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T-53 **ACTIVATION OF TLR-3 INDUCES IFN-LAMBDA EXPRESSION IN HUMAN NEURONAL CELLS**. L Zhou[1,2], X Wang[2], H Li[1], Y Zhou[1], S Hu[3], L Ye[2], W Hou[2], WZ Ho[2]; [1]Division of Histology and Embryology, Department of Anatomy, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430030 China; [2]Division of Allergy & Immunology, The Children's Hospital of Philadelphia,

Philadelphia, PA, 19104 USA; [3]Center for Infectious Diseases and Microbiology Translational Research, University of Minnesota Medical School, Minnesota, MN, 55455 USA.

T-54 **INCREASED CDK5 ACTIVITY IN THE HIPPOCAMPUS REGULATES THE DEPRESSIVE-LIKE BEHAVIORS IN CHRONIC MILD STRESS**. WL Zhu[1], L Lu[1]; [1]Peking University, National Institute on Drug Dependence, Beijing, 100191 China.

XIII. POSTER SESSION II: GENERAL POSTER SESSION 50-65

W-1 **IN VIVO IMPACT OF DELTA-9-THC-MEDIATED IMMUNOSUPPRESSION ON HIV PATHOGENESIS IN THE HUPBL-NOD-SCID/IL-2R-GAMMA-NULL MOUSE**. GC Baldwin[1], MD Roth[1], SM Kiertscher[1], KM Whittaker[1], J Zhuo[1]; [1]Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA, 90095-7363 USA.

W-2 **THE IMPACT OBSERVATION TO IMMUNE FUNCTION AND TRACE ELEMENTS IN 4 CASES OF AIDS TREATMENT BY ARTEMISIA**. L Cao[1], D Zhou[1]; [1]Department of AIDS Prevention, Center of Disease Control, Wuhan, 430020 China.

W-3 **EXPERIMENTAL HERPES SIMPLEX VIRUS-1 ENCEPHALITIS INDUCES NEURAL STEM CELL PROLIFERATION AND MIGRATION**. MC Cheeran[1], S Hu[1], MR Little[1], M Erickson[1], JR Lokensgard[1]; [1]CIDMTR, Department of Medicine, University of Minnesota Medical School, Minneapolis, MN, 55455 USA.

W-4 **ROLE OF DRD3 IN ACUTE AMPHETAMINE-INDUCED IL-10 PRODUCTION USING DRD3-KNOCKOUT MICE**. YJ Chen[1], JY Zhu[3], HB Zhang[2], SG Wei[2], CX Yan[2], HB Zheng[2], T Chen[2]; [1]Dept of Immunology and Pathogenic Biology and [2]Dept of Forensic Medicine, Xi'an Jiaotong Univ School of Med., Xi'an, 710061 China; [3]Mental Health, Xi'an Mental Health Hospital, Xi'an, 710077 China.

W-5 **MICROARRAY ANALYSIS OF LUNGS FROM INTRAVENOUS DRUG USERS WITH AND WITHOUT HIV INFECTION.** N Dhillon[2], A O'Brien-Ladner[2], S Buch[2]; [1]Department of Physiology and [2]Department of Medicine, Division Pulmonary/Critical Care, University of Kansas Medical Center, Kansas City, KS, 66160 USA.

W-6 **VECTOR-BASED GENERATION OF MONOCLONAL ANTIBODIES AGAINST THE CB2 RECEPTOR IN CB2-KO MICE**. A Harui[1], N Buckley[2], SM Kiertscher[1], MD Roth[1]; [1]Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA, 90095-1690 USA, [2]Biological Sciences Department, California State Polytechnic University, Pomona, CA, 91768 USA.

W-7 **INTERFERON LAMBDA INHIBITS HIV-1 INFECTION OF MACROPHAGES**. W Hou[1], X Wang[2], L Ye[2], ZQ Yang[1], WZ Ho[2]; [1]State Key Laboratory of Virology, School of Medicine, Wuhan University, Wuhan, 430071 China; [2]Division of Allergy and Immunology, The Children's Hospital of Philadelphia, Philadelphia, PA, 19104 USA.

W-8 **WIN55,212-2 INHIBITS RANTES/CCL5-INDUCED HUMAN MICROGLIA INTRACELLULAR CA2+ LEVELS AND MIGRATION**. S Hu[1], K Cushman[2], WS Sheng[1], SA Thayer[2], PK Peterson[1], RB Rock[1]; [1]Center for Infectious Diseases and Microbiology Translational Research and [2]Department of Pharmacology, University of Minnesota Medical School, Minneapolis, MN, 55455 USA.

W-9 **MIR-142-3P RESTRICTS CAMP PRODUCTION IN CD4+CD25- T CELLS AND CD4+CD25+ TREG CELLS BY TARGETING ADENYLYL CYCLASE 9 MRNA**. BO Huang[1]; [1]Department of Biochemistry and Molecular Biology, Tongji Medical College, Wuhan, 430030 China.

W-10 **TOXICOLOGY PROFILES AND BLOOD-BRAIN BARRIER PENETRANCE OF MONOCYTE-MACROPHAGE CARRYING NANOFORMULATED ANTIRETROVIRAL DRUGS**. GD Kanmogne[1], D. Barnes[1], A. Nowacek[1], B. Rabinow[2], H. Gendelman[1], S. Singh[1]; [1]Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE, 68198-5215 USA; [2]Global Research and Development, Baxter Healthcare, Chicago, IL, 60015-4625 USA.

W-11 **MUTANT HTT CAUSES ENDOPLASMIC RETICULUM STRESS THROUGH OXIDATIVE STRESS AND DISTURBANCE OF INTRACELLUAR CALCIUM**. H Li[1], Y Jiang[1], H Tan[1]; [1]Division of Histology & Embryology, Department of Anatomy, Tongji Medical College, Huazhong University of Science & Technology, Wuhan, 430030

China.

W-12 **PREVALENCE OF DRUG RESISTANT GENOTYPE AMONG THERAPY-NAÏVE PATIENTS OF HIV-1 INFECTION IN WUHAN , CHINA**. T Li[1]; [1]Division of Virology, Wuhan Centers for Disease Prevention & Control, Wuhan, 430022 China; [2]Division of Virology and Immunology, National Center for AIDS/STD Control and Prevention, Beijing, 100050 China.

W-13 **NOVEL MECHANISM OF NMDA RECEPTOR ACTIVATION BY HIV-1 TAT PROTEIN**. W Li[1], Y Huang[1], R Reid[1], J Steiner[1], T Malpica-llanos[1], T Darden[2], S Shankar[3], A Mahadevan[3], P Satishchandra[3], A Nath[1]; [1]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, 21287 USA; [2]Laboratory of Structural Biology, National Institute of Environmental Health Science, Research Triangle Park, NC, 27709 USA; [3]Departments of Neuropathology and Neurology, National Institute of Mental Health and Neuroscience, Bangalore, 560029 India.

W-14 **COMPLICATED PATTERN OF HIV-1 EVOLUTION AMONG DRUG ABUSERS AND SEXUALLY ACQUIRED CASES IN DEHONG, YUNAN PROVINCE, CHINA**. L Liu[1], H Wang[1], L Lu[2], M Jia[2], Y Ma[2], Y Zhang[2], Z Chen[1]; [1]AIDS Institute, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, China; [2]Yunnan Center, Center for Disease Control and Prevention, Kunming, 650022 China.

W-15 **MOLECULAR EPIDEMIOLOGY OF HUMAN ASTROVIRUS INFECTIONS IN WUHAN, CHINA**. MQ Liu[1], YH Wang[1], JS Peng[1], L Tang[1], Y Zhou[1], X Zhou[1], R Zhao[2], N Kobayashi[3]; [1]Department of Virology, Wuhan Centers for Disease Prevention & Control, Wuhan, 430015 China; [2]Department of Pathogen Biology, Huazhong University of Science and Technology, Wuhan, 430030 China; [3]Department of Hygiene, Sapporo Medical University School of Medicine, Sapporo, 060-8556 Japan.

W-16 **DEVELOPMENT OF MULTIFUNCTIONAL MAGNETIC NANOCARRIER FOR DRUG TARGETING TO BRAIN**. MP Nair[1], NH Gandhi[1], ZM Saiyed[1]; [1]Department of Immunology, College of Medicine, Florida International University, Miami, FL, 33199 USA.

W-17 **USE OF COCAINE AND CANABINOID RESULTS IN ALTERED PATTERNS OF HIV-1 LTR TRANSCRIPTION FACTOR BINDING SITE CONSERVATION DURING HIV DISEASE**. MR Nonnemacher[1], E Kilareski[1], B Aiamkitsumrit[1], N Parikh[1], BP Irish[1], S Lewis[2], J Jacobson[2], B Wigdahl[1]; [1]Department of Microbiology and Immunology, and [2]Division of Infectious Disease and HIV Medicine, Drexel University College of Medicine, Philadelphia, PA, 19102 USA.

W-18 **HIV-1-INFECTED AND/OR IMMUNE-ACTIVATED MACROPHAGES AFFECT HUMAN FETAL CORTICAL NEURAL PROGENITOR CELL DIFFERENTIATION THROUGH THE STAT3 PATHWAY**. H Peng[1], Y Wu[1], J Zheng[1]; [1]Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE, 68198-5880 USA.

W-19 **GENETIC VARIATION OF HEPATITIS C VIRUS IN A COHORT OF INJECTION HEROIN USERS IN WUHAN, CHINA**. JS Peng[1], X Wang[3], MQ Liu[1], DJ Zhou[1], J Gong[1], HM Xu[2], JP Chen[2], HH Zhu[1], W Zhou[1], WZ Ho[3]; [1]Wuhan Centers for Disease Control and Prevention, Wuhan, 430022 China; [2]Wuhan Psychiatric Health Center, Wuhan, 430030 China; [3]Division of Allergy & Immunology, Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, PA, 19104 USA.

W-20 **MICROARRAY ANALYSIS OF CELLULAR AND MOLECULAR BASIS OF METHAMPHETAMINE-INDUCED T CELL DYSFUNCTION**. R Potula[1], MR Brodie[3], F Yu[3], B Morsey[3], H Dykstra[1], Y Persidsky[1]; [1]Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA, 19140 USA; [2]Pharmacology and Experimental Neuroscience and [3]Department of Biostatistics, University of Nebraska Medical Center, Omaha, 68198 NE.

W-21 **HEPCIDIN AND IRON-ASSOCIATED NEURODEGENERATIVE DISORDERS**. ZM Qian[1], Y Ke[2]; [1]Laboratory of Brain Iron Metabolism, Hong Kong Polytechnic University, Hong Kong, China; [2]Department of Physiology, The Chinese University of Hong Kong Medical School, Hong Kong, China.

W-22 **WIN55,212-2 PROTECTS HUMAN DOPAMINERGIC NEURONS AGAINST GP120-INDUCED DAMAGE**. RB Rock[1], S Hu[1], W Sheng[1], PK Peterson[1]; [1]Center for Infectious Diseases and Microbiology Translational Research, University of Minnesota, Minneapolis, MN, 55455 USA.

W-23 **IMPACT OF MARIJUANA SMOKING ON THE IMMUNE RESPONSE TO HEPATITIS B VACCINATION**. MD Roth[1], DP Tashkin[1], G Ibrahim[1], SM Kiertscher[1]; [1]Division of Pulmonary & Critical Care, David Geffen School of Medicine at UCLA, Los Angeles, CA, 90095-1690 US.

W-24 **HEME OXYGENASE-1 REGULATION OF INFLAMMATORY MEDIATORS FROM IL-1-BETA-ACTIVATED HUMAN ASTROCYTES**. W Sheng[1], S Hu[1], PK Peterson[1], RB Rock[1]; [1]CIDMTR, Department of Medicine, University of Minnesota Medical School , Minneapolis, MN, 55455 USA.

W-25 **EFFECTS OF STRESS ON DECISION-MAKING PERFORMANCE IN HEROIN ADDICTS**. J Shi[1], XL Zhang[1], L Lu[1]; [1]National Institute on Drug Dependence, Peking University, Beijing, 100191 China.

W-26 **CAVEOLAE-ASSOCIATED SIGNALING MECHANISMS IN HIV-1-INDUCED DISRUPTION OF THE BLOOD BRAIN BARRIER**. M Toborek[1]; [1]Department of Neurosurgery, University of Kentucky Medical Center, Lexington, KY, 40536 USA.

W-27 **HIV-TAT-ACTIVATED T CELLS INHIBIT NEUROGENESIS THROUGH RELEASE OF GRANZYME B**. T Wang[1], T Johnson[1], PA Calabresi[1], A Nath[1]; [1]Department of Neurology, Johns Hopkins University, Baltimore, MD 21287 USA.

W-28 **CELLULAR MICRORNA EXPRESSION CORRELATES WITH SUSCEPTIBILITY OF MONOCYTES/MACROPHAGES TO HIV-1 INFECTION**. X Wang[1], L Ye[1], W Hou[1], Y Zhou[1], YJ Wang[1], DS Metzger[2], WZ Ho[1]; [1]Division of Allergy & Immunology, The Children's Hospital of Philadelphia and [2]Department of Psychiatry, The Center for Studies of Addiction, University of Pennsylvania School of Medicine, Philadelphia, PA, 19104 USA.

W-29 **OPIOIDS INHIBIT INTRACELLULAR ANTI-HIV-1 MICRORNA EXPRESSION AND POTENTIATES HIV INFECTION OF PERIPHERAL BLOOD MONOCYTES**. X Wang[1], Y Zhou[2], MQ Liu[2], L Ye[2], E Riedel[1], DJ Zhou[2], WZ Ho[1]; [1]Division of Allergy and Immunology, The Children's Hospital of Philadelphia, University of Pennsylvania, School of Medicine, Philadelphia, PA, USA 19104; [2]Division of Virology, Wuhan Center for Disease Prevention and Control, Wuhan, 430015 China.

W-30 **CHARACTERISTICS OF HEROIN USERS IN METHADONE MAINTENANCE TREATMENT CLINICS IN WUHAN, CHINA**. Z Wang[1], L Pulin[1], L Li[1], W Xia[1]; [1]Division of HIV/AIDS Prevention, Wuhan Center for Disease Control & Prevention, Wuhan, 430015 China; [2]Division of Allergy and Immunology, The Children's Hospital, Philadelphia, PA, 19104 USA; [3]Department of Psychiatry, the University of Pennsylvania School of Medicine, Philadelphia, PA, 19104 USA; [4]Department of Psychiatry, Yale University School of Medicine, New Haven, CT, 06519 USA

W-31 **BORNA DISEASE VIRUS P PROTEIN AFFECTS NEURAL TRANSMISSION THROUGH INTERACTING WITH GAMMA AMINOBUTYRIC ACID RECEPTOR-ASSOCIATED PROTEIN**. JG Wu[1], GQ Peng[1], Y Yan[1], SQ Wang[1], CL Zhu[1], J Hu[1], Y Zhu[1], FM Zhang[1]; [1]State Key Laboratory of Virology, Wuhan University, Wuhan, 430072 China.

W-32 **BORNA DISEASE VIRUS P PROTEIN INHIBITS NITRIC OXIDE SYNTHASE GENE EXPRESSION IN ASTROCYTES**. JG Wu[1], GQ Peng[1], FM Zhang[1], Q Zhang[1], K Wu[1], F Zhu[1]; [1]State Key Laboratory of Virology, Wuhan University, Wuhan, 430072 China.

W-33 **REGULATION OF NEURAL PROGENITOR CELL MIGRATION BY CHEMOKINES PRODUCED IN HIV-1 INFECTION IN SCID MICE**. YW Wu[1], HP Peng[1], HD Dou[1], YH Huang[1], JZ Zheng[1]; [1]Department of Pharmacology & Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE, 68198 USA.

W-34 **CHEMOKINE CCL2 ENHANCES EXCITATORY POSTSYNAPTIC CURRENTS (EPSCS) IN THE CA1 REGION OF RAT HIPPOCAMPAUS**. H Xiong[1], H. Tang[1], Y. Zhou[1], D. Hu[1]; [1]Department of Pharmacology & Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE, 68198-5880 USA.

W-35 **EFFECT OF RELAPSE PREVENTION ON DRUG ADDICTS BY 4C INTERVENTION MODE IN REEDUCATION-THROUGH-LABOR CENTERS**. YQ Yan[1], Q. He[2], J. Gong[1], NN Yang[1], ZZ Wang[2]; [1]Department for Chronic Disease Prevention & Control, Wuhan Centers for Disease Prevention & Control, Wuhan, 430015 China; [2]School of Public Health, Tongji Medical College, Huazhong University of Science & Technology,

Wuhan, 430030 China.

W-36 **ALCOHOL ENHANCES FULL CYCLE HEPATITIS C VIRUS INFECTION OF HUMAN HEPATOCYTES**. L Ye[1], SH Wang[1], X Wang[1], Y Zhou[2], DJ Zhou[2], WZ Ho[1]; [1]Division of Allergy & Immunology, The Children's Hospital of Philadelphia, Philadelphia, PA, 19104 USA; [2]Division of Virology, Wuhan Centers for Disease Control and Prevention, Wuhan, 430022 China.

W-37 **ACTIVATION OF TLR3 INHIBITS HIV INFECTION OF HUMAN MACROPHAGES**. Y Zhou[1], X Wang[1], L Ye[1], D Zhou[2], Q Hu[2], W Hou[1], WZ Ho[1]; [1]Division of Allergy & Immunology, The Children's Hospital of Philadelphia, Philadelphia, PA, 19104 USA; [2]Division of Virology, Wuhan Centers for Disease Prevention and Control, Wuhan, 430022 China.

W-38 **ACTIVATION OF TOLL-LIKE RECEPTORS INHIBITS HERPES SIMPLEX VIRUS-1 INFECTION OF HUMAN NEURONAL CELLS**. Y Zhou[1,2], L Ye[2], Q Wan[2], L Zhou[2], X Wang[2], JL Li[2], SX Hu[3], DJ Zhou[1], WZ Ho[2]; [1]Wuhan Centers For Disease Prevention and Control, Wuhan, 430022 China; [2]Division of Allergy & Immunology, The Children's Hospital of Philadelphia, Philadelphia, PA, 19104 USA; [3]Center for Infectious Disease and Microbiology Translational Research, University of Minnesota Medical School, Minneapolis, MN 55455 USA.

W-39 **CATECHOL-O-METHYLTRANSFERASE (COMT) GENE VARIANTS ARE ASSOCIATED WITH NOVELTY SEEKING AND SELF DIRECTIVENESS IN CHINESE HEROIN DEPENDENT PATIENTS**. M Zhao[1], S Yu[1], J Du[1], H Chen[1], C Fan[1], D Wang[1]; [1]Shanghai Mental Health Center, Medical School of Shanghai Jiao Tong University, Shanghai, 200030 China.

W-40 **DIMINISHED TOLL LIKE RECEPTOR-4-MEDIATED INNATE IMMUNITY IN NEONATAL BRAINS**. H Zhou[1]; [1]Department of Biological Sciences, Seton Hall University, South Orange, NJ, 07079 USA.

W-41 **CHARACTERISTICS OF HEROIN USERS IN METHADONE MAINTENANCE TREATMENT CLINICS IN WUHAN, CHINA**. W Zhou[1], P Liu[1], L Luo[1]; [1]Division of HIV/AIDS Prevention, Wuhan Center for Disease Control and Prevention, Wuhan, 430015 China; [2]Division of Allergy and Immunology, The Children, Philadelphia, PA, 19104 USA; [3]Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, PA, 19104 USA; [4]Department of Psychiatry, Yale University School of Medicine, New Haven, CT, 06519 USA.

W-42 **EFFECTS OF CCK-8 AND ITS RECEPTOR ANTAGONIST ON μ-OPIOID RECEPTOR IN DIFFERENT BRAIN REGIONS OF MORPHINE WITHDRAWAL RATS.** D Wen , B Cong , C-L Ma, Y-J Zhang, S-J Li, Z-Y Ni. Department of Forensic Medicine, Basic Medical College, Hebei Medical University, Hebei Key Laboratory of Forensic Medicine, Shijiazhuang, 050017 China

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ABSTRACTS

II. Opening Session

THE PREVENTION AND TREATMENT OF DRUG ABUSE AND HIV IN CHINA

1. **DRUG USE, HIV/HCV AND PREVENTION STRATEGY IN WUHAN**. DJ Zhou[1], W Zhou[1], X Wang[1], PL Liu[1], ZZ Yao[1], J Xu[1], JS Peng[1]; [1]Wuhan Centers for Disease Control and Prevention, Wuhan, 430022 China.

   Wuhan is the largest city in central China with a population of over 8,000,000 people. With the economical development, drug abuse such as opioids, has become a major public health problem in Wuhan city. The cumulative number of registered drug users in Wuhan increased from 11 000 in 1995 to 45 000 in 2007. The majority of drug users (90%) are young people aged between 20 and 39 years, live in urban (95%) and unemployed people (57.1%); 70% of them is injecting drug use, about 50% sharing needle. Drug abuse-related viral infections such as HIV and HCV have also increased in the city. Anti-HCV positive rate among drug users reached to 88.5%. Between 2000 and 2008, the cumulative number of the subjects with HIV/AIDS raised 26 folds. Injecting drug users (IDUs) made up over 40% of these cases by the end of 2007. However, HIV prevalence has now increased rapidly among men who have sex with men and among female sex workers. Although HIV/AIDS prevalence in Wuhan still remains low (0.014%), there is potential for an explosive spread of HIV/AIDS if preventative measures are not employed. Harm reduction strategies such as methadone maintenance treatment (MMT) and needle-syringe programs (NSP) have commenced implementing to reduce the risk of HIV infection among heroin users. Condom use promotion is carried out among 12,000-36,000 commercial sex workers in the city. Since Wuhan is the hinge of traffic and transportation in central China, it is important to consider both permanent residents and floating populations in future surveillance and intervention efforts.

2. **DRUG ABUSE AND TREATMENT IN CHINA**. W Hao[1]; [1]Mental Health Institute, Second Xiangya Hospital, Central South University, Changsha, 410011 China.

   Drug abuse in China can be traced to the late Qing Dynasty, and illicit drugs reemerged in China in the 1980s and the reemergence was mainly connected with global drug trafficking activities. The number of drug users documented officially by Chinese public security departments increased from 70,000 in 1990 to 1.16 million by 2006. At present, heroin is still main illicit drug and the current heroin users in China are about 700,000, accounting for 78.3% of all illicit drug users. Two trends of drug addiction in China: First, the prevalence rate of opiate addiction in some areas has begun to slow down or plateau, while amphetamine-type stimulants (mainly methamphetamine, MDMA, etc) and ketamine use are increasing rapidly. Second, intravenous drug use remains the most important route of transmission (51.2%-61.6%) of HIV/AIDS in China. In China, most of the pharmacological treatments that are used in the west, especially those for acute withdrawal symptoms, are available now. Furthermore, China has also developed some locally unique treatments, including Traditional Chinese Medicine, which includes herbal medicine, acupuncture and electro-acupuncture et al. In recent years, there have been two new developments in drug addiction treatment in China. First, residential therapeutic community have integrated into drug treatment facilities Second, integrated community based approaches have been set up in some areas. MTT has been implemented as pilot studies underway. The first eight MMT clinics were set up in early 2004, and now we have more than 500 MMT clinics. Supported by National 11.5 major project.

3. **DRUG TREATMENT AS HIV PREVENTION IN CHINA: SCIENTIFIC FINDINGS AND PUBLIC HEALTH IMPLICATIONS.** D Metzger[1]; [1]University of Pennsylvania, Department of Psychiatry, Philadelphia, PA. 19104 USA.

   In many countries and communities around the world, a disproportionate amount of HIV infection, morbidity and mortality is attributable to injection drug use. In China injection drug use is known to be a primary factor in initiating and sustaining the AIDS epidemic among both injectors and, through sexual transmission, to non-injection drug using populations. In evaluating the findings of studies conducted over the past 20 years, it is clear that effective drug treatments can play an important role in controlling the transmission of HIV. There is a

preponderance of evidence to show that when drug users enter treatment, their injection related risk behaviors decline; that when those in treatment are compared to untreated drug users, those in treatment have a lower rates of risk behavior and lower incidence of new HIV infections; and, that HIV positive drug users in treatment are more adherent to anti retroviral medication than those who are not in treatment. Collectively, the data also suggest that effective drug treatments view drug abuse and dependence as treatable medical conditions with biological, psychological and social characteristics. China's response to HIV infection among IDUs has evolved from one centered on a criminal justice approach to a public health approach. Efforts over the past ten years have been impressive and include the expansion of needle exchange programs and the largest scale-up of methadone treatment in history. Central to the sustained effectiveness drug treatment and community responses to HIV among injection drug users will be the need to view addiction as a treatable medical condition.

4. **INHIBITORY LONG-TERM DEPRESSION IN THE HIPPOCAMPUS IS ADAPTED TO OPIOID ADDICTION WITH A COMBINATORIAL PLASTICITY MECHANISM.** L Xu, HL Han; Key Laboratory of Animal Models and Human Disease Mechanisms, Kunming Institute of Zoology, the Chinese Academy of Sciences, Kunming, Yunnan, 650223 China, and Graduate School of the Chinese Academy of Sciences, Beijing, 100039 China.

The persistence of opioid addiction is a major clinical problem. It likely engages memory mechanisms that may in part attribute to adaptations of excitatory synaptic plasticity in the hippocampus. It remains unclear how inhibitory synaptic plasticity in the hippocampus is adapted to opioid addiction. Here we report that neither single *in vivo* morphine exposure nor subsequent acute withdrawal affects inhibitory long-term depression (I-LTD) in CA1 pyramidal neuron of the rat hippocampal slice, which is usually dependent on cannabinoid receptor 1 (CB1R). In marked contrast, repeated *in vivo* morphine exposure blocks I-LTD induction, and subsequent acute withdrawal enhances I-LTD dramatically. This phenomenon is attributed to a combinatorial plasticity containing both CB1R- and L-type calcium channel-mediated components. Thus, the adaptations of hippocampal I-LTD by a novel combinatorial plasticity with repeated *in vivo* opioid exposure and acute withdrawal may contribute, at least partially, to the persistence of opioid addiction. This work is supported by grants from the NSFC (30530250) and Basic Research Program of the MOST (2006CB500808).

III. Plenary Lecture I

STATE OF THE ART OF NEURAL STEM CELL BIOLOGY: The Yin and Yang of Neural Stem Cells

STATE OF THE ART OF NEURAL STEM CELL BIOLOGY: THE YIN AND YANG OF NEURAL STEM CELLS. WC Low[1]; [1]Department of Neurosurgery, University of Minnesota Medical School, Minneapolis, MN, 55455 USA.

Neural stem cells within the central nervous system can be found in specialized niches within the adult brain. During development, neural stem cells give rise to the diversity of cells found in the central and peripheral nervous systems. In the adult brain neural stem cells appear to provide a source of new cells within discrete regions of the brain, and for repair after injury. As opposed to their reparative functions, neural stem cells can also be a source of tumorigenesis. Recent studies now demonstrate that stem-like cells within the tumor mass are responsible for the self renewing properties of brain tumors. This lecture will present an overview of the reparative and tumorigenic potentials of neural stem cells in the mammalian brain, and discuss approaches to enhance the reparative processes, and approaches to target brain tumor stem cells for eradication.

IV. Symposium #1

GLOBAL PERSPECTIVES ON VIRAL & OPPORTUNISTIC INFECTIONS OF THE CNS

1. GLOBAL CHALLENGES OF EMERGING CNS INFECTIONS. PK Peterson[1], [1]University of Minnesota Medical School, Minneapolis , MN, 55455 USA.

After several decades of complacency regarding the importance of infectious diseases as a threat to public health, the era of "emerging and re-emerging infections" was ushered in during the end of the 20 th century. Avian influenza virus H5N1 and SARS are recent examples of the serious consequences these new or newly recognized infections can have on human health as well as the global economy. The underlying factors that explain the emergence of these infections include human behaviors (in particular, explosive population growth and travel across national borders), new or altered microbial species, and the transmission of pathogens from animal to human hosts (i.e. zoonoses). A large number of pathogens have a predilection for infecting nervous tissue, and of these neurotropic agents, at least 17 can be regarded as emerging pathogens. In this symposium, the pathogenesis of several agents that cause severe viral encephalitis or bacterial meningitis will be discussed by other presenters. In this talk, the epidemiology and clinical features of four additional neurotropic agents will be highlighted that underscore different features of emerging CNS infections: Nipah virus, enterovirus 71, West Nile virus, and new variant Creutzfeldt-Jacob disease. Also, research from our laboratory on the potential role of glial cells and lymphocytes in neuropathogenesis will be reviewed. Finally, the important gaps in knowledge regarding the etiology and pathogenesis of encephalitis as well as great need for effective therapies will be emphasized.

2. HUMAN ENDOGENOUS RETROVIRUS W FAMILY ENVELOPE GLYCOPROTEIN PLAYS A ROLE IN SCHIZOPHRENIA DEVELOPMENT BY ACTIVATING BRAIN-DERIVED NEUROTROPHIC FACTOR AND DOPAMINE D3 RECEPTOR THROUGH CALCIUM-DEPENDENT ERK SIGNALING PATHWAY. JG Wu[1], YN Chen[1], W Li[1], W Wei[1], GQ Peng[1], YX Mu[1], Y Yu[1], WJ Huang[1], ST Rasool[1], Y Zhu[1]; [1]State Key Laboratory of Virology, Wuhan University, Wuhan, 430072 China.

Human endogenous retroviruses (HERV) are dispersed over 8% of the human genome. Activation of the HERV W family members may link to the pathogenesis of multifactorial diseases such as cancer, autoimmune disease, multiple sclerosis, and Schizophrenia. We previously demonstrated that HERV-W pol gene was expressed in 34.5% individuals with recent-onset Schizophrenia suggesting HERV-W activation may link to the disease. In this study, we investigated the potential molecular mechanisms involved in schizophrenia development regulated by HERV-W. Our results showed that HERV-W envelop glycoprotein (env) is expressed in peripheral blood mononuclear cells (PBMCs) isolated from 22 of 60 (36.6%) recent-onset Schizophrenia patients, but not detected in healthy individuals. The expression of dopamine D3 receptor (D3DR) gene is enhanced in Schizophrenia patients. HERV-W Env protein is involved in the activation of brain-driven neurotrophic factor (BDNF) expression, which is then required for the enhancement of D3DR transcription. We further demonstrated that Env initiates the calcium-dependent signaling pathway by affecting extracellular Ca2+ entry, stimulating the phosphorylation of ERK1 and ERK2, and enhancing the binding of CREB to the promoter of BDNF gene, which results in the activation BDNF expression. These results provided evidence that HERV-W plays a role in the regulation of neural factors and also provide insights into our understanding the potential role of HERV-W in the pathophysiology of cognitive dysfunction in Schizophrenia development.

3. FUNCTIONAL ANALYSIS OF HUMAN CYTOMEGALOVIRUS, AN OPPORTUNISTIC PATHOGEN CAUSING COMMON INFECTIONS IN CNS. F Liu[1]; [1]School of Public Health, University of California, Berkeley, CA, 94720 USA.

The objectives of our research are (1) to study the biology of human herpesvirus infection (e.g. cytomegalovirus) and (2) to develop new therapeutic agents and approaches for treatment of diseases caused by these herpesviruses. Human herpesviruses are among the most medically important viruses. For example, herpes simplex viruses (HSV) are the causative agents of cold sores and genital herpes and are associated with CNS infections while Epstein Barr virus (EBV) and

Kaposi's sarcoma-associated herpesvirus (KSHV) are associated with a variety of human cancers. Our research primarily focuses on cytomegalovirus (CMV), which is a leading cause of CNS-associated birth defects in newborns and a major cause of blindness and death in immunocompromised patients such as AIDS patients. Little is known about the roles of viral genes in CMV replication and pathogenesis. Very few drugs are available for effective treatment of human herpesvirus infections. The emergence of drug-resistant strains (e.g. CMV resistant to ganciclovir and foscarnet) has posed a need to develop novel drugs and strategies to combat these infections. To address these public health issues, our current research activities focus on (1) studying the functions of viral genes in pathogenesis and identifying new viral targets for antiviral development and (2) generating novel therapeutic agents and studying their antiviral mechanisms and efficacies. In this report, I will summarize our recent progress on these research activities.

4. NEUROIMMUNE RESPONSES TO EXPERIMENTAL HERPES SIMPLEX VIRUS BRAIN INFECTION. JR Lokensgard[1], M Cheeran[1], CP Marques[1], S Hu[1]; [1]Center for Infectious Diseases and Microbiology Translational Research, University of Minnesota Medical School, Minneapolis, MN, 55455 USA.

Infection with HSV-1 stimulates microglial cell-driven pro-inflammatory chemokine production which precedes the presence of brain-infiltrating systemic immune cells. A predominantly macrophage (CD45hiCD11b+Ly6Chi) and neutrophil (CD45hiCD11b+Ly6G+) infiltrate is seen early during infection. By 14 d p.i., the phenotypic profile shifts to a predominantly lymphocytic (CD45hiCD3+) infiltrate which can be detected until at least 60 d p.i., long after clearance of infectious virus, with CD8+ and CD4+ T-cells present at a 3:1 ratio respectively (30 d p.i.). This T lymphocyte infiltration parallels increased IFN-g mRNA expression in the brain. Microglial cells respond to INF-g by producing inducible nitric oxide synthase (iNOS) and activation of resident microglia (CD45intCD11b+) can be detected until at least 30 d p.i., as assessed by MHC class II. Expression of both iNOS and heme oxygenase (HO)-1, a marker of oxidative stress, are highly elevated within 7 d p.i. and remain elevated for at least 21 d. The presence of viral infection-induced oxidative brain damage can be demonstrated by immunohistochemical staining for both 3-nitrotyrosine and 8-hydroxydeoxyguanosine (8-OH-dG), as well as by quantitative assessment of 8-isoprostane levels. Together, these studies show HSV brain infection results in early macrophage and neutrophil infiltration into the brain followed by prolonged T lymphocyte retention and microglial activation. Similar prolonged neuroimmune activation and oxidative stress may contribute to the neuropathological sequelae observed in herpes encephalitis patients. Supported by MH-066703.

5. THE BRAIN'S RESPONSE TO JAPANESE ENCEPHALITIS VIRUS INFECTION: DO NEURAL STEM CELLS PLAY A ROLE?. A Basu[1]; [1]Molecular and Cellular Neuroscience, National Brain Research Center, Manesar, Haryana, 122050 India.

Japanese encephalitis virus (JEV), is one of the leading causes of encephalitis in humans, with approximately 3 billion people living in endemic areas in South-east Asia. The survivors of JE mostly have severe cognitive deficits, behavioural problems, learning difficulties and motor disorders. We hypothesize that depletion of neural progenitor cells (NPCs) by the virus culminates in neurological sequelae in JE survivors. Cellular infection and cell death was determined by Flow cytometry. BrdU administration in animals and in neurospheres was used to determine the proliferative ability of NPCs. Our findings indicate that JEV targets the primary neurogenic area of the brain, the subventricular zone (SVZ), and leads to massive loss of actively proliferating NPC population from this area. Instead, with progressive infection, JEV induces cell cycle arrest in the NPCs accompanied with the decrease in the levels of various mitogenic signals. The supression in proliferative ability of NPCs and their altered fate upon JEV infection provides a possible explanation for the neurological sequelae observed in JE survivors.

6. ETIOLOGY OF BACTERIAL MENINGITIS IN CHILDREN, RESISTANCE TO ANTIBIOTICS AND THE IMPACT OF VACCINATION. X Shen[1]; [1]Beijing Children's Hospital, Affiliated to Capital Medical University, Beijing, 100045 China.

Acute bacterial meningitis is an important cause of morbidity and mortality in children < 5 y.o. H. influenzae, S. pneumoniae and N. meningitidis are the most important agents in developing countries, accounting for almost 90% of reported cases of acute bacterial meningitis in young children. The start of this millennium has witnessed the virtual disappearance of Haemophilus invasive disease in some countries, emergence of pneumococcal strains that are resistant to multiple antibiotics, isolation of

pneumococci with tolerance to vancomycin, and outbreaks/clusters of meningococcal meningitis in several geographical areas. Overuse and inappropriate use of antibiotic are severe problems in pediatric clinical practices, resulting in changes to the pathogen profile of bacterial meningitis with an increase in opportunist species, especially in China over last twenty years. Conjugate vaccines developed in the 90's, especially type b H. influenzae (Hib), and more recently the heptavalent pneumococcal and serogroup C meningococcal vaccines, have changed the profile of these invasive diseases (direct effect) and of their carriage status (indirect effect). Bacterial meningitis has become an uncommon disease in the developed world. However, with limited resources and poor living conditions, developing countries are still affected by the devastating consequences of these infections. This lecture review aspects of epidemiology, etiology and vaccination prevention of bacterial meningitis as well as the antimicrobial susceptibility with emphasis on the pediatric population of China.

7. **OPIATES AND THE NEUROPATHOGENESIS OF TUBERCULOSIS.** T Molitor[1]; [1]University of Minnesota, St. Paul, MN, 55108 USA. (no abstract available)

V. Symposium #2

CO-INFECTIONS AND OTHER DISEASE PROCESSES IN HIV INFECTION

1. **HCV COINFECTION ASSOCIATED WITH DIFFERENT DISEASE PROGRESSION IN TWO COHORTS WHO ACQUIRED HIV-1 THROUGH DIFFERENT INFECTIOUS ROUTES**. XY Zhang[1], JQ Xu[1], B Su[2], HY Zhang[3], XS Xia[4], YM Shao[1]; [1]State Key Laboratory for Infectious Disease Prevention, National Center for AIDS/STD Prevention & Control, Beijing, 10021 China; [2]Anhui Provincial Center for Disease Control and Prevention, Hefei, 230061 China; [3]Dali City Center for AIDS/STD Control and Prevention, Dali, 671000 China; [4]Life Science and Technology, Kunming University of Science and Technology, Kunming, 650224 China.

Background: It remains controversial how HCV co-infection influences the disease progression during HIV-1 infection. This study aims to define the influence of HCV infection on the replication of HIV-1 and the disease progression in HIV-infected former plasma donors (FPDs) and injecting drug users (IDUs) naive to ART. Method: Study cohorts were established including168 HIV-1-infected FPDs from Anhui province and 157 IDUs from Yunnan province in China. Thereafter the cohorts were monitored periodically. Result: During the 33-month follow-up of FPDs cohort, only 35% HIV-1 mono-infected subjects remained their CD4+ T-cell counts above 200 cells/ml and retained on the cohort study, which was significantly lower than 56% for HIV/HCV group and 69% for HIV/HCV/ Toxoplasma group (p,0.05). CD4+ T cells in HIV mono infection group were consistently lower than that in HIV/HCV group. In accordance with those observations, HIV viral loads in HIV mono-infection group were consistently higher than that in HIV/HCV group though statistical significances were only reached at baseline (p = 0.04). However, among the HIV-infected IDUs, a different phenomenon was observed. CD4+ T-cell counts within HIV/HCV patients were significantly lower than that in HIV-1 mono-infected subjects (p=0.0079), and the CD4+ T-cell counts even lower when the subjects co-infected with HIV/HCV/TB (p=0.0064). Conclusions: These data indicated HCV co-infection with HIV-1 was associated with different disease progression. It will be highly interesting to further explore the underlying mechanisms in the future. Supported by Chinese Ministry of Health, NIH.

2. **ENDURING NEUROIMMUNE EVENTS THAT LEAD TO HAND (HIV-1 ASSOCIATED NEUROCOGNITIVE DISORDERS).** H Gelbard[1]; [1]University of Rochester Medical Center. NY, 14642-0001 USA.

28 years after the beginning of the AIDS epidemic, we are confronting the fact that more than one out of three people with HIV-1 develop some form of HIV-1 associated neurocognitive disorder (HAND). Highly active antiretroviral therapy (HAART), even with dramatic reduction of viral load, may reverse some symptoms of HAND (often on a transient basis), but neither cures or prevents the disease. Our laboratory has investigated the role of the phospholipid mediator platelet-activating factor (PAF) in normal and pathologic synaptic transmission as a key molecule involved in the neuropathogenesis of HAND. Our central hypothesis is that viral proteins from HIV-1 can disrupt normal PAF signaling between neuronal synapses by direct and enduring effects on CNS-trafficking

immune effector cells that amplify the effects of PAF and cause neurologic disease. Based on our previous data, we believe that prolonged exposure or increasing doses of PAF results in a continuum of reversible to irreversible synaptodendritic damage with failure of synaptic transmission due to mitochondrial dysfunction. In this seminar, we will discuss experimental models that support the concept of HAND as a disease of the neurologic synapse, and identify potential targets for therapeutic intervention that are discrete from viral targets for HAART.

3. **SMOKING/NICOTINE IN INFLAMMATION, IMMUNITY AND LUNG DISEASES.** M Sopori[1], N Mishra[1], S Razani-Boroujerdi[1], S Singh[1], J Rir-sim-ah[1], S Gundavarapu[1], T Boyd[2], V Kurup[3]; [1]Lovelace Respiratory Research Institute, Albuquerque, NM, USA 87108; [2]Ohio State University, Columbus, OH, 43210 USA; [3]VA Medical Center, Milwaukee, 53295 WI.

Smokers have higher incidence of lung cancer, COPD, and respiratory infections; however, some of the inflammatory diseases, such as ulcerative colitis, sarcoidosis, and allergic diseases and less prevalent among smokers. Nicotine, the major immunosuppressive compound in cigarette smoke, impairs both the adaptive and inflammatory immune responses, including T cell responses. We have evidence to show: 1. T cell express α7-nicotinic acetylcholine receptors that, unlike the neuronal nicotinic receptors, act exclusively through the second messenger system and in concert with the T cell receptor to raise intracellular calcium. 2. Chronic nicotine treatment suppresses several parameters of allergen-induced responses, including lung inflammation and atopy, but promotes mucous cell metaplasia. 3. Prenatal exposure to mainstream or secondhand cigarette smoke increases airway reactivity and lung inflammation; phosphodiesterase-D4 inhibitors attenuate airway reactivity, but not lung inflammation and atopy. 4. Anti-inflammatory properties of nicotine may promote the growth and dissemination of pathogens. 5. Muscarinic and nicotinic receptors may have a yin-yang-like effect on inflammation and immunity. Supported in part by NIH RO1-17003, RO1-04208-17, RO1-04208-7S; RO3HD38222; RO1DA017003; and a FAMRI grant).

4. **OVERVIEW OF SUBSTANCE ABUSE AND HEPATITIS C VIRUS INFECTION AND CO-INFECTIONS IN INDIA.** D. Basu[1]; Drug De-addiction & Treatment Centre, Department of Psychiatry, Postgraduate Institute of Medical Education & Research (PGIMER), Chandigarh, 160012 India.

Hepatitis C virus (HCV) infection can have devastating long-term sequelae. It is very common in injecting drug users (IDU) worldwide. India has a huge number of substance abusers, with an estimated 1.1 million IDU. Research on HCV prevalence in IDU and especially other substance use is sparse. This review identified 16 such studies. Some of these also studied prevalence of hepatitis B virus (HBV) and human immunodeficiency virus (HIV) infections and co-infection rates. The summary findings indicate that there are pockets of very high HCV seroprevalence (60-90%), otherwise the range is moderate (30-50%), though in real terms it still indicates the appreciable magnitude of the problem that may emerge as an epidemic if it goes unheeded. HCV infection seems to be more common in IDU than HBV and HIV infections, again pointing toward the urgent need to prioritise this area. Co-infection rates are low in most of the few studies available, but clearly more studies are needed. There is a glaring paucity of studies on risk behaviours that can be linked meaningfully to HCV infection and its consequences. The urgent future research needs in this important area are highlighted.

5. **HIV NEUROPATHOGENESIS AND NEUROAIDS BIOMARKERS**. JJ He[1], BO Kim[2], B Zhou[3], W Zou[4], Z Wang[5], L Chang[6]; [1]Center for AIDS Research, Indiana University School of Medicine, Indianapolis, IN, 46202 USA; [2]Department of Natural Sciences, Sanju National University, Sanju; [3]Stem Cell Laboratory, Whitehead Institute for Biomedical Research, Boston, MA, 02139 USA; [4]Department of Microbiology, University of Texas Southwestern Medical Center, Dallas, TX, 75390 USA; [5]Department of Medicine, Xi'an Jiaotong University Medical College, Xi'an, 710049 China; [6]Department of Medicine, University of Hawaii School of Medicine, Honolulu, HI, 96813 USA.

Neurological disorders develop in most HIV-1-infected people. The current approaches to diagnose HIV-associated neurological disorders and monitor the progression and the treatment efficacy of these disorders are neuropsychological battery testing, and neuroimaging. Over the past two decades, the challenge for clinical management of these disorders has been lack of more dynamic, sensitive, specific and readily accessible NeuroAIDS biomarkers. To identify potential NeuroAIDS biomarkers, we began by understanding the molecular mechanisms of the neurotoxicity of HIV-1 Tat protein, an important pathogenic factor in HIV-1 neuropathogenesis. We demonstrated that Tat expression in the bran was directly linked to astrocytosis, degeneration of neuronal dendrites,

neuronal apoptosis, and increased infiltration of activated monocytes and T lymphocytes through activation of GFAP expression, while administration of Ginkgo biloba extract markedly prevented Tat from inducing astrocytosis and loss of neuronal integrity through down-regulation of GFAP expression. Moreover, we showed that Tat-induced neuropathological phenotypes were significantly alleviated in GFAP-null/Tat transgenic mice. Lastly, we showed in a small cohort of NeuroAIDS patients that the CSF GFAP level was positively correlated with the severity of HIV-associated neurological disorders. Taken together, these findings suggest for the first time that astrocytosis characterized by GFAP up-regulation directly contributes to HIV-associated neurological disorders and that GFAP can be served as a NeuroAIDS biomarker. Supported by NIH.

6. MORPHINE, NEURIMMUNOMODULATION AND TUBERCULOSIS; A RODENT MODEL. PP Singh[1], S Singh Jhamb[1]; [1]National Institute of Pharmaceutical Education and Research, S.A.S. Nagar, 160062 India.

Opioids have been associated with an enhanced susceptibility to infections in both humans and animals. The increased incidence of infections in opioid addicts has been linked to opioid-induced immunosuppression in various infections including tuberculosis (TB). Recently, it has been reported that acute administration of a low dose of morphine provides protection from experimental TB in murine and *in vitro* models. A single dose of morphine (5 mg/kg) resulted in significant suppression of *Mycobacterium tuberculosis* infection in mice; paradoxically, in mice treated with higher doses of morphine (10- 50 mg/kg/day x1), the infection progressed akin to controls. Morphine at a higher dose of 100 mg/kg/day did not show any effect in *M. tuberculosis* infection in mice. However, *M. smegmatis* infection in mice was suppressed at higher doses of morphine (50 and 100 mg/kg/day x1), whereas lower doses appeared relatively ineffective. *In vitro*, low concentration of morphine (1 μM) showed maximal effect on *M. tuberculosis*- infected mouse peritoneal macrophages, whereas a 100-fold higher concentration (0.1 mM) effectively inhibited the growth of *M. smegmatis* in infected macrophages. The mechanism(s) of antimycobacterial activity appeared to be opioid receptor-mediated, and were apparently nitric oxide-dependent. In conclusion, morphine exerted dose-dependent effects on *M. tuberculosis* and *M. smegmatis* both *in vitro* and *in vivo*. These findings strongly suggest the possibility of exploring the role of opioids in the pathogenesis of TB and in the development of opioid-based drugs for the treatment of TB.

VI. Symposium #3

PRIMATE MODELS FOR STUDYING DRUG ADDICTION & VIRAL INFECTION

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1. AN SIV/CHINESE MACAQUE MODEL FOR DRUGS OF ABUSE RESEARCH. Z Chen[1]; [1]AIDS Institute, The University of Hong Kong, Hong Kong, China.

In addition to traditional Indian macaque models infected with SIV or chimeric simian/human immunodeficiency virus (SHIV), there has been recent interest in Chinese macaques for modeling these infections. A new SHIV, designated SHIV-B'WHU, was generated by replacing counterparts of SHIV with tat/rev/vpu/env genes derived from a primary, CCR5-tropic, subtype B' HIV-1 strain isolated from a Chinese patient. Viral replication and tropism were determined using rhesus PBMC and CCR5-specific cell lines, respectively. We observed that 4 passages of SHIV-B'WHU in Chinese macaques enhanced viral infectivity (viral load) without altering CCR5-tropism or being associated with sequence variation in env genes recovered from peripheral blood and tissue lymphocytes. Significant CD4+ T cell loss was found in small intestines of P2 but not of P3-P4 infected animals. This enhanced infectivity of SHIV-B'WHU warrants further development of the Chinese macaque model for vaccine and pathogenesis studies. In additional studies, a Chinese macaque-adapted SIVmac239 was evaluated for transmissibility via intravenous, intrarectal and intravaginal inoculations. All routes established productive infections in 3 Chinese macaques (peak viremia 10^7-10^8 copies/ml at ~14 days) with viral set-points >10^5-10^6 copies/ml. This profile is similar to that in Indian macaques. Four SIVmac251 strains have also been isolated from 4 Chinese macaques with end stage AIDS (CD4<100/ul) and the pathology of these macaques studied. These findings suggest Chinese macaques as valuable models for viral research.

2. **GENETIC DIVERSITY AND COMPARTMENTALIZATION OF SIV IN THE CNS AT EARLY STAGES OF INFECTION**. FJ Novembre[1], A Reeve[1]; [1]Microbiology and Immunology, Yerkes National Primate Research Center, Atlanta, GA, 30329 USA.

SIVsmmFGb induces neuropathology in over 90% of infected pigtailed macaques and is a reliable model of HIV central nervous system (CNS) infection. However, little is understood about how SIVsmmFGb genetic diversity, compartmentalization and evolution is affected by initial seeding of the CNS and by adaptive immune responses over the course of infection. We demonstrated that seeding of the CNS at one week post-infection reduces Env V1 region and Int genetic diversity, but has a variable effect on Nef. By two months post-infection, tissue-specific immune pressure impacted the diversity of Nef, but the effects of adaptive immunity on Envelope V1 region and Integrase diversity was similar in all tissues. At one week and two months post-infection, SIVsmmFGb env V1 region and nef genes formed distinct compartments between all CNS tissues, while int formed distinct compartments between most CNS tissues. Positive selection led to compartmentalization of the env V1 region at one week and two months post-infection, while compartmentalization of nef and int at both time points was due to negative selection. Positive selection of the env V1 region increased in some brain tissues, while nef and int sequences each saw increased negative selection, over time. Convergent evolution of env V1 region and nef, and divergent evolution of int, was noted between compartments. These results showing compartmentalization and evolution of an SIV quasispecies, may provide a basis for understanding genetic diversity and evolution and the role of specific genes in lentiviral neuropathogenesis. Supported by NIH R01 MH067769.

3. **MORPHINE AND RAPID DISEASE PROGRESSION IN NON-HUMAN PRIMATE MODEL OF AIDS: INVERSE CORRELATION BETWEEN DISEASE PROGRESSION & VIRUS EVOLUTION.** A Kumar[1], R Kumar[1], RJ Noel[2], V Rivera-Amill[2]; [1]Division of Pharmacology, School of Pharmacy, University of Missouri at Kansas City, Kansas City, MO, 64108 USA; [2]Ponce School of Medicine, Ponce, PR, 00716 USA.

Six morphine-dependent and 3 control male Indian rhesus macaques were intravenously inoculated with mixture of $SHIV_{KU}$, $SHIV_{89.6}P$ and SIV/17E-Fr. These animals were followed for a period of 56 weeks for CD4 and CD8 profile, viral loads in plasma and cerebrospinal fluid (CSF), relative distribution of 3 pathogenic viruses in blood and brain, binding as well neutralizing antibody levels and cellular immune responses. Both morphine-dependent and control macaques showed precipitous loss of $CD4^+$ T cells but CD4 recovery was found to better in more control animals than that in the morphine-dependent animals. The plasma and CSF viral load was significantly higher in morphine-dependent group than those in the control group. Five morphine-dependent succumbed to SIV/SHIV-induced AIDS at week 18, 19, 20, 51 and 162 post-infection with neurological problems in 4 of those 5 animals. Three morphine-dependent macaques (euthanized at weeks 18, 19 and 20) did not develop cellular or humoral immune responses whereas other 3 morphine-dependent and 3 control macaques developed both cellular and humoral immune responses. These animals showed inverse correlation between disease progression and virus evolution.

4. **M. TUBERCULOSIS INFECTION IN NON-HUMAN PRIMATES**. J Zhang[1], ZJ Tang[1], LH Sun[1], XD Li[1], QY Xian[1], Y Wang[1], M Dai[1], Y Rao[1], R Bao[1], RX Li[1]; [1]ABSL-3 Laboratory , Wuhan University, Wuhan, 430071 China.

Tuberculosis (TB) is the most common opportunistic infection disease and killer for individuals infected with HIV and AIDS. Because of HIV and M.TB co-infection, emergence of multidrug-resistant M.TB, and lack of sufficient efficacy of BCG vaccination, the morbidity and mortality of TB infection are increasing sharply in the World. Therefore, there is an urgent need for developing new vaccines and drugs against TB, which requires establishing appropriate animal models for TB infection. In our collaboration studies with Japanese and Korean investigators, we attempted to infect Chinese macaques with M.TB using different methods and doses of TB strains in order to establish clinical relevant models. We challenged 20 monkeys with M. TB strain H37RV by intratracheal instillation or directly inoculated M.TB strain MDR-TBOB35 into lungs of 14 monkeys with bronchoscope. During the period of six to nine months after TB strain inoculation, the animals became infected, which is evidenced by clinical manifestations, laboratory analyses, skin tests with PPD, bacterial burden in infected tissues and histopathology evaluations. Importantly, the processes of developing chronic active infection or latent infection of TB in these infected monkeys are similar to those seed in human. These data indicate that it is feasible to use Chinese macaques as a clinically relevant model for TB infection. The establishment of model for M.TB infection in non-human primates should provide an

ideal platform not only for studying the immunopathogenesis of TB disease but also for preclinical trails of vaccines and drugs against TB.

VII. Young Investigator's Symposium

1. **THE ROLE OF CANNABINOID RECEPTORS IN THE MODULATION OF TOLL-LIKE RECEPTOR (TLR) 4 EXPRESSION AND ANTIBODY CLASS SWITCHING IN MOUSE B LYMPHOCYTES**. M Agudelo[1], C Newton[1], T Sherwood[1], TW Klein[1]; [1]Molecular Medicine, School of Biomedical Sciences, College of Medicine, University of South Florida, Tampa, FL, 33612 USA.

   Recently we showed cannabinoids induce B cell antibody class switching from IgM to IgE and CB2 receptors were involved. In the current study, because CB2 is coupled to Gi/o proteins and negatively regulates adenylyl cyclase, we measured cannabinoid effects on cAMP accumulation in B cells. We also explored the possibility that cannabinoid treatment of B cells modulates cell functions other than antibody class switching such as surface marker and TLR expression. Splenic B cells were purified and activated with IL4 and anti-CD40 in the presence of the nonselective cannabinoid agonist, CP55940, the CB1 agonist, methanandamide, or CB2 agonists, JW015 and CB65. Treated cells were analyzed by flow cytometry for expression of different B cell surface markers and TLRs. We showed CP55940 caused a significant increase in surface expression of TLR 4, but had no effect on other markers. Additional experiments with cannabinoid receptor selective agonists and antagonists suggested both CB1 and CB2 receptors were involved in the TLR effect. Receptor involvement was also supported by cannabinoid inhibition of cAMP levels in forskolin stimulated B cells. Furthermore, B cells treated with the cAMP enhancing agents, forskolin or 3-isobutyl-1-methylxanthine, were not able to class switch to IgE. These results suggest cannabinoids negatively regulate cAMP in B cells resulting in increased IgE. In conclusion, cannabinoids induce B cell class switching through mechanisms involving CB1 and CB2; in addition, an increase in TLR4 might also be involved in drug effects on antibody production. Supported by Supported by NIH grant DA019824 from the National Institute on Drug Abuse.

2. **SELECTIVELY ENHANCED RETRIEVAL OF POSITIVE OR HEROIN-RELATED WORDS AFTER PSYCHOSOCIAL STRESS IN ABSTINENT HEROIN ADDICTS**. LY Zhao[1], J Shi[1], XL Zhang[1], L Lu[1]; [1]National Institute on Drug Dependence, Peking University, Beijing, 100191 China.

   Background: Stress exposure in addicted individuals provokes drug craving and recall of drug-related memories. These memories might be about euphoria and getting high or about withdrawal and unpleasant parts of the addiction and thereby reflect positively or negatively valenced material, respectively. This distinction in emotional valence is critical for developing an operational definition of stress-induced craving, which has been related to relapse to drug abuse. Methods: Three groups of participants(Addicts given Heroin Words, Addicts given Non-drug Words, and Controls given Non-drug Words) were assessed for 24-hour delayed recall of positively and negatively valenced and neutral word lists on two occasions 4 weeks apart□once in a non-stress control condition, and once after exposure to the Trier Social Stress Test in a counterbalanced design. Results: After stress, recall of positively and negatively valenced heroin words and positively valenced non-drug words was better than that under non-stress control condition in abstinent addicts. In the addicts recalling heroin words, post-stressor salivary cortisol correlated positively with recall of positive words. Conclusions: Since greater emotional activation in response to stress, as reflected in higher cortisol levels among these post-addicts, is associated with better positive and drug related word recall, an operational definition for stress-induced craving, which can lead to relapse, may be "selectively enhanced memory of drug use and the rewarding aspects".

3. **A HUMANIZED HUPBL-NOD/SCID/IL2R-GAMMA-NULL MODEL FOR EVALUATING THE IMPACT OF DRUG ABUSE ON HUMAN IMMUNE FUNCTION**. A Harui[1], SM Kiertscher[1], MD Roth[1]; [1]Pulmonary & Critical Care Medicine, University of California, Los Angeles, Los Angeles, CA, 90095-1690 USA.

   Immunoregulatory effects of cannabinoids have been well documented in conventional animal models and with human cells in vitro. However, the relevance of these findings to human immune function in substance abusers has been difficult to assess. We have developed a xenotransplant

model that will serve as a platform for evaluating the effects of substance abuse on the presentation of viral antigens and the development of effector, memory and regulatory T cell responses in vivo. Immunodeficient NOD/SCID/IL2r-gamma-null mice, which lack the gamma chain of IL-2 receptor, allow efficient engraftment and expansion of human peripheral blood leukocytes (huPBL). Over 3 weeks, these cells reconstitute the spleen and lymphoid organs of recipient mice with more than 70% of the spleen cells expressing human CD45 (~25-30 x106 human PBL/spleen). Animals exhibit a relatively normal CD4/CD8 ratio (~1.5:1) as well as reconstitution of the CD3/CD56 and CD45/CD20 subsets. Furthermore, we have demonstrated that these animals can be challenged with adenovirus, either as free vector or virally-infected dendritic cells, resulting in normal activation and expansion of anti-viral specific effector and regulatory T cells in vivo. In future studies, reconstituted huPBL-NOD/SCID/IL2r-gamma-null animals will be exposed to cannabinoids using different exposure algorithms and evaluated for the effects on antigen-specific immune responses. In addition, this model supports active HIV infection and will be used to study the biology, efficacy and potential adverse effects of adenoviral-based vaccines for HIV. Supported by NIH/NIDA R01-DA03018.

4. INCREASED CDK5 ACTIVITY IN THE HIPPOCAMPUS REGULATES THE DEPRESSIVE-LIKE BEHAVIORS IN CHRONIC MILD STRESS. WL Zhu[1], L Lu[1]; [1]Peking University, National Institute on Drug Dependence, Beijing, 100191 China.

Cyclin-dependent kinase 5 (Cdk5) has been implicated in learning and synaptic plasticity. Previous evidence suggests that neuronal plasticity and neurotrophins are involved in depression and bipolar disorder. Here, we explored if Cdk5 participates in the depressive-like behaviors in chronic mild stress (CMS)-treated rats. We found here that CMS caused a significant increase of Cdk5 activity and the membrane fraction of p35 protein as well as a decrease of cytosolic p35, a Cdk5 activator, in the dentate gyrus (DG) of the hippocampus. Conversely, microinjection of a Cdk5 inhibitor, butyrolactone, in DG subregion, but not in CA1 or CA3 of the hippocampus, reversed the depressive-like symptoms without affecting the symptoms of control rats. Furthermore, treatment with butyrolactone in DG, but not in CA1 or CA3 of the hippocampus, increased the cytosolic p35 level as well as decreased the membrane p35 level in CMS-administrated rats. The current results proposed that the development of depressive-like behaviors was regulated by the increased Cdk5 activity of the hippocampus. These findings suggested that the depressive-like behaviors induced by chronic mild stress may be mediated by the activation of Cdk5 in DG and the Cdk5/p35 complex could provide a potential target for development as a novel therapeutic for the treatment of depressive disorders. Supported by The National Natural Science Foundation of China (No. 30800362) and 973 Program (2007CB512302).

VIII. Plenary Lecture II

MOLECULAR BIOLOGY OF THE INCUBATION OF DRUG CRAVING

MOLECULAR BIOLOGY OF THE INCUBATION OF DRUG CRAVING. L Lu[1]; [1]National Institute on Drug Dependence, Peking University, Beijing, 100191 China.

Relapse to drug use can occur after prolonged withdrawal periods and is often precipitated by reexposure to cues previously paired with drug use. Using drug self administration model, we found that cue-induced drug craving increases over the first several weeks of abstinence and remains high over extended periods, a phenomenon that we named as incubation of drug craving. Cocaine seeking in rats in extinction and cue-induced reinstatement tests follows an inverted U-shaped curve, with higher responding 1 or 3 months after withdrawal than 1 day or 6 months after withdrawal. Time-dependent increases in BDNF in the VTA, nucleus accumbens, and amygdala have been observed after cocaine withdrawal. Exposure to cocaine cues increased ERK phosphorylation in the central amygdala 30 days, but not 1 day, after withdrawal. Thirty days after cocaine withdrawal, inhibition of central amygdala ERK phosphorylation decreased cocaine seeking. Intra-central amygdala injections of the mGluR2/3 agonist LY379268 attenuated the enhanced extinction responding on cocaine withdrawal day 21. During the first weeks of cocaine withdrawal, GDNF-dependent neuroadaptations were also observed in the VTA. The expression of morphine-induced place preference also progressively increased, or incubated, over the first 14 days after the last drug exposure, an effect associated with increased ERK and CREB phosphorylation in the central amygdala. Overall, the incubation of drug craving is suggested to be

mediated by glutamate and acute activation of the ERK-CREB pathway in the central nucleus of the amygdala.

IX. Symposium #4

BASIC MECHANISMS IN DRUG ABUSE AND NEUROBIOLOGY

1. OPIATE MECHANISMS IN THE IMMUNE SYSTEM: COMPARING PHARMACOLOGY AND KNOCKOUT APPROACHES. C. Gaveriaux-Ruff[1]; [1]IGBMC Institut Génétique Biologie Mol. Cell., Université de Strasbourg (UdS)/INSERM/CNRS, Illkirch, 67400 France.

Opiates are known to alter immunity. The mechanisms for these actions have been examined using pharmacological and molecular tools, and more recently by knockout approaches. All mu, delta and kappa receptor targeted exogenous opiates as well as the endogenous opioid tone produced by enkephalins, endorphins and dynorphins peptides can influence immune functions. Opiates can act on all immune cell types (neutrophils, monocytes/macrophages/ dendritic cells, lymphocytes), and their action may be dependent on cell maturation. Mu-receptor activation induces pro- and anti-inflammatory effects, and kappa-receptor activation decreases inflammatory responses by down-regulating cytokines and chemokines. Delta-receptor role has more difficult to assess, due to the lack of satisfactory in vivo agonists. Reports on mu-receptor knockouts have indicated the selective action of morphine on mu-receptor and the implication of endogenous mu-receptor tone in fever, neuroinflammation, stress-induced apoptosis, and allergic airway responses. Kappa-receptor knockouts show altered immune cell numbers and increased antibody response, while beta-endorphin and preproenkephalin knockouts exhibit altered cytokine patterns. These approaches have also highlighted a role for the opioid system in inflammatory pain. Opioid peptides produced by immune cells at the inflammation site control inflammatory pain by activating opioid receptors on primary afferent nociceptive neurons. Altogether a modulation of opioid activities by transcription factors, cytokines, chemokines and other proteins has been shown. Supported by Université de Strasbourg/INSERM/CNRS.

2. NOVEL MECHANISMS IN NEUROTOXICITY AND NEUROAIDS. O. Meucci[1]; [1]Department of Pharmacology and Physiology, Drexel University College of Medicine , Philadelphia, PA, 19102 USA.

Chemokines are widely expressed in the nervous system and play important roles in regulation of basic neuronal/glial functions, ranging from cell migration, differentiation, and survival, to neurotransmission and neuronal-glial communication. One of the chemokine/receptor pairs constitutively expressed in the CNS is CXCL12/CXCR4, which is essential to proper brain development and largely contributes to homeostasis. Alterations of CXCL12/CXCR4 signaling may lead to neuronal injury, dysfunction, and/or death and have thus been implicated in several neurologic disorders, including neuroAIDS. Importantly, CXCR4 participates to HIV-1 neuropathology at different levels: it regulates leukocytes trafficking and acts as HIV co-receptor mediating infection of target cells, but can also interact with HIV envelope proteins independently of infection, causing cellular damage. Our recent studies demonstrate that neuronal CXCR4 function is under control of the ubiquitous protein ferritin heavy chain, which in turn is up-regulated (both in vitro and in vivo) by exposure to mu-opioid agonists, such as morphine and DAMGO. Unlike other evidence of opioid-chemokine interactions, this particular regulatory mechanism seems to be neuron-specific, ligand-dependent, relatively long-lasting, and not caused by reduction of surface CXCR4 levels. Thus, enhanced neurotoxicity would result from unbalance of beneficial/toxic signals triggered by CXCR4 following stimulation by its natural ligand (CXCL12) or viral proteins - with potential important implications to drug abuse and neuroinflammation. Supported by NIH DA15014 & DA19808.

3. CANNABINOIDS AND IMMUNITY: THE ANTIBODY SURGE. T Klein[1], C Newton[1], M Agudelo[1], T Sherwood[1], L Nong[1]; [1]Molecular Medicine, College of Medicine/University of South Florida, Tampa, FL, 33612 USA.

Cannabinoids have been shown to modulate the function of T cells, macrophages, and dendritic cells. However, although B cells appear to express high levels of cannabinoid receptor mRNA and cannabinoids modulate antibody responses, many questions persist concerning the cannabinoid effects on and the role of cannabinoid receptors in the immunobiology of B cells. We have been

examining the effects of cannabinoids on antibody production by cultures of mouse purified B cells as well as examining the regulation of cannabinoid 2 receptor (CB2) gene expression in B cells from mice and humans. Our results show that cannabinoids induce antibody class switching from IgM to IgE and that the effect is partially CB2 mediated and dependent on downregulation of intracellular cAMP. We have also observed that B cells express select and unique CB2 gene transcripts and that transcription selection changes with B cell activation. Finally, we have shown that at the level of the whole animal, cannabinoid treatment can promote the production of IgE to standard antigens resulting from possibly drug effects on both T and B cell function. These results suggest that cannabinoids may under some conditions act as selective immune adjuvants capable of enhancing antibody production and furthermore suggest that the endocannabinoid system may be of importance in the regulation of allergy and other antibody-mediated diseases. Supported by NIDA/DA019824.

4. DETERMINATION OF BIOLOGICAL PATHWAYS UNDERLYING ADDICTION AND NEUROPROTECTION BY NICOTINE. MD Li[1]; [1]Department of Psychaitry & Neurobehavioral Science, University of Virginia, Charlottesville, VA, 22911 USA.

Nicotine, a natural alkaloid agonist present in cigarette smoke, exerts its pharmacological effect through nicotinic acetylcholine receptors, resulting in modulation of a diverse set of genes involved in various cellular and biochemical pathways. However, regarding which genes and biochemical pathways are modulated by nicotine, it is largely unknown. To identify those genes and pathways underlying nicotine treatment, we have been employing both genomics and functional genomics approaches in our study on genetics and pharmacology of nicotine using humans, animals and cultured cells. In this presentation, specifically, I will present some of our most recent findings on identification and characterization of susceptibility loci and genes for nicotine addiction in humans through genome-wide linkage and association analyses. The genes of interest in this presentation will include those related to immune modulation and neuroprotection such as Interleukin 15 and amyloid precursor protein-binding protein, family B, member 1. Then I will discuss several biochemical pathways identified through microarray and proteomic techniques using both in vivo and in vitro approaches, which include those for phosphatidylinositol (PI) signaling, PKB/AKT, NF-κB, and JNK signaling, growth factor/cytokine signaling, and ubiquitin-proteosome signaling. Finally, I will present our recent findings on the involvement of a number of genes from mitogen-activated protein kinases, nuclear factor kappa B and toll-like receptor pathways underlying nicotine's anti-inflammatory mechanism. Supported by NIH Grants DA-12844 and DA-13783.

5. METHAMPHETAMINE-INDUCED EFFECTS ARE ENHANCED IN THE PRESENCE OF HIV VIRAL PROTEINS. SL Chang[1]; [1]Institute of NeuroImmune Pharmacology, Seton Hall University, South Orange, NJ, 07079 USA.

HIV positive individuals reportedly use psychostimulant drugs, such as methamphetamine (METH), to a greater extent than HIV negative individuals. HIV-1 infection or the presence of HIV viral proteins alters dopaminergic neuronal terminals, leading to decreased dopamine (DA) release and physiological dopaminergic deficits. This neuronal alteration, in turn, could lead to the use and abuse of psychostimulant drugs, such as METH, that increase DA release and relieve those deficits. In the HIV-1 transgenic (HIV-1Tg) rat model, there is no viral replication; however, viral proteins are found in the blood circulation and various organs including brain. Thus, this rodent model mimics HIV-positive patients treated with anti-retroviral therapy in which there is a persistent low level HIV infection and the presence of HIV viral proteins without viral replication. We tested our hypothesis that the effects of METH are enhanced in the HIV-1Tg rat and found that (1) METH-induced locomotive activity (rearing) and stereotypical head movement was greater in HIV-1Tg rats than in non-transgenic control rats; (2) METH (1.0 mg/kg) induced a conditioned place preference (CPP) in HIV-1Tg rats, but not in control rats; and and (3) expression of the D1R dopamine receptor was elevated in the prefrontal cortex of HIV-1Tg rats. Taken together, our studies suggest that the effects of METH are enhanced in the presence of HIV viral proteins, and that D1R expression in the prefrontal cortex may play a role in METH addiction in HIV-positive individuals. Supported by K02-DA016149 and R21-DA019836

X. Symposium #5

NOVEL MECHANISMS IN NEUROTOXICITY AND NEUROAIDS

1. **IS HIV-1 INDUCED CNS DAMAGE CLADE SPECIFIC?** P Seth[1], M Mishra[1]; [1]Molecular and Cellular Neuroscience, National Brain Reserach Centre, Manesar, 122050 India.

HIV-1 directly affects the nervous system, inducing distinct neurological deficits and irreversible neuronal damage. These disorders develop in advanced stages of HIV infection and are referred to as HIV associated neurological deficits (HAND). Detailed studies into the molecular and cellular events during the neuropathogenesis of HAND are lacking, especially with respect to different HIV-1 clades. In India, >95% of HIV-1 infections are due to clade C. Despite the large population of HIV-1 infected individuals, HIV-1 related neurological deficits are rare among Indians compared to Western countries, where HIV-1 clade B is prevalent. It is not known whether the low incidence of HAND in India is due to HIV-1C clade (rather than HIV-1B) infections. We carried out studies to understand the neuropathogenesis of HIV-1C. Further, we investigated if HIV or its viral proteins modulate human neural precursor cells and diminish rescue/replenishment of the damaged neuronal pool. We investigated the effect of HIV-1 transactivating protein (Tat) on cell survival, growth, proliferation, and differentiation potential of human neural precursor cells using a novel human neurosphere cell culture. We observed that Tat modulates the proliferation of human neural precursor cells (decrease in size and incorporation of Brdu and other markers). In addition to this, we observed that toxicity to human neurons was clade specific, as HIV-1 Tat B was more neurotoxic than HIV-1 Tat C. We believe our study provides new insight into the neuropathogenesis of HIV-1 and how two HIV-1 clades can be different. Supported by Grant BT/PR6838/Med/14/881/2005 and BT/PR6615/Med/14/857/2005 from Dept of Biotechnology, New Delhi, India to P. Seth.

2. **THE ROLE OF CD38 AS A NOVEL PHARMACOLOGICAL PATHWAY IN THE MECHANISMS OF NEURO-AIDS.** A Ghorpade[1]*, S Banerjee[2], W Kou[1], K Borgmann[1], R Persidsky[2], L Wu[2]; [1] Department of Cell Biology and Genetics, University of North Texas Health Science Center, Fort Worth, TX, 76107 USA; and [2]Center for Neurovirology and Neurodegenerative Disorders, University of Nebraska Medical Center, Omaha, NE, 68198 USA.

Astrocytes are numerically the most abundant cell type in the CNS. A critical function of astrocytes is to regulate the level of extracellular glutamate, an excitatory neurotransmitter. Astrocytes express glutamate transporters, most prominently excitatory amino acid transporter 2 (EAAT2), that clears the vast majority of synaptic glutamate. This prevents excitotoxicity, the overactivation of glutamate receptors on the cell surface of neurons. However, neuroinflammatory conditions such as in neuro-AIDS and/or in drug abuse involving methamphetamine (METH) involve excitotoxic injury likely via impaired astrocyte glutamate uptake. CD38 is a 45 kD ectoenzyme involved in synthesis and translocation of the potent calcium (Ca^{2+}) mobilizing agents, cyclic adenosine diphosphate-ribose (cADPR) and nicotinic acid adenine dinucleotide phosphate (NAADP+). We investigated effects of cytokines, HIV-1 and METH on the expression of EAAT2 in astrocytes, their effects on glutamate uptake and the potential role of CD38 in these phenomena. Our results showed that IL-1β and METH treatment led to reduced levels of EAAT2. Furthermore, we detected that IL-1β time-dependently reduced glutamate uptake in astrocytes, which was completely reversed by co-incubation with 8-Br-cADPR, a specific cADPR-antagonist. Additionally, a decrease in EAAT2 expression induced by IL-1β and an increase in EAAT2 expression induced by blocking the CD38 signaling were demonstrated. Thus, we provide new evidence that CD38 upregulation in activated astrocytes may be a novel pharmacological pathway involved during neuroinflammatory conditions and in the context of METH abuse. (*Dr. Ghorpade is both the presenting and senior author)

3. **CNS IMMUNITY MODULATES SYNAPTIC PROTEIN ECONOMY IN HIV ENCEPHALITIS**. BB Gelman[1]; [1]Department of Pathology, University of Texas Medical Branch, Galveston, TX, 77555-0609 USA.

Upregulation of interferon response genes is a highly prevalent change in the brain of people with HIV-infection. It occurs in those with neurocognitive impairment, and also occurs in many subjects without apparent functional changes. One prevalent interferon response in HIV/AIDS is immunoproteasome induction, which modifies normal protein turnover in favor of antigen

presentation. In neurons, protein turnover through the proteasome occurs locally in synapses, and it plays a key role in regulating synaptic transmission. In this presentation, the effect of immunoproteasome induction on the turnover of neural proteins in the HIV infected CNS will be described and discussed. Strong relationships to dementia and encephalitis will be illustrated. Immunoproteasomes were localized to various neuronal elements including stucturally normal synapses and pathologically modified elements of neurons. A proteomic analysis of synaptosomes identified some synaptic proteins that exhibit altered steady state concentration when immunoproteasome induction takes place. Data will be discussed that show that changes occur at the circuit level, and are not always driven by the regional concentration of HIV or inflammatory cells in the brain. The standard paracrine model, which suggests that neurocognitive impairment is caused by local inflammatory neurodegeneration, needs to be reconsidered. An alternate concept will be presented, in which potentially reversible changes in neural protein economy, and other metabolic changes in the brain, drive nonlethal changes in neurons. Supported by 1U01MH083507 and R01 MH79886.

4. **MOLECULAR PATHOLOGY OF THE DOPAMINE TRANSPORTER IN HIV-1 AND COCAINE ABUSE**. RM Booze[1]; [1]Department of Psychology, University of South Carolina, Columbia, SC, 29223 USA.

Human immunodeficiency virus (HIV)-1 Tat protein plays a key role in the pathogenesis of both HIV-1-associated cognitive-motor disorder and drug abuse. Dopamine (DA) transporter(DAT) function is strikingly altered in patients with HIV-1-associated dementia and a history of chronic drug abuse. Our pharmacological studies described the first in vitro evaluation of potential mechanisms underlying the effects of Tat protein on DAT function. Rat striatal synaptosomes were incubated with recombinant Tat1-86 protein and DAT-specific ligands. Tat decreased dopamine uptake and altered cocaine-like ligand binding to the transporter. Kinetic analysis of dopamine uptake revealed that Tat (1 or 10 μM) decreased the Vmax value and increased the Km value in a dose-dependent manner. Additional studies using SPR techniques suggested that Tat and DAT proteins interacted in a direct manner. Additionally, computer modeling indicated potential sites for Tat-induced alteration of the transporter protein. These findings provide new insights into understanding the pharmacological mechanisms of HIV-1 induced dysfunction of the nervous system. Supported by DA13137

5. **COMPARATIVE STUDY ON CALCIUM-INFLUX TRIGGERING RESPONSE IN HUMAN MICROGLIA TO STIMULATORS BETWEEN AT-2-INACTIVATED HIV PARTICLES AND ITS ENVELOPE PROTEIN GP120**. YY Zeng[1], XY Huang[1]; [1]Institute for Tissue Transplantation & immunology, Jinan University, Guangzhou, 510632 China.

HIV incorporates a series of host-derived proteins during the duding process. HIV particle is a chimeric and recombinant nanoparticle with proteins encoded by genes from viral and host genomes. On the basis of structural characteristics, HIV particles must be of unique biological functions, which may be association with pathogenesis of AIDS. For a better understanding of their phathogenicity in HIV-associated dementia (HAD), a comparative study on calcium-influx triggering response in human microglia to stimulators between AT-2-inactivated HIV-1 particles (HIVp) and gp120. The level of intracellular calcium of human microglia, which was grown on coverslip and loaded with Fluo-4, was detected in various experimental processing, by real-time imaging with confocal microscopy. A much stronger calcium-influx response can be triggered by HIVp including R5 and X4 types than that that by gp120 in human microglia. Calcium-influx triggered by HIVp is weaker in the presence of gp120 than that in the absence of gp120 indicating partially overlay in the mechanism. In view that microglial activation, which is responsible for neuron loss in HAD, is calcium dependent, extracellular HIVp has potent effector on the pathogenesis of HAD. Study for the mechanism underlying HIVp acting as a stronger calcium-influx stimulator to gp120 is needed although host molecules on the surface of HIVp may be involved in this process. Supported by China 973 project 2006CB504200.

6. **THE USE OF ANTI-AGING CHINESE MEDICINAL HERB GOUQIZI (WOLFBERRY), EXERCISE AND SELF-ASSEMBLING PEPTIDE (SAP) IN PROMOTING NEUROPROTECTION**. KF So[1]; [1]Anatomy, Research Center of Heart, Brain, Hormone & Healthy Aging, The University of Hong Kong, Hong Kong, China.

Although the main target of HIV is the immune system, the CNS is also markedly affected leading to cognitive impairment. Since dendritic pruning, loss of synapses and cell death have been observed, novel treatments to protect the CNS may offer additional approaches to prevention and

treatment of the neurological symptoms in HIV patients. Using a rat glaucoma model, we showed that oral administration of Wolfberry significantly reduced the retinal ganglion cell loss against elevated intraocular pressure. In an Alzheimer's disease model, primary cortical neurons exposed to B-amyloid peptides resulted in apoptosis. Extract of Wolfberry markedly reduced the number of apoptotic neurons and it may depend on the inhibition of the JNK signaling pathway. By administrating high dosages of corticosterone in rats for 14 day, depression-like behavior was observed and spatial memory was affected. Suppressed hippocampal cell proliferation, decreased spine density and dendritic length were observed. We showed that voluntary exercise (wheel running) reversed these structural changes and improved spatial memory and decreased depression-like behavior. Using the rat visual system as a model, we showed that a designed SAP nanofiber scaffold creates a permissive environment not only for axons to regenerate through the site of an acute injury, but also to knit the brain tissue together. In experiments using a severed optic tract in hamsters, we showed that regenerated axons reconnect to target tissues and functional return of vision was demonstrated. Supported by Azalea (1972) Endowment Fund, HKU.

XI. Symposium #6

HOST INNATE FACTORS AND IMMUNOLOGIC AND BIOLOGIC OBSTACLES TO THE CONTROL OF HIV

1. COHORT STUDY ON HOST FACTORS OF HIV DISEASE PROGRESSION. Y Shao[1]; [1]National Center for AIDS/STD Control & Prevention, Chinese Center for Disease Control and Prevention, Beijing, 100050 China.

Background. Host factors, including host immunity and genetic background, are likely to influence the HIV disease progression. The purposes of this study are to describe the association of selected host factors with CD4+ counts and viral load in HIV-1 infected former blood donors (FBDs) who were infected with HIV from a common-source exposure to contaminated blood between 1992-1995, in Fuyang City, Anhui Province, China. This unique cohort helped define the precise role of host factors in restricting HIV-1 disease progression. **Methods.** 353 subjects were enrolled, including 294 HIV-positive FBDs and 59 HIV-seronegative individuals. Vγ2Vδ2 T cell count and function, the expression of NKG2A on cytotoxic natural killer (NK), HLA genotypes in HIV-1 infected individuals were measured and their association with CD4 T cell count and viral load were analyzed. **Results.** HIV-infected participants had significant positive correlations between CD4 T cell count and both total Vγ2Vδ2 T cell count ($P<0.001$) and functional (isopentenyl pyrophosphate-responsive) Vγ2Vδ2 T cell count ($P<0.001$). Significant reverse correlations between viral load and both total Vγ2Vδ2 T cell count ($P<0.05$) and functional Vγ2Vδ2 T cell count ($P <0.05$) were also found. Fewer cytotoxic NK cells and more dysfunctional NK cells were observed in patients with advanced clinical conditions. Higher NKG2A expression level in cytotoxic NK subset were found in later stages HIV infection, A reverse association between the percentage of NKG2A positive cells in cytotoxic NK subset and CD4 cell count was observed in all HIV-1 infected groups. Comparing with HIV-positive group, the frequency of HLA-A*03 were significantly higher. **Conclusions.** 1. The association of Vγ2Vδ2 T cells with disease progression in HIV-infected participants supports the view that intact Vg2Vd2 T cell populations are important for controlling HIV disease. 2. Fewer cytotoxic NK cells and higher NKG2A expression in cytotoxic NK subset was found in patients in late stage HIV infection. Such a phenomenon may relate to the escape of HIV-1-infected CD4+T cells from being attacked by NK cells. 3. Potential protective role of HLA-A*03 in HIV-1 infection and disease progression in a Chinese former blood donor Cohort was found.

2. SUBSTANCES OF ABUSE AND THE ADAPTIVE IMMUNE RESPONSE - IMPLICATIONS FOR HIV PATHOGENESIS. SM Kiertscher[1], GC Baldwin[1], MD Roth[1]; [1]Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA, 90095-1690 USA.

HIV infection and progression to AIDS involves a complex interaction between the host's immune system and a variety of cofactors. Among these cofactors, drugs of abuse are a major public health concern. Drugs of abuse may increase the risk for HIV transmission through needle sharing and/or exposure to high-risk sexual behaviors. Epidemiological evidence supports a role for substances of abuse as independent risk factors in the development of HIV/AIDS. Utilizing in vitro models, we

examined the capacity for substances of abuse to act as immunomodulators and evaluated the subsequent effect on HIV infection. Exposure of dendritic cells (DC) to either THC or cocaine modified their cell surface phenotype and cytokine/chemokine profile to favor increased HIV coreceptor expression, decreased costimulatory molecule expression, and increased Th2-related gene expression. In addition, the drug-exposed DC exhibited an altered ability to stimulate antigen-specific T cells, shifting the balance of Th1/Th2 cytokines and promoting susceptibility to HIV infection. To confirm these results in an in vivo system, we developed a huPBL-SCID mouse model in which severe combined immunodeficient mice are implanted with human PBL and then exposed to HIV alone, or in combination with injections of THC or cocaine. Systemic exposure to these drugs enhanced susceptibility to HIV infection, increased systemic viral load, and modified host immune cells in a manner similar to the in vitro models. These results suggest that drugs of abuse alter the immune response in a manner that enhances HIV infection. Supported by NIDA/NIH #DA03018 & #DA023386.

3. **HIV NEUROPATHOGENESIS: THE TIGHT ROPE WALK OF INNATE IMMUNITY**. SJ Buch[1], H Yao[1], P Fuwang[1], R Williams[1], N Dhillon[1]; [1]Department of Physiology, Kansas University Medical Center, Kansas City, KS, 66160 USA.

Virus neuroinvasion occurs as an early event, within weeks following HIV infection. Intriguingly, subsequent CNS complications manifest only decades after the initial virus exposure. Although CNS is regarded as an immune-privileged site, emerging evidence indicates innate immunity elicited by the CNS glial cells a critical determinant for establishment of protective immunity. Sustained expression of these protective immune responses however, can be a double-edged sword. Cytokines elaborated as protective immune mediators have the ability to function in networks and, can co-operate with other host/viral mediators to tip the balance from a protective to a toxic response in the CNS. Herein we present an overview of some of the key elements of the cerebral innate immunity in NeuroAIDS including the critical immune cell types of the CNS with their respective soluble immune mediators: (1) Co-operative interaction of IFN-g with the host/virus factors (PDGF/viral Tat) in the induction of neurotoxic CXCL10 by macrophages, the predominant brain-resident immune cell; (2) Astrocyte activation in response to interplay of viral & cellular factors; (3) Protective roles of PDGF & MCP-1 in neuronal survival against Tat toxicity & reciprocally, PDGF-mediated toxicity in the endothelial cells. Further modulation of these responses in the backdrop of drugs of abuse adds yet another level of complexity of the mutual interactions in the CNS. The yin and yang of HIV pathogenesis in the CNS is thus a result of the functional immunity network that is modulated by components of cerebral innate immunity. Supported by NIMH (MH068212) & NIDA (DA020392)

4. **INNATE AND ADAPTIVE FACTORS CONTROLLING HIV-1 GENOMIC ACTIVATION**. B Wigdahl[1], E Kilareski[1], B Aiamkitsumrit[1], N Parikh[1], BP Irish[1], S Lewis[2], J Jacobson[1,2], S Joyce B.[3], N Rajagopalan[2], M Nonnemacher[1]; [1]Department of Microbiology and Immunology, Center for Molecular Virology, Center for Neuroimmunology and CNS Therapeutics, Center for Clinical and Translational Medicine, Institute for Molecular Medicine and Infectious Disease; and [2]Division of Infectious Disease and HIV Medicine, Department of Medicine, Drexel University College of Medicine, Philadelphia, PA, 19102 USA; and [3]Freedom Foundation, 180 Henur Cross, Bangalore, 560043 India.

HIV-1 long terminal repeat (LTR) or viral promoter serves a number of important functions during the course of viral replication, first in the genomic activation of integrated provirus within initial target cells during viral transmission and then later in disease during activation of genomic expression with latent viral reservoirs. As an extension of an HIV-1 structural and functional genetic analyses during the course of disease performed in the pre-HAART era, during the past three years we have moved forward with a large-scale real-time cross-sectional and longitudinal assessment of an HIV-1-infected patient population within the greater Philadelphia region. To date, greater than 300 patients have been enrolled in the DREXELMED HIV-1 PATIENT COHORT. This will be expanded to more than 1,000 patients within the next 24 months and will be expanded further to include collaborative clinical and research databases based on HIV-1-infected subtype C patients in southern India. At present, specific sequence configurations within the LTR and other regions of the viral genome are being explored with regard to their utility as disease stage-, organ-, or cell-specific markers, their potential role in viral replication and pathogenesis, and as molecular determinants that may alter the threshold required to achieve HIV-1 genomic activation from latency, with regard to their relative conservation in context of comorbidity factors associated with HIV-1 disease, and their genotypic and/or phenotypic

conservation in HIV-1 subtype B or other subtypes, particularly subtype C. Supported by NINDS/NS046263; NINDS/NS032092; NIDA/DA019807.

5. INTRACELLULAR IMMUNITY AND HIV-1. WZ Ho[1]; [1]The Children's Hospital of Philadelphia, The University of Pennsylvania School of Medicine, Philadelphia, PA, 19104 USA.

Intracellular innate immunity is crucial for protecting host cells from viral infection. We have investigated the role of anti-viral cellular factors in HIV-1 infection of monocytes and macrophages. Although both monocytes and macrophages possess essential requirements for HIV-1 entry, peripheral blood monocytes are infrequently infected with HIV-1 in vivo and in vitro. In contrast, tissue macrophages and monocyte-derived macrophages in vitro are highly susceptible to infection with HIV-1 R5 tropic strains. Thus, we examined whether intracellular anti-HIV-1 factors contribute to differential susceptibility of monocytes/macrophages to HIV-1 infection. Freshly isolated monocytes from peripheral blood had significantly higher levels of the intracellular the anti-HIV-1 microRNAs (miRNA, miRNA-28, miRNA-150, miRNA-223, and miRNA-382). The suppression of these anti-HIV-1 miRNAs in monocytes facilitates HIV-1 infectivity, while increase of the antiHIV-1 miRNA expression in macrophages inhibited HIV-1 replication. We also demonstrated that the activation of Toll-like receptor 3 (TLR3) in monocytes/macrophages by Poly I:C, a double-stranded RNA as the ligand for TLR-3, induced not only the expression of intracellular type 1 IFNs but also the expression of the anti-HIV-1 microRNAs. In addition, Poly I:C treatment enhanced the expression of IFN regulatory factors (IRFs) 1, 5, 7 and 9 in monocytes /macrophages. These findings are in parallel with the observation that Poly I:C treatment significantly inhibited HIV-1 infection of peripheral blood monocytes and macrophages. Thus, our data provide compelling experimental evidence to support the notion that intracellular innate immunity contributes to protection of monocytes/macrophages from HIV-1 infection. Supported by grants NIDA012815 and NIDA022177.

XII. Poster Session I

Young Investigator's Poster Session

T-1 THE ROLE OF CANNABINOID RECEPTORS IN THE MODULATION OF TOLL-LIKE RECEPTOR (TLR) 4 EXPRESSION AND ANTIBODY CLASS SWITCHING IN MOUSE B LYMPHOCYTES. M Agudelo[1], C Newton[1], T Sherwood[1], TW Klein[1]; [1]Molecular Medicine, School of Biomedical Sciences,, College of Medicine, University of South Florida, Tampa, FL, 33612 USA.

Recently we showed cannabinoids induce B cell antibody class switching from IgM to IgE and CB2 receptors were involved. In the current study, because CB2 is coupled to Gi/o proteins and negatively regulates adenylyl cyclase, we measured cannabinoid effects on cAMP accumulation in B cells. We also explored the possibility that cannabinoid treatment of B cells modulates cell functions other than antibody class switching such as surface marker and TLR expression. Splenic B cells were purified and activated with IL4 and anti-CD40 in the presence of the nonselective cannabinoid agonist, CP55940, the CB1 agonist, methanandamide, or CB2 agonists, JW015 and CB65. Treated cells were analyzed by flow cytometry for expression of different B cell surface markers and TLRs. We showed CP55940 caused a significant increase in surface expression of TLR 4, but had no effect on other markers. Additional experiments with cannabinoid receptor selective agonists and antagonists suggested both CB1 and CB2 receptors were involved in the TLR effect. Receptor involvement was also supported by cannabinoid inhibition of cAMP levels in forskolin stimulated B cells. Furthermore, B cells treated with the cAMP enhancing agents, forskolin or 3-isobutyl-1-methylxanthine, were not able to class switch to IgE. These results suggest cannabinoids negatively regulate cAMP in B cells resulting in increased IgE. In conclusion, cannabinoids induce B cell class switching through mechanisms involving CB1 and CB2; in addition, an increase in TLR4 might also be involved in drug effects on antibody production. Supported by NIH grant DA019824 from the National Institute on Drug Abuse.

T-2 CAMP ELEVATION ENHANCES SUSCEPTIBILITY OF BONE MARROW PROGENITOR CELLS TO HIV-1 AND UPREGULATES HIV-1 LONG TERMINAL REPEAT-DIRECTED TRANSCRIPTION VIA THE PKA/CREB SIGNALING PATHWAY. A Banerjee[1], A Ferrucci[1], V Pirrone[1], B Wigdahl[1], MR Nonnemacher[1]; [1]Department of Microbiology and Immunology, Drexel University College of Medicine, Philadelphia, PA, 19102 USA.

Several studies have suggested that the bone marrow may serve as a reservoir for HIV-1 with infected cells of the myeloid lineage reseeding the virus into the peripheral blood. Hematopoietic CD34+/CD38+ stem cells have been shown to be refractile to HIV-1 infection. However, a number of studies have indicated that more differentiated bone marrow progenitor cells within the monocytic lineage are more susceptible to HIV-1 infection than stem cells. We have identified both the HIV-1 receptor CD4 as well as the co-receptors CXCR4 and CCR5 on the surface of human CD34+/CD38+ TF-1 bone marrow progenitor cells. Therefore, this cell system was utilized as an in vitro model to determine effects of intracellular cAMP elevation on the alteration of HIV-1 infection. To this end, the adenylyl cyclase-specific activator forskolin was shown to increase the level of cAMP and cell surface levels of the co-receptor CXCR4 in TF-1 cells. This was accompanied by a concomitant increase in replication of a X4 HIV-1 strain in these cells, suggesting an increase in HIV-1 susceptibility. In parallel, an increase in T-tropic HIV-1 promoter activity was also detected upon augmentation of intracellular cAMP concentration. Experiments focused on elucidating the underlying mechanisms for these observations have revealed the direct role of the Protein Kinase A pathway and the downstream transcription factor CREB. This assumes importance as HIV-1-infected patients have been found to have very high circulating levels of prostaglandin E2 (PGE2), a natural cAMP signaling pathway activator. Supported by DA19807.

T-3 COCAINE POTENTIATES GP120-MEDIATED TOXICITY IN NEURONS. C Bethel-Brown[1], H Yao[1], JE Allen[1], X Zhu[1], S Callen[1], SJ Buch[1]; [1]Department of Molecular and Integrative Physiology, University of Kansas Medical Center, Kansas City, KS, 66160 USA.

While it has been well documented that drugs of abuse such as cocaine, cause enhanced progression of HIV-associated neuropathological disorders, the underlying mechanisms mediating these effects remain poorly understood. The present study demonstrated that exposure of rat primary neurons to both cocaine and gp120 resulted in increased cell toxicity compared to cells treated with either factor alone. The combinatorial toxicity of cocaine and gp120 was accompanied by an increase in both caspase-3 activity and expression of the pro-apoptotic protein Bax. Furthermore, increased neurotoxicity in the presence of both the agents was associated with a concomitant increase in the production of intracellular reactive oxygen species and loss of mitochondrial membrane potential. Increased neurotoxicity mediated by cocaine and gp120 was ameliorated by NADPH oxidase inhibitor apocynin, thus underscoring the role of oxidative stress in this co-operation. Signaling pathways including c-jun N-teminal kinase (JNK), p38, extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinases (MAPK) and NF-κB were also identified to be critical in the neurotoxicity induced by cocaine and gp120. Taken together these findings, determined that the underlying molecular mechanisms in cocaine and HIV gp120-mediated neurotoxicity involve oxidative stress, mitochondrial and MAPK signal pathway. Supported by NIH MH068212, NIDA DA020392 and NIDA DA024442.

T-4 DIVERSITY IN INFECTION AND NEUROTOXICITY OF HIV-1 CLADES B AND C IN HUMAN MACROPHAGES: RELATION TO HIV NEUROPATHOGENESIS. A Constantino[1], Y Huang[1], A Lopez[1], H Zhang[2], C Wood[2], J Zheng[1]; [1]Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE, 68198 USA; [2]Nebraska Center for Virology, University of Nebraska Lincoln, Lincoln, NE, USA 68583.

HIV-1 clade C is currently responsible for over 50% of HIV infections worldwide. HIV-1-associated dementia continues to be a significant consequence of AIDS among clade B-infected individuals in the US and Europe; however, a lower incidence has been reported in regions including sub-Saharan Africa and Southeastern Asia, where clade C is prevalent. Studies on the potential differences between clade B and C neuropathology are scarce. We hypothesized that in comparison to clade B, clade C has reduced neuropathogenesis due to slower replication kinetics and reduced neurotoxicity in macrophages. Human monocyte-derived macrophages (MDM) were infected by laboratory-adapted, primary clade B, or clade C isolates using the same viral titer. Progress of infection was monitored by reverse transcriptase activity assay and p24 analysis. Supernatants from infected MDM were analyzed for inflammatory factor production and used to

treat primary rat cortical neurons to assess macrophage-mediated neurotoxicity. Clade B infection reached highest levels after 7-14 days, while clade C peaked at 21 days post-infection. Increased inflammatory factor and neurotoxicity was observed in clade B-infected macrophages as compared to clade C. We have demonstrated slower infection kinetics and reduced neurotoxicity by HIV-1 clade C infection, which may correlate to the low incidence of HAD in clade C-infected individuals. Understanding clade-specific neurotoxicity may identify common therapeutic targets to reduce the burden of neurological complications in HIV-infected individuals worldwide. Supported by DHHS/NIH 1R21MH083525-01

T-5 NEUROPROTECTIVE ROLES FOR APELIN IN HIV-ASSOCIATED EXCITOTOXIC INJURY. DR Cook[3], LA Odonnell[2], LH Tanyu[3], DR Lynch[3], KL Jordan-Sciutto[3], DL Kolson[3]; [1]Department of Neurology, School of Medicine , University of Pennsylvania , Philadelphia , PA, 19104-6140 USA; [2]Basic Science Division , Fox Chase Cancer Center , Philadelphia , PA, USA 19111; [3]Department of Pathology, School of Dental Medicine , University of Pennsylvania , Philadelphia , PA, 19104-6140 USA.

Excitotoxic neuronal injury through the N-methyl-D-aspartate receptor (NMDAR) occurs in many neurodegenerative disorders, including HIV-associated neurocognitive disorders (HAND). Certain G-protein coupled receptors (GPCRs), such as chemokine receptors, can counteract HIV-induced neurotoxicity by modulating cell survival pathways. APJ is a recently described GPCR that, like chemokine receptors, can serve as a co-receptor for HIV entry and is co-expressed in neurons with its ligand apelin. Thus, we hypothesize that apelin/APJ signaling represents an endogenous neuronal survival pathway, and that modulation of this pathway can promote survival during HIV-induced neurotoxicity. We have found that: (a) endogenous apelin is released from cultured neurons under basal conditions, during neuroinflammatory activation, and during NMDAR activation by NMDAR agonists or HIV, (b) antibody neutralization of endogenous apelin reduces neuronal survival, (c) recombinant apelin activates cell survival kinases Akt and ERK-1/2 in neuronal cultures, and (d) recombinant apelin protects neurons against excitotoxicity induced by NMDAR agonists or HIV. These studies suggest that apelin release following neuronal immune activation or injury can counteract HIV-induced neurotoxicity via activation of cell survival kinases. Further definition of the interactions between apelin/APJ signaling and immune activation, as well as the mechanism(s) of apelin-mediated neuroprotection, will improve our ability to develop therapeutics for HAND and other neurodegenerative disorders. Supported by T32 AI-07632 (DRC) and R01 NS043994, P01 NS27445 (DLK).

T-6 TRANSCRIPTIONAL FACTOR FOXO3A IN ASTROGLIOSIS. M Cui[1], H Peng[1], C Tian[1], Y Huang[1], J Zheng[1]; [1]Pharmacol. and Experimental Neuroscience, University of Nebraska Med. Center, Omaha, NE, 68198 USA.

Reactive astrogliosis, including astrocyte proliferation and activation, is one of the hallmarks of neurodegenerative diseases. Proinflammatory cytokines, including IL-1β and TNF-α, have been showed to mediate astrogliosis; however, the mechanisms by which this process occurs, are not well defined. FOXO3a, a transcription factor as downstream effecter of the Akt pathway, is considered an important regulator of cell cycle, apoptosis, and DNA repair. In this study, we investigate the role of FOXO3a in inflammatory factors mediated astrocyte proliferation. Our results demonstrated that IL-1β and TNF-α induced a significant increase of astrocyte proliferation as determined by Ki67 immunostaining. Cyclin D1, which marks the cell cycle progression, was also increased. FOXO3a, the main upstream regulator of cyclin D1, was phosphorylated and translocalized from the nucleus to cytoplasm with IL-1β and TNF-α stimulation. Wild-type FOXO3a (WT-FOXO3a) overexpression through adenovirus vector significantly upregulated down stream factor p27 and subsequently inhibited the CDK4 and cyclin D1. In contrast, dominant-negative FOXO3a (DN-FOXO3a) decreased p27 and upregulated the CDK4 and cyclin D1. Consequently, WT-FOXO3a inhibited astrocyte proliferation and DN-FOXO3a increased astrocyte proliferation. Overexpression of constitutively active Akt-1 and DN-Akt-1 demonstrated FOXO3a was a downstream factor of Akt-1. We conclude that Akt-1/FOXO3a/cyclin D1 pathway plays an important role in proinflammatory cytokine-induced astrogliosis. Supported by R01 NS 061642-01, NIH R01 NS 41858-01, R21 MH 083525-01 and P01 NS043985.

T-7 GHRELIN PROMOTE T CELL PROLIFERATION THROUGH MTOR PATHWAY. T Cui[1], D Taub[1]; [1]Laboratory of Immunology, NIA, NIH, Baltimore, MD, 21224 USA.

Orexigen hormone ghrelin is a brain-gut peptide with GH-releasing, apetide-inducing activities and anti-inflammation and a widespread tissue distribution. Ghrelin is the endogenous ligand of GH secretagogue receptor (GHSR), and both ghrelin and the GHSR are expressed in T cells. In our previous reports we found that ghrelin specifically inhibit the expression of proinflammation anorectic cytokines and promotes thymopoieses during aging. Now we further examined the effect of ghrelin on human and mouse T cell lines and its signal transduction. Real-time PCR were used to detect the gene mRNA. Ghrelin actives mTOR pathway in T cells was studies using immunoblotting and inhibitors of the PI3K and mTOR and antagonist of GHSR, Des-Lys-3-GHRP6. Our results show that 50ng/ml to 1ug/ml Ghrelin significantly increases GHSR transfected Do11.10 T cell's proliferation. Ghrelin caused a significant increase in the phosphorylated mTOR, TSC2, P70S6K, S6K, 4E-BP-1, eIF4G, eIF4E in immunoblotting. While the phosphorylated mTOR, P70S6K, S6K were abolished by inhibitor rapamycin, LY294002 and Des-Lys-3-GHRP6. Ghrelin also show significant increase mRNA expression of cell cycle gene CDK4, cyclin D1 and cyclin E1, Cell proliferation and anti-inflammation gene peroxisome proliferator-activated receptor (PPAR) gamma and alpha, mitochondrial UCP2 and Cpt1a. Our data document that ghrelin affects several T cell functions including T cell proliferation, metabolism, cell cycle, anti-inflammation. The mTOR pathway connects all of these functions. Supported by NIH intramural Research program.

T-8 GLYCOGEN SYNTHASE KINASE 3 BETA (GSK3B) AS A POTENTIAL THERAPEUTIC TARGET IN NEUROAIDS. DC Davidson[1], SB Maggirwar[1]; [1]Department of Microbiology and Immunology, University of Rochester, Rochester, NY, 14642 USA.

A number of HIV viral proteins, including Tat, that are secreted by HIV-infected cells activate macrophages/microglia in the CNS, either alone, or in combination with host factors, such as soluble CD40 ligand (aka CD154), leading to progressive development of neurocognitive impairment. In this context, we have previously shown that soluble CD40L levels are elevated in the plasma and CSF of HIV-1 infected individuals with cognitive impairment. Here we demonstrate that the anticonvulsant and mood stabilizing drug sodium valproate (VPA) reduces soluble CD40L levels in both plasma samples of HIV-1 infected individuals and in cultured human platelets. Additionally, previous reports indicate that VPA acts as an inhibitor of glycogen synthase kinase 3 beta (GSK3B), a multifaceted kinase involved in neuronal survival that is thought to be activated by the HIV-1 neurotoxin platelet-activating factor (PAF). Based on this, we hypothesize that GSK3B may play a role in the release of soluble CD40L from platelets, a mechanism that may be blocked with VPA treatment. Consistent with this notion, we show here that treatment of human platelets with VPA is able to partially reverse PAF-induced GSK3B activation. Furthermore, over-expression experiments using GSK3B mutants in human megakaryocytes suggest that GSK3B is involved in CD40L surface expression, which occurs prior to its release, in platelets. These findings not only offer insight into the possible mechanism of VPA in the context of neuroprotection, but also emphasize the potential of GSK3B as a therapeutic target in neuroAIDS.

T-9 POTENTIAL ROLE OF MICRORNA-124 IN HUMAN NEUROGENESIS UNDER NORMAL AND INFLAMMATORY CONDITIONS. TM Eidem[1], H Peng[1], C Tian[1], JC Zheng[1]; [1]Lab of Neurotoxicology, Department of Pharmacology & Experimental Neuroscience and [2]Department of Pathology and Microbiology, University of Nebraska Medical Center, Omaha, NE, 68198 USA.

Neurogenesis is influenced by many factors including small non-coding RNAs termed microRNAs (miRNAs). Specifically, miR-124 reduces astrocyte differentiation, encourages transcription of neuron-specific genes, and promotes neurite outgrowth during differentiation of mouse neural progenitor cells (NPCs), and it is required for maintenance of mature neurons. We hypothesize that miR-124 expression increases during the differentiation of human NPCs into neurons through the course of normal neurogenesis and expression of miR-124 is decreased under neuroinflammatory conditions, resulting in increased levels of gliogenesis and gliosis, a phenomenon associated with CNS injury and neurodegenerative diseases. Both miRNA microarray and qRT-PCR analysis have established that miR-124 is significantly upregulated at seven days post-differentiation of human NPCs into neurons. We are currently investigating the expression of miR-124 in NPCs differentiating under inflammatory conditions mediated by IL-1beta and TNF-alpha. In addition to miRNA expression, cell pathways and genes regulated by miR-124 are also being assessed using bioinformatics target prediction software and confirmed using qRT-PCR and

Western blotting. Elucidating these genes and pathways is important in understanding the mechanism(s) by which changes in neurogenesis, due to miR-124 expression, may occur. In conclusion, we have confirmed that miR-124 is associated with neurogenesis in the human NPC model and are continuing further research on the expression and function of this miRNA in normal and inflammatory conditions. Supported by NIH R01 NS 41858-01, R01 NS 061642-01, R21 MH 083525-01 and P01 NS043985.

T-10 ANTIRETROVIRAL TREATMENT DAMPENS CSF IP-10 ELEVATION AND ITS ASSOCIATED BRAIN RESPONSE IN HIV PATIENTS. U Feger[1], M Ricardo-Dukelow[1], T Ernst[1], E Nerurkar[1], E Volper[1], S Buchthal[1], H Nakama[1], L Chang[1]; [1]University of Hawaii at Manoa, Burns School of Medicine, Honolulu, HI, 96813.

HIV-1 infection of the central nervous system (CNS) can lead to the development of HIV-associated neurocognitive disorders (HAND) (Antorini et al). Antiretroviral therapy (ART) reduced the severity of HAND, possibly by modulating the immune response in the brain (McArthur et al.). To gain further insights into ART's modulatory effect, we conducted localized in vivo proton magnetic resonance spectroscopy (1H MRS) and measurements of cytokines in the cerebrospinal fluid (CSF) in HIV subjects without (HIV) or with antiretrovirals (HIV+ART) and seronegative (SN) controls. CSF IP-10 is significantly elevated in HIV (n=8) when compared to HIV+ART (n=16; p=0.042) and SN controls (n=7, p=0.024). Within the HIV group, IP-10 correlated in varying degrees with two glial markers, myo-inositol (r=0.656-0.726, p=0.04-0.08) and choline compounds (r=0.046-0.843, p=0.25-0.008), in four brain areas measured [frontal grey (FGM) and white matter (FWM), parietal grey matter (PGM) and basal ganglia (BG)]. These correlations were not seen in HIV+ART and SN controls. Furthermore, HIV subjects showed reduction of the neuronal marker N-acetylaspartate in both BG and PGM, when compared to HIV+ART (BG: p=0.06, PGM: p=0.01), and controls (BG: p=0.06, PGM: p=0.05). IP-10 is a chemokine secreted by glial cells upon stimulation and can induce viral replication as well as neuronal cell death (van Marle et al). Our data suggest that upon initiation of ART the immune response in the brain is dampened or shifted to neuroprotective processes, likely orchestrated by the resident glial cells. Supported by NIH (1R01MH61427; K24DA16170; K02DA16991 & 1U54NS56883). RCMI G12RR003061.

T-11 CCAAT ELEMENT MEDIATED REGULATION OF ASTROCYTE-TIMP-1 EXPRESSION IN CHRONIC NEUROINFLAMMATION. JA Fields[1], K Borgmann[1], A Ghorpade[1]; [1]Cell Biology and Genetics, University of North Texas Health Science Center, Fort Worth, TX, 76107 USA.

Many neurodegenerative disorders, including HIV associated dementia (HAD), are exacerbated by an imbalance between matrix metalloproteinases and their inhibitors, tissue inhibitors of metalloproteinases (TIMPs). Primary human astrocyte-TIMP-1 expression was initially increased in response to the inflammatory cytokine interleukin (IL)-1beta, but was down regulated during chronic stimulation. Regulation of the TIMP-1 promoter contributed to a decrease in astrocyte-TIMP-1 expression, and deletion of a CCAAT box in the TIMP-1 promoter restored expression levels during chronic activation. We investigated the role of CCAAT enhancer binding protein-beta (CEBP/beta) and CCAAT displacement protein (CDP) in astrocyte-TIMP-1 expression during chronic neuroinflammation. Treatment with IL-1beta resulted in robust increases in CEBP/beta mRNA and to a lesser extent, increases in CDP mRNA levels. Transient knockdown of CDP, by siRNA, increased TIMP-1 mRNA levels at 72 and 168 hour time points and increased the level of TIMP-1 in supernatants of chronically activated astrocytes. Western blot analysis of nuclear extracts of IL-1beta-treated astrocytes revealed increases in CEBP/beta and CDP protein levels. Furthermore, the ratio of transcriptional silencer to activator isoforms of CEBP/beta increased in response to IL-1beta treatment. This work shows CDP and CEBP/beta may be major players in the intracellular signaling cascade leading to decreased astrocyte-TIMP-1 expression during chronic neuroinflammation. Supported by NS48837.

T-12 INHIBITORY LONG-TERM DEPRESSION IN THE HIPPOCAMPUS IS ADAPTED TO OPIOID ADDICTION WITH A COMBINATORIAL PLASTICITY MECHANISM. HL Han[1], L Xu[1]; [1]Key Lab of AMHD, CAS, Kunming Institute of Zoology, Kunming, 650223 China.

The persistence of opioid addiction is a major clinical problem. It likely engages memory mechanisms that may in part attribute to adaptations of excitatory synaptic plasticity in the hippocampus. It remains unclear how inhibitory synaptic plasticity in the hippocampus is adapted to opioid addiction. Here we report that neither single in vivo morphine exposure nor subsequent

acute withdrawal affects inhibitory long-term depression (I-LTD) in CA1 pyramidal neuron of the rat hippocampal slice, which is usually dependent on cannabinoid receptor 1 (CB1R). In marked contrast, repeated in vivo morphine exposure blocks I-LTD induction, and subsequent acute withdrawal enhances I-LTD dramatically. This phenomenon is attributed to a combinatorial plasticity containing both CB1R- and L-type calcium channel-mediated components. Thus, the adaptations of hippocampal I-LTD by a novel combinatorial plasticity with repeated in vivo opioid exposure and acute withdrawal may contribute, at least partially, to the persistence of opioid addiction. Supported by NSFC (30530250 and 30500150) and MOST 973 program (2006CB500808 and 2007CB512303).

T-13 A HUMANIZED HUPBL-NOD/SCID/IL2R-GAMMA-NULL MODEL FOR EVALUATING THE IMPACT OF DRUG ABUSE ON HUMAN IMMUNE FUNCTION. A Harui[1], SM Kiertscher[1], MD Roth[1]; [1]Pulmonary & Critical Care Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA, 90095-1690 USA.

Immunoregulatory effects of cannabinoids have been well documented in conventional animal models and with human cells in vitro. However, the relevance of these findings to human immune function in substance abusers has been difficult to assess. We have developed a xenotransplant model that will serve as a platform for evaluating the effects of substance abuse on the presentation of viral antigens and the development of effector, memory and regulatory T cell responses in vivo. Immunodeficient NOD/SCID/IL2r-gamma-null mice, which lack the gamma chain of IL-2 receptor, allow efficient engraftment and expansion of human peripheral blood leukocytes (huPBL). Over 3 weeks, these cells reconstitute the spleen and lymphoid organs of recipient mice with more than 70% of the spleen cells expressing human CD45 (~25-30 $x10^6$ human PBL/spleen). Animals exhibit a relatively normal CD4/CD8 ratio (~1.5:1) as well as reconstitution of the CD3/CD56 and CD45/CD20 subsets. Furthermore, we have demonstrated that these animals can be challenged with adenovirus, either as free vector or virally-infected dendritic cells, resulting in normal activation and expansion of anti-viral specific effector and regulatory T cells in vivo. In future studies, reconstituted huPBL-NOD/SCID/IL2r-gamma-null animals will be exposed to cannabinoids using different exposure algorithms and evaluated for the effects on antigen-specific immune responses. In addition, this model supports active HIV infection and will be used to study the biology, efficacy and potential adverse effects of adenoviral-based vaccines for HIV. Supported by NIH/NIDA R01-DA03018.

T-14 HIV-1 VPR-MEDIATED CELL DEATH AND PROTEOME ALTERATION. F He[1], Y Zeng[1], X Wu[1], Y Ji[1], T Andrus[2], T Wang[1]; [1]Institute of Tissue Transplantation and Immunology, Jinan University, Guangzhou, 510630, [2]Department of Laboratory Medicine, University of Washington School of Medicine, Seattle, WA, 98109 USA.

As the only accessory protein incorporated in HIV-1 virions, viral protein R (Vpr) is able to mediate cell death via both intracellular and extracellular pathways, and is pathogenically associated with AIDS symptoms, including T cell depletion, blood brain barrier integrity loss and neuroAIDS. To investigate the mechanisms of Vpr-mediated cytotoxicity, we infected C8166 cells with a recombinant adenovirus carrying both vpr and GFP genes (rAd-vpr), as well as the vector control virus (rAd-vector). Significant G2/M phase cell cycle arrest was observed in the rAd-vpr infected cells. In addition, mitochondrial membrane potential and plasma membrane integrity loss were detected by JC-1 and propidium iodine assays. Two-dimensional electrophoresis and mass spectrometry analysis revealed that Vpr significantly affects the cellular protein profile. Proteomic alterations include the down-regulation of both mitosis-associated structural proteins, vimentin and prohibitin; up-regulation of cyclin binding proteins, such as 14-3-3 and galectin-1; and up-regulation of redox proteins, including thioredoxin and protein DJ-1. Our data suggest that intracellular Vpr can mediate cell death by disrupting mitochondrial function, cell cycle and plasma membrane integrity, as well as induce proteomic alterations of structural, regulatory, binding and redox protein regulation. These findings are the first to show proteomic modulation in concurrence with endogenously expressed, Vpr-mediated cell death, which implicate promising potential for developing new therapies targeting Vpr related cytotoxicity. Supported by NSFC-GD (5300413, TW) & 973 (2006CB504200, YZ).

T-15 MODULATION OF MONONUCLEAR PHAGOCYTE BIOLOGY BY HUMAN IMMUNODEFICIENCY VIRAL INFECTION AND CD4+ T CELL SUBSET CONTACT. XY Huang[1], YY Zeng[2], HE Gendelman[1]; [1]Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE, 68198-5800 USA; [2]Institute for Tissue Transplantation & Immunology, Jinan University, Guangzhou, 510632 China.

Mononuclear phagocytes (MP) serve both as primary orchestrators of innate and adaptive immunity and as reservoirs for microbial pathogens. The functions of MP include antigen presentation, secretion of bioactive molecules, microbial and debris clearance. MP is also amongst the first cells infected by human immunodeficiency virus (HIV). We posit that what drives function of the infected MP is its interactions with CD4+ T lymphocyte subsets. To this end we used two laboratory systems to elucidate this question. The first is rodent bone marrow derived macrophages (rBMM) and the second is human peripheral blood monocytes derived macrophage (hMDM) cocultivated with regulatory (Treg) or effector (Teff) T cells. For the former rBMM are infected with vesicular stomatitis/HIV-1Yu2 pseudotypes and the latter hMDM are infected with HIV-1Ada. In both systems HIV-1 infected rBMM or hMDM led to limited cell death, albeit giant cells were formed in 10% of hMDM cultures. Cocultivation of uninfected or HIV-1 infected rBMM or hMDM with Teff showed activated stellate and elongated morphologies but no effect on cell viability. However, in contrast, cocultivation of HIV-1 infected rBMM or hMDM with Treg showed accelerated BMM and MDM cytotoxicities. The former occured by rapid cell loss and the latter by clumping then cell fusion. We posit that Treg possess effector cell killing for HIV-1 infected MP not previously demonstrated and as such is a new adaptive immune surveillance mechanisms for HIV-1 infection.

T-16 BEHAVIORAL EVALUATIONS IN THE 1-METHYL-4-PHENYL-1,2,3,6-TETRAHYDROPYRIDINE MOUSE MODEL OF PARKINSON'S DISEASE. JA Hutter[1], AD Reynolds[1], HE Gendelman[1], RL Mosley[1]; [1]Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE, 68198 USA.

Parkinson's Disease (PD) is the most common neurodegenerative movement disorder in humans. The MPTP mouse model is widely used to study PD as it recapitulates many of the neuropathological hallmarks. However, few studies have successfully used MPTP-intoxicated mice to investigate PD-associated motor deficits. Tests of motor function in MPTP-intoxicated mice have yielded incongruous results, which may reflect in part the extent of the lesion, intra-animal variability, or overall sensitivity of the tests. We show the utility of the rotating rod (rotarod) and the open field activity test (OFAT) as motor function assessments in the MPTP mouse model. C57BL/6J mice, age 18-20 weeks old, were trained on a rotarod for 20 min daily and habituated in an OFAT chamber for 10 min daily for three days. Pretests were then conducted to establish baseline performance for each mouse. One day after pretesting, mice were treated with either 20 mg/kg MPTP or PBS. Post-MPTP intoxication, mice were tested weekly with the rotarod and OFAT. Post MPTP/PBS-treatment performance values were subtracted from pretest performance values and normalized to the performance values of the PBS controls. By both rotarod and OFAT assessment, we consistently found significant differences between MPTP- and PBS-treated mice. Furthermore, mice treated daily with L-DOPA showed significantly improved motor function compared to untreated MPTP mice. Our study shows both rotarod and OFAT can be used to study motor deficit in the MPTP mouse model of PD and suggests that these tests can be used to assess drug effectiveness.

T-17 MECHANISM OF T CELL ACTIVATION IN CNS- IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME WITH HIV INFECTION. T Johnson[2], P Calabresi[2], A Nath[2]; [1]Department of Pathology and [2]Department of Neurology, Johns Hopkins School of Medicine, Baltimore, MD, 21287 USA.

Immune Reconstitution Inflammatory Syndrome (IRIS) may emerge in HIV-infected patients after initiation of HAART. In some patients it rapidly progresses to cause severe encephalitis. CNS-IRIS is largely mediated via activated-T cells, which differentiates it from HIV encephalitis. This paradoxical infiltration with T cells in patients who were immune suppressed represents a treatment dilemma. To determine the mechanism of T cell activation, T cells from blood of HIV(-) donors were treated with 200 nM HIV-Tat protein in conjunction with 10 uM TPCK (NF-κB blocker), 100 nM RO-32-0432 (pan-PKC inhibitor) and 10 uM chloroquine. To map the region of Tat responsible for T cell activation, cells were exposed to 15-mer Tat peptides derived from HIV clade B. Culture supernatants were assayed for concentration of Granzyme B by ELISA. To determine if Tat

activated T cells were susceptible to HIV infection, PBMCs were pretreated with Tat and then exposed to HIV. Cell supernatants were assayed for p24. The mean+SEM was obtained from 5 donors and analyzed by ANOVA. The HIV protein Tat activates T cells in a dose-responsive manner to secrete effector molecules and increases the likelihood of HIV cellular infection ($p=0.03$). The mechanism of Tat activation is dependent on fusion of the lysosome and endosome as treatment with chloroquine decreased activation ($p=0.02$). The cysteine rich region of Tat is critical for mediating these effects ($p=0.01$). It also requires NF-κB signaling ($p=0.032$) but is independent of PKC activation. These pathways may represent novel therapeutic targets for IRIS. Supported by NIH grant: R01NS056884.

T-18 NF-KB FAMILY MEMBER RELB INHIBITS HIV-1 TAT-INDUCED SYNTHESIS OF TNF-ALPHA. MM Kiebala[1], SB Maggirwar[1]; [1]Department of Microbiology and Immunology, University of Rochester, Rochester, NY, 14642 USA.

HIV-1-associated dementia (HAD) occurs, in part, due to the inflammatory response to viral proteins, such as Tat, in the central nervous system. Here we demonstrate that TNF-alpha production in Tat-exposed microglial cells diminishes after 16h of treatment, which coincides with the increase in synthesis of NF-kB family member RelB. Based on this, we hypothesize that the inflammatory response to Tat is self-limiting. Since genetic ablation of RelB leads to development of multi-organ inflammation in mice, we further hypothesize that Tat-induced, newly synthesized RelB plays an important role in inhibiting cytokine production by microglial cells, possibly through formation of transcriptionally inactive RelB/RelA complexes. Consistent with this notion, we show here that over-expression of RelB in microglial cells inhibits Tat-induced TNF-alpha synthesis in a manner that involves transcriptional repression of the TNF-alpha promoter. Also, addition of Tat to CD11b+ cells isolated from RelB deficient mice leads to a high level of TNF-alpha production. Additional experiments revealed an induction of phosphorylation of RelA at Serine-256, a pre-requisite for protein-protein interaction between RelB and RelA, followed by RelB/RelA interaction in Tat-treated cells. Furthermore, it appears that the Rel-homology-domain within RelB is necessary for this interaction. We conclude that RelB may play a role in resolving cytokine synthesis by interfering with normal pathways sub-served by prototypical NF-kB. Our findings may have important therapeutic implications for the management of HAD.

T-19 IN VIVO MORPHINE TREATMENT SUPPRESSES TUMOR ANGIOGENESIS BY INHIBITING MONOCYTE MIGRATION AND RECRUITMENT TO THE TUMOR SITE. L Koodie[1], R Charboneau[1], L Liu[1], S Roy[1]; [1]Department of Pharmacology, Surgery, BTR, University of Minnesota, Minneapolis, MN, 55455 USA.

We have previously demonstrated that chronic morphine exposure inhibits tumor-cell-induced angiogenesis to suppress tumor growth and progression. Tumor derived chemokines stimulate the migration of peripheral blood monocytes to the tumor site. The recruitment of monocytes enhances tumor progression by increasing angiogenesis. Since morphine is a highly immunosuppressive agent, we further investigated the effect of morphine on monocyte migration and recruitment to conditioned media (CM) derived from long-term cultures of mouse lung cancer cells in a PVA sponge model. Our results show that morphine treatment, administered through pellet implantation delayed chemotactic migration to the PVA sponge. Characterization of PVA sponge cells derived from placebo treated mice revealed a significant increase in monocytes and differentiated inflammatory cells. In contrast, morphine inhibited the normal chemotactic response to CM by almost 66% ($p<0.00001$). When compared to placebo treatment, morphine significantly reduced the number of CD45+ nucleated hematopoietic progenitors ($p<0.0005$); CD11b+ monocytes ($p<0.00001$); CD14+ monocytes ($p<0.0001$); Ly6G+/CXCR2+ neutrophils ($p<0.04$), F4/80+macrophages ($p<0.005$); and CD11c+ dendritic cells ($p<0.001$). Taken together these results suggest that morphine treatment by inhibiting monocyte recruitment can decrease angiogenesis. Supported by NIDA/NIH.

T-20 ASTROCYTES ARE REGULATORS OF HIV-1 INFECTED MACROPHAGE INFLAMMATORY ACTIVITIES. SD Kraft-Terry[1], T Wang[1], P Ciborowski[1], HE Gendelman[1]; [1]College of Medicine, University of Nebraska Medical Center, Omaha, NE, 68198-5800 USA.

Astrocytes are regulators of neural homeostasis. Their roles in disease pathobiology have only recently, though incompletely, been elucidated. To this end, we used a proteomic platform to investigate human astrocyte-microglial crosstalk during human immunodeficiency virus type one

(HIV-1) infection. We hypothesize that blood derived brain macrophage secretions of viral and cellular neurotoxic products are kept in abeyance by astrocytes through control of secretory activities. 2-dimensional difference in-gel electrophoresis was used to examine changes within the human macrophage proteome between single and astrocyte-macrophage co-culture conditions with or without HIV-1 infection. Spots showing statistically significant protein differences were picked and analyzed by liquid chromatography tandem mass spectrometry. Preliminary results demonstrated astrocyte-induced increases in HIV-1 infected macrophage leukotriene A4 hydrolase, vimentin and tubulin alpha, and mitochondrial calcium binding proteins. These speak towards control of macrophage arachidonic acid metabolism, cell mobility, and mitochondrial functions. Our current studies center on expanding protein identifications during these cellular interactions by employing stable isotope labeling of amino acids in cell culture. These data support the contention that astrocytes affect macrophage function during HIV-1 infection. Supported by NIH/P01DA026146.

T-21 SYNERGISTIC POTENTIATION OF NEUROPATHOGENESIS BY MORPHINE AND TAT IN A PNEUMOCOCCAL PNEUMONIAE MODEL. A Krishnan[1], J Wang[1], R Charboneau[2], B Roderick[2], S Roy[1]; [1]Department of Surgery, University of Minnesota, Minneapolis, MN, 55455 USA; [2]Veterans Affairs Medical Center, Veterans Affairs Medical Center, Minneapolis, MN, 55417 USA.

Chronic drug users account for a third of all cases of AIDS in the USA and the progression to AIDS dementia is accelerated in opiate drug abusers. Clinically, microglia activation better correlates with HAD than productive HIV-1 infection in the CNS. Moreover, pneumoccoal pneumonia is the most common opportunistic infection in this population. We hypothesize that co-infection with S. penumoniae (S.p) may be a contributing factor in the increased prevalence of HAD in the opioid drug abusing population. Few studies have investigated the type of toll-like receptor (TLR) activation following S.p infection. Our studies show that S.p infection activates TLR 2, 4 & 9 mRNA expression levels in microglial cells, with a concurrent increase in proinflammatory cytokines (IL-6, TNF-α) levels, ROS and NO. This effect is further exacerbated in the presence of morphine. Activation of TLR 2, 4 & 9 with their specific ligands (Pam3cys, LPS & CpG) in the presence of morphine and TAT results in a synergistic 3 fold increase in TLR mRNA expression, proinflammatory cytokine levels and microglial ROS and NO. Addition of culture supernatants from microglial cells treated with the specific TLR ligands + morphine + TAT to neuronal cells increased neuronal apoptosis. Thereby, our findings clearly suggest that activation of microglial cells by morphine, TAT and S.p leading to an increase in proinflammatory cytokines, ROS and NO may contribute to the neuropathogenesis observed among opiate drug abuser. Supported by RO1 DA12104, RO1 DA 022935, KO2 DA015349, P50 DA11806 (to SR).

T-22 STUDY ON THE RELATIONSHIP BETWEEN BLOOD PRESSURE, LIPID AND FASTING PLASMA GLUCOSE VALUE IN VARITY WAIST CIRCUMFERENCE IN WUHAN ADULTS. CF Li[1], DJ Zhou[1], XH Liu[1], ZY Zhu[1], ZF Zhang[1], J Xia[1], J Gong[1]; [1]Wuhan institute of Chronic Disease Prevention, Wuhan Centers for Disease Prevention & Control, Wuhan, 430015 China.

Objective: To analyze the correlation of CVD risks such as blood pressure, fasting plasma glucose and lipid between normal waist circumference (WC) and abnormal WC in adults, Wuhan, P.R.China. Research design and methods: We selected 1879 adults from 2006 adults chronic diseases survey in Wuhan, P.R.China, by stratified-cluster sampling, which is representative and cross-sectional. Each participant was invited to complete a set of standardized questionnaires, physical examinations and laboratory tests, blood pressure, triglycerides, LDL and HDL cholesterol, fasting plasma glucose, and waist circumference (were categorized using standard clinical thresholds). ANOVA was used to examine differences in mean values, correlation coefficients and trend chi-square were used to analyze the relations for CVD risks according to WC tertiles. RESULTS: The prevalence rate of abdominal obesity is 51.8%. Blood pressure and lipid and fasting plasma value was increased by increasing of waist circumference value ($p=0.01$), and there is significant difference between normal waist circumference team and abnormal team ($p=0.01$). Except for HDL cholesterol's negative correlation with WC, other values is positive. The detection rate of hypertension, dyslipidemia and prevalence rate DM is raised with waist circumference increasing. Conclusion: Pay attention to the prevalent statue of abdominal obesity. Individuals with abnormal waist circumference have higher risks of hypertension, dyslipidemia and Diabetes Mellitus. Supported by Public Health Bureau of Wuhan, P.R.China.

T-23 INTERFERON LAMBDA INHIBITS HERPES SIMPLEX VIRUS TYPE 1 REPLICATION IN HUMAN NEURONAL CELLS. JL Li[1], L Zhou[2], X Wang[1], L Ye[1], WZ Ho[1]; [1]Division of Allergy & Immunology, The Children's Hospital of Philadelphia, Philadelphia, PA, 19104 USA; [2]Division of Histology and Embryology, Department of Anatomy, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430030 China.

Herpes simplex virus type I (HSV-1) can establish latent infection in the nervous system. Although type I interferons (IFN-α and -β) and type II interferon (IFN-γ) have been shown to have the ability to inhibit HSV-1 infection, the anti-HSV-1 effect of a novel member of the IFN family, IFN-Lambda, remains to be determined. Here we demonstrate that IFN-Lambda exhibits inhibition on HSV-1 replication in human neuronal cells. Human NT2-N neuronal cells and CHP212 neuroblastoma cell line were both found as supportive systems for HSV-1 infection. However, HSV-1 infection of neurons was significantly suppressed by IFN-Lambda treatment as evidenced by the reduced HSV-1 DNA synthesis and expression of HSV-1 antigens. This IFN-Lambda-mediated action on HSV-1 could be partially neutralized by antibody to IFN-Lambda receptor (IL-10R). Investigation of the mechanisms showed that IFN-Lambda induced the expression of Toll-like receptors 3 and 9 (TLR3 and 9) as well as IFN regulatory factor 7 (IRF-7), resulting in the activation of endogenous IFN-α in the neuronal cells. These findings suggest that IFN-Lambda may have therapeutic potential for treatment of HSV-1 infection in the central nervous system. Supported by NIH DA012815 and DA22177.

T-24 EXAMINING THE FITNESS OF HIV-1 QUASISPECIES CONTAINING SPECIFIC CORE/ENHANCER REGION BINDING SITE POLYMORPHISMS. L Li[1], MR Nonnemacher[1], K Flaig[1], BP Irish[1], E Kilareski[1], B Wigdahl[1]; [1]Department of Microbiology and Immunology, Drexel University College of Medicine, Philadelphia, PA, 19102 USA.

The HIV-1 promoter or LTR regulates viral gene expression by interacting with multiple viral and host factors. Studies have shown that specific sequence configurations within CCAAT enhancer binding protein (C/EBP) site I, and transcription factor Sp binding site III of peripheral blood (PB)-derived LTRs from HIV-1-infected patients are preferentially encountered in late stage HIV disease. Specifically, the 3T configuration of C/EBP site I and the 5T configuration of Sp site III were binding site variants found in low frequencies in PB-derived LTRs from patients at early stages, and at relatively high frequencies in patients in late stage disease in sequence analyses performed in the pre-HAART era. Based on gel shift and BIAcore technologies, the C/EBP 3T and Sp 5T binding site configurations have been shown to exhibit a lower binding affinity for C/EBP and Sp1 compared to the consensus subytpe B LTR configuration at these sites, respectively. In recent studies, the HIV-1 3T/5T LTR genotype has now been detected in HIV-1-infected patients in the DrexelMed Cohort and we are now exploring the relative fitness of HIV-1 quasispecies containing these specific sequence alterations. Transient expression analyses have shown that LTRs containing the Sp 5T binding site configuration exhibit a spectrum of basal and Tat-driven functional activities within cells of the monocytic lineage. These results suggest that the 5T and 3T/5T LTRs may be present in infectious viral quasispecies circulating in the peripheral blood and other compartments during mid- to late-stage HIV disease. Supported by DA019807.

T-25 UP-REGULATION IN SPINAL CORD AND LOCUS CERULEUS, BUT DOWN-REGULATION IN DORSAL ROOT GANGLIA FOR KAPPA-OPIOID RECEPTOR OF MORPHINE TOLERANT RATS. XY Li[1], L Sun[1], J He[1], ZL Chen[1], F Zhou[1], XY Liu[1], RS Liu[1]; [1]Department of Anesthesiology, Cancer Hospital, Peking Union Medical College, Beijing, 100021 China.

As a non-selective agonist of opioid receptors, morphine can also act on KOR when activating MOR and delta-opioid receptor (DOR). Although previous findings indicate that KOR plays an important role in morphine analgesia and antinociceptive tolerance, the reasons for the paradoxical effect of KOR in analgesia and anti-analgesia is still unclear. The present study, therefore, was designed to examine the changes of KOR in different regions in nervous system of morphine tolerant rats and aim to disclose the role of KOR in morphine analgesia and antinociceptive tolerance. We have successfully attained morphine tolerance in rats with s.c injection of morphine (10mg/kg) twice a day by 7 consecutive days. Then competitive real-time PCR was used to assess mRNA expression for KOR in related regions, including thalamus, hypothalamus, hippocampus, locus ceruleus (LC), periaqueductal gray (PAG), lumber-sacral spinal cord and dorsal root ganglia (DRG) of morphine tolerant rats and immunohistochemistry was used to evaluate KOR protein expression in those regions except for DRG. As an index of antinociceptive threshold, the tail flick

latency (TFL) after 7 days morphine injections restored to the baseline value. The expression of KOR increased in locus ceruleus and spinal cord but decreased in DRG significantly in morphine tolerant rats, although we have not found some significant changes of KOR in other regions. Consequently, we propose there should be a biphasic role of morphine on central and peripheral nervous systems, both contribute to the development of morphine tolerance. Supported by Fund of Capital Medical Development and Research (20052057) from Beijing Municipal Health Bureau, China.

T-26 BOVINE ISG15: A BALANCING MOLECULAR IN BIV/BHV SUPER-INFECTION. C Liu[1], X Li[1], YQ Geng[1]; [1]Nankai University, College of Life Sciences, Tianjin, 300071 China.

Viral super-infection, which is an aspect in virus research, can explain many interesting bio-phenomena. It has been reported that BIV/BHV super-infection can increase the level of replication of BIV. We have also found that bICP0 of BHV could promote the activation of BIV's LTR though the NF-κb or AP-1 cell signal pathways. However, our recent studies suggest that the story seems not to be finished. We found that bovine ISG15 played a role in balancing BIV/BHV super-infection. ISG15 is a unbiquitin-like modifier which can be stimulated by type I interferon. Real-time PCR and Western blotting assays suggest that the level of bovine ISG15 is increased in the fetal bovine lung cells (FBLs) infected with BIV. While, the over-expression of bovine ISG15 induced by poly I:C in FBLs can repress the replication of BIV. Immunoflurescence assays and chromatin immunoprecipitation assays demonstrate that IRF-3 can bind to the promoter of ISG15 gene and stimulate the expression of the gene in FBLs. A luciferase-reporter system of bovine ISG15 gene is established in 293T cells. In this system, the over-expression of bovine IRF-3 can active the promoter of ISG15 gene. The expression of bICP0 can repress the activation, and the effect is dose-dependent. In vivo, BHV infection can repress the induction of ISG15 in FBLs treated with poly I:C. Taken these together, ISG15 can repress the replication of BIV, and BHV can repress the expression of ISG15. So BHV can help BIV in super-infection. BIV/BHV is similar to HIV/HSV. Our work may be analogized to HIV/HSV super-infection. Supported by National Natural Science Foundation of China (30770081).

T-27 HEPATITIS C VIRUS-INDUCED L-FICOLIN TRIGGERS LECTIN COMPLEMENT PATHWAY-MEDIATED CYTOLYTIC ACTIVITY AND INFLAMMATORY RESPONSES. J Liu[1], XL Zhang[1]; [1]The State Key Laboratory of Virology and Immunology, Wuhan University School of Medicine, Wuhan, 430071 China.

Background & Aims: L-ficolin is a recently identified lectin pathway activator present in normal human plasma associated with infectious diseases but little is known about L-ficolin and viral hepatitis. Methods: To elucidate this, the L-ficolin levels in serum, PBMCs and DCs were analyzed. The mechanism of the interaction between L-ficolin and HCV were further investigated. Results: We found that L-ficolin levels in serum from 150 HCV patients were significantly higher than that from 126 HBV patients and 150 healthy controls, and its levels were correlated with the severity of fibrosis and the active state of HCV infection. We further found that L-ficolin expressions were significantly increased in PBMCs and DCs from HCV patients, or in HCVcc infected DCs and Huh7.5.1 cells in vitro study. Investigation of the mechanisms of the L-ficolin action on HCV demonstrated that L-ficolin protein could recognize and bind HCV via interactions with N-glycans of viral envelope glycoproteins E1 and E2, activating the lectin complement pathway-mediated cytolytic activity in HCVcc infected Huh7.5.1. Furthermore, L-ficolin could significantly stimulate the expressions of pro-inflammatory factor cyclooxygenase-2 (COX-2), and Prostaglandin E2 (PGE2) expressions from HCVcc-Huh7.5.1 cells. Conclusions: These findings suggest the new biological functions of L-ficolin and increased L-ficolin levels are closely related disease progression, liver inflammation and fibrosis in HCV-infected chronic liver disease.

T-28 AN ESSENTIAL ROLE FOR DELTA FOSB IN THE CHRONIC DRUG ADDICTION. F Liu[1], X Liu [1]; [1]Medicine College, Xi'an Jiaotong University, Xi'an, 710061 China.

The mesolimbic system is closely related to the drug addiction. Many types of chronic stimulations mediate the interaction between the extracelluar transmitter and its receptor. This interaction will activate the intracellular signaling pathway and gene transcription and expression. At last, the extracellular stimulations lead to the neuron long-term plasticity changes in the central nervous system. This process may be the main neural biological mechanism during the drug addiction's formation and retention. The transcription factor, delta FosB, accumulates in a region-

specific manner in brain in response to many types of chronic stimulation due to the unusual stability of the protein. This unique phenomenon is responsible for the long-term behavioral and neuron plasticity changes. So, delta FosB is the key molecular mechanism in the chronic drug addiction, and will be the new target in the treatment of drug addiction.

T-29 MORPHINE MODULATES DENDRITIC CELL IL-23 PRODUCTION THROUGH TLR2-ATF2 AND TLR4-IRF3 SIGNALING. J Ma[1], R Barke[2], R Charboneau[2], S Roy[1], J Wang[1]; [1]Department of Surgery, University of Minnesota, Minneapolis, MN, USA 55455; [2]Department of Surgery, Veteran Affair Medical Center, Minneapolis, MN, 55417 USA.

IL-23, produced by macrophages and dendritic cells (DCs), plays a critical role in innate immunity against bacterial infection. We have shown previously that chronic morphine treatment impairs host innate immune response and increases susceptibility to S. pneumoniae lung infection. To determine if and how morphine modulates IL-23, bone marrow derived dendritic cells (BMDCs) and macrophages (BMDMs) were treated with morphine and stimulated with S. pneumoniae, toll like receptor (TLR) ligands (LPS, LTA, CpG), and Nod2 ligand (MDP). Our results show that S. pneumoniae, LPS, LTA, and CpG induced IL-23 promoter activity in both BMDCs and BMDMs. Although significant IL-23 protein production was observed in S. pneumoniae, LPS, and LTA stimulated BMDCs, but little or no induction was seen with BMDMs. Morphine treatment significantly inhibited IL-23 production in DCs. These results suggest that IL-23 is produced by DCs through activation of TLR2 and TLR4 signaling as an innate immune response to pathogens. Moreover, morphine treatment decreased LPS induced IRF3 phosphorylation and LTA stimulated ATF2 phosphoralytion in DCs. To further determine if morphine modulates TLR2-ATF2 and TLR4-IRF3 signaling in DCs, IL-23 production following LPS and LTA stimulation was investigated using DCs transfected with ATF2 and IRF3 expression plasmid. Our studies show that over-expression of ATF2 and IRF3 attenuated the IL-23 inhibitory effect caused by morphine treatment. Overall, our results support the concept that morphine modulates IL-23 through TLR2-ATF2 and TLR4-IRF3 signaling in DCs. Supported by R01 DA12104, K02 DA015349, P50 DA11806, and R03 DA023353.

T-30 REDUCED REGULATORY T-CELL INFILTRATION IN RESPONSE TO MCMV BRAIN INFECTION OF IL-10-DEFICIENT MICE. MB Mutnal[1], MC Cheeran[1], L Morgan[1], S Hu[1], JR Lokensgard[1]; [1]Center for Infectious Diseases and Microbiology Translational Research, University of Minnesota, Twin Cities, MN, 55455 USA.

While wild-type mice control murine cytomegalovirus (MCMV) brain infection, the virus is lethal to animals deficient in interleukin (IL)-10. This increased mortality is associated with elevated levels of proinflammatory cytokines and chemokines in the central nervous system, but reduced lymphocyte infiltration. Separation of cells isolated from wild-type murine brain tissue into distinct populations using FACS, along with subsequent quantitative RT real-time PCR, showed that brain-infiltrating CD45(hi)/CD11b(low) cells were the source of IL-10 within the brain. In this study, we hypothesized that IL-10-producing regulatory T cells (Tregs) control excess neuroinflammatory responses in the brains of MCMV-infected animals. Adoptive transfer of both the CD4(+)CD25(+) and CD4(+)CD25(-) cell populations into IL-10 KO mice protected them from the lethal effect of MCMV brain infection. Following direct intracerebroventricular injection of MCMV into IL-10 knockout (KO) and wild-type mice, brain samples were analyzed at 5 days post-infection for presence of CD4(+)CD25(+)FoxP3(+) cells. Compared to wild-type mice, IL-10 KO animals were found to have significantly reduced Treg cell infiltration into the brain. Experiments are currently underway to further characterize the function and expansion of the lymphocyte populations used for adoptive transfer studies.

T-31 DIFFERENTIAL MODULATION BY MORPHINE OF FC GAMMA RECEPTOR MEDIATED PHAGOCYTOSIS FOLLOWING TLR-2 AND TLR-4 ACTIVATION. J Ninkovic[1], A Krishnan[1], S Roy[1]; [1]Department of Pharmacology, University of Minnesota, Minneapolis, MN, 55343 USA.

Morphine has been known to modulate innate immunity, resulting in inhibition of clearance and increased dissemination of bacteria. Clinically, opioid users and abusers show a greater susceptibility to gram positive bacterial (G+) infections then to gram negative (G-) bacterial infections. Our data shows that morphine treatment leads to greater inhibition of phagocytosis and decreased clearance of IgG opsonized (G+) bacteria, when compared to opsonized (G-) bacteria. (G+) and (G-) bacteria selectively activate TLR-2, and TLR-4 respectively. We therefore

investigated if TLR activation attributes to differential effects of morphine on Fc gamma receptor (FcgR) mediated phagocytosis. Our data shows that morphine treatment resulted in the upregulation of both TLR-2 and TLR-4 expression in macrophages. Interestingly, activation of TLR-4 by LPS in the presence of morphine increased phagocytosis and bacterial killing while activation of TLR-2 by LTA decreased phagocytosis and killing in morphine treated cells. In addition, potentiation of phagocytosis by morphine observed with TLR-4 activation in wt mice is abolished in primary macrophages isolated form TLR-4 -/- mice. In presence of morphine TLR-4 activation increases and TLR-2 activation decreases phagocytosis of opsonized bacteria. Based on this observation we hypothesize that the greater susceptibility to (G+) infection in morphine users may be due to simultaneous activation of TLR-2 by morphine. Ongoing studies will clarify the points of convergence of mu opiate receptor and TLR-2 signaling pathways on FcgR phagocytosis. Supported by RO1DA12104, RO1 DA022935, KO2 DA015349, P50DA11806 (to S.R.) and T32DA007097-26A1 (to J.N).

T-32 MONOCYTE CARRIAGE AND RELEASE OF NANOFORMULATED INDINAVIR, RITONAVIR AND EFAVIRENZ: IMPROVED PHARMACOKINETICS AND DRUG DELIVERY. A Nowacek[1], R Miller[2], J Kipp[2], J Mcmillan[1], H Dou[1], S Graham[2], M Chaubal[2], J Werling[2], B Rabinow[2], H Gendelman[1]; [1]Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE, 68198-5880 USA; [2]Global R&D, BPT, Medication Delivery, Baxter Healthcare, Round Lake, IL, 60073 USA.

Limitations of oral antiretroviral therapy (ART) for HIV-1 infection include systemic toxicities, limited pharmacokinetics, and failure of drug penetrance into viral sanctuaries such as the central nervous system (CNS). In an attempt to bypass these limitations we developed nanoformulations of ritonavir, indinavir, and efavirenz for cell-based drug delivery into HIV-1 target tissues. The combination used maximizes effective concentrations of ART drugs by reducing their degradation by the liver achieved via a ritonavir boost mechanism. Nanoparticles (NP) were manufactured to optimize monocyte drug uptake/release kinetics and carriage into sites of active viral replication. We measured drug concentrations in monocytes, monocyte-derived macrophages (MDM), and culture media by reverse phase high performance liquid chromatography. Comparisons amongst various formulations ensured optimal uptake and dissociation. Both cell types reproducibly and rapidly, within 30 minutes, phagocytized NP in levels exceeding the ED50 of one log or greater without cytotoxicity as measured by cell migration, cytokine secretion, and mitochondrial function. The drugs were released into culture media for > 14 days. Size, shape, and surfactant coating substantively affected the uptake/release kinetics and cell handling of NP. Moreover, we demonstrated that NP laden MDM injected intravenously can traverse the blood brain barrier and subsequently release drug into the surrounding parenchyma. These results support the contention that ART drug NP could be used for treatment HIV-1 infection of the CNS. Supported by NIH Grant: 34-5160-2028-012.

T-33 MU-OPIOID SPECIFIC AGONIST DAMGO REDUCES HIV-1 REPLICATION IN HUMAN TF-1 BONE MARROW PROGENITOR CELLS. N Parikh[1], A Banerjee[1], A Alexaki[1], B Wigdahl[1], MR Nonnemacher[1]; [1]Department of Microbiology and Immunology, Drexel University College of Medicine, Philadelphia, PA, 19102 USA.

Several studies now suggest that opioids modulate innate, humoral, and cell-mediated immunological processes. There are have been reports supporting both protective as well as exacerbating effects of mu-opioids in the final outcome of human/simian AIDS. In vitro studies have shown that under chronic exposure to mu-opioid receptor ligands like morphine there is increased replication of X4-tropic HIV-1 strains in cells of the monocyte/macrophage lineage. CD34+/CD38+ progenitor cells within the bone marrow are refractile to HIV-1 infection, probably due to their low level expression of HIV-1 co-receptors, CXCR4 and CCR5. We have utilized the human CD34+/CD38+ TF-1 erythromyeloid progenitor cell line to study the effects of the mu-opioid specific agonist DAMGO on cell surface expression of the HIV-1 co-receptor CXCR4 and concomitant HIV-1 susceptibility. Our studies have identified the presence of the mu-opioid receptor-1 isoform on TF-1 cells. Flow cytometry assays exhibit a downregulation of CXCR4 upon DAMGO treatment of TF-1 cells. In line with these observations, DAMGO reduced viral replication in these cells. We suggest a cell-type specific role of mu-opioids in modulating co-receptor expression and viral replication. Additional studies are underway to unravel the molecular mechanism underlying this phenomena. Supported by DA019807.

T-34 METHAMPHETAMINE AND HUMAN IMMUNODEFICIENCY VIRUS TYPE-1 NEF-MEDIATED INCREASE IN MONOCYTE CHEMOATTRACATNT PROTEIN-1 (MCP-1) EXPRESSION IN ASTROCYTES: IMPLICATION IN NEUROAIDS. K Patel[1], A Kumar[1]; [1]Pharmacology & Toxicology, University of Missouri - Kansas City, Kansas City, MO, 64108 USA.

Both methamphetamine and human immunodeficiency virus (HIV-1) are known to induce neuroinflammation and thereby might be playing an important role in dementia. Recent studies have shown that methamphetamine causes increase in intensity of virus replication. Furthermore, HIV prevalence has been reported to be higher among methamphetamine users compared to that among non users. Likewise, increased level of monocyte chemoattractant protein-1 (MCP-1) has also been implicated in neuroinflammation in many diseases including HIV/AIDS. In this study we report that both methamphetamine and HIV-1 Nef causes increased production of MCP-1 in astrocytes. A three-day treatment of astrocytes with 500 μM methamphetamine caused 10.79±5.6 fold higher expression of MCP-1 RNA which could be partially abrogated (50±4.24 percent) by use of metabotropic glutamate receptor 5 (mGluR5) antagonist 2-methyl-6-(phenylethynyl)pyridine (MPEP). Likewise, transfection of astrocytes with HIV-1 Nef caused 3.3±0.1 fold higher expression of MCP-1 RNA which could be almost completely abrogated by use of HIV-1 Nef specific siRNA. These results clearly suggest that MCP-1 over-expression could be a possible mechanism by which methamphetamine causes neuroinflammation. Experiments are underway to determine whether methamphetamine causes synergistic activity with HIV-1 Nef. Supported by NIH.

T-35 CEREBROSPINAL FLUID PROTEOMICS REVEALS POTENTIAL PATHOGENIC CHANGES IN THE BRAINS OF SIV-INFECTED MONKEYS. G Pendyala[1], SA Trauger[2], E Kalisiak[2], RJ Ellis[3], G Siuzdak[2], HS Fox[1]; [1]Department of Pharmacology & Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE, 68198 USA; [2]Department of Molecular Biology & Center for Mass Spectrometry, Scripps Research Institute, San Diego, CA, 92037 USA; [3]Department of Neurosciences & HNRC, University of California at San Diego, San Diego, CA, 92103 USA.

The HIV-1-associated neurocognitive disorder occurs in approximately one-third of infected individuals. It has persisted in the current era of anti-retroviral therapy, and its study is complicated by the lack of biomarkers for this condition. Since the cerebrospinal fluid is the most proximal biofluid to the site of pathology, we studied the cerebrospinal fluid in a nonhuman primate model for HIV-1-associated neurocognitive disorder. Here we present a simple and efficient liquid chromatography coupled mass spectrometry based proteomics approach that utilizes small amounts of cerebrospinal fluid. First, we demonstrate the validity of the methodology using human cerebrospinal fluid. Next, using the simian immunodeficiency virus infected monkey model, we show its efficacy in identifying proteins whose increased expression is linked to disease: alpha-1-antitrypsin, complement C3, hemopexin, IgM heavy chain and plasminogen. These resulting biomarkers then revealed an important facet of the disease that their presence does not just reflect the breakdown of the normal barriers that isolate the CNS, but that the expression of the genes encoding these proteins are markedly increased in the brain parenchyma itself during disease. In summary, this study reveals new central nervous system alterations in lentivirus-induced neurological disease, and the technique employed holds great potential in its applicability to other systems in which limited amounts of biofluids can be obtained.

T-36 AGE-DEPENDENT DIFFERENTIAL EXPRESSION OF HIV-1 VIRAL PROTEINS IN THE HIV-1 TRANSGENIC RAT. JS Peng[1], XQ Liu[1], DJ Zhou[3], XW Wu[2], SL Chang[1]; [1]Institute of NeuroImmune Pharmacology, Seton Hall University, South Orange, NJ, 07079 USA; [2]TongJi Medical College, Huazhong University of Science & Technology, Wuhan, 430030 China; [3]Wuhan Centers for Disease Control & Prevention, Wuhan, 430022 China.

In HIV-1 infection, HIV-1-related proteins can cause organ dysfunction. The HIV-1 transgenic (HIV-1Tg) rat was developed as a model of AIDS-related pathology and immune dysfunction. In the HIV-1Tg rat, HIV-1-related pathologies become more prominent with advancing age. We have hypothesized that differential expression of HIV-1 viral proteins is age-dependent. We developed highly specific real-time PCR assays to compare the expression of the HIV-1 proteins, tat, gp120, nef and vif in the tissues of adult HIV-1Tg rats at 2-3 mo of age with those at 10-11 mo of age. In the younger rats, mRNA expression of viral proteins was greatest in the spleen; whereas in the older rats, HIV-1 viral protein expression was greatest in the cerebellum and spinal cord. Viral protein mRNA levels in the spleens of the younger rats were significantly greater than those in the

older rats ($p < 0.01$). Conversely, viral protein mRNA levels in the spinal cord, cerebellum, and striatum in the older rats were significantly greater than those in the younger animals ($p < 0.01$). In the prefrontal cortex, tat and nef expression was significantly greater at 2-3 mo of age than at 10-11 mo of age ($p < 0.05$). Our data indicate that the differential expression of various HIV viral proteins in the HIV-1Tg rat is age-dependent, and suggest that the alteration in expression of HIV-1 viral proteins in various organs may be one of the mechanisms underlying the age-related pathologies seen with HIV-1 progression to AIDS Supported by R01 DA 007058, K02 DA 016149, and R21 DA019836 to SLC partially.

T-37 L-FICOLIN AND HIV. XL Peng[1], J Liu[1], XL Zhang[1]; [1]State Key Laboratory of Virology, Immunology Department, Wuhan University School of Medicine, Wuhan, 430071 China.

Human L-ficolin is a recently identified lectin pathway activator present in normal plasma associated with infectious diseases but little is known about L-ficolin and HIV infection. In the present study, we found that increased L-ficolin levels in HIV patients comparing to health controls. L-ficolin could bind to gp120 and activate lectin complement pathway. L-ficolin pretreated HIV pseudovirus decreased infection to human CD4+T cells. Our study suggest that L-ficolin can prevent HIV infection and plays an important role in HIV pathogenesis.

T-38 A NITRATED ALPHA-SYNUCLEIN VACCINE STRATEGY FOR PARKINSON'S DISEASE. AD Reynolds[1], DK Stone[1], RL Mosley[1], HE Gendelman[1]; [1]Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE, 68198 USA.

Studies of Parkinson's disease (PD) suggest linkages between alpha-synuclein aggregation and nitration for disease. We previously demonstrated that nitration of alpha-synuclein creates novel antigens capable of inducing innate and adaptive immune responses that exacerbate PD pathology in MPTP-intoxicated mice. Mice immunized with nitrated c-terminal tail of alpha-synuclein (N4YSyn) generate robust T cell proliferative and inflammatory secretory responses. The adoptive transfer of such T cells to MPTP-mice exacerbates nigrostriatal degeneration, whereas adoptive transfer of regulatory T cells (Treg) to MPTP mice is neuroprotective. To modulate the neuroprotective effects of Treg, we injected tolerogenic doses of vasoactive intestinal peptide (VIP) then transferred these splenocytes to MPTP-mice. These animals showed modest effects on glial activation and neuronal survival. Surprisingly, pooled splenocytes from N4YSyn-immunized and VIP-injected donors attenuates microglial activation and results in significant neuroprotection after adoptive transfer to MPTP-mice. This was due, in part, to diminished suppressive capabilities of Treg within the N4YSyn immunogenic population that is restored in the presence of Treg from VIP-treated donors. Importantly, the suppressive function of pooled Treg is significantly enhanced compared to Treg from either naïve or VIP-treated donors. These data suggest that interactions with Treg and N4YSyn-mediated immunity results in a phenotypic switch that promotes neuroprotective immune-mediated responses that may be used in developing a PD vaccine. Supported by 5P01NS31492, 2R37 NS36126, 2R01 NS034239, P20RR15635, U54NS43011, P01MH64570, and P01 NS43985, Patterson Fellowship.

T-39 MORPHINE INHIBITS NEURONAL SURVIVAL SIGNALING STIMULATED BY CXCR4 BY INCREASING BRAIN LEVELS OF FERRITIN HEAVY CHAIN. R. Sengupta[1], S. Burbassi[1], O. Meucci[1]; [1]Department of Pharmacology and Physiology, Drexel University College of Medicine, Philadelphia, PA, 19102 USA.

Intracellular signaling through the chemokine CXCL12 and its receptor CXCR4 plays a significant role in neuronal development and homeostasis. Recent work has shown that the over-expression of the intracellular iron binding protein ferritin heavy chain (FHC) can negatively regulate CXCR4 function in various cell lines. In addition, studies from our laboratory indicated that endogenous as well as synthetic mu-opioid agonists impair the pro-survival action of CXCR4 in primary neurons. The current study focuses on the role of FHC in the heterologous desensitization of CXCR4 by opioids. We found that CXCR4-induced Galphai/betagamma activities (i.e. activation of ERK/Akt, GTPgammaS incorporation, inhibition of AC) were suppressed following in vitro or in vivo morphine treatment. This inhibitory action required prolonged opioid treatment and de novo protein synthesis. Furthermore, both morphine and DAMGO increased neuronal levels of FHC at 6, 18 and 24hrs. An increase in FHC protein was also reported in the cortex of morphine-treated rats but not in MOR KO animals. The temporal pattern of cortical FHC protein expression in morphine-treated animals strongly correlated with alterations of brain CXCR4 function. The crucial role of

FHC in inhibition of neuronal CXCR4 was confirmed by siRNA. Overall these findings suggest that opiates interfere with normal CXCR4 function in the brain through upregulation of FHC. As a consequence opiates may exacerbate progression to neuroAIDS in HIV+ drug users by reducing the neuroprotective potential of CXCR4. This work was supported by NIH grants DA15014 and DA19808 to Olimpia Meucci.

T-40 SEQUENTIAL INFORMATION PROCESSING BY THE BASOLATERAL AMYGDALA AND THE NUCLEUS ACCUMBENS IS NECESSARY FOR HEROIN-INDUCED CONDITIONED IMMUNOMODULATION. JL Szczytkowski[2], DT Lysle[2]; [1]Neurobiology Curriculum and [2]Psychology Department, University of North Carolina at Chapel Hill, Chapel Hill, NC, 27599 USA.

Heroin induced suppression of inducible nitric oxide synthase (iNOS) and the proinflammatory cytokines, TNF-alpha and IL-1 beta, can be conditioned to environmental stimuli associated with drug administration. Recent studies in our laboratory have indicated that both the basolateral amygdala (BLA) and the nucleus accumbens (NAC) shell independently play critical roles in the expression of these conditioned effects. The present investigation sought to determine whether communication between these brain regions is necessary for heroin-induced conditioned immunomodulation by utilizing the functional disconnection procedure. Rats were given five conditioning trials in which they received an injection of heroin immediately upon placement into a conditioning chamber. Rats were then re-exposed to the conditioning chamber ten days later without further drug administration. Prior to re-exposure, rats received unilateral intra-BLA microinfusions of the dopamine D1 antagonist, SCH23390, and concomitantly the glutamate antagonist, AP-5, was infused into the contralateral NAC shell. Analyses using real-time RT PCR indicate that disconnection of the BLA from the NAC attenuates the suppressive effects of heroin associated environmental stimuli on nitric oxide production and proinflammatory cytokine expression. This study is important because it is the first to define a specific neural circuit involved in neural immune interactions.

T-41 DIFFERENTIAL EXPRESSION OF MU, DELTA AND KAPPA OPIOID RECEPTORS IN THREE PHENOTYPES OF HUMAN NEUROBLASTOMA CELLS. JD Walton[1], J Peng[1], RA Ross[2], SL Chang[1]; [1]Institute of NeuroImmune Pharmacology, Seton Hall University, South Orange, NJ, 07079 USA, [2]Department of Biological Sciences, Fordham University, Bronx, NY, 10458 USA.

Previous studies have suggested that cancer development may be associated with altered opioid receptor regulation. In this study, we examined the expression of the mu (MOR), delta (DOR), and kappa (KOR) opioid receptors in three different phenotypes of human neuroblastoma cells: SH-SY5Y, a neuroblastic cell type; BE(2)-C, an intermediate cancer stem cell; and SH-EP1, a substrate adherent type. We compared the copy number of the MOR, DOR and KOR receptors in the three neuroblastoma phenotypes using absolute quantitation of real-time polymerase chain reaction (PCR). Our preliminary data showed that SH-SY5Y cells, the model that is widely used to study opioid receptors, had the highest copies of MOR mRNA among these three cell lines, whereas the cancer stem cell, BE(2)-C, has higher expression of DOR than the other two cell lines. In addition, DOR expression was highest among the three receptors in both SH-SY5Y and BE(2)-C cells and SH-EP1 had higher expression of MOR than BE(2)-C. Absolute quantitation of real-time PCR offers the advantage of comparison based on copy number of the target, and the additional benefit of being able to compare the copy number of all three receptors in different cell types to better understand the implications and pharmacology of these opioid receptors. To our knowledge, we are the first to compare and report the differential expression of the mu, delta, and kappa opioid receptors in three different phenotypes of a human cancer cell line. Supported by R01 DA07058, R21 DA019836, and K02 DA016149 to SLC.

T-42 ROLE OF THE PPARγ PATHWAY IN MORPHINE INDUCED MACROPHAGE APOPTOSIS AND AUTOPHAGY. J Wan[1], S Roy[1]; [1]Department of Surgery, University of Minnesota, Minneapolis, MN, 55455 USA.

Morphine has been shown to induce macrophage apoptosis but the role of TLR4 activation underlying this event has not been extensively investigated. Caspases seem to play redundant roles in most apoptotic pathways and Caspase-3 has been recognized to be a crucial player in this process. Peroxisome proliferator activated receptor (PPARγ), which belong to the steroid-lipid nuclear receptor family, has been revealed to have combinatorial control over homeostasis and immune responses and has been suggested as an alternate therapuetic approach for the treatment

of inflammatory diseases. In this study we investigated the role of the PPARγ signaling pathway in TLR signaling and if morphine modulates this signaling pathway. Our results show that morphine treatment resulted in a significant increase in TLR4 induced increase in initiator caspase 8 and 9 implicating the involvement of both the intrinsic and extrinsic pathways in the apoptotic events. At later time points a significant increase in the effector caspase, Caspase 3 was observed to significantly increase following morphine treatment. Interestingly we also observed significant increase in autophagic events and a significant reduction in PPAR? activation. These studies will attempt to link these pathways to morphine induced modulation of TLR4 signaling leading to apoptosis and autophagy. Supported by R01 DA12104, K02 DA015349, P50 DA11806.

T-43 TRANSCRIPTIONAL REGULATION OF HUMAN MEMORY T CELLS DIFFERENTIATION. Q Wan[1], L Kozhaya[1], D Unutmaz[1]; [1]Department of Microbiology and Pathology, School of Medicine, New York University, New York, NY, 10016 USA.

During an immune response, naïve T (TN) cells are activated and proliferate in response to microbial antigens and generate various subsets of effector and memory T (TEM and TM respectively) cells with distinct functions. However, the molecular mechanisms that promote proliferation and clonal expansion of TN cells and how they are endowed with diverse effector functions remain poorly understood. We found that Krüppel like factor 2 (KLF2), which is important to maintain murine T cell quiescence, is rapidly downregulated upon activation of both human TN and TM cells, whereas it is maintained at relatively higher levels in differentiated effector memory T (TEM) cells subsets. Sustained ectopic expression of KLF2 in TN cells through lentiviral transduction inhibits their proliferative capacity upon reactivation and promotes their differentiation into TEM phenotypes. Additionally, KLF2 expressing cells display decreased phosphorylation of STAT5a upon IL-2 or IL-7 stimulation, which is similar to responsiveness of naturally occurring TEM cells. Sustained expression of KLF2 doesn't modify the cytokine secretion pattern of primary T cells by Th1 type cytokine secretion, whereas negatively regulates secretion of Th2 type cytokines. Finally, KLF2 overexpressing CCR7-CD45RO+ population also displays TEM cell characteristics. Our findings suggest that KLF2 might be an important key factor in human TEM cell differentiation and this would have implications in modulating immune responses against infections or in development of novel vaccines.

T-44 COMPLICATED PATTERN OF HIV-1 EVOLUTION AMONG INJECTION DRUG USERS AND SEXUALLY ACQUIRED CASES IN THE DEHONG PREFECTURE OF YUNNAN PROVINCE, CHINA. HB Wang[1], L Liu[1], MH Jia[2], YH Ma[2], ZW Chen[1]; [1]AIDS Institute, The University of Hong Kong, Hong Kong, China; [2]Yunnan Center for Disease Control and Prevention, Yunnan Center for Disease Control and Prevention, Kunming, 650022 China.

The HIV-1 epidemic in China remains increasing at an irrepressible rate. Since the identification of a large number of HIV-1 infections among injection drug users (IDUs) in Dehong in 1989, the viruses initially identified in this prefecture are likely responsible to major epidemics in the entire country. This study is to further investigate the HIV-1 evolution in Dehong. Reverse transcription polymerase chain reaction was used to amplify HIV-1 p17 and RT fragment from patient's serum. Among the total of 23 samples studied, eight (34.8%) were from IDUs, eight (34.8%) from sexually acquired cases, and seven (30.4%) from unknown risk factors cases. The p17 and an 413-bp RT fragments were obtained from all study subjects whereas an 1049-bp RT fragment was sequenced for nine individuals. Phylogenetic and recombination analysis of these genes suggested that ten patients (43.5%) harbored multiple new recombinant HIV-1 virus that are distinct from one another, including two CRF01_AE/C and eight CRF01_B/C recombinant virus. These new recombinant viruses were from 37.5% (3/8) sexually acquired cases, 44.4% (4/9) IDUs, and 42.8% (3/7) unknown risk factors cases, respectively. The other 13 patients (56.5%) harbored CRF01_AE (7/23), subtype C (4/23), and CRF01_C/B (2/23), which were similar to those previously identified. This is the first report that multiple new recombinant forms of HIV-1 are arising not only among IDUs but also among sexually acquired cases in Dehong. Our findings have implications for HIV-1 pathogenesis studies among drug abusers and vaccine development.

T-45 AN ORALLY DELIVERED ATTENUATED SALMONELLA VACCINE EXPRESSING EAST6-AG85B ELICITS FULL IMMUNE RESPONSE AND PROTECTION AGAINST MYCOBACTERIUM TUBERCULOSIS. QL Wang[1], XL Zhang[1]; [1]The State Key Laboratory of Virology, Immunology, Wuhan University School of Medicine, Wuhan, 430071 China.

Attenuated Salmonella enterica have been implicated attractive as potential live oral delivery vector vaccines because of their ability to elicit both mucosal and systemic immunity. In the present study, we generated two attenuated S. typhimurium aroA SL7207 vaccine strains namely SL (pV-Ag85B) and SL (pV-ESAT6-Ag85B), harboring the Mycobacterium tuberculosis (M. tb) H37Rv Ag85B and ESAT6-Ag85B fusion genes respectively. After oral administration to mice, the SL(pV-ESAT6-Ag85B) induced the highest specific IgA levels in the serum and mucosa of the stomach and intestine of the immunized animals among the other (SL(pV-Ag85B), DNA vaccine pVAX1-Ag85B and BCG) vaccinated groups, and much higher levels of specific serum IgG were observed compared to the SL(pV-Ag85B) and pVAX1-Ag85B. Moreover, among all other groups- including BCG group- the combination of SL(pV-ESAT6-Ag85B) with BCG vaccination, induced the strongest specific IFN-gamma producing T cells/CTL responses, and the highest levels of granzyme B expression of CD8+ T cells. In addition, after intravenous, and intranasal infection with virulent H37Rv, the mice immunized with SL(pV-ESAT6-Ag85B) combined with BCG had the longest survival period, the lowest numbers of CPU in lungs and spleens, and substantially improved postinfection lung pathology compared to the mice immunized with DNA vaccine or BCG. Our results show that SL (pV-ESAT6-Ag85B) can induce the highest full immune and protective efficacy, against M. tb especially when it is combined with BCG vaccination and could be used as a promising mucosal TB vaccine.

T-46 THE REMAINED SERA NEUTRALIZING ACTIVITY AGAINST VACCINIA VIRUS TIANTAN IN CHINESE PEOPLE ARE OBVIOUSLY REDUCED BY REMOVAL OF THE VIRAL H3L GENE. YU Wenbo[1]; [1]AIDS Institute, University of Hong Kong, Hong Kong, China.

As a preventive vaccine, vaccinia virus was once wildly used around the world, which finally led to the eradication of human smallpox. An immunodominant antigen p35 is a 324-amino-acid membrane-associated protein encoded by Vaccinia virus genome open reading frame H3L. H3L protein was the first epitope among Vaccinia virus that has been identified as the major neutralizing antibody target in human. In the course of our developing Tiantan as a new live vector for AIDS vaccine, we should consider the preexisting immunity in Chinese people. In this study, we collected more than 50 human plasma samples of Chinese people. Based on a flow cytometry method for the neutralizing analysis, we found that the neutralizing activities are common in these samples. All of the samples before 1981 have the detectable 50% inhibition titer (IT50) against Vaccinia virus Tiantan (VTT) above 20 and the average IT50 is 104. We managed to construct a H3L deletion Tiantan (VTT/H3L). The results showed H3L is not essential for Vaccinia Virus Tiantan to replicate on Vero, however the replication capacity of Tiantan is reduced due to the silence of H3L gene products. A head to head comparison showed that the IT50 of human plasma against the H3L negative virus is largely reduced. 5 of the 53 samples have no detectable neutralizing activity to the VTT/H3L. Concerning the remained 48 samples, the average IT50 declined from 110 to 24. However, VTT/H3L induced much higher neutralizing antibody than VTT in balb/c mice, that indicate the humoral immunity profiles are different in human and mice.

T-47 HIV-1 TAT CO-OPERATES WITH IFN-γ AND TNF-α TO INDUCE CXCL10 EXPRESSION IN HUMAN ASTROCYTES THROUGH AN OXIDATIVE STRESS MEDIATED PATHWAY. R. Williams[1], S. Buch[1]; [1]Department of Molecular & Integrative Physiology, University of Kansas Medical Center, Kansas City, KS, 66160 USA.

HIV-encephalitis, the pathological correlate of HIV dementia is characterized by glial activation, cytokine/chemokine dysregulation, oxidative stress (OS), and neuronal damage/loss. Glial activation rather than viral load is a better correlate of HIVE severity. Our findings have demonstrated that the concerted action of the pro-inflammatory cytokines IFN-γ/TNF-α and HIV-1 Tat can result in a dramatic induction of CXCL10 in astrocytes. Since glial activation is accompanied by increased OS, we hypothesized that enhanced expression of CXCL10 in stimulated astrocytes involves an OS pathway. To better understand the role of OS in CXCL10 expression we focused on NADPH oxidase, a mediator of OS. Specifically, our findings demonstrated that treatment of astrocytes with the combination of Tat/IFN-γ/TNF-α resulted in increased OS with a concomitant increase in CXCL10. Furthermore, OS and CXCL10 expression

were both significantly decreased in stimulated astrocytes pre-treated with the antioxidant apocynin, an inhibitor of NADPH oxidase. Additionally, pre-treatment with apocynin followed by stimulation resulted in decreased activation of the MAPK signaling pathways Jnk and Erk1/2 coinciding with a reduction in the activation of the transcription factor NF-κB. Since OS and CXCL10 levels are linked to disease severity, an antioxidant that lowers both could lead to therapeutic intervention strategies for those suffering from HIVE. This work was supported by funding from NINDS F31NS062665 (RW), NIMH MH068212, NIDA DA020392, NIDA DA024442 (SB).

T-48 SDF-1 INCREASES HUMAN NEURAL PROGENITOR CELL PROLIFERATION THROUGH PI3K/AKT/FOXO3A SIGNALING PATHWAY. YW Wu[1], HP Peng[1], MC Cui[1], NW Whitney[1], JZ Zheng[1]; [1]Department of Pharmacology & Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE, 68198 USA.

Background: Stromal cell-derived factor (SDF-1), a ligand for CXCR4, is critical in neural development particularly mediating neural progenitor cell (NPC) migration. However, SDF-1-mediated NPC survival and proliferation and how the involved signaling pathways including Akt and FOXO3a (forkhead box, class O3A) are regulated remain unclear. Aim: We test the hypothesis that SDF-1 increases human NPC proliferation through phosphatidylinositol 3-kinase (PI3K)/Akt and FOXO3a. Methods: Upon SDF-1 treatment, human NPC proliferation was determined by Ki67 immunostaining and/or BrdU incorporation as well as phophorylation of Akt and FOXO3a. The signaling pathways were identified by using inhibitors for CXCR4 (T140), G protein (PTX) and PI3K (LY294002) individually. The roles of Akt and FOXO3a in SDF-1-mediated NPC proliferation were confirmed by overexpression through adenovirus gene delivery system. Result: SDF-1 promoted human NPC survival and proliferation and induced phosphorylation of Akt and FOXO3a. SDF-1-mediated NPC proliferation was abolished by T140, PTX and LY294002 treatment. Moreover, overexpression of constitutively active Akt-1 and dominant negative FOXO3a increased the SDF-1-mediated NPC proliferation, while the overexpression of dominant-negative mutant Akt and wild-type FOXO3a abolished it. Conclusion: SDF-1 enhances human NPC proliferation through PI3K/Akt /FOXO3a, a downstream substrate of PI3K/Akt, may play an important role in human NPC survival and proliferation during brain development. Supported by NIH R01 NS 061642-01,R01 NS 41858-01,R21 MH 083525-01 and P01 NS043985.

T-49 FUNCTIONALLY IMPAIRED CD56+ T CELLS IN HEROIN USERS INFECTED WITH HEPATITIS C VIRUS. L Ye[1], W Hou[1], X Wang[1], DS Metzger[2], E Riedel[1], L Song[2], L Zhou[1], Y Zhou[3], DJ Zhou[3], WZ Ho[1]; [1]Division of Allergy & Immunology, The Children's Hospital of Philadelphia, and [2]Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, PA, 19104 USA; [3]Division of Virology, Wuhan Centers for Disease Control and Prevention, Wuhan, 430022 China.

CD56+ T cells, a subset of human T lymphocytes, express cell-surface molecular CD56 that is typically expressed by natural killer cells. CD56+ T cells are abundant in liver and play an important role in host innate immunity against viral infections. In this study, we investigated the in vivo impact of heroin use and/or hepatitic C virus (HCV) infection on the CD56+ T cell frequency and function. A total of 37 heroin users with (17) or without (20) HCV infection and 17 healthy subjects were included in the study. Although heroin use and/or HCV infection have little impact on CD56+ T cell frequency in PBMCs, unstimulated CD56+ T cells isolated from heroin users with or without HCV infection had significantly lower levels of IFN-gamma expression than those from normal subjects. HCV infection also impaired the ability of IL-12-stimulated CD56+ T cells to produce IFN-gamma, as there was a negative correlation between plasma levels of HCV RNA and IFN-gamma production by IL-12-stimulated CD56+ T cells from the subjects with HCV infection. Investigation of the mechanisms involved in the functional impairment of CD56+ T cells by HCV infection showed that heroin use and/or HCV infection significantly increased the expression of two important suppressors in IL-12 pathway, suppressor of cytokine signaling protein-3 (SOCS-3) and protein inhibitors of activated STAT-3 (PIAS-3). These findings provide compelling *in vivo* mechanistic evidence that heroin use and HCV infection impair CD56+ T-mediated innate immune function, which may account for HCV infection and persistence in liver. Supported by NIH DA012815 and DA22177.

T-50 EFFECTS OF STRESS ON DECISION-MAKING PERFORMANCE IN HEROIN ADDICTS. X Zhang[1], J Shi[1], L Lu[1]; [1]National Institute on Drug Dependence, Peking University, Beijing, 100191 China.

Aims: Craving of addictive substances by addicts is not under conscious control, even when the physiological symptoms of addiction have disappeared for yrs. They remain with deficient impulse control and impaired impulsive behaviors, a phenomenon that contributes to relapse in detoxified drug abusers. While several behavioral paradigms have evaluated the impulsive behaviors of patients with drug addiction, few studies have focused on the change of impulsive choice and the effects of stress on decision-making performance in heroin addicts after different lengths of abstinence. Methods: Subjects (20-45 y.o) with a DSM-IV diagnosis of substance dependence, who had been abstinent from heroin for 3-15d, or 1- 6 mo, or 1-2y were assessed for their decision-making performance using the Iowa Gambling Task (IGT) after obtaining written informed consent. Subjects who had been abstinent for >15d were also given stress challenge testing. Results: In contrast to the long-term abstinent groups (3m, 6m, 1y), the short-term abstinent group (3-15d) had higher impulsive choice. The 2y group had recovered to the normal decision-making performance, but after stress challenge they had higher than normal impulsive choice. Conclusions: These findings provide insight into the decision-making performance in heroin addicts after different lengths of abstinence and the effects of stress on their decision-making, which may help develop effective clinical psychotherapy and relapse prevention strategies. The neural mechanisms underlying the changes in decision-making performance need to be explored.

T-51 THE IMPACT OF ALCOHOL WITHDRAWAL ON SNK/SPAR MRNA EXPRESSION OF RAT HIPPOCAMPUS, PREFRONTAL CORTEX AND CEREBELLUM. YU Zhang[1], PH Piao[1], CK Sun[1]; [1]Institute for Brain Disorders, Dalian Medical University, Dalian, 116044 China.

It is regulating Snk-SPAR pathway that a powerful method to control synapse remodeling. We aims at observing and discussing the Snk/SPAR mRNA expression level on different brain regions, different withdrawal time, and different types of intervention with the impact of alcohol addiction, withdrawal and pharmacologic intervention. Male SD rats were adopted for establishment of animal model of alcohol dependence, low concentrations of ethanol aqueous solution were drunk containing freely for 30 days. Then they were divided randomly into 5 groups, 8 rats each. Group A is Control group, which the whole process had been drinking water; Group B is Addiction group, which the whole process had been drinking alcohol. Group C, Withdrawal group, after 30 days of drinking alcohol, altered alcohol to drinking water in the next 6 days. Group D, naloxone-intervened group, after 30 days drinking alcohol, they were drinking alcohol with naloxone injected intraperitoneally in the next 6 days. Group E, salidaroside-intervened group, treated as same as Group D, but altered naloxone to salidaroside. Hippocampus, prefrontal cortex and cerebellum were separated immediately from the fresh rat brains. RT-PCR was used to detect the expression of SNK/SPAR mRNA level. Conclusion: 1.The level of SPAR mRNA expression was regulated negatively by the level of Snk mRNA. 2. There were various levels on the expressions of Snk/SPAR mRNA in these brain regions, as well as different in response to withdrawal and drug. 3. Chronic alcohol consumption impact on SNK-SPAR pathway, withdrawal and drug can relieve that.

T-52 SELECTIVELY ENHANCED RETRIEVAL OF POSITIVE OR HEROIN-RELATED WORDS AFTER PSYCHOSOCIAL STRESS IN ABSTINENT HEROIN ADDICTS. LY Zhao[1], J Shi[1], XL Zhang[1], L Lu[1]; [1]National Institute on Drug Dependence, Peking University, Beijing, 100191 China.

Background: Stress exposure in addicted individuals provokes drug craving and recall of drug-related memories. These memories might be about euphoria and getting high or about withdrawal and unpleasant parts of the addiction and thereby reflect positively or negatively valenced material, respectively. This distinction in emotional valence is critical for developing an operational definition of stress-induced craving, which has been related to relapse to drug abuse. Methods: Three groups of participants(Addicts given Heroin Words, Addicts given Non-drug Words, and Controls given Non-drug Words) were assessed for 24-hour delayed recall of positively and negatively valenced and neutral word lists on two occasions 4 weeks apart; once in a non-stress control condition, and once after exposure to the Trier Social Stress Test in a counterbalanced design. Results: After stress, recall of positively and negatively valenced heroin words and positively valenced non-drug words was better than that under non-stress control condition in abstinent addicts. In the addicts recalling heroin words, post-stressor salivary cortisol correlated positively with recall of positive

words. Conclusions: Since greater emotional activation in response to stress, as reflected in higher cortisol levels among these post-addicts, is associated with better positive and drug related word recall, an operational definition for stress-induced craving, which can lead to relapse, may be selectively enhanced memory of drug use and the rewarding aspects.

T-53 ACTIVATION OF TLR-3 INDUCES IFN-LAMBDA EXPRESSION IN HUMAN NEURONAL CELLS. L Zhou[1,2], X Wang[2], H Li[1], Y Zhou[1], S Hu[3], L Ye[2], W Hou[2], WZ Ho[2]; [1]Division of Histology and Embryology, Department of Anatomy, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430030 China; [2]Division of Allergy & Immunology, The Children's Hospital of Philadelphia, Philadelphia, PA, 19104 USA; [3]Center for Infectious Diseases and Microbiology Translational Research, University of Minnesota Medical School, Minnesota, MN, 55455 USA.

We examined the gene expression and regulation of Type III interferon (IFN), IFN-lambda, in human neuronal cells. Human neuronal cells expressed endogenous IFN-lambda 1 but not IFN-lambda 2/3. Upon the activation of Toll-like receptor (TLR)-3 expressed in the neuronal cells by polyriboinosinic polyribocytidylic acid (PolyI:C), both IFN-lambda 1 and IFN-lambda 2/3 expression was significantly induced. The activation of TLR-3 also exhibited antiviral activity against pseudotyped HIV-1 infection of the neuronal cells. Human neuronal cells also expressed functional IFN-lambda receptor complex, interleukin-28 receptor alpha subunit (IL-28R alpha) and IL-10R belta, as evidenced by the observations that exogenous IFN-lambda treatment inhibited pseudotyped HIV-1 infection of the neuronal cells and induced the expression of APOBEC3G/3F, the newly identified anti-HIV-1 cellular factors. These data provide direct and compelling evidence that there is intracellular expression and regulation of IFN-Lambda in human neuronal cells, which may have an important role in the innate neuronal protection against viral infections in the CNS. Supported by NIH DA012815 and DA022177.

T-54 INCREASED CDK5 ACTIVITY IN THE HIPPOCAMPUS REGULATES THE DEPRESSIVE-LIKE BEHAVIORS IN CHRONIC MILD STRESS. WL Zhu[1], L Lu[1]; [1]Peking University, National Institute on Drug Dependence, Beijing, 100191 China.

Cyclin-dependent kinase 5 (Cdk5) has been implicated in learning and synaptic plasticity. Previous evidence suggests that neuronal plasticity and neurotrophins are involved in depression and bipolar disorder. Here, we explored if Cdk5 participates in the depressive-like behaviors in chronic mild stress (CMS)-treated rats. We found here that CMS caused a significant increase of Cdk5 activity and the membrane fraction of p35 protein as well as a decrease of cytosolic p35, a Cdk5 activator, in the dentate gyrus (DG) of the hippocampus. Conversely, microinjection of a Cdk5 inhibitor, butyrolactone, in DG subregion, but not in CA1 or CA3 of the hippocampus, reversed the depressive-like symptoms without affecting the symptoms of control rats. Furthermore, treatment with butyrolactone in DG, but not in CA1 or CA3 of the hippocampus, increased the cytosolic p35 level as well as decreased the membrane p35 level in CMS-administrated rats. The current results proposed that the development of depressive-like behaviors was regulated by the increased Cdk5 activity of the hippocampus. These findings suggested that the depressive-like behaviors induced by chronic mild stress may be mediated by the activation of Cdk5 in DG and the Cdk5/p35 complex could provide a potential target for development as a novel therapeutic for the treatment of depressive disorders. Supported by The National Natural Science Foundation of China (No. 30800362) and 973 Program (2007CB512302).

XIII. Poster Session II

Session 2 – General Poster Session

W-1 IN VIVO IMPACT OF DELTA-9-THC-MEDIATED IMMUNOSUPPRESSION ON HIV PATHOGENESIS IN THE HUPBL-NOD-SCID/IL-2R-GAMMA-NULL MOUSE. GC Baldwin[1], MD Roth[1], SM Kiertscher[1], KM Whittaker[1], J Zhuo[1]; [1]Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA, 90095 USA.

Marijuana (MJ) use is common among HIV seropositive individuals, where it is often used for recreational and/or medicinal purposes. The use of MJ in this setting has led to the common perception that MJ is a "safe drug". However, we and others have shown that immune cells express cannabinoid receptors and that MJ and the psychotropic cannabinoid delta-9-THC (THC) modulate the function of immune effector cells and skew cytokine production toward an immunosuppressive profile. Work from our laboratory also suggests that THC enhances HIV infectivity and increases the rate of viral replication in vivo. To define the mechanism underlying the effects of THC on HIV replication, we created mouse/human chimeras using the latest generation of immunodeficient host, the NOD-SCID/IL2rgammanull mouse, as a graft recipient for human lymphocytes (huPBL-NOD-SCID). Using this mouse model, we have recovered functional human T cells and have shown that THC treatment (10 mg/kg), in the absence of HIV infection, decreases the number CD4+ and CD4+/CD8+ cells and diminishes the production of IFN-gamma following ex vivo T-cell stimulation. Additionally, THC treatment prior to and following HIV infection results in a two- to three-fold increase in HIV+ human T-cells recovered from the spleens of infected huPBL-NOD-SCID mice when compared to control animals. Our results suggest that the capacity of THC to suppress host immunity may directly impact on the pathogenesis of HIV in vivo. Supported by NIH/NIDA DA03018 and DA023386

W-2 THE IMPACT OBSERVATION TO IMMUNE FUNCTION AND TRACE ELEMENTS IN 4 CASES OF AIDS TREATMENT BY ARTEMISIA. L Cao[1], D Zhou[1]; [1]Department of AIDS Prevention, Center of Disease Control, Wuhan, 430020 China.

To AIDS infected person without AIDS anti-virus treatment carries on the treatment with the Artemisia. The infected person usually changes better than before. The value of CD4+ number is risen. It is proved that Artemisia has the anti-AIDS virus's function.

W-3 EXPERIMENTAL HERPES SIMPLEX VIRUS-1 ENCEPHALITIS INDUCES NEURAL STEM CELL PROLIFERATION AND MIGRATION. MC Cheeran[1], S Hu[1], MR Little[1], M Erickson[1], JR Lokensgard[1]; [1]CIDMTR, Department of Medicine, University of Minnesota Medical School, Minneapolis, MN, 55455 USA.

Neurological deficits are common in patients surviving herpes encephalitis (HSE), which may in part be mediated by immune response to infection. Neural stem cells (NSCs) have been shown to respond to inflammatory cues, migrate to damaged sites, and differentiate into functional brain cells. But little is known about the response of NSCs to viral encephalitis. In this study, we found increased numbers of actively dividing BrdU-labeled cells in HSV-1 infected brains when compared to uninfected controls, particularly in the subventricular zone, a known NSC niche. To track NSC responses in vivo, NSCs derived from luciferase-transgenic mice were transplanted into the subventricular zone 5 d prior to intranasal HSV-1 infection. Luciferase activity from transplanted NSCs was 2-4 fold greater among infected animals during the first 3-12 dp.i and these increases declined thereafter. Interestingly, cranial bioluminescence was greater in the caudal third of the brain which was sustained up to 30 dp.i. NSC proliferation and migration during HSE correlated closely with changes in the neuroinflammatory response. In addition, infected brains showed signs of severe glial scarring at 30 dp.i. and preliminary studies have shown that pro-inflammatory cytokines drive NSC differentiation into astrocytes. Additional experiments are underway to determine if NSC responses in the HSV-1-infected brain are shaped by the inflammatory milieu. These studies will provide insights that may facilitate the development of novel therapies for the neurological deficits seen in the wake of viral encephalitis. Supported by MH-066703; AHC Faculty Development Grant, UMN

W-4 ROLE OF DRD3 IN ACUTE AMPHETAMINE-INDUCED IL-10 PRODUCTION USING DRD3-KNOCKOUT MICE. YJ Chen[1], JY Zhu[3], HB Zhang[2], SG Wei[2], CX Yan[2], HB Zheng[2], T Chen[2]; [1]Department of Immunology and Pathogenic Biology and [2]Department of Forensic Medicine, Xi'an Jiaotong University School of Medicine, Xi'an, 710061 China; [3]Mental Health, Xi'an Mental Health Hospital, Xi'an, 710077 China.

Objective: To study the effects of amphetamine (AM) administration on the production of interleukin-10 (IL-10) following an intraperitoneal injection (ip) of bacterial lipopolysaccharide (LPS; 150ug/kg) in mice and the role of dopamine D3 receptor involved in it. Methods: Dopamine D3 receptor knock-out mice (D3RKO) and wild type mice (C57BL/6J), both exhibited a similar genetic background, received either vehicle (saline) or AM (5 mg/kg ip) 10 min prior to LPS (150 ug/kg) in vivo immune challenge, were sacrificed 0, 30, 60, 90,120, or 240 min later by anesthetized with sodium pentobarbital. C57BL/6J and D3RKO mice received AM at different dose (0, 2, 5, 10 mg/kg) 10 min prior to either vehicle or LPS, and were sacrificed 60 min later. In anesthetized mice, blood was collected via cardiac puncture using a syringe without an anticoagulant. IL-10 of serum was measured by means of commercially available enzyme-linked immunosorbent assay. Results: Under the treatment of AM, the greatest effect was observed at 60 min after LPS challenge in both C57BL/6J and D3RKO mice. The administration of AM at dose of 5 mg/kg significantly increases LPS-induced IL-10 production in C57BL/6J mice, but significantly increases LPS-induced IL-10 production at dose of 2 mg/kg in D3RKO mice, versus other dose of AM ($P<0.05$). Conclusion: Our results showed that IL-10 plays a role in the immune suppression caused by AM. A smaller dose of AM increased IL-10 of D3RKO compared with wild type indicated that D3R mediates immune inhibition of AM. Supported by NSFC: 30572089; NCET-07-0662

W-5 MICROARRAY ANALYSIS OF LUNGS FROM INTRAVENOUS DRUG USERS WITH AND WITHOUT HIV INFECTION. N Dhillon[2], A O'Brien-Ladner[2], S Buch[2]; [1]Department of Physiology and [2]Department of Medicine, Division Pulmonary/Critical Care, University of Kansas Medical Center, Kansas City, KS, 66160 USA.

Rationale: HIV and Intravenous drug use (IVDU) has been associated with pulmonary arterial hypertension (PAH) independently or in combination. The extent and type of contribution each makes to the pathogenesis of PAH is not clearly understood. To obtain a better understanding of the interactions between HIV and IVDU that might result in - or the escalation of the development of PAH, we analyzed human lungs with and without HIV and/or IVDU history. Methods: We examined histology of human lung samples from normal (3), HIV (6), IVDU (3) and HIV/IVDU (6). Selected samples were then examined by microarray analysis. Results: HIV/IVDU group (4 of 6) showed signs of early pulmonary ateriopathy. Gene expression analysis by microarray of HIV+ IVDU vs. IVDU demonstrated significant up regulation of pro-inflammatory cytokines including IL-1β and IL-6. MCP-1, PDGF and HIF-1α, known to be involved in PAH, were also up regulated. Further, HIV+ IVDU lungs that had signs of early pulmonary arteriopathy demonstrated significant down-modulation of tight junction proteins (TJPs) such as claudin 3, claudin 4, ZO-1, ZO-3 and occludin when compared with IVDUs or HIV-infection alone. Conclusion: HIV infection appears to induce a unique inflammatory response in IVDU as compared to IVDU without HIV, particularly in regards to PDGF. The combination of HIV & IVDU results in additive loss of TJPs at the pulmonary endothelium and, most likely, contributes to the loss of vascular integrity in early PAH. Supported by Parker B. Francis Fellowship (ND), Lied Endowed Basic Science program (ND), DA020392-01(SB), Joseph A.Cates Foundation (AOL).

W-6 VECTOR-BASED GENERATION OF MONOCLONAL ANTIBODIES AGAINST THE CB2 RECEPTOR IN CB2-KO MICE. A Harui[1], N Buckley[2], SM Kiertscher[1], MD Roth[1]; [1]Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA, 90095-1690 USA, [2]Biological Sciences Department, California State Polytechnic University, Pomona, CA, 91768 USA.

High affinity monoclonal antibodies (mAb) against the human cannabinoid receptor 2 (CB2) would greatly facilitate studies into the biological effects of marijuana. We proposed that the use of CB2 knock out (CB2-KO) mice, which lack expression of functional CB2 protein, would facilitate generation of anti-CB2 mAb. However, a priming immunization with plasmids expressing CB2 (and CD40L) and boosting with a lentiviral vector expressing CB2 (LV-CB2), failed to induced anti-CB2 Ab. To assure that the immune cells in CB-2 KO mice were capable of functional Ab responses, CB2-KO and control mice were immunized twice with a control adenoviral vector (AdV) expressing

the Her2 antigen. Spleen cells and serum were collected for phenotyping and Ab detection. CB-2 KO mice exhibited normal spleen cell composition and produced anti-Her2 IgG and IgM Ab responses at levels equivalent to controls. We therefore tested several alternative vaccine strategies in a stepwise approach using combinations of plasmid, LV and AdV vectors expressing CB2. Primary immunization of CB2-KO mice with either plasmid-CB2 or LV-CB2, followed by boosting with AdV-CB2 failed to induce Ab responses. However, when AdV-CB2 was used for the priming immunization, followed by boosting with either AdV-CB2 or LV-CB2, anti-CB2 Ab responses were readily detected with the AdV-CB2/LV-CB2 prime/boost strategy producing the greatest response. Spleen cells from mice with CB2 Ab responses have been fused with myeloma cells and screening for positive mAb clones is in process. Supported by NIH/NIDA R21-DA021813.

W-7 INTERFERON LAMBDA INHIBITS HIV-1 INFECTION OF MACROPHAGES. W Hou[1], X Wang[2], L Ye[2], ZQ Yang[1], WZ Ho[2]; [1]State Key Laboratory of Virology, School of Medicine, Wuhan University, Wuhan, 430071 China; [2]Division of Allergy and Immunology, The Children's Hospital of Philadelphia, Philadelphia, PA, 19104 USA.

The newly identified type III interferon (IFN-Lambda) has antiviral activity against a broad spectrum of viruses. We thus examined whether IFN-Lambda has the ability to inhibit HIV-1 infection of blood monocyte-derived macrophages that expressed IFN-Lambda receptors. Both IFN-Lambda 1 and IFN-Lambda 2, when added to macrophage cultures, inhibited HIV-1 infection and replication. This IFN-Lambda-mediated anti-HIV-1 activity is broad, as IFN-Lambda could inhibit infection by both laboratory-adapted and clinical strains of HIV-1. Investigations of mechanism(s) responsible for the IFN-Lambda action showed that although IFN-Lambda had little effect on HIV-1 entry co-receptor CCR5 expression, IFN-Lambda induced the expression of CC-chemokines, the ligands for CCR5. In addition, IFN-Lambda up-regulated intracellular expression of type I IFNs and APOBEC3G/3F, the newly identified anti-HIV-1 cellular factors. These data provide direct and compelling evidence that IFN-Lambda, through both extracellular and intracellular antiviral mechanisms, inhibits HIV-1 replication in macrophages. These findings indicate that IFN-Lambda may have a therapeutic value in the treatment of HIV-1 infection. Supported by NIH DA012815 and DA022177

W-8 WIN55,212-2 INHIBITS RANTES/CCL5-INDUCED HUMAN MICROGLIA INTRACELLULAR CA2+ LEVELS AND MIGRATION. S Hu[1], K Cushman[2], WS Sheng[1], SA Thayer[2], PK Peterson[1], RB Rock[1]; [1]Center for Infectious Diseases and Microbiology Translational Research and [2]Department of Pharmacology, University of Minnesota Medical School, Minneapolis, MN, 55455 USA.

The beta-chemokine receptor CCR5, together with its ligand RANTES/CCL5, has been implicated in HIV neuropathogenesis. Previous studies have reported that calcium signaling is an important factor in the regulation of macrophage activation and migration. We have shown that RANTES/CCL5 induces an elevation in intracellular calcium concentration ([Ca2+]i) and stimulates migration of human microglia. Here, we examined whether this migratory activity is dependent on [Ca2+]i mobilization and tested the hypothesis that WIN 55,212 (WIN-2), a synthetic CB(1)/CB(2) agonist, would alter the activation of Ca2+ signaling and inhibit migration of microglial cells towards RANTES/CCL5. Using indo-1-based microfluorimetry, we found that treatment of microglia with WIN-2 (10-6 M) potently inhibited RANTES/CCL5-induced increase in [Ca2+]i . In addition, treatment of microglial cells with WIN-2 (3 x 10-8 to 3 x 10-6 M) was also found to suppress directed migration towards RANTES/CCL5. The inhibitory effects of WIN-2 were blocked by the CB2-specific antagonist SR144528, while the CB1 receptor-specific antagonist SR141716A displayed minimal effect. Taken together, these data suggest that WIN-2 mediates its suppressive effect on [Ca2+]i mobilization and migration of microglial cells through the CB2 receptor. Supported by NIH/NIDA DA025525.

W-9 MIR-142-3P RESTRICTS CAMP PRODUCTION IN CD4+CD25- T CELLS AND CD4+CD25+ TREG CELLS BY TARGETING ADENYLYL CYCLASE 9 MRNA. BO Huang[1]; [1]Department of Biochemistry and Molecular Biology, Tongji Medical College, Wuhan, 430030 China.

Cyclic adenosine monophosphate (cAMP) is a ubiquitous intracellular second messenger regulating diverse cellular functions. It has been found that CD4+CD25+ T regulatory (Treg) cells exert their suppressor function by transferring cAMP to responder T cells. Here, we show that miR-142-3p regulates the production of cAMP by targeting adenylyl cyclase (AC) 9 mRNA in

CD4+CD25- T cells and CD4+CD25+ Treg cells. miR-142-3p limits cAMP level in CD4+CD25- T cells by inhibiting AC9 production, whereas Foxp3 downregulates miR-142-3p to keep AC9/cAMP pathway active in CD4+CD25+ Treg cells. These findings disclose a novel molecular mechanism through which CD4+CD25+ Treg cells harbor high level of cAMP for their suppressor function, and also suggest that the microRNA controlling AC expression may restrict the final level of cAMP in different types of cells.

W-10 TOXICOLOGY PROFILES AND BLOOD-BRAIN BARRIER PENETRANCE OF MONOCYTE-MACROPHAGE CARRYING NANOFORMULATED ANTIRETROVIRAL DRUGS. GD Kanmogne[1], D. Barnes[1], A. Nowacek[1], B. Rabinow[2], H. Gendelman[1], S. Singh[1]; [1]Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE, 68198-5215 USA; [2]Global Research and Development, Baxter Healthcare, Chicago, IL, 60015-4625 USA.

A limitation of antiretroviral therapies (ART) reflects its pharmacokinetics, toxicity profiles, and eradication of virus from hidden sanctuaries including that of the central nervous system (CNS). We reasoned that one means to bypass these limitations was through the creation of drug-encapsulated nanoparticles (NP) that could be taken up by immunocytes and travel to sites of active viral replication including the CNS. To this end, our laboratories developed ART NP that are rapidly taken up by human monocytes and monocyte-derived macrophages (MDM) then enabling drug release into tissue and blood. What remain poorly understood are the functional consequences of this therapy to cells and tissue. Thus, our objectives were to assess the nanotoxicity of monocytes and MDM following loading with NP-coated indinavir (NP-IDV) and ritonavir (NP-RTV), and their modulation of the blood-brain barrier (BBB) function and integrity. Using 3 NP-IDV and NP-RTV formulations, we now show that drug uptake was dose-dependent and influenced by the NP surfactant type. NP-IDV and NP-RTV uptake slightly reduced monocyte and MDM viability, and altered cell adhesion and transendothelial migration. The data caution the need for proper dosage and surfactant constituent for NP-IDV and NP-RTV for monocyte and MDM loading in order to optimize pharmacokinetics for cell-based NP drug delivery. All together seeking optimal dosage and surfactants can minimize toxicity and improve NP uptake and tissue distribution for clinical use. (Dr. Kanmogne is both presenting and senior author). Supported by NIH: NINDS / Grant: 2PO1 NS043985.

W-11 MUTANT HTT CAUSES ENDOPLASMIC RETICULUM STRESS THROUGH OXIDATIVE STRESS AND DISTURBANCE OF INTRACELLUAR CALCIUM. H Li[1], Y Jiang[1], H Tan[1]; [1]Division of Histology & Embryology, Department of Anatomy, Tongji Medical College, Huazhong University of Science & Technology, Wuhan, 430030 China.

Huntington's disease (HD) is caused by expansion of a polyglutamine repeat in the amino-terminal region of huntingtin (Htt) protein. Polyglutamine expansion causes the mutant Htt to accumulate and aggregate in the nuclei and cytoplasm of neurons. Accumulation of unfolded and malfolded proteins induces endoplasmic reticulum (ER) stress (ERS), activating caspase-12 located on the ER, finally causing apoptosis. Little is known about the relationship between ERS and mutant Htt. Here, we analyzed the role of the ERS in cellular toxicity of mutant huntingtin. In neuroblastoma (N2a) cells, transfected mutant Htt induced upregulation of glucose-regulated protein 78 (GRP78), the chaperone that increases protein folding in the ER lumen, and activation of caspase-12. In HD transgenic mouse brain and N2a cells expressing mutant Htt, GRP78 was found to be colocalized with the aggregates of mutant Htt. Over-expression of GRP78 could inhibit formation of mutant Htt aggregates, reducing activation of caspase-12 and increasing cell viability, whereas silence of GRP78 by SiRNA promoted formation of mutant Htt aggregates, elevating activation of caspase-12 and enhancing the decrease in cell viability. Moreover, it was found that mutant Htt-induced upregulation of GRP78 and activation of caspase-12 could be significantly diminished by edaravone, a potent scavenger of free radicals, and by X2628, a blocker of IP3R which mediates Ca2+ release from ER. Thus, mutant Htt could stimulate ERS through inducing oxidative stress and Ca2+ release from ER, which may be involved in neurodegeneration in HD. Supported by National Natural Science Foundation of China (30430260).

W-12 PREVALENCE OF DRUG RESISTANT GENOTYPE AMONG THERAPY-NAÏVE PATIENTS OF HIV-1 INFECTION IN WUHAN , CHINA. T Li[1]; [1]Division of Virology, Wuhan Centres for Disease Prevention & Control, Wuhan, 430022 China; [2]Division of Virology and Immunology, National Center for AIDS/STD Control and Prevention, Beijing, 100050 China.

Highly active antiretroviral therapy (HAART) has dramatically reduced AIDS-related morbidity and mortality, but the drug resistant mutations have emerged due to highly divergence of HIV and selective pressure of antiretroviral therapy “ART” drugs. ART is widely employed in China since 2003. To better understand the prevalence of drug resistance before ART, we collected 74 plasma specimens of therapy-naïve patients in Wuhan urban area. The HIV viral RNA were extracted and the pol (PR and RT) gene were amplified by RT-PCR. The sequences were analyzed with HIV drug resistance database of Stanford University. The distribution of the most common resistance mutations was as follows: The mutations associated with nucleoside reverse transcriptase inhibitor (NRTI) is 5.4% (4/74), include K70N, L210F, L210V; with nonnucleoside reverse transcriptase inhibitor (NNRTI) is 9.5% (7/74), include L100I/L/V, K101K/N, V106L, V179D, V179T, P225S, P236S; with protease inhibitor (PI) is 20.3% (15/74), include L10V, L10I, V32L, L33F, A71V, A71T, N83D, but the major resistance associated with PI has only one (V32L). The drug resistant mutations ratio is low among the therapy-naïve patients in Wuhan urban area. Most available antiretroviral drugs are susceptible, but potential mutations are still exist. We will strength the testing of drug resistance mutations before and after ART.

W-13 NOVEL MECHANISM OF NMDA RECEPTOR ACTIVATION BY HIV-1 TAT PROTEIN. W Li[1], Y Huang[1], R Reid[1], J Steiner[1], T Malpica-llanos[1], T Darden[2], S Shankar[3], A Mahadevan[3], P Satishchandra[3], A Nath[1]; [1]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, 21287 USA; [2]Laboratory of Structural Biology, National Institute of Environmental Health Science, Research Triangle Park, NC, 27709 USA; [3]Departments of Neuropathology and Neurology, National Institute of Mental Health and Neuroscience, Bangalore, 560029 India.

Objective: To determine the molecular determinants of Human Immunodeficiency Virus-1 (HIV-1) Tat protein in the interaction with N-methyl D-aspartate (NDMA) receptor. Methods: Human embryonic kidney (HEK) 293 cells expressing NMDA receptor subunits NR1 and NR2A were used to study the activation of NMDA receptor and excitotoxicity mediated by HIV-1 Tat protein. Clade C Tat genes were cloned from the brain tissues of HIV-1 infected patients by nested PCR. Mutagenesis and structural modeling were used to study the role of Cys31 of Tat and Cys744 of NR1 in Tat-NMDA receptor interaction. Results: We demonstrated that Tat can be secreted into the culture supernatant to a concentration of 0.5ng/ml. Tat in supernatant binds directly to the NMDA receptor and is more potent than recombinant Tat protein in inducing excitotoxicity. To further dissect the mechanisms by which Tat activates the NMDA receptor, we modified Cys-rich domain of Tat and found its modification abolished Tat-NMDA receptor interaction. Most importantly, we found that clade C Tat variants with Cys31Ser mutation have a significantly attenuated excitotoxic response via NMDA receptor, indicating the critical role of Cys31 in Tat-NMDA receptor interaction. Our structural modeling suggests that Cys31 of Tat may form an inter-molecular disulfide bond with Cys744 of NR1 and disrupt the intra-molecular disulfide bond between Cys744 and Cys798, which is important for redox regulation of the receptor activation. By mutagenesis, we confirmed that Cys744Ala mutation of NR1, which abolishes the potential formation of Cys31-Cys744 disulfide bond, significantly attenuates Tat-NMDA receptor interaction and excitotoxicity of Tat. Conclusion: NMDA receptor can be activated by disruption of Cys744-Cys798 disulfide bond by HIV-1 Tat protein, suggesting a novel mechanism of NMDA receptor activation. Supported by NIH R01NS039253.

W-14 COMPLICATED PATTERN OF HIV-1 EVOLUTION AMONG DRUG ABUSERS AND SEXUALLY ACQUIRED CASES IN DEHONG, YUNAN PROVINCE, CHINA. L Liu[1], H Wang[1], L Lu[2], M Jia[2], Y Ma[2], Y Zhang[2], Z Chen[1]; [1]AIDS Institute, Li Ka Shing Faculty of Med., University of Hong Kong, Hong Kong, China; [2]Yunnan Center, Center for Disease Control and Prevention, Kunming, 650022 China.

The HIV-1 epidemic in China is rapidly increasing at an irrepressible rate. The first HIV-1 epidemic was found in Dehong in 1989 among injection drug users (IDUs). This study is designed to investigate the viral revolution and genetic structures of HIV-1 strains in the region. Reverse transcription polymerase chain reaction was used to amplify p17 and RT gene from patient’s serum. Among the total of 23 samples collected, 8 samples (34.8%) were from IDUs, 8 samples

(34.8%) from sexually acquired cases, and 7 samples (30.4%) from unknown risk factors cases. p17 and 413-bp RT fragments were obtained from all study subjects, whereas a 1049-bp RT fragment was from 9 individuals. Phylogenetic and recombination analysis of these sequences suggests that 10 patients (43.5%) harbored multiple new recombinant HIV-1 virus that are distinct from one another, including 2 CRF01_AE/C and 8 CRF01_B/C recombinant virus. Those new recombinant virus were from 37.5% (3/8) sexually acquired cases, 44.4% (4/9) IDUs, and 42.8% (3/7) unknown risk factors cases, respectively. The other 13 patients (56.5%) harbored CRF01_AE (7/23), subtype C (4/23), and CRF01_C/B (2/23), which were similar to those previously identified. This is the first report that multiple divers new recombination HIV-1 are arising not only among IDUs but also sexually acquired cases in Dehong. The emergence of the new generation of recombinants among sexually acquired cases may further complicate the HIV-1 epidemic among general Chinese population, and the development of effective vaccines to prevent the HIV-1 epidemic in China.

W-15 MOLECULAR EPIDEMIOLOGY OF HUMAN ASTROVIRUS INFECTIONS IN WUHAN, CHINA. MQ Liu[1], YH Wang[1], JS Peng[1], L Tang[1], Y Zhou[1], X Zhou[1], R Zhao[2], N Kobayashi[3]; [1]Department of Virology, Wuhan Centers for Disease Prevention & Control, Wuhan, 430015 China; [2]Department of Pathogen Biology, Huazhong University of Science and Technology, Wuhan, 430030 China; [3]Department of Hygiene, Sapporo Medical University School of Medicine, Sapporo, 060-8556 Japan.

Human Astrovirus (HAstV) is thought to be an important cause for viral gastroenteritis in young children after rotavirus. Between July 2007 and August 2008, we had collected stool specimens from 361 children and 301 adults with diarrhea visited to three important hospitals in Wuhan city. Of which, there are 49 (13.6%) in children and 7 (2.3%) in adults positive respectively for astrovirus RNA. Compared to the astrovirus infection rate (33/335, 9.87%) in 2004.6~2005.5 (J Clin Microbiol, 2007, 45:1308-9), there is no significant difference of infection rate in children between these two years. However, July is the highest incidence of astrovirus infection (16/30, 53%) in children, and there is no significant peak to be found in other months, it is difficult to explain this interesting finding. After RT-PCR and sequencing with primer pairs (Mon269/270), 51-astrovirus-positive samples could be classified into genotype 1, and no other genotypes was found. Sequence analysis of 348-bp in ORF2 could find that all of the astroviruses identified in this study showed very little or almost no divergence among themselves. Although all of strains in this study and most of strain in 2004/2005 can be classed into HAstV-1b lineage, they represent two different groups perspicuously. Our data clearly indicate that longtime monitor for astrovirus infection is important for this virus' prevention and control.

W-16 DEVELOPMENT OF MULTIFUNCTIONAL MAGNETIC NANOCARRIER FOR DRUG TARGETING TO BRAIN. MP Nair[1], NH Gandhi[1], ZM Saiyed[1]; [1]Department of Immunology, College of Medicine, Florida International University, Miami, FL, 33199 USA.
(Abstract not available online)

W-17 USE OF COCAINE AND CANABINOID RESULTS IN ALTERED PATTERNS OF HIV-1 LTR TRANSCRIPTION FACTOR BINDING SITE CONSERVATION DURING HIV DISEASE. MR Nonnemacher[1], E Kilareski[1], B Aiamkitsumrit[1], N Parikh[1], BP Irish[1], S Lewis[2], J Jacobson[2], B Wigdahl[1]; [1]Department of Microbiology and Immunology, and [2]Division of Infectious Disease and HIV Medicine, Drexel University College of Medicine, Philadelphia, PA, 19102 USA.

The human immunodeficiency virus type 1 (HIV-1) long terminal repeat (LTR) serves a number of critical functions in viral replication, one of which involves regulating the transcriptional activity of the integrated provirus. We have previously demonstrated that sequence variation at HIV-1 LTR C/EBP site I and Sp site III revealed sequence configurations that were found to increase in prevalence with disease severity and correlate with HIV-associated dementia (HAD). In contrast, LTR NF-κB sites I and II were highly conserved regardless of disease severity. Previous studies have demonstrated that substances of abuse modify HIV disease by altering the activation state of infected cells resulting in compromise of the immune system, thereby affecting viral replication. This in turn impacts the selection of viral quasispecies within a given patient. In conjunction with our ongoing analysis of the HIV-1 LTR ATF/CREB, C/EBP, NF-κB, and Sp transcription factor binding sites for specific genotypic variants that correlate with disease progression in the DREXELMED HIV-1 cohort, we have also characterized these sequence variations to determine if

use of drugs of abuse (specifically cocaine and canabinoids) impact the genotypic variants observed within these sites in LTRs isolated from patients in late stages of disease. To date, results have shown that use of either substance results in an overall decreased binding site conservation however, each binding site revealed a unique pattern of conservation relevant to the subtype B consensus sequence. Supported by DA019807, NS046263.

W-18 HIV-1-INFECTED AND/OR IMMUNE-ACTIVATED MACROPHAGES AFFECT HUMAN FETAL CORTICAL NEURAL PROGENITOR CELL DIFFERENTIATION THROUGH THE STAT3 PATHWAY. H Peng[1], Y Wu[1], J Zheng[1]; [1]Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE, 68198-5880 USA.

Active neurogenesis occurs throughout life and relies upon the proliferation, migration and proper differentiation of neural stem/progenitor cells (NPCs). Diminished adult neurogenesis is considered a potential mechanism in the pathogenesis of HIV-1-associated dementia (HAD). We previously demonstrated HIV-1-infected and activated monocyte-derived macrophages (MDM) inhibit NPC neurogenesis, while enhancing astrogliogenesis through the secretion of the inflammatory cytokine TNF-a. Here we test the hypothesis that HIV-1-infected/activated MDM-secreted TNF-α promotes NPC astrogliogenesis via activation of the transcription factor STAT3, a critical factor for astrogliogenesis. We show that LPS-activated MDM-conditioned medium (LPS-MCM) and HIV-infected/LPS-activated MDM-conditioned medium (HIV/LPS-MCM) decreased β-III-tubulin and increased glia fibrillary acidic protein (GFAP) expression, demonstrating an inhibition of neurogenesis and an induction of astrogliogenesis. Interestingly, the induction of NPC astrogliogenesis correlated to STAT3 activation. Moreover, LPS-MCM- and HIV/LPS-MCM-induced NPC astrogliogenesis and STAT3 activation were partially abrogated by soluble TNF-α receptors. Furthermore, STAT3-targeting siRNA decreased TNF-α-induced NPC astrogliogenesis. In conclusion, these observations demonstrate that HIV-1-infected/activated MDM-secreted TNF-α induces NPC astrogliogenesis through the STAT3 pathway. This study generates important data elucidating the role of brain inflammation in neurogenesis and may provide insight into new therapeutic strategies for HAD. Supported by NIHR01 NS 41858, P20 RR15635 and P01 NS043985.

W-19 GENETIC VARIATION OF HEPATITIS C VIRUS IN A COHORT OF INJECTION HEROIN USERS IN WUHAN, CHINA. JS Peng[1], X Wang[3], MQ Liu[1], DJ Zhou[1], J Gong[1], HM Xu[2], JP Chen[2], HH Zhu[1], W Zhou[1], WZ Ho[3]; [1]Wuhan Centers for Disease Control and Prevention, Wuhan, 430022 China; [2]Wuhan Psychiatric Health Center, Wuhan, 430030 China; [3]Division of Allergy & Immunology, Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, PA, 19104 USA.

Since the majority of heroin abusers use injection as the primary route of admission, heroin abuse contributes significantly to the transmission of hepatitis C virus (HCV). We determined HCV infection and its genotype distribution among injection heroin users in Wuhan, the largest city in the central China. Eight hundred seventy-eight (84%) out of 1046 serum specimens from the injection drug users were positive for HCV antibody. Out of randomly selected 122 specimens positive for HCV antibody, seventy-eight (64%) had detectable HCV RNA with genotype 6a as the predominant strain (50%), followed by 3b (32.2%), 1a (8.1%), 1b (6.5%), and 3a (3.2%). HCV RNA levels in male heroin users were significantly higher ($P = 0.013$) than those in the female subjects. Although there was no significant difference in HCV RNA levels among the specimens positive for HCV 6a and 1a/1b, the samples with 6a or 1a/1b contained higher levels of HCV RNA than the specimens positive for HCV 3b ($P = 0.019$, $P = 0.012$, respectively). These findings indicate that there is a high prevalence of HCV infection with genotypes 6a and 3b as predominated strains among injection heroin users in Wuhan, China. Supported by DA 12815 and DA 22177.

W-20 MICROARRAY ANALYSIS OF CELLULAR AND MOLECULAR BASIS OF METHAMPHETAMINE-INDUCED T CELL DYSFUNCTION. R Potula[1], MR Brodie[3], F Yu[3], B Morsey[3], H Dykstra[1], Y Persidsky[1]; [1]Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA, 19140 USA; [2]Pharmacology and Experimental Neuroscience and [3]Department of Biostatistics, University of Nebraska Medical Medical Center, Omaha, 68198 NE.

Methamphetamine (METH) abuse is implicated in immune deregulation, however little is known about the underlying molecular mechanism ensuing to altered T cell immune response. Recent studies have enumerated the deleterious effects of METH on various components of the complex

immune system either by enhancing or suppressing the functions of distinct immune cell types. Since T cells play a critical role in regulation of immune homeostasis, we applied a DNA microarray analysis to identify the affected genes in T cells exposed to METH. Gene expression profiles of purified (negative selection) human pan T cells treated with METH at resting or activated (anti-CD3/CD28) were compared with those of controls using Phalanx Human Whole Genome DNA Microarray. Differentially expressed genes were identified by linear modeling and grouped by a hierarchical clustering algorithm. A total of 163 genes were significantly differentially expressed (>1.5-fold change; P <0.01) in T cells exposed to METH as compared to controls. Functional profiling of modulated genes showed prominent transcript changes in categories pertaining to regulation of cell signaling (AKT3), proliferation and differentiation (DUSP4, PTPRD), cell-mediated immune responses (GZMB), transcriptional co-activation (NCOA1) and MAPK signaling (MAP3K4, RAC1). Top canonical pathways significantly affected included TR/RXR activation, Pro-Apoptosis, RAR activation, p53 signaling and G-protein coupled receptor signaling. Molecular and functional studies to confirm and extend the microarray findings are being performed. Supported by NIDA/R21 DA0249791.

W-21 HEPCIDIN AND IRON-ASSOCIATED NEURODEGENERATIVE DISORDERS. ZM Qian[1], Y Ke[2]; [1]Laboratory of Brain Iron Metabolism, Hong Kong Polytechnic University, Hong Kong, China; [2]Department of Physiology, The Chinese University of Hong Kong Medical School, Hong Kong, China.

Owing to the significant role of brain iron misregulation or increased brain iron in the pathogenesis of neurodegenerative disorders and the significant contribution of iron-mediated free radicals in the development of these disorders, the application of chelator (iron depletion) and direct or indirect antioxidant treatment may be useful therapeutic approaches in clinic if these agents can cross the blood-brain barrier. Recent studies including ours demonstrated that the brain has the ability to express hepcidin. Accumulated data showed that the iron regulatory hormone may also be a central player in brain iron homeostasis, playing an essential role in the communication of brain iron stores and utilization to the blood-brain barrier and in the regulation of iron transport in neurons, one of the major sites of iron utilization in the brain. Our recent findings showed that ventricle injection of hepcidin or “recombinated-hepcidin-adenovirus [rHP Adenovirus]” induces a significant decrease in iron level of four brain regions (cortex, hippocampus, striatum and substantia nigra) of rats pre-treated with a high iron diet. Smilar findings were also obtained by injection (i.v.) of “OX26-Hepcidin” (OX26: a monoclonal antibody to transferrin receptor). These results support the viewpoint that hepcidin does have a central role in brain iron metabolism and imply that it is possible to develop a novel therapeutic approach with this peptide to effectively prevent and ameliorate iron-associated neurodegenerative disorders by disrupting the chain of pathological events induced by increas Supported by HKRGC (CUHK466907-KY), JSNSF (05-BK2005430 & 04KJB310113), DG of CUHK (A/C: 4450226-KY and 4450273-KY), SZ-HK ICP.

W-22 WIN55,212-2 PROTECTS HUMAN DOPAMINERGIC NEURONS AGAINST GP120-INDUCED DAMAGE. RB Rock[1], S Hu[1], W Sheng[1], PK Peterson[1]; [1]Center for Infectious Diseases and Microbiology Translational Research, University of Minnesota, Minneapolis, MN, 55455 USA.

Despite the therapeutic impact of anti-retroviral therapy (ART), HIV-1-associated dementia (HAD) remains a serious threat to AIDS patients, and there currently remains no specific therapy for the neurological manifestations of HIV-1. Based upon recent work that the nigrostriatal dopaminergic area is a critical brain region for the neuronal dysfunction and death seen in HAD, that synthetic cannabinoids inhibit HIV-1 expression in human microglia and suppress production of inflammatory mediators in human astrocytes, as well as a substantial literature demonstrating neuroprotective properties of cannabinoids in other systems, experiments were designed to test the hypothesis that synthetic cannabinoids will protect dopaminergic neurons against the toxic effects of the HIV-1 protein gp120. Using a human midbrain cell culture model, which contains dopaminergic neurons, microglia, and astrocytes, experiments were performed to characterize the damage to dopaminergic neurons induced by gp120 by assessing functional impairment as measured by dopamine uptake, and to investigate neurotoxicity by assessing apoptosis and oxidative damage. By using this midbrain culture model, we were able to identify the relative sensitivity of dopaminergic neurons to gp120-induced damage, evaluate the extent of neuronal damage, and also show that CB1/CB2 agonist WIN55,212-2 blunts the gp120-induced neuronal damage. Supported by NIH/NIDA DA025525.

W-23 IMPACT OF MARIJUANA SMOKING ON THE IMMUNE RESPONSE TO HEPATITIS B VACCINATION. MD Roth[1], DP Tashkin[1], G Ibrahim[1], SM Kiertscher[1]; [1]Division of Pulmonary & Critical Care, David Geffen School of Medicine at UCLA, Los Angeles, CA, 90095-1690 US.

Tetrahydrocannabinol (THC) has potent immunosuppressive effects on dendritic cells and T cells in vitro. Alveolar macrophages from the lungs of marijuana smokers are also impaired in their ability to produce nitric oxide and kill bacteria. However, direct evidence linking marijuana smoking to impaired systemic immunity in humans is lacking. We therefore designed a prospective study where control subjects and habitual marijuana smokers, all naïve to hepatitis B (HepB), are vaccinated 3 times with a HepB vaccine. Marijuana smokers are exposed to marijuana under close observation on the day of each vaccination (four marijuana cigarettes, 3.75-3.95% THC, over 24 hrs) and serum collected to assess THC exposure levels. Vaccine induced changes in HepB antibody are assessed by commercial ELISA. HepB-specific T cell responses are monitored by serial blood samples collected before/after each vaccination. Dendritic cells are generated from each patient, cultured with/without recombinant HepB antigen, and used to assess the frequency of HepB-specific T cell proliferation (by CFSE dye dilution) and cytokine production (by intracellular cytokine assays). Three control subjects and one marijuana smoker have been enrolled to date. Control subjects develop HepB-specific T cell proliferation and IFN-g production that starts after the 2nd vaccination and increases dramatically after the 3rd, associated with a CD4 effector-memory phenotype. Responses in our marijuana smoker are pending. This approach should accurately assess the clinical impact of marijuana smoking on human adaptive immunity. Supported by NIDA/NIH #RO1-DA03018.

W-24 HEME OXYGENASE-1 REGULATION OF INFLAMMATORY MEDIATORS FROM IL-1-BETA-ACTIVATED HUMAN ASTROCYTES. W Sheng[1], S Hu[1], PK Peterson[1], RB Rock[1]; [1]CIDMTR, Department of Medicine, University of Minnesota Medical School , Minneapolis, MN, 55455 USA.

Heme oxygenase (HO)-1 has been shown to attenuate oxidative injury and reduce apoptosis. HO-1 can be induced by various stimuli such as nitric oxide (NO) or heme, released during cellular injury. Deleterious free heme is degraded by HO-1 to carbon monoxide, iron and biliverdin, which are potently anti-oxidant and anti-inflammatory. In this study, we sought to investigate the role of HO-1 in interlukin (IL)-1beta-activated human astrocytes. We used hemin (a component of hemoglobin) as an HO-1 inducer and tin protoporphyrin (SnPP) IX as an inhibitor of HO-1 activity. We have previously reported that astrocytes produce many inflammatory mediators such as NO, cytokines and chemokines when stimulated by IL-1beta. Although IL-1beta treatment alone induced undetectable amounts of HO-1 protein, HO-1 mRNA expression was upregulated. Pretreatment with hemin alone substantially induced both HO-1 mRNA and protein expression, and HO-1 mRNA expression was further enhanced when combined with IL-1beta treatment. On the contrary, IL-1beta-induced NO production was markedly inhibited by hemin. When pretreated with SnPP, the inhibitory effect of hemin on IL-1beta-induced NO production was blocked, suggesting the involvement of HO-1. Pretreatment with hemin also downregulated IL-1beta-induced cytokine and chemokine expression and SnPP attenuated hemin's inhibitory effect. These findings suggest that upregulation of HO-1 is beneficial as anti-inflammatory agent under pathological conditions. Supported by NIH/NIDA - DA025525.

W-25 EFFECTS OF STRESS ON DECISION-MAKING PERFORMANCE IN HEROIN ADDICTS. J Shi[1], XL Zhang[1], L Lu[1]; [1]National Institute on Drug Dependence, Peking University, Beijing, 100191 China.

Aims: Evidences from clinical studies indicate that the craving on drug in addicts is not under control of self-consciousness, although the physiological withdrawal symptoms disappeared for months or years. The deficient impulse control and impaired impulsive behaviors has been suggested to contribute to the occurrence of relapse in detoxified drug abusers. **Methods:** In the present study, we used Iowa Gambling Task (IGT) to assess decision-making performance in chronic heroin addicts. The subjects provided written informed consent before testing. All subjects were 20 to 45 years old and with a DSM-IV diagnosis of substance dependence to opiates. The subjects who had been abstinent from heroin for 3d, 7d, 15d, 1m, 3m, 6m, 1y, 2y were given decision-making performance test. The subjects who had been abstinent from heroin for 15d, 1m, 3m, 1y, 2y were given stress challenge and decision-making performance test. **Results:** We found that in contrast to long-term abstinent heroin users (3m, 6m, 1y), the short-term abstinent heroin

users (3d, 7d, 15d) had higher impulsive choice. The 2y group had recovered to the normal decision-making performance, but after stress challenge they had higher impulsive choice in contrast to normal control. **Conclusions:** The present study displays the decision-making performance in heroin addicts depend the abstinent time and stress increase decision-making performance in heroin addicts. The neural mechanisms underlying the change in decision-making performance of heroin addicts need to be explored deeply.

W-26 CAVEOLAE-ASSOCIATED SIGNALING MECHANISMS IN HIV-1-INDUCED DISRUPTION OF THE BLOOD BRAIN BARRIER. M Toborek[1]; [1]Department of Neurosurgery, University of Kentucky Medical Center, Lexington, KY, 40536 USA.

The mechanisms involved in disruption of the blood-brain barrier (BBB) in HIV-1 infection are poorly understood. We propose that caveolae provide the signaling platform, which regulates vascular toxicity of HIV-1. Treatment with HIV-1 protein Tat activated the caveolae-associated Ras pathway in human brain microvascular brain endothelial cells (HBMEC). Indeed, exposure to Tat resulted in a rapid and time-dependent increase in GTP-Ras. These effects were observed after a 3 min exposure and returned to the control levels in cells exposed to Tat for 30 min. These effects are specific because treatment with negative controls, such as bovine serum albumin or immunoabsorbed Tat, did not alter GTP-Ras levels in HBMEC. The effects of Tat on GTP-Ras levels were dose-dependent and a marked increase was observed in HBMEC exposed to 20 nM Tat. Tat-mediated upregulation of Ras was markedly attenuated by silencing of caveolin-1, a regulatory protein present in caveolae. Interestingly, exposure to Tat diminished the expression of several tight junction proteins, namely, occludin, zonula occludens (ZO)-1, and ZO-2 in the caveolar fraction of HBMEC. These effects were effectively protected by pharmacological inhibition of the Ras signaling and by silencing of caveolin-1. The present data indicate the importance of the Ras and Rho signaling in disruption of the integrity of the BBB in response to Tat exposure. They also demonstrate that caveolin-1 and PPARs may constitute critical modulators that control signaling pathways leading to the disruption of tight junction proteins. Supported by MH63022, MH072567, and NS39254.

W-27 HIV-TAT-ACTIVATED T CELLS INHIBIT NEUROGENESIS THROUGH RELEASE OF GRANZYME B. T Wang[1], T Johnson[1], PA Calabresi[1], A Nath[1]; [1]Department of Neurology, Johns Hopkins University, Baltimore, MD 21287 USA.

T cells invade the brain in HIV-infected patients on antiretroviral therapy (ART) resulting in an Immune Reconstitution Syndrome which over a period of months causes profound cerebral atrophy presumably from lack of regeneration within the brain. Currently available ART has no effect on Tat production from HIV-infected cells, hence we first determined if Tat could activate T cells and if the activated T cells could impact neurogenesis. Tat-treated uninfected human lymphocytes released granzyme B (GB), TNF-alpha, IL-1, IL-10 and IFN-gamma but had decreased production of IL-3 and IL-4. The culture supernatants (sups) from Tat-treated primary human T cells caused decreased proliferation of cultured human fetal neural progenitor cells (NPC) as determined by BrdU incorporation in these cells. Neuronal differentiation was also impaired as determined by immunostaining for beta-III-tubulin positive neurons while there was an increase in differentiation to astrocytes. These effects on NPC could be blocked by immunodepletion of GB from the sups and could be replicated by the use of recombinant GB. Furthermore, GB treatment of human microglia caused a time and dosage dependent increase of vascular endothelial growth factor which may cause damage to blood-brain barrier and recruit secondary inflammatory attack. Thus HIV-Tat is sufficient to cause T cells activation and the subsequent NPC dysfunction via the release of GB either through direct interactions with NPC or via interactions with microglia. Supported by Johns Hopkins NIMH NeuroAIDS center.

W-28 CELLULAR MICRORNA EXPRESSION CORRELATES WITH SUSCEPTIBILITY OF MONOCYTES/ MACROPHAGES TO HIV-1 INFECTION. X Wang[1], L Ye[1], W Hou[1], Y Zhou[1], YJ Wang[1], DS Metzger[2], WZ Ho[1]; [1]Division of Allergy & Immunology, The Children's Hospital of Philadelphia and [2]Department of Psychiatry, The Center for Studies of Addiction, University of Pennsylvania School of Medicine, Philadelphia, PA, 19104 USA.

Although both monocytes and macrophages possess essential requirements for HIV-1 entry, peripheral blood monocytes are infrequently infected with HIV-1 *in vivo* and *in vitro*. In contrast, tissue macrophages and monocyte-derived macrophages *in vitro* are highly susceptible to infection

with HIV-1 R5 tropic strains. We investigated intracellular anti-HIV-1 factors that contribute to differential susceptibility of monocytes/macrophages to HIV-1 infection. Freshly isolated monocytes from peripheral blood had significantly higher levels of the anti-HIV-1 microRNAs (miRNA, miRNA-28, miRNA-150, miRNA-223, and miRNA-382) than monocyte-derived macrophages. The suppression of these anti-HIV-1 miRNAs in monocytes facilitates HIV-1 infectivity, while increase of the anti-HIV-1 miRNA expression in macrophages inhibited HIV-1 replication. These findings provide compelling and direct evidence at the molecular level to support the notion that intracellular anti-HIV-1 miRNA-mediated innate immunity may have a key role in protecting monocytes/macrophages from HIV-1 infection. Supported by NIH, DA012815 and DA022177.

W-29 OPIOIDS INHIBIT INTRACELLULAR ANTI-HIV-1 MICRORNA EXPRESSION AND POTENTIATES HIV INFECTION OF PERIPHERAL BLOOD MONOCYTES. X Wang[1], Y Zhou[2], MQ Liu[2], L Ye[2], E Riedel[1], DJ Zhou[2], WZ Ho[1]; [1]Division of Allergy and Immunology, The Children's Hospital of Philadelphia, University of Pennsylvania, School of Medicine, Philadelphia, PA, USA 19104; [2]Division of Virology, Wuhan Center for Disease Prevention and Control, Wuhan, 430015 China.

Our recent study (Blood. 2009 113:671-4) demonstrated that freshly isolated monocytes from human blood expressed significantly higher levels of cellular anti-HIV microRNAs (miRNAs, miRNA-28, 125b, 150, and 382) than donor-matched macrophages. This observation can explain why peripheral blood monocytes are refractory to HIV infection in both *in vitro* and *in vivo*. In this study, we investigated effect of morphine on the expression of cellular anti-HIV miRNA in monocytes and macrophages. We found that morphine-treated monocytes and macrophages expressed lower levels of anti-HIV miRNAs than untreated cells. This finding is in parallel with the observation that when exposed to morphine, either *ex vivo* or *in vitro* monocytes became more susceptible to HIV infection than unexposed cells. The morphine actions on the miRNAs and HIV could be reversed by Naltrexone or CTAP. More importantly, our *in vitro* observation of the morphine action on the miRNAs was confirmed by the in vivo finding that heroin-dependant subjects had significantly lower levels of anti-HIV miRNAs (miRNA-28, 125b, and 150) in PBMC and macrophages than normal subjects. In addition, morphine impaired the ability of monocyte and macrophages to express type I interferons (IFN alpha/beta), which could induce the expression anti-HIV miRNAs in monocytes and macrophages. These findings provide both *in vitro* and *in vivo* evidence, demonstrating that morphine, through its inhibitory effect on intracellular anti-HIV innate immunity, promotes HIV infection of monocytes and macrophages. Supported by NIH DA012815, and DA022177.

W-30 CHARACTERISTICS OF HEROIN USERS IN METHADONE MAINTENANCE TREATMENT CLINICS IN WUHAN, CHINA. Z Wang[1], L Pulin[1], L Li[1], W Xia[1]; [1]Division of HIV/AIDS Prevention, Wuhan Center for Disease Control & Prevention, Wuhan, 430015 China; [2]Division of Allergy and Immunology, The Children's Hospital, Philadelphia, PA, 19104 USA; [3]Department of Psychiatry, the University of Pennsylvania School of Medicine, Philadelphia, PA, 19104 USA; [4]Department of Psychiatry, Yale University School of Medicine, New Haven, CT, 06519 USA.

Objectives: To determine the characteristics of the heroin users in the MMT clinics in Wuhan city. Methods: Socio-demographic and risk data from heroin dependent individuals undergoing MMT were collected at entry to MMT. Additionally, blood samples were collected and tested for HIV and HCV at entry, 6 and 12 months after MMT enrollment. Results: A total of 3074 individuals enrolled in 16 MMT clinics in Wuhan between Jan 2007 and Oct 2008 were investigated. 71.6% of them were male, 28.4% female, 61.1% were younger than 40 years, and 57.5% were unmarried at admission; 65.6% had middle school level education, 88.2% did not have stable job, and 59.0% depended on their family or friends for living payment during last six months; 66.2% were below 30 years old when they first began abusing drugs, 74.7% injected heroin during six months prior to MMT entry, and 83.8% reported lifetime history of sharing needles; 30.6% had more than two sex partners during last six months, and 82.1% had sex without condom at last time. At MMT entry, 1.1% were HIV positive and 75.2% HCV positive; 6 of the 3074 participants acquired HIV within 6 months after MMT enrollment; treatment retention rates at 6 and 12 months were 82.5% and 68.6%, respectively.. Conclusions: Heroin users entering MMT in Wuhan are at very high transmission risk for blood borne infections, as indicated by the high rates of IDU, needle sharing, sexual activity, and unprotected sexual activity, which suggests that behavioral drug and HIV risk

reduction counseling should be combined in services of MMT clinic. Supported by 5 R01 DA 014718-06.

W-31 BORNA DISEASE VIRUS P PROTEIN AFFECTS NEURAL TRANSMISSION THROUGH INTERACTING WITH GAMMA AMINOBUTYRIC ACID RECEPTOR-ASSOCIATED PROTEIN. JG Wu[1], GQ Peng[1], Y Yan[1], SQ Wang[1], CL Zhu[1], J Hu[1], Y Zhu[1], FM Zhang[1]; [1]State Key Laboratory of Virology, Wuhan University, Wuhan, 430072 China.

Borna disease virus (BDV) is one of the infectious agents causing diseases of central nervous system (CNS) in a wide range of vertebrate species and perhaps in human. The phosphoprotein (P) of BDV, an essential cofactor of viral RNA-dependent RNA polymerase, is required for the virus replication. To explore biological roles of P protein, we identified P protein-interacting cellular factors with functions in neurobiology. Results from phage display-based protein interaction screening revealed that gamma aminobutyric acid receptor-associated protein (GABARAP) is one of the partners of P protein. Direct binding between P and GABARAP was confirmed by co-immunoprecipitation, protein pull-down, and mammalian two-hybrid analysis. We also discovered that P protein co-localizes with GABARAP in the cells and shifts its localization from cytosol to nucleus. In addition, we demonstrated that P protein blocks the trafficking of gamma aminobutyric acid (GABA) receptors, the principal GABA-gated ion channel that plays important roles in neural transmission, to cell surface. GABARAP is originally identified as a linker between GABA receptors and microtubules to regulate receptors trafficking, and plays important roles in the regulation of GABA, an inhibitory neural transmitter. Thus, we proposed that during BDV infection, the viral P protein binds to GABARAP, forces GABARAP translocation from cytoplasm to nucleus, blocks GABA receptors trafficking to the cell membranes, and thus inhibits GABA entering into the cells, which result in neural disorder.

W-32 BORNA DISEASE VIRUS P PROTEIN INHIBITS NITRIC OXIDE SYNTHASE GENE EXPRESSION IN ASTROCYTES. JG Wu[1], GQ Peng[1], FM Zhang[1], Q Zhang[1], K Wu[1], F Zhu[1]; [1]State Key Laboratory of Virology, Wuhan University, Wuhan, 430072 China.

Borna disease virus (BDV) is one of the potential infectious agents involved in the development of central nervous system (CNS) diseases. Neurons and astrocytes are the main targets of BDV infection, but little is known about the roles of BDV infection in the biological effects of astrocytes. Here we reported that BDV inhibits the activation of inducible nitric oxide synthase (iNOS) in murine astrocytes induced by bacterial LPS and PMA. To determine which protein of BDV is responsible for the regulation of iNOS expression, we co-transfected murine astrocytes with reporter plasmid iNOS-luciferase and plasmid expressing individual BDV proteins. Results from analyses of reporter activities revealed that only the phosphoprotein (P) of BDV had an inhibitory effect on the activation of iNOS. In addition, P protein inhibits nitric oxide production through regulating iNOS expression. We also reported that the nuclear factor kappa B (NF-KB) binding element, AP-1 recognition site, and interferon-stimulated response element (ISRE) on the iNOS promoter were involved in the repression of iNOS gene expression regulated by the P protein. Functional analysis indicated that sequences from amino acids 134 to 174 of the P protein are necessary for the regulation of iNOS. These data suggested that BDV may suppress signal transduction pathways, which resulted in the inhibition of iNOS activation in astrocytes.

W-33 REGULATION OF NEURAL PROGENITOR CELL MIGRATION BY CHEMOKINES PRODUCED IN HIV-1 INFECTION IN SCID MICE. YW Wu[1], HP Peng[1], HD Dou[1], YH Huang[1], JZ Zheng[1]; [1]Department of Pharmacology & Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE, 68198 USA.

Background: It is suggested that the inhibition of neurogenesis are associated with HIV-1 associated dementia (HAD). Our previous data showed HIV-1-infected macrophages (HIV-MDM) regulate astrocyte stromal cell-derived factor 1 (SDF-1) production through IL-1β. How chemokines produced by HIV-induced inflammation regulate NPC migration remains unclear. Aim: We test the hypothesis that SDF-1 and monocyte chemoattractant protein-1 (MCP-1), produced in astrocytes by IL-1β stimulation, affect NPC migration thus influencing neurogenesis in HAD. Methods: The secretion of SDF-1 and MCP-1 in astrocytes upon IL-1β stimulation was determined by ELISA. Human NPCs parallel injected along with HIV-MDM, IL-1β, SDF-1 or MCP-1 intracranially into basal ganglion 1mm apart in SCID mice. 5 and 7 days after injection, 30?m-floating sections were harvested and subjected to immunohistochemistry for NPC migration qualification using confocal

images. Results: IL-1β -stimulated astrocytes produced SDF-1 and MCP-1 in a time and dose-dependent manner. NPCs survived after injection into basal ganglion and showed little migration toward the parallel PBS injection site. In contrast, NPC migrated dramatically toward IL-1β as well as SDF-1 or MCP-1 injection site. Furthermore, more NPCs migration toward the site of the HIV-MDM injection were observed compared with control MDM. Conclusion: Chemokine SDF-1 or MCP-1 secreted by astrocytes in the sites of HIV-MDM are attractive to neural progenitors and suggest that SDF-1 and MCP-1 play an important role in NPC migration in neuroinflammation. Supported by NIH R01 NS 061642-01,R01 NS 41858-01,R21 MH 083525-01 and P01 NS043985.

W-34 CHEMOKINE CCL2 ENHANCES EXCITATORY POSTSYNAPTIC CURRENTS (EPSCS) IN THE CA1 REGION OF RAT HIPPOCAMPAUS. H Xiong[1], H. Tang[1], Y. Zhou[1], D. Hu[1]; [1]Department of Pharmacology & Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE, 68198-5880 USA.

Neuroinflammation plays an important role in neurodegenerative diseases. It occurs as a massive invasion of blood-borne immune cells and activation of resident microglial cells. These immune competent cells secrete a variety of immune active molecules, resulting in neuronal dysfunction and injury. Among the immune active molecules is chemokine CCL2, which is upregulated in affected brain tissue and cerebrospinal fluid. We hypothesize that CCL2 directly influences synaptic activity, leading to neuronal dysfunction. To test this hypothesis, we studied effects of CCL2 on EPSCs in the CA1 region of rat hippocampal slices. Our results showed that bath application of CCL2 significantly enhanced EPSCs in a dose-dependent manner. In contrast, heat denatured CCL2 had no apparent effect. Quantal analysis revealed a pre-synaptic site of action. The CCL2-associated enhancement of EPSCs was partially blocked either by a NMDA receptor antagonist APV or by an AMPA receptor antagonist DNQX, suggesting that CCL2 act on both NMDA and AMPA receptors. In parallel studies, CCL2 was also found to induce neuronal injury as demonstrated by Hoechst 33342 staining. Taken together, these results suggest that CCL2 may influence neuronal physiology in addition to its attraction of immune cells to the affected site. Supported by NIH NINDS R01 NS041862.

W-35 EFFECT OF RELAPSE PREVENTION ON DRUG ADDICTS BY 4C INTERVENTION MODE IN REEDUCATION-THROUGH-LABOR CENTERS. YQ Yan[1], Q. He[2], J. Gong[1], NN Yang[1], ZZ Wang[2]; [1]Department for Chronic Disease Prevention & Control, Wuhan Centers for Disease Prevention & Control, Wuhan, 430015 China; [2]School of Public Health, Tongji Medical College, Huazhong University of Science & Technology, Wuhan, 430030 China.

Voluntary, compulsive and reeducation-through-labor (RTL) were three regular methods of rehabilitation for drug addicts in China.Nonetheless,relapse rates for these three methods were still very high from 90% to 99%,especially after they left rehabilitation centers. In current study, 4C (Confident-Care for-Cognition therapy-Coping skill) intervention,a psychologically based program,was used to prevent relapse in the RTL centers. Using a cluster randomized sampling 96 drug addicts were selected from Wuhan RTL centers. The 96 participants were randomly assigned to intervention and control group (48 for intervention group). Addicts in intervention group accepted the 4C intervention, and those in control group were in a regular management from RTL. Intervention effects and risk factors were assessed using survival analysis and multivariable Cox Regression. The abstinent rates of post-intervention in 6 months and 12 months were significantly higher in intervention group than in control group (41.5% versus 17.6 for 6 months, and 22.5% versus 13.7% for 12 months). The multivariable Cox Regression showed that family support, harmonious family atmosphere, non-injection drug using, shorter time of addiction, male and 4C intervention were protective for addicts to keep on abstinent. The 4C intervention program can prolong abstinent time and reduce relapse effectively. Psychological intervention and behavior rectification should be paid more attention as an important component of regular addict rehabilitation in RTL system in China. Longer follow-up is needed to better evaluate the lasting protective effects. Supported by International and Comparative Education Research Institute (No.yx06004).

W-36 ALCOHOL ENHANCES FULL CYCLE HEPATITIS C VIRUS INFECTION OF HUMAN HEPATOCYTES. L Ye[1], SH Wang[1], X Wang[1], Y Zhou[2], DJ Zhou[2], WZ Ho[1]; [1]Division of Allergy & Immunology, The Children's Hospital of Philadelphia, Philadelphia, PA, 19104 USA; [2]Division of Virology, Wuhan Centers for Disease Control and Prevention, Wuhan, 430022 China.

Alcohol drinking and hepatitis C virus (HCV) infection are both recognized as major causes of liver disease and they frequently coexist in patients with chronic liver disease. There is limited information at cellular and molecular levels about the impact of alcohol on full cycle HCV infection of and replication in human hepatocytes. We investigated the role of alcohol in HCV JFH-1 infection of human hepatocytes. Human hepatocytes pretreated with alcohol demonstrated increased susceptibility to HCV JFH-1 infection, as evidenced by enhanced expression of HCV RNA and protein in the cells. Alcohol, when added to HCV JFH-1-infected hepatocyte cultures, also enhanced viral replication. In addition, alcohol compromised the anti-HCV effect of recombinant IFN-alpha in hepatocytes. Investigation of the mechanisms responsible for the alcohol action revealed that alcohol inhibited the expression of the IFN regulatory factor (IRF)-5 and -7, the positive regulators of type I IFN production. In addition, alcohol suppressed the expression of signal transducer and activator of transcription (STAT)-1 and -2, two key elements in Janus Kinase (JAK) /STAT pathway, through which type I IFNs exert their antiviral activity. Alcohol also induced the expression of suppressors of cytokine signaling (SOCS)-2 and -3, the negative regulators in JAK /STAT pathway. These findings indicated that alcohol, through modulating the expression of key regulators in IFN pathway, inhibits intracellular type I IFN production and function, promoting HCV infectivity and persistence in human hepatocytes. Supported by NIH AA013547, DA012815 and DA22177.

W-37 ACTIVATION OF TLR3 INHIBITS HIV INFECTION OF HUMAN MACROPHAGES. Y Zhou[1], X Wang[1], L Ye[1], D Zhou[2], Q Hu[2], W Hou[1], WZ Ho[1]; [1]Division of Allergy & Immunology, The Children's Hospital of Philadelphia, Philadelphia, PA, 19104 USA; [2]Division of Virology, Wuhan Centers for Disease Prevention and Control, Wuhan, 430022 China.

In macrophages, Toll-like receptors (TLRs) induce protective immune response, including the activation of type I interferon (IFN-alpha/beta)-mediated antiviral pathway. TLR3 recognizes double-stranded RNA and induces multiple intracellular events responsible for innate anti-viral activities in macrophages. Here we demonstrated that exposure to poly I:C, a double-stranded RNA as the ligand for TLR-3, significantly inhibited human immunodeficiency virus type-1 (HIV-1) infection of peripheral blood monocyte-derived macrophage. This inhibitory effect of poly I:C on HIV-1 was time and dose-dependent. Investigation of the mechanisms showed that poly I:C treatment of macrophages induced the expression of CC-Chemokines, the ligands for HIV-1 coreceptor CCR5. Poly I:C-treated macrophages also expressed increased levels of intracellular IFN-α/β and newly identified cellular anti-HIV-1 factors: APOBEC3G and microRNAs (miRNA), including miRNA-28, 125b, 150, 233, and 382. In addition, poly I:C treatment enhanced the expression of IFN regulatory factors (IRFs) 1, 5, 7 and 9 in macrophages. These data provide direct experimental evidence that the activation of TLR3 enhances both extracellular and intracellular anti HIV-1 mechanisms, through which HIV-1 replication is inhibited in macrophages. Supported by NIH DA012815, DA022177 and Foerderer Fund.

W-38 ACTIVATION OF TOLL-LIKE RECEPTORS INHIBITS HERPES SIMPLEX VIRUS-1 INFECTION OF HUMAN NEURONAL CELLS. Y Zhou[1,2], L Ye[2], Q Wan[2], L Zhou[2], X Wang[2], JL Li[2], SX Hu[3], DJ Zhou[1], WZ Ho[2]; [1]Wuhan Centers For Disease Prevention and Control, Wuhan, 430022 China; [2]Division of Allergy & Immunology, The Children's Hospital of Philadelphia, Philadelphia, PA, 19104 USA; [3]Center Infectious Disease and Microbiology Translational Research, University of Minnesota Medical School, Minneapolis, MN 55455 USA.

Toll-like receptors (TLRs) play an essential role in initiating intracellular type I interferon (IFN)-mediated innate immunity against viral infections. We examined whether human neuronal cells (primary human neurons, NT2-N and CHP-212 cells) express TLRs and mount type I IFN-mediated innate immunity against herpes simplex virus-1 (HSV-1) infection. Human neuronal cells expressed TLR family members 1-10 and IFN-alpha/beta. The activation of TLR3 or TLR8 by double-stranded RNA (poly I:C) or single-stranded RNA (ssRNA) induced IFN-alpha/beta expression. In addition, HSV-1 infection of human neuronal cells induced IFN-α expression. Investigation of the mechanisms showed that poly I:C treatment enhanced IFN regulatory factors (IRFs) 1, 5, 7 and 9 expression, and ssRNA treatment induced IRFs 1 and 5 expression in human neuronal cells.

Importantly, the activation of TLR3 and TLR8 by poly I:C and ssRNA prior to HSV-1 infection decreased the susceptibility of the neuronal cells to infection. These observations indicate that human neuronal cells possess intracellular TLR-mediated innate immune protection against HSV-1 infection. Supported by NIH DA012815 and DA022177 and the Foerderer Fund.

W-39 CATECHOL-O-METHYLTRANSFERASE (COMT) GENE VARIANTS ARE ASSOCIATED WITH NOVELTY SEEKING AND SELF DIRECTIVENESS IN CHINESE HEROIN DEPENDENT PATIENTS. M Zhao[1], S Yu[1], J Du[1], H Chen[1], C Fan[1], D Wang[1]; [1]Shanghai Mental Health Center, Medical School of Shanghai Jiao Tong University, Shanghai, 200030 China.

BACKGROUND: Previous research suggests that personality traits, particularly novelty seeking (NS), increase the risk of substance abuse. Novelty seeking, one of the fundamental traits of the human temperament, is related to dopamine. Catechol-O-methyltransferase (COMT) is essential for dopamine inactivation. The aim of our study was to assess whether the COMT gene variants in heroin dependent patients is related to their personality traits. METHODS: 495 heroin dependent patients (234 male, 261 female, mean age 32.2 years old) from drug abuse rehabilitation centers in Shanghai completed Temperament and Character Inventory; TCI) assessment, meanwhile their DNA were collected and eight SNPs in the COMT gene (rs4818, rs4680 (Val158Met), rs174696, rs174699, rs737866, rs933271, rs1544325, rs5992500) were genotyped in all subjects. RESULTS: The novelty seeking scores were associated with genotypes of rs4818 (F=4.21, p=0.015), rs174699 (F=4.39, p=0.013) and rs737866 (F=3.54, p=0.03), and self directiveness scores were associated with rs737866 genotype (F=3.14, p=0.044). The patients with rs4818 CC genotype had higher novelty seeking scores than rs4818 CG genotype carriers (63.6 vs 61.5; p=0.014). Patients with rs174699 TT genotype had higher novelty scores than those with rs174699 TC or CC genotype (64.1 vs 61.9, 61.8; p=0.02, p=0.047). The patients with rs737866 CT genotype tended to have lower novelty seeking score (61.8 vs 63.4, p=0.086) and higher self directiveness scores than TT genotype carriers (58.0 vs 56.0, p=0.067). The patients with rs4818 C allele had higher novelty seeking and self directiveness in Chinese heroin dependent patients. Supported by Shanghai Narcotic Control Foundation.

W-40 DIMINISHED TOLL LIKE RECEPTOR-4-MEDIATED INNATE IMMUNITY IN NEONATAL BRAINS. H Zhou[1]; [1]Department of Biological Sciences, Seton Hall University, South Orange, NJ, 07079 USA.

Toll like receptor (TLR)-4-mediated innate immune response plays a key role in the host's immune defense against gram-negative bacterial infections. Peripheral treatment with gram-negative bacterial endotoxin, lipopolysaccharide (LPS), also is well-recognized to induce neuroinflammation in many experimental animal models characterized by increased expression of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-1β. The neonates are known to be more susceptible to bacterial infection than adults. Furthermore, evidence suggests that this may be due to altered immune function in the neonates. However, TLR-4-mediated neuroinflammation in the neonates have not been carefully examined. In this study, we treated one day old (P1) pups and young adult animals with LPS via intraperitoneal injection, and examined the expression of TLR4, cytokines, and chemokines in the brain. We found that the P1 brains exhibited much reduced induction of cytokines, namely TNF-α, IL-6, and IL-1β, and chemokines, namely macrophage chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP)-2, MIP-1β than adult brains following LPS treatment. Furthermore, P1 brains also express much less TLR-4 than adult brains. Our data suggest that P1 brains exhibit reduced neuroinflammation compared to adults following LPS treatment, and this reduction is associated with diminished TLR-4 expression in the neonatal brains.

W-41 CHARACTERISTICS OF HEROIN USERS IN METHADONE MAINTENANCE TREATMENT CLINICS IN WUHAN, CHINA. W Zhou[1], P Liu[1], L Luo[1]; [1]Division of HIV/AIDS Prevention, Wuhan Center for Disease Control and Prevention, Wuhan, 430015 China; [2]Division of Allergy and Immunology, The Children, Philadelphia, PA, 19104 USA; [3]Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, PA, 19104 USA; [4]Department of Psychiatry, Yale University School of Medicine, New Haven, CT, 06519 USA.

Objectives: To determine the characteristics of the heroin users in the MMT clinics in Wuhan city. Methods: Socio-demographic and risk data from heroin dependent individuals undergoing MMT were collected at entry to MMT. Additionally, blood samples were collected and tested for HIV

and HCV at entry, 6 and 12 months after MMT enrollment. Results: A total of 3074 individuals enrolled in 16 MMT clinics in Wuhan between Jan 2007 and Oct 2008 were investigated. 71.6% of them were male, 28.4% female, 61.1% were younger than 40 years, and 57.5% were unmarried at admission; 65.6% had middle school level education, 88.2% did not have stable job, and 59.0% depended on their family or friends for living payment during last six months; 66.2% were below 30 years old when they first began abusing drugs, 74.7% injected heroin during six months prior to MMT entry, and 83.8% reported lifetime history of sharing needles; 30.6% had more than two sex partners during last six months, and 82.1% had sex without condom at last time. At MMT entry, 1.1% were HIV positive and 75.2% HCV positive; 6 of the 3074 participants acquired HIV within 6 months after MMT enrollment; treatment retention rates at 6 and 12 months were 82.5% and 68.6%, respectively.. Conclusions: Heroin users entering MMT in Wuhan are at very high transmission risk for blood borne infections, as indicated by the high rates of IDU, needle sharing, sexual activity, and unprotected sexual activity, which suggests that behavioral drug and HIV risk reduction counseling should be integrated into services of MMT clinic. Supported by 5 R01 DA 014718-06.

W-42 EFFECTS OF CCK-8 AND ITS RECEPTOR ANTAGONIST ON μ-OPIOID RECEPTOR IN DIFFERENT BRAIN REGIONS OF MORPHINE WITHDRAWAL RATS. D Wen , B Cong , C-L Ma, Y-J Zhang, S-J Li, Z-Y Ni. Department of Forensic Medicine, Basic Medical College, Hebei Medical University, Hebei Key Laboratory of Forensic Medicine, Shijiazhuang, 050017 China

Cholecystokinin (CCK) is a neuropeptide found in many systems. There is a broad distribution in the central nervous system, with a variety of physiological functions. Reseach suggests that CCK receptor antagonists can alleviate the naloxone percipitated withdrawl syndrome, also can prevent the relapse of opioid abuse. To explore the possible mechanisms that CCK-8 and CCK receptor antagonist regulate morphine withdrawal syndrome, the effects of CCK-8, CCK_1 receptor antagonist (L-364,718), and CCK_2 receptor antagonist(LY-288,513) by i.p. and i.c.v. on μ-opioid receptor were observed by radioligand binding assay in prefrontal cortex(PFC), hippocampus(Hip), cauduate putamen (CPu) of morphine withdrawal rats. Our study showed that CCK-8 and CCK receptor antagonists could alleviate morphine withdrawal symptoms by regulating Bmax or/and Kd of μ-opioid receptor, with significant specificity in different brain regions. Supported by NSFC30672355.