolites and diffusion in young MJ users. MJ use may lead to disruption of brain organization or development. Longitudinal follow-up is ongoing to determine if these abnormalities will persist, resolve, or worsen. Supported by Queen Emma Research Fund, ONDCP & NIH K01- DA021203, K24-DA16170, K02-DA16991, U54-NS39406, U54-NS56883, P20-RR11091, G12-RR003061-21.

CELL MEDIATED NOVEL GENE THERAPY FOR NEUROAIDS.
Lu, Y[1]; [1]Department of Public Health Sciences, University of Hawaii, Honolulu, HI 96822.

Concept of cell-based vehicle has attracted great interest in the recent years and cell based drug delivery has become a distinct therapeutic strategy. Cell-based drug delivery is particularly relevant to neuroAIDS treatment since many antiretroviral drugs have little efficiency to cross the blood-brain barrier (BBB). Circulating blood monocytes and their derived macrophages are known to migrate across the BBB and enter the CNS under normal physiologic conditions and certain circumstances; these cells could be genetically modified for delivering anti-HIV-1 genes to the CNS in a noninvasive and nonsurgical manner. To test and develop this cell-based novel gene therapy for neuroAIDS, several defective lentivi ral vectors (DLV) were constructed for the expression of target transgenes including a soluble TNF receptor (sTNFR) and anti-HIV-Tat single chain antibody (scFv-Tat). High-tittered vector stocks enabled effective transduction of human neuronal cell lines and primary cultures of monocyte-derived macrophages (MDM) in vitro. DLV-mediated secretion of the transgenes in human cells was demonstrated to be stable at high level using ELISA and western blot assays. Biological activity of the secreted transgene products was confirmed through either specific protein binding assay or protein functional blocking analysis. In vitro protection assays showed these transgene products expressed from transduced cells were able to protect human neuronal cells from TNF-α, HIV-1 Tat- and gp120-mediated neurotoxicity. Finally, in vivo experimental tests using HIV-infected encephalitis (HIVE) SCID mice as a model demonstrated that significant number of DLV transduced primary mouse MDM are able to migrate across the BBB and enter the brain and verified substantial

expression of transgene products in the brain of experimental mice through immunohistochemical staining. In addition, the efficiency of CNS trafficking of these cells can be enhanced through the transient disruption of the BBB with bradykinin. These experimental methods and findings lay the initial groundwork for future in vivo studies on the ability of GFP-DLV-modified blood MDM to introduce anti-HIV-1 and neuroprotective genes into the CNS. Present findings support current concept and notion of using genetically modified MDM cells as novel and distinct therapeutic delivery approach to combat neuroAIDS. Supported by NIMH.

CORTISOL AND BEHAVIORAL REGULATION IN CHRONIC ACTIVE CANNABIS USERS. King, GR[1]; [1]Neuroscience and MRI Research Program, University of Hawaii, Honolulu, HI 96813.

Background: Cannabis is the most abused illegal drug in the United States. Acutely, cannabis impairs psychomotor processing and accuracy, but the chronic effects of cannabis use are more variable. Whether chronic active cannabis use in humans may alter psychomotor function, brain activation, and hypothalamic-pituitary-axis (HPA) function were evaluated in this study. Methods: 30 cannabis users (16 men, 14 women) and 30 non-drug user controls (16 men, 14 women) ages of 18- 44 years old were evaluated with neuropsychological tests that assessed motor behavior. Blood oxygen level dependent (BOLD)-functional MRI (fMRI) were performed on a 3 Tesla scanner during a visually paced finger-sequencing task, cued by a flashing checkerboard (at 2 or 4 Hz). Salivary cortisol was measured to assess HPA function. Results: Male, but not female, cannabis users had significantly slower performance on psychomotor speed tests. As a group, cannabis users had greater activation in BA 6 than controls, while controls had greater activation in the visual area BA 17 than cannabis users. Cannabis users also had higher salivary cortisol levels than controls (+ 87%, p= 0.002). Discussion: Chronic active cannabis use may lead to slower and less efficient psychomotor function, especially in the male users, as indicated by a shift from regions involved with automated visually guided responses to more executive or attentional control areas. These brain activities may be attenuated by the higher cortisol levels in the cannabis users, which may lead to less efficient visual-motor function. Supported by NIDA, U54-NS/DA-56883, K02-DA020569, 2K24-DA16170.

Kazuma Nakagawa

Vivek Nerurkar

Symposium VII: Spice and Bath Salts

Aron Lichtman

Anu Mahadevan

Brian Thomas

Mahmoud ElSohly

Banquet

BREAKING THE “ICE” PROBLEM: RESEARCH BEYOND THE MAINLAND AND BIOGENIC AMINES. Yamamoto, B[1]; [1]Department of Neurosciences, University of Toledo College of Medicine, Toledo, OH 43616.

Methamphetamine is a drug of abuse whose illicit use is spreading internationally. Due in part to the availability of methamphetamine, the growing problem of methamphetamine abuse is particularly evident in Hawaii, Asian countries and the Pacific Islands. Therefore, the problem of methamphetamine abuse and its consequences extend well beyond the U.S. mainland. In addition, evidence from human and animal studies indicates that it also produces neurobehavioral and neurochemical changes indicative of neurotoxicity. The traditional line of thinking has been that these neurological changes, including the long-term damage to dopamine and serotonin terminals, are initiated within the brain by biogenic amine and amino acid neurotransmitters. However, a different line of thinking will be discussed that links systemic toxicity to methamphetamine neurotoxicity. In addition, the possible roles of neuroinflammatory mediators, environmental stress, and targets other than biogenic amine terminals will also be considered. Supported by NIH-NIDA DA07606 and DA16866.

Young Investigator Poster Session

THE INTERACTIVE ROLE OF HISTONE DEACETYLASES AND CANNABINOID GENES IN ALCOHOL ABUSERS. Agudelo M[1], Yndart A[1], Morrison M[1], Napuri J[1], Khatavkar P[1], Nair MP[1]; [1]Department of Immunology, Institute of Neuro-Immune Pharmacology, Herbert Wertheim College of Medicine, Florida International University, Miami, FL 33199.

Histone deacetylases (HDACs) and HDAC inhibitors (HDACi) have been implicated in drug and alcohol addiction; and cannabinoid receptors (CBRs) have been shown to play a role in alcohol use disorders (AUDs). However, the interactive roles of HDACs and CBRs on alcohol-induced immune-dysregulation have not been elucidated yet. We hypothesize that alcohol can exert its deleterious effects on immune cells such as monocyte-derived dendritic cells (MDDCs) through HDACs and CBRs. The expression of class I HDACs (1, 2, 3, and 8) and CBRs (1, 2, and GPR55) in MDDCs from alcoholics and non-alcoholics was assessed by qRT-PCR. The ability of EtOH to modulate MDDCs surface markers and co-stimulatory molecules (CD11c, CD40, DC-SIGN, CD80, CD83, and CD86) was tested by qRT-PCR and flow cytometry. Our results show a significant upregulation of CB2, GPR55, and HDAC2 with a reciprocal downregulation of CB1 in MDDCs from alcoholics compared to non-alcoholics. Further, alcoholics showed higher levels of DC-SIGN and CD86. These findings were further confirmed in vitro using normal MDDCs treated with EtOH (0.05, 0.1 and 0.2%). MDDCs surface markers and co-stimulatory molecules were also shown to be modulated by the HDACi, trichostatin A, and the CB2 antagonist AM630 in vitro. Our results provide insights into alcohol mechanisms of dendritic cell dysregulation and suggest that alcohol is acting through mechanisms involving CBRs and HDACs. Supported by National Institute on Drug Abuse grants R01MH085259 and R01DA021537.

ROLE OF CYP2A6 IN NICOTINE METABOLISM MEDIATED OXIDATIVE STRESS AND HIV-1 REPLICATION. Ande A[1], Jin M[1], McArthur C[2], Kumar A[1], Kumar S[1]; [1]Division of Pharmacology & Toxicology, University of Missouri-Kansas City School of Pharmacy, Kansas City, MO 64108; [2]Department of Oral Biology, University of Missouri-Kansas City School of Dentistry, Kansas City, MO 64108.

To explore the role of cytochrome P450 2A6 (CYP2A6) in tobacco/nicotine-mediated oxidative stress and HIV-1 replication, we performed in vitro studies using HIV-1 models U937 monocytes-derived macrophages (MDM) and SVGA astrocytes and ex-vivo study using human monocytes of HIV+/smokers. Our results showed that CYP2A6 is predominantly expressed in MDM and astrocytes compared to CYP3A4, which is highly expressed in the liver. Further, results from LC-MS/MS using selective CYP2A6 inhibitor, tryptamine, clearly showed that CYP2A6 metabolizes nicotine into cotinine and NNK (nicotine-derived nitrosamineketone) and induces ROS in both MDM and astrocytes. Although CYP2A6 and other tobacco constituent-metabolizing CYP1A1 were not induced in MDM, they were significantly induced (3-fold) by nicotine in astrocytes. To delineate whether CYP2A6-mediated nicotine metabolism and oxidative stress is involved in enhanced HIV-1 replication, we are in the process of performing experiments with nicotine-treated HIV-infected MDM. Furthermore, our ex-vivo preliminary studies using monocytes from healthy, HIV+, smokers, and HIV+/smokers showed an altered levels of CYP1A1 and CYP2A6 and antioxidant genes (e.g. SOD1 and catalase). We are now in the process of performing extensive analysis of the expression of these genes and HIV-1 viral load (HIV-1 RNA and p24). Taken together, these results will test our hypothesis that CYP2A6 and CYP1A1 are involved in tobacco/nicotine-mediated HIV-1 replication. This study has clinical relevance because smoking is 3-times higher among HIV+ population than normal. Supported by NIH-DA031616-01 (Dr. Santosh Kumar).

L-DOPA INCREASES TYROSINE HYDROXYLASE EXPRESSION ON GABAERGIC NEURONS FOLLOWING 1-METHYL-4-PHENYL-1,2,3,6-TETRAHYDROPYRIDINE-INTOXICATION. Anderson KM[1], Kuenstling MV[1], Szlachetka AM[1], Hutter-Saunders JLA[1], Mosley RL[1]; [1]Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha,

NE 68198.

The therapeutic potential L-3,4-dihydroxyphenylalanine (L-DOPA) was previously studied as a potential drug for combating the neurodegeneration characteristic of Parkinson's disease. This study found that mice treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and treated with L-DOPA for 35 days resulted in improved motor function and increased numbers of tyrosine hydroxylase (TH) immunoreactive (TH+) neurons in the substantia nigra pars compacta (SNpc) compared to MPTP-mice given no drug. We hypothesized that increased number of TH+ neurons are derived from a phenotypic shift of GABAergic neurons that upregulate TH. Dual immunostaining of the ventral midbrain for TH and glutamic acid decarboxylase-67 (GAD-67), a marker for GABAergic neurons, and stereological analysis of, demonstrated a significant increase in GAD67+/TH+ neurons in mice intoxicated with MPTP and treated with L-DOPA compared to mice treated with PBS or MPTP alone. This finding suggests that in response to the loss of DA neurons upon MPTP assault and L-DOPA treatment, TH transcription and expression is triggered in GABAergic neurons of the SNpc leading to a reparative phenotypic shift.

TIMP-1 ATTENUATES STAUROSPORINE- AND HIV-1-INDUCED APOPTOSIS IN HUMAN NEURONS THROUGH MODULATION OF BCL-2 FAMILY AND MITOCHONDRIAL MEMBRANE PERMEABILITY. Ashutosh A[1], Chao C[1], Tang L[1], Borgmann K[1], Ghorpade A[1]; [1]Department of Cell Biology and Anatomy, University of North Texas Health Science Center, Fort Worth, TX 76107.

The tissue inhibitor of metalloproteinases-1 (TIMP-1) is strongly upregulated in reactive astrocytes due to acute exposure to proinflammatory cytokines in neuroinflammatory disease, HIV-1-associated dementia (HAD). Since TIMP-1 displays pleotropic functions in addition to modulation of MMPs activity, its induction likely serves multiple roles. We have previously demonstrated that prolonged exposure of proinflammatory stimuli same as in chronic neuroinflammation in HAD down regulates TIMP-1 levels, which led us to hypothesize neuroprotective role of TIMP-1 in HIV-1-induced neuronal toxicity. In this study, primary human neurons in culture were exposed to a model neurotoxin, staurosporine (STS) and HIV-1 to induce apoptosis. Our results showed that TIMP-1 has specific, direct, MMP-independent potential of neuroprotection from HIV-1- and STS-induced apoptosis. Further, TIMP-1 suppresses elevated levels of major proapoptotic protein, Bax; and increases antiapoptotic proteins, Bcl-2 and Bcl-xL, in order to protect from programmed cell death. Furthermore, we observed that TIMP-1 inhibits mitochondrial membrane permeability pore (mPTP) formation, caspase-3 activity and DNA fragmentations induced by HIV-1 and STS. Together, these findings describe novel function, mechanisms and direct role of TIMP-1 in neuroprotection suggesting its therapeutic potential in HIV-1-associated dementia and possibly in other neurodegenerative diseases. Supported by NIH/RO1NS048837.

DIFFERENTIAL EFFECTS OF HIV-1B AND HIV-1C INFECTION ON SYNAPTIC PLASTICITY GENES: IMPLICATION IN HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS. Atluri, VSR[1], Pilakka-Kanthikeel S[1], Nair MP[1]; [1]Department of Immunology, Institute of Neuro-Immune Pharmacology, Herbert Wertheim College of Medicine, Florida International University, Miami, FL 33199.

Previous reports suggest that HIV-1 Clade B is more neuropathogenic than Clade C, although the mechanism of this differential effect is yet to be elucidated. We have interrogated 84 key human synaptic plasticity genes expression profiles in HIV-1B and HIV-1C infected primary human astrocytes by using human synaptic plasticity RT Profile PCR Array. Results show that 17 key synaptic genes (ADCY1 and 8, GRIN1, GRIN2C, GRM1, 2 and 4, MMP9, PRKCG, PRKG1, RELN, TNF, NOS1, PPP1R14A, ARC, KIF17, GRIA4) were significantly (≥3 fold) down-regulated in HIV-1B infected primary human astrocytes compared to uninfected control cells. These differentially expressed genes were functionally categorized into immediate/late response, long-term potentiation/depression, cell adhesion, extracellular matrix and proteolytic processing, CREB cofactors, neuronal receptors, postsynaptic density, apoptosis and other genes. In HIV-1C infected primary human astrocytes, none of the genes were either significantly up- or down-regulated. This

study supports the notion that Clade B is more neuropathogenic than Clade C and down-regulation of human synaptic plasticity genes may be attributed for the increased incidence of HIV-associated neurocognitive disorders (HAND) in Clade B infected patients. Supported by NIH grants 5R01DA021537 and 1R01DA027049.

MEMRI: A BIOMARKER FOR NEUROAIDS. Bade AN[1], Poluektova LY[1], Gorantla S[1], Gendelman HE[1], Boska MD[2], Liu Y[2]; [1]Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198; [2]Department of Radiology, University of Nebraska Medical Center, Omaha, NE 68198.

Introduction: A pathological correlate for HIV-1 associated dementia is HIV-1 encephalitis (HIVE). We posit that Mn2+ enhanced MRI (MEMRI) can be used to detect early pathobiologic events for HIVE, notably astrogliosis. Methods: We compared MEMRI against histological evaluation for HIVE. Thirty two five-week-old male NOD.Cg-Prkdcscid Il2rgtm1Wjl/Sz (NSG) mice were divided into 3 groups. Group 1 (n=12) were murine HIVE where NSG mice were injected into the caudate/putamen with HIV-1 infected human monocyte-derived macrophages (MDM) and Mn2+. Group 2 (n=8) was murine HIVE alone. Group 3 (n=12) NSG mice injected with Mn2+ and uninfected human MDM. Mn2+ was injected i.p. for 8 days before imaging as a 30 mg/kg/day. Mice were scanned at 4, 8, 15 and 28 days after induction of HIVE using T1 mapping and T1-wt MRI. Mice were euthanized then brains removed and embedded in paraffin. Five μm thick sections were cut and labeled with mouse monoclonal antibodies for HLA-DR, HIV-1p24, GFAP and Iba-1. Results: On day 8 and 15, MEMRI enhancement was observed at the injection sites in Group 1 mice. No enhancement was observed in Groups 2 and 3. The immunohistological results showed human MDM in and around the injection. HIV-1 infection and glial activation were found at the same regions. A replicate in vitro study showed neuronal and glial Mn uptake linked to inflammation. Based on these, we hypothesize that the signal enhancement results from the increased neuronal activity as a result of gliosis stimulating Mn uptake. As such MEMRI may be developed as biomarker for neuroAIDS. Supported by NIH K25MH089851.

ETHANOL INCREASES THE SURFACE EXPRESSION OF AMPA RECEPTORS BY MECHANISMS THAT INVOLVE ALTERATIONS IN THE BIOPHYSICAL PROPERTIES OF NEURONAL MEMBRANES. Bae M[1], Tovar-Y-Romo LB[1], Bandaru VVR[1], Haughey NJ[1]; [1]Department of Neurology, Johns Hopkins Medical Institutions, Baltimore, MD 21287.

HIV-infected subjects who abuse alcohol exhibit greater deficits in cognitive tasks that assess frontal lobe function as compared to HIV-infected subjects who do not abuse alcohol. Here we provide evidence that alcohol impairs neuronal function by mechanisms that involve alterations in the biophysical properties of neuronal membranes that facilitate the surface expression of calcium permeable AMPA receptors. Ethanol rapidly extracted specific lipids from neuronal membranes within 2 min. In this time frame GM1 gagliosides collapsed into focal aggregates, and the surface expression of AMPA receptors was increased in these microdomains. The effects of ethanol on GM1 and AMPA distribution were reversed by the addition of soluble cholesterol back into the membranes. Increased surface expression of AMPA receptors following ethanol involved a PKC-dependent phosphorylation of the C-terminal serine 831. Although surface expression was enhanced by ethanol, AMPA-evoked calcium bursts were depressed in the presence of ethanol. Immediately following the removal of ethanol, AMPA-evoked calcium transients were enhanced in regions of the membrane where AMPA receptors were clustered. These findings suggest that ethanol intoxication may modify the biopysical properties of neuronal membranes to increase the surface expression of AMPA receptors. Ethanol appears to both increase the surface expression and directly inhibits the function of AMPA receptors. During ethanol withdrawal AMPA receptor activity is dramatically increased for prolonged periods of time. Supported by NIH grant R01AA017408.

LIPOPOLYSACCHARIDE INDUCED VIRAL REPLICATION IN SIV-INFECTED CHINESE RHESUS MONKEYS. Bao R[1], Ye L[1], Dai M[1], Rao Y[1], Zhang J[1], Guo M[1], Wang Y[1], Huang ZX[1], Xian QY[1], Tang ZJ[1], Ho WZ[2], Wu K[1]; [1]State Key Laboratory of Virology, the Center for Animal Experiment/Animal Biosafety Level III Laboratory, Wuhan University, Wuhan, 430071; [2]Department of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140.

Bacteria infection increases the circulating microbial products such as lipopolysaccharide (LPS), which is currently considered to play an important role in immune activation, viral replication, and progression of HIV infection to AIDS. To investigate the effect of LPS on SIV replication, we used SIV-infected Chinese Rhesus macaques as an in vivo HIV infection model. The SIV-infected monkeys were intravenously injected with LPS. The serum LPS levels, determined by Amebocyte Lysate assay, increased dramatically within 4h post-injection and returned to normal level at 6h post-injection. In vivo administration of LPS to SIV-infected monkeys resulted in a 10-fold increase of SIV viral load at 24h post-injection. This increase of plasma SIV RNA was transient, as SIV RNA load returned to the level prior to the LPS injection at 48h post LPS injection. The subsequent injection of LPS failed to induce SIV RNA expression. The mechanism investigation showed that, upon LPS injection, the absolute CD4+ T cell counts decreased significantly, whereas HLA-DR+ CD4+ T cells counts increased moderately. The levels of several inflammatory cytokines (IL-4, IL-6, and IL-8) and toll-like receptors (TLR-3, TLR-9) were also elevated. These data suggest that LPS administration to Chinese Rhesus monkeys can induce a transient but significant increase in SIV replication, which could be due to the increase in the viral target cells and immune activation. Future studies are necessary to determine molecular mechanisms responsible for LPS-mediated enhancement of SIV replication. Supported by Mega-Projects of Science Research for the 11th Five Year Plan, China, 2009ZX10004-402.

PDGF-BB INDUCTION OF MCP-1: IMPLICATIONS FOR HAND. Bethel-Brown C[1], Yao H[1], Yang L[1], Buch S[1]; [1]Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198.

MCP-1 has been implicated as an important biomarker for HAND. The mechanisms, in part revolve around its ability to recruit monocytes into the CNS. In addition to its chemotactic activity, MCP-1 is also known to disrupt the blood brain barrier. We have previously demonstrated that in astrocytes HIV-1 Tat up-regulates the expression of PDGF-BB, a known cerebrovascular permeant as well as an inducer of MCP-1. Since astrocytes are in close proximity to the endothelium comprising the neovascular unit, we hypothesized that PDGF-BB released by the activated astrocytes could augment the expression of MCP-1. The present study was aimed at exploring the molecular mechanisms involved in PDGF-BB mediated upregulation of MCP-1. Exposure of human primary and A172 astrocytes to recombinant PDGF-BB protein increased the production and release of MCP-1 at both RNA and protein levels. PDGF-mediated induction of MCP-1 involved activation of ERK1/2, JNK, p38 MAPK, PI3K/Akt pathways and the downstream transcription factor, NFκB. Chromatin Immunoprecipitation assays demonstrated increased binding of NFκB to the MCP-1 promoter following PDGF-BB exposure. Functionally, conditioned media from PDGF-BB-treated astrocytes enhanced monocyte transmigration and barrier permeability in an in vitro model system of human brain microvascular endothelial cells, an effect that was blocked by tyrosine kinase receptor antagonist and neutralizing MCP-1 antibody. These results thus underpin the role of HIV-activated astrocytes in mediating exaggerated monocyte recruitment into the brain via the chemokine MCP-1. Supported by NIH MH068212.

CATECHOLAMINE PRODUCTION BY VAGINAL EPITHELIAL CELLS: A NON-NEURONAL IMMUNOMODULATORY MECHANISM? Brosnahan AJ[1], Jones BJ[1], Vulchanova-Hart L[1], Brown DR[1]; [1]Department of Veterinary and Biomedical Sciences, College of Veterinary Medicine, University of Minnesota, Saint Paul, MN 55108.

We have previously reported (JNIP 5: S41, 2010) that epithelial cells in human vaginal tissue

are immunoreactive for the norepinephrine transporter, which is normally expressed by neurons and is a site of cocaine action. We extended this initial finding by testing the hypothesis that vaginal epithelial cells produce and release catecholamines, and that these substances alter epithelial cell interactions with pathogens. Immunohistochemical experiments indicated that immunoreactivities for the catecholamine-synthesizing enzymes tyrosine hydroxylase and dopamine beta-hydroxylase were present in two different human vaginal epithelial cell lines (ATCC CRL-2616 and a line generated at the University of Iowa). Furthermore, both epithelial cell lines were capable of synthesizing and secreting norepinephrine and dopamine in nanomolar concentrations; preliminary results indicated that catecholamine secretion is stimulated by Staphylococcus aureus peptidoglycan (10 ug/ml), a component of the bacterial cell wall. As previously observed (JNIP 6: S26, 2011), 10 uM norepinephrine, but not dopamine, enhanced interleukin-6 and interleukin-8 secretion in response to staphylococcal toxic shock syndrome toxin-1 (10-100 ug/ml). Norepineprhine also enhanced innate cytokine and chemokine responses to peptidoglycan (10 ug/ml). Based on these findings, we hypothesize that vaginal epithelial cells may constitute a non-neuronal source of norepinephrine, which is capable of modulating immune responses to pathogenic microorganisms and their exotoxins. Supported by NIDA DA-10200 and NIDA T32DA007097.

STABLE EXPRESSION OF ANTI-HIV TAT SINGLE CHAIN VARIABLE FRAGMENT INTRABODY IN HUMAN NEURONAL CELLS AS A POTENTIAL THERAPY FOR NEUROAIDS. Byron MM[1], Lu Y[1]; [1]Office of Public Health Sciences, University of Hawaii at Manoa, Honolulu, HI 96822.

HIV Tat, vital for HIV replication, is a potent neurotoxin causing HIV-Associated Dementia (HAD). To test whether stable production of Tat antibody in the brain could block Tat and provide protection from HAD, our research integrates anti-HIV-1 Tat single chain variable fragment (scFv) intrabodies with a novel gene therapy method utilizing monocytes for gene delivery. HIV-based lentiviral vectors were constructed to express HIV-Tat scFv antibodies or control scFv with CMV promoter and GFP as an indicator gene. High titer vectors were generated through transfection of 293T cells and efficiently transduced 80-100% of human macrophage (CHME-5) and neuroblastoma (HTB-11) cell lines, determined by GFP quantification. Expression of anti-Tat scFv (>800 ng/mL), detected using ELISA, was stable long-term (>25 passages) and intracellular production was confirmed through immunofluorescent staining. Western Blot and Immunoblot demonstrated biological function of secreted anti-Tat scFv by its specific binding to HIV-Tat protein. Long-term observation (>150 days) revealed no apparent change as compared to normal cells in cell growth and morphology. Genetic expression analysis of 24 housekeeping genes revealed no significant differences between transduced and nontransduced cell lines. Anti-HIV Tat scFv significantly protected neuronal cells from Tat- and gp120-mediated neurotoxicity. This study facilitates development and potential use of constructed lentiviral vectors to deliver anti-Tat scFv to the brain for neurotherapeutic intervention using genetically modified cells as a vehicle. Supported by National Institute of Mental Health.

LIPOPOLYSACCHARIDE ALTERS THE INTRACELLULAR CONCENTRATION OF SAQUINAVIR IN MACROPHAGES THROUGH ALTERED EXPRESSION LEVELS OF MRP-1 AND MDR1. Cao L[1], Silverstein PS[1], Earla R[1], Kumar A[1]; [1]Division of Pharmacology and Toxicology, School of Pharmacy, University of Missouri-Kansas City, Kansas City, MO 64108.

MDR1 (P-gp, ABCB1) and multidrug resistance-associated protein 1 (MRP-1, ABCC1) are both involved in the cellular efflux of HIV-1 protease inhibitors. As such, the expression levels and activities of these proteins will determine the intracellular concentrations of antiretrovirals in HIV-infected cells. Our hypothesis is that inflammation will alter the expression and activities of MDR1 and MRP-1, thereby changing the intracellular concentrations of antiretrovirals. To determine the effects of inflammation on protease inhibitors in macrophages, we treated THP-1 macrophages with LPS and determined the effects on MRP-1 and MDR1 at the levels of mRNA, protein and functional activity, as well as the effects on the intracellular concentration of saquinavir. At the level

of mRNA, treatment of THP-1 macrophages with 100 ng/ml LPS resulted in a 300% increase in MRP-1 expression and a 30% decrease in MDR1 expression. Changes in protein levels, as well as measures of the functional activities of these transporters reflected the mRNA changes observed. Furthermore, treatment of THP-1 macrophages with LPS resulted in a 60% increase in the intracellular concentration of saquinavir. This demonstrates that differential regulation of MRP-1 and MDR1 leads to increased intracellular concentration of saquinavir. Thus, because these two transporters bind antiretrovirals based upon very different physical characteristics, the reciprocal regulation of these transporters may result in differential effects (i.e. either increase or decrease) on the various HIV-1 protease inhibitors they transport. Supported by NIDA DA 025011.

BUPRENORPHINE DECREASE THE INFLAMMATORY RESPONSE OF MONOCYTES IN THE CONTEXT OF NEUROAIDS. Carvallo L[1], Lopez L[1], Che FY[1], Lim J[1], Eugenin E[1], Nieves E[2], Madrid-Aliste C[3], Fiser A[3], Weiss L[1], Angeletti RH[2], Berman JW[1]; [1]Department of Pathology, Albert Einstein College of Medicine, Bronx, NY 10461; [2]Department of Developmental and Molecular Biology, Albert Einstein College of Medicine, Bronx, NY 10461; [3]Department of Systems and Computational Biology & Department of Biochemistry, Albert Einstein College of Medicine, Bronx, NY 10461.

HIV-1 enters the brain early in the course of infection and despite successful antiretroviral therapy greater than 50% of HIV infected people exhibit HIV-associated neurocognitive disorders (HAND). Many HIV infected opiate abusers have increased inflammation that contributes to HAND. Buprenorphine (bup) is used to treat opioid addiction. The effects of bup on the transmigration of HIV infected monocytes (MON) across the Blood Brain Barrier (BBB) that contributes to inflammation are unknown. We hypothesize that bup will alter junctional proteins (JP) on MON and BBB to change the ability of MON to transmigrate into the CNS in response to CCL2, a chemokine elevated in the CNS of HIV infected people. We showed that CCL2 increased HIV infected MON transmigration across BBB. We are studying the effects of bup and CCL2 on JP of human MON and brain microvascular endothelial cells (BMVEC) necessary for MON to cross the BBB. We showed that CCL2 increased JAMA phosphorylation while CCL2+bup decreased this effect. As this phosphorylation is associated with migration, bup could decrease neuroinflammation. CCL2 induces cell projections on MON which are associated with a migratory phenotype. CCL2+bup decrease these projections. By proteomics we quantified membrane peptides of MON and showed increased phosphorylation of leukosialin and RNA binding proteins with bup+CCL2. In BMVEC, CCL2 decreased JAMA phosphorylation and CCL2+bup increased it. As JP are important in barrier integrity, bup could alter this property. Our data demonstrate important mechanisms by which bup may impact NeuroAIDS. Supported by NIDA, Grant # 5P20DA026149-02, Einstein Proteomics Center for Study of the Neurological Consequences of HIV and Substance Abuse.

INTRACELLULAR CB2 RECEPTOR AND RECEPTOR TRAFFICKING IN HUMAN IMMUNE CELLS. Castaneda JT[1], Kiertscher SM[2], Harui A[2], Roth MD[2]; [1]Molecular Toxicology, University of California Los Angeles, Los Angeles, CA 90095; [2]Pulmonary & Critical Care Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095.

Cannabinoids activate cannabinoid receptors type 1 (CB1) and 2 (CB2) and induce complex downstream signaling events. While expression of CB2 predominates in immune cells, the distribution and function of CB2 within different human leukocyte subsets is poorly understood. Using a monoclonal antibody against the C-terminal portion of CB2, we readily detected CB2 on the surface of fresh human B cells, but this expression was downregulated when treated with THC. In contrast, CB2 was not detected on the surface of T cells or monocytes. However, all three cell types demonstrated high intracellular CB2 protein (after permeabilization). We hypothesize that receptor internalization and signaling through intracellular CB2 might play an important role in mediating the biologic effects of cannabinoids. In order to study this hypothesis, we developed a model trafficking assay using human A549 lung tumor cells expressing high levels of CB2 (A549-CB2). As in human B cells, A549-CB2 cells exhibit both extracellular and intracellular CB2. When

exposed to THC, cell surface CB2 expression rapidly declines in a concentration- and time-dependent manner while intracellular CB2 expression increases. Pretreatment with AM630, a CB2-specific antagonist, failed to block receptor loss. In the future, this intracellular trafficking assay will be applied to human B cells to study the interrelationships between CB2 receptor location, ligand binding, internalization, and signaling. This work should provide important new insight into how cannabinoids and CB2 receptor pathways function in human immune cells. Supported by NIH/NIDA Grants #R21-DA021813 and R01-DA03018.

TRANSFORMING GROWTH FACTOR β-1 BLOCKER RESCUES HIV-1 NEF MEDIATED SPATIAL LEARNING IMPAIRMENT IN SPRAGUE DAWLEY RATS. Chompre G[1], Loucil R[1], Rivera-Amil V[3], Porter JT[2], Noel Jr R[1]; [1]Biochemistry Department, Ponce School of Medicine and Health Sciences, Ponce, 00732; [2]Pharmacology Department, Ponce School of Medicine and Health Sciences, Ponce, 00732; [3]Microbiology Department, Ponce School of Medicine and Health Sciences, Ponce, 00732.

People with HIV associated neurological disturbances (HAND) continue suffering neurological dysfunction even with combined ART. HAND may develop by the action of viral toxins such as Nef. Viral toxins cause the release of pro-inflammatory molecules resulting in learning impairment. Previous studies in our lab showed that astrocytes expressing Nef produce high levels of TGFβ-1 and Chemokine (C-C motif) ligand (CCL2) in vitro and in vivo. In addition, we showed that unilateral infusion of Nef-expressing astrocytes into the hippocampus of rats causes learning impairment. We found the learning impairment was related to increased expression of CCL2, infiltration of macrophages, and loss of neurons in the hippocampus. However, the role of TGFβ-1 signaling in the learning impairment in our model remains unclear. To test this, we infused rats with Nef expressing astrocytes into the right hippocampus and then treated orally with a TGFβR1 blocker, SD208 (10 mg/kg) daily for seven days. Rats were tested for learning using novel location recognition model. We found that animals treated with Nef and the TGFβR1 blocker showed improved learning compared to the rats treated with Nef and placebo. In addition, brain tissues from rat treated with TGFβR1 blocker showed a decrease in phospho-SMAD-2, and GFAP immunoreactivity. Moreover, we saw that astrocytes expressing Nef treated with the TGFβR1 blocker showed decrease the CCL2 expression in vitro. In conclusion, Nef mechanism occurs in part through TGFβ signaling. This may open avenues for new therapeutic strategies to complement cART. Supported by PSM Behavioral Core and Molecular Biology Core Lab (RR003050), and MBRS RISE program (GM082406).

ASTROCYTE TRACE AMINE ASSOCIATED RECEPTOR-1-INDUCED CAMP REGULATES EXCITOTOXICITY: A MECHANISTIC COMMONALITY OF METH AND HIV-1-INDUCED NEUROTOXICITY. Cisneros I[1], Borgmann K[1], Ghorpade A[1]; [1]Cell Biology and Anatomy, University of North Texas Health Science Center, Fort Worth, TX 76107.

Methamphetamine (METH) is a psychostimulant that results in euphoric effects, heightening the libido and impairing users judgement increasing an individual's risk for acquiring human immunodeficiency virus (HIV-1). HIV-1 results in cognitive effects, such as HIV-associated dementia (HAD), characterized by similar neuropathologies as METH abuse. Astrogliosis is a key pathological feature of METH exposure and HAD, but astrocytes role is unclear in METH/HIV-1-induced neurotoxicity. Excitatory amino acid transporters (EAATs) are the facilitators in regulating glutamate concentrations and are localized in astrocytes. METH/HIV-1-induced excitotoxicity is associated with the dysregulation of EAAT-2. Astrocytes sensitivity to METH led to the investigation of astrocyte trace amine associated receptor 1 (TAAR1) as a potential receptor mechanism for METH-induced effects in astrocytes. TAAR1 is a G-protein coupled receptor, activated by METH, inhibiting dopamine uptake, inducing efflux, and triggering DAT internalization. Preliminary mRNA and protein data suggests significant TAAR1 expression in primary human astrocytes. Activation of TAAR1 by known agonist, β-phenylethylamine (β-PEA), and METH, was measured by intracellular cAMP changes. We propose that TAAR1 is a receptor mechanism for

METH-induced cAMP increases in astrocytes and contributes to the regulation of METH/HIV-1-induced neurotoxicity. Results will contribute to an understanding of astrocytes direct effect of TAAR1 activation, and uncover indirect mechanisms of combined effects of HIV-1/METH in central nervous system.

HIV X4 AND X4R5 VIRUSES EXHIBIT DECREASED TOTAL ANTI-OXIDANT CAPACITY IN A PUERTO RICAN COHORT OF HIV-INFECTED WOMEN. Colon K[1], Zenon F[1], Delgado G[3], Rivera-Amill V[4], Noel R[4], Wojna V[2], Melendez LM[1]. [1]Departments of Microbiology and [2]Neurology, University of Puerto Rico Medical Sciences, San Juan, 00936; [3]Department of Biology, University of Puerto Rico Rio Piedras, San Juan, 00936; [4]Department of Microbiology, Ponce School of Medicine, Ponce, 00730.

HIV infection of target cells is triggered by the recognition of the CD4 receptor and a coreceptor, CCR5 or CXCR4. The principal region that determines the viral tropism is the variable loop 3 (V3 loop) of the envelope protein gp120. In this study, we describe the role of HIV-gp120 sequences in antioxidant dysfunction in HIV-positive women with cognitive impairment. We hypothesize that specific sequence changes within the HIV-1 gp120 will cause antioxidant dysfunction leading to HIV-associated neurocognitive disorders (HAND). HIV isolates derived from 21 HIV-infected women with or without neurocognitive disorders were previously characterized for cellular tropism and co-receptor usage. Supernatant from day 14 post-infection was used to measure total antioxidant capacity (TAC) in vitro and to extract viral RNA. The gp120 gene was amplified using nested PCR with primers that recognize conserved sequences. The PCR products were cloned into pCR2.1 or pcDNA3.1/V5-HIS and sequenced. Co-receptor prediction was obtained with the Web PSSM Software. One-way ANOVA was used for statistical analysis. Our results demonstrate that TAC from supernatant tends to decrease with HAND. For tropism, TAC was significantly decreased for X4-tropic ($p<0.001$) and X4/R5-tropic viruses ($p<0.05$) compared to R5-tropic viruses. Our data suggest that X4- and X4/R5 tropism caused a decrease in the TAC leading to antioxidant imbalance that may partially explain the role of gp120 sequences in macrophage dysfunction and cognitive dysfunction. Supported by R01-MH08316-01, R25-GM061838, G12RR03051, G12RR003050, and SNRP-NINDS-1-U54NS431.

NICOTINE SUPPRESSES TLR3-MEDIATED INFLAMMATION THROUGH A CALCIUM SIGNALING MECHANISM. Cui WY[1], Chang SL[2], Polanowska-Grabowska R[3], Saucerman JJ[3], Li MD[1]; [1]Department of Psychiatry and Neurobehavioral Sciences, University of Virginia, Charlottesville, VA 22911; [2]Institute of NeuroImmune Pharmacology and Department of Biology, Seton Hall University, South Orange, NJ 07079; [3]Department of Biomedical Engineering, University of Virginia, Charlottesville, VA 22903.

Nicotine, the primary psychological stimulant of tobacco, exerts suppressive effects on inflammation and confers increased susceptibility to viral infections. To characterize nicotine's anti-inflammatory effects during viral infections, in this study, we first examined RNA expression of 51 key genes within the innate immune pathways using a quantitative RT-PCR array. We then determined the protein level for two key genes, interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), in poly(I:C)-induced macrophages using ELISA. We found that poly(I:C)-induced innate immune signaling was significantly suppressed by nicotine at both the RNA and protein levels and demonstrated that such alteration was mediated by the α7 nicotinic acetylcholine receptor (nAChR). Importantly, all these results were confirmed in both RAW264.7 cell line and primary peritoneal macrophages. Furthermore, to reveal mechanism underlying this effect, we employed a protein array containing 1318 kinase-related antibodies to examine nicotine's effects on poly(I:C)-triggered kinases at the phosphorylation level, and found that a cluster of calcium-elicited kinases was suppressed by nicotine. Finally, we used Western blotting and calcium imaging experiments to confirm some of our findings from the protein array experiments. Taken together, our results indicate that nicotine has significant suppressive effects on poly(I:C)-induced TLR-related pathways, and that calcium signaling is actively involved in the immunosuppressive effects of

nicotine during viral-induced inflammation. Supported by NIH grants DA-013783, DA-016149 and DA-026356.

EFFICACY AND SAFETY TESTS OF LONG-ACTING NANOFORMULATED ANTI-RETROVIRAL DRUGS IN HIV-1 INFECTED HUMANIZED MICE. Dash PK[1], Gorantla S[1], Roy U[1], Knibbe J[1], Balkundi S[1], McMillan J[1], Gelbard HA[2], Poluektova LY[1], Gendelman HE[1]; [1]Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198; [2]Center for Neural Development and Disease, University of Rochester School of Medicine and Dentistry, New York, NY 14642.

Background: Compliance, escape from immune surveillance and cumulative toxicities underlie treatment failures for antiretroviral therapies (ART) for HIV disease. To this end our laboratories developed atazanvir (ATV) and ritonavir (RTV) nanoformulations (referred to as nanoART). Methods: Newborn NOD/SCID-IL-2γcnull mice were transplanted with human CD34+ hematopoietic stem cells and infected at 22 weeks of age with HIV-1ADA. After eight weeks of infection five mice were injected subcutaneously (sc) at weekly intervals with nanoART at 250mg/kg at 1:1 ATV/RTV concentration for six dosages, and six animals remain as untreated control. Additional 5 uninfected animals were treated by similar schedule for evaluation of the drug safety profile. Animals were sacrificed 17 weeks after infection for analysis of tissue drug levels, viral loads and histopathology. Results: All HIV-1 infected and treated animals survived study and retained human hematopoiesis. Eight weeks after viral infection all animals showed sustained viral load with a median value of 1.63×10^5 HIV-1 RNA copies/ml. After 4 weekly drug injections the viral loads were below the levels of detection and three weeks after the final nanoART treatment viral replication rebounded to levels observed in untreated animals. NanoART treatment preserved damage of human lymphoid tissue by HIV-1 and prevented reduction of CD4+ T cells. Conclusion: The development of long-acting nanoART is now realized and enabling efficient control of HIV-1 replication in humanized mice. Future works in monkeys and in human are being planned.

EXCESS SOLUBLE CD40L CONTRIBUTES TO BLOOD BRAIN BARRIER PERMEABILITY IN A MOUSE MODEL OF HIV-ASSOCIATED NEUROCOGNITIVE DISORDER (HAND). Davidson DC[1], Hirschman MP[1], Sun A[1], Kasischke KA[1], Schifitto G[2], Maggirwar SB[1]; [1]Department of Microbiology and Immunology, University of Rochester School of Medicine and Dentistry, Rochester, NY 14642; [2]Department of Neurology, University of Rochester School of Medicine and Dentistry, Rochester, NY 14642.

Despite the use of antiretroviral therapies, a majority of HIV infected individuals still develop HAND, indicating that host inflammatory mediators, in addition to viral proteins, may be contributing to these disorders. Consistently, we have previously shown that levels of the inflammatory mediator soluble CD40 ligand (sCD40L) are elevated in the circulation of HIV infected, cognitively impaired individuals. Here we demonstrate that the non-nucleoside reverse transcriptase inhibitor efavirenz induces the release of sCD40L in HIV infected individuals, thus further contributing to excess plasma concentrations of this mediator. Recent studies from our lab implicate a role for the CD40/CD40L dyad in blood brain barrier (BBB) permeability and interestingly, sCD40L is thought to regulate BBB permeability in other inflammatory disorders of the CNS. Using complementary multiphoton microscopy and quantitative analyses in wild type and CD40L knockout mice, we now reveal that the HIV transactivator of transcription (Tat) can induce BBB permeability in a CD40L dependent manner. This permeability is limited to the BBB and was found to be a result of aberrant platelet activation induced by Tat. Furthermore, Tat treatment led to an increase in Gr1 positive monocytes, indicating an expansion of the inflammatory subset of cells in these mice. Exploring the mechanisms by which the BBB becomes compromised during HIV infection has the potential to reveal novel targets, thereby aiding in the development of adjunct therapies for the management of HAND, which are currently lacking. Supported by National Institutes of Health grants RO1 NS054578 and RO1 NS066801.

C/EBPβ REGULATES MULTIPLE IL-1β-INDUCED HUMAN ASTROCYTE INFLAMMATORY GENES VIA A P38 DEPENDENT PATHWAY. Fields JA[1], Ghorpade A[1]; [1]Cell Biology and Anatomy, University of North Texas Health Science Center, Fort Worth, TX 76107.

C/EBPβ regulates gene expression in multiple organ systems and cell types, including the CNS and astrocytes. C/EBPβ is detectable in brains of HIV–associated dementia (HAD) patients and astrocytes increase C/EBPβ expression in response to IL-1β, TNF-α, HIV-1 and LPS. Despite its prevalence in the CNS, little is known about how C/EBPβ contributes to astrocyte gene expression during neuroinflammation. Here, we sought to define a role for C/EBPβ in regulating the human astrocyte inflammatory response, using IL-1β as the inflammatory stimulus. C/EBPβ knockdown in human astrocytes affected expression of 60% of IL-1β-regulated genes; both increasing and decreasing mRNA levels. C/EBPβ knockdown blocked IL-1β-mediated COX2 expression and a p38-selective small molecule inhibitor blocked increases in C/EBPβ and COX2 mRNA expression. C/EBPβ knockdown enhanced IL-1β-mediated BDKRB2 expression while an ERK1/2-selective small molecule inhibitor blocked IL-1β-mediated BDKRB2 mRNA expression. Interestingly, the ERK1/2-selective small molecule inhibitor increased IL-1β-mediated C/EBPβ expression. A p38-selective small molecule inhibitor blocked IL-1β-mediated C/EBPβ translocation to the nuclei and COX2 expression, whereas the ERK1/2-selective small molecule inhibitor enhanced C/EBPβ translocation to nuclei and COX2 expression. These data suggest that C/EBPβ is part of a transcriptional complex that directs the IL-1β-mediated inflammatory response. Delineating C/EBPβ activity during the astrocyte inflammatory response may lead to effective therapies for HAD and other CNS pathologies. Supported by NINDS/NIH-1F31NS072006-01.

MORPHINE EXACERBATED RESPONSE TO HIV-1 TAT-DEPENDENT SYNAPTODENDRITIC INJURY IS MEDIATED BY [CA2+]I STORES AND ATP DEPLETION. Fitting S[1], Zou S[2], Knapp PE[2], Hauser KF[1]; [1]Department of Pharmacology & Toxicology, Virginia Commonwealth University, Richmond, VA 23298; [2]Department of Anatomy & Neurobiology, Virginia Commonwealth University, Richmond, VA 23298.

Synaptodendritic organization and spine density are disrupted by Tat and/or morphine in vivo (as assessed in Golgi-impregnations and by electron microscopy); with combined opioid and Tat induction causing synergistic dendritic pathology at 7-10 days following continuous exposure to both (Fitting et al., Am J Pathol, 2010). Parallel in vitro studies (primary striatal neuron culture) that showed nearly identical dendritic swellings as seen in vivo, examined the mechanisms underlying synaptodendritic injury. Within a 10 min time window Tat caused significant focal increases in [Na+]i and [Ca2+]i along the dendrites within the first 2 min, which were partially attenuated by NMDA and AMPA receptor antagonists MK801 and CNQX. In contrast, Tat ± morphine treatment caused significant sustained increases in [Na+]i and [Ca2+]i, as well as corresponding increases in focal dendritic swellings. Importantly, Tat ± morphine-induced initial losses in ion homeostasis and increased [Ca2+]i production were attenuated by RyR and IP3 inhibitors as well as Pyruvate, indicating the importance of [Ca2+]i stores and ATP. The Tat and morphine-driven excitotoxic, glutamatergic dysregulation of [Ca2+]i homeostasis appears to be an important event in opioid-HIV-1 Tat synergistic interactions, and is likely to be critical in underlying the loss of synaptic connectivity. The studies outlined herein will contribute to better therapeutic approaches toward allaying the CNS consequences of opioid abuse-HIV-1 comorbidity. Supported by NIDA DA018633, DA027374.

HIV-1 VIRAL PROTEIN R (VPR) MEDIATED INDUCTION OF PRO-INFLAMMATORY CYTOKINES IL-6, IL -8 AND RANTES IN THE ASTROCYTES VIA P38 MAPK AND NF-κB PATHWAY. Gangwani MR[1], Kumar A[1]; [1]Department of Pharmacology and Toxicology, University of Missouri-Kansas City, Kansas City, MO 64108.

The HIV-1 accessory protein Vpr is a protein with several critical functions including activation of HIV-1 LTR transcription and the transport of the preintegration complex into the nucleus. Vpr plays an important role in the pathogenesis of AIDS, both centrally and peripherally. Glial activation is

one of the prominent features of HIV-1-associated neurological disorders (HAND) and the level of glial activation is positively correlated with the severity of HAND. In view of this, we sought to address whether Vpr can induce glial activation and the secretion of proinflammatory cytokines IL-6, IL-8 and RANTES. The transfection of SVGA astrocytes with Vpr showed time-dependent induction of these cytokines with peak mRNA levels of (12.5 ± 1.16 fold for IL-6; 3.42 ± 0.4 fold for IL-8 and 29.76 ± 2.24 fold for RANTES) and peak protein levels (10.46 ± 0.73 fold for IL-6; 3.28 ± 0.10 fold for IL-8 and 107.26 ± 2.42 fold for RANTES). To determine whether these effects were mediated by the NF-κB pathway, the cells were pretreated with chemical antagonists of p38 MAPK (SB 203580) and NF-κB (Bay 11-7082: IκB-α; SC-514: IKK2) pathway. All three inhibitors abrogated Vpr-mediated induction of these cytokines. This strongly suggests the involvement of the NF-κB and p38 pathways in Vpr-mediated induction of inflammatory cytokines in astrocytes. Currently the studies are underway to determine the role of 4 p38 isoforms by utilizing specific siRNA's. Supported by NIDA (DA025528).

ALCOHOL MODULATES P2X RECEPTORS IN EMBYRONIC STEM CELL DERIVED MICROGLIA: POTENTIAL ROLE IN MICROGLIA IMMUNE REGULATION. Gofman L[1], Cenna J[1], Potula R[1]; [1]Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140.

A wealth of scientific evidence underscores the deleterious effects of alcohol abuse on the neuroimmune system. However, it still remains unclear how alcohol exposure deregulates microglia immunoregulatory and neuroprotective mechanisms. Microglia express various cell surface P2 nucleotide purinoreceptors. Purinergic receptors and the associated signaling cascades have emerged as a pivotal regulator of immune cell inflammatory response in the central nervous system (CNS) and recently have shown to be important mediators of ethanol (EtOH)-induced effects. Using Embryonic Stem cell-derived microglial (ESdM) as a cellular tool to study the function of microglia, we investigated the effects of alcohol on microglia purinergic receptors. mRNA and immunohistochemical analysis of ESdM cells showed strong expression of metabotropic P2Y6, 12 and inotropic P2X3,4,7 receptors. Treatment with EtOH (50-100mM) for 24-48hrs had no effect on P2Y6 and P2Y12 mRNA expression. However, P2X4 and P2X7 mRNA expression in EtOH treated ESdM were 2.5 and 1.5 folds higher respectively compared to controls. Furthermore, our result show that direct exposure of 50mM EtOH significantly increased microglia [Ca2+]c concentration suggesting impending changes that could likely contribute to altered microglial activation, and cytokine release. Exploring the role of purinoreceptor in microglia-mediate neuroprotection will aid to elucidate the processes that contribute to neurodegeneration associated with alcohol abuse. Supported by TUSM Developmental Funds.

SIV/TB COINFECTION OF CHINESE RHESUS MONKEYS. Guo M[1], Zhang J[1], Wang Y[1], Tang ZJ[1], Xian QY[1], Rao Y[1], Dai M[1], Bao R[1], Huang ZX[1], Wang X[1], Ho WZ[2], Ye L[1]; [1]Animal Experiment/Animal Biosafety Level III Laboratory, Wuhan University, Wuhan, 430071; [2]Department of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140.

Tuberculosis (TB) is the leading cause of the death among HIV-infected patients. HIV infection is also a risk factor for reactivation of latent TB infection to active disease. To establish an animal model for TB and HIV coinfection is critical to the understanding of the pathological interactions between these two pathogens. In this study, we first inoculated Chinese Rhesus monkeys (CRMs) with SIV mac239 strain. The animals became infected as evidenced by continued presence of plasma SIV RNA and protein and a significant decrease in CD4+/CD8+ T cell ratio, which was negatively associated with plasma SIV RNA levels. At week 6 post-SIV infection, the animals were intra-bronchially inoculated with M.tb H37Rv strain. Comparing with SIV mono-infected monkeys, the coinfected animals had little differences in SIV viral load and CD4+/CD8+ T cell ratio. In contrast, chest X-ray showed that the coinfected monkeys had disseminated lesions in both left and right lungs, while the lung lesions in TB mono-infected monkeys were localized in right lung.

All three coinfected animals died at week 16, 18, 19 post-tb infection respectively, while the animals infected with M.tb or SIV only are still alive. The necropsy demonstrated a disseminated M.tb infection not only in the lungs but also in other organs including spleen, pancreas, liver, kidneys and heart. These data demonstrated the success in establishing SIV and TB coinfection model using CRMs. Our ongoing studies will further investigate the mechanisms involved in the interactions between SIV and M.tb on disease progression in CRMs. Supported by Mega-Projects of Science Research for the 11th Five Year Plan, China, 2009ZX10004-402.

METHAMPHETAMINE INDUCES TAAR1 RECEPTOR EXPRESSION IN NAÏVE T LYMPHOCYTES: ROLE IN IMMUNOMODULATION. Haldar B[1], Cenna J[1], Fan S[1], Potula R[1]; [1]Departments of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140.

The recently discovered novel transmembrane G protein coupled receptor, trace amine-associated receptor 1 (TAAR1) represents a potential direct target for drugs of abuse and monoaminergic compounds, including amphetamines. Recently TAAR1 mRNA up-regulation in human lymphocytes following in vitro stimulation with PHA has been noted. For the first time, our studies have illustrated that there is an induction of TAAR1 mRNA expression in naive T lymphocytes in response to methamphetamine (METH). METH treatment for 6 hrs significantly ($p= 0.02$) increases TAAR1 mRNA expression. Furthermore 24 hrs post METH exposure, TAAR1 protein expression showed significant increase ($p=0.01$) by immunocytochemistry and an increased expression was also observed by flow cytometry. These data suggest that METH has an immunomodulatory effect that is attributable to the activity of the receptor. In vitro using our cloned human TAAR1 expression plasmid METH activated TAAR1 receptors and triggered accumulation of intracellular cAMP. Our results also show presence of TAAR1 in human lymph nodes from HIV-1 infected patients with and without history of METH abuse. The expression of TAAR1 on lymphocytes was largely in the paracortical lymphoid area of the lymph nodes with enhanced reactivity to TAAR1 receptor in lymph nodes of HIV-1 infected METH abuser. Taken together, the ability of METH to activate TAAR1 in vitro, along with the expression of TAAR1 in T lymphocytes in the peripheral lymphoid organ such as lymph node suggests that TAAR1 may play a role in METH-mediated immune modulatory properties. Supported by NIH/1R01DA031064-01.

MECHANISMS BY WHICH A CB2-SELECTIVE CANNABINOID INHIBITS T-CELL FUNCTION. Hartzell RR[2], Meissler JJ[1], Adler MW[1], Eisenstein TK[1]; [1]Center for Substance Abuse Research, Temple University School of Medicine, Philadelphia, PA 19140; [2]Department of Microbiology and Immunology, Temple University School of Medicine, Philadelphia, PA 19140.

We have previously shown that CB2-selective agonists inhibit the Mixed Lymphocyte Reaction (MLR), an in vitro correlate of organ graft rejection, via CB2 receptors. An effect on T-cells was postulated, as CB2 agonists inhibited IL-2 release, and full inhibition occurred when purified CD3+ cells, but not CD11b+ cells, were treated. Current studies explored further the mechanisms for the anti-inflammatory properties of this class of cannabinoids. A PCR T-cell activation array was used to generate a gene expression profile of mouse spleen cells cultured in an MLR, with and without the CB2 selective agonist, O-1966. mRNA was extracted from CD3+ T-cells purified by flow cytometry. O-1966 treated T-cells showed a significant reduction in expression of CD40 ligand and CyclinD3 in the MLR. In addition, there was an increase in IL-10 mRNA expression, and of other molecules in immunosuppressive pathways. An increase in IL-10 protein in culture supernatants was confirmed by ELISA. Further, flow purified T-cells treated with anti-CD3 and anti-CD28 in the presence of O-1966 showed decreased proliferation. O-1966 treatment was also shown to increase the percentage of Treg-cells in the MLR culture, as assessed by the number of Foxp3+CD4+ cells detected by flow cytometry. Together, these results show that a CB2 agonist can suppress T-cells in the MLR by inducing anti-inflammatory cytokines and suppressor T-cells, and by inhibiting direct T-cell activation. These data support the potential of this class of

compounds as useful therapies to prolong graft survival in transplant patients. Supported by NIDA grants DA13429, DA06650, and T32-DA07237.

HIV TAT MEDIATES DOWN REGULATION OF β-CATENIN SIGNALING IN ASTROCYTES THROUGH ITS INTACT CYSTEINE-RICH REGION AND LOSS OF β-CATENIN LEADS TO SIGNIFICANT IMPAIRMENT OF EXCITATORY AMINO ACID TRANSPORTER 2. Henderson LJ[1], Narasipura SD[1], Min S[1], Al-Harthi L[1]; [1]Department of Immunology and Microbiology, Rush University Medical Center, Chicago, IL 60612.

HIV has evolved many mechanisms to overcome host restriction factors. We have determined that β-catenin signaling restricts HIV transcription in many cell types, including astrocytes. To assess if HIV has a mechanism to overcome β-catenin signaling-mediated restriction of replication, we evaluated the impact of HIV transactivator of transcription (Tat) on β-catenin signaling. We demonstrate that either soluble HIV-1 clade B Tat1-86 or Tat cDNA reduced the expression of active β-catenin protein in primary progenitor derived astrocytes (PDAs) by 78%. Further, Tat cDNA transfection diminished activity of β-catenin/TCF reporter (TOPflash) in PDAs (59%) and U87MG astrocytoma (41%). Disruption of the dicysteine motif (C30C31) by mutation (C30G) or transfection with clade C Tat restored TOPflash activity in PDAs. We next determined the impact of diminished β-catenin on astrocyte function. β-catenin knockdown dramatically reduced expression of glutamate transporter Excitatory Amino Acid Transporter 2 (EAAT2), as measured by western blot and RT-PCR in PDAs. Collectively, these data demonstrate that the Tat dicysteine motif is required for inhibition of β-catenin in astrocytes and that signals that disrupt β-catenin lead to inhibition of EAAT2 expression. Because glutamate is the most abundant neurotransmitter in the CNS and must be tightly regulated, our findings indicate that β-catenin pathway is critical for CNS health and that reduced β-catenin signaling in the brain can contribute to dysregulation of glia. Supported by F31 NS071999 to LJH and R01NS 060632 to LA.

MORPHINE-INDUCED CONDITIONED PLACE PREFERENCE AND REINSTATEMENT AFTER EXTINCTION IN HIV-1 TRANSGENIC RATS. Homji NF[1], Vigorito MV[1], Liu CL[1], Chang SL[1]; [1]Institute of NeuroImmune Pharmacology, Seton Hall University, South Orange, NJ 07079; [2]Department of Biological Science, Seton Hall University, South Orange, NJ 07079.

The prevalence of morphine addiction in HIV-1 infected persons is higher than the healthy population. The mu-opioid receptor (MOR) which mediates the actions of morphine is shown to be up-regulated in HIV-1 transgenic (HIV-1Tg) rat. In this study, we used the conditioned placement preference (CPP) test, a popular model to study the motivational effects of drugs, to investigate if HIV-1Tg rats are more sensitive to the addictive properties of morphine than control animals as indicated by drug-primed or stress-induced reinstatement of a morphine CPP. The HIV-1Tg and F344 rats were conditioned with three doses of 3.5 mg/kg morphine. Following extinction both HIV-1Tg and F344 rats were randomly divided into two groups. One group was administered a morphine prime with 1 mg/kg and 3.5 mg/kg morphine on 2 consecutive days, respectively. These animals were tested for reinstatement on each day following morphine treatment. The second group was administered foot-shock and tested for reinstatement. HIV-1Tg rats did not show reinstatement on either dose of morphine compared to the F344 rats, which showed reinstatement at 3.5mg/kg of morphine. Both HIV-1Tg rats and F344 showed re-instatement when foot-shock was administered. The failure of the HIV-1Tg rats to show drug-primed reinstatement suggests a memory deficit as the drug failed to serve as a reminder of the incentive value of drug-associated cues. Supported by NIH/NIDA R01 DA007058 and K02 DA016149.

CD40 LIGAND INDUCES BRAIN PERICYTE CELL DEATH: IMPLICATIONS FOR HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS (HAND). Jackson JW[1], Davidson DC[1], Maggirwar SB[1]; [1]Department of Microbiology and Immunology, University of Rochester Medical Center, Rochester, NY 14642.

The neurovascular unit of the blood-brain barrier (BBB) is comprised of pericytes, endothelial

cells (ECs), astrocytes, and neurons. Pericyte interaction with ECs of the brain microvasculature provides structural support and is involved in regulation of EC gene expression, both of which are vital in maintaining BBB integrity. HIV infection results in increased BBB permeability due, in part, to the robust inflammatory response within the central nervous system. Soluble CD40 ligand (sCD40L) is a pro-inflammatory mediator thought to be abundantly released by platelets, and we have previously shown that there are increased levels of sCD40L in the plasma and cerebral spinal fluid of HIV infected patients with cognitive impairment. Using sodium fluorescein assays, we now reveal that the HIV transactivator of transcription (Tat) induces BBB leakiness in wild type, but not CD40L knockout, mice. Consistent with this notion, multiple cell viability assays demonstrate that treatment of cultured human brain pericytes with CD40L results in cell death, independent of caspase 3 activity and conventional apoptosis. We hypothesize that the increased CD40L levels found during HIV infection lead to the death of brain resident pericytes, thus contributing to loss of BBB integrity. In support of this notion, we are currently analyzing pericyte numbers in wild type and CD40L knockout mice. These observations will not only provide a better understanding of BBB permeability during HIV infection, but will also introduce pericytes as a major player in the field of HIV induced neuroinflammation. Supported by National Institute of Health grants RO1 NS054578 and RO1 NS066801.

CYP2E1-MEDIATED ALCOHOL METABOLISM INDUCES EXPRESSIONS OF CYP2A6 AND CYP2E1 THROUGH OXIDATIVE STRESS-INDUCED PKC SIGNALING CASCADES IN MONOCYTES AND ASTROCYTES. Jin M[1], Kumar A[1], Kumar S[1]; [1]Division of Pharmacology and Toxicology, School of Pharmacy, University of Missouri-Kansas City, Kansas City, MO 64108.

Cytochrome P450 2A6 (CYP2A6) and CYP2E1 are known for nicotine and alcohol metabolisms, respectively, those are known to cause oxidative stress-associated liver damage and lung cancer. Tobacco/nicotine and alcohol have also been implicated in HIV-1 replication. Our previous findings showed that alcohol induced CYP2A6 and CYP2E1 in monocytes and astrocytes, but the mechanism is unknown. Therefore, this study was designed to examine the molecular mechanism of alcohol-mediated inductions of CYP2A6 and CYP2E1. We applied qRT-PCR, western blotting and flow cytometry to examine mRNA, protein expression, and reactive oxygen species, respectively. Our results using CYP2E1 selective inhibitor, diallyl sulfide, and an antioxidant Vitamin C showed that alcohol-induced expressions of CYP2A6 and CYP2E1 were mediated through alcohol metabolism by CYP2E1 that leads to increased oxidative stress. Further, using specific inhibitors (Staurosporine for PKC, U0126 for MEK/Erk and SB600125 for JNK), we showed that alcohol induced CYP2A6 and CYP2E1 through oxidative stress-activated PKC pathway. The results showed that CYP2A6 was induced through the induction of MEK/Erk resulting into Nrf2 translocation, while CYP2E1 was induced through JNK phosphorylation resulting into c-Jun phosphorylation and translocation. In conclusions, these findings provide a novel pathway for alcohol-mediated CYP2A6 and CYP2E1 inductions. This study has clinical relevance because tobacco consumption is 3-time higher among alcoholics (45%) compared to normal (15%), which is further increased in HIV+ population (90%). Supported by NIH-DA031616-01(Kumar, S.).

PSYCHOLOGICAL DISTRESS AND DEPRESSED MOOD IN HIV PATIENTS AND METHAMPHETAMINE USERS. Katayama N[1], Munsaka SM[1], Jiang C[1], Nakama H[1], Chang L[1]; [1]Department of Medicine, MRI Research Program, John A. Burns School of Medicine, University of Hawaii at Manoa, Honolulu, HI 96822.

Introduction: HIV infection and Methamphetamine (METH) abuse are common co-morbid disorders. Prior studies showed drug abuse in HIV patients may lead to more self-report of mental distress and psychiatric symptoms. However, it is unclear whether HIV patients who use METH are at greater risk for psychiatric distress. Method: We assessed 134 subjects [32 seronegative non-drug user controls (SN), 37 HIV+, 28 HIV+METH, and 37 METH only] for depressive symptoms with the Center for Epidemiological Studies Depression Scale (CES-D) and Symptom Checklist 90-

R (SCL 90-R). Result: HIV+METH subjects had higher SCL 90-R scores in almost all subscales and CES-D than the other three controls, and reached significance for group differences for the majority of them (p-values<0.0001-0.005). HIV subjects also had higher SCL 90-R subscale scores (except for paranoia) and CES-D than SN (p-values<0.0006-0.048). METH subjects had higher obsessive-compulsive, interpersonal sensitivity, depression, and psychoticism subscales as well as higher CES-D than SN (p-values<0.0006-0.03). HIV and HIV+METH subjects had higher somatization score in SCL 90-R than METH users. Conclusion: These findings suggest that METH use in the setting of HIV leads to greater risk for psychiatric distress than either condition alone. Treatments or interventions need to target both HIV and psychiatric symptoms in these individuals. Correlations with these symptoms and neuroinflammatory changes, measured with MR spectroscopy or cerebrospinal fluid cytokine levels, are needed to further assess these subjects. Supported by NINDS, NIDA (U54NS56883-05, 2K24-DA16170) and NCRR (G12RR003061, P20RR11091).

EFFECTS OF ANTIRETROVIRAL DRUGS ON HUMAN MACROPHAGES ACTIVATION. King J[1], Akay C[1], Jordan-Sciutto K[1]; [1]Department of Pathology School of Dental Medicine, University of Pennsylvania, Philadelphia, PA 19104.

Combination antiretroviral therapy (cART) has decreased the incidence of HIV-Associated dementia (HAD), but less severe forms of cognitive, behavioral, and motor impairments, termed HIV associated neurocognitive disorder (HAND) persist in 30-50% of HIV positive patients. Neuronal damage in HIV-infected patients has been attributed to the presence of astrocytosis, perivascular inflammatory macrophages, microglial nodules, and multinucleated giant cells, suggesting an inflammatory process underlies the pathogenesis of HAND. This had led us to hypothesize that antiretrovirals contribute to the persistence of HAND in HIV positive patients. As microglial and astrocytic activation play seminal roles in mediating neuronal damage, we sought to address whether antiretrovirals provoke an inflammatory response in human macrophages leading to the release of pro-inflammatory markers and assessed levels of tumor necrosis factor (TNF)-α, CD86 and CD11b as well as anti-inflammatory cell markers, CD206 and CD163 in primary macrophages and astrocytes. The results indicate that treatment with the protease inhibitor Ritonavir alone enhanced the presence of CD11b in human macrophages. This enhancement was associated with chemotaxis and alterations in gene expression. However there was no change in anti-inflammatory marker expression in the Ritonavir treated macrophages. These results establish a more defined link between the inflammatory response and cART in HIV infected individuals and offer a potential explanation for the increased prevalence of HAND in the post-cART era. Supported by NIH R01 NS056885, 5K12GM081259.

MOTOR SLOWING IN HIV-INFECTED METHAMPHETAMINE USERS. Kraft-Terry SD[1], Nakama H[1], Jiang C[1], Chang L[1]; [1]Division of Neurology, Department of Medicine, John A. Burns School of Medicine, University of Hawaii at Manoa, Honolulu, HI 96813.

Introduction: Methamphetamine (METH)-dependence causes dopamine-induced oxidative damage to surrounding dopaminergic neurons. HIV-infection is also known to have neurotoxic effects on the dopamine system as a result of glial activation and secretion of toxic viral proteins. We hypothesized that combined METH-dependence and HIV-infection would lead to additive neurotoxic effects to the dopaminergic system. Methods: We performed a 2x2 cross-sectional study in 55 METH-dependent subjects [age 39.8±1.2 years; 25 HIV+ (23 men, 2 women,) 30 HIV(-) (25 men, 5 women)] and 64 non-METH users [age: 40.4±1.4 years, 34 HIV+(31 men, 3 women), 30 HIV(-) (27 men, 3 women)]. Participants were evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) and the Grooved pegboard task. Z-scores were calculated from a large normative database, adjusted for both the subjects' age and education level. Results: HIV+ subjects had greater tremor scores on UPDRS than non-HIV subjects (2-way non-parametric ANOVA-p=0.01). HIV+ subjects also tended to have more bradykinesia than non-HIV subjects (2-way non-parametric ANOVA-p=0.06). In contrast, the METH subjects were slower on the Grooved

Pegboard task, with lower z-scores than non-METH users (2-way ANOVA-p<0.001) and HIV+METH-users had the lowest motor z-scores of all groups. Conclusion: The dopaminergic system is affected differently by HIV infection and METH abuse. However, the HIV+METH group having the lowest motor z-score suggests that METH-dependence and HIV-infection have additive neurotoxic effects on the dopaminergic system. Supported by NINDS, NIDA (U54NS56883-05, 2K24-DA16170) and NCRR (G12RR003061, P20RR11091).

CYCLOOXYGENASE (COX) ENZYMES AND PROSTAGLANDIN E2 (PGE2) MODULATE WEST NILE VIRUS (WNV)-INDUCED NEUROINFLAMMATION, AND REGULATE THE PRODUCTION OF NEUROINFLAMMATORY MOLECULES INCLUDING MATRIX METALLOPROTEINASES (MMPS). Kumar M[1], Verma S[1], Nerurkar VR[1]; [1]Department of Tropical Medicine, Medical Microbiology and Pharmacology, John A. Burns School of Medicine/University of Hawaii, Honolulu, HI 96813.

Inflammatory responses triggered initially to clear WNV infection, later become detrimental and contribute to blood-brain barrier (BBB) disruption and neuronal death. COX enzymes and its product PGE2 regulate production of several inflammatory cytokines and MMPs. We previously demonstrated that multiple MMPs produced by WNV infected-astrocytes mediate disruption of an in vitro BBB model. In this study, we characterized the pathophysiological consequences of COX-2 expression in human brain cortical astrocytes (HBCA) and mice following WNV infection. While COX-1 mRNA expression did not change, WNV infection significantly induced mRNA and protein expression of COX-2 in HBCA. Similarly, PGE2 level was also enhanced significantly in infected HBCA and was blocked in the presence of COX-2 specific inhibitor, NS-398. Treatment of infected HBCA with NS-398 attenuated the expression of MMP in a dose-dependent manner. In addition, the expression of IL-1β, -6 and -8, which were markedly elevated in infected HBCA, exhibited a significant reduction in the presence of NS-398. Similarly, mRNA and protein expression of COX-2 increased dramatically in the mice brain at days 6 and 8 after infection with WNV, which correlated with the peak virus titers and increase in cytokines in the brain. These results provide first evidence that WNV-induced COX-2/PGE2 regulates the expression of downstream inflammatory mediators and link it with BBB disruption and neuroinflammation. Further in vivo studies using COX inhibitors are warranted to investigate their therapeutic potential to manage WNV disease. Supported by Hawaii Community Foundation, G12RR003061 (RCMI), P20RR018727 (COBRE), NIH.

THERANOSTIC DEVELOPMENTS OF SMALL MAGNETITE ANTIRETROVIRAL PARTICLES-SMART. Li T[1], Liu X[1], Kabanov AV[3], Kayandan S[2], Riffle JS[2], Gendelman HE[1], Balasubramaniam S[2], Davis RM[2]; [1]Department of Pharmacology & Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198; [2]Department of Chemical Engineering, Virginia Tech, Blacksburg, VA 24061; [3]Department of Pharmaceutical Sciences and Center for Drug Delivery and Nanomedicine, University of Nebraska Medical Center, Omaha, NE 68198.

Our laboratories developed a novel drug delivery system utilizing monocyte-derived macrophages (MDM) to carry antiretroviral therapies (ART) to cell and tissue sites of HIV-1 infection. Although nanoformulated ART were tested in vitro for uptake, release and antiretroviral efficacy, more complex approaches are needed to determine drug biodistribution and efficacy in animals. To address this, small magnetite-containing ART (SMART) polymer nanoparticle systems were developed. First, we combined ART and superparamagnetic iron oxide particles into hydrophobic cores of polymer particles utilizing its hydrophilic shell to stabilize the particles. Second, we administered the SMART to MDM and observed, as a result, changes in the transverse relaxivity. Next, we prepared SMART by flash nanoprecipitation using rapid micromixing to effect high supersaturations and kinetically controlled aggregation of hydrophobic ART and magnetite using block copolymers to sterically stabilize the particles. The resulting MART particles have narrow size distributions with polydispersity indices typically in the range 0.1-0.15. The magnetite-PDLLA particles were not cytotoxic at levels needed to achieve an effective drug concentration for antiretroviral activities. Importantly, SMART was taken up within eight hours by

MDM. We posit that with flash precipitation, we can enable combined therapeutic and diagnostic drug delivery using image-guided detection. Supported by National Institutes of Health grants 1P01 DA028555 and a research grant from Baxter Healthcare.

EFFECT OF METHAMPHETAMINE ON LPS-INDUCED PRO-INFLAMMATORY CYTOKINE PRODUCTION IS MEDIATED BY MAPK AND NF-κB PATHWAYS. Liu X[1], Silverstein PS[1], Kumar A[1]; [1]Division of Pharmacology and Toxicology, University of Missouri-Kansas City, Kansas City, MO 64108.

Although the effects of methamphetamine (MA) on the CNS have been well studied, less is known about the effects of MA in the periphery. In order to determine the potential interactions of MA and bacterial infection on the induction of inflammatory cytokines we treated U937-differentiated macrophages with bacterial LPS and MA (individually as well as in combination) and then measured cytokine production at the mRNA and protein levels. Treatment with both LPS and MA resulted in increased mRNA levels of TNF-α (57 ± 14.3-fold), IL-8 (24.3 ± 3.9-fold) and IL-1β (15.0 ± 7.0-fold), and also increased nuclear translocation of the p50 subunit of NF-κB. For all three cytokines, the level of induction seen when treated with both MA and LPS was higher than that observed when treated with LPS alone. Treatment of differentiated U937 cells with MA and LPS, along with the IKK inhibitor SC-514 significantly abrogated the expression levels of TNF-α (86.0%), IL-8 (73.1%) and IL-1β (47%). All expression levels are relative to inhibitor only. In order to determine the signaling pathways involved in the induction of these cytokines, cells were treated with inhibitors of p38 MAPK (SB203580), MEK1/2 (U-0126), and PI3K (LY294002). The induction of TNF-α was abrogated by treatment with all three inhibitors, while IL-8 induction was abrogated by the p38 and MEK1/2 inhibitors and IL-1β induction was abrogated only by the p38 inhibitor. These results indicate that MA and LPS interact to increase the induction of inflammatory cytokines in U937 macrophages. Supported by NIDA grant DA 025528.

CHRONIC MORPHINE INHIBITS WOUND HEALING BY MODULATING TLR4 SIGNALING. Ma J[1], Roy S[2]; [1]Department of Surgery, University of Minnesota, Minneapolis, MN 55455; [2]Departments of Surgery and Pharmacology, University of Minnesota, Minneapolis, MN 55455.

Skin injury evokes both innate and adaptive immune responses to restore tissue integrity. TLRs play a critical role in host responses to injurious insults. Previous studies demonstrated that chronic morphine administration delays wound healing by inhibiting immune cell recruitment to the wound site. In this study, we investigated the role of TLR2 and TLR4 in morphine modulation of neutrophil recruitment following injury. Full excisional wounds were created on the skin of wildtype (WT), TLR2(-/-) and TLR4(-/-) mice. Our results demonstrate that chronic morphine treatment of WT mice, significantly inhibited neutrophil recruitment and wound closure when compared to placebo treatment. Interestingly, wound closure was inhibited in placebo treated TLR2(-/-) mice when compared to placebo treated WT mice implicating a protective effect of TLR2 in wound closure. Chronic morphine resulted in a further decrease in neutrophil recruitment, significant delay in wound closure and greater inflammation in TLR2(-/-) mice. Interestingly morphine induced inhibition of both neutrophil recruitment and wound closure were abolished in the TLR4(-/-) mice. These results indicate that chronic morphine treatment inhibited neutrophil recruitment following wounding by modulating TLR4 signaling. The reduction in neutrophil recruitment was attributed to altered early expression of TNF-α and IL-1β. Taken together, our findings indicate differential regulation of wound healing by both TLR2 and TLR4 but morphine modulation of wound healing is mediated by activation of TLR4 signaling. Supported by RO1 DA12104, RO1 DA 022935, KO2 DA015349, P50 DA11806 (to S.R.).

COCAINE ACCENTUATES HIV DISEASE PROGRESSION BY DOWN REGULATING ANTI-HIV MIRNA “MIR-125B” IN CD4+ T CELLS. Mantri C[1], Pandhare J[1], Dash C[1]; [1]Laboratory of Retrovirology and Epigenetics, Center for AIDS Health Disparities Research, Vanderbilt Meharry Center For AIDS Research, Meharry Medical College, Nashville, TN 37221.

Epidemiological studies suggest that HIV positive cocaine users have: a) lower CD4+ T cell counts, b) accelerated decline of CD4+ T cells, c) increased risk of AIDS progression, and d) greater risk of AIDS-related death. However, neither the mechanism by which cocaine enhances HIV-1 pathogenesis nor the effects of cocaine on CD4+ T cell biology is clearly understood. Since CD4+ T cells are the primary targets for HIV-1 infection/replication, the first step to unravel the mechanism by which cocaine contributes to HIV/AIDS is to decipher how cocaine modulates CD4+ T cell biology. Uncovering cocaine-induced molecular alterations in CD4+ T cells will reveal novel pathways and potential biomarkers that will be instrumental in addressing the effects of cocaine on HIV pathogenesis. Micro-RNAs (miRNA) play a critical roles in innate immunity against infections. Drugs of abuse such as cocaine and methamphetamine alter the functioning of the immune system in several ways, making the immune cells vulnerable to infection. Our recent work demonstrates that cocaine down regulates anti-HIV miRNA, miR-125b, in naïve, resting as well as activated CD4+ T cells. Intriguingly, cocaine induced down regulation of miR-125b resulted in the activation of naïve CD4+ T cells and increase in HIV-1 replication. These findings suggest that cocaine may increase HIV disease progression by: 1) making the CD4+ T cells more susceptible to infection and 2) activating the naïve CD4+ T cell population and thereby accelerating CD4+ T cell decline. Details of these findings will be presented in the meeting. Supported by NIH/DA024558 and DA030896.

PROTEOMIC PROFILING OF MONOCYTE DERIVED MACROPHAGES DURING NANOART TREATMENT. Martinez-Skinner A[1], Veerubhotla R[1], Balkundi S[1], Liu H[1], Xiong H[1], McMillan J[1], Gendelman HE[1]; [1]Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68105.

Access to medicines in resource limited settings, malabsorption syndromes, drug toxicities and compliance limits the effectiveness of antiretroviral therapy (ART). To this end, nanoformulations of crystalline ART (nanoART) including ritonavir, atazanavir and efavirenz were developed in our laboratories for monocyte-macrophage based drug delivery demonstrating cell and tissue depots, reductions in viral replication, and limited systemic toxicities. Despite such benefits the effect on cellular functions remained unknown. To this end, we used proteomic approaches and notably, pulse stable isotope labeling of amino acids in cell culture (pSILAC), to evaluate macrophage function during nanoART carriage. A broad range of protein cluster changes were seen and included those linked to free radical scavenging, antigen presentation, cell mobility, phagocytosis, and cellular differentiation and development as well as modifications in lipid metabolism. These profiles were reflective of cell activation and coincided with electrophysiological changes in macrophage potassium channels. These data demonstrate how nanoART-macrophage interactions can facilitate drug loading and effect enhancements in macrophage ART carrying capacities to facilitate their role as cell drug depots. These results also illustrate the utility of this approach for targeted drug delivery for a broad range of patient needs during progressive viral infection. Supported by 1P01 DA028555, 2R01 NS034239, 2R37 NS36126, P01 NS31492, P20RR 15635, P01 MH64570, and P01 NS43985.

MORPHINE INCREASES INFLAMMATORY ACTIVITY IN THE INTESTINES BY INHIBITING MIR155 AND MIRNA146A. Meng J[1], Yu H[2], Banerjee S[1], Roy S[1]; [1]Department of Pharmacology, University of Minnesota, Minneapolis, MN 55455; [2]Department of Surgery, University of Minnesota, Minneapolis, MN 55455.

Inflammatory bowel disease is a pathological inflammatory condition of the bowel due to disruption of tolerance mechanism to gut microbiota and over-exuberant action of gut associated lymphoid tissue (GALT). The mu opioid receptor (MOR) has been implicated in the development and pathogenesis of inflammatory diseases since MOR antagonism improves clinical and inflammatory activities of patients with Crohn's disease, suggesting that aberrant MOR activation may be involved in excess gut inflammation. LPS exhibits a biphasic profile in proinflammatory cytokine activation. While short term treatment results in profound inflammatory cytokine

production, prolong treatment results in LPS tolerance. In the present study, we show that prolonged morphine treatment in vivo prevents LPS tolerance and leads to sustained activation of proinflammatory cytokines, TNF alpha, IL-6 and IL-17 in the mesenteric lymph node (MLN). Similar increase in IL-6 and IL-17 were observed ex vivo when MLN were stimulated with prolonged LPS treatment in the presence of morphine. Morphine's effects were also validated in J774 cell line. LPS induced miR155 and miR146a play important roles in mediating endotoxin tolerance. Our data show that morphine can decrease LPS-induced miR155 and miR146a production. Thus, we hypothesize that morphine can increase inflammatory activity in the intestines by inhibiting miR155 and miRNA146a production in GALT. This study for the first time provides a mechanism for the sustained gut inflammation following morphine treatment, paving the way for future therapeutic strategies. Supported by RO1 DA12104 ; RO1 DA022935; KO2 DA015349, P50 DA11806.

ENHANCED COCAINE SENSITIZATION IN ADULT FEMALE HIV-1 TRANSGENIC RATS. Moran LM[1], Booze RM[1], Webb KM[1], Mactutus CF[1]; [1]Department of Psychology, University of South Carolina, Columbia, SC 29208.

Drugs of abuse that act primarily on the dopaminergic (DAergic) system, such as cocaine (Coc), may exacerbate HIV-1 infection and consequent behavioral and neurological manifestations. Adult male rats that are administered an intra-accumbal infusion of the HIV-1 protein Tat show attenuated Coc sensitization compared to control animals. In the present study, we used the HIV-1 transgenic (Tg) rat, which constitutively expresses 7 of the 9 HIV-1 genes, to assess sensitization to Coc across repeated administration. Adult female Sprague-Dawley rats (HIV-1 Tg, n=9; control, n=11) were administered saline (day 1), followed by 10 days of Coc (10 mg/kg, i.p.) and a final Coc challenge after 7 days of abstinence. The distance traveled and time spent in the periphery of the locomotor activity test chamber were initially the same for the two groups, but distance traveled increased significantly in the HIV-1 Tg group relative to controls, and time spent in the periphery decreased at a slower rate in the HIV-1 Tg group relative to controls. The HIV-1 Tg group had significantly lower distance traveled and time spent in the center compared to the control group across all tests. Differences in Coc sensitization between the two groups are consistent with the emerging alterations in the DA system reported in this animal model and suggest functional consequences of chronic low level of exposure to the HIV-1 proteins which resemble the suppression of infection in HIV-1 positive individuals under combined antiretroviral therapy. Supported by DA013137; HD043680.

MARIJUANA USE MAY INCREASE SUSCEPTIBILITY TO HIV INFECTION AND NEUROINFLAMMATION. Munsaka SM[1], Feger U[1], Nerurkar V[2], Chang L[1]; [1]University of Hawaii, John A. Burns School of Medicine, Department of Medicine, Honolulu, HI 96813; [2]University of Hawaii, John A. Burns School of Medicine, Department of Tropical Medicine, Medical Microbiology and Pharmacology, Honolulu, HI 96813.

Cannabinoids modulate cellular immune responses and alter cytokine secretion in vitro. The goal of this study was to examine the effects of marijuana on peripheral and CNS immune markers in marijuana (MJ) and HIV+marijuana (HIV+MJ) users. PBMCs were isolated from HIV+MJ users, n=18, HIV subjects, n=14, HIV-seronegative MJ users n=11 and seronegative controls (SN, n=14). Cells were stained for CD16 and CCR5 and were analyzed by flow cytometry. CSF cytokine expression from age-matched subjects was measured by Luminex. Inflammatory CD14+CD16+ monocytes were significantly higher in HIV+MJ users than HIV+ subjects (23.1% vs. 11.9%, $p=0.004$), and in MJ users compared to SN subjects (25.7% vs. 10.2%, $p<0.001$). The CD14+CD16+ phenotype correlated positively with the amount of lifetime marijuana use ($r=0.56$, $p=0.027$). CCR5 expression was higher in MJ users than SN subjects (24.5% vs. 8.4%, $p=0.003$), however; HIV+MJ users had lower CCR5 expression than HIV subjects (13.4% vs. 18.5%, $p=0.011$). Inflammatory cytokines were higher in the HIV+MJ users than the other three groups ($p<0.05$). Higher amounts of inflammatory monocytes in HIV+MJ and MJ groups, and their correlation with lifetime MJ use, suggest THC-induced inflammation in the periphery. Higher CCR5

expression in MJ users than SN subjects, but lower expression in HIV+MJ users than HIV subjects, suggests that MJ use may render SN more susceptible to HIV infection but may be downregulated in HIV. Furthermore, the higher expression of inflammatory cytokines in CSF of HIV+MJ suggests that marijuana may promote neuroinflammation. Supported by NIMH (2R01MH61427); NIDA (2K24DA16170); NINDS & NIDA (U54NS56883); NCRR (5P20RR016467).

INFLAMMATORY EFFECTS ON NEURONAL AUTOPHAGY. Ninemire C[1], Fox HS[1]; [1]Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198.

Neuroinflammation caused by HIV, has demonstrated altered autophagy rates in neurons. Autophagy clears long-lived proteins, organelles and protein aggregates. The normal or enhanced activity of this system has become a common theme in protection from neurodegenerative diseases. The activated immune response from neuroinflammation creates a harsh environment for cellular homeostasis, given this state of cytotoxicity, we propose the autophagy process is hindered through signaling pathways of released cytokines from glial cells and preventing neuronal survival. Here we will study the relationship between autophagy and neuroinflammation from HIV infection. Previous work in our group found neuronal autophagy of primary neurons to be altered by SIV infected supernatant. Our goal is to tease out the component(s) of the immune response that is affecting neuronal autophagy. First we will screen individual cytokines and measure the effects on autophagy in differentiated SH-SY-5Y cells. LC3-II, a marker for autophagosomes, will be measured on a western blot analysis to determine the cytokine effect on autophagy changes. Preliminary data reveals TNFα decreasing autophagic flux in the presence of a neuronal autophagy inducer, N10-substituted phenoxazine (10-NCP), which works through an mTOR-independent pathway. The next step will look at the receptor and pathway of the cytokine signaling in SH-SY-5Y and how it affects the autophagy process. The biochemical process of cytokine signaling will unravel the mechanism of autophagy disruption and subsequent neurodegeneration in neuroAIDS. Supported by R01 MH073490.

CHRONIC MORPHINE TREATMENT DIFFERENTIALLY MODULATES MACROPHAGE PHAGOCYTIC AND BACTERICIDAL MECHANISMS FOLLOWING TLR2 AND TLR4 ACTIVATION. Ninkovic J[1], Roy S[1]; [1]Department of Surgery, Division of Basic and Translational Research, School of Medicine, University of Minnesota, Minneapolis, MN 55455.

The most frequent community acquired opportunistic infection in opioid abusers is infection with Gram-positive (G+) Streptococcus pneumoniae. To our knowledge, no studies have investigated if morphine treatment differentially modulates clearance of (G+) vs (G-) bacteria by macrophages. Upon infection, bacterial clearance is initiated by phagocytosis followed by bactericidal mechanisms. In this study, we show that chronic morphine treatment leads to greater intracellular bacterial growth of (G+), when compared to (G-) bacteria which selectively activate TLR2 and TLR4 respectively. We first investigated if morphine modulates TLR expression and if TLR activation contributes to the differential effects of morphine on phagocytosis of (G+) and (G-) pathogens. Our results show that chronic morphine treatment upregulates TLR2 and TLR4 expression. Interestingly, activation of TLR2 alone led to decreased, while activation of TLR4 led to increased bacterial phagocytosis in both vehicle and morphine treated cells. These differential effects of TLR activation on phagocytosis are abolished in macrophages isolated from TLR2KO and TLR4KO mice. Additionally, bactericidal mechanisms such as ROS release and phagosomal maturation were more significantly suppressed in chronic morphine treated macrophages following internalization of (G+) when compared to (G-) bacteria. Based on these observations we conclude that morphine induced-increase in TLR2 expression and activation by (G+) bacteria leads to decreased phagocytosis and bacterial killing, thereby increasing susceptibility to (G+) infection. Supported by F31 DA026264-01A1 (to JN) and RO1 DA12104, RO1 DA12104, RO1 DA022935, KO2 DA015349, P50 DA11806 (to SR).

DIFFERENTIAL EFFECTS OF HIV-1 CLADE B AND CLADE C ON THE EXPRESSION OF SILENT INFORMATION REGULATOR2 HOMOLG-1 (SIRT1). Pichili VB[1], Nair MP[1]; [1]Department of Immunology, Institute of NeuroImmune Pharmacology, Herbert Wertheim College of Medicine, Florida International University, Miami, FL 33199.

Silent Information Regulator2 Homolg-1 (SIRT1) is a class III deacetylase sirtuin, a mammalian homologue of the yeast transcriptional repressor silent information regulator 2 homolog-1. SIRT1 is involved in regulation of aging, oxidative stress, metabolism control, mitochondrial anti-oxidant capacity. Recently, SIRT1 has been shown to have a physiological role in learning, memory, neuronal plasticity and cognition in mice. SIRT1 requires nicotinamide adenine dinucleotide (NAD+) as a cofactor, which links its activity to the metabolic state of the cell and is dependent on the redox state of the cell. HIV infection is known to hamper the redox status by decreasing the levels of NAD. Alteration in the NAD/NADH ratio affects the SIRT1 activity. We hypothesize that HIV viral infection significantly inhibits SIRT1. Further, we hypothesize that clade B and C virus exhibit differential effects in neural cells by down regulating SIRT1. Primary human astrocytes were separately infected with HIV-1 clade B and clade C virus. RNA was extracted, reverse transcribed and analyzed by qRTPCR. Cell lysates were prepared and analyzed by western blots to examine the protein expression levels. Results indicate that HIV-1 clade B significantly down regulated the expression of SIRT1 gene, protein as well as enzyme activity as compared to the Clade C virus in identical astrocyte cultures. These studies suggest that SIRT1 may play a role in the neuropathogenesis and differentially regulated in HIV clades and may be of therapeutic significance. Supported by NIH Grants RO1DA021537,R37DA025576.

COCAINE DOWN REGULATES MICRORNA-146A WITH A RECIPROCAL UPREGULATION OF CXCR-4: IMPLICATIONS IN HIV IMMUNOPATHOGENESIS. Pilakka-Kanthikeel S[1], Napuri J[1], Nair MP[1]; [1]Department of Immunology, Institute of NeuroImmune Pharmacology, Herbert Wertheim College of Medicine, Florida International University, Miami, FL 33172.

Drugs of abuse like cocaine and morphine modulate HIV co-receptor / chemokine receptor expression leading to increased immunopathogenesis of HIV infection. CXCR-4 is previously shown to be a target for microRNA (miR)-146a. Based on this, we hypothesize that cocaine down regulates miR-146a with a reciprocal upregulation of CXCR-4 expression, making the cells more susceptible to HIV infection. Monocyte Derived Dendritic cells from normal healthy individuals were transfected with miR-146a mimic and miR-146a specific inhibitor in separate experiments, followed by cocaine (1-10nM) treatment for 48 hrs. Non-transfected cells served as controls. Transfected and non-transfected cells were analyzed for the expression of CXCR-4 by flow-cytometer and miR-146a by quantitative RT-PCR. Cocaine significantly suppressed miR-146a and upregulated CXCR-4 expression in a dose dependent fashion. Transfection of miR-146a mimic reversed cocaine mediated CXCR-4 upregulation, whereas transfection with miR-146a inhibitor increased expression of CXCR-4. These results suggest that cocaine plays an important role in immune pathogenesis of HIV infection potentially, by down regulating miR146a leading to upregulation of CXCR-4 receptors. Further studies on the role of miR-146a are of therapeutic significance in cocaine using HIV infected subjects. Comparison between groups was made with the Student's t-test or Mann–Whitney test. $p<0.05$ was considered significant. Supported by 5R01DA027049 and 1R37DA025576.

INVOLVEMENT OF GLIAL CCR5 IN MORPHINE AND TAT-MEDIATED NEURODEGENERATION. Podhaizer EM[1], Zhang Y[2], Knapp PE[3], Hauser KF[1]; [1]Pharmacology & Toxicology, Virginia Commonwealth University, Richmond, VA 23298; [2]Medicinal Chemistry, Virginia Commonwealth University, Richmond, VA 23298; [3]Anatomy & Neurobiology, Virginia Commonwealth University, Richmond, VA 23298.

Opioid abuse enhances the pathogenesis of HIV-1. Previous studies showed that combined morphine and Tat produce synergistic neurotoxicity and this is dependent on glia. CCR5 is well known for its interactions with gp120 to mediate HIV-1 infection, but may also interact with Tat

indirectly. Additionally, CCR5's interactions with the mu-opioid receptor make it a good target to assess opioid-HIV-1 interactions. We hypothesized that glial CCR5 mediates morphine and Tat interactive neurodegeneration. To determine CCR5's involvement, neuronal survival was assessed with morphine, Tat, or the combination, in the presence or absence of the CCR5 antagonist, maraviroc (MVC). MVC selectively blocked the interactive toxicity of the combined treatments. CCR5 inhibition also suppressed modest reductions in neurite length in response to morphine and Tat treatment. An experiment using CCR5-/- glia showed a significantly delayed onset of the neurotoxic response and suppressed morphine and Tat toxicity, suggesting that glial CCR5 is critical for morphine and Tat's neurotoxic effects. Because of the role of CCR5 in glial inflammatory signaling, NF-κB p65 nuclear translocation and cytokine/chemokine release were assessed. MVC produced a modest but significant decrease in NF-κB activation and suppressed RANTES and MCP-1 secretion. Activation of CCR5 by beta-chemokine ligands showed neurotoxicity, suggesting that Tat and morphine's upregulation of CCR5 ligands by glia appear to be one mechanism by which opioids and HIV-1 proteins mediate their neurodegenerative effects. Supported by NIDA P01 DA019398, T32 DA007027.

N-FORMYL-METHIONINE-LEUCINE-PHENYLALANINE (FMLP) COATED NANOART. Puligujja P[1], Meyer J[1], McMillan J[1], Gendelman HE[1], Liu X[1]; [1]Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68128.

Our laboratories developed the idea that mononuclear phagocytes (MP; monocytes, dendritic cells and macrophages) can be used as carriers for antiretroviral therapy (ART). To this end ritonavir, atazanavir and efavirenz nanoformulations (called, nanoART) were manufactured and tested for entry, release, and antiretorivral activities in primary cells. The formulations were coated with an activating and chemotactic peptide, N-formyl-methionine-leucine-phenylalanine (fMLP)-modified poloxamer to facilitate cell targeting. We theorized that fMLP would stimulate the MP, enhancing particle uptake while causing down-regulated CCR5 and CXCR4, thereby inhibiting virus. Thus, fMLP-tagged nanoART were made with sizes of 269-277 nm, zeta potentials of -17.1 to -19.2 mv and polydispersities of 0.144-0.166. Micellar formulations were < 50 nm with PDIs of 0.17-0.23. Integrity of the fMLP coating was substantiated by 1H nuclear magnetic resonance studies. Cell uptake was assessed from 1 to 8 hours with/out stimulation with lipopolysaccharide, tumor necrosis factor alpha (TNF-α) + interferon gamma (IFN-γ) or granulocyte colony stimulating factor. Our results demonstrate that fMLP coated particles show enhanced uptake into human monocyte-derived macrophages, regardless of stimulus with the greatest effect in TNF-α + IFN-γ stimulated cells. Flow cytometry assays confirmed altered macrophage phenotypes. We posit that accelerated particle uptake and immune modulatory functions of fMLP-tagged nanoART make it an attractive candidate for development as a vehicle for antiretroviral drug delivery. Supported by Carol Swarts, MD Neuroscience Lab, NIH 1P01 DA028555, 2R01 NS034239, 2R37 NS36126, P01 NS31492, P20RR 15635, P01 MH64570, P01 NS43985.

DETERMINING THE ROLE OF A UNIQUE POPULATION OF ACTIVATED CD8+ T CELLS IN THE BRAIN AFTER HIV INFECTION. Richards MH[1], Poluektova L[2], Al-Harthi L[1]; [1]Department of Immunology and Microbiology, Rush University Medical Center, Chicago, IL 60612; [2]Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198.

CD8+ T cells play a critical role in anti-HIV immunity. They infiltrate the brain early in HIV/SIV infection but their role, whether pathogenic or protective, in the brain is unclear. In the delicate environment of the CNS, highly activated CD8+ T cells may on one hand control HIV replication but on the other lead to bystander damage through inflammatory mediators. We and others have identified a unique subset of highly activated CD8+ T cells that express CD4 dimly on their surface (double positive (DP) T cells). DP T cells account for approximately 60% of HIV- specific T cell responses in HIV Long Term Non-Progressors. Using the NOD/SCID/IL-2rγc-/- (NSG) mice reconstituted with human peripheral blood lymphocytes, we identified DP T cells in the brain. DP T

cells constituted 5-10% of the CD3+ T cell population in the brain. Both DP T cells and CD4 single positive T cells were permissive to HIV infection, at three weeks post-infection the majority of CD4 single positive T cells were depleted while the DP T cells remained. Interestingly, culturing of human progenitor-derived astrocytes with supernatants from primary activated CD8+ T cell that are enriched in DP T cells caused a significant activation of astrocytes, as measured by expression of IFNγ and HLA-DR. These data demonstrate the presence of DP T cells in the CNS which persist despite HIV infection. They also provide a model by which astrocytes and inflammatory mediators from activated CD8+ T cells can lead to CNS activation and pathogenesis. Supported by R01NS060632-LA.

CYSTATIN B INHIBITS THE IFN-β RESPONSE BY PREVENTING STAT-1 TRANSLOCATION AND DECREASING LEVELS OF STAT-1PY: IMPLICATION OF HIV REPLICATION IN MACROPHAGES. Rivera-Rivera L[1], Colón K[1], Meléndez LM[1]; [1]Department of Microbiology and NeuroAIDS Program, University of Puerto Rico-Medical Sciences Campus, San Juan, 00935.

Our group recently showed that Cystatin B, a cysteine protease inhibitor, is upregulated in blood monocyte-derived macrophages (MDM) compared to placental macrophages, which are less susceptible than MDM to HIV-1 infection. Intracellular expression of cystatin B was increased in HIV-1-infected MDM at 12 dpi and in the secretome of HIV-infected MDM, suggesting that this protein is activated during HIV infection. A direct connection between cystatin B and HIV replication was demonstrated using small interfering RNA against cystatin B. Subsequently, the signaling mechanisms for cystatin B in HIV replication were related to its interaction with signal transducer and activator of transcription-1 (STAT-1). Whereas STAT-1 activates HIV-1 replication, high levels of tyrosine phophorylated STAT-1 (STAT-1PY) have been associated with HIV-1 inhibitory activity. In MDM, high levels of cystatin B and low levels of STAT-1PY may promote HIV replication. In the present study, we used luciferase reporter gene assays, immunofluorescence and western blots in Vero cells, which are IFN deficient. We demonstrated that cystatin B inhibited the IFN-β response in Vero cells by preventing STAT-1 translocation to the nucleus and decreasing levels of STAT-1PY. The discovery of this mechanism of cystatin B regulation of STAT-1 phosphorylation could inform the development of new therapeutic that aim to inhibit the long terminal repeat (LTR)-mediated HIV replication by modulating the site of STAT1 phosphorylation in favor of tyrosine instead inhibiting STAT-1 expression. Supported by NIH grants R01 MH083516-01.

DEPRESSION MANAGEMENT RESULTS IN INCREASED TREATMENT ADHERENCE AND IMPROVED IMMUNE SYSTEM FUNCTION IN HIV-1 INFECTED PUERTO RICANS. Rivera-Rivera Y[1], Toro V[1], Cappas-Ortiz N[1], Rivera-Amill V[1]; [1]Microbiology Department, Ponce School of Medicine & Health Sciences, Ponce, 00717.

Human immunodeficiency virus is characterized for its effects on the immune system and also at the oxidant/antioxidant homeostasis. Depression plays a crucial role in the HIV/AIDS progression and health status of HIV-1 infected population. Our long term goal is to promote mental health among people diagnosed with HIV/AIDS through an integrated health care service to positively influence overall physical health and maintenance of an effective antiretroviral treatment resulting in fuller, more productive lives. Our objective is to assess the impact of integrated medical health care in depression levels and CART (combination antiretroviral therapy) adherence on immunological system function and oxidant/anti-oxidant balance in patients with HIV/AIDS. A retrospective study by Toro et al. 2011 indicated that the average level of depression in HIV-infected patients was significantly lower than the initial value and patients with ≤90% adherence demonstrated a significant improvement on their adherence to antiretroviral treatment following an integrated behavioral care intervention. In addition, the average HIV viral load (2,205.13 ± 7,557.22) was significantly lower than the initial value (54,278.38 ± 54,592.39, $p<.05$). Based on these observations, the work proposed herein will specifically address the how management of depression and CART treatment adherence affect immune system parameters (viral load, T cell counts, and the inflammatory profile) and determine if the intervention at the patient-health care

provider interaction can change the oxidant/antioxidant balance. Supported by NCRR-RCMI RR003050.

IN VIVO WEST NILE VIRUS INFECTION MODULATES THE MARKERS OF BLOOD-BRAIN BARRIER INTEGRITY. Roe K[1], Kumar M[1], Lum S[1], Orillo B[1], Nerurkar VR[1], Verma S[1]; [1]Department of Tropical Medicine, Medical Microbiology and Pharmacology, University of Hawaii at Manoa, Honolulu, HI 96813.

West Nile virus (WNV) encephalitis is characterized by neuroinflammation, neuron death and blood-brain barrier (BBB) disruption. However, the mechanisms associated with BBB disruption are unclear. Interactions between tight junction proteins (TJP) and adherens junction proteins (AJP) of the brain microvascular endothelial cells are responsible for maintaining BBB integrity. Herein, we characterized the relationship between BBB disruption and expression kinetics of key TJP, AJP and matrix metalloproteinases (MMPs) in the mice brain following WNV infection. A dramatic increase in BBB permeability was observed at later time points of central nervous system (CNS) infection and did not precede virus-CNS entry. WNV-infected mice exhibited significant reduction in the protein levels of TJP and AJP which correlated with increased levels of MMPs and infiltrated leukocytes in the brain. Intracranial inoculation of WNV also demonstrated increased extravasation of IgG and MMP expression in the brain implicating virus replication in the CNS in BBB disruption. These data suggest that altered expression of junction proteins is a pathological event associated with WNV infection and may explain the molecular basis of the BBB disruption. We propose that during high viremia, early virus entry and replication in the brain leads to the initiation of the BBB disruption, followed by unrestricted entry of the leukocytes and a second wave of WNV into the CNS. These data further implicate role of MMPs in BBB disruption and strategies to interrupt this process may influence the WNV disease outcome. Supported by Hawaii Community Foundation (20050405), RCMI Program (G12RR01) and COBRE (P20RR018727).

GLYCOGEN SYNTHASE KINASE 3β (GSK3β) INHIBITION PREVENTS MONOCYTE (MO) MIGRATION ACROSS BLOOD BRAIN BARRIER (BBB) VIA SUPPRESSION OF RAC1-GTPASE AND FUNCTIONAL ACTIVATION OF β-INTEGRIN. Rom S[1], Reichenbach NL[1], Fan S[1], Dykstra H[1], Ramirez S[1], Persidsky Y[1]; [1]Department of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140.

GSK3β was identified as a potent regulator of immune responses; however, its effects in leukocytes remain largely undefined. Here, we tested the idea that GSK3β inhibition in Mo can diminish their ability to engage brain endothelium and migrate across the BBB. TNF-α stimulation of human brain microvascular endothelial cells (BMVEC) and application of relevant chemokines in BBB models increased Mo adhesion/migration (5-7-fold). Mo pretreatment with inhibitors diminished adhesion (50%) and migration (90%). Mo interactions with BMVEC decreased transendothelial electrical resistance (measure of barrier integrity). GSK3β suppression in Mo led to substantial attenuation of BBB injury. As β-integrins (like very late antigen, VLA-4) play a crucial role in Mo rolling and adhesion, we studied functional activation of VLA-4 after stimulation with a peptide mimicking Mo engagement by VCAM-1. Peptide stimulation resulted in 14-20-fold up-regulation of active VLA-4 in Mo; VLA-4 was suppressed 40-60% by GSK3β inhibitors. Since small GTPases like Rac1 control leukocyte movement, we assessed Rac1 activation in Mo with relevant stimuli and showed its suppression by GSK3β inhibitors. Cells treated with GSK3β inhibitors showed increased levels of phosphorylated (inhibitory) sites of actin-binding proteins, cofilin and vasodilator-stimulated phosphoprotein, which control functional activation of beta-integrins. In summary, these results indicate that inhibition of GSK3β directly affects cytoskeleton rearrangement and adhesion via suppression of Rac1 suppressing inflammatory leukocyte responses. Supported by NIAAA/AA015913, NIMH/MH65151.

DIFFERENTIAL PROLIFERATION OF NEURAL STEM/PROGENITOR CELLS DURING HERPES SIMPLEX ENCEPHALITIS. Rotschafer JH[1], Cheney-Peters D[1], Cheeran MCJ[1]; [1]Veterinary

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Endogenous neural stem/progenitor cells (NSCs) respond to inflammatory cues in the brain to proliferate, migrate, and differentiate into neurons or glial cells. However, little is known about NSC response to inflammation during herpes encephalitis (HSE). Using a murine model for HSE, change in numbers of endogenous NSCs was studied at 3, 6, 10, 15, and 30 days post infection (d.p.i). A transient increase in the number of Nestin(+)CD45(-) cells was observed at 6 d.p.i, but this NSC population decreased significantly at 15 and 30 d.p.i. This transient increase correlated with increased expression of ki67 in CD45(-) brain cells at 3-6 d.p.i. which subsequently decreased through 30 d.p.i. Proliferating cell nuclear antigen (PCNA) was localized primarily to doublecortin expressing neuroblasts and Sox2 expressing NSCs at 3 d.p.i but was not detected at 15 d.p.i. These data suggest differential temporal modulation of proliferative responses in the brain during HSE. Gene expression analysis was performed by RT-PCR to identify factors inhibiting neurogenesis during chronic HSE. Among the genes assessed, bone morphogenic protein-4 and fibroblast growth factor-2 were substantially down regulated in HSE. Studies are underway to identify mechanisms by which modulation of growth factor alters neurogenesis during HSE. Insights obtained from these studies may help identify points of intervention for new therapeutic and preventative strategies to combat neurological deficits ensuing viral encephalitis. Supported by NINDS/RO1 NS065817, NIDA/T32 DA007097.

IMAGING DENDRITIC CELL TRAFFICKING INTO THE CENTRAL NERVOUS SYSTEM DURING STEADY-STATE AND UNDER NEUROINFLAMMATION. Sagar D[1], Lamontagne A[1], Foss C[2], Khan Z[1], Pomper M[2], Jain P[1]; [1]Department of Microbiology and Immunology, PA Biotech Center, Drexel University College of Medicine, Doylestown, PA 18902; [2]Department of Radiology, Johns Hopkins University, Baltimore, MD 21231.

In healthy individuals, infiltration of dendritic cells (DCs) and other lymphocytes into the central nervous system (CNS) is tightly controlled by the highly specialized blood-brain barrier (BBB). Our interest lies in elucidating the path that DCs take while transmigrating across the BBB into an inflammed CNS. We detected the migration of DCs and other leukocytes by non-invasive in vivo imaging (Near Infra-Red, SPECT-CT, and bioluminescence) in mice with experimental autoimmune encephalomyelitis and glioblastoma multiforme. Moreover, histology confirmed MCP-1 presence in brain EAE lesions colocalizing with DCs emerging from perivascular spaces. To further characterize mechanism of DC trafficking, we utilized an in vitro BBB model consisting of human brain microvascular endothelial cells (HBMECs). In these studies, both non-activated and activated DCs exhibited a more efficient transmigration pattern during steady-state as well as under the influence of MCP-1. Extensive in vitro imaging of DCs along with HBMECs in transwells confirmed our observations and suggested an early breach of BBB permeability by MCP-1 supported by its colocalization with CCR2 receptor on HBMECs. Overall, these one of-a-kind comprehensive studies are first to demonstrate that MCP-1 is important in chemoattraction of DCs to the BBB, making these cells more responsive to neuroinflammation. Our results also suggest that MCP-1-mediated breach of the BBB permeability allows an easy passage to all types of leukocytes; however, chemoattraction itself could be influenced by cell type and cellular activation.

AGE AND ETHANOL CONCENTRATION-DEPENDENT EFFECTS OF ACUTE BINGE DRINKING IN THE HIV-1 TRANSGENIC RAT. Sarkar S[1], Mao X[1], Liu C[1], Chang SL[1]; [1]Institute of NeuroImmune Pharmacology, Seton Hall University, South Orange, NJ 07079.

Binge drinking is a common form of alcohol abuse. Alcoholic beverages vary significantly in ethanol (EtOH) concentration. We previously showed EtOH concentration dependent activation of supraoptic nucleus in the hypothalamus. In HIV infected population, incidence of alcohol abuse is 50%. We reported age dependent expression of HIV-1 viral proteins in HIV-1 transgenic (HIV-1Tg) rat. Thus, we hypothesized that there are age and EtOH concentration dependent effects of binge drinking in the HIV-1 infected population. Blood EtOH concentration (BEC) was measured in F344 rats after gavage (i.g.) administration of 0%, 20%, or 52% EtOH. Using absolute quantitative real-

time RT-PCR, we compared expression of HIV-1 viral protein, Tat, in brain, spleen, and liver of adult and adolescent HIV-1Tg rats following i.g. administration of 0% 20% or 52% EtOH for 3 d (4.8 g/kg per d). We also assessed age dependent motor function deficits in HIV-1Tg rats 1 d after exposure to 20% EtOH. BEC was significantly higher in the 52% group compared to the 20% group at 90 min post treatment. In adults, Tat expression (copies/μg of total RNA) was significantly increased in the brain, liver, and spleen of the 52%, but not the 20% group. In adolescents, Tat expression was increased in the brain and liver of the 52% group, but not in spleen. A significant reduction in locomotor activity occurred in EtOH-treated adult HIV-1Tg rats, although no difference was observed in adolescents. Our data indicate that binge drinking can have age and EtOH concentration dependent effects in the course of HIV-1 infection. Supported by K02 DA016149 & RC2 AA019415 to SL Chang.

MODULATION OF EXPERIMENTAL HERPES ENCEPHALITIS-ASSOCIATED NEUROTOXICITY THROUGH SULFORAPHANE TREATMENT. Schachtele SJ[1], Hu S[1], Lokensgard JR[1]; [1]Center for Infectious Disease & Microbiology Translational Research, University of Minnesota, Minneapolis, MN 55455.

Reactive oxygen species (ROS) produced by brain-infiltrating macrophages and resident microglia are pivotal to pathogen clearance during viral brain infection. Unchecked free radical generation is also responsible for damage and toxicity of host tissue bystander to the primary infection. The unwanted effects of excessive ROS are combated by local cellular production of antioxidant enzymes, including heme oxygenase-1 (HO-1) and glutathione peroxidase-1 (Gpx1). In this study, we show that experimental murine herpes encephalitis triggers robust ROS production and antioxidant upregulation in the brain. This antioxidant response is insufficient to prevent neurotoxicity and mortality associated with viral brain infection. We hypothesized that enhancing antioxidant responses in astrocytes, the major free radical combating cell in the brain, would mitigate the effects of ROS-mediated neurotoxicity both in vitro and during viral brain infection. We demonstrate that sulforaphane (SFN), a potent stimulator of antioxidant responses, enhanced HO-1 and Gpx1 expression in astrocytes through the activation of the nuclear factor-E2-related factor 2 (Nrf2). SFN treatment was effective in reducing neurotoxicity associated with HSV-stimulated microglial ROS production. Systemic injections of SFN during active HSV infection reduced neuroinflammation via a decrease in brain-infiltrating leukocytes, macrophage-produced ROS, and activated microglia. These data support a key role for astrocyte-associated antioxidants in modulating oxidative stress and neuronal damage in response to viral infection. Supported by R01MH-066703 from the National Institute of Mental Health.

SIGNALING MECHANISMS INVOLVED IN METHAMPHETAMINE-MEDIATED INCREASE IN THE EXPRESSIONS OF IL-6/IL-8 IN ASTROCYTES. Shah A[1], Kumar A[1]; [1]Pharmacology & Toxicology, University of Missouri-Kansas City, Kansas City, MO 64108.

Methamphetamine (MA) is one of the most commonly used drugs of abuse and CNS toxicity of MA is well documented, but the mechanisms contributing to this toxicity have not been fully elucidated. In this study, we investigated the effect of MA on the proinflammatory cytokines/chemokines, IL-6 and IL-8 in an astrocytic cell line. The IL-6/IL-8 levels were found to increase by 4.6 ± 0.2 fold and 3.5 ± 0.2 fold, respectively, after exposure to MA for 3 days. The involvement of the NF-κB pathway was explored as one of the possible mechanism(s) responsible for the induction of IL-6 and IL-8 by MA. We found that exposure of astrocytes to MA results in activation of NF-κB through the phosphorylation of IκB-α, followed by translocation of NF-κB from the cytoplasm to the nucleus. The MA-mediated increases in IL-6/IL-8 were significantly abrogated by SC514, an IKK antagonist. In addition, treatment of cells with a specific inhibitor of mGluR5 revealed that MA-mediated expression levels of IL-6 and IL-8 were abrogated by this treatment by 42.6 ± 5.8 % and 65.5 ± 3.5%, respectively. Also, LY294002, an inhibitor of the Akt/PI3K pathway abrogated the MA-mediated induction of IL-6 and IL-8 by 77.9 ± 6.6 % and 81.4 ± 2.6 %, respectively. Thus, our study demonstrates the involvement of an NF-κB-mediated signaling

mechanism in the induction of IL-6 and IL-8 by MA. Furthermore, we showed that blockade of mGluR5 can protect astrocytes from MA-mediated increases of proinflammatory cytokines/chemokines suggesting mGluR5 as a potential therapeutic target in treating MA-mediated neurotoxicity. Supported by NIDA (DA025528).

MORPHINE AND HIV-1 TAT AS COMORBIDITIES ADDITIVELY REDUCE GUT BARRIER FUNCTION. Sindberg G[1], Meng J[2], Molitor T[1], Roy S[3]; [1]Veterinary Population Medicine, College of Veterinary Medicine, University of Minnesota, Saint Paul, MN 55108; [2]Department of Pharmacology/Medical School, University of Minnesota, Minneapolis, MN 55455; [3]Basic and Translational Research Division/Department of Surgery/Medical School, University of Minnesota, Minneapolis, MN 55455.

Much recent attention has been placed on the role of gut homeostasis as the source of inflammation for HIV progression to AIDS. As a comorbidity to HIV, opiates have been observed to enhance pathogenesis of HIV, but these interactions have primarily been studied in the CNS. Studies in humans or primates imply that gut epithelial cells are affected by both HIV/SIV and morphine separately; however these models have drastic limitations for studying gut that do not allow the effects to be directly examined. Given that HIV-1 Tat is the first protein translated upon infection and has broad effects on multiple cells, we examine its effect on epithelial cell lines, as well as gut tissues from the murine Tat86 transgenic model, with or without the addition of morphine. Our results show that chronic morphine in Tat86 mice additively enhances bacterial translocation and disrupts tight junctions measured by immunofluorescence of tight junction proteins occludin/ZO-1. Both Caco2 (human large intestine) and IEC-6 (rat small intestine) cell lines show a decrease in barrier function mediated by Tat in the presence of morphine and exacerbated by TLR2 (LTA) and TLR2 (LPS) signaling using trans-epithelial resistance (TER). Notably, these additive effects are observed in both small and large intestine, whereas morphine alone has effects in the small intestine only. Based on these observations, we conclude that morphine and HIV-1 Tat have additive effects as comorbidities, which likely contributes to the enhanced inflammation and pathogenesis observed in opiate using HIV patients. Supported by NIH/T32 DA007097, NIH/RO1 DA12104, NIH/RO1 DA022935, NIH/KO2 DA015349, NIH/P50 DA11806.

DETECTION OF CIRCULATING PLATELET-MONOCYTE COMPLEXES IN HUMAN IMMUNODEFICIENCY VIRUS TYPE-1 INFECTED INDIVIDUALS. Singh MV[1], Davidson DC[1], Kiebala M[1], Maggirwar SB[1]; [1]Department of Microbiology and Immunology, University of Rochester Medical Center, Rochester, NY 14642.

Activated platelets form transient aggregates with monocytes in circulation and have a half-life of approximately 30-60 minutes. These complexes are increased in various inflammatory conditions and are an early marker of myocardial infarction. Chronic inflammation is one of the hallmarks of HIV infection. Increased CD16+ inflammatory monocytes have been observed in these individuals, especially in CNS of individuals with HIV-associated encephalopathy, probably as a result of increased interaction with platelets. However, narrow detection period and platelet activation during sample processing pose significant problems in detecting platelet-monocyte complexes (PMCs). We have standardized a method addressing these difficulties, to enumerate PMCs involving CD16+ or CD16- monocytes in whole blood using flow cytometry. Blood collected from healthy individuals was treated with either collagen (for platelet activation) or LPS (for monocyte activation) and subsequently used to study effect of these treatments on PMC formation. We also validated the use of this method to quantify PMCs ex vivo in HIV infected individuals. Our in vitro results demonstrate that platelet activation, but not monocyte activation, resulted in significant increase in PMC formation. In HIV infected individuals there was a significant increase in CD16+ PMCs and platelet activation, when compared with HIV uninfected control individuals. Furthermore, PMC percentages correlated positively with platelet activation. These findings

improve our ability to detect PMCs and shed light on HIV pathogenesis. Supported by National Institute of Health grants RO1 NS054578 and RO1 NS066801.

MODULATION OF NA-K ATPASE ACTIVITY OF RAT BRAIN SYNAPTOSOME BY NOREPINEPHERINE AND SEROTONIN. Sinha S[1,2], Mallick BN[2], Sundaram S[1]; [1]Centre for Biotechnology, University of Allahabad, Allahabad, 211002; [2]School of Life Science, Jawaharlal Nehru University, New Delhi, 110067, India.

Sleep and wakefulness are behavioral and physiological activities. It is a modified form of the basic rest activity cycle. Humans usually fall asleep by entering in non Rapid Eye movement sleep, a phase accompanied by characteristic changes in the Encephalogram (EEG). The person next moves to REM sleep, which is characterized not only by rapid eye movements but also by inhibition of skeletal muscle tone. These two states alternate with each other during sleep cycle. It has been found that REM sleep is generated as a result of excitation of Cholinergic PS on neurons and inhibition of monaminergic PS off neurons. Moreover the REM sleep deprivation induced increase in Na-K ATPase activity which is partially mediated by NE. Serotonin has been found to increase during REM sleep. These facts implicate that both serotonin and norepinepherine are involved during REM sleep. The present study has been initiated to find out the effect of Norepinepherine and Serotonin and the blockers Prazosin and Propranolol in different permutations and combinations on Na-K ATPase activity. Brain from the male wistar rats was extracted and subjected to homogenization, synaptosome was prepared and Na-K ATPase activity was estimated under the influence of NE, 5HT, Prazosin and Propranolol in different combinations. Both NE and 5HT increase the Na-K ATPase activity individually and also synergistically when used in combination but in presence of receptor antagonists a decrease is observed. Moreover Prazosin and Propranolol also decrease the basal values of Na-K ATPase activity.

FUNCTIONAL PROPERTIES OF AN IN VITRO MODEL OF THE BLOOD-BRAIN BARRIER FOLLOWING CHRONIC MORPHINE EXPOSURE. Strazza M[1], Pirrone V[1], Wigdahl B[1], Nonnemacher MR[1]; [1]Department of Microbiology and Immunology and Institute for Molecular Medicine and Infectious Disease, Drexel University College of Medicine, Philadelphia, PA 19102.

About one-third of human immunodeficiency virus type 1 (HIV-1) cases leading to acquired immunodeficiency syndrome (AIDS) in the United States have been attributed to injection drug use, frequently involving the abuse of opioids. Opioid abuse by HIV-1-infected individuals leads to more rapid disease progression, increased viral replication and peripheral viral load, and increased incidence and severity of neurocognitive abnormalities compared to non-drug abusers. The blood-brain barrier (BBB) is an obstacle that must be overcome during neuroinvasion and HIV-associated neurocognitive disorders (HAND) development. HIV-1 proteins can directly impact BBB permeability, and drugs of abuse including cocaine and methamphetamine have been shown to increase BBB leakiness and cellular transmigration. Previous in vitro and in vivo studies addressing the role of mu-opioids in altering BBB suggest that exposure increases cellular transmigration and overall barrier leakiness. In this study, a human brain microvascular endothelial cell (hBMEC) line, hCMEC/D3, was used to establish an in vitro transwell model of the BBB to investigate the effects of chronic morphine treatment on barrier structure and function. We observed hCMEC/D3 cells form a confluent monolayer with a basal rate of passage of a 70 kDa tracer molecule comparable to primary hBMECs. Future experiments will investigate the impact of chronic morphine treatment on transcellular migration of mononuclear cells, tight junction protein expression, adhesion molecule surface expression, and cytokine/chemokine secretion. Supported by National Institute of Neurological Disorders and Stroke R01 NS32092; National Institute on Drug Abuse R01 DA19807; National Institute of Mental Health T32 MH079785.

NEUROINFLAMMATION AND DEPRESSIVE SYMPTOMS IN HIV PATIENTS AND METHAMPHETAMINE USERS. Tanizaki N[1], Munsaka S[2], Nerurkar V[2], Jiang C[3], Chang L[3]; [1]Biomedical Science (Clinical Research), John A. Burns School of Medicine, University of Hawaii,

Honolulu, HI 96813; [2]Department of Tropical Medicine, Microbiology and Pharmacology, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI 96813; [3]Department of Medicine, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI 96813.

Introduction: Neuroinflammation and depression are often associated with HIV infection and methamphetamine (METH) use. Elevations in cytokines have been reported in depressed individuals, but how CSF cytokine levels might be related to depressive symptoms in HIV subjects and METH users is unknown. Methods: From a 2x2 cross-sectional study, 59 subjects [12 seronegative (SN) controls, 15 HIV, 13 HIV+METH users, and 19 METH only] were evaluated for depressive symptoms with the Center for Epidemiological Studies Depression Scale (CES-D), and had lumbar punctures for CSF analyses using a 42-plex panel of cytokines. Results: HIV subjects had elevated IL-1α, TNF-α, eotaxin, fractalkine, GM-CSF, IFN-α, IL-10, MCP-1, MIP-1β, and sCD40L (p=<0.0001-0.02). METH users had elevated TGF-α (p=0.01). HIV and HIV+METH users with higher CSF eotaxin levels tended to have higher CES-D scores (HIV: r=0.51, p=0.07; HIV+METH: r=0.55, p=0.08), while METH users with higher levels of eotaxin had lower CES-D scores (r=-0.41, p=0.11, interaction-p=0.01). In all subjects combined, higher fractalkine was correlated with higher CES-D (r=0.25, p=0.058), while lower IL-4 was associated with higher CES-D (r=-0.34, p=0.01). Conclusion: Ten of the cytokines were elevated in HIV subjects and TGF-α was elevated in METH subjects. However, only HIV subjects with higher fractalkine and CSF eotaxin had more depressive symptoms. Therefore, not all of these cytokines contribute to depressive symptoms in our subjects. Lower IL-4 also may contribute to depressive symptoms in these individuals. Supported by NINDS, NIDA (U54NS56883-05, 2K24-DA16170) and NCRR (G12RR003061, P20RR11091).

ASTROCYTE-ELEVATED GENE-1 PROTECTS HUMAN ASTROCYTES FROM OXIDATIVE STRESS-INDUCED DNA DAMAGE: A POSSIBLE ROLE IN NEUROINFLAMMATORY DISORDERS. Vartak N[1], Borgmann K[1], Tang L[1], Ghorpade A[1]; [1]Department of Cell Biology and Anatomy, University of North Texas Health Science Center, Fort Worth, TX 76107.

Astrocyte elevated gene-1 (AEG-1), a novel human immunodeficiency virus (HIV-1)- and tumor necrosis factor (TNF)-α-inducible oncogene, has engendered tremendous interest in the field of cancer research as a therapeutic target for many metastatic aggressive tumors. However, little is known of its role in astrocyte behavior and function during HIV-1 infection in the brain, and whether it contributes towards the development of HIV-1-associated neurocognitive disorders (HAND). Based on its putative role as a metastasis adhesion protein in cancer, here we investigate whether AEG-1 induction in astrocytes alters their responses to reactive astrogliosis, a hallmark feature of neuroinflammatory disorders. Analysis of a cohort of HIV+ and HIV- patient brain mRNAs revealed a significant increase in AEG-1 mRNA levels in HIV+ patients, which was further supported by subsequent in vitro studies. A dramatic increase in the nucleolar localization of AEG-1 protein was noted following treatment with hydrogen peroxide (H2O2), an inducer of ROS, which further hinted towards its plausible role in the nucleolus. Therefore, here we investigated whether AEG-1 protects or sensitizes the astrocytes to oxidative stress-induced DNA damage and whether it plays a role in astrocyte recruitment to injury site by increasing their proliferative potential. We have performed DNA fragmentation ELISA, MTT and in-vitro cell migration assays to address this question. Findings in this study suggest that AEG-1 may play a role in protecting astrocytes from oxidative damage and increase their migratory potential. Supported by NIMH R01 MH087345-01.

LONGITUDINAL ANALYSIS OF INTRA-HOST HIV-1 ENVELOPE SPECIES DURING THE COURSE OF HAND. Vazquez-Santiago FJ[1], Melendez LM[2], Plaud-Valentin M[2], Noel RJ[1], Wojna V[2], Rivera-Amill V[1]; [1]Microbiology Department, Ponce School of Medicine and Health Sciences, Ponce, 00730; [2]Medical Sciences Campus, University of Puerto Rico, San Juan, 00936.

A considerable fraction of HIV-1-infected individuals continue to present neurocognitive complications despite combined antiretroviral treatment. HIV-1 envelope (env) genetic heterogeneity has been detected within the CNS of HAND subjects. Our aim is to study the intra-

host HIV-1 env sequences at multiple time points by using computational tools. We hypothesize that longitudinal and inter-compartmental changes in HIV-1 env contribute to HAND pathology. Paired plasma and CSF from HIV+ Puerto Rican women from the SNRP at the UPR Medical Sciences Campus were collected at 12-month intervals. Viral RNA was extracted, amplified by PCR methods, cloned into pCR2.1, and sequenced. The C2V4 region of env were aligned using Bioedit 7.0.9. Neighbor-joining phylogenetic reconstruction and genetic distances were calculated using MEGA 5.0.5. Phylogenetic analysis consistently showed genetic variants unique to the CSF. Env diversity was higher for plasma than for CSF whereas divergence increased over time. No changes in glycosylation sites within the V3 were seen; however for the V4, the glycosylation pattern was different. Low CSF heterogeneity indicates that certain strains might be suited for CNS infection. Our findings suggest that genetic variability of env is an important mechanism for persistent neuropathology during HAND. These findings allow a better understanding of the intra-host viral dynamics and bring new insights as to when neurotropic variants emerge. These observations provide novel prospects as to whether the early use of entry inhibitors can prevent infection to the CNS. Supported by MBRS-RISE GM082406, P20RR11126, G12RR003050, R01-MH08316-01, SNRP U54 NS43011.

RIG-I SENSES HIV-1 INFECTION AND MEDIATES TYPE I INTERFERON RESPONSE IN HUMAN MACROPHAGES: RELEVANT TO HIV-1-ASSOCIATED NEUROCOGNITIVE DISORDERS. Wang M[2], Huang Y[1], Huang J[3], Zheng JL[1]; [1]University of Nebraska Medical Center, Department of Pharmacology and Experimental Neuroscience, Omaha, NE 68198-5930; [2]Shanghai Jiaotong University, School of Medicine, Shanghai, 200025; [3]Chinese Academy of Sciences, Graduate University, Beijing, 100049.

HIV-1 enters the brain within weeks of initial infection as Mononuclear Phagocytes (MP) cross the blood brain barrier. These HIV-1 infected MP are thought to be a reservoir for viral replication, and thus drive the pathogenesis of HIV-1 associated neurocognitive disorders (HAND). Despite many reports describing the innate immune response to HIV-1 infection, which protein(s) sense HIV-1 in human macrophages remains unknown. Retinoic acid inducible gene I (RIG-I) is a cytosolic protein that senses HIV-1 infection in plasmacytoid dendritic cells. In this work we examine the effect of RIG-I on type I interferon response in HIV-1-infected macrophages. Our results show that RIG-I was significantly increased in HIV-1-associated dementia tissues compared with HIV-1-infected individuals without dementia or HIV serum-negative controls. In human MDM or microglia, infection with macrophage-tropic HIV-1ADA or primary HIV-1 clade B and C isolates significantly increased Rig-I mRNA and protein levels compared to uninfected control. The upregulation of RIG-I was correlated with STAT1 phosphorylation, indicating its association with interferon response. Furthermore, siRNA silencing of Rig-I reduced STAT1 phosphorylation and the downstream type I interferon response genes. These observations suggest that RIG-I senses HIV-1 infection and induces Type-I IFN response in human MP. Determining the molecular mechanism of HIV-1 sensing and immune response in MP will help us to further understand the neuropathogenesis of HAND. Supported by R01 NS41858-01, R01 NS061642-01, 3R01 NS61642-2S1, R21 MH083525-01, P01 NS043985, and P20RR 15635-01 (JZ) and National Natural.

FOXO3A IS INVOLVED IN THE PROPER GENERATION OF INDUCED PLURIPOTENT STEM CELL (IPSC). Wang YX[1], Tian CH[1], Zheng JL[1]; [1]University of Nebraska Medical Center, Department of Pharmacology and Experimental Neuroscience, Omaha, NE 68198-5930.

iPSCs have been successfully generated from various somatic cells, which represents a fascinating breakthrough in the field of regenerative medicine. Our previous studies have demonstrated that Foxo3a played important roles not only in HIV-mediated macrophage apoptosis, but also in inflammation-induced reactive astrogliosis. Recently, Foxo3a was reported to be essential for the homeostasis of mouse neural and hematopoietic stem cell. However, the role of Foxo3a in the reprogramming of somatic cells is still unclear. Thus, in this study, we investigate Foxo3a function in the reprogramming process of iPSCs. Firstly, we used MEFs from Foxo3a-wild

type and -null mice as parental cells to generate iPSCs through ectopic expression of Yamanaka factors. Our data showed that the reprogramming efficiency of Foxo3a-null MEFs was dramatically decreased and the occurrence of iPSC colonies was delayed compared to Foxo3a-wild type MEFs. Secondly, we compared the proliferation, self-renew and differentiation of these two kinds of iPSCs. The results demonstrated that both of these iPSCs expressed high levels of ES cell markers, exhibited strong alkaline phosphatase activity and formed three typical germ layers in teratoma. However, Foxo3a-null iPSCs showed impaired differentiation capability to neuronal lineages in vitro. These results suggest that Foxo3a affects the initiation of reprogramming and the differentiation of resulting iPSCs, which will help us better understand the function of Foxo3a and provide alternative strategy to enhance the efficiency of iPSC generation.

HUMAN HEPATIC STELLATE CELLS SUPPRESS HEPATITIS C VIRUS REPLICATION IN HUMAN HEPATOCYTES. Wang YZ[1], Ye L[1], Wang X[1], Li JL[1], Song L[1], Ho WZ[1]; [1]Department of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140.

There is limited information about the role of hepatic stellate cells (HSC) in liver innate immunity against hepatitis C virus (HCV). We thus examined whether HSC can produce antiviral factors to inhibit HCV replication in human hepatocytes. HSC expressed functional Toll-like receptor 3 (TLR-3) and retinoic acid-inducible gene I (RIG-I). When stimulated with the TLR-3 ligand (polyinosine-polycytidylic acid, poly I:C) or RIG-I ligand (5' triphosphate double stranded RNA, 5'ppp-dsRNA), HSC expressed significantly higher levels of interferon-β (IFN-β) and IFN-λ than control cells. When HCV JFH-1-infected hepatocytes were coculutred with HSC stimulated with poly I:C or incubated in media conditioned with supernatant (SN) from poly I:C-stimulated HSC, HCV replication was significantly suppressed. This HSC SN action on HCV replication was mediated through type I IFNs as well as type III IFNs, which was evidenced by the observations that antibodies to IFN-α/β or IFN-lambda receptors could neutralize HSC-mediated anti-HCV effect. Investigation of the mechanisms showed that the HSC SN-mediated anti-HCV effect was related to the induction of IFN-stimulated gene expression in hepatocytes. These observations provide compelling evidence at cellular and molecular levels that HSC may have a crucial role in liver innate immunity against HCV infection. Supported by National Institutes of Health (DA12815, DA22177, and DA27550).

THE EFFECTS OF DOPAMINE ON LEUKOCYTE TRANSMIGRATION ACROSS THE HUMAN BLOOD BRAIN BARRIER AND ITS ROLE IN THE PATHOGENESIS OF NEUROAIDS. Williams DW[1], Calderon TM[1], Coley JS[1], Gaskill PJ[1], Carvallo L[1], Eugenin EA[1], Berman JW[1]; [1]Pathology, Albert Einstein College of Medicine, Bronx, NY 10461.

HIV enters the CNS early after primary infection and results in HIV associated neurocognitive disorders (HAND) in 40-60% of HIV infected individuals, despite antiretroviral therapy. One mechanism that contributes to the entry of HIV into the brain is the migration of monocytes across the blood brain barrier (BBB). We showed that CD14+CD16+ monocytes preferentially transmigrate across our model of the BBB in response to CCL2 and SDF-1, chemoattractants elevated in the CNS of individuals with HAND. HIV results in the exuberant transmigration of these cells resulting in BBB damage. The junctional proteins ALCAM, JAM-A, PECAM-1, and CD99 are critical to this process, as blocking antibodies inhibit monocyte transmigration. Drugs of abuse may alter the incidence and/or severity of HIV neuropathogenesis. Dopamine, a neurotransmitter whose presence extracellularly is central to many drugs of abuse, increases viral replication in macrophages, demonstrating the potential of drugs of abuse to exacerbate HAND. We found that monocytes and T cells, another cell type which may be involved in the HIV pathogenesis of substance abusers, express dopamine receptors at the mRNA and protein levels, indicating that dopamine may affect the function of these cells. We found a cooperative increase in monocyte and T cell transmigration across the BBB in response to SDF-1 in the presence of dopamine, suggesting that it may worsen HAND by promoting the recruitment of other cell types, in addition to

monocytes, to the CNS, potentially compromising BBB integrity and contributing to neuroinflammation. Supported by NIMH/95262005, NIMH/95262924, NIDA/95265535.

D-SERINE POTENTIATES NMDA RECEPTOR-MEDIATED EVOKED EPSCS IN RAT HIPPOCAMPAL NEURONS: IMPLICATIONS FOR HIV-ASSOCIATED NEUROTOXICITY. Xia J[1], Liu H[1], Wu L[1], Huang Y[1], Xiong H[1]; [1]Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198-5880.

D-serine is an N-methyl-D-aspartate receptor (NMDAR) co-agonist that is generated primarily in glial cells, and it has been suggested to play a critical role in the NMDAR-mediated neurotoxicity in neurodegenerative diseases. Increasing evidence shows that human immunodeficiency virus-1 (HIV-1)-infected and/or immune-activated glial cells release multiple excitotoxic factors, leading to neuronal injury and death by producing excessive activation of NMDARs in HIV-associated dementia (HAD). Thus, D-serine was hypothesized to be released from immune-activated glial cells in HAD and to contribute to the NMDAR-mediated neurotoxicity in HIV-associated neuronal injury. In the present study, using high performance liquid chromatography (HPLC) and cell viability assay, we found that gp120 treatment induced a significant release of D-serine from astrocytes, which enhanced the NMDAR-mediated excitotoxicity to hippocampal neurons. We also used whole-cell patch clamp recording to examine the effect of D-serine on NMDAR-mediated evoked excitatory postsynaptic currents (eEPSCNMDAR) in the CA1 region of rat hippocampal slices. Bath application of D-serine increased the amplitude of eEPSCNMDAR in a concentration-dependent manner, and this was specifically abolished by enzymatic degradation or by a selective NMNDAR antagonist 5,7-dichlorokynurenic acid (DCKA). D-serine potentiated eEPSCNMDA predominantly via activation of extrasynaptic NR2B-containing NMDARs. Our results implicate an underlying mechanism and therapeutic target for HIV-1-associated neuronal injury and death. Supported by NIH 5R01NS063878.

COCAINE-MEDIATED UPREGULATION OF GLIAL FIBRILLARY ACIDIC PROTEIN: IMPLICATION FOR ASTROCYTE ACTIVATION IN HAND. Yang L[1], Yao H[1], Bethel-Brown C[1], Buch S[1]; [1]Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198.

Despite the success of ART, almost 60% of HIV-infected individuals develop cognitive impairments referred to as HIV-associated neurological disorders (HAND). Adding complexity to this is the use of illicit drugs such as cocaine by these individuals. One of the hallmark features of HAND is reactive astrocytosis, exemplified by enhanced expression of GFAP, cellular hypertrophy, and astrocyte proliferation. While the role of HIV proteins in mediating astrocytosis is well characterized, few studies have explored whether cocaine can also mediate astrocytosis thereby exacerbating disease progression. Herein we investigated the role of cocaine in triggering astrocyte activation as evidenced by upregulated expression of GFAP both in vitro & in vivo. Exposure of astrocytes to cocaine resulted in astrocyte proliferation associated with increased expression of GFAP mRNA and protein, an effect that was abrogated by pretreatment of cells with a sigma1-receptor antagonist. Using a pharmacological approach, we provide evidence for phosphorylation of ERK1/2, p38 & JNK signaling pathways with the subsequent downstream activation of the early growth response gene (Egr-1) in this process. Corroboration of these findings in vivo demonstrated increased expression of GFAP in the brain of mice following cocaine injection. These findings suggest that cocaine binding to its receptor activate astrocytes via the phosphorylation of MAPK and downstream Egr-1 signaling pathways. These findings could have implications for enhanced progression of HAND in HIV-1 infected cocaine addicts. Supported by MH-068212, DA020392, DA023397, DA024442.

INHIBITORY EFFECT OF NANOZYMES ON AMYLOID BETA AGGREGATION AND OXIDATIVE STRESS: A NEW THERAPEUTIC IMPLICATION FOR ALZHEIMER'S DISEASE. Zhang G[1], Kiyota T[1], Batrakova EV[2], Gendelman HE[1]; [1]Department of Pharmacology and Experimental

Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198; [2]Department of Pharmaceutical Sciences, University of Nebraska Medical Center, Omaha, NE 68198.

Alzheimer's disease (AD) is a common, devastating and age-linked progressive neurodegenerative disorder. Soluble oligomeric aggregates of amyloid beta peptides (Abeta) affect the neuropatholobiology of AD by potentiating microglia activation and neuronal damage. Thus, therapeutic strategies directed at regulating oligomeric Abeta aggregation and consequent microglial oxidative stress and inflammatory responses could be valuable to halt disease progression. The antioxidant enzyme catalase which serves, in part, to decompose hydrogen peroxide, can effect Abeta folding through direct binding interactions between it and a region of Abeta (amino acid residues 25-35). We hypothesized that delivery of the antioxidant catalase into the brain using nanoparticles could inhibit Abeta aggregation and attenuate the reactive oxygen species (ROS) production. To begin to tackle this problem we now demonstrate that catalase and nanoformulated catalase particles (nanozymes) specifically inhibit Abeta1-42 peptide to form high molecular weight aggregates or small oligomeric species such as trimers and tetramers. Released nanozymes from monocyte-derived macrophages as a drug delivery carrier significantly inhibited Abeta1-42 peptide oligomerization and scavenged of hydrogen peroxide. Furthermore, primary cell-based viability assays supported the fact that catalase or nanozymes protect neurons from damage caused by Abeta1-42 oligomeric aggregates. These data, taken together, support a therapeutic role for nanozymes to limit Abeta aggregates and the linked neurotoxicity. Supported by NIH / 2R37 NS36126.

TLR3 ACTIVATION EFFICIENCY BY LOW AND HIGH MOLECULAR WEIGHT POLY I:C . Zhou Y[1], Wang X[1], Li JL[1], Wang YZ[1], Ye L[2], Guo M[2], Song L[1], Ho WZ[1]; [1]Department of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140; [2]State Key Laboratory of Virology, the Center for Animal Experiment/Animal Biosafety Level III Laboratory, Wuhan University, Wuhan, 430070.

Toll like receptor-3 (TLR-3) plays a critical role in initiating type I interferon (IFN)-mediated innate immunity against viral infections. Double-stranded RNA (dsRNA), a common intermediate product of viral replication, activates TLR-3 for activation and induces the subsequent signaling cascades. Polyinosinic-polycytidylic acid (poly I:C), a synthetic analog of dsRNA, has been commonly used as a TLR-3 agonist. However, the activation efficiency of TLR-3 by poly I:C is influenced by various factors. In this study, we examined the stimulatory effects of two commercially available poly I:C (high molecular weight, HMW and low molecular weight, LMW) on TLR3 activation in various human cell types by determining the induction of type I and type III IFNs as well as the antiviral effect. We demonstrated that the efficiency of TLR-3 activation by HMW poly I:C was significantly higher than that by LMW poly I:C in different cell lines tested. Transfection of poly I:C into cells was necessary for introducing poly I:C into certain types of cells, as the direct addition of poly I:C into these cells failed to activate TLR-3. In contrast, both HMW and LMW poly I:C could efficiently induce TLR-3 activation in macrophages and a neuroblastoma cell line (CHP212) without transfection. Furthermore, we demonstrated that methamphetamine or morphine treatment compromised poly I:C mediated induction of type I IFNs in macrophages. The observations of this study support the concept of developing efficient TLR-3 ligands for antiviral against HIV and other viruses. Supported by National Institute on Drug Abuse/ DA012815; DA027550; DA022177.

GENERAL POSTER SESSION ABSTRACTS

(*in alphabetical order*)

BRAIN IMMUNOPHILIN IN HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS. Achim CL[1], Vinters HV[2], Tatro ET[1], Moore DJ[1], Soontornniyomkij B[1], Gospodarev V[1], Gouaux B[1], Masliah E[1], Grant I[1], Soontornniyomkij V[1]; [1]HIV Neurobehavioral Research Program, School of Medicine, University of California San Diego, San Diego, CA 92093; [2]Neuropathology and Neurology, Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA 90095.

FK506 binding protein (FKBP)-51 and FKBP52 control glucocorticoid receptor (GR) sensitivity. Dysregulation of proteins involved in GR-mediated signaling can lead to maladaptive stress response and aging-related cognitive decline. As chronic stress is associated with HIV infection, we hypothesize that altered cortical expression of these proteins is associated with HIV-associated neurocognitive disorders (HAND). We used quantitative immunohistochemistry to assess expression levels of these proteins in the mid-frontal gyrus of 55 HIV-infected subjects free of cerebral opportunistic diseases compared to 20 age-matched non-HIV controls. The immunoreactivity normalized to the neuroanatomic area measured (IRn) for FKBP51 was increased in HIV subjects both in the cortex and subcortical white matter, while no significant alterations were observed for GR or FKBP52. Notably, the cortical FKBP51 IRn was higher in HAND subjects than in cognitively normal HIV subjects. No significant changes in FKBP51 IRn were found with respect to major depressive disorder, hepatitis C virus infection, methamphetamine use, or antiretroviral treatment in HIV subjects. In conclusion, the increased cortical expression of FKBP51 might represent negative feedback in an attempt to reduce GR sensitivity in the setting of chronic stress-induced elevation of GR-mediated signaling inherent in HIV infection. The increased cortical FKBP51 expression might lead to down-regulation of protein translation mediated by Akt/mammalian target of rapamycin kinase signaling and thereby contribute to HAND. Supported by MH81482, DA26306, DA27513, MH62512, MH83506, MH59745, AG16570, AI35040.

THE ROLE OF EARLY ENDOSOMAL SIGNALING IN HIV-1 INDUCED AMYLOID BETA ACCUMULATION IN BRAIN ENDOTHELIAL CELLS. Andras IE[1], Toborek M[1]; [1]Biochemistry and Molecular Biology, University of Miami School of Medicine, Miami, FL 33136.

Clinical evidence indicates increased amyloid deposition in HIV-1-infected brains. Our previous study have shown that HIV-1 exposure increased amyloid beta accumulation at the blood brain barrier (BBB) level in a model of human brain microvascular endothelial cells (HBMEC). HIV-1 exposure also increased the levels of early endosomal antigen-1 (EEA1) in HBMEC. In this study we proposed to investigate the role of EEA1 in amyloid beta accumulation in HBMEC. We found that EEA1 and amyloid beta partly colocalized in HBMEC cytoplasm and nuclei. Moreover, EEA1 and amyloid beta nuclear entry was increased in the presence of HIV-1. Because early endosomes are involved in nuclear signaling via Smads, and Smad signaling was linked to amyloid beta pathology, we investigated the involvement of the Smad pathway in this process. In our cells, nuclear Smad2 level increased after amyloid beta exposure. This effect was further augmented by the presence of HIV-1. EEA1 silencing decreased Smad2 and amyloid beta nuclear entry in HBMEC. Our data show that amyloid beta is transported into the endothelial nucleus by the early endosomes and may involve the Smad signaling pathway. Supported by MH63022, MH072567, NS39254 and DA027569.

THERAPEUTIC TREATMENT OF AICAR FOR MICROGLIAL INFLAMMATION IN ALZHEIMER'S DISEASE. Ayasolla KR[1], Rahimipour S[2], Malhotra A[1], Singhal PC[1]; [1]Feinstein Institute for Medical Research, Hofstra North Shore-LIJ School of Medicine, Great Neck, NY 11021; [2]Department of Chemistry, Bar-Ilan University, Ramat Gan, 52900 Israel.

Introduction: Pro-inflammatory cytokines have been detected in AD brain and seem to play a

role in the pathogenesis of AD. Our earlier reports investigated glial cell responses to LPS and Abeta , by upregulating the expression of cytokines TNF-α, IL-1β, and IL-6, as well iNOS and COX-2. The present study was undertaken to investigate the therapeutic benefits of AICAR (a potent activator of AMP-activated protein kinase) in blocking the pro-oxidant/proinflammatory responses in microglia. Objectives: Our main objectives were a) to understand activation as well release of cytokines from activated microglia in response to accumulated Aβ, and therapeutic benefits of AICAR. Experimental methods : BV-2 microglia were used in these studies to understand LPS/ SMase/Aβ stimulated signaling mechanisms of NFκB pathway leading to the release of NO, ROS generation , release of inflammatory cytokine (TNF-α, IL-1β, IL-6) as well the scavenging macrophage like phagocytic functions of microglia. Results: AICAR inhibits LPS, and Smase activated cytokine release and NO production. AICAR also seem to promote Aβ phagocytosis . Further we observed a reduction in the stress signaling with a significant lowering in p-ERK, p-p38, p-Akt (ser 473) as well significant reduction of proteins such as p-NIK, p-IKK a/b and in p-p65 translocation. Conclusions: Microglia plays an active role in triggering the immune cytokine responses in the neuro-inflammatory process of AD. Hence AICAR treatment is effective in blocking cytokine release by possibly regulating NFκB pathways.

PATHOGENS, TLRS, IL-17 SIGNALING AND THEIR CROSSTALK IN BRONCHIAL MUCOSA. Banerjee S[1], Ninkovic J[1], Ma J[1], Meng J[2], Roy S[1]; [1]Surgery, University of Minnesota, Minneapolis, MN 55455; [2]Pharmacology, University of Minnesota, Minneapolis, MN 55455.

Both Toll-like receptors and Interleukin-17 signaling pathways are predisposed to protect from pathogens, where local and systemic inflammation being the hallmark response to the attacking pathogen. While initial inflammatory response is beneficial towards containment of an infection, a persistent hyper-inflammation is detrimental to mucosal integrity. Absence of relevant TLRs or the IL-17 receptor has been independently shown to result in downregulation of hyper- inflammation both in vitro and in vivo. Conversely, pathogen mediated hyper-inflammation in lung and gut mucosa is associated with elevated IL-17 levels. On the other hand, chronic Morphine has been shown to increase the pathogenic load in lung infections, while its role in modulating the barrier integrity largely remains unexplored. Our study specifically focuses on the barrier function of the bronchial epithelium, and we show that these cells are capable of inducing the “first response” to gram positive pathogenic signal, involving IL-17 and its signaling. We also demonstrate that upon encountering S. pneumoniae signal in the lung compartment, there is a concomitant release of TLR2 mediated IL-17 by the epithelial cells. We show that the first messengers in both pathways bind to each other and this might be a mechanism to keep hyper-inflammation under control in the lung mucosa, where TLR2 signal dominates that of IL-17R. Finally, we show that chronic morphine modulates the interaction between the key molecules and impairs effective response to pathogens in the mucosa. Supported by NIH grants RO1 DA 12104, RO1 DA 022935, KO2 DA 015349, P50 DA011806.

REGULATION OF MIR-146A BY IL-1β IN ASTROCYTES. Banerjee S[1]; Dejos M[1]; Datta PK[1]; [1]Neuroscience/Center for Neurovirology, Temple University, Philadelphia, PA 19140.

MicroRNAs (miRNAs) constitute a group of small non-coding RNA molecules generally 18-22 base-pairs in length and are considered to be negative regulators of gene expression at the level of post-transcription. In the present study we investigated the molecular mechanism of miR-146a expression by the proinflammatory cytokine, IL-1β in astrocytes since in HIV-1-infected brain activation of astrocytes by proinflammatory cytokines contributes to neurodegeneration. Our studies demonstrate that induction of mir-146a expression by IL-1β in astrocytes is dependent on the activation of NF-κB and C/EBP transcription factors. Furthermore, our studies also suggest that C/EBP mediated induction of mir-146a promoter is dependent on the presence of functional NF-κB binding sites since mutation of both sites prevents activation of the promoter by C/EBP-beta and -delta. Our studies also demonstrate that overexpression of mir-146a in astrocytic cells inhibits

glutamate transporter, EAAT2 expression through a miR-146a-binding site within the 3' UTR of EAAT2. Supported by NIH/NIDA.

PLATELET-DERIVED GROWTH FACTOR RESTORES HIV TAT AND COCAINE-MEDIATED IMPAIRMENT OF NEUROGENESIS: ROLE OF TRPC 1 CHANNELS. Buch S[1], Yao HH[1]; [1]Pharmacology, University of Nebraska Medical Center, Omaha, NE 689198.

Platelet-derived growth factor-BB (PDGF-BB) has been reported to provide tropic support for neurons in the central nervous system (CNS) in our previous. However, whether PDGF-BB regulates neurogenesis especially in the context of HIV-associated neurological disorder (HAND) and drug abuse, remains largely unknown. In this study we demonstrate that pre-treatment of rat hippocampal neuronal progenitor cells (NPCs) with PDGF-BB restored proliferation impaired by HIV Tat & cocaine via the cognate receptors. We identify the essential role of transient receptor potential canonical (TRPC) channels in PDGF-BB-mediated proliferation. Parallel but distinct ERK/CREB, PI3K/Akt signaling pathways with downstream mTOR/p70S6K/4E-BP and NF-kB were critical for proliferation. Blocking TRPC 1 channel suppressed PDGF-mediated proliferation as well as PDGF-BB-induced ERK/CREB and mTOR/p70S6K/4E-BP activation thereby underscoring its role in this process. In vivo relevance of these findings was further corroborated in HIV Tat transgenic mice wherein hippocampal injection of recombinant rAAV2-PDGF-B restored impaired NPC proliferation induced by Tat and cocaine. Together these data underpin the role of TRPC channel as a novel target regulating cell proliferation-mediated by PDGF-BB with implications for therapeutic intervention for reversal of impaired neurogenesis inflicted by HIV Tat and cocaine. Supported by DA020392, DA023397 and DA024442 (SB).

DOPAMINE INCREASES CXCL12-MEDIATED T CELL TRANSMIGRATION ACROSS THE BLOOD BRAIN BARRIER. Calderon TM[1], Gaskill PJ[1], Lopez L[1], Eugenin EA[1], Berman JW[2]; [1]Department of Pathology, Albert Einstein College of Medicine, Bronx, NY 10461; [2]Departments of Pathology and Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, NY 10461.

The prevalence of HIV-associated neurocognitive disorders (HAND) is increasing in infected individuals on cART. HIV entry into the CNS occurs early after viral infection, establishing a viral reservoir and chronic neuroinflammation. Drug abuse is proposed to exacerbate HAND and increase neuroinflammation, characterized by an increased influx of T cells. The T cell chemokine CXCL12 (SDF-1) is constitutively expressed in the CNS and is increased with HIV infection. Many drugs of abuse increase CNS extracellular dopamine levels and we hypothesize that dopamine alters the transmigration of T cells across the blood brain barrier (BBB) in response to CXCL12. Using our in vitro model of the human BBB, we show that there is a significant increase in human T cell transmigration in response to CXCL12 (25 or 50 ng/ml) and dopamine (10 or 20 μM) when compared to CXCL12 alone. Dopamine by itself does not increase transmigration. Significant D4 dopamine receptor (D4R) levels are detected on the surface of T cells from multiple donors by FACS and D4R is minimally detected on T cells activated with PHA and IL-2. In some donors, D5R is detected on resting T cells and D1R and D5R on activated T cells. Dopamine activation of D4R may contribute to increased CXCL12-mediated transmigration of resting T cells. This increased transmigration does not involve changes in expression of the CXCL12 receptor, CXCR4, in resting T cells as indicated by FACS. Thus, dopamine may increase CXCL12-mediated T cell influx into the CNS, contributing to increased neuroinflammation in HIV-infected drug abusers. Supported by: NIDA and NIMH.

MINOCYCLINE PROTECTS MICE AGAINST WEST NILE VIRUS (WNV)-ASSOCIATED SEVERE DISEASE. Chapagain ML[1], O'Connell M[1], Lazaga NB[1], Kumar M[1], Volper EA[1], Verma S[1], Nerurkar VR[1]; [1]Department of Tropical Medicine, Medical Microbiology and Pharmacology, John A. Burns School of Medicine, Honolulu, HI 96817.

Purpose: WNV causes potentially fatal encephalitis. However, no therapeutic drugs or vaccines

are available to prevent or treat WNV infection in human. Objective of this study was to determine the role of minocycline, for WNV-associated encephalitis. Methods: Age and gender matched, 8- to 12-weeks old C57BL/6 mice were inoculated with 1,000 plaque-forming unit of WNV, and were either untreated or treated with minocycline (40 mg/kg/day) and monitored for 3 weeks after infection. Mice survival was analyzed using Log-rank (Mantel-Cox) tests, viremia was quantitated by plaque assay or real-time PCR (qRT-PCR) and cytokines were measured by Luminex assay. Results: Over 80% of WNV-infected mice succumbed to death, whereas 31% and 62% of WNV-infected mice treated with minocycline beginning on day 3 and day 1 after infection, respectively survived (Chi-square 12.40, df 3, p= 0.0061). There was no difference in the viremia, however, at day 9 after infection three-fold less viral RNA was observed in the brain of mice treated with minocycline. Moreover, WNV induced chemokine ligands CXCL-9, IP-10 and MCP-1 in the blood and CXCL-9, IP-10, MCP-1 and eotaxin in the brain. Minocycline selectively reduced the expression of CXCL-9 and eotaxin in the blood and brain. Conclusions: Our data suggest that minocycline, a semi-synthetic, highly lipophilic, tetracycline antibiotic may modulate transmigration of specific subsets of leukocytes by altering expression of their specific ligands and/or receptors and may control brain inflammation and promote survival of WNV-infected mice. Supported by Institutional Funds, DoD (W81XWH-07-2-0073), RCMI (G12RR03061), and COBRE (P20RR018727), NIH.

INFECTION OF CHINESE MACAQUES BY A NEUROTROPIC SIVMAC251/CNS WITHOUT AND WITH TETRAHYDROCANNABINOL (THC). Chen Z[1], Qiang W[2], Cong Z[2], Liu L[1], Qin C[2], Molina P[3]; [1]AIDS Institute of Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China; [2]Institute of Laboratory Animal Science, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [3]Department of Physiology, Louisiana State University Health Sciences Center, New Orleans, LA 70119.

It has been suggested that substances and HIV/SIV proteins may exhibit neurotoxic synergism. It is, therefore, desirable to generate a pathogenic macaque model using a neurotropic SIV to study the substance abuse. We sought to isolate a neurotropic SIV and to determine the chronic effect of delta9-tetrahydrocannabinol (THC) on viral infection in Chinese macaques. Sixteen animals were divided into four study groups: THC+SIV+, THC+SIV-, THC-SIV+ and THC-SIV- with four macaques per group. One month post THC administrations, macaques in group one and three were challenged with SIV. A novel SIVmac251/CNS strain was successfully isolated from CNS of an end-staged SAIDS Chinese macaque. SIVmac251/CNS displayed enhanced pathogenicity compared to its parental SIVmac251. During the THC study, three infected macaques developed paralyzed limbs, 1/4 in group one and 2/4 in group three, and died of SAIDS with high viral loads before the cessation of THC. THC, however, did not seem to affect peak and steady state plasma viral/proviral loads between THC treated and untreated infected animals. On average group-one macaques maintained significantly better body weight compared with group-three animals, which might contribute to relatively modest progression of simian AIDS in group-one macaques. As an active ingredient of Marinol as an appetite stimulant for AIDS patients, THC maintained the body weight of infected macaques. Our findings provide useful information on the SIVmac251/CNS-Chinese macaque model and the effects of THC in both infected and un-infected animals. Supported by HKU-UDF and NIH.

DANGER SIGNAL HMGB1 MEDIATES ETHANOL-INDUCED NEUROINFLAMMATION THROUGH TLR AND RAGE RECEPTORS. Crews FT[1], Vetreno R[1]; [1]Bowles Center for Alcohol Studies, University of North Carolina, Chapel Hill, NC 27599.

Ethanol increases neuroimmune gene expression through NFkB, a transcription factor that increases expression of innate immune cytokines, oxidases and proteases. We discovered that ethanol acts through release of High-mobility group box 1 (HMGB1), an endogenous DANGER signaling protein. DANGER signals activate Receptor for advanced glycation end products (RAGE) and Toll-like receptors (TLR). Studies in brain slice cultures find ethanol treatment increases

HMGB1 mRNA and immunohistochemistry (+IR) as well as releasing HMGB1 into the culture medium (ELISA). HMGB1 is an agonist at TLR-RAGE receptors that activate NFkB, a transcription. Ethanol activation of NFkB transcription of proinflammatory genes is blunted by siRNA and drugs that blunt HMGB1-TLR-RAGE signaling. Chronic ethanol treatment of mice (5 gm/kg/day, 10 days) increases mRNA and protein (+IHC) for HMGB1, TLR, NADPH oxidase and other innate immune genes in frontal cortex. These increases are associated with elevated markers of reactive oxygen species and neurodegeneration. These studies support the hypothesis that chronic ethanol releases HMGB1 activating TLR-RAGE receptors that stimulate NFkB transcription of neuroimmune genes that amplify proinflammatory responses causing neurotoxicity. Human post-mortem brain assessments find that alcoholic brain shows increased levels of DANGER signaling that correlate with markers of cytotoxicity and years of drinking alcohol. These studies suggest HMGB1-TLR-RAGE DANGER signals are activated in brain by ethanol. Supported by NIAAA.

EPIGENETIC MECHANISMS INVOLVED IN THE INDUCTION OF THE COMPLEMENT C3 GENE IN ASTROCYTIC CELLS IN RESPONSE TO IL-1β. Datta PK[1]; Rappaport J[1]; [1]Neuroscience, Temple University, Philadelphia, PA 19140.

Uncontrolled synthesis of the complement component C3 by HIV-1 induced proinflammatory cytokine IL-1β in the brain can lead to neuroinflammation and neurodegeneration. We have demonstrated earlier that IL-1β induces C3 synthesis in astrocytes and monocytes in a C/EBP dependent manner. To investigate epigenetic regulations, we observed that C3 promoter contains no CpG islands for DNA methylation. Therefore, we investigated whether epigenetic modifications at the chromatin level of C3 gene are involved in the transcriptional activation of the gene in response to IL-1β in astrocytes. Our studies demonstrate that overexpression of Brahma-related gene-1 (BRG-1), a protein contained in an ATP-dependent chromatin remodeling complex, and histone acetyltransferase (HAT), p300 further induces IL-1 beta mediated C3 expression at the promoter level. Furthermore, overexpression of histone-lysine methyltransferase, H3 lysine 9-specific 3 (G9a) inhibited IL-1β mediated C3 expression at the promoter level. On the contrary, overexpression of mutant form of BRG-1 (K798R, mutation in ATP binding site) inhibited transcriptional response of the C3 promoter by IL-1β, while a mutant form of G9a failed to repress C3 promoter activation by IL-1β. Together, these data suggest that epigenetic modifications of the chromatin of the C3 gene are involved in the transcriptional activation of the gene in response to IL-1β. These observations demonstrate that targeting chromatin modifiers may have potential as novel therapeutic strategies for inhibiting IL-1β mediated C3 gene regulation. Supported by NIH/NIDA Career Development Award.

ENHANCED PULMONARY VASCULAR REMODELING IN MORPHINE TREATED SIV-INFECTED MACAQUES: IMPLICATION IN HIV-ASSOCIATED PULMONARY ARTERIAL HYPERTENSION. Dhillon N[1], Cheney P[2], Tawfik O[3], O'Brien-Ladner A[1]; [1]Department of Medicine, Division of Pulmonary and Critical Care Medicine, University of Kanas Medical Center, Kansas City, KS 66160; [2]Department of Molecular and Integrative Physiology, University of Kanas Medical Center, Kansas City, KS 66160; [3]Department of Pathology, University of Kansas Medical Center, Kansas City, KS 66160.

Rationale: Our recent published findings showing enhanced pulmonary vascular remodeling in HIV-infected lung tissues from IV heroin and/or cocaine abusers indicate that intravenous drug use (IVDU) and HIV-1 potentially act in concert to cause pulmonary arteriopathy. In this study we used simian immunodeficiency (SIV) macaque model as a biological tool to explore the association of drug abuse and HIV-infection to obtain a better understanding of HIV-PAH's development. Methods: The archival lung tissues from 11 male SIVmacR71/17E-infected rhesus macaques exposed (n=6) or unexposed (n=5) to morphine (2.5mg/kg, QID) for up to 59 weeks were assessed for histological evidence of pulmonary vascular lesions and compared with morphine exposed un-infected controls (n=5). Results: No difference was observed in the viremia on treatment of SIV-infected macaques with morphine. However, significant vascular remodeling was found in the

SIV+morphine group, including moderate to severe medial hypertrophy, intimal lesions, endothelial disruption with adventitial thickening or luminal obstruction and presence of early and complex plexiform lesions. In contrast, only less severe lesions with mild focal, medial and intimal lesions or adventitial remodeling were observed in two of the five macaques in the SIV group. Pulmonary arteriopathy was more advanced in the morphine group compared to the SIV group as almost all of them showed a disrupted endothelial layer with swollen cells and mild to moderate medial hypertrophy. Analysis of lung extracts suggested an up-regulation endothelial injury and inflammatory markers in macaques from SIV+ morphine group. Conclusion: The presence of complex lesions in SIV+Morphine group suggests that SIV and morphine together potentiates the incidence and severity of pulmonary arteriopathy. Supported by Parker B. Francis Fellowship (ND), NIH-DA031589 (ND), AHA-11SDG7500016 (ND) and NIH-DA12827 (PC).

MORPHINE TREATMENT IN THE CONTEXT OF OPPORTUNISTIC INFECTION INDUCES DIFFERENTIAL IMMUNE CELL TRAFFICKING INTO THE CNS BY MODULATING TLR AND CHEMOKINE RECEPTOR EXPRESSION. Dutta R[1], Yu H[1], Charboneau R[2], Barke R[2], Roy S[1,2]; [1]Department of Surgery, University of Minnesota, Minneapolis, MN 55455; [2]Department of Surgery, Veterans Affairs Medical Center, Minneapolis, MN 55417.

Opioid drug abusers are at a higher risk for HIV associated neurocognitive disorders (HAND). However, studies investigating co-infection with bacterial opportunistic infection in the context of HIV-1 are limited. The goal of the present study was to investigate if co-infection with S. pneumoniae (Sp) in HIV infected drug abusers accelerates HAND. In vivo bioluminescent imaging showed morphine (MS) treatment increases ($p<0.05$) bacterial dissemination into the CNS, both in wild type and Tattg mice. Further we investigated the trafficking pattern of immune cells into the CNS following adoptive transfer of luciferase tagged splenocytes. MS treatment significantly increased immune cell infiltration into the CNS of mice injected with HIV-1 Tat protein and co-infected with Sp. FACS analysis showed significant infiltration of CD3+, F480+ and Ly6C+ immune cells into the CNS of MS treated bacterial F480+ infected Tattg group. Tat along with MS selectively increased trafficking of CD3-CCR5 phenotype. However, trafficking of CXCR4 phenotype on CD3, F480 and Ly6C were observed only in the presence of Sp. In addition, MS treatment significantly increases TLR2 and TLR4 expression on CD3 and F480, Ly6C population respectively in bacterial infected Tattg mice. BBB integrity is lost in the same group of mice. Trafficking of these populations into the CNS was decreased in TLR2-/- and TLR4-/- mice. Data suggests that MS treatment in the context of opportunistic infection induces differential immune cell trafficking into the CNS, leading to sustained proinflammatory responses thus contributing to HAND. Supported by NIH Grants RO1 DA12104, RO1 DA022935, KO2 DA15349, P50 DA 11806 (to Sabita Roy).

METHAMPHETAMINE ALTERS BLOOD BRAIN BARRIER FUNCTIONS FACILITATING CENTRAL NERVOUS SYSTEM INFECTION. Eugenin EA[1], Nosanchuk JD[2,3], Martinez LR[3,4]; [1]Departments of Pathology, Albert Einstein College of Medicine, Bronx, NY 10461; [2]Department of Medicine (Division of Infectious Diseases), Albert Einstein College of Medicine, Bronx, NY 10461; [3]Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, NY 10461; [4]Department of Biomedical Sciences, Long Island University, C. W. Post Campus, Brookville, NY 11548.

Methamphetamine (METH) is a major drug of abuse in the United States. METH is a strong addictive central nervous system (CNS) stimulant that mimics and has longer lasting pharmacological effects than cocaine. The blood brain barrier (BBB) is a unique interface that in part functions to prevent microbial invasion of the CNS. Although there is substantial evidence of the effects of cocaine on BBB function, the effects of METH on brain vasculature have not been studied extensively. The encapsulated AIDS-associated pathogenic fungus Cryptococcus neoformans (Cn) frequently infects the CNS; globally there are ~1 million cases of CNS cryptococcosis every year. In addition, Cn is an excellent model organism for the study of CNS

susceptibility due to the availability of tools such as specific antibodies and well-established animal models. Hence, we hypothesized that METH alters the innate immunity function and BBB integrity increasing susceptibility to cryptococcosis, including CNS infection. In this study, we demonstrated the detrimental impact of METH on host immune function in response to a systemic fungal challenge. Mice that received METH prior to Cn infection displayed increased fungal burden, increased pulmonary inflammation, and decreased survival. METH abrogates normal macrophage function, resulting in an inability to control the disease. Furthermore, our results suggest that METH modifies the expression of adhesion molecules at the level of the endothelial cells of the BBB. Therefore, METH may disrupt the BBB integrity in vitro via the modulation of the expression of tight junction proteins which may result in extensive brain alterations including an increase in the susceptibility of the CNS to cryptococcal infection. We believe this interdisciplinary project may lead to develop better public health strategies to deal with this burden on our society. Supported by NIH-NIAID grant 1K22A1087817-01A1, NIH AI-51519 and MH076679.

IDENTIFICATION OF INTRACELLULAR TOXIC SIGNALS REQUIRED FOR BYSTANDER KILLING THROUGH GAP JUNCTIONS FROM HIV INFECTED ASTROCYTES TO UNINFECTED ASTROCYTES. Eugenin EA[1], Berman JW[1,2]; [1]Departments of Pathology, Albert Einstein College of Medicine, Bronx, NY 10461; [2]Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, NY 10461.

HIV entry into the central nervous system (CNS) is an early event after infection, resulting in neurological dysfunction in a significant number of individuals. As people with AIDS live longer, the prevalence of cognitive impairment is increasing, despite antiretroviral therapy. The mechanisms that mediate CNS dysfunction are still not well understood, but probably is a combination of inflammation, viral infection and/or replication. In addition, to those mechanisms we recently demonstrated that HIV infection of astrocytes mediated survival of HIV infected cells and bystander killing of surrounding uninfected cells by a mechanism gap junction dependent. Now in this report we characterize the mechanism of HIV mediate protection of infected astrocytes with emphasis in mitochondrial dysregulation and identify the intracellular factors that mediated bystander killing of uninfected cells. Our findings describe a novel mechanism by which HIV maintain survival of HIV infected astrocytes and we identify IP3, calcium and Cytochrome C as key signals involved in bystander killing of uninfected cells in contact with HIV infected astrocytes by a gap junction dependent mechanism. Thus, our data provide novel mechanisms of HIV survival and toxicity in the current NeuroAIDS era, were viral replication is not a major component due to effective antiretroviral treatments. Our findings identify new potential therapeutic targets to reduce the devastating consequences of NeuroAIDS. Supported by MH52974, MH070297 and MH076679.

MOTOR FUNCTION AND NEUROMETABOLITES IN CHILDREN WITH PRENATAL METHAMPHETAMINE OR NICOTINE EXPOSURE. Fukaya E[1], Chang L[1], Loehaugen G[2,3], Skranes J[2,3], Alicata D[1], Cunningham E[1], Jiang C[1], Ernst T[1]; [1]Department of Medicine, John A. Burns School of Medicine, University of Hawaii Manoa, Honolulu, HI 96813; [2]Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, Trondheim, Norway; [3]Department of Pediatrics, Sorlandet Hospital, Arendal, Norway.

The development of motor skills in children is essential and influences other areas of maturation including cognition and social integration. Whether prenatal methamphetamine (pMETH) or prenatal nicotine (pNIC) exposure affects motor development in children is not well studied. Method: Motor skill ability and neurometabolites were evaluated in children with pMETH or pNIC exposure. The Movement Assessment Battery for Children-2 was used to assess motor skill competence across 3 categories: Manual Dexterity (MD), Aiming and Catching (AC) and Balance (BAL). Scores of 16 stimulant exposed children (7.2±0.3 years old; 6 pNIC, 1 pMETH, 9 pMETH+NIC; 9 boys) and 48 non-exposed children (7.2±0.1 years old; 24 boys) were compared. Proton magnetic resonance spectroscopy (MRS) was performed in 56 of these children (16 stimulant exposed, 40 non-exposed). Results: Exposed subjects scored worse on MD (-17%,

p=0.02) and BAL (-13%, p=0.02), which led to lower overall test scores (-11%, p=0.02), compared to controls. No group difference was found on AC. On MRS, exposed children with higher N-acetylaspartate (NAA) in the anterior cingulate had lower BAL component scores (r=-0.50, p=0.05), while non-exposed children with higher NAA in the anterior cingulate tended to have higher BAL component scores (r=0.21, p=0.23; interaction p=0.02). Conclusions: Prenatal METH or NIC exposure may lead to motor deficits in children. The altered relationship between neuronal marker NAA in the anterior cingulate cortex and motor function suggest an abnormal neurodevelopment in children with stimulant exposure. Supported by 1R01-DA21016, RC2DA029475, 2K24DA016170, K02-DA16991, U54 NS056883, G12RR003061.

DOPAMINE MEDIATED INCREASES IN HIV REPLICATION IN MACROPHAGES ARE DUE IN PART TO INCREASED VIRAL ENTRY. Gaskill PJ[1], Berman JW[1]; [1]Department of Pathology, Einstein, Bronx, NY 105302; Department of Microbiology and Immunology, Einstein, Bronx, NY 10530.

Macrophages are central to the development of HIV-associated neurological diseases (HAND) as major targets for HIV infection in the CNS. The neurological complications of HIV are a major issue among HIV-infected drug abusers, potentially due to the elevated CNS dopamine levels which mediate the effects of drug abuse. We showed previously that elevated dopamine increases HIV replication in macrophages by increasing the number of macrophages infected with HIV. Additionally, we demonstrated macrophages express dopamine receptors (DR) and other dopaminergic proteins through which dopamine may alter HIV infection and other macrophage functions. Our recent data demonstrate that the increased number of macrophages infected with HIV in the presence of dopamine may be due to a dopamine mediated increase in HIV entry into macrophages. Using HIV-virions containing β-lactamase, our data show HIV enters more macrophages in cultures exposed to dopamine. Both the increase in HIV entry and in HIV replication occur at a wide range of dopamine concentrations, and the magnitude of these effects varies by donor. We are currently identifying the receptors involved in this effect using DR agonists. These findings suggest elevated dopamine levels will increase the number of CNS macrophages infected by HIV, potentially increasing the production of inflammatory cytokines and neurotoxic viral proteins. Thus, dopamine may have an significant role in the development of HIV infection of the CNS and may be a common mechanism by which drugs of abuse exacerbate HAND in HIV infected drug-abusers. Supported by NIDA, NIMH.

HAART PROMOTES AMYLOID BETA DEPOSITION IN VITRO AND IN VIVO VIA BACE ACTIVATION. Giunta B[1], Jin J[1], Sadic E[1], Lam L[1], Li L[1], Tan J[2]; [1]College of Medicine, Department of Psychiatry and Neurosciences/Neuroimmunology Laboratory, University of South Florida, Tampa, FL 33613; [2]College of Medicine, Department of Psychiatry and Neurosciences, Silver Child Development Center, University of South Florida, Tampa, FL 33606.

We evaluated the effects of HAART medications (AZT, 3TC, Indinavir, and Abacavir) alone and in combination on: 1) Aβ40, 42 generation in murine N2a cells transfected with the human “Swedish” mutant form of APP and 2) microglial phagocytosis of FITC-Aβ42 peptides in murine N9 microglia. We found HAART compounds (10 μM) increase Aβ generation (~50-200%) in SweAPP N2a cells and inhibit microglial phagocytosis of FITC-Aβ42 peptides in murine microglia. The most significant amyloidogenic effects were observed when HAART were combined ($p<0.05$) (Giunta et al., 2011). HAART effects in vivo are likely to occur over long term exposures (Kiebala et al. 2010). We then examined the EFV containing regimen: EFV /AZT/3TC in vitro (Fig 1). SweN2a cells treated with EFV or EFV/3TC/AZT increased ROS production, β-secretase expression, and Aβ generation. Then in a short-term two-week pilot study in Tg2576 mice. We intraperitoneally (IP) administered EFV/3TC/AZT combined or singly (Fig 2). We found EFV promoted significantly more β-secretase expression, and oligomeric Aβ generation. On the other hand, AZT was the least potent. We then examined ROS levelevels in primary neurons from brains of Balb/C wild type mice. We found EFV promoted significantly more ROS (Fig 3). Finally we performed an Aβ

phagocytosis assay and found that EFV inhibits microglial phagocytosis of Aβ40,42 peptide (Fig 4) suggesting the majority of the toxic properties of the 3TC/AZT/EFV regimen in terms of APP processing and microglial phagocytosis are dependent upon EFV at clinically relevant dose. Supported by 1 K08 MH082642-01A1 (Giunta-PI) (NIH/NIMH).

HUMANIZED MICE TO ASSESS THE HIV-1 CLADE-SPECIFIC DIFFERENCES: APROPOS OF VIRAL VIRULENCE AND NEUROPATHOLOGY. Gorantla S[1], Makarov E[1], Akther S[1], Wood C[2], Gendelman HE[1], Poluektova L[1]; [1]Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198; [2]Nebraska Center for Virology, University of Nebraska at Lincoln, Lincoln, NE 68588.

Effect of HIV-1 genetic variation on viral transmission and pathogenesis is still not understood. Contradicting human reports exist with the occurrence of HIV-associated neurocognitive disorders (HAND) in clade C infected individuals. In vitro studies showed low replication fitness of Subtype C virus in peripheral mononuclear cells leaving the question: what renders the epidemic succes! s of subtype C transmission? Humanized mice with functional human immune system provide the best platform to investigate clade-specific differences in viral virulence, cytopathicity and neurotoxicity. Methods: To this end we infected humanized NOD/scid/gcnull mice, reconstituted at birth with human CD34+ stem cells, using HIV-1ADA (clade-B) or C1157 (Clade C primary isolate). Blood was collected every 2w post infection to measure viral load and CD4, CD8 T cells by FACS analysis. At 8-12w, mice were sacrificed to collect spleen, lymph nodes and brain for immunohistology. Results: Predominance of viral replication in clade C infected mice is observed. Even with higher viral loads, CD4+ T cell depletion was minimal in clade C infected mice compared to significant depletion in clade B infection. Higher percentage of clade C infected mice had signs of meningitis. However, neuropathology in different regions of brain was comparable between both clades. Conclusion: Elucidating differences in viral replication pattern and the relationship to neurotoxicity between HIV-1 clades B and C in humanized mice provide important insights needed to clarify the disparity seen in HAND incidence.

PURINERGIC RECEPTORS ARE REQUIRED FOR HIV-1 INFECTION OF PRIMARY HUMAN MACROPHAGES. Hazleton JE[1], Berman JW[1,2], Eugenin EA[1]; [1]Departments of Pathology, Albert Einstein College of Medicine, Bronx, NY 10461; [2]Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, NY 10461.

Macrophages play a significant role in HIV infection, viral rebound, and in the development of NeuroAIDS. However, the function of host proteins in viral replication is incompletely characterized in macrophages. Purinergic receptors, P2X and P2Y, are major components of the macrophage immune response to pathogens, inflammation and cellular damage. We demonstrate that these receptors are necessary for HIV infection of primary human macrophages. Inhibition of purinergic receptors results in a significant reduction in HIV replication in macrophages. This inhibition is independent of viral strain and is dose dependent. We also identify that P2X1, P2X7 and P2Y1 receptors are involved in viral replication. We show that P2X1, but not P2X7 or P2Y1, is necessary for HIV entry into macrophages. We demonstrate that interaction of the HIV surface protein gp120 with macrophages stimulates an increase in ATP release. Thus, we propose that HIV's binding to macrophages triggers a local release of ATP that stimulates purinergic receptors and facilitates HIV entry and subsequent stages of viral replication. Our data implicate a novel role for a family of host proteins in HIV replication in macrophages and suggest new therapeutic targets to reduce the devastating consequences of HIV infection and AIDS. Supported by the National Institutes of Mental Health grants MH075679 to J.W.B., MH076679 to E.A.E. and NIH Centers for AIDS.

TCF4 BINDS DIRECTLY TO THE HIV LTR AND ASSOCIATES WITH NUCLEAR MATRIX PROTEIN SMAR1 TO REPRESS HIV TRANSCRIPTION IN ASTROCYTES. Henderson LJ[1], Narasipura SD[1], Adarichev V[2], Kashanchi F[3], Al-Harthi L[1]; [1]Department of Immunology and Microbiology, Rush University Medical Center, Chicago, IL 60612; [2]Department of Medicine,

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Astrocytes are generally restricted in HIV replication but under certain triggers can support productive HIV infection. We previously established that inhibiting β-catenin signaling triggers productive HIV replication in astrocytes. We also determined that knockdown of β-catenin or its transcriptional partner TCF4 enhances docking of elongation-competent RNA Polymerase II, suggesting that β-catenin/TCF4 repress HIV at the level of transcription. To directly assess the impact of β-catenin/TCF4 on HIV transcription, we evaluated whether β-catenin/TCF4 associate directly with HIV LTR. We identified four novel TCF4 binding sites on the LTR located at -336, -143, +66 and +186 from the +1 transcription initiation site. Strongest binding was observed at the -143nt site. By chromatin immunoprecipitation we confirmed that TCF4 and β-catenin are docked on the LTR at -143nt but are removed when this site is deleted. Furthermore, deletion or mutation of the -143nt TCF4 binding site in combination with knockdown of β-catenin or TCF4 enhanced basal HIV LTR activity by 4-fold in astrocytes that stably express an LTR-luciferase construct but had no effect on Tat-mediated transactivation. We further show that TCF4 is associated with nuclear matrix protein SMAR1 at -143nt site. These data suggest that β-catenin/TCF4 interact with SMAR1 at -143nt and may render this region inaccessible to transcriptional machinery. Disrupting this complex in astrocytes may account for a more permissible state for HIV productive replication. Supported by F31 NS071999 to LJH and R01NS 060632 to LA.

EXECUTIVE FUNCTIONING AND CORTISOL RESPONSES IN YOUNG CHILDREN WITH PRENATAL STIMULANT EXPOSURE. Hernandez AB[1], Cloak CC[1], Dowland S[1], Carlson S[2], Ernst TM[1], Chang L[1]; [1]Department of Medicine, University of Hawaii, Manoa , John A. Burns School of Medicine, Honolulu, HI 96813; [2]Institute of Child Development, University of Minnesota, Minneapolis, MN 55455.

Introduction: A significant portion of women continues to use stimulants (STIM), including methamphetamine (METH, up to 5%) and nicotine (NIC, ~16%), during their pregnancy. Whether prenatal STIM exposure affects executive function and stress response in children is unknown. Methods: Neuropsychological performance and salivary cortisol levels before and after an MRI scan (as a stressor) were evaluated in 140 children ages 3-5 years. 83 were exposed prenatally to STIM (47.4±0.8 months old, 50 boys; 27 NIC-exposed, 18 METH-exposed, 38 METH+NIC exposed) and 57 were unexposed to drugs (Controls: 46.6±0.6 months old, 28 boys). Results: No significant group differences were seen on four executive function tests: Day/Night (Stroop), Grass/Cloud (Stroop), Separated Cool Card Sort (SCCS, set-shift), and Gift Delay (inhibitory control). However, girls performed better than boys on the Grass/Cloud ($p=0.02$) and SCCS ($p=0.007$). Although salivary cortisol levels showed no group difference at baseline, the controls had elevated cortisol while the STIM group had no change in cortisol (a blunted stress response) after the MR scan (interaction-$p=0.03$). Unexposed girls who had a higher stress response showed trends for poorer performance. Conclusion: Prenatal STIM exposure may not impact early executive function but may lead to a blunted stress response in these children. The lack of a cortisol response in the STIM group may also be due to their adaptation to chaotic home environments. Longitudinal follow-ups with neuroimaging and HOME assessments of these children are ongoing. Supported by NIH (1R01-DA21016; 2K24-DA16170; K02-DA16991; K01-DA21203; 1U54-NS56883; 1P20-RR11091; 5G12-RR003061).

PERSISTENT HUMORAL IMMUNE RESPONSES IN THE CNS LIMIT RECOVERY OF REACTIVATED MURINE CYTOMEGALOVIRUS. Hu S[1], Mutnal MB[1], Lokensgard JR[1]; [1]Center for Infectious Diseases and Microbiology Translational Research, University of Minnesota Medical School, Minneapolis, MN 55455.

Previously we have determined that CD8+ T lymphocytes are required to restrict acute, productive MCMV infection within the central nervous system (CNS). In this study, we investigated

the contribution of humoral immune responses in control of viral brain infection. We examined B-lymphocyte-lineage cells and assessed their role in controlling the recovery of reactivated virus from latently-infected brain tissue. Brain infiltrating leukocytes were first phenotyped using markers indicative of B-lymphocytes and plasma cells. Results obtained during these studies showed a steady increase in the recruitment of B-lymphocyte-lineage cells into the brain. Further, MCMV-specific antibody secreting cells were detected within the infiltrating leukocyte population using an ELISPOT assay. Immunohistochemical studies of brain sections revealed co-localization of CD138+ cells with either IgG or IgM. Additional immunohistochemical staining for MCMV early antigen 1 (E1, m112-113), a reported marker of viral latency in neurons, confirmed its expression in the brain during latent infection. Finally, using B-cell deficient (Jh-/-) mice we demonstrated that B lymphocytes control recovery of reactivated virus from latently-infected brain tissue. A significantly higher rate of reactivated virus was recovered from the brains of Jh-/- mice when compared to Wt animals. Taken together, these results demonstrate that MCMV infection triggers accumulation and persistence of B-lymphocyte-lineage cells within the brain which produce antibodies and! play significant role in controlling reactivated virus. Supported by National Institute of Neurological Disorders and Stroke/R01NS-038836.

FOXO3A REGULATES INFLAMMATORY MONONUCLEAR PHAGOCYTE ACTIVATION IN HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS. Huang Y[1], Zheng J[1]; [1]Department of Phamacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198 5930.

Aberrant immune activation is considered a critical factor in the pathogenesis of HIV-associated neurocognitive disorders (HAND). In HAND, HIV-1-infected and immune-activated brain mononuclear phagocytes (MP; perivascular macrophages and microglia) drive excessive inflammation within the central nervous system. FOXO3a, a predominant Forkhead transcription factor expressed in MP, plays an important role in the regulation of metabolism and innate immunity. In the present study, we investigated the involvement of FOXO3a in the activation of MP during HAND. Our data demonstrated that inflammatory stimuli regulated the phosphorylation of FOXO3a, a critical post-translational modification that decreases the activity of FOXO3a. Overexpression of FOXO3a through an adenovirus delivery system reduced TNF-α production in HIV-1-infected macrophages. In contrast, when challenged with inflammatory stimuli, microglia isolated from FOXO3a knockout mice demonstrated increased inflammatory cytokine expression and neurotoxin glutamate production compared with microglia from wild type mice, suggesting that FOXO3a inhibits microglia inflammatory response and neurotoxic potential. This immunomodulatory function of FOXO3a was further confirmed in a murine brain inflammation model where we intracranially injected cytokines into the basal ganglia of FOXO3a knock out or wild type FVB mice. These findings support that FOXO3a activity is an underlying component of the inflammatory environment perpetuated by HIV-1 infection and that modifying its function may have therapeutic benefits in HAND. Supported by R01 NS 41858-01, R01 NS061642-01, 3R01NS61642-2S1, R21 MH 083525-01, P01 NS043985, and P20 RR15635-01 (JZ).

PHAGOCYTIC UPTAKE OF HIV-1-INFECTED APOPTOTIC T CELL BODIES FACILITATES HIV-1 ENTRY INTO RENAL TUBULAR CELLS. Husain M[1], Lan X[1], Goel H[1], Singh P[1], Malhotra A[1], Singhal PC[1]; [1]Department of Medicine/Nephrology, Hofstra North Shore-LIJ School of Medicine, Great Neck, NY 11021.

Renal tubular cells have been reported to serve as a reservoir for HIV-1 in humans. Entry of HIV-1 in these cells, however, remains to be determined. Since phagocytic activity of proximal renal tubular cells is well documented, we hypothesized that HIV-1 may enter tubular cells by phagocytosis of apoptotic fragments of HIV-1-infected T cells. We evaluated the expression of PD-1 on CD4 T cells and PD-L1 on HK2 and primary tubular (PTEpiC) cells with or without morphine. Then, control or HIV-1 infected T cells were co-cultured with HK2 cells followed by analysis of T cell apoptosis by FACS and HIV-1 expression in HK2 by RT-PCR. To examine uptake of apoptotic

T cells or fragments, GFP reporter T cells were infected with NL4-3 virus followed by co-cultivation with HK2. Further, MT2 cells were infected with NLC4-3EGFP reporter virus and co-cultured with PTEpiC. PD-1 expression was found in 12% of CD4 cells while 65% HK2 cells showed PD-L1 expression. Co-culture revealed significant apoptosis in T cells and HIV-1 expression in HK2 cells while use of inhibitors of apoptosis/phagocytosis reversed the above observations. Significant number of HK2 and PTEpiC showed partial GFP expression indicating phagocytosis of apoptotic T cells or their fragments. Morphine enhanced the expression of PD-L1 in PTEpiC. These observations do indicate induction of T cell apoptosis and subsequent phygocytosis of HIV-laden apoptotic bodies by tubular cells and thus the transfer of HIV-1. Increase in PD-L1 on PTEpiC by morphine may enhance T cells apoptosis and therefore, may increase viral entry too. Supported by NIDDK.

LECTIN MEDIATED CNS RECRUITMENT OF DENDRITIC CELLS. Jain P[1], Sagar D[1], Foss C[2], Khan ZK[1], Pomper M[2]; [1]Department of Microbiology and Immunology, Drexel University College of Medicine, Doylestown, PA 18902; [2]Department of Radiology, Johns Hopkins University, Baltimore, MD 21210-2519.

Although it has been established that dendritic cells (DCs) are pivotal players in the development of CNS autoimmune inflammation, the molecular mechanisms of how circulating DCs gain access to the CNS have not been understood. In this respect, importance of glycan binding proteins such as C type lectin (DC-SIGN), sialic acid binding Ig-like lectins (Siglec-10) and selectins (slex and L-selectin) remain to be evaluated. Our current efforts in studying the importance of DC-specific lectin receptors to delineate the mechanistic efficacy of these cells during transmigration sheds light on the ability of DCs to be better responders that other immune cells. While both MCP-1 dependent chemotaxis and lectin binding underlie a common mechanism of DC transmigration irrespective of disease model, the functional potential of these cells can only be expressed once they encounter disease-specific antigen in the CNS. Uncontrolled antigen presentation can give rise to neuroinflammatory disease such as multiple sclerosis, while defective presentation capability can allow tumors to evade immune cells and metastatize. We have found that antigen presentation functionality of DCs is indeed compromised in vitro upon mimicking hypoxic conditions found in a tumor micro-environment. Also, T cell proliferation, important for generating anti-tumor response has been shown to be affected during hypoxia conditions. Thus, DC-BBB interaction can be selectively exploited to positively or negatively regulate migration in order to potentiate cancer immunothe! rapeutic strategies or suppress autoimmunity.

DYNAMICS OF DENDRITIC CELLS AND T CELLS IN HTLV-1 ASSOCIATED ONCOGENESIS AND NEUROINFLAMMATION: IMPLICATIONS IN IMMUNOMODULATORY THERAPIES AND DIAGNOSTIC TOOLS. Jain P[1], Manuel S[1], Makedonas G[2], Betts M[2], Gardner J[2], Goedert J[3], Khan ZK[1]; [1]Department of Microbiology and Immunology, Drexel University College of Medicine, Doylestown, PA 18902; [2]Department of Microbiology and Immunology, University of Pennsylvania School of Medicine, Philadelphia, PA 19104; [3]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD 20892-7335.

Human T-cell leukemia virus type 1 (HTLV-1) is the etiologic agent of two immunologically distinct diseases: adult T-cell leukemia (ATL) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). Although the HTLV-1-specific CD8+ cytotoxic T cell response is seen in both pathogenic states, its actual significance in preventing viral load and controlling disease progression remains questionable. Utilizing a newly standardized dendritic cell and a T cell polychromatic antibody cocktail, we investigated the immune activation of these cells in a patients' cohort from Jamaica including HTLV-1 seronegative controls, asymptomatic carriers (ACs), ATL, and HAM/TSP. Extensive immune profiling revealed that CD8+ T cells from both HAM/TSP and ATL patient samples demonstrated some functional responses, albeit to a much lesser extent than those responses seen in ACs. Furthermore, DCs from HTLV-1-diseased individuals exhibited an altered maturation and adhesion phenotype as compared to ACs. The expression of an inhibitory

molecule PD-1 and its ligand, PD-L1 was upregulated in CTLs and DCs, respectively in both diseased groups. While comparing the matched proviral loads to the flow cytometry results, we identified uni! que immune signatures distinguishing ACs from ATL and HAM/TSP patients. Collectively, these results suggest that modulation of both DCs and CD8+ T cells and/or blockade of the PD-1/PD-L1 pathway may be useful in therapeutic interventions of ATL and/or HAM/TSP.

ANTIRETROVIRAL ACTIVITY AND BRAIN PENETRANCE OF FOLATE-COATED NANOFORMULATED ANTIRETROVIRAL DRUGS. Kanmogne GD[1], Roy U[1], Liu Z[1], McMillan J[1], Gorantla S[1], Balkundi S[1], Smith N[1], Alnouti Y[2], Gautam N[2], Poluektova L[1], Kabanov A[2], Bronich T[2], Gendelman HE[1]; [1]Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE, 68198-5215; [2]Department of Pharmaceutical Sciences, University of Nebraska Medical Center, Omaha, NE, 68198-6025.

Despite the effectiveness of combination antiretroviral therapy (cART) in reducing morbidity and mortalities, HIV-associated neurocognitive disorders remains a highly prevalent co-morbid condition. This may be due, in part, to the poor ART penetrance into the CNS and continuance of the brain viral reservoir. Thus, even when ART can reduce viral load in the periphery, productive HIV infection can continue in the CNS. Increasing ART penetration in the brain could help reduce the CNS viral load and diminish injury and death of neural cells. We previously demonstrated macrophage uptake of nanoformulated crystalline antiretroviral drugs (nanoART; atazanavir, ritonavir, indinavir, and efavirenz), and demonstrated that nanoART transfer from mononuclear phagocytes to human brain microvascular endothelial cells can be realized through cell-to-cell contacts. To translate the cell assays into relevant animal models of disease ritonavir and atazanavir nanoformulations were injected into HIV-1 infected NOD/scid-gamma-null mice reconstituted with human peripheral blood lymphocytes. Atazanavir and ritonavir levels in brains of mice treated with folate-coated nanoART were 3 to 4-fold higher than in mice treated with non-coated particles. This was associated with decreased viral load in the spleen and brain, and diminished brain CD11b-associated glial activation. We postulate that folate modification of nanoART could facilitate drug entry into the brain. Supported by NIH grants RO1MH081780 (to GDK), 1P01DA028555, and P01 NS043985 (to HEG and GDK).

MONONUCLEAR PHAGOCYTE INTERCELLULAR CROSSTALK FACILITATES TRANSMISSION OF CELL TARGETED NANOFORMULATED ANTIRETROVIRAL DRUGS TO HUMAN BRAIN ENDOTHELIAL CELLS. Kanmogne GD[1], Liu X[1], McMillan J[1], Balkundi S[1], Zhou Y[2], Gendelman HE[1], Singh S[1]; [1]Departments of Pharmacology and Experimental Neuroscience , University of Nebraska Medical Center, Omaha, NE 68198-5215; [2]Center for Biotechnology, University of Nebraska-Lincoln, Lincoln, NE 68588.

Despite the successes of antiretroviral therapy (ART) HIV-associated neurocognitive disorders remains prevalent in infected people. This is due, in part, to incomplete ART penetrance across the blood-brain barrier (BBB) and the establishment of viral sanctuaries within the central nervous system. In efforts to improve ART delivery our laboratories developed a macrophage-carriage system for nanoformulated crystalline antiretroviral drugs (nanoART; atazanavir, ritonavir, indinavir, and efavirenz). We demonstrate that nanoART transfer from mononuclear phagocytes (MP) to human brain microvascular endothelial cells (HBMEC) can be realized through cell-to-cell contacts, which can facilitate drug passage across the BBB. Co-culturing of donor MP containing nanoART with recipient HBMEC facilitates intercellular particle transfer. NanoART uptake was observed in up to 52% of HBMEC with limited cytotoxicity. Folate-coating of nanoART increased MP to HBMEC transfer to up to 77%. We postulate that monocyte-macrophage transfer of nanoART to brain endothelial cells could facilitate drug entry into the brain. Supported by NIH grants RO1MH081780 (to GDK), 1P01DA028555, P01 NS043985, and P20 RR15635 (to HEG and GDK).

POTENTIATING DENDRITIC CELLS TO TARGET HYPOXIC ENVIRONMENT OF BRAIN TUMOR. Khan ZK[1], Masih S[1], Karatas E[1], Sagar D[1], Jain P[1]; [1]Department of Microbiology and

Immunology, Drexel University College of Medicine, Doylestown, PA 18902.

Recent studies clearly demonstrated the ability of dendritic cells (DCs) to migrate into the central nervous system (CNS) during neuroinflammation; however, their potential as immunotherapeutic for CNS disorders still remains to be exploited. Glioblastoma multiforme (GBM) is the most common type of brain tumor, as well as the most malignant with mean survival time of 1 year. The most difficult problem to treat tumors is their hypoxic microenvironment that changes the phynotypic characteristic of immune cells. In hypoxic conditions, HIF-1α, a transcription factor, stimulates various genes that promote angiogenesis and tumor growth, is accumulated in large amounts. Our hypothesis is to equip DCs with anti-HIF-1α through antisense RNA technology in order to improve their antigen presenting capacity under hypoxic conditions. We began our experiment with cloning antisense sequence HIF-1α under CMV promoter and a hypoxia-response elements (3X HRE) sequence just before CMV promoter, which helps promote the transcription of asHIF-1α. Monocytes were separated from fresh PBMC's and differentiated into MDDCs (monocyte derived dendritic cells) using IL-4 and GM-CSF. Initial transfection results using the pRNAT-CMV3.2/Neo vector showed desired efficiency and confirmed the ability of MDDCs to take up the plasmid. Experiments are ongoing to assess the potential of plasmid-bearing DCs in vitro as well as in vivo in a mouse model of glioblastoma. This translational approach has applicability in eradicating tumors by DC-based vaccination or being adjunct to existing radio- and chemotherapy.

MCP-1 EXHIBITS PROFOUND EFFECT ON THE TRAFFICKING OF DENDRITIC CELLS INTO THE CENTRAL NERVOUS SYSTEM. Khan ZK[1], Sagar D[1], Rahman S[1], Manuel S[1], Jain P[1]; [1]Department of Microbiology and Immunology, Drexel University College of Medicine, Doylestown, PA 18902.

Immune cell infiltration across the blood-brain barrier (BBB), uncontrolled activation and antigen presentation are influenced by chemokines secreted at the neurovasculature. MCP-1 is one such potent chemoattractant known to be secreted by the astrocytes found at the BBB. It is upregulated in most CNS disorders, making it a key factor in chemoattracting leukocytes to transmigrate into the CNS. To characterize the mechanisms of leukocyte trafficking in the presence of MCP-1, we have studied transmigration by utilizing the one-cell and three-cell in vitro models of the BBB consisting of primary human brain-derived microvascular endothelial cells (HBMVEC), astrocytes and neurons. To investigate efficacy of transmigration, dendritic cells (DCs), monocytes, CD4 and CD8 T cells were compared in the absence and presence of MCP-1. We have demonstrated that non-activated DCs exhibit a greater migratory potential compared to other immune cells tested during steady state. Activation of these cells enhances their trafficking across the BBB. Similarly, stimulation with the chemokine MCP-1 facilitates transmigration of both non-activated and activated leukocytes with DCs again being the top responding cells. These observations were also complemented by in vitro imaging data. We have also determined that the one-cell model of BBB is comparable to the three-cell BBB model. In summary, the findings in this study indicate that MCP-1 plays an important role in enhancing transmigration of immune cells, particularly DCs, across the BBB, suggesting its potential use in immune therapy.

NEUROIMMUNE INTERACTION IN THE ADRENAL GLAND OF HUMANIZED MICE: A POSSIBLE ROLE DURING HIV-1 INFECTION. Knibbe J[1], Makarov E[1], Gutti T[1], Dash PK[1], Gorantla S[1], Poluektova L[1]; [1]Pharmacology Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68168.

Background: The adrenal gland (AG) produces steroids (from cortex) and catecholamines (from medulla) to influence stress and anxiety-related behavioral and physiological phenotypes. The less investigated region between cortex and medulla, called the x-zone became the interest of this study because we found human immune cells after transplantation of CD34+ hematopoietic stem cells into NOD/scid/γ_c^{null} (hu-NSG) mice. Much remains unknown of AG and x-zone function in hu-NSG during HIV-1 infection. This finding may demonstrate an important neuroimmune interaction in relation to HIV-1 infection of humanized mice. Methods: AGs were collected from NSG mice: 8

humanized and 7 control mice, with ages ranged from 6-18 months. 5μ-thickness sections of tissues were stained with HLA-DR and tyrosine hydroxylase (TH) antibodies. The ratio of cortex:medulla (c:m), number and distribution of human cells were analyzed. Results: All healthy mice had a smaller medulla than cortex, with human cells in the x-zone. Females had ~3.95:1 c:m ratio and males had ~2.6:1. Healthy appearing infected hu-NSG had ~3.7:1. Animals that developed signs of sickness showed significant reduction of the cortex with inverted c:m ratios and sporadic, multinucleated human cells in medulla and cortex. Older mice had normal c:m ratios, but TH+ zone was irregular and spread-out. Conclusion: From the analyzed AG data we assume aging, presence of human immune activated cells, and HIV-1 infection affects the steroid-producing cortical part of mouse AG. Correlation of morphology of AG with function needs to be investigated.

ACCELERATED CAUDATE ATROPHY IN HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART)-TREATED HIV SUBJECTS OVER THREE YEARS. Kogachi S[1], Chang L[1], Sadino J[1], Jiang CS[1], Ernst TM[1]; [1]Department of Medicine, John A. Burns School of Medicine, University of Hawaii at Manoa, Honolulu, HI 96813.

HIV infection is associated with cortical and subcortical brain atrophy, which can affect cognitive abilities. Few studies evaluated longitudinal brain changes in HIV subjects. Methods: Neuropsychological tests and structural MRI were performed at baseline and annually (up to 3 years) in 70 subjects: 35 seronegative controls (SN) ages 47.4±1.6 years and 35 HIV+ subjects ages 43.7±2.3 years maintained on HAART (14 had HIV-associated neurocognitive disorder). Automated morphometry assessed volume changes in 16 subcortical regions. Repeated measures ANCOVAs were performed (time and status as main effects, baseline age and scanner upgrade as covariates). Results: HIV subjects had CD4 counts (409.5±28.6/mm3), nadir CD4 (183.1±27.1/mm3), log viral load (2.7±0.2), HIV dementia scales (14.2±0.3), Karnofsky scores (92.0±1.6) and global cognition scores (-0.3±0.1). HIV subjects showed smaller volumes than SN in all regions, especially the thalamus, over 3 years. Both groups had smaller volumes in the right thalamus, right caudate, and right hippocampus 2-3 years later compared to baseline. HIV subjects showed greater atrophy than SN over 3 years in both caudates (interaction-$p<0.006$). Conclusion: Despite HAART, HIV subjects continue to show accelerated atrophy in the caudates and smaller subcortical structures compared to SN over 3 years. These findings are consistent with prior studies, showing greater caudate atrophy (prior to HAART) and premature brain atrophy in HIV patients. A larger sample size and longer duration of follow-ups are needed to further assess the aging effects. Supported by 2R01-MH61427; 2K24-DA16170, U54NS56883; G12RR003061.

CENTRAL ROLE OF CYTOCHROMES P450 (CYP) IN ALCOHOL-MEDIATED OXIDATIVE STRESS AND ALCOHOL-ANTIRETROVIRAL THERAPY (ART) INTERACTIONS. Kumar S[1], Jin M[1]; [1]University of Missouri-Kansas City, School of Pharmacy, Kansas City, MO 64108.

Mild-to-moderate alcohol consumption, which is highly prevalent in HIV+ persons, is known to increase HIV-1 replication, reduce ART efficacy, and increase ART toxicity. We hypothesize that 1) CYP2E1 plays a central role in alcohol-mediated HIV-replication through increased oxidative stress and 2) CYP3A4 plays a central role in alcohol-mediated reduced ART efficacy and increased ART toxicity. CYP2E1 metabolizes alcohol and causes oxidative stress-mediated liver toxicity, while CYP3A4 metabolizes ARTs, especially protease inhibitors (PI). To test our hypotheses we used in-vitro HIV-1 model monocyte-derived macrophage (MDM) cell line, U937 and recombinant CYP3A4 enzyme, in addition to ex-vivo monocyte samples from alcoholic/HIV+ persons. Initial results demonstrated the expression of CYP2E1 and CYP3A4 and their further inductions by alcohol in U937 cells. Subsequently, we demonstrated the role of oxidative stress dependent MEK/Erk-JNK pathway in alcohol-mediated induction of CYP2E1 in U937. The in vitro inhibition studies using recombinant enzyme showed unique interactions of eight PIs with CYP3A4. The PIs-CYP3A4 interactions were selectively altered by alcohol, suggesting that alcohol selectively alters CYP3A4-mediated metabolism of PIs. Finally, our preliminary ex-vivo study showed very high induction of

CYP2E1 and CYP3A4 in alcoholic and HIV+ persons. Future studies using HIV-infected MDM and alcoholic/HIV+ human monocytes are underway. The current and future studies would help find novel interventions and optimal ART regimens for alcoholic/HIV+ persons. Supported by NIH grants DA031616-01 and AA015045.

IMPULSIVENESS AND RISKY BEHAVIOR IN HIV-INFECTED AND NICOTINE SMOKING INDIVIDUALS. Lau EK[1], Chang L[1], Holt J[1], Jiang CS[1], Lum M[1]; [1]Department of Medicine, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI 96813.

Introduction: HIV+ individuals have higher prevalence of stimulant drug abuse, including nicotine smoking. Both HIV and stimulant use may be related to increased impulsiveness. Whether these factors are additive or interactive is unknown. Methods: A 2x2 study was performed, with 23 seronegative (SN, 13 non-smokers, 10 smokers) and 17 HIV+ subjects (13 non-smokers, 4 smokers). Each completed the Barratt Impulsiveness Scale-11 (BIS, which assesses attention, motor, self-control, cognitive complexity, perseverance and cognitive instability), the Iowa Gambling Task (IGT, choosing cards out of 4 decks to maximize money won), and the Balloon Analogue Risk Task (BART, a computerized test for risky behavior), during functional MRI (fMRI). Results: HIV subjects had higher BIS total scores than SN (+10.2%, p=0.028). HIV smokers netted less money than HIV non-smokers, while SN smokers performed better than SN non-smokers (interaction-p=0.04). Similarly, HIV smokers had greater losses in total money than HIV non-smokers, while SN smokers lost less than SN non-smokers (interaction-p=0.035). HIV subjects also won less money on the BART than SN (p=0.01). Conclusion: Our findings suggest that: 1) HIV subjects had higher impulsivity. 2) Nicotine smoking may lead to more risk-taking in HIV subjects, who preferred the higher risk decks that led to less money, but may promote relaxation in SN subjects. Nicotine smoking may increase impulsivity in HIV subjects, and may lead to a higher risk for HIV transmission and drug abuse. Correlations with fMRI data are ongoing. Supported by NIH Grant Support: (2K24-DA16170, U54NS56883, G12RR003061).

FUNCTIONAL ROLE OF MICRORNAS IN HIV-ASSOCIATED NEPHROPATHY. Malhotra A[1], Rai P[1], Singhal PC[1]; [1]Feinstein Institute for Medical Research, Hofstra North Shore-LIJ School of Medicine, Great Neck, NY 11021.

We have demonstrated the activation of mTOR pathway in HIV-associated nephropathy (HIVAN) and rapamycin (R), an inhibitor of mTOR pathway has been used to attenuate polycystic kidney disease in animal experimental models. However, the precise role of microRNAs, endogenous RNA oligonucleotides which specifically target mRNA and regulate gene expression in HIVAN is not functionally known. Methods: Kidneys were harvested from FVB/N and Tg26 mice at 8wks of age (n=3). In another group, mice were given rapamycin (5mg/kg, ip, alternate day; Tg+R) for 4 weeks. Total RNA from renal tissue (n=3) was isolated from FVB/N (controls), Tg26 and Tg+R by Triozol reagent (Invitrogen). A complete miRNA microarray was performed in these groups and a data analysis was generated. Real-Time qPCR was performed to confirm the miRNA microarray data by using forward primers and universal qPCR primers (Invitrogen). Results: TG26 mice showed altered expressions of mir-145(C=18793±2273,Tg=8454±1255, and R=13910±3232, Arbitrary Units; AU; $p<0.04$), mir-16(C=11594±1393, Tg=5758±1898, and R=10373±3484 AU; $p<0.05$), mir-30c (C=22517±2908, Tg=15486±1992, and R=19537±4178 AU; $p<0.07$), mir-466 (C=8274±1038, Tg=12856±1754, and R=9623±3237 AU; $p<0.09$) which were reversed by R. These results were confirmed by qRT-PCR. Conclusions: These microRNAs have been considered to play key roles in many cellular processes such as proliferation, differentiation and apoptosis by inhibiting targeted gene expression. Our results demonstrate that the above selective bioregulators could have a functional impact in HIVAN. Supported by Funding: NIDDK Support.

MENINGES AS POTENTIAL ORGANIZERS OF NEUROGENESIS, NEURO-INFLAMMATION, NEURO-IMMUNE AXIS, RESPONSE TO INJURY AND KEY PLAYERS IN NEUROLOGICAL DISORDERS. Mercier F[1], Arikawa-Hirasawa E[2], Chyba M[3], Douet V[4], Cho Kwon Y[3], Vellinga D[1],

Chang L[4]; [1]Department of Tropical Medicine, Medical Microbiology and Pharmacology, JABSOM, University of Hawaii, Honolulu, HI 96822; [2]Research Institute for Diseases of Old Age, Juntendo University Faculty of Medicine, Tokyo, 113-8421, Japan; [3]Department of Mathematics, University of Hawaii, Honolulu, HI 96822; [4]MR Research Center, Queen's Medical Center, JABSOM, University of Hawaii, Honolulu, HI 96813.

Meninges are typically described as brain coverings without role in brain function. In fact, meninges deeply penetrate th! e brain structure as falx cerebri, tentorium cerebelli, vascular adventitia, choroid plexus stroma and sulci. Meningeal cells connect to each other by gap junctions to form a continuous network throughout the dura, pia-arachnoid and internal meninges. We found that internal meninges comprise a developed system of extracellular matrix (ECM), including fractones, the specialized ECM of the subventricular zone (SVZ). Fractones contain collagens, laminins and heparan sulfate proteoglycans (HSPG) and appear as ultrastructurally visible fragments (fractals) contacting multiple processes of glia, neurons, neural stem cells. We have shown that fractone-associated HSPG capture and promote growth factor activity in the brain ventricle walls; 6OHDA ablation of meningeal cells at the brain surface modifies neurogenesis in the SVZ, the principal neurogenic niche; mechanical brain injury raises expression of HSPG in the meninges of the wounded site. We also found deep anatomical alterations of the meninges and fractones in BTBR T+ tf/J mice, animal! model for autism. Together, our results support the view that meninges and fractones form a functional apparatus that organizes growth factor/cytokine activity throughout the brain and plays a crucial role in autism. We currently investigate whether meninges/fractones are deteriorated by substances of abuse, and develop mathematical models to understand the role of meninges/fractones in neural alterations leading to autism. Supported by NIH RCMI 5G12/A103061; NIH R21 NS057675; NSF DUE-0634624, Japanese Society for the Promotion of Sciences S09109.

HIV-1 LTR SINGLE NUCLEOTIDE POLYMORPHISMS (SNPS) CORRELATE WITH DISEASE PARAMETERS. Nonnemacher MR[1], Pirrone V[1], Aiamkitsumrit B[1], Shah S[1], Wojno A[1], Passic S[1], Blakey B[1], Zhong W[1], Moldover B[3], Feng R[4], Randazzo C[4], Downie D[2], Lewis S[2], Jacobson J[2], Wigdahl B[1]; [1]Department of Microbiology and Immunology, Institute for Molecular Medicine and Infectious Disease, Drexel University College of Medicine, Philadelphia, PA 19102; [2]Department of Medicine, Division of Infectious Diseases and HIV Medicine, Drexel University College of Medicine, Philadelphia, PA 19102; [3]B-Tech Consulting, Ltd, N/A, Philadelphia, PA 19130; [4]Department of Biostatistics and Epidemiology, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, PA 19104.

The long terminal repeat (LTR) regulates HIV-1 gene expression by interacting with multiple host and viral factors. Cross-sectional studies in the pre-HAART era demonstrated that single nucleotide polymorphisms (SNPs) in C/EBP site I and Sp site III from peripheral blood-derived LTRs increased in frequency as disease severity increased and correlated with HIV-1-associated dementia. Current studies focus on the identification of LTR signatures derived from peripheral blood proviral DNA that can be used as molecular markers to identify HIV-1-infected individuals more prone to developing advanced disease and/or neurologic disease. A prospective, longitudinal study was conducted on 458 HIV-1 seropositive patients currently enrolled in the DREXELMED HIV/AIDS Genetic Analysis Cohort in Philadelphia, PA. History of clinical parameters and comorbities were collected approximately every 6 months. The collection of extensive clinical parameters on these patients have allowed for cross-population and longitudinal analyses of the impact of these parameters on the development of SNPs during the course of disease. To date, SNPs have been identified that associated with CD4 T-cell count and viral load. In addition, SNPs were identified that associated with change in CD4 T-cell count and change in viral load. These results suggest that the HIV-1 genomic swarm may evolve during the course of disease in response to selective pressures that lead to changes in prevalence of LTR SNPs that may be predictive of more advanced HIV disease and that may result in alterations in viral function. Supported by NIH/NINDS: R01 NS32092; NIH/NIDA: R01 DA19807; NIH/NIMH: T32 MH079785.

PANNEXIN1 HEMICHANNELS ARE CRITICAL FOR HIV INFECTION OF HUMAN PRIMARY CD4+ T LYMPHOCYTES. Orellana JA[1], Williams DW[2], Sáez JC[3], Berman JW[2,4]; Eugenin EA[2]. [1]Departamento de Neurología, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile; [1]Departments of Pathology, Albert Einstein College of Medicine, Bronx, NY 10461; [3]Departamento de Fisiología, Pontificia Universidad Católica de Chile, Santiago, Chile. [4]Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, NY 10461.

Human immunodeficiency virus-1 (HIV) is a major public health issue and infection of CD4+ T lymphocytes is one of its major features. While several cellular proteins have been identified that facilitate viral infection and replication, the role of hemichannels in these processes has not been well characterized. We now show that HIV isolates, R5 and X4, induced biphasic opening of Panx1 hemichannels. There was a transient early (5-30 min) and a later persistent (48-120 h) opening of Panx1 hemichannels. This HIV mediated Panx1 hemichannel opening was dependent on HIV's binding to CD4 and CCR5/CXCR4 receptors. The blocking of Panx1 hemichannels by reducing channel opening or protein expression by using antibodies/peptides or siRNA, completely inhibited HIV replication in CD4+ T lymphocytes. Thus, our findings demonstrate that another host protein, Panx1 hemichannels, is essential for HIV infection/replication. Supported by MH52974, MH070297 and MH076679.

CEREBROSPINAL FLUID MIRNA PROFILE IN HIV-ASSOCIATED NEUROLOGICAL DISORDERS. Pacifici M[1], Delbue S[4], Ferrante P[2], Jeansonne D[1], Kadri F[1], Nelson S[3], Peruzzi F[1]; [1]Lousianna State University Health Sciences Center, Neurological Cancer Center and Stanley Scott Cancer Center, School of Medicine, New Orleans, LA 70112; [2]Department of Public Health and Microbiology-Virology, University of Milan, Milan, 20123; [31]Lousianna State University Health Sciences Center and Alcohol Research Center, School of Medicine, New Orleans, LA 70112; [4]Ettore Sansavini Health Science Foundation, University of Milan, Milan, 20123.

HIV-associated neurological disorders (HAND) comprise cognitive, motor and behavioral impairments of various entities which affect a substantial number of HIV-1 infected individuals. Understanding the biology of brain HIV-1 infection and identifying markers for its pathological manifestations, including HIV-Encephalitis, are of critical importance and it continues to be an active field of research. MicroRNAs are short non-coding RNAs that modulate gene expression by translational repression. Because of their high stability in intracellular as well as extracellular environments, miRNAs have been recently emerged as important biomarkers in several human diseases, but they have not been tested in the CSF of HIV-positive individuals. Here, we present results of a pilot study aimed to investigate a putative miRNA signature in the CSF of HIV-positive individuals with neurological disorders. We utilized a high throughput approach of miRNA detection arrays and focused on the identification of differentially expressed miRNAs in the CSF of ten HIV-positive individuals compared to ten HIV-negative samples. The group of HIV+ individuals contained nine cases of HAND and, among those, four had HIVE. All the HIV- samples had non-viral acute disseminate encephalomyelitis and no signs of cognitive impairment. Comparison analysis revealed 23 down-regulated miRNAs ($p < 0.1$) in HAND compared to the HIV-negative group and, interestingly, no miRNA was found up-regulated in this group. Comparison between HIVE and HIV- groups showed 36 differentially regulated miRNAs ($p < 0.1$), of which only three were upregulated. Although validation with an independent number of clinical samples is required before trying definite conclusion, this work offers the base for future investigation. Supported by NIH MH 079751 and P60 AA009803-18.

COCAINE INDUCED ALTERATIONS IN THE METABOLIC SIGNATURES OF CD4+ T CELLS: IMPLICATIONS IN HIV/AIDS AND DRUG ABUSE BIOLOGY. Pandhare J[1], Mantri C[1], Dash C[1]; [1]Laboratory of Retrovirology and Epigenetics, Center For AIDS Health Disparities Research, Vanderbilt-Meharry Center for AIDS Research (CFAR), Meharry Medical College School of

Medicine, Nashville, TN 37221.

Cocaine a common drug of abuse among HIV-infected persons serves as a cofactor for susceptibility to HIV infection and disease progression, and its abuse has been independently associated with poorer clinical outcomes. In addition to indirect effects on psychosocial stability that limit adherence to medical care and HIV treatments, data also suggest direct effects of cocaine on CD4+ T cell depletion and enhanced HIV replication. HIV-1 glycoprotein gp120 has been shown to cause apoptosis of uninfected (bystander) CD4+ T cells. We hypothesize that cocaine may exacerbate the effect of HIV-1 gp120 on CD4+ T cell decline in drug abusing HIV positive individuals. Using primary human CD4+ T cells we demonstrate that HIV-1 gp120 and cocaine affect the pathways important in preserving the redox balance resulting in the induction of apoptosis in CD4+ T cells. These effects were potentiated by the synergistic action of cocaine and gp120 and were mediated by p53. Induction of p53 resulted in 1) upregulation of the catalytic activity of proline oxidase (POX) a mitochondrial inner membrane enzyme that can generate ROS, and 2) downregulation of glucose 6 phosphate dehydrogenase (G6PD) important for the pentose phosphate pathway and a key component for generating NADPH essential for maintaining glutathione in a reduced state. Thus from our studies we conclude that cocaine and HIV-1 gp120 burden the cellular environment by increasing the oxidative stress in CD4+ T cells. Supported by Vanderbilt-Meharry Center for AIDS Research (CFAR).

BLOOD BRAIN BARRIER DISRUPTION BY METHAMPHETAMINE IS REGULATED BY CAVEOLAE-DEPENDENT ENDOCYTOSIS AND ACTIN CYTOSKELETON REARRANGEMENT. Park M[1], Lim B[2], Wylegala A[1], Toborek M[1]; [1]Department of Biochemistry and Molecular Biology, University of Miami School of Medicine, Miami, FL 33136; [2]Department of Biology, Centre College, Danville, KY 40422.

Methamphetamine (METH) is a drug of abuse with neurotoxic effects, which include blood-brain barrier (BBB) disruption. The present study focuses on the role of caveolae-dependent endocytosis and actin nucleation in METH-induced BBB disruption. Exposure to 10 μM METH increased phosphorylation of caveolin-1 (cav-1), a major component of caveolae, and endocytosis of occludin in hCMEC/D3 cells (human cerebral microvascular endothelial cell line). The involvement of functional caveolae in METH-induced alterations of occludin expression was confirmed by co-immunoprecipitation, lipid-rafts fractionation, and depleting of cav-1 with specific siRNAs. Because multiple stages of endocytosis are energetically unfavorable and require force-generating machinery to occur, actin polymerization has been proposed to be involved in these processes. In fact, actin polymerization was significantly increased by METH exposure and both occludin and phosphorylated cav-1 co-localized with actin filaments. Blocking of METH-induced actin polymerization by inhibition of actin nucleation with CK-666 resulted in inhibition of cav-1 and coronin1b phosphorylation. Because phosphorylation of coronin1b regulates actin nucleation, we propose that actin filamentous nucleation can be one of the targets of METH-induced and caveolae-dependent internalization of tight junction proteins in BBB. Supported by DA027569, MH63022, MH072567, and NS39254.

MICRORNA-124 DEACTIVATES HUMAN HIV-1-INFECTED AND CLASSICALLY ACTIVATED MACROPHAGES/MICROGLIA: IMPLICATION FOR NEUROGENESIS. Peng H[1], Jia B[1], Zhu B[1], Chen Q[1], Wang M[1], Yunlong H[1], Zheng J ; [1]Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68105.

Macrophages/microglia (M/M) activation, depending on the conditions, can either enhance or suppress neurogenesis. microRNA-124 (miR-124) has been shown to deactivate M1 (classically activated pro-inflammatory) M/M and skew their polarization toward an M2 (alternatively activated growth-promoting) phenotype. Our previous studies demonstrated that HIV-1-infected M1 macrophages inhibit neurogenesis and promote astrogliogenesis through the secretion of pro-inflammatory cytokines (IL-1β, TNF-α and IL-6). In the present study, we investigated whether miR-124 is able to polarize or deactivate HIV-1-infected M1 macrophages and promote neurogenesis.

Primary human monocyte-derived macrophages (MDMs) and microglia were treated with LPS (M1 activator) or IL-4 (M2 activator) to promote their differentiation into M1 or M2 phenotype, respectively. The expression levels of miR-124, pro- and anti-inflammatory cytokines were determined by real time RT-PCR. We found that miR-124 is expressed in microglia but absent in peripheral MDMs. miR-124 expression correlated inversely with the M1 activation of microglia. M1 microglia downregulated miR-124 compared with unpolarized microglia, whereas M2 microglia upregulated miR-124. Furthermore, HIV-1 infection strongly potentiated M1 macrophage-induced pro-inflammatory cytokine production. Over-expression of miR-124 in HIV-1-infected MDMs inhibited M1 macrophage-induced pro-inflammatory cytokine production. In conclusion, miR-124 may represent a new strategy to promote brain regenerative process through direct M/M state towards a pro-neurogenic phenotype. Supported by NIH/R21 NS066841, R01 NS41858, R20RR15635, P01NS43985.

POLY(ADP-RIBOSE) POLYMERASE (PARP) INHIBITION IN BRAIN ENDOTHELIUM PROTECTS THE BLOOD BRAIN BARRIER (BBB) UNDER PHYSIOLOGIC AND NEURO-INFLAMMATORY CONDITIONS. Persidsky Y[1], Rom S[1], Fan S[1], Reichenbach N[1], Dykstra H[1], Ramirez SH[1]; [1]Department of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140.

HIV-associated neurodegeneration is driven by chronic inflammatory responses and BBB injury mediated by pro-inflammatory factors as well as migration of leukocytes across BBB. Treatment approaches targeting inflammation and HIV replication should be beneficial for amelioration of HIV associated neurocognitive disorders. Recently, inhibitors of PARP-1 emerged as potent anti-inflammatory and immunomodulatory compounds. We explored the idea that PARP inhibition in brain endothelium can shield BBB. We found that PARP suppression in primary human brain microvascular endothelial cells (BMVEC) improved BBB integrity and augmented expression of tight junction proteins. PARP inhibitors prevented barrier disruption caused by oxidative stress and the inflammatory factor, CD40 ligand. PARP inhibition in BMVEC diminished human monocyte adhesion to TNFα stimulated BMVEC (up to 65%) and migration (80-100%) across BBB models, decreased expression of adhesion molecules (ICAM, VCAM) and decreased the activity of the GTPases, RhoA/Rac1 (controlling BBB integrity and monocyte migration across the BBB). PARP inhibitors down regulated expression of inflammatory genes and dampened secretion of pro-inflammatory factors that were increased by TNFα in BMVEC. In vivo treatment with a PARP inhibitor decreased enhanced BBB permeability in mice with systemic inflammation. All these results point to the relevance of PARP suppression in protection of the BBB in the setting of HIV-1 infection. Supported by NIMH, NIAAA.

ACTIVATION OF CANNABIOID RECEPTOR 2 (CB2) ATTENUATES LEUKOCYTE-ENDOTHELIAL INTERACTIONS AND BLOOD-BRAIN BARRIER (BBB) DYSFUNCTION UNDER INFLAMMATORY CONDITIONS. Persidsky Y[1], Haskó J[2], Skuba A[3], Fan S[1], Dykstra H[1], Rechenbach N[1], Krizbai I[2], Zhang M[1], Tuma R[4], Son Y[3], Ramirez SH[1]; [1]Department of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140; [2]Institute of Biophysics, Biological Research Center, Szeged, Hungary; [3]Shriners Hospitals Pediatric Research Center and Department of Anatomy and Cell Biology, Temple University School of Medicine, Philadelphia, PA 19140; [4]Department of Physiology, Temple University School of Medicine, Philadelphia, PA 19140.

Previous studies showed that modulation of the CB2 during neuroinflammation could produce potent neuroprotective and anti-inflammatory effects. However, little is known about how selective activation of the CB2 affects the activated state of the brain endothelium and BBB function. Using human brain tissues affected by HIV encephalitis and human brain endothelial cells (BMVEC) stimulated by TNFα or IL1β we demonstrated that the CB2 is upregulated during inflammatory insult. We then examined whether the CB2 agonists could attenuate inflammatory responses at the BBB using a mouse model of LPS-induced encephalitis and highly selective CB2 agonists. Two-

photon intravital microscopy revealed that administration of two CB2 agonists greatly diminished leukocyte adhesion in deep ascending cortical post-capillary venules. BBB permeability assessments with small and large fluorescent tracers showed that CB2 agonists were effective at preventing barrier leakiness after LPS administration. To determine whether the effects by CB2 agonists on barrier protection are not only due to the CB2 modulation of immune cell function, we tested the agonists in-vitro with barrier forming primary BMVEC. The addition of CB2R agonist increased trans-endothelial electrical resistance and increased the amount of tight junction proteins present in membrane fractions. CB2 agonists decreased the induction of ICAM and VCAM expression in BMVEC exposed to pro-inflammatory mediators. These results suggest that pharmacological CB2 ligands offer a new strategy for BBB protection during neuroinflammation. Supported by NIAAA, NIMH, NIDA.

NEUROCHEMICAL COMPOSITION CORRELATED WITH VARIANCE IN ATTENTION AND HYPERACTIVITY/IMPULSIVITY SCORES: A MULTIVOXEL SPECTROSCOPY STUDY. Pritchett A[1], Chang L[1], Saito A[1], Keating B[1], Alicata D[1], Jiang CS[1], Cloak C[1], Lohaugen G[3], Skranes J[2], Ernst T[1]; [1]Department of Medicine, University of Hawaii John A. Burns School of Medicine, Honolulu, HI 96813; [2]Department of Laboratory medicine, Children's and Women's Health, Norwegian University of Science and Technology, Trondheim, Norway; [3]Department of Pediatrics, Sorlandet Hospital, Arendal, Norway.

Attention-Deficit/Hyperactivity Disorder (ADHD) involves widespread dysfunction in brain areas associated with attention and cognition. Proton magnetic resonance spectroscopy (1H-MRS) may detect neuronal or glial metabolite abnormalities that may contribute to developmentally inappropriate attention and impulsivity. Method: 1H-MRS (4 brain regions) was performed on 105 healthy children and adolescents (ages 5-17 years, 50 boys, 55 girls). Guardians of the children also completed DuPaul ADHD Rating Scale IV Home edition, which assesses the frequency of inattention (IA) and hyperactive/impulsive (HI) symptoms. Results: Across all subjects, higher IA scores was associated with higher N-acetyl-aspartate (NAA) in anterior cingulate cortex (ACC, r=0.22, P=0.03) and higher total creatine in frontal white matter (tCr FWM, r=0.20, P=0.04). 12 of these children with a formal diagnosis of ADHD had higher NAA than age-sex-matched controls (+13%, P=0.02). Glutamate in ACC was correlated with total score (r=0.20, P=0.04) and subscale scores: IA (r=0.19, P=0.05), HI (r=0.17, P=0.09). Conclusions: The elevated NAA in children with ADHD and the associa! tion across subjects between higher neuronal metabolites (NAA and glutamate in ACC and tCr in FWM) of those with higher IA scores suggest altered neuronal organization (e.g., increased density) and less efficient pathways in brain regions involved in executive functions in children with attention problems. These neurometabolite abnormalities may contribute to the symptoms in ADHD and hence may be useful for diagnosis and treatment monitoring. Supported by NIH (1R01-DA21016, RC2DA029475, 2K24DA016170, K02-DA16991, U54 NS056883, G12RR003061).

EFFECTS OF APOE-EPSILON4 ALLELE AND HIV ON CORTICAL BRAIN STRUCTURES. Sadino J[1], Chang L.[1], Andres MA[2], Ernst TM[1]; [1]Department of Medicine, John A. Burns School of Medicine, University of Hawaii at Manoa, Honolulu, HI 96826; [2]Pacific Biosciences Research Center, University of Hawaii at Manoa, Honolulu, HI 96826.

The APOE4(e4) allele may contribute to HIV-associated neurocognitive disorder (HAND) by causing premature brain atrophy in subcortical gray matter and cognitive deficits. This study assessed possible effects of e4 on cortical brain regions in HIV subjects and seronegative controls (SN). Methods: We evaluated 175 subjects (71 SNe4-, 30 SNe4+, 52 HIV+e4-, 22 HIV+e4+; 19–71 years old) and performed automated morphometry (FreeSurfer) of cortical area, thickness, and volume (normalized to intracranial volume) in 71 regions. Results: Compared to SN, HIV subjects had thinner cuneus, isthmus cingulate, posterior cingulate, and lingual right cortices (Simes corrected-$p<0.0011$). HIV subjects also had smaller volumes than SN in 35 regions across all lobes (corrected-$p<0.0008$), but no group differences in surface areas were observed in any region.

Subjects with ε4 allele had larger volumes than those without e4 in 7 regions (in the frontal, occipital, and parietal lobes). The only region that showed an HIV by e4 interaction was the right parsopercularis, where SNe4+ subjects had larger volumes while HIV+e4+ subjects had smaller volumes compared to their corresponding e4- groups (ANCOVA-p=0.02). Conclusion: Cortical thinning and smaller cortical volumes in HIV patients are consistent with prior reports. In contrast to our prior study of the subcortical regions, APOE-ε4 did not affect most of the cortical structures of HIV subjects more than those in SN. However, all subjects had some brain regions with larger volumes, which suggest an antagonistic pleiotropic effect of the ε4 allele. Supported by NIH (2R01MH61427, 2K24DA016170, 1R24DA027318, and 1U54-NS056883).

A COMBINED OPIATE AGONIST AND ANTAGONIST TRETMENT REDUCES ALCOHOL INHIBITORY EFFECTS ON OPIATE RECEPTOR DIMERIZATION AND CYTOLYTIC FUNCTIONS OF NK CELLS AND REDUCES MAMMARY TUMOR GROWTH. Sarkar DK[1], Sengupta A[1], Zhang C[1], Boyadjieva N[1]; [1]Endocrine Program, Rutgers University, New Brunswick, NJ 08901.

We have recently shown that there exists a negative feedback interaction between mu-opioid receptor (MOR) and the delta-opioid receptor (DOR) in splenocytes controlling natural killer (NK) cell functions. Whether or not receptor dimerization is involved in the feedback interaction between these receptors and in the alcohol action on NK cells is tested. We used splenocytes of animals chronically fed with alcohol or control diet and treated with vehicle or a MOR antagonist naltrexone and/or a DOR agonist DPDPE for 4 weeks. We show that MOR and DOR monomeric and dimeric proteins existed in splenocytes. Chronic treatment with alcohol increased the level of MOR and DOR heterodimer, while naltrexone reduced the level of MOR but increased levels of DOR monomer and homodimer. DPDPE promoted naltrexone effects on receptor dimerization. Opioid receptor homodimerization was positively associated, while receptor heterodimerization was negatively associated with the ligand binding and cell function. A combined treatment of an MOR antagonist and a DOR agonist was able to reverse the immune suppressive effect of alcohol and reduce the growth and progression of carcinogen-induced mammary tumors in rats. These data identify a role of receptor dimerization in the DOR and MOR feedback interaction in NK cells, and further elucidate the potential for developing a combined opioid antagonist and agonist therapy for the treatment of alcohol-induced immune incompetence and cancer. Supported by a NIH/NIAAA grant R21 AA016296.

CANNABINOID RECEPTOR EXPRESSION IN HUMAN FETAL NEURAL PRECURSOR CELLS. Sheng WS[1], Hu S[1], Rock RB[1]; [1]The Center for Infectious Diseases & Microbiology Translational Research, University of Minnesota Medical School, Minneapolis, MN 55455.

Neural precursor cells (NPCs) are a self-renewing, multipotent population of cells that are capable of differentiating into neurons, astrocytes, and oligodendrocytes. These cells contribute importantly to brain patterning, memory formation, and brain repair. Recently reports of endocannabinoid and synthetic cannabinoid modulation of rodent NPC proliferation were shown. In this study we used different gestation stages (8-20 wk) of human fetal brain tissues and NPCs derived from 8-12 wk fetal brain specimens to investigate the expression of cannabinoid receptors. We then studied the response of NPCs to the treatment with synthetic cannabinoid compounds WIN55,212-2 and methanandamide (a stable analogue of anandamide, an endogenous CB1 receptor agonist). We found moderate to high expression levels of CB1 receptor in all human brain specimens and in NPCs while CB2 receptor expression levels were very low to undetectable by real-time PCR. Induction of NPC proliferation assessed by 3H-thymidine incorporation was found after treatment with WIN55,212-2 or methanandamide (10^{-15} to 10^{-9} M). These findings indicate that expression of cannabinoid receptors likely plays a role in fetal development. Currently, we are investigating the effects of other synthetic cannabinoid ligands and selective cannabinoid receptor antagonists on NPC functions. Supported by NIH (NIDA) DA025525.

CORTICAL AND WHITE MATTER DEVIATIONS RELATE TO COGNITIVE DEFICITS IN VERY-LOW-BIRTH-WEIGHT (VLBW) YOUNG ADULTS. Skranes J[1], Loehaugen GCC[2], Eikenes L[3], Bjuland KJ[1], Haberg A[4], Brubakk A-M[1]; [1]Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, 7489 Trondheim; [2]Department of Pediatrics, Sorlandet Hospital, Arendal, Norway; [3]Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway; [4]Department of Neuroscience, Norwegian University of Science and Technology, Trondheim, Norway.

Perinatal brain injury in very low birth weight (VLBW) children affects grey and white matter and is associated with neurocognitive deficits that persist into adulthood. The aim of study was to investigate the relationship between cortical surface area and white matter microstructure and cognitive function in VLBW young adults. Method: 49 VLBW (birth weight ≤ 1500 grams) and 59 term born controls were assessed cognitively at age 19 with Wechsler Adult Intelligence Scale (WAIS)-III. An automated MRI technique at 1.5 Tesla for morphometric analyses of cortical surface area and diffusion tensor imaging to investigate fractional anisotropy (FA) in white matter tracts were performed in both groups. Results: Low IQ was associated with reduced surface area in specific cortical regions in the VLBW young adults. The IQ indices that contributed the most to the associations were the Working Memory Index and the Processing Speed Index. These indices were also related with FA reduction in central white matter tracts like corpus callosum, and association tracts in external capsule and sup. long. fascicle leading to the affected cortical areas. Conclusions: Cognitive deficits in young adults born with VLBW were related with both grey and white matter abnormalities indicating perinatal brain injury with permanent consequences for brain structure and functioning. Supported by the Research Council of Norway (NevroNor-project) and Central Norway Regional Health Authority.

WNT SIGNALING IN NEUROAIDS. Tang S-J[1], Gelman B[1], Shi Y[1], Li B[1]; [1]Department of Neuroscience and Cell Biology, University of Texas Medical Branch, Galveston, TX 77555.

HIV-1/AIDS patients often develop neurological complications, such as neurocognitive deficits and neuropathic pain. We are interested in elucidating the CNS host mechanisms that interact with HIV toxins to cause NeuroAIDS-related neural damages. Our current studies focus on the Wnt signaling, which plays important roles in neurogenesis, axon outgrowth, dendritic arborization, and synapse differentiation. Previous studies from our group demonstrated that Wnt proteins in central neurons are synthesized and secreted in response to synaptic activation and that the synaptic activity-gated Wnt signaling regulates long-term potentiation (LTP). More recently, we found that Wnt signaling was specifically up-regulated in the spinal cord dorsal horn (SDH) from the HIV-1 patients who had developed chronic pain. This finding indicates that the dysregulated Wnt signaling probably is an important host factor in the SDH that facilitates the development of HIV-1-associated chronic pain. We further found that HIV-1-related chronic pain was also associated with the activation of astrocytes in the SDH. In addition, our studies on animal models revealed that HIV-1 gp120 rapidly induced Wnt expression in the SDH and that Wnt signaling controlled astroglial activation and cytokine expression. The results collectively suggest that gp120 may contribute to the SDH neuropathogenesis of HIV-1-associated chronic pain by aberrantly activating Wnt signaling and astrocytes. Supported by Whitehall Foundation.

NEUROPATHOGENIC MECHANISMS BY HIV-1 CLADE B AND C: ROLE OF LIPID RAFTS. Thangavel S[1], Santiago EM[1], Nair MPN[1]; [1]Institute of NeuroImmune Pharmacology (NIP), College of Medicine, Florida International University, Miami, FL 33199.

Aim: Previous studies suggest that infections with HIV-1 B and C clade differentially contribute to the neuropathogenesis of HIV-associated neurocognitive disorder (HAND). Sterol deficiency and lipid rafts modification upregulate rate limiting enzyme, 3-hydroxy- 3-methylglutaryl (HMG)-CoA reductase (HMGCR) and sterol regulatory element binding proteins (SREBP), which are known to play a significant role in neuropathogenesis of HAND. We hypothesize that clade B and C Tat exert differential effects on neuronal cell SK-N-MC by upregulation of HMGCR and SREBP leading to

HAND. Methods: RNA extracted from SK-N-MC cells treated with HIV-1 clade B and C Tat 50 ng/ml at 48h was reverse transcribed and analyzed by quantitative real-time PCR to determine HMGCR and SREBP gene expression and the cell lysates were analyzed for protein levels by western blot. Results: Results indicate that HIV-1 clade B Tat significantly upregulated HMGCR and SREBP gene expression, and protein modification compared with clade C Tat. Conclusions: These studies suggest that HIV-1 B and C Tat may play a differential role in the sterol synthesis implicates neuropathogenesis of HAND. Supported by NIH grants R37DA025576 and R01DA021537.

EFFECTS OF COCAINE ON HIV INFECTION OF QUIESCENT T CELLS. Vatakis DN[1], Kim SG[1], Zhuo J[1], Baldwin GC[1], Zack JA[1]; [1]Department of Medicine, Division of Hematology and Oncology, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095.

Stimulant use such as cocaine has been shown to impact the human immune system. In regards to the human immunodeficiency virus (HIV) infection, a number of studies have indicated that cocaine users are at an increased risk for infection and display more rapid disease progression and morbidity. However due to many variables such as adherence to antiretroviral therapy, use of multiple classes of drugs and co-infections among others, it is difficult to fully appreciate the impact drug abuse has on HIV disease. We hypothesize that cocaine will influence the kinetics of HIV infection in quiescent cells by increasing their permissiveness to infection. To this end, quiescent cells were exposed to cocaine for one or three days. Based on our data, 1-day cocaine exposure had no detectable effects. However, 3-day exposure, when compared to quiescent cells, resulted in increased reverse transcription kinetics, higher levels of viral cDNA, increased viral RNA and protein synthesis. When compared to pre-stimulated T cells, the 3-day treated cocaine cells demonstrate delays in HIV cDNA integration. In addition, the 3-day treated cells progressed to the G1b phase of the cell cycle, displayed slight increases in T cell activation marker expression, and a marked increase in the levels of CCR5. Therefore, cocaine exposure increases the permissiveness of quiescent cells to HIV infection through minor changes in their cell state. These patterns are currently being examined in vivo using the BLT humanized mouse model. Supported by National Institute of Drug Abuse/R21 DA031036-01A1.

ALCOHOL INHIBITS INTRACELLULAR HIV RESTRICTION FACTORS AND ENHANCES HIV INFECTION OF CORD BLOOD MONOCYTE-DERIVED MACROPHAGES (CBMDM). Wang X[1], Mastrogiannis DS[2], Dai M[1], Ye L[1], Li JL[1], Wang YZ[1], Song L[1], Sakarcan S[1], Ho WZ[1]; [1]Department of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140; [2]Department of Obstetrics, Gynecology and Reproductive Sciences, Temple University School of Medicine, Philadelphia, PA 19140.

Recent government surveys indicate that about 1 in 12 pregnant women drink during pregnancy while 1 in 30 pregnant women report binge drinking. Approximately 6,000 to 7,000 HIV-infected women give birth each year in the United States, resulting in 280 to 370 new perinatal infections despite the wide availability of potent anti-retroviral treatment. In vitro investigations have shown that alcohol enhances HIV infection of adult monocyte-derived macrophages and lymphocytes. In this investigation, we examined whether alcohol has the ability to inhibit intracellular innate HIV restriction factors and enhance HIV infection of cord blood monocyte-derived macrophages (CBMDM). We demonstrated that alcohol treatment of CBMDM significantly inhibited the expression of several key HIV restriction factors: anti-HIV microRNAs, tetherin, APOBEC3G and APOBEC3H. In addition, alcohol suppressed the expression of IFN regulatory factor 7 (IRF-7) and RIG-I, the critical modulators in IFN pathway. The suppression of these innate restriction factors was associated with reduced production of type I IFNs and the enhancement of HIV infection of CBMDM. These findings suggest that that maternal alcohol consumption can be potentially harmful as it may facilitate HIV infection/replication, promoting vertical transmission of HIV. Supported by NIH DA12815, DA22177, and DA27550.

POTENTIATION OF NMDA RECEPTOR-MEDIATED EPSCS BY D-SERINE: IMPLICATIONS FOR HIV-1-ASSOCIATED NEUROTOXICITY. Xia JX[1], Xiong H[1]; [1]Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198.

Increasing evidence indicates that HIV-1-infected, immune activated glial cells release soluble factors leading to neuronal injury via N-methyl-D-aspartate receptors (NMDARs). However, the identities of soluble NMDAR agonist-like substances are not well assayed. In the present study, we observed treatment of human astrocytes with HIV-1 glycoprotein 120 (gp120) or lipopolysaccharide (LPS) significantly increase astrocyte production of D-serine, an NMDAR co-agonist, as detected by high performance liquid chromatography (HPLC). Bath application of D-serine differentially enhanced NMDAR-mediated EPSCs (EPSCNMDAR), but not α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor (AMPA)-mediated EPSCs (EPSCAMPAR). The D-serine-mediated increase of EPSCNMDAR was dose-dependent and blocked by 5,7-Dichlorokynurenic acid (5,7-DCKA), an NMDAR antagonist which binds to the glycine-binding site. The D-serine enhancement of EPSCNMDAR is mainly mediated via NR2B-containing NMDAR (NR2BR)-mediated EPSC (EPSCNR2BR), but not NR2A-containing NMDAR (NR2AR). Further investigation revealed that D-serine enhances EPSCNR2BR via extra-synaptic NR2BRs. The activation of NR2BRs by D-serine is associated with neuronal injury as the blockade of NR2BRs with specific antagonist ifenprodil. Taken, together, these results showed that HIV-1-infected, immune activated glial cells produce soluble D-serine resulting neuronal injury via NR2BRs. Supported by NIH grant 1R01 NS063878.

NONMUSCLE MYOSIN LIGHT-CHAIN KINASE MEDIATES MICROGLIAL MIGRATION INDUCED BY HIV TAT: INVOLVEMENT OF B1 INTEGRINS. Yao HH[1], Buch S[1]; [1]Department of Pharmacology, University of Nebraska Medical Center, Omaha, NE 68198.

Introduction: HIV Tat released from HIV-infected cells has been shown exhibit chemotactic activity. Activated microglia are a hallmark feature of HIV-associated neurological disorder (HAND). These cells can migrate to the signal elicited by HIV Tat released from infected cells. We hypothesized that the microglial adhesion/migration mediated by Tat will involve actin rearrangement and the activation of its upstream non-muscle myosin light chain kinase (MYLK) and integrins. Methods: Microglial migration was assessed by both Boyden and Dunn Chamber. Role of Cdc42 was assessed by GLISA. F-actin polymerization was examined by palladin staining and flow cytometry. HIV Tat was stereotactically injected in the mice hippocampus followed by transplantation of AAV-GFP transduced mice microglia in the corpus calloseum. Results: Intra-hippocampal injection of HIV Tat1-72 into mice resulted in migration of AAV-GFP transfected microglia to the Tat-injected site. Molecular mechanisms of this process involved Tat-mediated activation of VEGFR1 receptor, leading to inside-out activation of MYLK & β1 integrin, resulting subsequently in outside-in activation of the downstream Pyk2, Src, and Cdc42. This ultimately culminated into actin rearrangement and the ensuing migration of microglia. Conclusions: Our findings for the first time have identified two novel phenomena: a) RGD-independent activation of β1 integrin by HIV Tat and, b) Involvement of MYLK in Tat-mediated microglial migration. Supported by DA020392, DA023397 and DA024442 (SB) and DA030285 (HY).

AZITHROMYCIN INHIBITS HEPATITIS C VIRUS REPLICATION IN HEPATOCYTES. Ye L[1], Guo M[1], Li J-L[2], Wang X[2], Wang Y-Z[2], Zhou Y[2], Ho W-Z[2]; [1]The Center for Animal Experiment/Animal Biosafety Level III Laboratory, Wuhan University, Wuhan, 430071, China; [2]Department of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140.

Azithromycin is a potent antibiotic and is frequently used in treatment of patients for mycobacterial infections. Azithromycin has well-established antibacterial and anti-inflammatory effects. Preliminary evidence showed that azithromycin may also have antiviral effects. In this study, we investigated the effect of azithromycin on HCV infection/replication in human hepatocytes. Azithromycin treatment of hepatoctyes before, during, or after HCV infection

significantly suppressed full cycle viral replication, as evidenced by decreased expression of HCV RNA, protein, and production of infectious virus. Investigation of the mechanism(s) demonstrated that the azithromycin's inhibition of HCV replication is due to its disruption of autophagy machinery, which is required for the initiation of HCV viral replication and also contributes to HCV particle assembly and/or egress. These data indicate that azithromycin, a potent antibacterial medicine, may be beneficial for people infected with HCV. Future studies are necessary to determine clinical significance of the in vitro anti-HCV effect of azithromycin. Supported by NIDA grants DA12815, DA22177 and DA27550.

SIV INFECTION OF CHINESE RHESUS MONKEYS. Ye L[1], Bao R[1], Guo M[1], Dai M[1], Rao Y[1], Zhang J[1], Wang Y[1], Xian Q-Y[1], Huang Z-X[1], Wang X[1], Yang Z-J[1], Ho W-Z[2]; [1]The Center for Animal Experiment/Animal Biosafety Level III Laboratory, Wuhan University, Wuhan, 430071, China; [2]Department of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140.

India-origin rhesus monkeys infected with simian immunodeficiency virus (SIV) have been used for many years as an animal model for HIV/AIDS in humans. However, this animal model has several limitations including AIDS developing much more rapidly than HIV-infected humans and the severe shortage supply. To further determine whether Chinese rhesus monkeys (CRMs) are suitable for SIV infection, we infected CRMs with SIVmac239 through two approaches, intravenous and vaginal inoculation. The SIVmac239 used in this study was directly collected from CEMX174 cell cultures without adaptive passages in CRMs or monkey PBMCs. All 15 animals inoculated with SIVmac239 became infected as evidenced by the plasma SIV RNA/p27 protein expression. Plasma viral load reached to the peak level at ~ day 14 postinfection and then declined to a stable level, although fluctuated during the course of infection. The CD4+/CD8+ ratio had a ~ 50% drop at the early stage of infection (30 days postinfection) and subsequently recovered to a mediate level that was still lower than the original one. The two infection approaches, intravenous and vaginal inoculation, did not result in a significant difference in virological and immunological changes in the infected animals. No clinical symptom was observed in SIVmac239 infected monkeys within the 32-week experiment. These data demonstrated the success in establishing SIV infection model using CRMs. The ongoing studies will further investigate the SIV/AIDS pathogenesis in CRMs and explore the feasibility of this model for evaluating anti-AIDS drugs and vaccines. Supported by NIDA grants DA12815, DA22177 and DA27550.

DIFFERENTIAL REGULATION OF IL-33 BY HIV-1 B AND C CLADE INFECTION IN HUMAN ASTROCYTES (HA): ROLE IN NEUROPATHOGENESIS. Yndart A[1], Agudelo M[1], Nair MPN[1]; [1]Department of Immunology, Institute of Neuro-Immune Pharmacology, Herbert Wertheim College of Medicine, Florida International University, Miami, FL 33199.

Experimental and clinical evidence suggests differences in manifestation of HIV-associated neurocognitive disorders (HAND) between clade B and C-infected subjects with clade B being more neuropathogenic than clade C. Although the exact mechanisms of these differential effects are not elucidated yet, it is suggested that pro-inflammatory cytokines may play a significant role in the complex regulatory mechanisms of neuropathogenesis of HIV-1 infection. One of the newly described members of the IL-1 family, IL-33 is abundantly expressed in the CNS. IL-33 has also been shown to activate T Lymphocytes and microglia cells, suggesting a possible role in neuroimmune inflammatory processes. We hypothesize that IL-33 and other proinflammatory cytokines are differentially dysregulated by HIV clades. HA were infected with HIV1 B or C viruses and the RNA was extracted and quantitated for IL-33, TNFα and IL-6 by q-RT-PCR. Cytokines secretion was measured in culture supernatants by ELISA whereas intracellular IL-33 protein expression was detected by western blot. The HIV infection was confirmed by p24 ELISA. Our results indicated that HA infected with HIV-1 B showed higher level of proinflammatory cytokines TNFα and IL-6 compared to HIV-1 C infected cultures. In particular, IL-33 was found to be significantly upregulated in HIV1-B infected cultures. These results suggest that IL-33 may play a

significant role in differential neuropathogenesis induced by HIV-1B and C infection and may serve as a potential therapeutic target to control HAND. Supported by NIH/1R01MH085259 and 5R01DA021537.

ADENOSINE DEAMINASES AS DRUG CANDIDATES FOR THE TREATMENT OF HIV INFECTION. Zavialov A[1], Lu Y[1]; [1]Department of Public Health, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI 96822.

Adenosine deaminases (ADAs) play an important role in a wide range of physiological processes in the body by controlling adenosine concentration. Genetic defects leading to ADA1 inactivation result in severe combined immunodeficiency (SCID), while excessive expression or mutation of ADA2 is accompanied by abnormalities in organ development and immune system function. Clinical studies have shown that the levels of ADA2 in biological fluids are altered in pathophysiological conditions, suggesting that ADA2 activity could be a convenient marker for the diagnosis of immune diseases such as tuberculosis, HIV infection and breast cancer. Recently, we isolated human ADA2, identified and cloned the ADA2 gene CECR1 and solved the crystal structure of ADA2. Our functional studies have revealed a new cytokine/growth factor function of ADAs in addition to their ADA activity. We have shown that the enzymes interact with adenosine receptors (ADOR) and facilitate the proliferation and differentiation of T cells in the presence of activated monocytes or dendritic cells. Therefore, we propose that ADAs alone or in combination with adenosine receptor antagonists or agonists could be used to treat immune disorders, neurological disorders and cancers. In particular, we will study the effect of adenosine deaminases and adenosine receptors on the efficiency of gene therapy for HIV dementia, which involves the macrophage-based delivery of HIV antigens into the brain. Supported by NIMH grant from the National Institute of Health (NIMH079717-01A2); Finnish Academy of Science (grants 2).