Society on NeuroImmune Pharmacology (SNIP)

19th Scientific Conference

Conrad San Juan Condado Plaza
San Juan, PR

April 3-6, 2013

Previous Conferences:1993 Toronto Hilton, Canada; 1994 Breakers, Palm Beach, FL; 1995 Bristol Court, San Diego, CA; 1996 Caribe Hilton, San Juan, PR; 1997 Opryland Hotel, Nashville TN; 1998 Scottsdale Princess, Scottsdale, AR; 2000 NIH Mazur Auditorium, Bethesda MD; 2001 Emory University, Atlanta, GA; 2002 Clearwater Beach Hilton, Clear Water, FL; 2004, La Fonda Hotel, Santa Fe, NM; 2005 Clearwater Beach Hilton, Clear Water, FL; 2006 La Fonda Hotel, Santa Fe, NM; 2007 City Center Marriott Hotel, Salt Lake City, UT; 2008 Francis Marion Hotel, Charleston, SC; 2009 Pearl Plaza Howard Johnson, Wuhan, China; 2010 Manhattan Beach Marriott, Manhattan Beach, CA; 2011 Hilton Clearwater Beach Resort, Clear Water Beach, FL; 2012 Hawaii Prince Hotel, Honolulu, HI

TABLE OF CONTENTS

Twenty Years of SNIP

By Bob Donahoe

A BRIEF HISTORY: In San Juan we proudly celebrate twenty years of the Society on NeuroImmune Pharmacology (SNIP). The first Conference that led to the formation of SNIP was held in Toronto, in 1993. It was initially conceptualized and organized at a meeting of the Committee (now College) on Problems of Drug Dependence (CPDD) in Keystone, CO, in 1992.

CPDD had been sponsoring posters and symposia on immunopharmacology (IP) since 1984. By the 1992 meeting, interest in IP had grown tremendously and for the first time CPDD scheduled two symposia on the topic. Attendance approached 90 scientists. Upon exiting the second symposium, excitement among attendees was palpable. Animatedly, Dr. Burt Sharp began chatting up the idea: *"We need to hold our own meetings."* That evening, in John Madden's condo, a working group (Drs. Burt Sharp, John Madden, Bob Donahoe, Marty Adler, Toby Eisenstein, Tom Rogers, Tom Klein and Jean Bidlack) met to effect such an effort. The proposal evolved to organize a satellite meeting the following year with CPDD in Toronto. Marty Adler, being the Executive Secretary of CPDD, spearheaded the joint-meeting arrangements. John Madden and Burt Sharp, working with guidance from Dr. Charles Sharp from the NIDA program office, obtained a NIDA-sponsored R13 Grant to help support this first 'SNIP' meeting, and especially to support expenses of jury-selected young investigator travel awardees (YITAs) to the meeting.

Several subsequent satellite conferences were held with CPDD and one with Neuroscience. In 2000, 'SNIP's' first 'independent' meeting was held at NIH. The high attendance there encouraged talk among the working group and other 'regulars' to consider forming, "*Our own society*." In the fall of 2000, Bob Donahoe organized a meeting to initiate a new society in the office of Burt Sharp at the University of Tennessee, College of Medicine, in Memphis. Attending were Bob, Burt, John Madden and Rick Weber (*photo below*). With communicated input from the working group, they set the groundwork for a society—choosing the SNIP name by a vote of the principals involved, which included, Phil Peterson, Tom Klein, Tom Rogers, Jean Bidlack and Toby Eisenstein. Interim officers were chosen. Corporate papers were filed and tax-exempt status obtained. An R13 grant application was funded to hold the first official SNIP conference at Emory University in Atlanta, in 2001. There, the first society officers were elected. Notably, the SNIP Treasury was initially financed through the generous personal contributions of a group of 40 Charter Members, to whom all SNIP members are indebted.

Attendees at first organizational meeting of SNIP (2000)

Left to Right: *Bob Donahoe, Burt Sharp, Rick Weber, John Madden*

[An in-depth history of SNIP is at: www.s-nip.org/confrences/history.]

SNIP CHARTER MEMBERS: *Martin Adler, Barbara Bayer, Jean Bidlack, Guy Cabral, Linda Chang, Sulie Chang, Paul Cheney, Ronald Chuang, Robert Donahoe, Toby Eisenstein, Howard Fox, Herman Friedman, Clair Gaveriaux-Ruff, Karl Goodkin, Steve Henriksen, John Holliday, Thomas Jerrells, Norbert Kaminski, Steve Keller, Tom Klein, Mahendra Kumar, Donald Lysle, John Madden, Fred Marsteller, Bonnie Miller, Tom Molitor, Madhaven Nair, Avindra Nath, Phillip Peterson, Fernando Renaud, Thomas Rogers, Sabita Roy, Walter Royal, Burt Sharp, Charles Sharp, Pravin Singhal, Mohan Sopori, George Stefano, Richard Weber, James Zadina*

Acknowledgements

The Society on NeuroImmune Pharmacology expresses its deep appreciation for the contributions made by so many individuals and institutions in support of this 19th SNIP Scientific Conference in San Juan, Puerto Rico. The scientific program was developed by the Ad Hoc Meetings Committee chaired by Sabita Roy, Phil Peterson, and Shilpa Buch. Special thanks go to the Meeting Organizer, Bob Donahoe, and to the local organizing committee: Loyda Melendez and Richard Noel (co-chairs) and members Vanessa Rivera, Valerie Wojna, and Annabell Segarra. A special thank you to NIDA for their continued long term support for the mission of SNIP and our annual conference.

Sponsors and Contributors

The Society on NeuroImmune Pharmacology (SNIP) sincerely thanks following sponsors who have generously contributed to different activities during 19th Society of NeuroImmune Pharmacology Meeting.

1. **National Institute on Alcohol and Alcoholism** $15,000
   To support Symposium #1 (Neuroimmune Activation Contributes to Addiction Neurobiology) and Travel Scholarship to support young investigators involved in alcohol research.
2. **National Institute of Mental Health** $7000
   Partial sponsorship of Symposium #6: (Neuropathology of HIV-1 in an Aging Population)
3. **Department of Surgery-Basic and Translation Division, University of Minnesota Medical School** $6000
   Partial sponsorship of Reception
4. **Institute of Neuroimmune Pharmacology and Center for Personalized Nano Medicine, HW College of Medicine, FIU** $5000
   Graduate trainee associated expenses, partial sponsorship of Early Career Investigator Lunch
5. **Dr. Brian Wigdahl, Drexel University** $5,000
   Partial sponsorship of Early Career Investigator Lunch
6. **Dr. Pravin Singhal** $3,000
   Early Career Investigator Travel Award
7. **Drs. Howard Fox /Shilpa Buch** $5,000
   Bill Narayan Memorial Lecture
8. **Drs. Tom Molitor /Sabita Roy** $2,500
   Grants Writing Workshop Lunch
9. **Dr. Jose Lasalde**, Vice President for Research & Technology, University of Puerto Rico $2,000
   Program Book Printing
10. **Dr. Kenira Thompson**, Dean for Research, Ponce School of Medicine $1,000
    Partial sponsorship of Early Career Investigator Lunch

2012-2013 Council, Officials & Committees

Sabita Roy, Ph.D.
President
Professor of Surgery & Director, Division of Infection, Inflammation & Vascular Biology
University of Minnesota Academic Health Center,
Minneapolis, MN 55455

Howard S. Fox, MD, Ph.D.
President Elect
Professor
University of Nebraska Medical Center
Omaha, NE 68198-5800

Guy A. Cabral, Ph.D.
Past President
Professor, Microbiology and Immunology
Chair, Graduate Program Committee Virginia Commonwealth University
School of Medicine
Richmond, VA 23298

Shilpa Buch
Secretary
Professor and Vice Chair
Research Department of Pharmacology and Experimental Neuroscience
University of Nebraska Medical Center
Omaha, NE 68198-5880

Anil Kumar Ph.D.
Treasurer
Chair and Professor
Division of Pharmacology and Toxicology
UMKC School of Pharmacy
Kansas City, MO 64108

Anuja Ghorpade, Ph.D.
Council Member
Membership Committee Chair
Professor and Chair Department of Cell Biology and Anatomy
University of North Texas Health Science
Fort Worth, TX, 76107

Sulie L. Chang, Ph.D.
Council Member
Meetings Committee Chair
Professor and Director
Institute of Neuroimmune Pharmacology
Seton Hall University
South Orange, NJ 07079

Sanjay Maggirwar, Ph.D.
Council Member
Communications Committee Chair
Associate Professor
Department of Microbiology and Immunology
University of Rochester Medical Center
Rochester, NY 14642

Kurt F. Hauser, Ph.D.
Council Member
Professor
Department of Pharmacology and Toxicology
Virginia Commonwealth Univ. School of Med.
Richmond, Virginia 23298-0613

Linda Chang MD
Council Member
Professor of Medicine
John A. Burns School of Medicine
University of Hawaii at Manoa
The Queen's Medical Center
Honolulu, Hawaii 90095-7363

Wenzhe Ho, MD M.Ph.
Council Member
Professor, Dept. Pathology & Laboratory Medicine, Dept. Anatomy and Cell Biology
Temple University School of Medicine
3500 N. Broad Street, Philadelphia, PA 19140

Michal Toborek, MD, Ph.D.
Council Member
Professor and Vice-Chair for Research
Dept of Biochemistry and Molecular Biology
University of Miami School of Medicine
Miami, FL 33136

Christoph Stein, MD
Council Member, International
Direktor
Klinik für Anaesthesiologie und Operative Intensivmedizin
Freie Universität Berlin, Benjamin Franklin,
Hindenburgdam 30 D-12200 Berlin

Prati Pal Singh, Ph.D.
Council Member, International
Professor, Department of Pharmacology and Toxicology, In-Charge, Centre of Infectious Diseases, National Institute of Pharmaceutical Education and Research
Punjab, India

Robert M. Donahoe, Ph.D.
Conference Director
Adjunct Professor
Department of Pathology,
University of Utah, School of Medicine
Salt Lake City, UT 84112

Santosh Kumar, Ph.D.
Early Career Investigator Committee Chair
Assistant Professor
Pharmacology and Toxicology, School of Pharmacy, University of Missouri-Kansas City
Kansas City, MO 64108

Howard E. Gendelman, MD
Ex Officio, Editor-in-Chief, JNIP
Larson Professor of Internal Medicine and Infectious Diseases
Chair, Department of Pharmacology and Experimental Neuroscience
University of Nebraska Medical Center
Omaha, NE 68198-5880

Pravin C. Singhal, MD
Ad hoc Member
Director, Renal Research Molecular Laboratory
Professor of Medicine, Hofstra North Shore LIJ Medical School,
Great Neck, NY 11021

Executive Committee

President: Sabita Roy
President elect: Howard Fox
Secretary: Shilpa Buch
Treasurer: Anil Kumar
Past President: Guy Cabral

Meetings Committee

Sulie L. Chang, Chair; Michael Roth, Linda Chang

Ad Hoc Meetings Committee

Co-Chairs: Sabita Roy, Phil Peterson, Shilpa Buch; Guy Cabral, Howard Fox, Anil Kumar, Marcus Kaul, Pravin Singhal, Richard Noel, Michael Toborek, Kelly Jordan- Sciutto, Bob Donahoe, Santosh Kumar

Early Career Investigator Committee

Santosh Kumar, Chair; Michael Nonnemacher, Sylvia Kiertscher, Vanessa Rivera Amill, Prasun K Datta, James Haorah, Samikkannu Thangavel, Tom Molitor, Anuja Ghorpade, Rosemarie Booze, Wenzhe Ho, Shao-Jun Tang, Walter Royal, Loyda Melendez

Communications Committee

Sanjay B. Maggirwar, Chair; Rosemarie Booze, Shilpa Buch, Anil Kumar, Larisa Poluektova, Mohan Sopori

Membership Committee

Anuja Ghorpade, Chair; Norbert Kaminski, Patricia Molina, Jialin Zheng

Finance and Audit Committee

Anil Kumar, Chair; Linda Chang, Bob Donahoe

Election Nominating Committee

Shilpa Buch, Chair; Howard Fox, Guy Cabral, Sabita Roy, Anil Kumar

Society Awards Committee

Howard Fox, Chair; Yuri Persidsky, Tom Klein, Lena Al-Harthi, Peter Gaskill

Journal Publications Committee

Sabita Roy, Chair; Guy Cabral, Howard Fox

Public Relations Committee

Sabita Roy, Chair; Bob Donahoe, Phil Peterson, Clair Gaveriaux-Ruff, Howard Fox

Annual Society Awards

Each year the Society recognizes a few of its members who have exemplified unique qualities of leadership, service and/or scholarship on behalf of the Society and its mission. The following awards are bestowed annually.

Herman Friedman Founders Award

For Visionary Contributions in the Establishment and Continued Development of the Society

This award is named in honor of Herman Friedman, PhD, a man who promoted the study of drugs of abuse, infections, and immunity, promoted meetings among scientists based on this theme, and was a founding member of the Society. He passed away in 2007. This award recognizes individuals whose contribution to SNIP was visionary and served as a key to the founding of the Society and/or its continued development and perpetuation.

Distinguished Services Award

For Extraordinary Service to Society and to the Accomplishment of its Mission

The Distinguished Services Award recognizes an individual whose efforts and commitment to the society has been both consistent and exemplary over protracted years of service.

Outstanding Service And Support Award

For Extraordinary Service to Society and to the Accomplishment of its Mission

This award is given in recognition of individuals who are not necessarily investigators or members, but who have provided extraordinary service in facilitating the operation of Society initiatives. Examples would include individuals who often work “behind the scenes” to facilitate the Society by work on its publications, fundraising, and/or in the organization or conduct of meetings and symposia.

Wybran Award

For Extraordinary Contributions that Help to Integrate the Fields of NeuroImmunology, Drugs Of Abuse, and Immunity to Infection

Joseph Wybran, MD, was trained in Immunology and worked for some time in the USA before returning to his Brussels home. He was a seminal contributor through the 1970s and into the 1980s to the integration of the fields of neuroimmunology, drugs of abuse and immunity to infection. As a measure of the impact that his science had on the field of neuroimmune pharmacology, his seminal paper published in the Journal of Immunology 1979 regarding the ability of endogenous and exogenous opioids to modulate T cell rosette formation in a naloxone reversible way was the most cited research article through the early 1980s. He was killed, presumably, by terrorists reacting to his leadership and participation in Jewish causes. He was shot in his car in the parking lot of his work, October 3, 1989 in Brussels. Sadly, this tragedy occurred at the peak of Joe’s career. The Wybran Award was created to memorialize Joe’s scientific prestige in the area of neuroimmune pharmacology. It is meant, most particularly, to serve as a remembrance of his leading contributions that underpin SNIP. The Wybran Award is the highest honor bestowed by SNIP in recognition of the very best scientific contributions that have resulted in the preservation and expansion of the field of Neuroimmune Pharmacology.

Early Career Investigator Travel Award Winners 2013

In order to promote interest in the field of Neuroimmune Pharmacology and to recognize the excellent work being done by Early Career investigators in this field, the Society provides Early Career Investigator Travel Awards (ECITA) to graduate students and post-doctorate trainees (within 5 years of Ph.D.) working with a SNIP Member and seeking funds to attend the annual conference of the Society on NeuroImmune Pharmacology. For the 2013 SNIP Scientific Conference, a total of 66 abstracts were submitted. Of which 22 graduate students and 13 post-doctorate fellows were awarded. Of these 35 awardees, 9 awards were conferred to students and post-doctorate fellows working in alcohol-related research and these awards were sponsored by NIAAA. The ECITA awards were made in 3 categories: $750+registration waiver, $500+registration waiver, and $500. In addition, 6 students who were among the top candidates were awarded with "Certificate for Excellence". However, they were not given travel awards because they were the 3rd candidates from the same mentor. Finally, the top 3 from each graduate student post-doctorate fellow categories were selected for symposium presentation.

ECITA Awardees	Mentor	University
Pre-Doctoral		
Amma, AB	Dash, CV	Meharry Medical College
Bertrand, SJ	Booze, RM	University of South Carolina
Cao, L	Kumar, A	University of Missouri- Kansas City
Chen, Q	Zheng, JC	University of Nebraska Medical Center
Cisneros, I	Ghorpade, A	University of North Texas Health Science Center
Coley, JS	Berman, JW	Albert Einstein College of Medicine
Festa, L	Meucci, O	Drexel University College of Medicine
Gangwani, MR	Kumar, A	University of Missouri- Kansas City
Liu, X	Kumar, A	University of Missouri- Kansas City
Loucil, R	Noel, Jr, RJ	Ponce School of Medicine and Health Sciences
Mamik, MK	Ghorpade, A	University of North Texas Health Science Center
Meng, J	Roy, S	Veterans Affairs Medical Center
Moran, LM	Mactutus, CF	University of South Carolina
Sen, S	Amini, S	Temple University School of Medicine
Shah, A	Kumar, A	University of Missouri- Kansas City
Sindberg, GM	Roy, S	University of Minnesota
Strazza, M	Nonnemacher, M	Drexel University College of Medicine
Vartak, N	Ghorpade, A	University of North Texas Health Science Center
Wang, Y	Zheng, JC	University of Nebraska Medical Center
Williams, DW	Berman, JW	Albert Einstein College of Medicine
Yang, L	Buch, S	University of Nebraska Medical Center
Zhou, Y	Ho, WZ	Temple University School of Medicine
Post-Doctoral		
Ashutosh, F	Ghorpade, A	UNT Health Science Center
Castro, V	Toborek, M	University of Miami
Kiebala, M	Maggirwar, SB	University of Rochester
Lan, X	Singhal, PC	Feinstein Institute for Medical Research
Ma, J	Roy, S	University of Minnesota
Mantri, SK	Dash, CV	Meharry Medical College

Pilakka-Kanthikeel, S	Nair, M	Florida International University
Wang, YZ	Ho, WZ	Temple University School of Medicine
Zhao, L	Zheng, JC	University of Nebraska Medical Center

ECITA-alcohol Awardees	**Mentor**	**University**
Pre-Doctoral		
Ande, A	Kumar, S	University of Missouri- Kansas City
Fergoson, LB	Harris, RA	University of Texas, Austin
Franklin, T	Sarkar, DK	Rutgers University
Gofman, L	Potula, R	Temple University School of Medicine
Parikh, N	Wigdahl, B	Drexel University College of Medicine
Teng, S	Molina, P	Louisiana State University Health Sciences Center
Post-Doctoral		
Agudelo , M	Nair, M	Florida International University
Bethel-Brown, C	Buch, S	University of Nebraska Medical Center
Vetreno, RP	Crew, FT	University of North Carolina, Chaper Hill

The SNIP recognizes the service of ECITA committee members (Drs. S. Kumar (Chair), Booze, Datta, Ghorpade, Haorah, Ho, Kiertscher, Meléndez, Molitor, Nonnemacher, Royal, Tang, Thangavel, and Rivera), and thank them for their wonderful job in reviewing the ECITA applications. Professor Arthur Falek, of Emory University, who passed away in 2005, was widely known for his mentorship. In 1982, he was the first recipient of a NIDA grant in the field of NeuroImmune Pharmacology. He held grants in this area of research for 20 more years, until his retirement in 2002. He was an early and ever enthusiastic promotor of SNIP and Early Career Investigators. Accordingly, the ECITA awards are tendered in his honor.

The Society Welcomes our Plenary Speakers

Dr. Benjamin K. Chen is an Associate Professor in the Division of Infectious Diseases, Department of Medicine at the Icahn School of Medicine at Mount Sinai. Dr. Chen began his training in HIV virology with Nobel Laureate David Baltimore and then with Dr. Peter S. Kim and has maintained an interest in the HIV-host cell interactions for 20 years. The work from his laboratory has advanced our understanding of how the assembly and production of HIV in T cells is coordinated by the cell-cell contacts and how these contacts called virological synapses (VS) enhance infection. Using recombinant infectious forms of HIV to facilitate measurement of the steps of the virus life cycle his laboratory revealed that cell adhesion induced by the viral Env protein induces the active recruitment of the assembling viral components to the cell-cell junction. Studies from the lab have also visualized a endocytic entry pathway that is mediated by the VS, measured the resistance of the VS to neutralization by patient sera, and revealed the simultaneous transmission of multiple genetic copies of HIV by VS. Current studies in the laboratory have focused on the role of cell-to-cell infection in a parenteral model of HIV transmission in humanized mice supported by an Avant Garde Award from the NIH. The goal of these studies is to visualize VS in vivo and to characterize how they participate in viral spread in vivo. He is also a Burroughs Wellcome Investigator in the Pathogenesis of Infectious Diseases. Overall, the studies in the laboratory examine how immune cells actively participate in HIV dissemination and examine a novel paradigm that may help us to understand many aspects of HIV pathogenesis.

Dr. Kanneganti is an Associate Member in the Department of Immunology at St. Jude Children's Research Hospital. Her laboratory focuses on studying the molecular mechanisms of host defense and inflammation. Dr. Kanneganti has published over 100 papers, many in prestigious journals including Nature, Cancer Cell, Nature Immunology, Nature Reviews Immunology and Immunity. She has made seminal contributions to our understanding of how the innate immune system recognizes and responds to pathogens and how mutations in these sensing systems and signaling affect the development of infectious, inflammatory, and autoimmune diseases in humans. Dr. Kanneganti regularly presents her findings at national and international symposia and at major research institutions throughout the world. She has consistently been active in postdoctoral and graduate student training. Web page: www.stjude.org/kanneganti

Jon Lindstrom. Department of Neuroscience, Medical School of the University of Pennsylvania. Research in my laboratory involves nicotinic acetylcholine receptors (AChRs) of both muscles and nerves. We discovered that myasthenia gravis (MG) is caused by an antibody-mediated autoimmune response to muscle α1* AChRs, developed experimental autoimmune MG (EAMG) as an animal model of MG, developed an immunodiagnostic assay for MG, discovered the main immunogenic region (MIR) and determined its structure, and have developed a specific immunosuppressive therapy for EAMG. We made monoclonal antibodies as model autoantibodies and as probes for characterizing neuronal AChRs. We are characterizing the structures and functional properties of human neuronal AChR subtypes expressed in Xenopus oocytes and transfected cell lines. We found that nicotine acts as a pharmacological chaperone to promote assembly of α4β2* AChRs. Subunit concatamers proved especially useful for expressing complex AChR subtypes important for addiction to nicotine such as (α6β2)(α4β2)β3. We are collaborating in development of positive allosteric modulators selective for α5* AChRs for smoking cessation therapy.

Tariq M. Rana, Ph.D., is Professor and Director of the RNA Biology Program at Sanford-Burnham. Dr. Rana's laboratory has discovered fundamental structural and functional features of small RNAs required for gene silencing. In addition, his laboratory has uncovered mechanisms involving small RNAs and RNA-protein complexes in regulating host-pathogen interactions. Dr. Rana received his Ph.D. from the University of California at Davis and he was an American Cancer Society fellow at the University of California at Berkeley. He is a recipient of numerous awards including a Research Career Award from the National Institutes of Health in 1996. Dr. Rana has advised a number of biotechnology companies and has served as a member of several Scientific Advisory Boards. Prior to joining the faculty of the Sanford-Burnham, Dr. Rana was a Professor of Biochemistry and Molecular Pharmacology and Founding Director of a Program in Chemical Biology at the University of Massachusetts Medical School. Dr. Rana joined Sanford-Burnham in 2008 to establish the Program for RNA Biology.

Prof. dr. Bert 't Hart (59) is a medical biologist with a PhD in immunology. As postdoc I led a research group in ethnopharmacology, working on the immunologically active principles of medicinal plants. In 1989 I joined the Dutch Primate Centre/BPRC to work on the development and research of non-human primate models for immune-mediated inflammatory disorders. My initial research was in rheumatoid arthritis, but in later years I switched to multiple sclerosis and Parkinson's disease. Currently I am chairman of the Immunobiology department of the Biomedical Primate Research Centre and hold the chair in Neuroimmunology at the University Medical Centre in Groningen.

SNIP Administrative Meetings

Tuesday, April 2, 2013

1:00pm	**Opening of Conference Office (Almendros, Ocean Tower, Mezzanine level)**
3:00 – 4:00pm	**SNIP Executive Committee Meeting (President's Suite)**
4:00 -6:30pm	**SNIP Meetings /Program Committee (Horizonte, Ocean Tower, Mezzanine level)**
7:30pm	**SNIP Council Dinner**

Wednesday, April 3, 2013

All business meetings on April 3 will take place in Boardroom II, Lagoon Tower, Mezzanine level.

8:00 – 8:20am	**Awards Committee**
8:20 – 9:05am	**ECITA Committee**
9:05 – 9:50am	**Communications Committee**
9:50 – 10:20am	**Membership Committee**
10:20 – 11:00am	**Finance Committee**
11:00 – 11:45am	**Elections Committee**
12:00 – 1:00pm	**Lunch**
1:00 – 3:00pm	**Council Meeting and Committee Reports**
2:00pm	**Conference Office Opens (Almendros, Ocean Tower, Mezzanine level)**
3:00-6:00pm	**Registration Opens (Ponce de Leon Foyer, Ocean Tower, Mezzanine level**

Scientific Sessions

Wednesday, April 3, 2013

5:00-8:00pm **Opening Reception and Poster Session 1**

(Brisas del Mar,Ocean Tower, Lobby level)

Please have posters numbered 1-40 mounted by 4:45pm.

Posters W-1 through W-40 to be presented from 5-6:20pm, and then removed.

Posters W-41through W-80 to be mounted from 6:20-6:40 and presented until 8pm.

Sponsored by the Department of Surgery, University of Minnesota

Poster titles listed by assigned Poster Board Numbers

(see *Journal of Neuroimmune Pharmacology for complete abstracts)*

EARLY CAREER INVESTIGATOR POSTER SESSION TITLES

W-1. COCAINE ENHANCES HIV-1 INTEGRATION IN CD4+ T CELLS BY MODULATING THE EPIGENETIC DNA SIGNATURES OF HOST GENOME. Amma, A.B. 1, Pandhare, J 1, Mantri, C.K. 1, Dash, CV 1; 1Center for AIDS Health Disparities Research, Department of Biochemistry and Cancer Biology, Meharry Medical College, Nashville, TN 37208.

W-2. ROLE OF CYTOCHROME P450 (CYP) IN SMOKING AND ALCOHOL MEDIATED OXIDATIVE STRESS: IMPLICATIONS WITH HIV-1 PATHOGENESIS. Ande, A 1, Sinha, N 1, McArthur, C 2, Kumar, S 1; 1Division of Pharmacology & Toxicology, UMKC School of Pharmacy, Kansas, MO 641082Department of Oral Biology, UMKC School of Dentistry, Kansas, MO 64108.

W-3. HIV-1 LTR SINGLE NUCLEOTIDE POLYMORPHISMS (SNPS) THAT CORRELATE WITH CLINICAL DISEASE PARAMETERS ARE FOUND IN BOTH THE PERIPHERAL BLOOD AND BRAIN COMPARTMENTS. Antell, G 1, Nonnemacher, M 2, Pirrone, V 2, Dampier, W 2, Aiamkitsumrit, B 2, Williams, J 2, Shah, S 2, Wojno, A 2, Passic, S 2, Blakey, B 2, Zhong, W 2, Moldover, B 4, Feng, R 5, Downie, D 3, Lewis, S 3, Jacobson, J 3, Wigdahl, B 2; 1School of Biomedical Engineering and Health Sciences, Drexel University, Philadelphia, PA 191022Microbiology and Immunology, Drexel University College of Medicine, Philadelphia, PA 191023Division of Infectious Disease and HIV Medicine, Department of Medicine, Drexel University College of Medi cine, Philadelphia, PA 191024B-Tech Consulting, LTD, B-Tech Consulting, LTD, Philadelphia, PA 191305Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, PA 19104.

W-4. EFFECT OF METHAMPHETAMINE AND GP120 ON AUTOPHAGY IN SVGA ASTROCYTES. Cao, L 1, Kumar, S 1, Kumar, A 1; 1Division of Pharmacology and Toxicology, School of Pharmacy, University of Missouri-Kansas City, Kansas City, MO 64108.

W-5. UPREGULATION OF THE ALPHA7-NICOTINIC ACETYLCHOLINE RECEPTOR IN A TRANSGENIC MOUSE MODEL THAT EXPRESSES THE HIV COAT PROTEIN GP120. Capó-Vélez, C.M. 1, Morales, B 1, Melendez, R. 2, Lasalde-Dominicci, J.A. 1; 1Department of Biology, University of Puerto Rico, Rio Piedras Campus, San Juan, PR 009312Department of Anatomy and Neurobiology, University of Puerto Rico, Medical Sciences Campus, San Juan, 00936.

W-6. CXCR7, A NOVEL RECEPTOR OF CXCL12, MEDIATES MIGRATION AND SIGNALING OF NEURAL PROGENITOR CELLS IN VITRO. Chen, Q 1, Li, Y 1, Song, A 1, Zhu, B 1, Peng, H 1, Huang, Y 1, Tian, C 1, Xu, D 1, Zheng, J. C 1; 1Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198.

W-7. TRANSIENT METHAMPHETAMINE-ASSOCIATED HYPERTHERMIA MODULATES ASTROCYTE TRACE AMINE ASSOCIATED RECEPTOR-1 (TAAR1) ACTIVATION AND EXACERBATES HIV-1-INDUCED NEURODEGENERATION. Cisneros, IE 1, Ghorpade, A 1; 1Cell Biology and Anatomy, University of North Texas Health Science Center at Fort Worth, Fort Worth, TX 76107.

W-8. DOPAMINE MEDIATED CHANGES IN THE BLOOD BRAIN BARRIER AND NEUROINFLAMMATION IN THE CONTEXT OF CNS HIV INFECTION AND SUBSTANCE ABUSE. Coley, JS1, Calderon, TM1, Lopez, L1, Berman, JW1; 1Dept. of Pathology, Albert Einstein College of Medicine, Bronx, NY 10461.

W-9. EFFECT OF GP120 IN CATHEPSIN B AND CYSTATIN B EXPRESSION IN HIV PATIENTS. Colon, K 1, Delgado, G 2, Melendez, LM 1; 1Microbiology Department, University of Puerto Rico - Medical Sciences Campus, San Juan, PR 009352Biology Deparment, University of Puerto Rico - Rio Piedras Campus, San Juan, PR 00931.

W-10. HIV-1 ENVELOPE GLYCOPROTEIN GP120 TRIGGERS A SENESCENCE PHENOTYPE IN CULTURED HUMAN ASTROCYTES. Crowe, EP 1, Sell, C 1, Torres, C 1; 1Dept. of Pathology and Laboratory Medicine, Drexel University College of Medicine, Philadelphia, PA 19102.

W-11. DISRUPTION OF THE CHOLINERGIC ANTI-INFLAMMATORY RESPONSE IN THE HIV CONTEXT. Delgado-Velez , M 1, Baez-Pagan , C 1, Gerena, Y 6, Quesada , O 3, Santiago-Perez , L 1, Wojna , V 5, Melendez, L 4, Silva, W 7, Lasalde-Dominicci, J 1; 1Dept of Biology, Dept of Chemistry, Dept of Physical Sciences, University of Puerto Rico, Río Piedras Campus, San Juan, PR 009314; Dept of Microbiology and Medical Zoology, Internal Medicine, Dept of Pharmaceutical Sciences, School of Pharmacy, Dept of Physiology, Univ of Puerto Rico, Medical Sciences Campus, San Juan, PR 00936.

W-12. GENOMIC SIGNATURE OF PPAR AGONISTS IN BRAIN AND LIVER: ROLE IN ALCOHOL CONSUMPTION. Ferguson, LB 1, Blednov, YA 1, Harris, RA 1; 1Waggoner Center for Alcohol and Addiction Research, University of Texas at Austin, Austin, TX 78712.

W-13. INVOLVEMENT OF GLIA AND CYTOKINES IN HIV-INDUCED CHANGES OF FERRITIN HEAVY CHAIN PROTEIN EXPRESSION IN CORTICAL NEURONS. Festa, L 1, Meucci, O 1; 1Department of Pharmacology and Physiology, Drexel University College of Medicine, Philadelphia, PA 19102.

W-14. NEONATAL ETHANOL EXPOSURE CAUSES LONG-TERM ALTERATION IN MICROGLIA SENSITIVITY AND RESPONSE TO STRESS. Franklin, T 1, Sarkar, D.K. 1; 1Endocrine Program, Rutgers University, New Brunswick, NJ 08901.

W-15. HIV-1 VIRAL PROTEIN R (VPR) INDUCES THE PRODUCTION OF PRO-INFLAMMATORY CYTOKINES IL-6, IL -8 AND RANTES IN THE ASTROCYTES VIA DIFFERENT MECHANISMS. Gangwani, MR 1, Kumar, A 1; 1Division of Pharmacology and Toxicology, University of Missouri Kansas City, Kansas City, MO 64108.

W-16. HIV PROTEASE INHIBITORS PROMOTE AMYLOIDOGENIC APP PROCESSING VIA PHOSPHO-EIF2A-DEPENDENT TRANSLATIONAL UPREGULATION OF BACE1. Gannon, P 1, Akay, C 1, Yee, A 1, Odeleye, A 1, Clements, J 2, Mankowski, J 2, Zink, C 2, Jordan-Sciutto, K 1; 1School of Dental Medicine, University of Pennsylvania, Philadelphia, PA 191042School of Medicine, Johns Hopkins University, Baltimore, MD 21205.

W-17. ALCOHOL ALTERS MICROGLIA FUNCTION THROUGH P2X4 RECEPTOR SIGNALING. Gofman, L 1, Cenna, JM 1, Potula, R 1; 1Department of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140.

W-18. COCAINE REGULATES NEURONAL EXPRESSION OF RXR-Γ: IMPLICATIONS FOR RETINOIC ACID RESPONSIVE GENES AND NEURONAL PLASTICITY. Kovalevich, J 1, Corley, G 1, Ozdemir, AY 1, Yen, W 1, Kim, JK 1, Rawls, S 1, Langford, D 1; 1Neuroscience, Temple University School of Medicine, Philadelphia, PA 19140.

W-19. FUNCTIONAL ADAPTATION OF NMDA RECEPTORS FOLLOWING HIV-1 TAT-INDUCED POTENTIATION. Krogh, KA1, Thayer, SA1 ; Department of Pharmacology, University of Minnesota Medical School, Minneapolis, MN 55455

W-20. HEDGEHOG PATHWAY PLAYS A VITAL ROLE IN HIV-ASSOCIATED NEPHROPATHY. Lan, X 1, Cheng, K 1, Plagov, A 1, Chandel, N 1, Rai, P 1, Malhotra, A 1, Singhal, PC 1; 1Renal Molecular Research Laboratoy, Feinstein Institute for Medical Research, Great Neck, NY 11021.

W-21. THE ROLE OF PI3K/AKT/CREB-1 AND JAK/STAT SIGNALING IN HIV-1 NEF-MEDIATED INCREASE OF IL-6 IN ASTROCYTES. Liu, X 1, Kumar, A 1; 1Pharmacology & Toxicology, School of Pharmacy, University of Missouri-Kansas City, Kansas City, MO 64108.

W-22. PROTEOMIC FINGERPRINTS OF PRIMARY HUMAN ASTROCYTES TREATED WITH HIV-1 CLADE B AND C PROTEINS: ROLES OF ENDOPLASMIC RETICULUM STRESS IN NEURO-AIDS. López, SN, Rodríguez, M., Amadeo, W, Cubano, L, Alves, J, Boukli, N; Department of Microbiology and Immunology, Biomedical Proteomic Facility, Universidad Central del Caribe, Bayamón, PR 00960.

W-23. HIV-1 NEF EXPRESSION IN RAT HIPPOCAMPUS INCREASES SMALL INTESTINE PERMEABILITY AND DECREASES OCCLUDIN TIGHT JUNCTION PROTEIN. Loucil, R 1, Isidro, RA 2, Chompre, G 1, Hernandez, S 2, Cruz, ML 2, Isidro, AA 2, Appleyard, CB 2, Noel, Jr, RJ 1; 1Department of Biochemistry, Ponce School of Medicine and Health Sciences, Ponce, PR 007162Department of Physiology and Pharmacology, Ponce School of Medicine and Health Sciences, Ponce, PR 00716.

W-24. CHEMOKINE CXCL8 MODULATES HIV-1 REPLICATION IN HUMAN MONOCYTE-DERIVED MACROPHAGES. Mamik, MK 1, Borgmann, K 1, Ghorpade, A 1; 1Cell Biology and Anatomy, University of North Texas Health Science Center, Fort Worth, TX 76107.

W-25. DISTINCT INDUCTION OF IL-17 ISOFORMS BY MORPHINE CONTRIBUTES TO DIFFERENTIAL BARRIER DISRUPTION IN THE SMALL INTESTINE AND COLON. Meng, J 1, Ma, J 2, Banerjee, S 2, Wang, F 1, Charboneau, R 3, Roy, S 2; 1Department of Pharmacology, University of Minnesota, Minneapolis, MN 554552Department of Surgery, University of Minnesota, Minneapolis, MN 554553Department of Surgery, Veterans Affairs Medical Center, Minneapolis, MN 55417.

W-26. DEFICITS IN ATTENTION, A CORE COMPONENT OF EXECUTIVE FUNCTION, IN FEMALE HIV-1 TRANSGENIC RATS. Moran, L.M. 1, Booze, R.M. 1, Mactutus, C.F. 1; 1Behavioral Neuroscience Program, Department of Psychology, University of South Carolina, Columbia, SC 29208.

W-27. INDUCTION OF IL-6 AND IL-8 CYTOKINES BY HIV-1 TAT INVOLVES A COMMON TRANSCRIPTION FACTOR NUCLEAR FACTOR-KAPPA B BUT DIFFERENT SIGNALING PATHWAYS. Nookala, A, Kumar, A; Division Pharmacology & Toxicology, UMKC School of Pharmacy, Kansas city, MO 64108.

W-28. COCAINE ALTERS CYTOKINE SIGNATURES WITHIN PATIENTS IN THE DREXELMED HIV/AIDS GENETIC ANALYSIS COHORT. Parikh, N 1, Williams, J 1, Pirrone, V 1, Nonnemacher, M 1, Aiamkitsumrit, B 1, Passic, S 1, Blakey, B 1, Frantz, B 1, Moldover, B 2, Feng, R 3, Downie, D 4, Lewis, S 4, Jacobson, JM 4, Wigdahl, B 1; 1Microbiology and Immunology, Drexel University College of Medicine, Philadelphia, PA 191022B-Tech Consulting, Ltd, B-Tech Consulting, Ltd, Philadelphia, PA 191303Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, PA 191044Medicine/Division of Infectious Disease and HIV Medicine, Drexel University College of Medicine, Philadelphia, PA 19102.

W-29. CCR5-EXPRESSING NEURONS AND GLIA AS SITES OF CONVERGENCE FOR HIV-1 TAT AND OPIOID INTERACTIONS. Podhaizer, EM 1, Zhang, Y 2, Knapp, PE 3, Hauser, KF 1; 1Dept. of Pharmacology & Toxicology; 2Dept. of Medicinal Chemistry; 3Dept. of Anatomy & Neurobiology, Virginia Commonwealth University, Richmond, VA 23298.

W-30. PROTEOMICS APPROACH OF ALCOHOL INDUCED ER STRESS IN HUMAN MICROGLIA CELLS. Ricardo J Carrero, Yanilda Ramos, Sheila Lopez, Janaina Alves, Hiram Escobales, Madeline Rodríguez, and Nawal Boukli. Universidad Central del Caribe, Bayamón, PR 00960.

W-31. ROLE OF DEPRESSION ON PRO-INFLAMMATORY AND OXIDATIVE STRESS RESPONSES IN HIV-INFECTED PUERTO RICANS. Rivera-Rivera Y, Toro-Rodriguez V, Cappas-Ortiz N, Rivera-Amill V; Dept. of Microbiology, and Deptt of Clinical Psychology Ponce School of Medicine & Health Sciences, Ponce, PR 00716.

W-32. HIV-1 CLADE B ACTIVATES PRO-APOPTOTIC PROTEIN SIGNATURES IN HUMAN MICROGLIA. Rodriguez, M 1, Escobales, H 1, Lopez, SN 1, Alves, JM 1, Cubano, L 1, Boukli, NM 1; 1Biomedical Proteomic Facility, Universidad Central del Caribe, Bayamon, PR 00956.

W-33. POLY(ADP-RIBOSE) POLYMERASE-1 (PARP) INHIBITION DECREASES HIV-1 REPLICATION IN PRIMARY HUMAN MONOCYTE-DERIVED MACROPHAGES (MDM). Rom , S 1, Reichenbach, NL 1, Persidsky, Y 1; 1Department of Pathology & Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19046.

W-34. PACAP27 IS A NEW NEUROPROTECTIVE COMPOUND AGAINST TAT-MEDIATED NEUROTOXICITY. Rozzi SJ, Borelli G, Ryan K, Steiner J, Palchik G, Avdoshina V, Mocchetti I; Department of Neuroscience, and the Department of Pharmacology & Physiology, Georgetown University, Washington, DC 20007; National Institute of Neurological Disorders and Stroke NINDS), National Institutes of Health, Bethesda, MD 20892.

W-35. ANTI-APOPTOTIC ROLE OF HEXOKINASE IN HIV-1 INFECTED MACROPHAGES. Sen , S 1, Datta, PK 2, Khalili, K 2, Amini, S 1; 1Biology , Temple University , Philadelphia , PA 191212Neuroscience/ CNAC, Temple University School of Medicine, Philadelphia , PA 19140.

W-36. INFECTION WITH ECOHIV, A NOVEL MURINE MODEL OF HIV, AND MORPHINE COMPROMISE GUT BARRIER FUNCTION AND BACTERIAL CLEARANCE. Sindberg, GM 1, Sharma, U 2, Meng, J 3, Banerjee, S 2, Volsky, D 4, Molitor, T 5, Roy, S 2; 1Comparative and Molecular Biosciences, University of Minnesota, Saint Paul, MN 551082Department of Surgery, University of Minnesota, Minneapolis, MN 554553Department of Pharmacology, University of Minnesota, Minneapolis, MN 554554Molecular Virology Division, St. Luke's-Roosevelt Hospital Center/Columbia University, New York, NY 100195Department of Veterinary Population Medicine, University of Minnesota, Saint Paul, MN 55108.

W-37. GLIAL P2X4 RECEPTORS MEDIATE OPIOID AND HIV-1 ASSOCIATED NEURODEGENERATION. Sorrell, ME 1, Zou, S 2, Knapp, PE 2, Hauser, KF 1; 1Department of Pharmacology and Toxicology; 2Department of Anatomy and Neurobiology, Virginia Commonwealth University, Richmond, VA 23298.

W-38. STRUCTURAL AND FUNCTIONAL ALTERATIONS IN AN IN VITRO MODEL OF THE BLOOD-BRAIN BARRIER FOLLOWING PROLONGED EXPOSURE TO MORPHINE. Strazza, M 1, Pirrone, V 1, Lin, W 2, Feng, R 2, Wigdahl, B 1, Nonnemacher, M 1; 1Microbiology and Immunology, Drexel University College of Medicine, Philadelphia, PA 191022 Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, PA 19104.

W-39. ACUTE ALCOHOL INTOXICATION IS ASSOCIATED WITH SUSTAINED NEUROINFLAMMATION WITHOUT EXACERBATION OF EARLY NEUROBEHAVIORAL OUTCOMES POST TRAUMATIC BRAIN INJURY. Teng, S 1, Molina, P 1; 1Department of Physiology, Louisiana State University Health Sciences Center, New Orleans, LA 70112.

W-40. NEUROTOXIC EFFECTS OF HIV-1 VPR EXPRESSION IN ASTROCYTES . Torres, L. and Noel Jr., RJ; Biochemistry Dept, Ponce School of Medicine & Health Sciences, Ponce, PR 00732.

W-41. ASTROCYTE-ELEVATED GENE-1 PROTECTS HUMAN ASTROCYTES FROM OXIDATIVE STRESS-INDUCED DNA DAMAGE: A POTENTIAL SURVIVAL MECHANISM IN HAND. Vartak-Sharma, N 1, Ghorpade, A 1; 1Department of Cell Biology and Anatomy, University of North Texas Health Science Center, Fort Worth, TX 76107.

W-42. EFFECT OF HIV-1 GP120 ON THE GLUTAMIC ACID METABOLIC SYSTEM IN HUMAN ASTROCYTES. Vázquez-Santiago, FJ 1, Meléndez, LM 2, Wojna , V 3, Noel, RJ 1, Rivera-Amill, V 1; 1Microbiology Department, Ponce School of Medicine and Health Sciences, Ponce, PR 007162Microbiology and Medical Zoology Department, University of Puerto Rico Medical Science Campus, San Juan, PR 009363Specialized Neuroscience Research Program, University of Puerto Rico Medical Science Campus, San Juan , PR 00936.

W-43. COCAINE SELF-ADMINISTRATION POTENTIATES EXCITATORY RESPONSES OF RAT CORTICAL NEURONS TO HIV-1 TAT PROTEIN. Wayman, WN 1, Napier, TC 1, Hu, X-T 1; 1Department of Pharmacology and the Center for Compulsive Behavior and Addiction, Rush University Medical Center, Chicago, IL 60612.

W-44. THE EFFECTS OF DOPAMINE ON CD14+CD16+ TRANSMIGRATION ACROSS THE HUMAN BLOOD BRAIN BARRIER AND ITS ROLE IN THE PATHOGENESIS OF NEUROAIDS. Williams, DW 1, Calderon, TC 1, Lopez, L 1, Morgello, S 2, Berman, JW 1; 1Pathology, Albert Einstein College of Medicine, Bronx, NY 104612Neurology, Neuroscience, Pathology, Mount Sinai Medical Center, New York, NY 10029.

W-45. ANKYRIN-RICH MEMBRANE SPANNING PROTEIN (ARMS) PLAYS A CRUCIAL ROLE IN HIV-1 TAT-INDUCED ACTIVATION OF MICROGLIAL CELLS. Wooten, AK 1, Jackson, J 1, Kiebala, M 1, Maggirwar, SB 1; 1Department of Microbiology and Immunology, University of Rochester School of Medicine and Dentistry, Rochester, NY 14642.

W-46. SELENOGLYCOPROTEINS SUPPRESS ADHESION OF BREAST CANCER CELLS TO HUMAN BRAIN ENDOTHELIUM VIA A MECHANISM INVOLVING NF-KB. Wrobel JK, Choi JJ, Xiao R, Kwiatkowski S, Power R, Toborek M; Department of Biochemistry and Molecular Biology, University of Miami Miller School of Medicine, Miami, FL 33136; Nutrigenomics Research Centre, Alltech, Nicholasville, KY 40356.

W-47. SIGMA-1 RECEPTOR PROTECTS AGAINST HIV TAT-MEDIATED ER STRESS RESPONSE IN ASTROCYTE:IMPLICATION FOR HAND. Yang, L 1, Mori, M 2, Buch, S 1; 11Dept. of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, omaha, NE 681982Dept. of Toxicology, School of Pharmacy and Pharmaceutical Sciences, Hoshi University, Tokyo, 142-8501.

W-48. EFFECT OF COCAINE IN THE PLASMA OF HIV SEROPOSITIVE WOMEN BY 18O ISOTOPIC LABELLING. Zenon, F 1, Cruz, A 1, Melendez, L 1, Segarra, A 1, Jorge , I 2, Vazquez, J 2, Serrano , H 1; 1University of Puerto Rico Medical Sciences Campus, School of Medicine/UPR-RCM, San Juan, PR 009362Cardiovascular Proteomics Laboratory, Centro Nacional de Investigaciones Cardiovasculares/Centro de Biología Molecular “Severo Ochoa”, Madrid, E-28029.

W-49. THE INTERACTIVE ROLE OF ALCOHOL AND CANNABINOIDS ON DENDRITIC CELL FUNCTION. Agudelo, M, Yndart, A, Morrison, M, Muñoz, K, Raymond, A, Nair, MP; 1Dept. of Immunology/Institute of NeuroImmune Pharmacology, Herbert Wertheim College of Medicine, Miami, FL 33190.

W-50. CALPAIN-MEDIATED DEGRADATION OF MDMX/MDM4 EXPRESSION CONTRIBUTES TO HIV-INDUCED NEURONAL DAMAGE. Akay, C 1, Colacurcio, D 1, Daniels, M 1, Kolson, DL 2, Jordan-Sciutto, KL 1; 1Department of Pathology , School of Dental Medicine, 2Department of Neurology, The Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104.

W-51. HIV-1 CLADE B EXPRESS NEURONAL APOPTOTIC PROTEOMIC FINGERPRINTS. Alves, JM, Carrero, RJ, Rodriguez, M, Lopez, SN, Cubano, L, Boukli, NM; Biomedical Proteomics Facility - Department of Microbiology and Immunology, Universidad Central del Caribe, Bayamón, PR 00960.

W-52. MORPHINE IMPAIRS LYSOSOMAL ACIDIFICATION LEADING TO COMPROMISED BACTERIAL KILLING. Anand, V 1, Koodie, L 2, Banerjee, S 1, Sindberg, G 3, Ma, J 1, Roy, S 1; 1Division of BTR/ Department of Surgery, 2Dentistry, Pharmacology, University of Minnesota, Minneapolis, MN 554553; Department of Veterinary Biosciences, University of Minnesota, Saint Paul, MN 55108.

W-53. EFFECT OF NICOTINE ON SYNAPTIC PLASTICITY GENE EXPRESSION IN HIV-1 INFECTION: IMPLICATION IN HAND. Atluri, VSR 1, Sudheesh, PK 1, Samikkannu , T 1, Vijaya, P 1, Ding, H 1, Raymond, AD 1, Nair, M 1; 1Department of Immunology, Institute of NeuroImmune Pharmacology, Herbert Wertheim College of Medicine, Florida International University, Miami, FL 33199.

W-54. CHARACTERIZATION OF SINGLE NUCLEOTIDE POLYMORPHISMS OF THE HUMAN ALPHA7 NICOTINIC RECEPTOR REVEALS ALTERATIONS IN FUNCTIONALITY AND RESPONSE TO BUPROPION: POTENTIAL IMPLICATIONS TO THE PATHOGENESIS AND TREATMENT OF HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS. Báez-Pagán, C.A. 1, Aviles-Pagán, E. 1, Aponte-Santiago, N.A. 1, Holder-Viera, M. 1, Lasalde-Dominicci, J.A. 1; 1Department of Biology, University of Puerto Rico, Río Piedras Campus, San Juan, PR 00931.

W-55. ROLE OF HIV TAT PROTEIN IN THE REGULATION OF GENE EXPRESSION IN MACROPHAGE. POSSIBLE MECHANISM IN DRUG ABUSERS. Carvallo, L 1, Fajardo, J.E 2, Berman, JW 1; 1Department of Pathology, Albert Einstein College of Medicine, Bronx, NY 104612Department of Systems and Computational Biology , Albert Einstein College of Medicine, Bronx, NY 104613Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, NY 10461.

W-56. POTENTIAL PROTECTIVE ROLE OF THE TIGHT JUNCTION PROTEIN OCCLUDIN AGAINST HIV-1 INFECTION OF PERICYTES . Castro, V 1, Lüthen, M 2, Toborek, M 1; 1Biochemistry and Molecular Biology, University of Miami. Miller School of Medicine, Miami, FL 33136 2Department of Biology, Freie Universität-Berlin, Berlin, 14195.

W-57. REPEATED COCAINE ADMINISTRATION EXACERBATED HIV-1 TAT-MEDIATED CORTICAL EXCITABILITY VIA OVER-ACTIVATING L-TYPE CALCIUM CHANNELS. Chen, L 1, Napier, TC 1, Hu, X-T 1; 1Dept. of Pharmacology and Center for Compulsive Behavior and Addiction, Rush University Medical Center, Chicago, IL 60612.

W-58. HUMAN PRIMARY ASTROCYTES EXPRESS CD99: POTENTIAL ROLE IN HIV BRAIN INFECTION. Daep, CA 1, Eugenin, E 1; 1Public Health Research Institute, University of Medicine and Dentistry of New Jersey, Newark, NJ 07107.

W-59. MECHANISM FOR ACCELERATED NEUROPATHOGENESIS IN DRUG ABUSE/HIV MODEL: ROLE OF SYSTEMIC INFECTION AND TOLL -LIKE RECEPTORS. Dutta, Raini 1, Roy, Sabita 1; 1Department of Surgery, University of Minnesota, Minneapolis, MN 55455.

W-60. HIV-1 VIRAL PROTEINS DISRUPT NEURON AUTOPHAGY FUNCTION AND AUTOPHAGOSOME FORMATION: MECHANISMS IN HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS. Fields, J 1,

Dumaop, W 1, Adame, A 1, Masliah, E 1; 1Department of Pathology, University of San Diego, California, La Jolla, CA 92093.

W-61. PLATELET ACTIVATION BY COCAINE IN HIV PATIENTS INVOLVES IKK. Kiebala, M 1, Singh, M 1, Maggirwar, SB 1; 1Department of Microbiology and Immunology, University of Rochester School of Medicine and Dentistry, Rochester, NY 14642.

W-62. IN VITRO AND IN VIVO EXPOSURE TO COCAINE ENHANCES HIV INFECTION IN QUIESCENT T CELLS. Kim SG1, Dixit D2, Jung J2, Rovner RJ2, Zack JA1,2, Baldwin GC1, Vatakis DN1; 1Department of Medicine, Division of Hematology and Oncology, 2Department of Microbiology, Immunology and Molecular Genetics, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095.

W-63. MORPHINE DISRUPTS LEUKOCYTE ENDOTHELIAL TRANS-CELLULAR MIGRATION. Koodie, L 1, Roy, S 2; 1Dentistry, Pharmacology, University of Minnesota, School of Medicine, Minneapolis, MN 554552Division of Basic Translational Research, Department of Surgery, University of Minnesota, Minneapolis, MN 55446.

W-64. METHAMPHETAMINE MODULATES ANTI-HIV-1 MIRNA EXPRESSION TO REGULATE HIV-1 REPLICATION IN CD4+ T CELLS AND MACROPHAGES. Mantri, CK 1, Velamarti Mantri, J 1, Pandhare Dash, J 1, Dash, CV 1; 1CAHDR, Meharry Medical College, Nashville, TN 37208.

W-65. INSOMNIA CORRELATES WITH IMMUNE DYSREGULATION BUT NOT WITH HCT/OX SYSTEM DYSFUNCTION IN HIV-INFECTED WOMEN. Menéndez-Delmestre, R 1, López, R 2, Matos, M 1, Skolasky, RL 3, Vélez, J 1, Ginebra, T 1, Wojna, V 1; 1NeuroAIDS Program, .2Division of Neurology, Univ. of Puerto Rico, Medical Sciences Campus, San Juan, PR 009353Department of Orthopaedics, Johns Hopkins University, Baltimore, MD 21287.

W-66. T-CELL RECONSTITUTION DURING MURINE ACQUIRED IMMUNODEFICIENCY SYNDROME (MAIDS) PRODUCES NEUROINFLAMMATION AND MORTALITY IN ANIMALS HARBORING OPPORTUNISTIC VIRAL BRAIN INFECTION. Mutnal, MB 1, Schachtele, SJ 1, Hu, S 1, Lokensgard, JR 1; 1Neuroimmunology Laboratory, Center for Infectious Diseases and Microbiology Translational Research, University of Minnesota , Minneapolis, MN 55455.

W-67. CLASS I HISTONE DEACETYLASES AND A LYSINE-SPECIFIC HISTONE METHYLTRANSFERASE, SUV39H1, PROMOTE HIV LATENCY IN ASTROCYTES. Narasipura, SD 1, Min, S 1, Al-Harthi, L 1; 1Department of Immunology/Microbiology, Rush University, Chicago, IL 60612.

W-68. METHAMPHETAMINE-INDUCED INCREASES IN PLASMA AMMONIA PRODUCE NEUROINFLAMMATION AND BLOOD-BRAIN BARRIER DISRUPTION. Northrop, NA1, Halpin, LE1, Yamamoto, BK 1; 1Dept. of Neurosciences, Univ. of Toledo College of Medicine, Toledo, OH 43614.

W-69. NEUROINFLAMMATION IN YOUNG ADULT HIV-1 TRANSGENIC RATS. Persons, AL 1, Chen, L 1, Wayman, WN 1, Hu, X-T 1, Napier, TC 1; 1Department of Pharmacology and Center for Compulsive Behavior and Addiction, Rush University Medical Center, Chicago, IL 60612.

W-70. COCAINE DOWNREGULATES SAHMD1 EXPRESSION AND FACILITATES HIV-1 INFECTION IN ASTROCYTES. Pilakka-Kanthikeel, S 1, Raymond, S 1, Atluri, V 1, Nair, M 1; 1Department of Immunology, Institute of NeuroImmune Pharmacology, Herbert Wertheim College of Medicine, Florida International University, Miami, FL 33199.

W-71. MEDIUM SPINY NEURONS IN THE NUCLEUS ACCUMBENS OF HIV-1 TRANSGENIC FEMALE RATS: DIOLISTIC ASSESSMENT OF SYNAPTODENDRITIC ALTERATIONS. Roscoe, RF, Mactutus, CF, Booze, RM; Dept. of Psychology, University of South Carolina, Columbia, SC 29208.

W-72. PERSISTENT CD8 T CELLS HINDERS NEUROGENESIS DURING HERPES SIMPLEX ENCEPHALITIS. Rotschafer, JH 1, Roach, E 1, Cheeran , MCJ 1; 1Veterinary Population Medicine, University of Minnesota, St. Paul , MN 55108.

W-73. MAGNETIC-NANOFORMULATION OF M-OPIOID RECEPTOR ANTAGONIST (CTOP) FOR TREATMENT OF MORPHINE-INDUCED NEUROPATHOGENESIS IN HIV INFECTION. Sagar, Vidya 1, Pilakka-Kanthikeel , S. K. 1, Priestap, H. 2, Atluri, V. S. R. 1, Ding, H. 1, Guduru, R. 1, Khizroev, S. 1, Nair, M.P. 1; 1Center for Personalized Nanomedicine, Institute of NeuroImmune Pharmacology, Department of Immunology, Herbert Wertheim College of Medicine, Florida International University, Miami, FL 331992Department of Biological Sciences, College of Arts and Sciences, Florida International University, Miami, FL 33199.

W-74. DIFFERENTIAL INDUCTION OF POST-ENCEPHALITIC REGULATORY T-CELLS BY DISTINCT BRAIN CELL POPULATIONS. Schachtele, SJ 1, Mutnal, MB 1, Hu, S 1, Lokensgard, JR 1; 1Center for Infectious Disease & Microbiology Translational Research, Univ. of Minnesota, Minneapolis, MN 55407.

W-75. A MURINE MODEL OF HIV RECAPITULATE KEY FEATURES OF HIV-1 INFECTION IN THE CONTEXT OF OPIOID ABUSE. Sharma, U 1, Banerjee, S 1, Sindberg, G 2, Charboneau, R 3, Volsky, DJ 4, Roy, S 1; 1Department of Surgery, University of MInnesota, Minneapolis, MN 554552Comparative and Molecular Biosciences, University of MInnesota, Minneapolis, MN 554553Department of Surgery, Veterans Affairs Medical Center, Minneapolis, MN 554174Molecular Virology Division, St. Luke's-Roosevelt Hospital Center, New York, NY 10019.

W-76. ADOLESCENT BINGE DRINKING PERSISTENTLY INCREASES NEUROIMMUNE SIGNAL EXPRESSION IN THE ADULT PREFRONTAL CORTEX. Vetreno, R.P. 1, Qin, L. 1, Crews, F.T. 1; 1Bowles Center for Alcohol Studies, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599.

W-77. GLUTAMINASE 1 IS ESSENTIAL FOR THE SURVIVAL, DIFFERENTIATION, AND PROLIFERATION OF NEURAL PROGENITOR CELLS. Wang, Y 1, Huang, Y 1, Zhao, L 1, Li, Y 1, Zheng, J 1; 1Dept of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68105.

W-78. HEPATITIS C VIRUS IMPAIRS TOLL-LIKE RECEPTOR-3 SIGNALING AND INHIBITS IFN-LAMBDA 1 EXPRESSION IN HUMAN HEPATOCYTES. Wang, Y.Z. 1, Li, J.L. 1, Wang, X. 1, Ye, L. 1, Zhou, Y. 1, Thomas, R.M. 1, Ho, W.Z. 1; 1Department of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140.

W-79. EXERCISE MODULATES REDOX-SENSITIVE SMALL GTPASE ACTIVITY IN THE BRAIN MICROVASCULATURE IN A MODEL OF BRAIN METASTASIS FORMATION. Wolff, G 1, Park, M 1, Andras, IE 1, Kim, HJ 1, Toborek, M 1; 1Biochemistry and Molecular Biology, Univ. of Miami, FL 33136.

W-80. ANTI-INFLAMMATORY EFFECT OF DEXAMETHASONE -HPMA COPOLYMER IN A MURINE MODEL OF HIV-1 ENCEPHALITIS. Zhao, L1, Huang, Y1, Wang, D2, Zheng, J.C1; 1Dept. of Pharmacology & Experimental Neuroscience; 2Dept. of Pharmaceutical Sciences, College of Pharmacy, Univ. of Nebraska Medical Center, Omaha, NE 68198.

Please remember to take down all posters after the session.

Thursday, April 4, 2013

All sessions held in Ponce de Leon Rooms A/C, Ocean Tower, Mezzanine level unless otherwise listed.

7:00-8:00am **Continental Breakfast for Conference Registrants**
(*Ponce de Leon Foyer*)

8:00-8:15am **INTRODUCTION TO THE MEETING**

Welcome from the Society on NeuroImmune Pharmacology
Sabita Roy Ph.D.- SNIP President
(University of Minnesota, Minneapolis)

8:15 – 8:55am **PLENARY LECTURE 1: Benjamin Chen, M.D., Ph.D.-** Mount Sinai School of Medicine, NY.

2009 Avant-Garde Award for Innovative HIV-AIDS Research
Title: Visualizing HIV dissemination through virological synapses.

Introduction by Dr. Chandravanu Dash PhD. – Meharry Medical College School of Medicine, Nashville, Tennessee

8:55 -11:20am **SYMPOSIUM #1: Neuroimmune Activation by Alcohol, Drugs and/or AIDS Contributes to Addiction Neurobiology**

Co-Chairs: *Fulton Crews, Ph.D.*– UNC Medical School, Chapel Hill, NC
Changhai Cui, Ph.D.– NIAAA, NIH, Bethesda, MD

8:55-9:00am **Introductory Remarks: Changhai Cui, Ph.D.-** NIAAA, NIH, Bethesda, MD

9:00-9:25am **Lecture 1: Dr. Fulton T. Crews-** UNC Medical School, Chapel Hill, NC

Title: Ethanol activates HMGB1/TLR-RAGE Signaling inducing innate immune genes in brain.

9:25-9:50am **Lecture 2: Dr. Dipak Sarkar-** Rutgers University, New Brunswick, NJ

Title: Microglial mediation of alcohol programming of the neuroendocrine-stress axis influencing alcohol-drinking behavior.

9:50-10:15am **Lecture 3: Dr. R. Adron Harris, Ph.D.-** Waggoner Center, University of Texas

Title: Neuroimmune regulation of alcohol consumption, opportunities for therapeutics?

10:15-10:40am **Lecture 4: Dr. Mark Hutchinson, PhD-** School of Med. Sciences, University of Adelaide

Title: The proinflammatory hypothesis of addiction: clinical and preclinical evidence

10:40-10:50am **Coffee Break**

10:50-11:15am **Lecture 5: Dr. Sietse Jonkman, Ph.D., Scripps Research Inst., Jupiter, FL**

Title: miRNA132 promotes cocaine addiction through NFkB signaling

11:15-11:20am **Concluding Remarks** Sulie L. Chang, PhD, Seton Hall University

11:20-11:50am **PLENARY LECTURE 2: Thirumala-Devi Kanneganti, Ph.D.-** St. Jude Children's Research Hospital

Title of talk: Mediators of Inflammatory Responses

Introduction: Dr. Prasun Datta, Ph.D.- Temple University, Philadelphia

11:50-12:55pm **Meet the Mentors Luncheon** *(Ponce de Leon B)*

11:50-12:55pm **Lunch on your own (for those not attending Meet the Mentors Lunch)**

1:00-2:00 pm **SNIP Annual Business Meeting** *(Ponce de Leon A/C)*
All Society Members Welcome
ECITA should attend. All trainee members of SNIP highly encouraged to participate.
Prizes will be given by raffle to those in attendance.

2:00-4:30 pm **SYMPOSIUM II: Emerging Trends in Substance Abuse, HIV Infection and Neuropathogenesis**

Co-Chairs: *Kelly Jordan-Sciutto, Ph.D.-* University of Pennsylvania
Thomas Rogers, Ph.D.- Temple University, Philadelphia, PA

2:00 –2:25pm **Lecture 1: Jag Khalsa, Ph.D.-** NIDA/NIH

Title: Clinical implications of Neuro-Immune Pharmacology

2:25-2:50pm **Lecture 2: Olimpia Meucci, M.D.-** Drexel University, Philadelphia

Title: The FHC-CXCR4 connection and its relevance to HAND and drug abuse

2:50-3:15pm **Lecture 3: Lena Al-Harthi, Ph.D.-** Rush University, Chicago

Title: Astrocytes and NeuroAIDS: The Wnt/β-catenin connection in virus/host interaction and neuropathogenesis

3:15-3:25pm **Coffee Break**

3:25 – 3:50pm **Lecture 4: Shilpa Buch, Ph.D.-** University of Nebraska

Title: HIV and Morphine mediated regulation of neuronal dysfunction: blaming the Messenger

3:50-4:15pm **Lecture 5: Joan Berman, Ph.D**.- Albert Einstein College of Medicine, Bronx, NY

Title: Dopamine mediated neuroinflammation and CNS damage in the context of HIV infection: A common mechanism of drugs of abuse

4:15-4:30pm **Lecture 6: Santanu Banerjee. Ph.D.-** University of Minnesota

Title: Morphine attenuation of LPS tolerance-Role of miRNA

4:35 – 7:35 pm **Poster Session 2** *(Brisas del Mar,Ocean Tower, Lobby level)*
(Coffee Break during Poster Session)
Please have posters numbered 1-40 mounted by 4:00pm.
Posters T-1 through T-40 to be presented from 4:35-5:55pm, and then removed.
Posters T-41 through T-75 to be mounted at 6pm and presented until 7:35pm.

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

GENERAL POSTER SESSION TITLES

T-1. LONG-TERM HIV-1 INFECTION OF HUMANIZED MICE LEADS TO BEHAVIORAL ABNORMALITIES. Akhter, S 1, Epstein, A 1, Poluektova, L 1, Gendelman, HE 1, Gorantla, S 1; 1Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center , Omaha, NE 68198.

T-2. HUMAN NEUROGENESIS IN NSG MICE FOR HAND PATHOGENESIS STUDIES. Akhter, SA, Knibbe, J, Wu, L, Li, Y, Peng, H, Gorantla , S, Poluektova, LY; Univ. of Nebraska Medical Center, Department of Pharmacology and Experimental Neuroscience, Omaha, NE 68198.

T-3. FORMATION OF D1/NMDA RECEPTOR COMPLEXES MEDIATES HIV-1 PROTEINS+METH SYNAPTODENDRITIC INJURY. Aksenova, M.V. 1, Mactutus, C.F. 1, Booze, R.M. 1; 1Psychology Department, University of South Carolina, Columbia, SC 29208.

T-4. HIV-1 INDUCED AMYLOID BETA ACCUMULATION IN BRAIN ENDOTHELIAL CELLS. Andras IE, Toborek M; Department of Biochemistry and Molecular Biology, University of Miami School of Medicine, Miami, FL 33136.

T-5. HIV INTERACTS WITH NEURONAL TUBULIN: A MECHANISM FOR MICROTUBULAR NETWORK IMPAIRMENT?. Avdoshina, V 1, Sahab, ZJ 2, Rozzi, SJ 3, Lim , ST 1, Mocchetti, I 1; 1Department of Neuroscience, Georgetown University Medical Center, Washington, DC 200572Department of Molecular Oncology, Georgetown University Medical Center, Washington, DC 200573Interdisciplinary Program in Neuroscience, Georgetown University Medical Center, Washington, DC 20057.

T-6. MANGANESE ENHANCED MAGNETIC RESONANCE IMAGING (MEMRI) REFLECTS HUMAN NEUROPATHOLOGY IN A MURINE MODEL OF HIV-1 ASSOCIATED NEUROCOGNITIVE DISORDERS (HAND). Bade, AN 1, Gorantla, S 1, Poluektova, LY 1, Makarov, E 1, Gendelman, HE 1, Boska, MD 2, Liu, Y 2; 1Department of Pharmacology and Experimental Neuroscience, University of

Nebraska Medical Center, Omaha, Omaha, NE 681982Department of Radiology, University of Nebraska Medical Center, Omaha, Omaha, NE 68198.

T-7. WITHAFERIN A INHIBITS IL-1BETA MEDIATED INDUCTION OF MIR-146A EXPRESSION IN HUMAN ASTROCYTES BY DOWN-REGULATING NF-KB SIGNALING. Banerjee, S 1, Datta, P.K 1; 1Department of Neuroscience/ Center for Neurovirology, Temple University School of Medicine, Philadelphia, PA 19140.

T-8. HIV-1 TAT/COCAINE-INDUCED SYNAPTODENDRITIC INJURY IS PREVENTED BY ESTROGENIC COMPOUNDS. Bertrand, SJ 1, Aksenova, MV 1, Mactutus, CF 1, Booze, RM 1; 1Psychology Department, University of South Carolina, Columbia, SC 29208.

T-9. ROLE OF IL-1 SIGNALING IN REGULATION OF BEHAVIORAL EFFECTS OF ETHANOL AND BENZODIAZEPINES. Blednov YB, Harris RA; Waggoner Center for Alcohol and Addiction Research, University of Texas, Austin, TX 78712.

T-10. HISTONE DEACETYLASE DEREGULATION IN HIV-1-INFECTED MACROPHAGES EXPOSED TO METHAMPHETAMINE. Burns, AC 1, Olszowy, P 1, Ciborowski, P 1; 1Pharmacology & Experimental Neuroscience , University of Nebraska Medical Center, Omaha, NE 68198.

T-11. DOPAMINE INCREASES CD14+CD16+ MONOCYTE TRANSMIGRATION ACROSS THE BBB. Calderon, TM 1, Lopez, L 1, Williams, DW 1, Gaskill, PJ 1, Eugenin, EA 2, Berman, JW 1; 1Department of Pathology, Albert Einstein College of Medicine, Bronx, NY 104612Public Health Research Institute (PHRI) and Department of Immunology and Molecular Genetics, University of Medicine and Dentistry of New Jersey, Newark, NJ 07103.

T-12. CHRONIC MORPHINE PREVENTS GP120-MEDIATED CELL DEATH BY ALTERING THE PROBDNF PROCESSING. Campbell, L 1, Passeri, E 1, Mocchetti, I 1, Bachis, A 1; 1Department of Neuroscience, Georgetown University, Washington, DC 20057.

T-13. POTENTIAL PROTECTIVE ROLE OF THE TIGHT JUNCTION PROTEIN OCCLUDIN AGAINST HIV-1 INFECTION OF PERICYTES. Castro, V 1, Lüthen, M 2, Toborek, M 1; 1Biochemistry and Molecular Biology, University of Miami. Miller School of Medicine, Miami, FL 33136 2Department of Biology, Freie Universität-Berlin, Berlin, 14195.

T-14. MORPHINE-INDUCED EIPIGENETIC FACTORS PROMOTE MACROPHAGE APOPTOSIS VIA ACTIVATION OF THE RENIN ANGIOTENSIN SYSTEM. Chandel, N 1, Malhotra, A 1, Singhal, PC 1; 1Hofstra University, North-Shore Long-Island Jewish Medical Health system, Great Neck, NY 11021.

T-15. NEURAL STEM CELL PROLIFERATION IS MODULATED BY DIFFERENTIAL FGF-2 EXPRESSION DURING EXPERIMENTAL HERPES SIMPLEX ENCEPHALITIS. Cheeran M C-J, Rotschafer JH, Hu S, Low WC; Veterinary Population Medicine, University of Minnesota, St. Paul, MN 55108; Center for Infectious Diseases and Microbiology Translational Research, Department of Medicine, and Department of Neurosurgery and Stem Cell Institute, University of Minnesota, Minneapolis, MN 55455.

T-16. CXCR7, A NOVEL RECEPTOR OF CXCL12, MEDIATES MIGRATION AND SIGNALING OF NEURAL PROGENITOR CELLS IN VITRO. Chen, Q 1, Li, Y 1, Song, A 1, Zhu, B 1, Peng, H 1, Huang, Y 1, Tian, C 1, Xu, D 1, Zheng, J. C 1; 1Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198.

T-17. POST-TRANSLATIONAL MODIFICATIONS OF HISTONE H4 IN HUMAN IMMUNODEFICIENCY VIRUS-1 INFECTED HUMAN MACROPHAGES EXPOSED TO METHAMPHETAMINE AND ANTIRETROVIRAL DRUGS. Ciborowski P, Burns A, Olszowy PP; Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198-5800.

T-18. IMPACT OF SUBSTANCE ABUSE ON HIV-1 LTR SINGLE NUCLEOTIDE POLYMORPHISMS (SNPS) AND DISEASE PROGRESSION IN A CLINICAL COHORT. Dampier, W 1, Nonnemacher, M 1, Pirrone,

V 1, Williams, J 1, Aiamkitsumrit, B 1, Wojno, A 1, Passic, S 1, Blakey, B 1, Zhong, W 1, Moldover, B 3, Feng, R 4, Downie, D 2, Lewis, S 2, Jacobson, J 2, Wigdahl, B 1; 1Dept. of Microbiology and Immunology, Drexel University College of Medicine, Philadelphia, PA 191022Division of Infectious Disease and HIV Medicine, Dept. of Medicine, Drexel University College of Medicine, Philadelphia, PA 191023B-Tech Consulting, LTD, B-Tech Consulting, LTD, Philadelphia, PA 191304Dept. of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, PA 19104.

T-19. ROLE OF EPIGENETICS IN ASTROCYTIC EAAT2 GENE EXPRESSION BY IL-1 BETA. Datta, P 1; 1Neuroscience, Temple University School of Medicine, Philadelphia, PA 19140.

T-20. HIV-TAT AND COCAINE MEDIATED DOWN-REGULATION OF BMP RECEPTOR AXIS IN PULMONARY ARTERIAL SMOOTH MUSCLE CELLS: IMPLICATIONS FOR HIV-PAH. Dhillon NK, Dalvi P, O'Brien-Ladner A; Internal Medicine, University of Kansas Medical Center, Kansas City, KS 66160.

T-21. DUAL MECHANISM ENHANCED BBB CROSSING BY TRANSFERRIN CONJUGATED FLUORESCENT MAGNETIC LIPOSOME. Ding H, Agudelo M, Kanthikeel SP, Guduru R, Sagar V, Atluri V, Thangavel S, Nair MN; Department of Immunology, Florida International University, Miami, FL 33199.

T-22. ROLE OF CYP2A6 IN NICOTINE METABOLISM STUDIED USING NEWLY DEVELOPED LC-MS/MS-SPE METHOD IN HIV-1 MODELS MONOCYTES AND ASTROCYTES, AND PLASMA FROM HIV-INFECTED SMOKERS. Earla, R 1, Ande, A 1, Mitra, AK 1, Kumar, A 1, Kumar , S 1; 1University of Missori-Kansas City, UNKC School of Pharmacy, Kansas City, MO 64108.

T-23. NEUROPROTECTIVE ROLE OF PHOSPHODIESTERASE INHIBITOR IBUDILAST ON NEURONAL CELL DEATH INDUCED BY HIV-1 AND MORPHINE ACTIVATED GLIA. El-Hage, N 1, Zou, S 2, Snyder, S 1, Podhaizer, EM 1, Beardsley, PM 1, Knapp, PE 2, Hauser, KF 1; 1Department of Pharmacology and Toxicology , Virginia Commonwealth University, Richmond , VA 232982Department of Anatomy and Neurobiology, Virginia Commonwealth University, Richmond , VA 23298.

T-24. METHAMPHETAMINE ALTERS GAP JUNCTIONAL COMMUNICATION BETWEEN NEURONS AND ASTROCYTES: POTENTIAL ROLE IN CNS COMPROMISE AND DRUG DEPENDENCY. Eugenin E, Nosanchuck J, Martinez L, Castellano P; Microbiology and Molecular Genetics, and the Public Health Research Institute, UMDNJ, Newark, NJ 07103; Department of Biomedical Sciences, Albert Einstein College of Medicine (Long Island University-Post, Brookville, NY) Bronx, NY 10461

T-25. HIV INFECTION OF ASTROCYTES INCREASED RELEASE OF DICKKOF-1 (DKK1) PROTEIN BY A HEMICHANNEL-DEPENDENT MECHANISM. Eugenin, E 1, Orellana, JA 2, Saez, JC 2, Bennett, M 3, Berman, J 3, Morgello, S 4; 1Microbiology and Molecular genetics, Public Health Research Institute (PHRI)/UMDNJ, Newark, NJ 071032Physiology, Pontificia Univ Catolica de Chile, Santiago, 3Albert Einstein College of Medicine, Bronx, NY 104614neurology, Mount Sinai, NY, NY 10010.

T-26. EXPOSURE TO FLAME RETARDANT BDE-47 INDUCES OCCLUDIN DISRUPTION AND VCAM-1 EXPRESSION IN HUMAN BRAIN ENDOTHELIAL CELLS. Eum, SY 1, Choi, JJ 1, Andra, IE 1, Park , M 1, Toborek, M 1; 1Department of Biochemistry & Molecular Biology, University of Miami Miller School of Medicine, Miami, FL 33136.

T-27. ACTIVATION OF MACROPHAGE DOPAMINE RECEPTORS MAY EXACERBATE HAND BY INCREASING HIV ENTRY INTO MACROPHAGES AND ALTERING MACROPHAGE FUNCTIONS. Gaskill, PJ, Berman, JW Dept of Pathology, Albert Einstein College of Medicine, Bronx, NY 10461.

T-28. ANGIOTENSIN II AND IV IN GLUCOSE TOLERANCE AND OXIDATIVE STRESS OF HUMAN NEURONAL CELLS. Gerena, Y 1, Sierra, J 2, Sánchez-Courtney, Y 3, Méndez, J 4, Pérez, S 2, Hilera, C 2, Wojna, V 5; 1Pharmaceutical Sciences Dept., University of Puerto Rico, Medical Sciences Campus, San Juan, PR 009362Rio Piedras Campus, University of Puerto Rico, Rio Piedras, PR 009313Medicine, San Juan Bautista, Caguas, PR 007254Earth Institute, Columbia University, New

York, NY 100275Neurology Division, University of Puerto Rico, Medical Sciences Campus, San Juan, PR 00936.

T-29. POTENTIAL ROLE OF GP120 IN HIV-INDUCED AIRWAY MUCUS FORMATION AND LUNG DISEASE. Gundavarapu, S 1, Mishra, N.C. 1, Singh, S.P. 1, Langley, R.J. 1, Buch, S 2, Sopori, M.L 1; 1Respiratory Immunology Division, Lovelace Respiratory Research Institute, Albuquerque, NM 8710822Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198.

T-30. MODULATION OF HUMAN CD4 AND CD8 T CELLS CELL CYCLE ENTRY AND PROGRESSION TO METHAMPHETAMINE. Haldar, B 1, Cenna, J M 1, Potula, R 1; 1Department of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140.

T-31. METHAMPHETAMINE (METH) MEDIATED IMMUNE DYSREGULATION IN AN ANIMAL MODEL OF CHRONIC VIRAL INFECTION. Haldar, B 1, Cenna, JM 1, Gofman, L 1, Potula, R 1; 1Department of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140.

T-32. MECHANISMS OF CEREBRAL HEMORRHAGIC LESIONS IN DRUG ABUSE NEUROAIDS. Haorah, J 1, Abdul Muneer, PM 1, Szlachetka, A 1; 1University of Nebraska Medical Center, Omaha, NE , Neurovascular Oxidative Injury Laboratory, Dept. of Pharmacology and Experimental Neuroscience, Omaha, NE 68198-5215.

T-33. EXOSOME-MEDIATED SHUTTLING OF MICRORNA-29 REGULATES HIV TAT AND MORPHINE-MEDIATED NEURONAL DYSFUNCTION. Hegde R1, Callen S2, Hu G2,Yao H2, Chaudhuri AD2, Duan M2, Yelamanchili SV2, Wen H2, Cheney PD1, Fox HS2,Buch S1,2. 1Department of Molecular and Integrative Physiology, University of Kansas Medical Center, Kansas City, Kansas 66160, USA; 2Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198.

T-34. DAMAGE CONTROL IN VIVO: NEUROPROTECTIVE LIPOCALIN-2 IS UPREGULATED IN BRAINS OF HIV-1/GP120-TRANSGENIC MICE. Hoefer, M. M. 1, Maung, R. 1, De Rozieres, C. M. 1, Dowling, C. C. 1, Catalan, I. C. 1, Sanchez, A. B. 1, Kaul, M. 1; 1Infectious and Inflammatory Disease Center, Sanford-Burnham Medical Research Institute, La Jolla, CA 92037.

T-35. BRAIN CELLS MODULATE ENCEPHALITOGENIC T-CELL RESPONSES VIA PD-1: PD-L1. Hu S, Schachtele SJ, Mutnal MB, Sheng WS, Lokensgard JR; Center for Infectious Diseases and Microbiology Translational Research, University of Minnesota, Minneapolis, MN 55455.

T-36. OPIATES DEACTIVATE REDOX-SENSITIVE STRESS RESPONSE PROGRAM IN T CELLS. Husain, M 1, Rehman, S 2, Chandel, N 2, Lan, X 2, Malhotra, A 2, Singhal, PC 2; 1Department of Biotechnology, Jamia Millia Islamia, New Delhi , 1100252Feinstein Institute for Medical Research, Hofstra North Shore LIJ Medical School, Great Neck, NY 11021.

T-37. REGULATION OF CYTOCHROME P450 2E1 EXPRESSION BY ETHANOL: ROLE OF OXIDATIVE STRESS-MEDIATED PKC/JNK/SP1 PATHWAY. Jin, M1, Ande, A1, Kumar, A1, Kumar, S1; 1Division of Pharmacology and Toxicology, Univ. of Missouri-Kansas City, Kansas City, MO 64108.

T-38. E2F1 AT THE SYNAPSE: NOVEL FUNCTIONS FOR A CELL CYCLE TRANSCRIPTION FACTOR IN A NON-CELL CYCLE CONTEXT. Jordan-Sciutto KL, Ting JH, Schleidt S, Wu J, Marks, DR; Department of Pathology/Dental Medicine, University of Pennsylvania, Philadelphia, PA 19104.

T-39. THE ROLE OF CELL CYCLE PROTEIN E2F1 IN HIV-INDUCED NEUROTOXICITY. Jordan-Sciutto, KL 1, Zyskind, JW 1, Wang, Y 1, Akay, C 1, Kolson, DL 2; 1Department of Pathology/Dental Medicine, 2Department of Neurology/Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104.

T-40. MAGNETO-ELECTRIC NANOPARTICLES FOR NON-INVASIVE BRAIN STIMULATION. Khizroev, S. 1, Yue, K. 1, Guduru, R. 1, Liang, P. 2, Hong, J. 1, Nair, M. 1; 1Center for Personalized NanoMedicine/Institute of Neuro-Immune Pharmacology/Department of Immunology, Herbert Wertheim College of Medicine/Florida International University, Miami, FL 331992Department of Electrical Engineering, University of California, Riverside, CA 92521.

T-41. VOLUNTARY EXERCISE REDUCES THE EFFECTS OF METHAMPHETAMINE ON THE EXPRESSION OF MULTIDRUG REGISTANCE TRANSPORTERS IN BRAIN ENDOTHELIUM. Kim, HJ 1, Zhang, B 1, Park, M 1, Toborek, M 1; 1Biochemistry and Molecular Biology, University of Miami, Miami, FL 33136.

T-42. CYTOKINE PROFILES IN ANTIRETROVIRAL TREATED MACROPHAGES AND ASTROCYTES. King, J 1, Chan, J 1, Jordan-Sciutto, K 1; 1Department of Pathology, University of Pennsylvania, Philadelphia, PA 19104.

T-43. FEASIBILITY OF THE CONDITIONAL DEPLETION OF MOUSE MICROGLIA: IMPLICATION FOR HUMANIZED MOUSE MODEL IMPROVEMENT. Knibbe J, Gutti T, Akhter S, Bade A, Liu Y, Gorantla S, Poluektova L; University of Nebraska Medical Center, College Of Medicine / PEN Department, Omaha, NE 68114.

T-44. INTERPLAY OF COCAINE ABUSE AND HIV-1 TAT PROTEIN ON OLIGODENDROCYTE FUNCTION: IMPLICATIONS FOR HIPPOCAMPAL DEMYELINATION AND PROGRESSION OF HAND. Kovalevich, J 1, Yen, W 1, Ozdemir, AY 1, Langford, D 1; 1Neuroscience, Temple University School of Medicine, Philadelphia, PA 19140.

T-45. ASHWAGANDHA (WITHANIA SOMNIFERA) REVERSES B-AMYLOID INDUCED NEURONAL TOXICITY: IMPLICATIONS IN HAND. Kurapati, V.K.R 1, Atluri, V.S.R 1, Samikkannu, T 1, Yndart, A.A 1, Nair, M.P.N 1; 1Immunology, Florida International University, College of Medicine, Miami, FL 33199.

T-46. ETHANOL DOWN REGULATES T CELL VITAMIN D RECEPTOR THROUGH MODULATION OF EPIGENETIC FACTORS. Lan, X 1, Chandel, N 1, Lederman, R 1, Valecha, G 1, Malhotra, A 1, Singhal, PC 1; 1Feinstein Institute for Medical Research, Hofstra North Shore LIJ Medical School, Great Neck, NY 11021.

T-47. ETHANOL DOWN REGULATES T CELL VITAMIN D RECEPTOR THROUGH MODULATION OF EPIGENETIC FACTORS. Lan, X, Chandel, N, Lederman, R, Valecha, G, Malhotra, A, Singhal, PC; Feinstein Institute Medical Research, Hofstra North Shore LIJ Medical School, Great Neck, NY 11021.

T-48. PINCH IN THE CELLULAR STRESS RESPONSE TO TAU-HYPERPHOSPHORYLATION. Langford, D 1, Ozdemir, AY 1, Rom, I 1, Kovalevich, J 1, Yen, W 1, Adiga, R 1, Dave, R 1; 1Neuroscience, Temple University School of Medicine, Philadelphia, PA 19140.

T-49. LPS INDUCES IMMUNE ACTIVATION AND SIV REPLICATION IN CHINESE RHESUS MACAQUES. Li, J-L 1, Bao, R 1, Guo, M 2, Ye, L 3, Zhang, J 1, Dai, M 1, Rao, Y 1, Wang, Y 1, Xian, Q-Y 1, Huang, Z-X 1, Tang, Z-J 1, Persidsky, Y 3, Ho, W-Z 3; 1The Center for Animal Experiment/Animal Biosafety Level III Laboratory, Wuhan University School of Medicine, Hubei, 4300712State Key Laboratory of Virology, Wuhan University School of Medicine, Wuhan, PA 4300713Department of Pathology and Laboratory Medicine, Temple University School of Medicine , Philadelphia, PA 19140.

T-50. HIV-1 TAT PROTEIN INCREASES MICROGLIAL OUTWARD K CURRENT AND RESULTANT NEUROTOXIC ACTIVITY. Liu, J 1, Collins, C 1, Xu, P 1, Chen, L 1, Xiong, H 1; 1Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198-5880.

T-51. ANTIRETROVIRAL THERAPY REVERSES HIV-MEDIATED SUPPRESSION OF ANTIVIRAL CELLULAR FACTORS. Liu, MQ 1, Zhao, M 2, Zhou, W 1, Peng, JS 1, Wang, X 3, Wang, F 1, Zhou, DJ 1, Ho, WZ 3; 1Department of Virology, Wuhan Centers for Disease Prevention & Control, Wuhan,

4300152Wuhan AIDS Care Center, Wuhan Municipal Institute of Dermatosis, Wuhan, 4300303Department of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19104.

T-52. MIR-9 PROMOTES MICROGLIAL ACTIVATION BY TARGETING MCPIP: IMPLICATIONS FOR HAND. Ma, R 1, Yao, H 1, Buch, S 1; 1Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198.

T-53. EFFECT OF HIV-1 SUBTYPE C INFECTION ON IMMUNE AND NERVOUS SYSTEM FUNCTION AND BIOLOGY IN A HUMANIZED MOUSE MODEL OF HIV/AIDS. Makarov, E 1, Adem, S 1, Wood, C 2, Poluektova, L 1, Gendelman, HE 1, Gorantla, S 1; 1Dept. of Pharmacology and Experimental Neuroscience, Univ. of Nebraska Medical Center, Omaha, NE 681982Nebraska Center for Virology, Univ. of Nebraska at Lincoln, Lincoln, NE 68583.

T-54. CLINICAL CORRELATION WITH CD4 COUNT AND MENTAL DIAGNOSIS AMONG HIV INFECTED DRUG USERS. Munoz-Caamano, K., Raymond, A., Yndart, A., Pilakka-Kanthikeel, S., Nair, MPN.; Dept. of Immunology, Institute of NeuroImmune Pharmacology, Herbert Wertheim College of Medicine, Florida International University, Miami, FL 33199.

T-55. THC-INDUCED DYSREGULATION IN MICRORNA TRIGGERS MYELOID-DERIVED SUPPRESSOR CELLS AND CONSEQUENT SUPPRESSION OF T CELL RESPONSES TO GP120 OF HIV. Nagarkatti M, Hegde V, Nagarkatti P; Dept. of Pathology, Microbiology and Immunology, University of South Carolina School of Medicine, Columbia, SC 29209.

T-56. HIV-1 LTR SINGLE NUCLEOTIDE POLYMORPHISMS (SNPS) CORRELATE WITH CLINICAL DISEASE PARAMETERS. Nonnemacher, M 1, Pirrone, V 1, Dampier, W 1, Aiamkitsumrit, B 1, Williams, J 1, Shah, S 1, Wojno, A 1, Passic, S 1, Blakey, B 1, Zhong, W 1, Moldover, B 3, Feng, R 4, Downie, D 2, Lewis, S 2, Jacobson, J 2, Wigdahl, B 1; 1Department of Microbiology and Immunology, Drexel University College of Medicine, Philadelphia, PA 191022Division of Infectious Disease and HIV Medicine, Department of Medicine, Drexel University College of Medicine, Philadelphia, PA 191023B-Tech Consulting, LTD, B-Tech Consulting, LTD, Philadelphia, PA 191304Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, PA 19104.

T-57. ALCOHOL MEDITATED INDUCTION OF PROINFLAMMATORY CYTOKINES IN HUMAN ASTROCYTES. Nookala, A, Gangwani, M, Rey, JP, Shah, A, Kumar, S, Kumar, A; Pharmaoclogy & Toxicology, UMKC-School of Pharmacy, Kansas City, MO 64108.

T-58. TAT-MEDIATED CHANGES OF MALAT1 LONG NON-CODING RNA AFFECTS THE STRUCTURE AND FUNCTION OF SC35 NUCLEAR SPECKLES DOMAINS IN NEURONS. Pacifici, M 1, Kadri, F 1, Jeansonne, D 1, Peruzzi, F 1; 1LCRC, LSUHSC School of Medicine, New Orleans, LA 70112.

T-59. HIV-RELATED PAIN AND GP120 IN THE BRAIN. Palma, J, Geller, E, Adler, M, Eisenstein, T, and Benamar, K. Center for Substance Abuse Research (CSAR), Temple University School of Medicine, Philadelphia, Pennsylvania, USA.

T-60. METHAMPHETAMINE-INDUCED OCCLUDIN ENDOCYTOSIS IS MEDIATED BY THE ARP2/3 COMPLEX-REGULATED ACTIN REARRANGEMENT. Park, M 1, Kim, HJ 1, Toborek, M 1; 1Department of Biochemistry and Molecular Biology, University of Miami School of Medicine, Miami, FL 33136.

T-61. COMORBIDITY OF ALCOHOLISM, HIV INFECTION AND HEPATITIS C: IN VIVO BRAIN IMAGING. Pfefferbaum A, Zahr NM, Sullivan EV; Center for Health Science, SRI International, Menlo Park, CA 94025; Department of Psychiatry, Stanford University School of Medicine, Stanford, CA 94305.

T-62. LONGITUDINAL STUDY OF HIV-1 INDUCED NEUROPATHOGENESIS IN HUMANIZED NOD/SCID-IL 2RECEPTOR GAMMA CHAIN-NULL (NSG) MOUSE MODEL. Potula, R 1, Zuluaga-Ramirez, V 1,

Reichenbach, N 1, Cenna, JM 1, Persidsky , Y 1; 1Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140.

T-63. SPECTRUM OF AUTOPSY HIV NEUROPATHOLOGY IN THE POST ANTI-RETROVIRAL THERAPY (ART) ERA: EXPERIENCE IN A SINGLE URBAN TERTIARY TEACHING HOSPITAL. Potula, R, Zhang, M, Ramirez, SH, Persidsky, Y, Mukherjee, A; Pathology and Laboratory Medicine, Temple Univ. Hospital and School of Medicine, Philadelphia, PA 19140.

T-64. SERUM DETECTION OF SHED EXTRACELLULAR MICROVESICLES FROM BRAIN ENDOTHELIAL CELLS: SEROLOGICAL INDICATORS OF BLOOD BRAIN BARRIER (BBB) DISRUPTION DURING NEUROINFLAMMATION. Ramirez, SH 1, Persidsky, Y 1, Rom, S 1, Dykstra, H 1; 1Department of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140.

T-65. COCAINE ENHANCES HIV-1 REPLICATION IN MONOCYTE DERIVED MACROPHAGES BY REGULATING THE ACTIVATING TRANSCRIPTION FACTOR-2 (ATF-2). Ranjan, A 1, Pandhare-Dash, J 1, Mantri, C K 1, Dash, CV 1; 1CAHDR, Meharry Medical college, Nashville, TN 37208.

T-66. HIV NEUROPATHOGENESIS: ROLE OF NEF+ EXOSOMES (EXNEF), METHAMPHETAMINE AND OPIATES. Raymond, A.D. 1, Yndart-Arias, A. 1, Agudelo, M. 1, Munoz, K. 1, Alturi, V.S. 1, Pilakka, S. 2, Thangavel, S. 2, Nair, M.P. 1; 1Department of Immunology, Florida International University, Herbert Wertheim College of Medicine; 2Institute of NeuroImmune Pharmacology, Florida International University, Miami, FL 33199.

T-67. SELECTIVE ACTIVATION OF CANNABINOID RECEPTOR 2 (CB2) IN LEUKOCYTES SUPPRESSES THEIR ENGAGEMENT OF THE BRAIN ENDOTHELIUM AND PROTECTS THE BLOOD BRAIN BARRIER (BBB). Rom S, Zuluaga-Ramirez V, Dykstra H, Reichenbach NL, Persidsky Y; Department of Pathology & Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140.

T-68. MAGNETIC-NANO FORMULATION OF M-OPIOID RECEPTOR ANTAGONIST (CTOP) FOR TREATMENT OF MORPHINE-INDUCED NEUROPATHOGENESIS IN HIV INFECTION. Sagar, Vidya 1, Pilakka-Kanthikeel , S. K. 1, Priestap, H. 2, Atluri, V. S. R. 1, Ding, H. 1, Guduru, R. 1, Khizroev, S. 1, Nair, M.P. 1; 1Center for Personalized Nanomedicine, Institute of NeuroImmune Pharmacology, Department of Immunology, Herbert Wertheim College of Medicine, Florida International University, Miami, FL 331992Department of Biological Sciences, College of Arts and Sciences, Florida International University, Miami, FL 33199.

T-69. CANNABINOID BLOCKADE OF HIV-1 GP120-INDUCED EFFECTS ON HUMAN FETAL NEURAL PRECURSOR CELLS. Sheng, WS 1, Hu, S 1, Rock, R B 1; 1CIDMTR, Department of Medicine, University of Minnesota, Minneapolis, MN 55455.

T-70. INTERPLAY OF HIV-1 GP120 AND OPIATES DURING THE PATHOGENESIS OF HIV-ASSOCIATED CHRONIC PAIN. Tang, S.-J. 1, Shi, Y. 1, Yuan, S. 1; 1Department of Neuroscience and Cell Biology, University of Texas Medical Branch, Galveston, TX 77555.

T-71. IMMUNOPATHOGENIC MECHANISMS OF HIV-1 CLADE B AND C: ROLE OF DOPAMINERGIC SYSTEM. Thangavel, S 1, Rao, K.V.K 1, Raymond, A 1, Ding, H 1, Atluri , V.S.R 1, Nair, M.P 1; 1Institute of NeuroImmune Pharmacology (NIP), College of Medicine,, Florida International University, Miami, FL 33199.

T-72. HEROIN USE INHIBITS ANTI-HIV MICRORNA EXPRESSION IN CD4+ T CELLS. Wang, X 1, Peng, JS 2, Liu, MQ 2, Zhou, Y 1, Wang, F 2, Zhou, W 2, Zhou, DJ 2, Ho, WZ 1; 1Dept. of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 191402Dept. of Virology, Wuhan Centers for Disease Prevention & Control, WUHAN, 430015.

T-73. DYSREGULATION OF IL-33 AND ST2 IN HIV1 B AND C CLADES. Yndart A, Agudelo M, Munoz-Caamano K, Raymond A, Nair M; Immunology Department, College of Medicine, Florida International University, Miami, FL 33199.

T-74. URMC-099: A MIXED-LINEAGE KINASE-3 (MLK3) INHIBITOR WITH THE POTENTIAL TO ERADICATE HUMAN IMMUNODEFICIENCY VIRUS INFECTION. Zhang G, Dash PK, Wiederin JL, Ciborowski PS, Goodfellow VS, McMillan JM, Smith NA, Gorantla AS, Gelbard, HA, Gendelman HE; University of Nebraska Medical Center, School of Medicine, Omaha, NE 68198; Califia Bio., Inc, San Diego, CA 92121; University of Rochester Medical Center, School of Medicine and Dentistry, Rochester, NY 14642.

T-75. INTERMOLECULAR INTERACTION BETWEEN HIV-1 TAT PROTEIN AND DOPAMINE TRANSPORTER DISRUPTS THE PHYSIOLOGICAL FUNCTION OF DOPAMINE SYSTEM. Zhu, J 1, Midde, NM 1, Huang, X 3, Gomez, AM 1, Booze, RM 2, Zhan, CG 3; 1South Carolina College of Pharmacy, University of South Carolina, Columbia, SC 292082Psychology, University of South Carolina, Columbia, SC 292083College of Pharmacy, University of Kentucky, Lexington, KY 40536 .

Please remove all posters at the end of the session

Friday, April 5, 2013

6:30-8:00am **JNIP Editorial Board Meeting** *(Ponce de Leon B)*

7:00-8:00am **Continental Breakfast for Conference Registrants**
(*Ponce de Leon Foyer*)

8:00 – 8:40am **PLENARY LECTURE 3: Jon M Lindstrom Ph.D.-** University of Pennsylvania

Title: Nicotinic acetylcholine receptors: Targets of nicotine and autoantibodies

Introduction: Mohan Sopori, Ph.D.- Lovelace Respiratory Research Institute, Albuquerque, NM

8:40-10:10am **SYMPOSIUM III: Physiological and Pathological Role of Nicotinic Receptors**

Co-Chairs: *Madhavan Nair, Ph.D.-* Florida International University
Mohan Sopori, Ph.D.- Lovelace Respiratory Research Institute

8:40-9:05am **Lecture 1: Eliot R Spindel, Ph.D.-** Oregon Health and Science University

Title: LYNX1 and other LY-6 proteins are a family of endogenous regulators of nicotinic signaling: Implications for lung disease and lung cancer

9:05 – 9:30am **Lecture 2: Mohan Sopori, Ph.D.-** Lovelace Institute

Title: Nicotinic Receptors in Airway mucus formation in Health and Disease.

9:30-9:50am **Lecture 3: Santosh Kumar, Ph.D.-** UMKC

Title: Role of cytochrome P450 enzymes in tobacco/nicotine-mediated effects on HIV-1 model systems

9:50-10:10am **Lecture 4: Venkata Subba Rao Atluri, Ph.D.-** Florida International University

Title: Effect of nicotine on synaptic plasticity gene expression in HIV-1 infection: implication in HAND

10:10-10:20am **Coffee Break**

10:20-10:50am **Plenary Lecture 4: Bert t' Hart, Ph.D.-** Biomedical Primate Research Center, The Netherlands

Title: Mysterious Role of B lymphocytes in neuroinflammation

Introduction: Howard Gendelman, M.D.- University of Nebraska

10:50-12:25pm **Symposium IV: Animal Models of HIV infection and Drug Abuse Session**

Co-Chairs: *Shilpa Buch, Ph.D.*- University of Nebraska
Marcus Kaul, Ph.D.- Sanford-Burnham Institute

10:50-11:15am **Lecture 1: Howard Fox, M.D., Ph.D.-** University of Nebraska, Omaha,NE

Title: Interaction of methamphetamine and HIV – A systems approach

11:15-11:40am **Lecture 2: Ken Williams, Ph.D.-** Boston College, Chestnut Hill, MA

Title: Monocyte and Macrophage Activation in SIV Pathogenesis

11:40-12:05pm **Lecture 3: Fatah Kashanchi, Ph.D.-** George Mason University, Manassas, VA

Title: Exosomes and their function in vitro and in vivo

12:05-12:25pm **Lecture 4: Marco Salemi, Ph.D.-** University of Florida, Gainsville, FL

Title: Phylodynamic analysis of brain infection in the SIV infected macaque model of NeuroAIDS

12:30 - 1:30pm **Early Career Investigators Grant Writing Workshop Session**

Co-Chairs: *Albert Avila, Ph.D.*- National Institute on Drug Abuse/NIH
Eduardo Montalvo Ph.D.- CSR, National Institutes of Health

1.30- 2.10pm **Bill Narayan Lecture: Avi Nath, M.D.-** NINDS, National Institute of Health

Title: Eradication of HIV reservoirs from the brain

Introduction: Shilpa Buch Ph.D.- University of Nebraska, Omaha

2:10 – 4:10pm **Symposium V: Cannabinoids, HIV Pathogenicity, and Other Infectious Disease Processes**

Organizers: *Vishnudutt Purohit, Ph.D.*-National Institute on Drug Abuse, NIH
Guy A. Cabral, Ph.D.- Virginia Commonwealth University

Co-Chairs: *Rao Rapaka, Ph.D.*- National Institute on Drug Abuse, NIH
Guy A. Cabral, Ph.D.- Virginia Commonwealth University

2.10-2.15pm **Introductory Comments - Rao Rapaka, Ph.D.-** Chief, Chemistry and Physiological Systems Research Branch (CPSRB), NIDA, NIH

2:15 – 2:40pm **Lecture 1: Melissa Jamerson, Ph.D.-** Virginia Commonwealth University School of Medicine, Richmond, VA

Title: Cannabinoids mediate macrophage-like cell responsiveness to HIV-specified gene products

2:40-3:05pm **Lecture 2: Mitzi Nagarkatti, Ph.D.-** University of South Carolina School of Medicine, Columbia, SC

Title: THC-induced dysregulation in microRNA triggers myeloid-derived suppressor cells and consequent suppression of T cell responses to gp120 of HIV.

3:05-3:30pm **Lecture 3: Nicole LeCapitaine, Ph.D.-** University Health Sciences Center, New Orleans, LA

Title: Unraveling the impact of cannabinoids on HIV disease: a system-wide approach.

3:30 – 3:55pm **Lecture 4: Norbert Kaminski, Ph.D.-** Director for Integrative Toxicology, Michigan State University, East Lansing, MI

Title: Role of antigen presenting cells and the cannabinoid receptors 1 and 2 in Δ9-tetrahydrocannabinol impairment of the inflammatory response to influenza infection

3:55-4:00pm **Summary and Conclusion – Vishnudutt Purohit, Ph.D.-** NIDA,NIH

Afternoon and Evening Free!!!

Saturday, April 6, 2013

7:00-8:00am **Continental Breakfast for Conference Registrants**
(*Ponce de Leon Foyer*)

8:00 – 8:40am **PLENARY LECTURE 5: Tariq Rana, Ph.D.-** Sanford-Burnham Institute

Title: Meeting Places for RNAi and Antiviral Defense Machine

Introduction: Marcus Kaul, Ph.D.- Sanford-Burnham Institute

8:40 -10:.35am **SYMPOSIUM VI: Neuropathology of HIV-1 in an Aging Population**

Co-Chairs: *Jeymohan Joseph, Ph.D.*- National Institute of Mental Health, Bethesda
Michal Toborek M.D., Ph.D.- University of Miami School of Medicine

8:40-8:45am **Introductory Remarks: Jeymohan Joseph, Ph.D.**- NIMH, NIH

8:45-9:10am **Lecture 1: Gary Landreth, Ph.D.-** Case Western Reserve University, Cleveland, OH

Title: Therapeutic approaches to amyloid clearance and improved cognitive function"

9:10-9:35am **Lecture 2: Eliezer Masliah, Ph.D.-** University of California, San Diego

Title: Autophagy and HIV-1 brain infection

9:35-9:55am **Lecture 3: Valerie Wojna, M.D.-** University of Puerto Rico, San Juan, PR

Title: HAND and Host Factors in Women on CART: Role of β-amyloid

9:55-10:05am **Coffee Break**

10:05-10:30am **Lecture 4: Lynn Pulliam, Ph.D.-** University of California, San Francisco

Title: HIV regulation of amyloid beta production

10:25-10:45am **Lecture 5: Ibolya Andras, M.D.-** University of Miami School of Medicine

Title: HIV-1 induced amyloid beta accumulation in brain endothelial cells"

10:50-10:55am **Concluding Remarks**

10:55-am 12:05 **Symposium VII: Early Career Investigator Symposium**

Co-Chairs: *Santosh Kumar, Ph.D.*- UMKC
Mike Nonemacher, Ph.D.- Drexel University, Philadelphia

11:00-11:30am **Pre doctoral Presentations**

Lecture 1: Ankit Shah, M.S.- School of Pharmacy, Univ. of Missouri-Kansas City

Title: HIV-1 protein gp120 and methamphetamine co-operate synergistically to increase oxidative stress in astrocytes: Role of cytochrome P450

Lecture 2: Yu Zhou, M.S.- Temple University School of Medicine

Title: HCV infection and heroin use dysregulate the circulating miRNA expression

Lecture 3: Sarah J. Bertrand, B.S.- University of South Carolina

Title: HIV-1 Tat/cocaine-induced synaptodendritic injury is prevented by estrogenic compounds

11:35-12:05pm **Post Doctoral Presentation**

Lecture 1: Crystal Bethel-Brown, Ph.D.- University of Nebraska Medical Center

Title: Cooperative effects of HIV-1 Tat and ethanol on human brain endothelial cell permeability involves modulation of PDGF/PDGF-R axis

Lecture 2: Fnu Ashutosh, Ph.D.– Univ. of North Texas Health Science Center

Title: A nanotechnology approach to protect human neurons from oxidative stress

Lecture 3: J Ma, Ph.D – Department of Surgery, University of Minnesota

Title: Methamphetamine disrupts gut barrier function in a murine EcoHIV infection model

12:05-12:30pm **Lunch on your own**

12:30-1:30pm **Future Perspective – NeuroAIDS, Substance Abuse Think Tank**

Co-Chair: *Yuri Persidsky, M.D., Ph.D.- Temple University, Philadelphia, PA*
Kendall Bryant, Ph.D.- NIAAA

1:30 – 3:15pm **Symposium VIII: Local Host Symposium – HIV, Drug Abuse, and NeuroImmune Pharmacology Research in Puerto Rico**

Co-Chairs: *Richard J. Noel Jr., Ph.D.*- Ponce School of Medicine
Loyda Melendez, Ph.D.- UPR - Medical Sciences Campus

1:30-1:50pm **Lecture 1: Vanessa Rivera-Amill, Ph.D.-** Ponce School of Medicine

Title: Integrated Behavioral Care Reduces Depressive Symptoms and Improves Psychological and Physical Health in HIV Patients.

1:50-2:10pm **Lecture 2: Annabell Segara Ph.D.-** UPR - Medical Sciences Campus

Title: Sex steroids modulation of the behavioral response to cocaine.

2:10-2:30pm **Lecture 3: Steven Treistman, Ph.D.-** UPR - Neurobiology Institute

Title: Molecular tolerance: Routes to drug adaptation viewed from the level of an individual channel protein"

2:30-2:50pm **Lecture 4: Loyda Melendez, Ph.D.-** UPR - Medical Sciences Campus

Title: Cathepsin B and cystatin B in HIV infection and neurocognitive disorders.

2:50-3:10pm **Lecture 5: Jose Lasalde, Ph.D.-** UPR - Rio Piedras

Title: The alpha7 nicotinic acetylcholine receptor in HIV: Potential implications to HIV-associated neurocognitive disorders and inflammation.

3:10-3:15pm **Concluding Remarks**

7:00 – 10:00pm **EVENING BANQUET AND AWARDS CEREMONY**

Hosted by Howard Fox, M.D., Ph.D.- incoming SNIP President

Special Dinner Presentation: David Shurtleff, Ph.D.- NIDA, NIH

Meeting Adjourned!

Sunday, April 7, 2013

Departure Day

19th SNIP SCIENTIFIC CONFERENCE

REGISTERED PARTICIPANT LIST

Bert A 't Hart
Dept. Immunobiology, Biomedical Primate Research Centre
Lange Kleiweg 161
Rijswijk, AL 2288GJ
Netherlands
hart@bprc.nl

Amma Addai
Meharry Medical College
Department of Biochemistry and Cancer Biology
1005 Dr. D.B. Todd, Jr. Blvd
Nashville, TN 37208
aaddai09@email.mmc.edu

Martin W Adler
Temple Univ School of Medicine
3500 N. Broad St.
Philadelphia, PA 19140
baldeagl@temple.edu

Marisela Agudelo
Herbert Wertheim College of Medicine, Florida International University
10480 SW 228th terrace
Miami, FL 33190
magudelo@fiu.edu

Cagla Akay
University of Pennsylvania, School of Dental Medicine, Dept of Pathology
240 South 40th Street
Room 312, Levy Building
Philadelphia, PA 19104
akayc@upenn.edu

Marina Aksenova
Psychology Department,
University of South Carolina
1512 Pendleton St
Barnwell College
Columbia, SC 29208
Aksenova@mailbox.sc.edu

Lena Al-Harthi
Rush University Medical Center
1735 West Harrison St.
Chicago, IL 60612
Lena_Al-Harthi@rush.edu

Janaina Alves
Universidad Central Del Caribe
PO BOX 60327
Bayamon, PR 00960-6032
abaez@uccaribe.edu

Vidhu Anand
University of Minnesota Surgery BTR
515 Delaware Street SE
MMC 195 Mayo
Minneapolis, MN 55455
vanand@umn.edu

Anusha Ande
Division of Pharmacology
UMKC School of Pharmacy
2464 Charlotte St., HSB 3219
Kansas City,MO64108
aakhd@mail.umkc.edu

Ibolya-Edit Andras
University of Miami
1011 NW 15th St.
Gautier Rm 528B
Miami, FL 33136
IAndras@med.miami.edu

Gregory Antell
Microbiology and Immunology,
Drexel University College of Medicine
245 N. 15th Street
Philadelphia, PA 19102
gregory.c.antell@gmail.com

Fnu Ashutosh
UNT Health Science Center
3500 Camp Bowie Blvd
Fort Worth, TX 76107
fnu.ashutosh@unthsc.edu

Venkata Subba Rao Atluri
Herbert Wertheim College of Medicine, FIU
11200 SW 8th St.
Miami, FL 33199
vatluri@fiu.edu

Valeriya Avdoshina
Department of Neuroscience
3970 Reservoir Rd. NW
NRB, EG-19A
Washington DC 20057
va44@georgetonw.edu

Albert Avila
NIH/National Institute on Drug Abuse
6001 Executive Blvd.
Suite 4282, MSC 9555
Rockville, MD 20852
aavila@nida.nih.gov

Alessia Bachis
Department of Neuroscience,
Georgetown University
3970 Reservoir Rd. NW
Washington DC, 20057
bachisa@georgetown.edu

Carlos A. Baez-Pagan
University of Puerto Rico
PO Box 223360
San Juan, PR 931
Puerto Rico
cbaezpagan@gmail.com

Santanu Banerjee
University of Minnesota
515 Delaware St. SE
Minneapolis, MN 55455
banerjes@umn.edu

Roderick Allen Barke
Minneapolis Veterans Affairs
University of Minnesota,
Department of Surgery,
Director, Specialty Care PSL (112)
Minneapolis, MN 55417
Roderick.Barke@va.gov,
barke009@umn.edu

Usman Barlass
University of Minnesota
515 Delaware Street SE
Minneapolis, MN 55455
ubarlass@umn.edu

Joan W Berman
Albert Einstein College of Medicine
Department of Pathology
1300 Morris Park Avenue
Bronx, NY 10461
joan.berman@einstein.yu.edu

Sarah J Bertrand
Psychology Department,
University of South Carolina
1512 Pendleton Street
Barnwell College
Columbia, SC 29208
sbertrand114@gmail.com

Crystal Bethel-Brown
Univ of Nebraska Medical Center
17116 Chutney Drive
Omaha, NE 68136
c.bethelbrown@unmc.edu

Yuri A Blednov
University of Texas at Austin
1 University Station, A4800
Austin, TX 78712
yablednov@austin.utexas.edu

Rose Booze
University of South Carolina
1512 Pendleton Street
Columbia, SC 29208
booze@mailbox.sc.edu

Kathleen Borgmann
University of North Texas Health Science Center
3500 Camp Bowie Blvd, RES 202
Fort Worth, TX 76107
kathleen.borgmann@unthsc.edu

Dr. Nawal Boukli
Biomedical Proteomics Facility
Universidad Central del Caribe
School of Medicine

Ave. Laurel, Sta. Juanita
Bayamon, PR 00956
nawal.boukli@uccaribe.edu

Shilpa J Buch
Univ of Nebraska Medical Center
985880 Nebraska Medical Center
DRC 8011
Omaha, NE 68198
sbuch@unmc.edu

Guy A Cabral
Virginia Commonwealth University
School of Medicine
1101 E. Marshall Street
Richmond, VA 23298-0678
gacabral@vcu.edu

Tina M.Calderon
Albert Einstein College of Medicine
Dept. of Pathology, 1300 Morris Park Ave., Forchheimer 727
Bronx, NY 10461
tina.calderon@einstein.yu.edu

Shannon E Callen
Univ of Nebraska Medical Center
985880 Nebraska Medical Center
DRC 8052
Omaha, NE 68198
scallen@unmc.edu

Yisel Cantres-Rosario
University of Puerto Rico
Medical Sciences Campus
Biomedical Building 1, Room 301
San Juan, PR 935
yisel.m.cantres@upr.edu

Lu Cao
Division of Pharmacology
College of Pharmacy
University of Missouri-Kansas City
2464 Charlotte Street
Kansas City, MO 64108
lc7x5@mail.umkc.edu

Ricardo Carrero
Biomedical Proteomics Facility
Universidad Central del Caribe
Ave. Laurel, Sta. Juanita
Bayamon, PR 00956
411rcarrero@uccaribe.edu

Loreto Carvallo
Albert Einstein College of Medicine
1300 Morris Park Avenue
Bronx, NY 10461
lcarvall@einstein.yu.edu

Victor Manuel Castro Villela
University of Miami
Miller School of Medicine Dpt. Biochemistry and Molecular Biology
1011 NW 15th street
Miami, FL 33130
vcastrovillela@med.miami.edu

Richard G Charboneau
Department of Surgery
University of Minnesota
515 Delaware St SE
Minneapolis, MN 55455
charb019@umn.edu

Maxim C-J Cheeran
Veterinary Population Medicine
College of Veterinary Medicine,
University of Minnesota
1365 Gortner Avenue
St. Paul, MN 55108
cheeran@umn.edu

Benjamin K Chen
Mount Sinai School of Medicine
One Gustave Levy Place, Box 1630
New York, NY 10029
ben.chen@mssm.edu

Lihua Chen
Rush University Medical Center
1735 W. Harrrion ST.
Chicago, IL 60612
lihua_chen@rush.edu

Qiang Chen
Department of Pharmacology and Experimental Neuroscience,
Univ of Nebraska Medical Center
985930 Nebraska Medical Center
Omaha, NE 68198
qche1@unmc.edu

Pawel Ciborowski
Univ of Nebraska Medical Center,
Department of Pharmacology and Experimental Neuroscience
985800 Nebraska Medical Center
Omaha, NE 68198-5800
pciborowski@unmc.edu

Irma Elisa Cisneros
University of North Texas Health Science Center
3500 Camp Bowie Blvd
Fort Worth, TX 76107
icisnero@live.unthsc.edu

Jacqueline Seki Coley
Albert Einstein College of Medicine
1300 Morris Park Avenue
Forchheimer 727, Bronx, NY 10461
jacqueline.coley@phd.einstein.yu.edu

Krystal Colon-Rivera
University of Puerto Rico - Medical Sciences Campus
Biomedical Bldg 1
San Juan, PR 935
krystal.colon@upr.edu

Fulton T. Crews
Univ of North Carolina, Chapel Hill
Bowles Center for Alcohol Studies
1021 Thurston-Bowles Building,
Chapel Hill, NC 27599-7178
ftcrews@med.unc.edu

Elizabeth Patricia Crowe
Drexel University College of Medicine
245 N. 15th St., MS435
Philadelphia, PA 19102
epc27@drexel.edu

Changhai Cui
NIH/NIAAA/DNB
5635 Fishers Lane, Room 2067
Rockville, MD 20852-1796
changhai@mail.nih.gov

Carlo Amorin Daep
Univ of Medicine and Dentistry of NJ
ICPH Public Health Research institute
225 Warren St RBL2220
Newark, NJ 7003
daepcp@umdnj.edu

William Dampier
Drexel University College of Medicine
245 N. 15th Street
Philadelphia, PA 19102
judowill@gmail.com

Chandravanu Dash
Center for AIDS Health Disparities
1005 Dr. DB Todd Jr Blvd
Old Hospital Bldg-CAHDR
Nashville, TN 37221
cdash@mmc.edu

Prasun Datta
Neuroscience
Temple University School of Medicine
3500 N. Broad Street
Philadelphia, PA 19140
dattapk@temple.edu

Navneet K. Dhillon
University of Kansas Medical Center
3901 Rainbow Blvd.
Kansas City, KS 66160
ndhillon@kumc.edu

Hong Ding
Immunology Department, Herbert Wertheim College of Medicine
Florida International University
11200 SW 8th St AHC1-308
Miami, FL 33199
hding@fiu.edu

Robert M Donahoe
University of Utah
PO Box 342
Eden, UT 84310
robert.donahoe@path.utah.edu

Raini Dutta
Department of Surgery

University of Minnesota
420 Delaware St SE
Minneapolis, MN 55455
rdutta@umn.edu

Ravinder Earla
UMKC School of Pharmacy
2464 Charlotte Street
Kansas City, MO 64108
earlar@umkc.edu

Toby K Eisenstein
Center for Substance Abuse
Temple University School of Medicine
3500 North Broad Street
Philadelphia, PA 19140
tke@temple.edu

Nazira El-Hage
Virginia Commonwealth University
410 N. 12th Street, Rm. 746
Richmond, VA 23298
nelhage@vcu.edu

Sung Yong Eum
Department of Biochemistry &
Molecular Biology, University of Miami
Miller School of Medicine
1011 NW 15th Street
Miami, FL 33136
seum@med.miami.edu

Laura B Ferguson
University of Texas at Austin, Institute
for Neuroscience, Waggoner Center
for Alcohol Addiction
Austin, TX 78712
laurazeavin@gmail.com

Lindsay Festa
Drexel University College of Medicine
245 N. 15th Street
Philadelphia, PA 19103
lindsay.festa@gmail.com

Jerel A Fields
University of California San Diego
4702 Mission Blvd #2
San Diego, CA 92109
jafields@ucsd.edu

Howard Steven Fox
Univ of Nebraska Medical Center
985800 Nebraska Medical Center
Omaha, NE 68198
hfox@unmc.edu

Tina C Franklin
Rutgers University
67 Poultry Farm Rd
New Brunswick, NJ 8901
tinaf@eden.rutgers.edu

Mohitkumar Rajkumar Gangwani
Department of Pharmacology
University of Missouri Kansas City
2464 Charlotte Street
Kansas City, MO 64108
mrgdrc@mail.umkc.edu

Patrick Joseph Gannon
University of Pennsylvania
4101 Baltimore Avenue
Philadelphia, PA 19104
gannonp@mail.med.upenn.edu

Peter Jesse Gaskill
Albert Einstein College of Medicine
1300 Morris Park Avenue
Bronx, NY 10461
peter.gaskill@einstein.yu.edu

Howard E Gendelman
Univ of Nebraska Medical Center
985880 Nebraska Medical Center
DRC 8008
Omaha, NE 68198-5880
HEGENDEL@UNMC.EDU

Yamil Gerena
University of Puerto Rico-Medical
Sciences Campus, Department of
Pharmaceutical Sciences
P.O. Box 365067
San Juan, PR 00936-5067
yamil.gerena@upr.edu

Anuja Ghorpade
UNTHSC
3500 Camp Bowie BLvd
RES 202
Fort Worth, TX 76107
anuja.ghorpade@unthsc.edu

Larisa Gofman
Temple University School of Medicine
3500 N. Broad Street
MERB 880A Department of Pathology
Philadelphia, PA 19140
lgofman@temple.edu

Santhi Gorantla
Univ of Nebraska Medical Center
985880 Nebraska Medical Center
Omaha, NE 68198
sgorantla@unmc.edu

James Haorah
Univ of Nebraska Medical Center
985215 Nebraska Medical Center
Omaha, NE 68198-5215
Jhaorah@unmc.edu

R. Adron Harris
University of Texas at Austin,
Waggoner Center for Alcohol &
Addiction Research
2500 Speedway, MBB 1.124
Austin, TX 78712
harris@austin.utexas.edu

Norman Haughey
Johns Hopkins University SOM
600 N Wolfe Street
Baltimore, MD 21287
Nhaughe1@jhmi.edu

Kurt Hauser
Virginia Commonwealth University
RM439, 1217 E. Marshall St.
Richmond, VA 23298
kfhauser@vcu.edu

Johnny J He
University of North Texas Health
Science Center
3500 Camp Bowie Blvd
Fort Worth, TX 76107
johnny.he@unthsc.edu

Ramakrishna Hegde
University of Kansas Medical Center-
Physiology Department
3901 Rainbow Boulevard
Kansas City, KS 66160
rhegde2@kumc.edu

Charles Hinkin
UCLA School of Medicine
15865 Royal Haven Place
Sherman Oaks, CA 91403
chinkin@ucla.edu

Wenzhe Ho
Temple University
3500 N Broad St
Philadelphia, PA 19140
wenzheho@temple.edu

Shuxian Hu
Univ of Minnesota Medical School
3-432 TRF, 2001 6th St. SE
Minneapolis, MN 55455
huxxx031@umn.edu

Xiu Ti Hu
Dept. of Pharmacology
Rush University Medical Center
Cohn Research Building, Rm 414
1735 W. Harrison Street
Chicago, IL 60612
xiu-ti_hu@rush.edu

Mark R Hutchinson
University of Adelaide
Frome Rd
Adelaide, AL 5005, Australia
mark.hutchinson@adelaide.edu.au

Joseph Wiliam Jackson
University of Rochester
601 Elmwood Ave
Rochester, NY 14642
joseph_jackson@urmc.rochester.edu

Melissa June Jamerson
Virginia Commonwealth University
1101 East Marshall Street

Sanger Hall Room 7065
Richmond, VA 23298
hrickomj@vcu.edu

Sietse Jonkman
Scripps Research Institute Florida
110 Scripps Way
Jupiter, FL 33458
sjonkman@scripps edu

Kelly L Jordan-Sciutto
University of Pennsylvania
240 S 40th St
Room 312 Levy
Philadelphia, PA 19104
jordank@upenn.edu

Jeymohan Joseph
National Institute of Mental Health
Rm 6110
6001 Executive Boulevard
Bethesda, MD 20852
jjeymoha@mail.nih.gov

Norbert E Kaminski
Michigan State University
1129 Farm Lane
315 Food Safety and Toxicology Bldg
East Lansing, MI 48824
kamins11@msu.edu

Thirumala-Devi Kanneganti
St. Jude Children's Research Hospital
262 Danny Thomas Place, MS 3511
Memphis, TN 38105
thirumala-devi.kanneganti@stjude.org

Marcus Kaul
Sanford-Burnham Medical Research Institute
10901 North Torrey Pines Road
La Jolla, CA 92037
mkaul@sanfordburnham.org

Jag H Khalsa, PhD, MS
National Institute on Drug Abuse, NIH
6001 Executive Blvd., Room 4137
Bethesda, MD 20892
jag.khalsa@nih.gov

Michelle M Kiebala
University of Rochester School of Medicine and Dentistry
601 Elmwood Ave., Box 672
Rochester, NY 14642
michelle_kiebala@urmc.rochester.edu

Hyun-Jung Kim
University of Miami
1011 NW 15th St.
Miami, FL 33136
hjkim@med.miami.edu

Jennifer Margaret King
University of Pennsylvania
Philadelphia, PA 19143
kingjen@dental.upenn.edu

Lisa Koodie
University of Minnesota
3900 Plymouth Blvd. #215
Plymouth, MN 55446
kood0006@umn.edu

Jane Kovalevich
Temple University
3500 N. Broad Street, MERB 750
Philadelphia, PA 19140
jane.kovalevich@temple.edu

Edmundo Kraiselburd
UPR Medical School
GPOBox 365067
San Juan, PR 936
Edmundo.kraiselburd@upr.edu

Kelly Allen Krogh
University of Minnesota Medical School, Department of Pharmacology
1150 Hennepin Ave #2004
Minneapolis, MN 55403
kelly.krogh@gmail.com

Adarsh M Kumar
Department of Psychiatry and Behavioral Sciences
Univ. of Miami, Miller School of Medicine
1120 NW 14th Street, (CRB 1462)
Miami, FL 33136 United States
akumar@med.miami.edu

Anil Kumar
UMKC School of Pharmacy
2464 Charlotte Street
HSB 3255
Kansas City, MO 64108
kumaran@umkc.edu

Mahendra Kumar
Department of Psychiatry and Behavioral Sciences
Univ. of Miami, Miller School of Medicine
1120 NW 14th Street (CRB 1461)
Miami, FL 33136 United States
mkumar@med.miami.edu

Santosh Kumar
University of Missouri-Kansas City
2464 Charlotte St.
Kansas City, MO 64018
kumarsa@umkc.edu

Xiqian Lan
Feinstein Institute for Research, Hofstra North Shore LIJ Medical
225 Community Drive
Great Neck, NY 11021
xlan@nshs.edu

Gary E Landreth
Case Western Reserve University
Neurosciences, E649, SOM
10900 Euclid Ave
Cleveland, OH, 44106
gel2@case.edu

Dianne Langford
Temple UniversitySchool of Medicine
Department of Neuroscience
3500 N. Broad St, MERB 750
Philadelphia, PA 19140
tdl@temple.edu

Nicole Jane LeCapitaine
LSU Health Sciences Center
Department of Physiology
1901 Perdido Street
New Orleans, LA 70115
nlecap@lsuhsc.edu

Jon Martin Lindstrom
Department of Neuroscience
Medical School, Univ. of Pennsylvania
217 Stemmler Hall
Philadelphia, PA 19104-6074
jslkk@mail.med.upenn.edu

Jianuo Liu
Department of Pharmacology and Experimental Neuroscience
Univ of Nebraska Medical Center
600 S. 42nd Street
Omaha, NE 68198-5880
jnliu@unmc.edu

Xun Liu
Division of Pharmacology
University of Missouri-Kansas City
2464 Charlotte Street
Kansas City, MO 64108
xlfn3@mail.umkc.edu

James R. Lokensgard
University of Minnesota
3-220 LRB/MTRF
2001 6th St. S.E.
Minneapolis, MN 55455
loken006@umn.edu

Sheila Lopez
Biomedical Proteomics Facility
Universidad Central del Caribe
School of Medicine
Ave. Laurel, Sta. Juanita
Bayamon, PR 00956
sheila_natalie@yahoo.com

Raisa Loucil
Ponce School of Medicine
395 Zona Industrial Reparada #2
Ponce, PR 716
r.loucil@gmail.com

Jing Ma
Department of Surgery
University of Minnesota
420 Delaware Street SE, MMC195

Minneapolis, MN 55455
maxxx221@umn.edu

Sanjay B Maggirwar
Univ of Rochester Medical Center
601 Elmwood Avenue, Box 672
Rochester, NY 14642
sanjay_maggirwar@urmc.rochester.edu

Eugene O Major
NIH, NINDS
10 Center Drive
Bldg 10/RM 3B14
Bethesda, MD 20892
majorg@ninds.nih.gov

Manmeet K Mamik
Cell Biology and Anatomy, University of North Texas Health Science Center
3500 Camp Bowie Blvd, RES 232
Fort Worth, TX 76107
makaur@live.unthsc.edu

Chinmay K Mantri
CAHDR, Meharry Medical College
1005 Dr Db Todd Jr Blvd
Old Hospital Building, 5th Floor
Nashville, TN 37208
cmantri@mmc.du

Neysha Martinez-Orengo
Ponce School of Medicine
395 Zona Industrial Reparada #2
Ponce, PR 716
ney2sonara@yahoo.com

Yvonne McCommon
UMKC School of Pharmacy
2464 Charlotte Street
HSB 3255
Kansas City, MO 64108
mccommony@umkc.edu

Loyda Melendez
University of Puerto Rico, Medical Sciences Campus
Department of Microbiology A-367
PO Box 365067
San Juan, Puerto Rico 936
loyda.melendez@upr.edu

Raissa Menendez-Delmestre
University of Puerto Rico, Medical Sciences Campus
NeuroAIDS Program
Biomedical Bldg 1 Suite 332
San Juan, PR 935
raissa.menendez@upr.edu

Jingjing Meng
Department of Pharmacology, University of Minnesota
6-120 Jackson Hall
321 Church St. SE
Minneapolis, MN 55455
mengx062@umn.edu

Olimpia Meucci
Drexel University College of Medicine
245 North 15th Street, NCB 8221
Philadelphia, PA 19072
omeucci@drexelmed.edu

Italo Mocchetti
Georgetown Univ Medical Center
3970 Reservoir Rd, WP13 NRB
Washington, DC 20057
moccheti@georgetown.edu

Patricia E Molina
LSUHSC, Department of Physiology
1901 Perdido St. Rm 7205
New Orleans, LA 70112
PMolin@lsuhsc.edu

Thomas W. Molitor
University of Minnesota
1365 Gortner Ave., 225 VMC
St. Paul, MN 55108
molit001@umn.edu

Eduardo Montalvo
National Institutes of Health
6701 Rockledge Drive
Bethesda , MD 20892
montalve@csr.nih.gov

Landhing Mary Moran
University of South Carolina
1204 Main Street
Columbia, SC 29201
moranl@email.sc.edu

Karla Munoz
Immunology Department, Herbert Wertheim College of Medicine - Florida International University
11200 SW 8th St, AHC1-308
Miami, FL 33199
liortiz@fiu.edu

Manohar B Mutnal
University of Minnesota
2001 6th ST SE
3-430 LRB/MTRF
Minneapolis, MN 55455
mutna001@umn.edu

Mitzi Nagarkatti
University of South Carolina- School of Medicine, Dept. of Pathology, Microbiology and Immunology
6439 Garners Ferry Rd.
Columbia, SC 29208
Mitzi.Nagarkatti@uscmed.sc.edu

Prakash S. Nagarkatti
Office of Research
University of South Carolina
915 Bull Street
Columbia, SC 29208
Prakash@mailbox.sc.edu

Madhavan Nair
Immunology Department, Herbert Wertheim College of Medicine - Florida International University
11200 SW 8th St, AHC1-308
Miami, FL 33199
liortiz@fiu.edu

Celeste Napier
Rush University Medical Center
1735 W Harrison Street, Cohn 424
Chicago, IL 60612
celeste_napier@rush.edu

Srinivasa Doddamane Narasipura
Dept of Immunology/Microbiology
Rush University
1735 W Harrison Street
Chicago, IL 60612
srinivasa_narasipura@rush.edu

Avindra Nath
National Institutes of Health, NINDS
9000 Rockville Pike
10 Center Drive, Bldg 10/Room 7C103, Bethesda, MD 20892
natha@ninds.nih.gov

Richard J Noel Jr
Ponce School of Medicine
Department of Biochemistry
395 Industrial Reparada, Zona 2
Ponce, PR 717
rnoel@psm.edu

Michael Nonnemacher
Drexel University College of Medicine
245 N. 15th Street
Philadelphia, PA 19102
michael.nonnemacher@drexelmed.edu

Anantha Ram Nookala
Division of Pharmacology
University of Missouri Kansas City
2464, Charlotte St., HSB 3207
Kansas City, MO 64110
anfh3@mail.umkc.edu

Nicole Alia Northrop
Univ of Toledo College of Medicine
3000 Arlington Ave, Mail Stop #1007
Toledo, OH 43614
nicole.fazo@utoledo.edu

Michael Olin
University of Minnesota
Department of Pediatrics
540 Delaware St. SE
Minneapolis, MN 55455
olin0012@umn.edu

Nirzari Parikh
Drexel University College of Medicine
245 N. 15th Street
Philadelphia, PA 19102

np344@drexel.edu
Minseon Park
Dept. of Biochem & Molecular Biology
Univ of Miami School of Medicine
1011 NW 15th St.
Gautier Bldg room. 528B
Miami, FL 33136
mspark@med.miami.edu

Rahul V Pawar
Imaging Consultants of Essex
Saint Barnabas Medical Center
77 Park Avenue
Hoboken, NJ 7030
rvp325@yahoo.com

Juliana Perez-Laspiur
University of Puerto Rico, Medical Sciences Campus
Department of Microbiology A-367
San Juan, Puerto Rico 936
jplaspiur@gmail.com

Yuri Persidsky
Temple University School of Medicine
3500 North Broad Street
Pathology Room 842MERB
Philadelphia, PA 19140
yuri.persidsky@tuhs.temple.edu

Amanda Lee Persons
Rush University Medical Center
1735 W Harrison Street, Cohn 463
Chicago, IL 60612
amanda_l_persons@rush.edu

Francesca Peruzzi
Cancer Center at LSU Health Sciences Center
533 Bolivar Street
New Orleans, LA 70131
fperuz@lsuhsc.edu

Adolf Pfefferbaum
SRI International
333 Ravenswood Avenue, BN168
Menlo Park, CA 94025
dolf@synapse.sri.com

Sudheesh Pilakka-Kanthikeel
Institute of NeuroImmune Pharamcology, Dept of Immunology, Florida International University
11200 SW 8th St, HLS 1
Miami, FL 33174
spilakka@fiu.edu

Elizabeth Mary Podhaizer
Dept. of Pharmacology & Toxicology
Virginia Commonwealth University
410 N. 12th Street, Rm. 746
Richmond, VA 23298
podhaizere@mymail.vcu.edu

Raghava Potula
Pathology and Laboratory Medicine
3500 N Broad Street, MERB 854A
Philadelphia, PA 19140
raghava.potula@tuhs.temple.edu

Servio Heybert Ramirez
Temple Univ School of Medicine
Dept of Pathology & Lab. Medicine
3500 N. Broad Street, MERB 844
Philadelphia, PA 19140
servio@temple.edu

Tariq Rana
Sanford Burnham Med. Res. Institute
10901 N. Torrey Pines Rd.
La Jolla, CA 92037 United States
trana@sanfordburnham.org

Kesava Rao
Immunology Department, Herbert Wertheim College of Medicine - Florida International University
11200 SW 8th St, AHC1-308
Miami, FL, 33199
krao@fiu.edu

Andrea Raymond
Immunology Department, Herbert Wertheim College of Medicine - Florida International University
11200 SW 8th St, AHC1-308
Miami, FL 33199
liortiz@fiu.edu

Linda Rivera
Department of Microbiology
UPR Medical Science Campus
San Juan, PR. 00936
linda.rivera2@upr.edu

Vanessa Rivera-Amill
Department of Microbiology
Ponce School of Medicine
395 Zona Industrial Reparada 2
Ponce, PR 716
vrivera@psm.edu

Yainyrette Rivera-Rivera
Department of Microbiology
Ponce School of Medicine
388 Zona Industrial Reparada 2
Ponce, PR 716
yainyrr@yahoo.com

Robert Bryan Rock
University of Minnesota
McGuire Translational Res. Facility
2001 6th Street SE
Minneapolis, MN 55455
rockx012@umn.edu

Jose W. Rodriguez
Universidad Central del Caribe
School of Medicine
P.O. Box 60327
Bayamon, PR 960 United States
jwrodriguez@uccaribe.edu

Madeline Rodriguez
Biomedical Proteomics Facility
Universidad Central del Caribe
School of Medicine
Ave. Laurel, Sta. Juanita
Bayamon, PR 00956
rodriguez_madeline@yahoo.com

Thomas J Rogers
Temple University School of Medicine
3500 N. Broad Street, CILR
Philadelphia, PA 19140
rogerst@temple.edu

Slava Rom
Temple University School of Medicine
3500 North Broad Street
Pathology-8th Floor MERB
Philadelphia, PA 19140
slava.rom@temple.edu

Robert Francis Roscoe
University of South Carolina
457 Lake Estate Dr
Chapin, SC 29036
roscoerf@email.sc.edu

Jessica Helen Rotschafer
Veterinary Population Medicine, University of Minnesota
1365 Gortner Ave, 225 VMC North
St. Paul, MN 55110
rots0006@umn.edu

Sabita Roy
University of Minnesota
425 Delaware St
Minneapolis, MN 55455
royxx002@umn.edu

Summer J Rozzi
Georgetown University
Department of Neuroscience
3801 Newark St NW #C429
Washington, DC 20016
sjr65@georgetown.edu

Vidya Sagar
Ctr for Personalized Nanomedicine
Institute of NeuroImmune Pharm.
Florida International University
1200 SW 8th St, University Park
Miami, FL 33199
vsaga001@fiu.edu

Dipak K Sarkar
Endocrine Program, Rutgers Univ
67 Poultry Farm Lane
New Brunswick, NJ 8901
sarkar@aesop.rutgers.edu

Scott James Schachtele
University of Minnesota
2001 6th St. SE
Minneapolis, MN 55455-3007

sjschach78@gmail.com

Christina Joanne Schier
Department of Pharm. & Toxicology
Virginia Commonwealth University
P.O. Box 980613
Richmond, VA 23298
cjschier@vcu.edu

Annabell C Segarra
University of Puerto Rico, School of Medicine, Dept of Physiology
PO Box 365067
San Juan, PR 00936-5067
annabell.segarra@upr.edu

Christian Sell
Drexel University College of Medicine
Department of Pathology
245 N 15th Street, Room 5605
Philadelphia, PA 19102
christian.sell@drexelmed.edu

Satarupa Sen
Temple University
1220 North Broad Street
Philadelphia, PA 19121
satarupa.temple@gmail.com

Horacio Serrano
Univ. of Puerto Rico, Med. Sciences
Dept of Biochemistry Office A-620-C
PO Box 365067
San Juan, Puerto Rico 936
horacio.serrano@upr.edu

Ankit Shah
University of Missouri-Kansas City
2464 Charlotte St
Kansas City, MO 64108
abs9t2@umkc.edu

Umakant Sharma
Department of Surgery
University of Minnesota
11-197 Moos Tower, MMC 195,
420 Delaware Street SE
Minneapolis, MN 55455
usharma@umn.edu

Wen S Sheng
University of Minnesota
3-430 TRF, 2001 6th St. SE
Minneapolis, MN 55455
sheng008@umn.edu

Peter Steven Silverstein
University of Missouri-Kansas City
2464 Charlotte Street
Kansas City, MO 64108
silversteinp@umkc.edu

Gregory Michael Sindberg
University of Minnesota
11-196 Malcolm Moos Tower
515 Delaware St. SE
Minneapolis, MN 55455
sind0017@umn.edu

Pravin C Singhal
Hofstra North Shore LIJ Med. School
Div. Kidney Disease & Hypertension
100 Community Drive
Great Neck, NY 11021
singhal@lij.edu

Mohan Sopori
Immunology Division, Lovelace Respiratory Research Institute
2425 Ridgecrest Dr., SE
Albuquerque, NM 87108
msopori@lrri.org

Mary Ellen Sorrell
Dept. of Pharm. & Toxicology
Virginia Commonwealth University
1320 Perry St.
Richmond, VA 23224
sorrellme@vcu.edu

Eliot R Spindel
OHSU-ONPRC
505 NW 185th Ave
Beaverton, OR 97007
SPINDELE@OHSU.EDU

Marianne Strazza
Drexel University College of Medicine
245 N. 15th Street
Philadelphia, PA 19102
mstrazz@gmail.com

Edith V Sullivan
Stanford University School of Med.
Psychiatry & Behavioral Sciences
401 Quarry Road
Stanford, CA 94305-5723
edie@stanford.edu

Shao-Jun Tang
Dept Neuroscience and Cell Biology
University of Texas Medical Branch
301 Univ. Blvd
Galveston, TX 77555
shtang@utmb.edu

Sophie Xu Teng
LSU Health Sciences Center
Physiology Department
1901 Perdido St. Rm 7205
New Orleans, LA 70112
xteng@lsuhsc.edu

Samikkannu Thangavel
Florida International University
11200 SW 8th St AHC2-693
Miami, FL 33199
Liortiz@fiu.edu

Michal Toborek
Univ of Miami School of Medicine
1011 NW 15th Street
Gautier Bldg. Room 517
Miami, FL 33155
mtoborek@med.miami.edu

Lilith Torres
Ponce School of Medicine
395 Zona Industrial Reparada #2
Ponce, PR 716
litorres@stu.psm.edu

Steven N. Treistman
Institute of Neurobiology
University of Puerto Rico
201 Boulevard del Valle
San Juan, PR 901
steven.treistman@upr.edu

Neha N Vartak
University of North Texas Health Science Center
3805 Modlin Ave.
Fort Worth, TX 76107
nvartak@live.unthsc.edu

Dimitrios Nikolaos Vatakis
David Geffen School of Med., UCLA
615 Charles Young Dr South
BSRB 173, M/C 736322
Los Angeles, CA 90095
dvatakis@ucla.edu

Fabian Vazquez-Santiago
Ponce School of Medicine
388 Zona Industria Reparada 2
Ponce, PR 716
fvazquezsantiago@yahoo.com

Ryan Peter Vetreno
Univ of North Carolina at Chapel Hill
Bowles Center for Alcohol Studies
104 Manning Dr
Chapel Hill, NC 27599-7178
rvetreno@email.unc.edu

Xu Wang
Temple University
3500 N Broad St
Philadelphia, PA 19140
xuwang@temple.edu

Yi Wang
Department of Pharmacology and Experimental Neuroscience
Univ of Nebraska Medical Center
985930 Nebraska Medical Center
Omaha, NE 68198-5930
yi.wang@unmc.edu

Yizhong Wang
Department of Pathology
Temple University School of Medicine
3500 N Broad Street, MERB 881A
Philadelphia, PA 19140
yzwang@temple.edu

Wesley N Wayman
Pharmacology Department Rush University Medical Center
1735 W Harrison St

Cohn Building Room 463
Chicago, IL 60612
wesley_n_wayman@rush.edu

Brian Wigdahl
Drexel University College of Medicine
245 North 15th Street
Philadelphia, PA 19102
bwigdahl@drexelmed.edu

Dionna Whitney Williams
Albert Einstein College of Medicine
1300 Morris Park Avenue
Forchheimer 727
Bronx, NY 10461
dionna.williams@phd.einstein.yu.edu

Kenneth C Williams
Boston College
140 Commonwealth Avenue
Chestnut Hill, MA 1950
kenneth.williams.3@bc.edu

Valerie Wojna
University of Puerto Rico
Medical Sciences Campus
PO Box 365067
San Juan, PR 00936-5067
valerie.wojna1@upr.edu

Gretchen Wolff
University of Miami
1011 NW 15th St
Miami, FL 33136
g.wolff11@med.miami.edu

Alicia Kozue Wooten
University of Rochester
601 Elmwood Ave, Box 672
Rochester, NY 14642
alicia_wooten@URMC.rochester.edu

Jagoda Krystyna Wrobel
Univ of Miami Miller School of Med
Dept of Biochemistry & Mol. Biology
1011 NW 15th St., Room 528
Miami, FL 33136
jwrobel@med.miami.edu

Huangui Xiong
Department of Pharmacology and
Experimental Neuroscience
Univ of Nebraska Medical Center
Omaha, NE 68198-5880
hxiong@unmc.edu

Bryan Yamamoto
University of Toledo College of Med
Department of Neurosciences
3000 Arlington Ave, Mail Stop 1007
Toledo, OH 43614
Bryan.Yamamoto@utoledo.edu

Adriana Yndart Arias
Immunology Department, Herbert
Wertheim College of Medicine -
Florida International University
11200 SW 8th st AHC1-308
Miami, FL 33199
ayndarta@fiu.edu

Frances Michelle Zenon
University of Puerto Rico
Medical Sciences Campus
Biomedical Building I, Room #301
San Juan, PR 935
frances.zenon@upr.edu

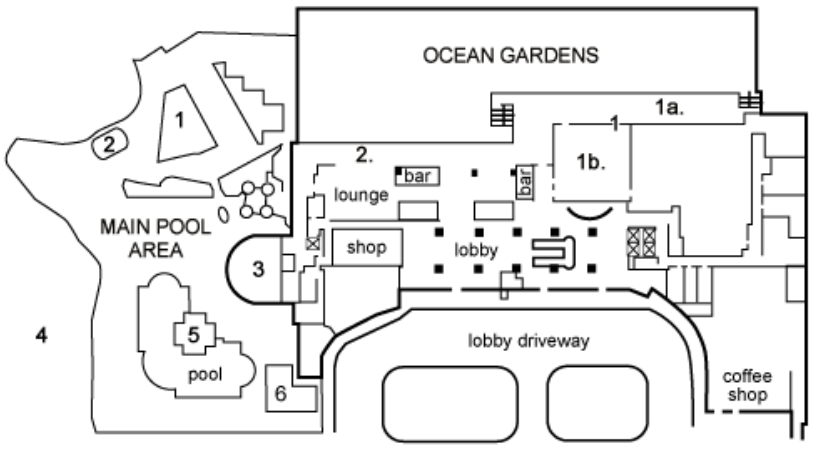
Lixia Zhao
Univ of Nebraska Medical Center
42nd and emile street
Omaha, NE 68198
lzhao@unmc.edu

Yu Zhou
Temple University School of Medicine
Pathology Dept., MERB
3500 N Broad St, Room 881a
Philadelphia, PA 19140
yu.zhou@temple.edu

Jun Zhu
Department of Drug Discovery and
Biomedical Sciences
South Carolina College of Pharmacy
University of South Carolina
75 Sumter St
Columbia, SC 29208
zhuj@sccp.sc.edu

A special thank you to NIDA for their continued long term support for the mission of SNIP.

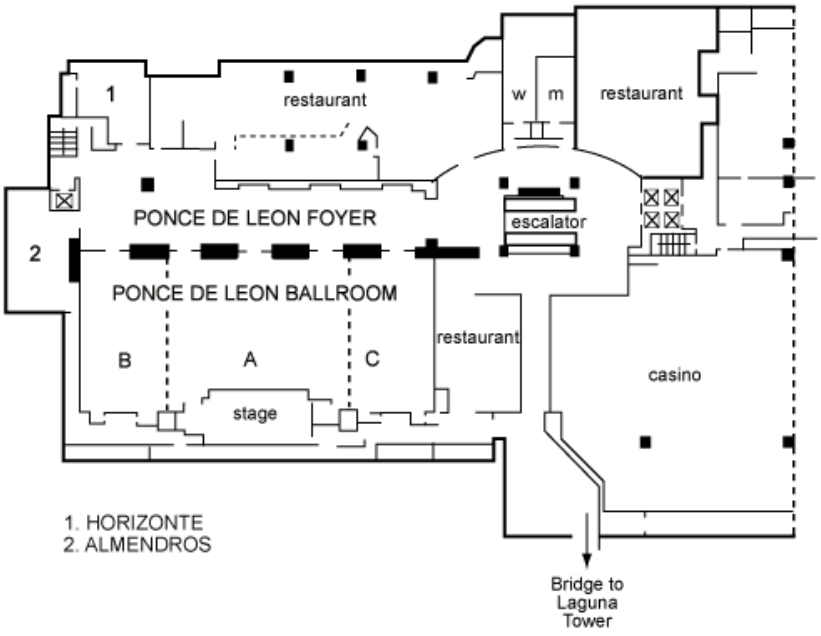
CONRAD SAN JUAN, CONDADO PLAZA
OCEAN TOWER LOBBY LEVEL



1. Salt Water Pool
2. Jacuzzi
3. Pool Restaurant
4. Beach Area
5. Pool Bar
6. Water Slide

1. BRISAS DEL MAR AND
   BRISAS DEL MAR TERRACE
   1a. BRISAS DEL MAR TERRACE
   1b. BRISAS DEL MAR
2. ETERNAL TERRACE

CONRAD SAN JUAN, CONDADO PLAZA
OCEAN TOWER MEZZANINE LEVEL



INDIVIDUAL ABSTRACTS

DEFICITS IN ATTENTION, A CORE COMPONENT OF EXECUTIVE FUNCTION, IN FEMALE HIV-1 TRANSGENIC RATS. Moran LM, Booze RM, Mactutus CF; Behavioral Neuroscience Program, Department of Psychology, University of South Carolina, Columbia, SC 29208.

Nearly half of all individuals with HIV-1 are afflicted with HIV-1-associated neurocognitive disorders (HAND), the most prominent feature of which is impaired executive function. In the present study, we characterized the cognitive performance of 4-6 month-old female ovariectomized Fisher-344 HIV-1 transgenic (HIV-1 Tg; n=41) and non-transgenic control rats (n=43) using a visual signal detection task to assess attention. All animals obtained 70% accuracy after two months of training, but twice as many control animals compared to HIV-1 Tg animals met this performance level after only one month. The temporal domain, i.e., signal duration, was subsequently manipulated. A decrease in hits and an increase in misses as a function of decreased signal duration were observed for both groups; however, the HIV-1 Tg group was more adversely affected. In contrast to the performance of controls, the HIV-1 Tg rats did not display differential target detection (hits vs. misses) at the 500 or 100 msec durations. Assessment of visual prepulse inhibition before and after operant testing confirmed that the HIV-1 Tg animals were able to detect even a 20 msec visual stimulus despite the presence of cataracts, and thus, their impaired performance in the operant task was not the result of a vision impairment. The present data suggest that chronic low level exposure to HIV-1 proteins in the HIV-1 Tg rat, which resembles the suppression of infection in HIV-1 positive individuals under CART, results in deficits in attention, and thus support the use of the HIV-1 Tg rat to model HAND. **Supported by DA013137, HD043680.**

COOPERATIVE EFFECTS OF HIV-1 TAT AND ETHANOL ON HUMAN BRAIN ENDOTHELIAL CELL PERMEABILITY INVOLVES MODULATION OF PDGF/PDGF-R AXIS. Bethel-Brown C, Buch S. Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198.

HIV-associated neurocognitive disorder (HAND) remains a growing problem in HIV-infected individuals and has shown to be exacerbated by alcohol use. Although the detailed molecular mechanisms involved in HAND remain poorly understood, Blood-Brain Barrier (BBB) modulation by HIV/HIV proteins & alcohol (EtOH) use leading to neuroinflammation appears in part, to be critical for disease pathogenesis. Since the vascular permeant PDGF-BB & its receptor have been shown to be modulated by HIV, we hypothesized that EtOH could potentiate HIV-mediated endothelial barrier permeability via modulation of the PDGF-BB/PDGFR axis. Specifically, our findings demonstrated that exposure of HBMECs to EtOH (50mM) resulted in PDGF-BB induction, and that Notch-1 activation was critical in this process. Reciprocally, Notch-1 inhibition resulted in abrogation of EtOH-mediated induction of PDGF-BB. Chromatin Immunoprecipitation (ChIP) assays demonstrated increased binding of the Notch downstream effector, CSL to the human PDGF-BB promoter following EtOH exposure. Intriguingly, HIV Tat mediated the phosphorylation of the cognate PDGF-Î²R. Functional relevance of HIV Tat & EtOH on BBB integrity was demonstrated by down-regulation of tight junction proteins and an increase in endothelial permeability. These results provide evidence of modulation of PDGF/PDGF-Î²R axis in the context of HIV & EtOH mediated modulation of brain endothelial permeability with implications for Notch-1 as a potential adjunctive therapeutic target for HAND. **Supported by Johns Hopkins NIMH Center for Novel Therapeutics of HIV-associated Cognitive Disorders**

THE ROLE OF PI3K/AKT/CREB-1 AND JAK/STAT SIGNALING IN HIV-1 NEF-MEDIATED INCREASE OF IL-6 IN ASTROCYTES. Liu X, Kumar, A; Pharmacology & Toxicology, School of Pharmacy, University of Missouri-Kansas City, Kansas City, MO 64108.

The life expectancy of individuals infected with human immunodeficiency virus 1 (HIV-1) has significantly increased. However, HIV-associated neurocognitive disorders (HAND) are still highly prevalent. HIV-1 Nef expression in astrocytes is associated with moderate to severe dementia of AIDS patients. It is believed that production of pro-inflammatory cytokines by astrocytes is one of the primary mechanisms leading to HAND. In the present study IL-6 mRNA and protein levels can be significantly induced in Nef-tranfected SVGA astrocytes in a time-dependent manner. The peak level of IL-6 mRNA is 15.05 ±1. 82 fold at 6 h post transfection. To determine the role of PI3K/Akt, cells were pretreated with a PI3K inhibitor, LY294002, before transfection and the expression levels of IL-6 were significantly decreased at both mRNA and protein level. Furthermore, when treated with Nef recombinant protein, the ratio of phosphorylated Akt to total Akt was increased to 1.2 ± 0.1 fold within 20 min and the expression level of CREB-1 (1.23 ±0.1 fold at maximum) also increased leading to the induction of IL-6. Also, pretreatment with the JAK1 inhibitor piceatannol and STAT3 inhibitor cryptotanshinone showed significant inhibition of IL-6 expression following Nef transfection. This suggests that the JAK/STAT pathway is involved in Nef-induced pro-inflammatory cytokine production in astrocytes. Taken together these results suggest possible mechanisms in HIV-1 Nef-mediated neuroinflammation during HAND. **Supported by DA025528 and DA025011 to AK.**

MEDIUM SPINY NEURONS IN THE NUCLEUS ACCUMBENS OF HIV-1 TRANSGENIC FEMALE RATS: DIOLISTIC ASSESSMENT OF SYNAPTODENDRITIC ALTERATIONS. Roscoe RF, Mactutus CF, Booze, RM; Department of Psychology, University of South Carolina, Columbia, SC 29208.

Medium spiny neurons (MSN) of the nucleus accumbens are involved in motivated behaviors; depression and substance abuse are often co-morbid with HIV-1 infection, although the mechanism for such behavioral changes is unknown. HIV-1 transgenic rats constitutively express 7 of 9 HIV-associated proteins at a low level, and may represent a useful model for studying alterations in neuronal morphology associated with HIV-1 behavioral deficits. In this experiment, we analyzed the dendritic spines of MSNs in the nucleus accumbens core (NAcc) of HIV-1 transgenic F-344 adult female rats vs. F-344 adult female control rats (N=10). All rats were sacrificed while in diestrus, perfused with 4% paraformaldehyde and the forebrains sectioned at 200 microns. MSNs were DiOlistically labeled utilizing the indocarbocyanine dye DiI and a Helios gene gun (Bio-rad). Analysis of MSN dendritic spine density revealed that control animals had an average spine density of 49 per 70 microns and HIV-1 transgenic animals had an average spine density of 35 per 70 microns. Similarly, the branching quantity of MSNs of the NAcc was decreased in HIV-1 trangenic rats relative to control (average of 3.5 primary branches vs. 6). Collectively, these results indicate significant synaptodendritic alterations in the GABAergic MSNs of the NAC core region occur as a consequence of chronic, low-level exposure to HIV-1 associated proteins. **Supported by NIH DA013137, DA031604, HD043680**

ANTI-APOPTOTIC ROLE OF HEXOKINASE IN HIV-1 INFECTED MACROPHAGES.

Sen S, Datta PK, Khalili K, Amini S; Biology, Temple University, Philadelphia, PA 19121; Neuroscience/CNAC, Temple University School of Medicine, Philadelphia, PA 19140.

Viruses have devised various strategies to protect infected cells from apoptotic clearance. HIV-1 infected macrophages are long lived and considered to be viral reservoirs. We provide evidence that HIV-1 protects infected macrophages from apoptosis by modulating the host glycolytic pathway. Glycolytic enzyme Hexokinase (HK) and product of its enzymatic activity Glucose 6 phosphate (G-6-P) are known to play a non-metabolic role in resisting and supporting apoptosis, respectively. Increased association of HK with voltage dependent anion channel of mitochondrial outer membrane can resist apoptosis by maintaining mitochondrial membrane integrity. On the other hand increased G-6-P pool in cytoplasm can force HK to dissociate from mitochondrial membrane and induce apoptosis by cytochrome c leakage. In this study we analyzed regulation of HK that converts glucose to G-6-P and Glucose-6-phosphate-dehydrogenase (G6PD) that converts G-6-P in to fructose 6 phosphate, in response to HIV-1 activation in chronically infected U1 cell line. We found that HIV-1 replication in U1 cell induces HK expression followed by translocation of HK from cytoplasm to mitochondria of cell. We also observed that viral replication increases the enzymatic activity of G6PD. As a consequence HK can associate strongly with mitochondrial membrane and this association is kept under tight control by rapidly turning over G-6-P through increased activity of G6PD enzyme. Hence our work suggests Hexokinase as a new therapeutic target for intervention to curtail viral persistence in the macrophage. **Supported by NIMH/CNAC to KK, NINDS/PO1 to SA, NIDA/RO1 to KD.**

HIV-1 PROTEIN GP120 AND METHAMPHETAMINE CO-OPERATE SYNERGISTICALLY TO INCREASE OXIDATIVE STRESS IN ASTROCYTES: ROLE OF CYTOCHROME P450. Shah A, Kumar A; Division of Pharmacology & Toxicology, UMKC School of Pharmacy, Kansas City, MO 64108.

HIV-1 gp120 has been shown to have neurotoxic potential in the CNS via several mechanism(s) including production of proinflammatory cytokines and chemokines and oxidative stress. Moreover, among various risk factors, drug abuse is thought to have a direct implication in the pathology of HIV associated neuroinflammation. Recently, we have shown that gp120 and methamphetamine (MA) interact with each other synergistically to induce proinflammatory cytokine IL-6. In the present study, we demonstrate functional implication of synergistic co-operation between gp120 and MA to induce oxidative stress and cell death in astrocytes. Both MA and gp120 induce the ROS production in dose and time-dependent manner and Cytochrome P450 2E1 (CYP2E1) was found to be involved in this process. Both gp120 and MA induced CYP2E1 expression at the levels of mRNA (>3.2 fold) and protein (~1.4 fold) and inhibition of CYP2E1 significantly reduced the ROS production (30-60%) by either gp120 or MA alone as well as combination of gp120 and MA. Inhibition of CYP2E1 was further shown to have protective effect on cell-survival in the astrocytes treated with gp120 or/and MA. This is a novel mechanism addressing the mechanism(s) underlying the synergistic co-operation between gp120 and MA to induce oxidative stress in astrocytes. **Supported by DA025528 and DA025011 to AK.**

HIV-1 TAT/COCAINE-INDUCED SYNAPTODENDRITIC INJURY IS PREVENTED BY ESTROGENIC COMPOUNDS. Bertrand SJ, Aksenova MV, Mactutus CF, Booze RM; Psychology Department, University of South Carolina, Columbia, SC 29208.

HIV-1 Tat and cocaine act synergistically to produce neuronal death; however, synaptic loss and dysfunction are predictive of HAND. The temporal relationship for synaptic loss vs. cell death in HAND/substance abuse is unclear, and early therapeutic intervention to reverse synaptic loss may slow the trajectory to cognitive impairments. In the present study, primary rat midbrain cell cultures (21 days in vitro) were co-treated with a subtoxic dose of HIV-1 Tat (10nM) and physiological levels of cocaine (1.6ÂµM). After 24 hours, F-actin puncta density was determined along MAP-2 positive neurites. HIV-1 Tat+cocaine produced a significant reduction in F-actin puncta density, suggesting that Tat+cocaine act synergistically to cause synaptodendritic injury. The estrogen receptor agonist daidzein (a soy derived compound), metabolized by bacterial flora in the gut, forms the potent metabolite S-Equol. Treatment of cell cultures with S-Equol (50nM) or its enantiomer, R-Equol (50nM), prevented the neuronal injury induced by HIV-1 Tat+cocaine. Additionally, we found that pre-treatment with the estrogen receptor antagonist tamoxifen (100nM) abolished synaptodendritic protection, suggesting S- and R-Equol act through an estrogen receptor mediated mechanism to prevent injury. Collectively, these results suggest that the estrogen receptor is a valid target for early therapeutic intervention in maintaining synaptic integrity in HIV-1+cocaine neurotoxicity. **Supported by DA013137, DA031604, HD043680, GM081740.**

SIGMA-1 RECEPTOR PROTECTS AGAINST HIV TAT-MEDIATED ER STRESS RESPONSE IN ASTROCYTE:IMPLICATION FOR HAND. Yang L, Mori M, Buch S; Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198; Department of Toxicology, School of Pharmacy and Pharmaceutical Sciences, Hoshi University, Tokyo, 142-8501.

Although ART can effectively suppress viral suppression, expression of viral proteins such as Tat remains unaffected. This in turn, could lead chronic activation of glia resulting in neuroinflammation. ER stress has recently been implicated to play an important role in the impairment of CNS homeostasis in HIV+ patients. In response to ER stress, cells activate a set of tightly controlled regulatory programs, the unfolded protein response (UPR), to restore normal functioning of the ER. However, if ER stress is sustained and the adaptive UPR fails to eliminate unfolded/misfolded proteins, balance shifts to apoptosis as a mechanism for clearing stressed proteins. We hypothesized that Tat mediated activation/apoptosis of astrocytes involves the ER stress response. Our preliminary data demonstrates that HIV Tat induced ER stress in astrocytes, with activation of the three UPR pathways-PERK, ATF6 & IRE1. This was accompanied by disruption of calcium homeostasis, generation of reactive oxidative stress (ROS) & induction of apoptosis. Of particular interest is the chaperone Sigma-1 Receptor (σ1-R) that is critical for ER stress. Intriguingly, over-expression of σ1-R in astrocytes significantly decreased Tat-mediated ROS generation & inhibited expression of pro-apoptotic CHOP protein. Reciprocally, knocking down σ1-R resulted in decreased expression of the anti-apoptotic Bcl2 & increased cellular apoptosis. Thus, σ1-R could be envisioned as a critical modulator of glial cell survival and may be an important target for therapeutic intervention in HAND. **Supported by NIMH/5R01MH068212.**

MIR-9 PROMOTES MICROGLIAL ACTIVATION BY TARGETING MCPIP: IMPLICATIONS FOR HAND. Ma R, Yao H, Buch S; Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198.

In keeping with the emerging interest in the molecular mechanisms controlling the magnitude of microglia-mediated inflammatory responses in the CNS, a new and exciting aspect of gene regulation has been discovered in recent years â€" the mammalian microRNAs (miRNA). The highly conserved microRNA-9 (miR-9) plays a critical role in neuronal precursors as well as in axonal extension. Its role in inflammatory responses mediated by microglia however, remains poorly understood. The present study was undertaken to identify the role of miR-9 in microglial activation in the CNS. Herein we have identified unique roles of miR-9 in mediating both the microglial inflammatory response as well as microglial migration through distinct signaling pathways. MiR-9-mediated regulation of both these processes involved down-regulated expression of a key target protein, macrophage-chemoattractant protein inducible peptide (MCPIP) that has been implicated in controlling inflammation. Our studies using the rat primary microglial implicate that miR-9 mediated cellular activation involved activation of the NF-kB pathway. Intriguingly, miR-9 mediated control of microglial migration involved the Î²-catenin pathway. In vivo administration of lentivurus-premiR-9 resulted in increased microglial activation and migration, thus validating our cell culture findings. These findings underpin the role of miR-9 regulated MCPIP as a molecular switch determining microglial activation and migration with implications for various neurodegenerative disorders including HAND. **Supported by NIMH/5R01, MH068212.**

DIFFERENTIAL INDUCTION OF POST-ENCEPHALITIC REGULATORY T-CELLS BY DISTINCT BRAIN CELL POPULATIONS. Schachtele SJ, Mutnal MB, Hu S, Lokensgard JR; Center for Infectious Disease & Microbiology Translational Research, University of Minnesota, Minneapolis, MN 55407

Persistently activated microglial cells contribute to ongoing brain injury. Our laboratory has shown that following murine herpesvirus brain infection (HSV-1 or MCMV) ~90% of CD11b(+)CD45(int) microglia chronically express MHC class II (>30 d p.i.). Our preliminary data also show that elevated numbers of immunosuppressive regulatory T-cells (Tregs) are retained within post-encephalitic brains. Although it is clear that Tregs help blunt inflammation within the brain, the reciprocal actions of resident brain cells on Treg induction and retention following infection are unknown. These in vivo and in vitro studies use Foxp3-diphtheria toxin receptor (DTR)-GFP transgenic mice which, upon administration of low-dose diphtheria toxin, results in the specific depletion of naturally occurring (n)Tregs from the donor cells. Adoptive transfer of Treg-depleted CD4(+)Foxp3(-) T-cells into virus-infected TCRÎ² knockout mice will then be used to assess the ability of the brain microenvironment to induce CD4(+)Foxp3(+) Tregs in vivo. In vitro experiments will go on to determine differential effects of distinct brain cell populations on CD4(+) lymphocyte transition into a Treg phenotype. Addition of Treg-depleted CD4(+) T-cells, isolated from Foxp3-DTR-GFP animals, to resting or antigen-stimulated astrocyte, microglial cell or neuronal cell cultures will be used to assess induction of Tregs, as indicated by stimulation of Foxp3 expression. Results generated from these studies will determine whether post-encephalitic microenvironments promote transition of CD4(+) T-cells into Tregs. **Supported by R01NS-038836-14.**

COCAINE ENHANCES HIV-1 INTEGRATION IN CD4+ T CELLS BY MODULATING THE EPIGENETIC DNA SIGNATURES OF HOST GENOME. Amma AB, Pandhare J, Mantri CK, Dash, CV; Center for AIDS Health Disparities Research, Department of Biochemistry and Cancer Biology, Meharry Medical College, Nashville, TN 37208.

Drug abuse is a powerful cofactor for HIV infection, pathogenesis and treatment. Cocaine, a commonly used drug among HIV-1 positive individuals, has been demonstrated to increase HIV-1 replication in cell cultures, peripheral blood mononuclear cells (PBMCs) and animal models. Recently, our laboratory has reported that cocaine enhances HIV-1 replication in primary CD4+ T cells by targeting viral post entry steps. Therefore, the goal of this study is to examine the effects of cocaine on integration, a critical post entry step in HIV-1 life cycle. During HIV-1 replication, the viral genome is reverse transcribed into a double stranded DNA (dsDNA) by HIV-1 reverse transcriptase. This viral dsDNA is transported into the nucleus in the form of a pre-integration complex (PICs) and integrates into the host genome. Our data demonstrates that cocaine treatment enhances HIV-1 integration in CD4+ T cells. Interestingly, DNA demethylating agent (5-aza-2'-deoxycytidine) also increased HIV-1 integration in CD4+ T cells. Given that HIV-1 integration has been suggested to be disfavored in methylated DNA targets, we hypothesize that cocaine enhances integration by reducing the global DNA methylation signature of the host genome. Our studies using isolated PICs from infected cells illustrate that integration is reduced in methylated target DNA in comparison to un-methylated DNA. We believe understanding of the mechanism by which cocaine modulates HIV-1 integration will aid in the discovery of novel targets that can synergize with integrase inhibitors as part of an approach to cure HIV/AIDS. **Supported by #2T32H007735-17 from NIH/NHLBI to Dr SE Adunyah.**

ACUTE ALCOHOL INTOXICATION IS ASSOCIATED WITH SUSTAINED NEUROINFLAMMATION WITHOUT EXACERBATION OF EARLY NEUROBEHAVIORAL OUTCOMES POST TRAUMATIC BRAIN INJURY. Teng S, Molina P; Department of Physiology, Louisiana State University Health Sciences Center, New Orleans, LA 70112.

Approximately 1.7 million people sustain a traumatic brain injury (TBI) annually, and acute alcohol intoxication (AAI) contributes to 36% to 51% of TBI incidents in the U.S. Although AAI is associated with the risk of injury, conflicting reports have failed to establish whether AAI significantly impacts TBI outcomes. The aim of our study was to determine whether AAI aggravates neurobehavioral and neuroinflammatory sequelae from TBI. Male Sprague-Dawley rats were surgically instrumented with gastric and vascular catheters prior to fitting with a female Luer-lock over a 5 mm left lateral craniotomy. After a 3 day recovery, animals received a primed (2.5 g/kg) 15 h constant (300 mg/kg/h) intragastric alcohol infusion. TBI was induced by lateral fluid percussion. AAI at the time of TBI did not alter apnea duration (15.3+5.3 sec vs. 26.5+8 sec), righting reflex (716+118 vs. 522+83), and neurobehavioral outcome scores (Δ2.2+0.6 vs. Δ3.9+0.6). TBI resulted in a localized inflammatory response as reflected by increased myeloperoxidase (MPO) activity in the ipsilateral (10-fold; $p<0.05$) cortex 24 h post-TBI. AAI did not alter MPO activity but markedly exacerbated neuroinflammation as reflected by significantly ($P<0.05$) higher IL-1, IL-6, TNFα, and MCP-1 mRNA expression as compared to the dextrose-treated animals at 24 h post-TBI. These results show dissociation between neuroinflammation and clinical neurobehavioral measures following TBI in AAI. The clinical implications of enhanced neuroinflammation to long term recovery in the AAI TBI victim warrant further investigation. **Supported by DOD-W81XWH-11-2-0011; NIAAA-AA7577.**

COCAINE ENHANCES HIV-1 REPLICATION IN MONOCYTE DERIVED MACROPHAGES BY REGULATING THE ACTIVATING TRANSCRIPTION FACTOR-2 (ATF-2). Ranjan A, Pandhare-Dash J, Mantri CK, Dash, CV; CAHDR, Meharry Medical college, Nashville, TN 37208.

Macrophages are important target cells for the HIV-1 in vivo. Due to their capacity to infiltrate virtually all organs including the brain, macrophages play critical role in HIV-1 neuropathogenesis since they serve as the primary reservoirs of HIV in the central nervous system. It is well established that drugs of abuse increase HIV-1 replication in macrophages, however the detailed molecular mechanisms remain to be fully understood. By using a THP1 macrophage (THPmac) model, we propose a novel mechanism by which cocaine accentuates HIV replication in macrophages. Our results demonstrate that cocaine treatment induced the phosphorylation and nuclear translocation of the ATF-2 concomitant with downregulation of histone deacetylase-3. ATF-2 is a member of the ATF-CREB family of transcription factors, which have been implicated in the transactivation of the HIV-1 long terminal repeat (LTR) promoter. Importantly, the activation of ATF-2 has been well characterized to be negatively regulated by HDAC-3 expression. Our data also reveal that cocaine-induced activation of ATF-2 increased TNF-Î± expression both at transcript and protein levels. TNF-Î± is known to activate NF-kappaB that is essential for sustained HIV-LTR activation. We observed increased activation and nuclear translocation of NF-kappaB in THP-1 macrophages in the presence of cocaine resulting in enhanced stimulation of the HIV-1 LTR and in enhanced viral replication. Therefore, our results indicate that in THP-1 macrophages, cocaine-induced repression of HDAC-3 promotes activation of ATF-2 resulting in increased HIV-1. **Supported by NIDA/NIH.**

INFECTION WITH ECOHIV, A NOVEL MURINE MODEL OF HIV, AND MORPHINE COMPROMISE GUT BARRIER FUNCTION AND BACTERIAL CLEARANCE.

Sindberg GM, Sharma U, Meng J, Banerjee S, Volsky D, Molitor T, Roy S; Comparative and Molecular Biosciences, University of Minnesota (UM), Saint Paul, MN 55108; Department of Surgery, UM, Minneapolis, MN 55455; Department of Pharmacology, UM, Minneapolis, MN 55455; Molecular Virology Division, St. Lukes-Roosevelt Hospital Center/Columbia University, NY, NY 10019; Department of Veterinary Population Medicine, UM, Saint Paul, MN 55108.

Compromised gut barrier function, which is exacerbated by opiates, is believed to be integral for early pathogenesis of HIV; however no mouse model currently exists to study the epithelial and immune interactions in the gut. EcoHIV was developed to simulate HIV pathogenesis by genetically altering HIV to infect mouse cells by substituting gp80 from Murine Leukemia Virus for gp120 of HIV. Our study shows that chronic morphine in EcoHIV treated mice additively enhances bacterial translocation from the gut to systemic tissues beyond what is seen in either treatment alone. Additionally, histology of EcoHIV infected and morphine treated animals show a drastic change in intestinal structures and disrupts tight junction organization as measured by immunofluorescence using the tight junction protein occludin. Interestingly, an in vitro measure of barrier function (ECIS) using mouse IEC4 cells was modulated solely by the presence of LPS and not EcoHIV or morphine. This implicates TLR4 activation as having a strong role in barrier dysfunction in our model, consistent with studies in human HIV which implicate LPS as a biomarker for disease progression. One potential source of these bacterial products is a lack of clearance: our lab has observed that morphine reduces macrophage clearance of bacterial products, and similar data is reported for HIV-infected human macrophages. Thus, we suspect that EcoHIV and morphine act together to reduce macrophage-mediated clearance in the gut, which contributes to systemic bacterial translocation and models what is observed in human HIV pathogenesis. **Supported by NIH/T32 DA007097, NIH/RO1 DA12104, NIH/RO1 DA022935, NIH/RO1 DA031202, NIH/K05 DA033881, NIH/P50 DA011806, NIH/R01 DA034582.**

MECHANISMS OF COCAINE-INDUCED ENHANCEMENT OF HIV REPLICATION IN MONOCYTE DERIVED MACROPHAGES. Swepson CB, Pandhare J, Dash CV; Biochemistry, Meharry Medical College, Nashville, TN 37208.

The prevalence of HIV- associated neurocognitive disorders (HANDs) is increasing among infected individuals. Caused by progressive HIV infection in the brain, HANDs are a result of subsequent inflammation and damage within the central nervous system (CNS). Macrophages are the primary target for HIV replication in the CNS and have been shown to play a major role in the progression to these diseases. While in vitro studies demonstrate increased HIV replication in macrophages when drugs of abuse are present, the mechanisms for this enhancement are not completely understood. It has been previously shown that drugs of abuse, including cocaine and methamphetamine, have the ability to increase transcription of cellular, as well as, integrated viral genes. These events correlate with clinical evidence of higher viral loads and exacerbated AIDS progression in HIV infected drug abusers compared to non-abusers with HIV. We hypothesize that HIV replication is increased in monocyte derived macrophages (MDMs) via cocaine induced epigenetic modification. Our results demonstrate for the first time that cocaine induced activation of the p38/Erk/MAPK signaling pathways leads to induction of mitogen- and stress-activated protein kinase 1 (MSK1). Our findings suggest that activated MSK1 initiates epigenetic modification of histone 3, ultimately enhancing transcription of cellular and integrated viral genes. Increased HIV replication in primary MDMs as a result of cocaine induced histone 3 modification may play a role in the acceleration of the development of HANDs. **Supported by T32 grant #2T32H007735-17 from NIH.**

WITHAFERIN A INHIBITS IL-1BETA MEDIATED INDUCTION OF MIR-146A EXPRESSION IN HUMAN ASTROCYTES BY DOWN-REGULATING NF-KB SIGNALING. Banerjee S, Datta PK; Department of Neuroscience/Center for Neurovirology, Temple University School of Medicine, Philadelphia, PA 19140.

Neuroinflammation plays a critical role in pathogenesis of numerous neurodegenerative disorders including NeuroAIDS. Release of pro-inflammatory cytokines such as interleukin (IL)-1beta from infiltrating macrophages, activated microglia, astrocytes, and dysregulation of inflammation-associated microRNAs such as miR-146a within the brain can accelerate the development of HIV Associated Neurocognitive Disorders. Thus, we investigated the mechanism of IL-1beta expression of the miR-146a gene using isolated human fetal astrocytes and an astroglial cell line. Furthermore our studies demonstrate that activation of the miR-146a gene by IL-1beta required the p65/RelA subunit of NF-kB and was dependent on NF-kB response elements located in the proximal gene promoter. Our findings demonstrate that IL-1beta-induced IKKbeta, IkBalpha and p65 phosphorylation regulate NF-kB activation in human fetal astrocytes and in an astroglial cell line. Additionally, our results indicate that p65 phosphorylation of serine 276 constitutes an essential step in the p65-dependent IL-1beta induced transcriptional expression of miR-146a. As a therapeutic approach we assessed the anti-inflammatory effects of steroidal lactone, Withaferin A (WA) isolated from *Withania somnifera* on miR-146a expression. WA dose dependently inhibited IL-1Î² induced miR-146a expression. When examined for the mechanism, we found that WA inhibited IL-1Î² induced IKKbeta, IkBalpha and p65 phosphorylation. Thus, Withaferin A may have potential therapeutic application in inflammation-associated neurodegenerative disorders. **Supported by NIH/NIDA to PKD.**

MAGNETO-ELECTRIC NANOPARTICLES FOR NON-INVASIVE BRAIN STIMULATION. Khizroev S, Yue K, Guduru R, Liang P, Hong J, Nair M; Center for Personalized NanoMedicine/Institute of Neuro-Immune Pharmacology/Department of Immunology, Herbert Wertheim College of Medicine/Florida International University, Miami, FL 33199; Department of Electrical Engineering, University of California, Riverside, CA 92521.

This presentation will give an overview of a new nanotechnology that exploits unique multi-functional properties of magneto-electric nanoparticles (MENs) to artificially stimulate the neural activity deep in the brain. Specifically, this technology provides a unique way to efficiently couple electric signals in the neural network to the magnetic dipoles in the nanoparticles with the purpose to enable non-invasive approach. Simulations of the effect of MENs for non-invasively stimulating the brain of a patient with Parkinsons Disease to bring the pulsed sequences of the electric field to the levels comparable to those of healthy people show that the optimized values for the concentration of the 20-nm nanoparticles (with the magneto-electric (ME) coefficient of 100 V cm-1 Oe-1 in the aqueous solution) is 3 x 10^6 particles/cc and the frequency of the externally applied 300-Oe magnetic field is 80 Hz. In-vitro Scanning Probe Microscopy (SPM) experiments were conducted to demonstrate the new underlying physics that enables the energy of remote magnetic fields to be efficiently transferred into the electric charge energy in the vicinity of MENs.

Supported by NIH DA027049.

A NANOTECHNOLOGY APPROACH TO PROTECT HUMAN NEURONS FROM OXIDATIVE STRESS. Ashutosh Dr, Viola M, Labhasetwar V, Ghorpade A; Cell Biology and Anatomy, UNT Health Science Center, Fort Worth, TX 76107; Department of Biomedical Engineering, Cleveland Clinic, Cleveland, OH 44195.

Neuroinflammation-associated excessive production of reactive oxygen species (ROS) is a common molecular basis in pathogenesis of several neurodegenerative diseases e.g. HIV-1-associated dementia, Parkinson's and Alzheimer's disease. ROS damage cellular components and are a major contributor of neuronal injury. Catalase, an antioxidant enzyme, is a well-known therapeutic target that converts H2O2 into water. However, medical use of catalase is greatly restricted by its labile nature and inadequate delivery. Here, we evaluated a nanotechnology approach that utilizes FDA approved, PLGA nanoparticles loaded with catalase (NP-CAT) in delivering catalase to protect primary cultured human neurons from oxidative damage. A rapid uptake of NPs by human neurons was observed. NPs formulation itself did not show any sign of neurotoxicity. Moreover, NPs release active catalase enzyme within 1h and sustained for over a month. The data show that human neurons are highly sensitive to H_2O_2-induced toxicity. Importantly, NP-CAT-mediated delivery of catalase efficiently protected human neurons from H_2O_2-mediated oxidative stress. NP-CAT significantly inhibited H_2O_2-induced protein oxidation, DNA damage, opening of mitochondrial membrane transition pores, cell membrane integrity loss and restored the cell morphology, neurite network and MAP-2 expression. Brain targeting of these catalase-loaded detoxifying NPs may find wide therapeutic applications for oxidative stress associated acute and chronic neurodegenerative disorders. **Supported by NIH/1R01NS070896-01.**

METHAMPHETAMINE-INDUCED INCREASES IN PLASMA AMMONIA PRODUCE NEUROINFLAMMATION AND BLOOD-BRAIN BARRIER DISRUPTION. Northrop NA, Halpin LE, Yamamoto BK; Department of Neurosciences, University of Toledo College of Medicine, Toledo, OH 43614.

Recently we have shown that the psychostimulant, methamphetamine (Meth), produces liver damage. In models of acute liver failure, increased plasma ammonia mediates brain edema and disruption of blood-brain barrier (BBB) tight junction proteins. Neurotoxic doses of Meth that are hepatotoxic also disrupt the BBB and increase cyclooxygenase-2 (COX-2) in the brain. Since COX plays a causative role in models of hepatic encephalopathy and BBB disruption, we hypothesized that Meth-induced increases in COX-2 and disruption of BBB structure and function are mediated by increased plasma ammonia. A neurotoxic Meth regimen (10mg/kg, ip, q 2hr, x4) to rats increased plasma ammonia by 86±12% 2hr after the last Meth injection, compared to saline controls. Meth also significantly increased COX-2 protein by 67±36%. This finding was paralleled by the decreased expression of tight junction proteins, occludin by 51±8% and claudin-5 by 51±7%, and increased BBB permeability as measured by FITC-dextran extravasation, compared to saline controls 24hr after treatment. Pretreatment with lactulose (5.3g/kg, po, q 12hr), a drug that increases the excretion of ammonia, prevented the Meth-induced increases in ammonia as well as increases in COX-2 and BBB disruption. These data indicate that Meth-induced increases in ammonia produce neuroinflammation and BBB disruption and suggest that COX activity mediates the BBB disruption. These findings identify a novel mechanism of Meth-induced BBB disruption and novel consequences of Meth-induced liver damage that include neuroinflammation and BBB disruption. **Supported by NIH DA07606.**

DOPAMINE MEDIATED CHANGES IN THE BLOOD BRAIN BARRIER AND NEUROINFLAMMATION IN THE CONTEXT OF CNS HIV INFECTION AND SUBSTANCE ABUSE. Coley JS, Calderon TM, Lopez L, Berman JW; Department of Pathology, Albert Einstein College of Medicine, Bronx, NY 10461.

CNS complications due to HIV infection persist despite current antiretroviral therapies. HIV enters the CNS by the transmigration of infected monocytes across the blood brain barrier (BBB). Production of viral and neurotoxic factors by these cells leads to infection and/or activation of perivascular macrophages, microglia, and astrocytes, resulting in neuroinflammation leading to HIV-associated neurocognitive disorders (HAND). Many drug abusers have higher infiltration of monocytes and perhaps T-cells into the CNS, which may contribute to increased neuroinflammation. Drugs of abuse, such as methamphetamine and cocaine, increase extracellular dopamine in the CNS. Additionally, SDF-1, a chemokine that is chemotactic for monocytes and T-cells, is increased in the CNS during HIV infection. Our laboratory demonstrated that a more mature monocyte subset (CD14+CD16+) is permissible to HIV infection and preferentially transmigrates across our in vitro human BBB model. We hypothesize that increased CNS dopamine in HIV-infected drug abusers increases migration of CD14+CD16+ monocytes into the CNS, contributing to the chronic neuroinflammation that causes HAND. We showed dopamine receptor expression on CD14+CD16+ monocytes by flow cytometry and qRT-PCR. Using a chemotaxis assay, we found that dopamine alone and with SDF-1 induces chemotaxis of CD14+CD16+ monocytes. We are also examining the effects of SDF-1 and dopamine on junctional proteins of the BBB, as these proteins are involved in maintaining its integrity and facilitating transmigration. **Supported by NIDA R01 DA025567.**

HEDGEHOG PATHWAY PLAYS A VITAL ROLE IN HIV-ASSOCIATED NEPHROPATHY. Lan X, Cheng K, Plagov A, Chandel N, Rai P, Malhotra A, Singhal PC; Renal Molecular Research Laboratory, Feinstein Institute for Medical Research, Great Neck, NY 11021.

HIV-associated nephropathy (HIVAN) is characterized by heavy proteinuria, rapidly progressive renal insufficiency, and distinct morphological changes in the kidney. HIV-induced epithelial-mesenchymal transition (EMT) and proliferation of renal cells are important involved mechanisms contributing to the progression of kidney injury. In this study, we tested the role of hedgehog pathway in the HIV-induced EMT and fibrosis of kidney. We used the Tg26 mice, the most commonly used HIVAN mouse model, to investigate the activation of hedgehog pathway by HIV. Immunofluorescent staining, Western blot, and real time PCR results showed that the expression of hedgehog pathway related molecules, including sonic hedgehog (SHH), PTCH, gli1, and gli2, were significantly increased in renal tissues of Tg26 mice. In vitro study, we used recombinant sonic hedgehog and HIV virus to treat human podocytes and human renal proximal tubular epithelial kidney cells (HRPTEC); in these studies, both methods not only activated the hedgehog pathway but also enhanced the expression of EMT and proliferation molecular markers. On the other hand, the blockage of hedgehog pathway with Gant58, a specific blocker for gli1 transcription activity, dramatically decreased HIV-induced kidney cell EMT and proliferation. These results indicate that hedgehog pathway plays a vital role in HIVAN, and our study provides insight into a new target for HIVAN therapeutic strategy.

PROTEOMIC FINGERPRINTS OF PRIMARY HUMAN ASTROCYTES TREATED WITH HIV-1 CLADE B AND C PROTEINS: ROLES OF ENDOPLASMIC RETICULUM STRESS IN NEURO-AIDS. López SN, Rodríguez M, Amadeo W, Cubano L, Alves J, Boukli N; Department of Microbiology and Immunology, Biomedical Proteomic Facility, Universidad Central del Caribe, Bayamón, PR 00960.

It is suggested that the degree of neuro-AIDS vary according to the HIV-1 clade.The cellular basis and mechanisms underlying HIV-1 neuropathogenesis is complex and poorly understood. Because astrocytes are critical for central nervous system function, they are important cells to consider in the context of HIV-1 neuropathogenesis.
Exploiting proteomics, we hypothesize that clade B and C induce differential protein expression profiles on primary human astrocytes. In the current study, we used a differential proteomic analysis of primary human astrocytes treated with HIV-1 clade B and C by two-dimensional gel electrophoresis (2DE), followed by liquid chromatography-tandem mass spectrometry and protein identification to establish homologies and dissimilarities in protein expression. A total of 69 and 72 proteins were modulated by HIV-1 clade B and clade C, respectively, as analyzed on 2D maps by PD Quest software. Among the proteins significantly upregulated by HIV-1 are Annexin A5 and Cyclophilin A (pro-apoptotic factors), Protein Disulfide Isomerase and Elongation factor 2 (Endoplasmic Reticulum stress markers), Vimentin (structural protein). In addition, HIV-1 clade C has upregulates significantly, HSP60 (ER Chaperone) and 14-3-3 protein (essential anti-apoptotic signal) as compared to HIV clade B. These suggest that HIV-1 clade B and C induce a differential protein profile in astrocytes. This demonstrates that HIV-1 clade B appears to induce pro-apoptotic and ER stress markers while clade C seem to be related to the generation of protective and anti-apoptotic mechanism in astrocytes. **Supported by NIH-RCMI Biomedical Proteomics Facility 2G12RR03035.**

EXERCISE MODULATES REDOX-SENSITIVE SMALL GTPASE ACTIVITY IN THE BRAIN MICROVASCULATURE IN A MODEL OF BRAIN METASTASIS FORMATION.

Wolff G, Park M, Andras IE, Kim HJ, Toborek M; Biochemistry and Molecular Biology, University of Miami, Miami, FL 33136.

Tumor cell extravasation into the brain requires passage through the blood-brain barrier, which is a highly protected microvascular environment that is fortified with tight junctions (TJ). Activation of redox-sensitive small GTPases (Ras kinase) can lead to the disruption of TJs and promote tumor cell extravasation. There is evidence that exercise can alter the oxidation status of the brain microvasculature and protect against tumor cell invasion. In the current study we injected D122 cells (murine Lewis lung carcinoma) into mouse brain microvasculature in order to study blood-borne brain metastasis formation. Mice exercised for five weeks using a running wheel. The average voluntary running distance was 3.6 ±1.4 km/day. Mice were injected with $1x10^6$ tumor cells and 48-hours later microvessels were isolated. Oxidative stress measurements revealed a trend toward increased reactive oxygen species in both the exercise and tumor cell injected groups. Ras activity was increased in the sedentary mice injected with tumor cells but was similar to control in the exercise tumor cell group. TJ (occludin and claudin-5) protein expression was similar between the exercise tumor and vehicle treated groups, however ZO-1 and junctional adhesion molecule-A protein levels trended toward increased expression in the tumor cell groups. These data indicate that initial steps in metastasis formation involve a localized increase in reactive oxygen species and activation of small GTPases. Importantly, they suggest that exercise plays a role in modulating Ras signaling in the brain microvasculature.

Supported by NIH/NCI R0CA133257.

EFFECT OF NICOTINE ON SYNAPTIC PLASTICITY GENE EXPRESSION IN HIV-1 INFECTION: IMPLICATION IN HAND. Atluri VSR, Sudheesh PK, Samikkannu T, Vijaya P, Ding H, Raymond, AD, Nair, M; Department of Immunology, Institute of NeuroImmune Pharmacology, Herbert Wertheim College of Medicine, Florida International University, Miami, FL 33199.

HIV-associated neurocognitive disorder (HAND) is characterized by development of cognitive, behavioral and motor abnormalities, and occurs in approximately 50% of HIV infected individuals. In US, the prevalence of cigarette smoking range from 35-70% in HIV-infected individuals compared to 20% in general population. However the synergistic effects of nicotine and HIV-1 infection and the underlying mechanisms in the development of HAND have not been clearly elucidated yet. Primary human astrocytes were infected with HIV-1 in the presence or absence of nicotine at different concentrations for 7 days. Among 84 human synaptic plasticity genes analyzed using human synaptic plasticity PCR array, 8 genes were significantly down regulated (4-43 folds) with nicotine (100ÂµM) while 33 synaptic plasticity genes were down regulated (3-43 folds) with HIV. Out of these 33 genes, 14 genes were significantly further down regulated with HIV infection plus nicotine treatment. Interestingly, 10 genes were significantly dysregulated (3-31 folds) by both nicotine and HIV-1 plus nicotine treated cells. Further, confocal microscopy of SK-N-MC cells showed a decrease in synaptic density in HIV-nicotine treated cells in comparison to nicotine or HIV treated cells. These studies suggest that nicotine significantly dysregulates the synaptic plasticity gene expression and may be correlated with increased risk for HAND in HIV infected smokers. **Supported by NIH grants: 5R01DA021537 and 1R01DA027049.**

MANGANESE ENHANCED MAGNETIC RESONANCE IMAGING (MEMRI) REFLECTS HUMAN NEUROPATHOLOGY IN A MURINE MODEL OF HIV-1 ASSOCIATED NEUROCOGNITIVE DISORDERS (HAND). Bade AN, Gorantla S, Poluektova LY, Makarov E, Gendelman HE, Boska, MD, Liu Y; Department of Pharmacology and Experimental Neuroscience; and Department of Radiology, University of Nebraska Medical Center, Omaha, Omaha, NE 68198.

Although antiretroviral therapy has decreased the prevalence of HAD (HIV-associated dementia), the overall prevalence of HAND (HIV-associated neurocognitive disorder) has remained unchanged affecting from 39 to 52% of infected patients. The means for better diagnosis and monitoring of HAND from its earliest stages to more severe disease could improve disease outcomes by separating HAND from other neurologic disorders as well as better defining when to initiate antiretroviral or adjunctive therapies. Importantly, the diagnosis of HAND is one of exclusion of other CNS disorders and as such could be improved if disease biomarkers were available and acquired either from cerebrospinal fluid tests or by neuroimaging. We used Mn2+ enhanced MRI (MEMRI) to evaluate changes in the brain of humanized mice due to HIV-1 Clade-C infection, providing imaging biomarkers of brain dysfunction. These methods will be useful for testing experimental therapies for HIV-1 infection and HAND. The changes of MEMRI signal intensity in hippocampus and amygdala indicated that HIV-1 infection caused the deviation of Mn2+ accumulation from uninfected state, suggesting neuronal pathology in these regions. The elevated signal intensity on hippocampus in infected mice suggests excitatory neurotoxicity causing increased Mn2+ uptake, whereas the decreased signal intensity on amygdala may result from neuronal dropout. Since the function of both hippocampus and amygdala include memory, the abnormal signal intensity in the infected mice may suggest memory deficit in these animals.

HUMAN PRIMARY ASTROCYTES EXPRESS CD99: POTENTIAL ROLE IN HIV BRAIN INFECTION. Amorin Daep C, Eugenin E; Public Health Research Institute, University of Medicine and Dentistry of New Jersey, Newark, NJ 07107.

CD99 is an intracytoplasmic glycoprotein found in a variety of cells. Its role ranges from cell differentiation, apoptosis, and leukocyte transmigration across the endothelium. Infection of the CNS occurs following the transmigration of HIV-infected macrophages across the BBB leading to NeuroAIDS and CNS deterioration. This is facilitated by the interactions of macrophages with adhesion molecules expressed within the BBB. Despite previously being identified to be present on endothelial cells, neither the role of CD99 in BBB semi-permeabilty nor its expression among other cells comprising the BBB, namely, astrocytes, have been elucidated. This study shows that primary human astrocytes robustly express CD99 as verified by Western blot and Immunofluoresence assay. We have also identified that CD99 expression is negatively impacted by methamphetamine with a 2.8-fold decrease 6 hours post-treatment as compared with the untreated controls. Recovery of CD99 levels occurs at T = 24 hours post-treatment. This suggests that usage of the narcotic could increase the window of opportunity for HIV and neurotrophic pathogens to infect the CNS leading to the progression of NeuroAIDS and other CNS diseases. Currently the role of CD99 and Meth in the HIV infection of the CNS is being identified. Determining the role of these molecules in the BBB semi-permeability and synaptic regulation may provide further insight into the NeuroAIDS pathogenesis and the design of anti-HIV therapies.

METHAMPHETAMINE DISRUPTS GUT MUCOSAL IMMUNITY IN A HIV INFECTION MODEL. Ma J, Sindberg G, Meng JJ, Wang FY, Roy S; Department of Surgery and Department of Pharmacology, University of Minnesota, Minneapolis, MN 55455; Department of Veterinary Biosciences, University of Minnesota, Saint Paul, MN 55108.

METH) is a highly addictive psychostimulant that is one of the most widely abused illicit drugs, with an estimated over 35 million users worldwide. Multiple lines of evidence suggest that chronic METH abuse is the major factor for the increased risks of infections with human immunodeficiency virus (HIV) and possibly other pathogens, due to its immunosuppressive property. During HIV infection, microbial translocation is a major contributor of immune activation. However, very little is known on how METH modulates gut mucosal immune function in the context of HIV infection. Herein, we investigated the effects of METH on HIV enteropathogenesis by using a chimeric model of HIV infection (EcoHIV). We report that METH alone does not induce significant bacterial translocation, however, in the presence of HIV infection, METH treatment results in extraintestinal growth of bacteria in liver, lung and mesenteric lymph node (MLN) in mice. METH and HIV-treated mice gavaged with GFP labeled E.coli and fluorescence signals were detected in MLN, indicating that METH treatment promotes bacterial translocation of commensal bacteria from the gut lumen. This translocation correlated with up-regulated HIV p24 core antigen levels in plasma, liver and lung and increased proinflammatory cytokines TNF-Î±, IL-1Î² and IL-6 production in lung and MLN. This study provides the evidence to investigate the underlying mechanisms responsible for the action of METH on modulating mucosal immunity in the context of HIV infection. **Supported by RO1 DA12104, RO1 DA022935, RO1 DA031202, K05DA033881, P50 DA011806, R01 DA034582.**

INDUCTION OF IL-6 AND IL-8 CYTOKINES BY HIV-1 TAT INVOLVES A COMMON TRANSCRIPTION FACTOR NUCLEAR FACTOR-KAPPA B BUT DIFFERENT SIGNALING PATHWAYS. Nookala A, Kumar A; Division of Pharmacology & Toxicology, UMKC School of Pharmacy, Kansas city, MO 64108.

The incidence of HAND is increased in HIV individuals on HAART and this may be associated with increased life expectancy. Several HIV proteins including HIV-1tat have been implicated in this phenomenon. The present study was undertaken with the objective of determining the effects of the HIV-1 viral protein Tat on astrocytes. SVGA astrocytes were transiently transfected with Tat plasmid and expression of IL-6 and IL-8 was studied. The maximal IL-6 and IL-8 RNA and protein levels were observed at 6h and 48h post transfection, respectively. Inhibitor studies were performed to identify the mechanisms by which these cytokines were up-regulated. Treatment with the NFKB inhibitor (either BAY or SC514) resulted in decreased expression of IL-6 and IL-8 mRNAs by 47.9% and 40.1%, respectively. Treatment with a PI3K/AKT inhibitor (LY 294002) decreased the expression of IL-6 mRNA by 52.9% with no effect on the expression of IL-8. Treatment with a JNK inhibitor (SP600125) resulted in decreased expression of IL-8 mRNA by 57.9%. We also treated with STAT3 inhibitor (Cryptotanshinone) that resulted in decreased production of IL-6 mRNA by 47.2% and IL-8 mRNA by 43.1%, while treatment with a JAK3 inhibitor (Janex-1) resulted in decreased production of IL-6 and IL-8 mRNA by 60.7% and 29.5% respectively. The inhibition at the protein level for all inhibitors was consistent with inhibition at the mRNA level. To prove the autocrine effect, astrocytes were treated with IL-6 protein that resulted in the increased production of IL-6 mRNA by greater than 2-fold. **Supported by grants DA025528 & DA025011 to AK.**

DISTINCT INDUCTION OF IL-17 ISOFORMS BY MORPHINE CONTRIBUTES TO DIFFERENTIAL BARRIER DISRUPTION IN THE SMALL INTESTINE AND COLON. Meng J, Ma J, Banerjee S, Wang F, Charboneau R, Roy S Department of Pharmacology and Department of Surgery, University of Minnesota, Minneapolis, MN 55455; Department of Surgery, Veterans Affairs Medical Center, Minneapolis, MN 55417.

Opioids are the gold standard for pain management in malignant pain due to its well-established efficacy while opioid therapy for nonmalignant pain associated with chronic inflammatory diseases like IBD remains controversial. In all patients presenting to an IBD clinic, the frequency of opioid use ranged from 3% to 13%. However, the roles of μ-opioid receptors in intestinal inflammation remain controversial: while some studies report a specific opiate showed potential anti-inflammatory effects in the human colon tissues, others claim that antagonism of the opioid receptor leads to reversal of inflammation and therapy with the opioid antagonist promotes mucosal healing in Crohn's disease. We investigated the profile of pro-inflammatory cytokine production in MLN following morphine treatment. Interestingly, IL-17A, but not IL-17F, was up-regulated by morphine. And only IL-17A disrupted the barrier function of small intestinal epithelial cells. In contrast, the colonic epithelial cells only showed compromised barrier in the presence of IL-17F. The differential responses of small intestinal and colonic epithelial cells to IL-17A and -17F were consistent with our previous in vivo observation: that morphine treatment only led to tight junction disruption in small intestine but not colon. The specific effects of morphine on IL-17A and differential responses of small intestinal and colonic epithelial cells to specific IL-17 may explain the contradictory results from human studies, which may provide novel personalized therapeutic strategies to control pain and inflammation in IBD patients. **Supported by RO1 DA12104, RO1 DA022935, RO1 DA031202, K05 DA033881, P50 DA011806, R01 DA034582.**

COCAINE DOWNREGULATES SAHMD1 EXPRESSION AND FACILITATES HIV-1 INFECTION IN ASTROCYTES. Pilakka-Kanthikeel S, Raymond S, Atluri V, Nair M; Department of Immunology, Institute of NeuroImmune Pharmacology, Herbert Wertheim College of Medicine, Florida International University, Miami, FL 33199.

Human immunodeficiency virus 1 (HIV-1) remains one of the leading causes of death worldwide. HIV penetrates CNS during early infection, establishing a viral reservoir. Even though astrocytes are infected by HIV, unlike microglia and brain macrophages, they are not productively infected. Non-productive infection could be significant to neuropathogenesis. Previous studies suggest that cocaine upregulates HIV infectivity and associated morbidilty. Although the potent antiretroviral therapies have significantly improved the morbidity in HIV patients, the biggest challenge is the inability of HAART to eradicate the virus from the reservoirs. The mechanisms leading to the establishment of HIV reservoir in vivo are still not fully understood. Recently identified restriction factor, SAM domain and HD domain-containing protein 1 (SAHMD1), which hydrolyses dNTPs has been shown to restrict HIV infection in resting CD4+ T cells. We hypothesize that increased SAHMD1 expression may lead to non-productive infection in astrocytes and cocaine may reverse SAHMD1 mediated non-productive infection. Our results show that astrocytes displayed higher expression level of SAHMD1 by quantitative RT-PCR , flowcytometry and western blot analysis, and cocaine significantly down-regulates SAHMD1, which in turn up-regulates viral replication in astrocytes. These results suggest that SAMHD1 plays a significant role in non-productive HIV infection in astrocytes and cocaine may reactivate the latent viral infection by modulating SAHMD1. **Supported by NIH Grant R37DA025576.**

HIV-1 VIRAL PROTEIN R (VPR) INDUCES THE PRODUCTION OF PRO-INFLAMMATORY CYTOKINES IL-6, IL-8 AND RANTES IN THE ASTROCYTES VIA DIFFERENT MECHANISMS. Gangwani MR, Kumar A; Division of Pharmacology and Toxicology, University of Missouri Kansas City, Kansas City, MO 64108.

The HIV-1 accessory protein Vpr plays an important role in the pathogenesis of disease; however, its role in neuroinflammation is not well characterized. The present study was designed to study the role of HIV-1 vpr in glial activation which is one of the prominent features of HIV-1-associated neurological disorders (HAND). In view of this, we sought to address whether Vpr can induce proinflammatory cytokines IL-6, IL-8 and RANTES in astroglial cells. The transfection of SVGA astrocytes with Vpr caused time-dependent induction of these cytokines with peak mRNA levels of (12.5 ± 1.16 fold for IL-6; 3.42 ± 0.4 fold for IL-8 and 29.76 ± 2.24 fold for RANTES) and peak protein levels (10.46 ± 0.73 fold for IL-6; 3.28 ± 0.10 fold for IL-8 and 107.26 ± 2.42 fold for RANTES). To determine the mechanism involved in the secretion of these cytokines various pathways were explored using pharmacological inhibitors. Chemical antagonists of p38MAPK (SB203580), PI3K/Akt (LY294002), NF-κB (Bay 11-7082: IκB-α; SC-514: IKK2) and Jak/STAT (AG490) pathway showed varying degrees of inhibition in the production of different cytokines by Vpr. NF-kB was found to be involved in up-regulation of all 3 cytokines but IL-6 involved p38 MAP kinase and PI3k/Akt pathway whereas IL-8 expression was mediated by JNK pathway. Currently, studies are underway to determine the role of Jak/STAT pathway and to determine whether there is any involvement of autocrine or paracrine loop in the production of these cytokines. **Supported by grants DA025528 and DA025011 to AK.**

COCAINE ALTERS CYTOKINE SIGNATURES WITHIN PATIENTS IN THE DREXELMED HIV/AIDS GENETIC ANALYSIS COHORT. Parikh N, Williams J, Pirrone V, Nonnemacher M, Aiamkitsumrit B, Passic S, Blakey B, Frantz B, Moldover B, Feng R, Downie D, Lewis S, Jacobson JM, Wigdahl B; Microbiology and Immunology, and Medicine/Division of Infectious Disease and HIV Medicine, Drexel University College of Medicine, Philadelphia, PA 19102; B-Tech Consulting, Ltd, Philadelphia, PA 19130; Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, PA 19104.

HIV infection is prevalent among substance abusers. We evaluated the relationship between illicit drug use and HIV-1 disease progression in HIV-1-infected patients enrolled in the DREXELMED HIV/AIDS Genetic Analysis Cohort in Philadelphia, PA. Patients within the cohort are assessed approximately every 6 months for HIV-1 clinical markers and history of illicit drug, alcohol, and medication use. Drug abuse was found to be common with 87.6% of patients admitting past use, 29.7%, currently abusing drugs; and 36.2% testing positive for drug use at the time of visit. Utilizing the drug screens at the time of visit, it was found that the cohort could be categorized as non-users (PN), preferential cocaine users (PC), and multidrug users (PM). The overall health of the PN subcohort is better than that of the PC subcohort. Peak and current viral loads in PN are substantially lower than those in PC and PM patients. Since, cocaine is known to have immunomodulatory effects, the cytokine profiles of PN, PC, and PM (where cocaine was one of the drugs abused) individuals were analyzed and compared to understand the effects of cocaine on cytokine modulation and HIV-1 disease progression. Among the 30 cytokines investigated, differential levels of various cytokines, were established within the PN, PC, and PM subcohorts. The cytokine profiles have also been associated with clinical parameters such as age, gender, viral load, CD4+ T cell count and neurocognitive impairment status. In conclusion, illicit drug use appears to facilitate HIV-1 disease progression based on these assessments. **Supported by R01 NS32092; and a grant from the National Institutes on Drug Abuse.**

STRUCTURAL AND FUNCTIONAL ALTERATIONS IN AN IN VITRO MODEL OF THE BLOOD-BRAIN BARRIER FOLLOWING PROLONGED EXPOSURE TO MORPHINE. Strazza M, Pirrone V, Lin W, Feng R, Wigdahl B, Nonnemacher M; Microbiology and Immunology, Drexel University College of Medicine, Philadelphia, PA 19102; Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, PA 19104.

Opioid abuse by human immunodeficiency virus type 1 (HIV-1)-infected individuals leads to more rapid disease progression, increased viral replication and peripheral viral load, and increased incidence and severity of neurocognitive abnormalities compared to non-drug abusers. The blood-brain barrier (BBB) is an obstacle that must be overcome during neuroinvasion and development of HIV-associated neurocognitive disorders (HAND). Previous studies addressing the role of mu-opioids in altering BBB permeability suggest that exposure increases cellular transmigration through an uncharacterized mechanism. In this study, a human brain microvascular endothelial cell (hBMEC) line, hCMEC/D3, was used to establish an in vitro transwell model of the BBB to investigate the effects of chronic (24, 48, 72 h) morphine treatment on barrier structure and function. We observed that hCMEC/D3 cells form a confluent monolayer with a basal rate of passage of a 70 kDa tracer molecule comparable to primary hBMECs. We have shown that these cells express μ-opioid receptor, and that chronic morphine treatment induces changes in mRNA levels of tight junction proteins and cellular adhesion molecules. Functionally, an increase in PBMC transmigration was observed following chronic morphine exposure, in the absence of increased overall barrier leakiness. Results suggest that morphine activates hCMEC/D3 cells creating a cellular environment permissive to transmigration. These studies may uncover a mechanism through which morphine disrupts periphery-CNS homeostasis leading to accelerated HAND. **Supported by R01 NS32092 to BW.**

HEPATITIS C VIRUS IMPAIRS TOLL-LIKE RECEPTOR-3 SIGNALING AND INHIBITS IFN-LAMBDA 1 EXPRESSION IN HUMAN HEPATOCYTES. Wang YZ, Li JL, Wang X, Ye L, Zhou Y, Thomas RM, Ho WZ; Department of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140.

Toll-like receptor-3 (TLR-3) activation plays an important role in the innate immune responses to viral infections. We show here the activation of TLR-3 signaling pathway by poly I:C, a synthetic mimic of dsRNA, could induce high level expression of interferon (IFN)-λ1 in human hepatocytes. The induced IFN-λ1 contributed to poly I:C-mediated inhibition of hepatitis C virus (HCV) Japanese fulminant hepatitis-1 (JFH-1) replication in hepatocytes. This inhibitory effect of poly I:C on HCV replication, however, was compromised by HCV infection of hepatocytes. Investigation of the mechanisms showed that HCV infection suppressed the expression of poly I:C-induced IFN-λ1 and IFN-stimulated genes (IFN-stimulated gene 56, ISG-56; myxovirus resistance A, MxA and 2'-5'-oligoadenylate synthetase 1, OAS-1), the key antiviral elements in IFN signaling pathway. Among the HCV nonstructural (NS) proteins tested, NS3/4A, NS5A and NS5B had the ability to inhibit poly I:C-induced IFN-λ1 expression in hepatocytes. These observations provide the experimental evidence that HCV and its proteins impair TLR-3 signaling and inhibit intracellular IFN-λ1/ISG expression in hepatocytes, which may account for HCV persistence in the liver. **Supported by NIH DA22177.**

MODULATION OF HUMAN CD4 AND CD8 T CELLS CELL CYCLE ENTRY AND PROGRESSION TO METHAMPHETAMINE. Haldar B, Cenna JM, Potula R; Department of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140.

Methamphetamine (METH) is a highly addictive central nervous system stimulant and toxic drug of abuse. METH is also deleterious to different immune cell types. However, further research needs to be done to understand the mechanisms by which METH mediates T cell immune dysregulation. Our earlier study showed that METH exposure results in mitochondrial oxidative damage, loss of IL-2 production and proliferation of T cells. The current study was done to investigate the effects of METH on cell cycle entry and progression in both CD4 and CD8 T cells. Genes responsible for positive and negative regulation of cell cycle progression were differentially regulated in METH treated CD4 and CD8 T cells. Cell cycle analysis indicated that, compared to the controls, a significant number of both CD4 and CD8 T cells exposed to METH remain arrested in G1 phase. Furthermore, METH exposure significantly decreased cyclin E and cyclin dependent kinase 2 (CDK2) expression in both CD4 and CD8 T cells in all 3 interphases of the cell cycle. The expression of transcription factor E2F1, required for the timely regulation of numerous genes essential for DNA replication and cell cycle progression, significantly decreased in T cells after METH exposure. Our results provide evidence that METH exposure alters cell cycle entry and progression. The decreased expression of cyclin E, CDK2, and E2F1 are contributory to the impaired cell cycle progression of METH-exposed T cells. **Supported by R21 DA0249791 and R01 DA031064 to RP.**

ALCOHOL ALTERS MICROGLIA FUNCTION THROUGH P2X4 RECEPTOR SIGNALING. Gofman L, Cenna JM, Potula R; Department of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140.

Alcoholism is the third leading cause of preventable death in the United States. A wealth of scientific evidence underscores the deleterious effects of alcohol abuse on microglia, the resident immune cells of the CNS. Purinergic signaling plays a key role in regulating microglial function and, more significantly, purinergic receptors have been shown to be important mediators of alcohol-induced effects. Our previous results have shown up-regulation of purinergic receptors in alcohol treated embryonic stem cell-derived microglia (ESdM). Here, we investigate the up regulation of the purinergic receptor P2X4, and its effects on microglia function in response to alcohol. Alcohol decreased migration of microglia towards Fractalkine (CXCL3) by 75 percent following 48 hours of treatment compared to control ($p<0.001$). Fractalkine-dependent migration was confirmed to be P2X4 receptor-dependent through the use of 5-BDBD, a P2X4 selective antagonist, which reversed the effects 2.3 fold as compared to alcohol alone. Similarly, 48 hours of alcohol treatment significantly decreased microglia phagocytosis by 15 percent compared to control ($p<0.002$). 5-BDBD pre-treatment prior to alcohol treatment significantly increased microglial phagocytosis ($p<0.03$). Our findings support P2X4 receptor involvement in microglia immune function suggesting purinergic activation may play a role in modulating microglia function in the context of alcohol abuse. Exploring the role of purinoceptors in microglia-mediated neuroprotection may elucidate processes that contribute to alcohol abuse. **Supported by grants from NIH.**

O-1966, A CB2-SELECTIVE CANNABINOID AGONIST, BLOCKS T-CELL ACTIVATION IN THE MIXED LYMPHOCYTE REACTION. Robinson RH, Meissler JJ, Adler MW, Eisenstein TK; Center for Substance Abuse Research; Department of Microbiology and Immunology; Department of Pharmacology, Temple University, Philadelphia, PA 19140.

We have previously shown that CB2-selective agonists inhibit the Mixed Lymphocyte Reaction (MLR), an in vitro correlate of organ graft rejection, via CB2 receptors. The cannabinoids directly affect T-cells and significantly decrease expression of mRNA for several markers of immune activation and for molecules involved in cell division. In addition, there was an increase in mRNA expression of molecules involved in immunosuppressive pathways, including IL-10. The increase in IL-10 was confirmed by measuring IL-10 protein in MLR culture supernatants. Furthermore, there was an increase in regulatory T-cells (Tregs) in the MLR. Current studies explored further the mechanisms for the suppressive properties of this class of cannabinoids. The importance of increased IL-10 levels in the inhibition of proliferation and increase in Tregs in O-1966 treated cells in the MLR was studied using an anti-IL-10 antibody in MLR cultures. Pretreatment with anti-IL-10 resulted in a partial reversal of inhibition of proliferation and blocked the increase of Tregs. The effect of O-1966 on T-cells was further examined by measuring the activation of the several transcription factors in T-cells from the MLR. O-1966 treatment resulted in a dose-dependent decrease in the active nuclear forms of NF-Î°B and NFAT. Further, T-cells in the MLR treated with O-1966 had decreased expression of CD4, a co-receptor with the T-cell receptor. These data support the potential of this class of compounds as useful therapies to prolong graft survival in transplant patients. **Supported by DA13429, DA06650, and T32-DA07237.**

CXCR7, A NOVEL RECEPTOR OF CXCL12, MEDIATES MIGRATION AND SIGNALING OF NEURAL PROGENITOR CELLS IN VITRO. Chen Q, Li Y, Song A, Zhu B, Peng H, Huang Y, Tian C, Xu D, Zheng JC; Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198.

Neural progenitor cell (NPC) migration is an essential process for both proper brain development and neuroregeneration after brain injury. Although CXCL12 and its receptor CXCR4 are known to regulate NPC migration, recent data have suggested that CXCL12 binds to its novel receptor CXCR7 with higher affinity than to CXCR4; however, the exact role of CXCR7 in CXCL12-mediated NPC migration is unknown. To determine the role of CXCR7 in CXCL12-mediated NPC migration, we used in vitro NPC cultures derived from CXCR4 knockout, CXCR7 knockout and their corresponding wild type mice. Both CXCR4 and CXCR7 were expressed on NPCs in developing mouse brain and adherent cultures in vitro by immunostaining. CXCL12 mediated NPC migration in transwell assays and stripe assays, and antagonists for either CXCR4 or CXCR7 blocked the migration. Surprisingly, NPCs from CXCR4 knockout mice migrated to CXCL12, and CXCR7 antagonist completely blocked the migration. To determine the signaling for CXCR7-mediated NPC migration, we found Erk1/2 could be activated in CXCR4 knockout NPCs after CXCL12 treatment by western blotting, suggesting that CXCR7 can activate Erk1/2, which is associated with migration. Erk1/2 inhibitor blocked CXCL12-mediated migration of CXCR4 knockout NPCs, indicating that Erk1/2 activation is essential for CXCR7-mediated NPC migration. These results reveal an essential role of CXCR7 for CXCL12-mediated NPC migration that will be important to understand neurogenesis during development and neural repair after brain injury, and provide a target for modulating NPC migration. **Supported by R01 NS41858-01, R01 NS061642-01, 3R01NS61642-2S1, R21 MH083525-01, P01 NS043985.**

GLUTAMINASE 1 IS ESSENTIAL FOR SURVIVAL, DIFFERENTIATION, AND PROLIFERATION OF NEURAL PROGENITOR CELLS. Wang Y, Huang Y, Zhao L, Li Y, Zheng J; Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68105.

Glutaminase is the enzyme that converts glutamine into glutamate, which serves as a key excitatory neurotransmitter and one of the energy providers for cellular metabolism. Previous studies have revealed that mice lacking glutaminase 1 (GLS1), the dominant isoform in brain and kidney, died shortly after birth due to disrupted glutamatergic transmission, suggesting the critical role of GLS1 in synaptic network. However, whether GLS1 regulates neurogenesis, a process by which neurons are generated from neural progenitor cells (NPCs), is unknown. Using a human NPC model, we found that both GLS1 isotypes, kidney-type glutaminase (KGA) and glutaminase C (GAC), were upregulated during neuronal differentiation and correlated with the increase of neuronal marker microtubule-associated protein 2 (Map2). To study the functional impact of GLS1 on neurogenesis, we used small interference RNA targeting GLS1 and determined the expressions of neuronal genes by real-time RT-PCR and immunocytochemistry. siRNA silencing of GLS1 significantly reduced expression of Map2, indicating that GLS1 is essential for neurogenesis. To unravel the specific process(es) of neurogenesis being affected, we further studied survival and proliferation of NPCs in vitro. siRNA silencing of GLS1 induced significantly larger number of TUNEL+ cells and fewer Ki67+ cells, suggesting critical roles of GLS1 for the survival and proliferation of NPCs. These data suggest that GLS1 may become a new therapeutic target to properly regulate critical processes of neurogenesis.

TRANSIENT METHAMPHETAMINE-ASSOCIATED HYPERTHERMIA MODULATES ASTROCYTE TRACE AMINE ASSOCIATED RECEPTOR-1 (TAAR1) ACTIVATION AND EXACERBATES HIV-1-INDUCED NEURODEGENERATION. Cisneros IE, Ghorpade A; Cell Biology and Anatomy, University of North Texas Health Science Center at Fort Worth, Fort Worth, TX 76107.

Methamphetamine (METH) is a highly abused and addictive psychostimulant. METH heightens sexual arousal and decreases inhibition increasing the probability for acquiring human immunodeficiency virus-1 (HIV-1). HIV-1 results in cognitive effects, such as HIV-associated dementia (HAD) characterized by similar neurotoxic mechanisms as METH. Astrogliosis and hyperthermia are key pathological features of METH exposure and HAD. In context of our studies, METH abuse increases brain temperature by approximately 2Â° C, mimicking a fever common during early HIV-1 infection. A moderate increase in brain temperature exacerbates neuroinflammatory processes synergistically effecting METH/HIV-1-associated neurodegeneration. Astrocytes sensitivity to METH led to the investigation of astrocyte TAAR1 as a receptor mechanism for METH-induced effects in astrocytes. We have shown astrocyte TAAR1 thermoregulatory responses directing the expansion of our studies to investigate METH-associated hyperthermia in METH/HIV-1-induced astrocyte activation. Data suggests expression of functional astrocyte TAAR1. Furthermore, TAAR1 is regulated in the presence of transient hyperthermia. Elevated temperatures increased GFAP expression and cytokine secretion. We propose activation of astrocyte TAAR1 mediates METH/HIV-1-induced neurodegeneration, further modulated by METH-associated hyperthermia. The results will lead to understanding of the mechanisms and pathological features associated with METH and HIV-1 neurodegeneration and potential therapeutic targets in the CNS. **Supported by 1R01 DA025566.**

ASTROCYTE-ELEVATED GENE-1 PROTECTS HUMAN ASTROCYTES FROM OXIDATIVE STRESS-INDUCED DNA DAMAGE: A POTENTIAL SURVIVAL MECHANISM IN HAND. Vartak-Sharma N, Ghorpade, A; Department of Cell Biology and Anatomy, University of North Texas Health Science Center, Fort Worth, TX 76107.

Astrocyte elevated gene-1 (AEG-1), a novel human immunodeficiency virus (HIV-1)- and tumor necrosis factor-Î-inducible oncogene, has generated significant interest in the field of cancer research as a therapeutic target for many metastatic aggressive tumors. However, little is known of its role in astrocyte behavior and function during HIV-1 central nervous system (CNS) infection, and whether it contributes towards the development of HIV-1-associated neurocognitive disorders (HAND). Based on its putative role in cancer as a chemotherapy resistance marker, we investigated whether AEG-1 induction in astrocytes alters their responses to oxidative stress, a hallmark feature of neuroinflammatory diseases. Analysis of AEG-1 mRNA levels in an aging cohort of HIV-1 seropositive and seronegative human brain tissues showed a significant positive correlation to aging. A dose-dependent increase in AEG-1 astrocyte nucleolar localization was noted following treatment with oxidative stress stimuli, hydrogen peroxide, as assayed by immunostaining and confocal microscopy. Cell death and cell survival assays to quantify apoptotic nuclei, mitochondrial depolarization and activity, and cell membrane permeability demonstrated a novel role of AEG-1 in protecting astrocytes from oxidative stress-induced damage. These findings suggest that AEG-1 may play a role in protecting astrocytes from oxidative stress-induced DNA damage, a plausible mechanism of astrocyte survival during HIV-1 CNS infection-induced toxicity. **Supported by R01 MH087345-01.**

PERSISTENT CD8 T CELLS HINDERS NEUROGENESIS DURING HERPES SIMPLEX ENCEPHALITIS (HSE). Rotschafer JH, Roach E, Cheeran MCJ; Veterinary Population Medicine, University of Minnesota, St. Paul , MN 55108.

HSE is characterized by chronic inflammation dominated by CD8 T cells. Persistent virus-specific CD8 T cells produce interferon-1, which has been shown to impair NSC proliferation. Furthermore, during chronic HSE, endogenous neural stem cell (NSC) proliferation is decreased in a FGF-2 dependent manner. We demonstrate, here, that depletion of CD8 T cells between 15 and 20 d p.i. increased endogenous NSC numbers. A 5-fold increase in CD45(-)nestin(+) NSCs was seen in animals treated with CD8 depleting antibody compared to isotype treated controls. However, expression of the proliferation marker, Ki-67, in CD45(-) brain cells was similar in both antibody and isotype treated animals at 20 d p.i. Further experiments are underway to determine other cell types affected by persistent CD8 T cells in the brain. To determine the mechanisms of CD8 T cell effects on NSC, changes to the inflammatory milieu in the brain were assessed. Increased infiltrating inflammatory macrophages were found with CD8 T cell depletion. However, microglia and CD4 T cell numbers were not altered. Interestingly, MHC II expression on microglia and expression of CD62L and CD103 expression on CD4 T cells was decreased with CD8 T cell depletion, indicating an altered neuroimmune activation state. Studies are underway to determine if changes in immune cells reflect altered cytokine and growth factor expression profiles that may affect neurogenesis in the adult brain. These studies will help identify therapeutic interventions to enhance neurogenesis during viral encephalitis. **Supported by RO1NS065817, T32DA007097.**

INVOLVEMENT OF GLIA AND CYTOKINES IN HIV-INDUCED CHANGES OF FERRITIN HEAVY CHAIN PROTEIN EXPRESSION IN CORTICAL NEURONS.

Festa L, Meucci O; Department of Pharmacology and Physiology, Drexel University College of Medicine, Philadelphia, PA 19102.

Ferritin is a ubiquitous protein involved in iron sequestration and storage, composed of two different subunits, heavy chain (FHC) and light chain (FLC). Recent evidence has identified a novel role for FHC as a negative regulator of the chemokine receptor CXCR4. Our lab has previously demonstrated that mu-opioid receptor agonists, including morphine, upregulate FHC protein levels in neurons, which results in inhibition of neuroprotective signaling mediated by CXCR4. Furthermore, in vivo data indicate greater expression of FHC and inhibition of CXCR4 activation in brain tissue of HIV+ drug abusers compared to controls. The aim of this study was to investigate potential components of HIV infection that could contribute to the upregulation of FHC in neurons. Our data indicate that the inflammatory cytokines tumor necrosis factor-alpha and interleukin-1 beta, as well as the HIV envelope glycoprotein (gp120), preferentially upregulated FHC protein expression, but not FLC, in neurons. While both cytokines induced increases in FHC in both the presence and absence of glia, gp120 only caused significant changes in neuronal/glial bilaminar co-cultures, suggesting glia are necessary for the increase seen in FHC protein levels by gp120. In support of this, the presence of an IL-1 beta neutralizing antibody (or receptor antagonist) in gp120-treated bilaminar cultures abrogated neuronal FHC upregulation. Overall, these studies suggest that opiates and HIV can synergistically act on FHC and deprive neurons of important neuroprotective actions driven by CXCR4. **Supported by DA15014; DA032444; MH097623.**

HISTONE DEACETYLASE DEREGULATION IN HIV-1-INFECTED MACROPHAGES EXPOSED TO METHAMPHETAMINE. Burns AC, Olszowy P, Ciborowski P; Pharmacology & Experimental Neuroscience , University of Nebraska Medical Center, Omaha, NE 68198.

It has been shown that chromatin remodeling and control of gene transcription in HIV-cells occurs via epigenetic mechanisms that involve histone deacetylases (HDACs), a family of enzymes modifying acetylation of histones. We have also shown that exposure of macrophages to methamphetamine (METH) leads to changes in histone acetylation patterns; however the dynamics of the two insults is unknown. Since the macrophage is a key part of the innate immunity system and the target of HIV, it's important to understand the molecular mechanisms regulating phenotypic and functional characteristics of these cells. In our studies we use an in vitro model of human monocyte derived macrophages (MDM) from healthy donors, which are infected with HIVADA and/or exposed to METH. Proteins levels of HDAC1 were elevated in the cytosol in HIV infected MDM compared to control; however the levels of HDAC1 transcript remain unchanged. In the cytosol and in the nucleus, METH treatment of MDM lowered the levels of HDAC1 from control and from HIV to HIV/METH. The latter observation led us to speculate that HIV infection and/or METH exposure may alter intracellular location of these critical regulatory factors and lead to observed changes in patterns of histones PTMs. From these data, we hypothesize that the insults of HIV infection and exposure to METH differentially regulate HDAC1, which alter PTM of histones, thus altering the phenotype of the macrophage. Further testing is required but our results show the possible mechanism of the treatments is to regulate transcription by altering the location of HDAC1.

ANTI-INFLAMMATORY EFFECT OF DEXAMETHASONE -HPMA COPOLYMER IN A MURINE MODEL OF HIV-1 ENCEPHALITIS. Zhao L, Huang Y, Wang D, Zheng JC; Department of Pharmacology and Experimental Neuroscience, and the Department of Pharmaceutical Sciences, College of Pharmacy, University of Nebraska Medical Center, Omaha, NE 68198.

Chronic and unchecked inflammation plays an important role in the process of HIV-1 associated neurocognitive disorders (HAND). Therefore, anti-inflammation agents have been actively under development as a therapeutic approach for HAND. However, blood-brain barrier (BBB) permeability, side effects, specificity for inflammatory site, and the drug's sustainability in vivo are the main hurdles to the development of novel anti-inflammatory agents. N-(2-hydroxypropyl) methacrylamide (HPMA) copolymer holds therapeutic promise in that it can readily cross BBB and slowly release drug over a long period of time. Using the severe combined immunodeficient (SCID) mice injected with monocyte-derived macrophages (MDM), we found that HPMA copolymer crossed the BBB and accumulated in microglia, and to a less extent in astrocytes, in and adjacent to the MDM injection site. Next, we tested dexamethasone, a well-characterized anti-inflammation agent, in conjugation with HPMA copolymer. In in vitro cultured MDM, Dexamethasone-HPMA copolymer (p-Dex) significantly decreased both TNF and LPS-induced inflammatory chemokine MIP1-Î² release. Furthermore, in the murine HIV Encephalitis model, when HIV-1-infected MDM were stereotactically injected into the basal ganglia of the SCID mice, intravenous injection of p-Dex significantly decreased GFAP levels, a hallmark of astrogliosis and inflammation. These data suggest that p-Dex can be used as an effective anti-inflammation agent to treat HAND. **Supported by R01 NS41858-01, R01 NS061642-01, 3R01NS61642-2S1, R21 MH083525-01, P01 NS043985, P20 RR15635-01.**

METHAMPHETAMINE MODULATES ANTI-HIV-1 MIRNA EXPRESSION TO REGULATE HIV-1 REPLICATION IN CD4+ T CELLS AND MACROPHAGES. Mantri CK, Velamarti-Mantri J, Pandhare-Dash J, Dash CV; CAHDR, Meharry Medical College, Nashville, TN 37208.

Methamphetamine (Meth) is the second most frequently used illicit drug in the United States. Meth is associated with increased risk of HIV-1 acquisition, higher viral loads, and increased HIV-1 neuropathogenesis. Meth has been shown to increase HIV-1 replication in different in vitro models e.g. macrophages, microglia and dendritic cells. However, the effects of Meth on HIV-1 replication in CD4+ T cells, the primary targets of HIV-1 remains poorly understood. To investigate this, we infected primary CD4+ T cells with HIV-1 and treated them with Meth. Surprisingly, Meth decreased HIV-1 replication in CD4+ T cells in a concentration dependent manner. This is in contrast to an earlier report that demonstrated Meth increased HIV-1 replication in CD4+ T cells. To define the mechanism by which Meth regulates HIV-1 replication, we tested the expression of the cellular anti-HIV miRNAs. Real time analysis indicated that Meth increased the expression of three anti-HIV miRNAs miR-125b, miR-150 and miR-28-5p in CD4+ T cells. Knock down experiments confirmed a direct correlation between anti-HIV miRNA and HIV-1 replication. In parallel, when we used monocyte-derived macrophages, Meth increased HIV-1 replication and decreased expression of these anti-HIV-1 miRNAs. These data illustrate the complex interaction between Meth and HIV-1. Currently, we are investigating the differential effects of Meth on these cell types. **Supported by NIDA/NIH.**

PLATELET ACTIVATION BY COCAINE IN HIV PATIENTS INVOLVES IKK. Kiebala M, Singh M, Maggirwar SB; Department of Microbiology and Immunology, University of Rochester School of Medicine and Dentistry, Rochester, NY 14642.

Recent work has indicated that platelets, which are anucleate, circulating blood cells, play a central role in inflammatory disorders such as malaria and atherosclerosis. Importantly, large clinical studies have suggested a strong influence of platelets on the outcome of neurological impairment associated with HIV infection. We, and others, have shown that HIV infection is associated with increased levels of molecules that activate platelets, including sCD40L and PAF. Additionally, cocaine, which is a drug commonly abused by HIV patients, is involved in platelet activation. We show here that HIV patients receiving antiretroviral therapy have significantly higher levels of platelet activation than healthy subjects, measured by CD62P expression, and that this activation is further increased in HIV patients that have reported cocaine use. Recent reports indicate that NF-κB inhibitors can impair platelet function, thus suggesting a non-traditional, yet important role for NF-κB in platelets. Based on this, we hypothesize that IKK activation is central for platelet activation induced by HIV and cocaine. As such, cocaine can directly activate platelets and there is increased IκBα phosphorylation and degradation in platelets from HIV patients. Furthermore, kinase assays indicate that there is increased IKK activity in platelets from HIV patients. A better understanding of intracellular signaling targets, such as IKK, that play a crucial role in regulating platelet activation in response to HIV infection and cocaine could reveal potential targets to dampen HIV-induced inflammation. **Supported by R01 NS066801.**

CHEMOKINE CXCL8 MODULATES HIV-1 REPLICATION IN HUMAN MONOCYTE-DERIVED MACROPHAGES. Mamik MK, Borgmann, K, Ghorpade A; Cell Biology and Anatomy, University of North Texas Health Science Center, Fort Worth, TX 76107.

Chemokine CXCL8 is an important neutrophil chemoattractant implicated in various neurodegenerative disorders. We previously reported that HIV-1 infection is linked to upregulation of CXCL8 in brain tissue. We also reported that SHP2 and MAPK pathways regulate the expression of CXCL8 in human astrocytes. In the post-ART era, low level of productive replication of HIV-1 in brain is a critical component of neuropathogenesis regulation. The present study investigated the effect of CXCL8 on productive infection of HIV-1 in human monocytes-derived macrophages (MDM). We also employed human promonocytic cell line U937 as an efficient transfection system. Human MDM were infected with blood and brain-derived HIV-1 isolates, HIV-ADA and HIV-JRFL. Treatment with CXCL8 led to significant upregulation ($p<0.01$) in HIV-1 p24 levels in supernatants of HIV-infected MDM, as determined by ELISA. Reverse transcriptase (RT) activity was significantly increased ($p<0.01$) in HIV-infected MDM treated with CXCL8. We compared the formation of 2-LTR circles in CXCL8 treated vs untreated HIV-infected MDM by RT-PCR, as a measure of viral genome integration. Transient transfection of U937 cells with HIV-LTR construct containing luciferase reporter gene resulted in increased luciferase activity when treated with CXCL8. The results show that CXCL8 mediates productive infection of HIV-1 in MDM and induces HIV-1 LTR promoter activity in U937 cells. Detailed understanding of the mechanisms involved could aid in therapeutic intervention strategies by modulating levels of this chemokine in the brain. **Supported by R01MH087345-02.**

ELEVATED LEVELS OF SOLUBLE CD40L CAUSE INCREASE IN CIRCULATING PLATELET-MONOCYTE COMPLEXES: POSSIBLE ROLE IN HIV-ASSOCIATED NEURO-INFLAMMATION. Singh M, Davidson D, Ramirez S, Silva J, Maggirwar S; Department of Microbiology and Immunology, University of Rochester Medical Center, Rochester, NY 14642; Department of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140.

Background: Transient complexes between activated platelets and monocytes (PMCs) are increased in inflammatory conditions like cardiovascular diseases. Chronic inflammation is a hallmark of HIV infection and HIV infected individuals exhibit increased platelet activation. HIV infection also causes increase in CD16+ inflammatory monocytes in CNS of neurocognitively-impaired individuals probably due to interaction with activated platelets.
Methods: PMCs were quantified from 36 HIV+ and 37 HIV- individuals and also after whole blood treatment with CD40L using flow cytometry. Imagestream, SEM and TEM were used to study PMC morphology. Immunohistochemistry was used to detect PMCs in brain tissue samples from HIV+ and HIV- individuals. Graph pad prism was used for statistical analysis. Results: CD16+ PMCs were significantly increased in HIV+ individuals ($p= 0.01$) and correlated positively with platelet activation ($p=0.008$). There were 1-4 platelets per monocyte in a complex. CD40L caused increase in PMCs ($p=0.006$) and this increase was through the interaction of p-selectin on platelets with monocytic PSGL-1. Numerous PMCs were lined onto the lumen of CNS capillaries and only the monocytes extravasated into brain parenchyma of tissue samples from HIV infected individuals. Conclusions: In HIV infected individuals, the increase in activated platelets leads to amplification of platelet-monocyte complexes in circulation. Monocytes in these complexes migrate to CNS and may contribute substantially towards HIV-associated neuro-cognitive impairment. **Supported by RO1 NS066801.**

MORPHINE-INDUCED EIPIGENETIC FACTORS PROMOTE MACROPHAGE APOPTOSIS VIA ACTIVATION OF THE RENIN ANGIOTENSIN SYSTEM.

Chandel N, Malhotra A, Singhal PC; Hofstra University, North-Shore Long-Island Jewish Medical Health system, Great Neck, NY 11021.

Background: We previously reported that morphine has potential to induce apoptosis of macrophages. However, the involved mechanism is far from clear. We hypothesize that morphine-induced epigenetic factors down regulate VDR and activate the renin-angiotensin system (RAS) DNA damage and apoptosis. Methods: Murine macrophages (J 774.16 cells) were treated with morphine (10-8 -10-6M) for 24 hours followed by protein extraction and probing for VDR, Renin, angiotensinogen (AGT), Ac-H3/H4 and DNMTs (n=3). Total RNA was extracted from & probed for VDR, Renin and AGT, Ac-H3/H4 and DNMTs. AngII content was measured by ELISA in cells/media. To determine the role of AngII in morphine-induced macrophage apoptosis, cells were incubated in media containing buffer, morphine (10-8M), losartan ((10-7M, an AngII blocker), or losartan + morphine for 24 hours followed by apoptosis assay by TUNEL. To find the role of epigenetic factor on VDR down regulation, macrophages were pre-treated with 5-azacytidine (5 ÂµM)& morphine. Additionally, a Chip assay was done to see the H3K4 (Me) 2/3 & Ac-H3/H4 acetylation on VDR promoter. Results: Morphine down regulated VDR & activated RAS in the form of enhanced renin and AGT expression & increased AngII levels in macrophages. Morphine modulated Dnmt-3b(3-fold) & HDACs expression. Enhanced CpG methylation of VDR was blocked by 5-azacytidine. Chip-experiments indicated that Morphine decreased Histone3 acetylation & H3K4 trimethylation at VDR promoter. Losartan inhibited apoptosis. It appears that morphine-induced macrophage apoptosis was mediated through the RAS activation.
Supported by NIH/RO1 DK84910-01.

EFFECT OF METHAMPHETAMINE AND GP120 ON AUTOPHAGY IN SVGA ASTROCYTES. Cao L, Kumar S, Kumar A; Division of Pharmacology and Toxicology, School of Pharmacy, University of Missouri-Kansas City, Kansas City, MO 64108.

Methamphetamine (METH) is a commonly used drug of abuse among HIV-infected individuals. Previous studies have revealed that METH abusers who are infected with HIV-1 show greater neuropathological dysfunction than either METH users or HIV-positive individuals alone. Autophagy is an intracellular activity that is known to eliminate dysfunctional organelles during deprivation condition to protect the cells from apoptotic cell death. In addition to its protective role, autophagy could also be destructive leading to cell death, which is called autophagic cell death. This study is designed to investigate t he additive/synergistic role of METH in HIV protein gp120-induced autophagy and apoptotic cell death in SVGA astrocytic cell lines. Therefore, we treated SVGA astrocytes with 200 pM gp120 IIIb protein and 1mM methamphetamine alone and in combination and measured autophagy marker protein LC3II. The results showed an increase in the levels of LC3II in either METH or gp120-teated SVGA by 2-3 fold, and the levels of LC3II was further increased to 4-5 fold when the cells were treated simultaneously with both METH and gp120. The results suggest that both METH and gp120 work together in additive manner causing increased autophagic activity. We are now in the process of determining the mechanism of METH and gp120-mediated autophagy and its relationships with apoptotic cell death that will be discussed in the poster. This study is novel and has clinical relevance because METH use in HIV-infected populations is highly prevalent and shows exacerbated neuron damage. **Supported by DA025528 and DA025011 to AK.**

POTENTIAL PROTECTIVE ROLE OF THE TIGHT JUNCTION PROTEIN OCCLUDIN AGAINST HIV-1 INFECTION OF PERICYTES. Castro V, Lathen M, Toborek M; Biochemistry and Molecular Biology, University of Miami, Miller School of Medicine, Miami, FL 33136; Department of Biology, Freie Universitat-Berlin, Berlin, 14195.

The blood-brain barrier (BBB) is the interface between the blood and the brain parenchyma where the brain endothelium forms a functional unit together with neurons, pericytes, astrocytes and the extracellular matrix. Tight junctions (TJ) are key regulators of the BBB permeability. The C-terminal domain of the TJ protein occludin is needed for the proper TJ formation and function. Disruption of the BBB and TJs, as occurs during HIV infection, leads to neuroinflammation and neurodegeneration and can contribute to HIV-associated dementia. Pericytes can be infected by HIV but they do not support high viral replication rates. Here, we show that human primary BBB pericytes infected with HIV proliferate and, surprisingly, do not exhibit oxidative stress. Upon infection, they overexpress ZO-1, occludin, and connexin-43 in a cell-cell communication-dependent manner. Molecular modeling of the C-terminal domain of occludin revealed structural similarities with known oxidoreductases. Furthermore, HEK-293 cells overexpressing occludin exhibited a reduced NADH content, and their occludin-containing lysates showed a higher NADH/NAD+ conversion rate than untransfected cells. Moreover, upon HIV-infection, the viral replication in occludin-expressing HEK-293 cells was reduced to levels similar to those in infected pericytes. Our results indicate that overexpression of occludin in HIV infected pericytes is linked to reduced oxidative stress potentially preventing HIV proliferation. In addition, they reveal that occludin can modulate the cellular redox conditions. **Supported by NIH MH072567, MH098891, DA027569.**

POTENTIAL ROLE OF GP120 IN HIV-INDUCED AIRWAY MUCUS FORMATION AND LUNG DISEASE. Gundavarapu S, Mishra NC, Singh SP, Langley RJ, Buch S, Sopori ML; Respiratory Immunology Division, Lovelace Respiratory Research Institute, Albuquerque, NM 87108; Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198.

Lung diseases such as asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD), and lung infections are major causes of morbidity and mortality among HIV-infected patients even on HAART. Airway mucus hypersecretion is a key pathophysiological feature in these diseases and contributes to airway obstruction. Moreover, mucus is an excellent milieu for bacterial and fungal growth. Although smoking is a major cause of COPD and highly prevalent in HIV-infected people, HIV may be an independent risk factor for COPD and asthma. Using normal human bronchial epithelial (NHBE) cells we show that nicotine and acetylcholine induce mucus formation via the α7-nicotinic acetylcholine receptor (α7-nAChR)-γ-aminobutyric acid (GABA)ARα2 pathway and the nAChR antagonists suppress allergen/cigarette smoke-induced mucus formation in vivo and in vitro (1). Interestingly, NHBE cells also express CXCR4, and X4-tropic gp120 induces mucus formation in these cells that is blocked by antagonists of CXCR4, α7-nAChRs, and GABAAR. Moreover, even after anti-retroviral therapy, autopsied lung tissues from SIV-infected macaques and HIV-infected patients exhibit significant levels of gp120 and increased expression of mucus and GABAARα2 (2). Thus, the α7-nAChR-GABAARα2 pathway plays a critical role in response to allergen/cigarette smoke- and gp120-CXCR4-induced mucus production in the lung. The excessive mucus formation in HIV-infected lungs may contribute to lung diseases and lung infections in HIV patients, and inhibitors of α7-nAChR, GABAAR, and CXCR4 may have therapeutic potential. **Supported by US Army Medical Research and Material Command (GW093005), NIH (R01-DA017003) and LRRI (IMMSPT).**

A MURINE MODEL OF HIV RECAPITULATE KEY FEATURES OF HIV-1 INFECTION IN THE CONTEXT OF OPIOID ABUSE. Sharma U, Banerjee S, Sindberg G, Charboneau R, Volsky DJ, Roy, S; Department of Surgery, University of Minnesota, Minneapolis, and the Department of Comparative and Molecular Biosciences, University of Minnesota, Minneapolis, MN 55455; Department of Surgery, Veterans Affairs Medical Center, Minneapolis, MN 55417; Molecular Virology Division, St. Luke's-Roosevelt Hospital Center, New York, NY 10019.

Bacterial translocation and systemic LPS are hallmarks of HIV infection that are potentiated in chronic drug abusers. To delineate the underlying mechanism a murine model of EcoHIV was used. Mice were implanted with morphine pellet (25mg/mice), and infected with EcoHIV (1Ã—106pg/mice) by IP injection while untreated mice served as control. Following inoculation, mice were sacrificed at different time points and blood, peritoneal macrophages and tissues including mesenteric lymph node, spleen, liver, lung were collected for analysis. Bacterial growth and proinflammatory cytokines IL-6 and TNF-Î± were significantly greater in morphine treated EcoHIV injected animals when compared to morphine or EcoHIV alone injected animals, while no bacterial translocation was observed in control animals. Interestingly, HIV p24 protein levels were significantly higher in the morphine implanted animals when compared to placebo groups suggesting greater infectivity in morphine treated mice. The effect of morphine was reversed following methylnaltrexone treatment. FACS analysis of peripheral blood showed increase in double positive CCR5/CXCR4 in CD8+ T-cell and CD11b+ macrophage cells, while CD4+ T-cells showed increase in only CCR5 expression. This observation is consistent with that observed in HIV infected drug abusers. Mechanism by which these receptors are modulated their trafficking will be focus of this study. **Supported by RO1 DA12104, RO1 DA022935, RO1 DA031202, K05 DA033881, P50 DA0118061, R01 DA034582.**

HIV-1 NEF EXPRESSION IN RAT HIPPOCAMPUS INCREASES SMALL INTESTINE PERMEABILITY AND DECREASES OCCLUDIN TIGHT JUNCTION PROTEIN. Loucil R, Isidro RA, Chompre G, Hernandez S, Cruz ML, Isidro AA, Appleyard CB, Noel, Jr, RJ; Department of Biochemistry and the Department of Physiology and Pharmacology, Ponce School of Medicine and Health Sciences, Ponce, PR 00716.

Gastrointestinal (GI) pathologies are still a common problem during HIV infection despite the use of combination antiretroviral therapies (cART). Intestinal inflammation, increased permeability, and villous atrophy are involved in the development of chronic diarrhea that provokes malabsorption. Even though cART successfully controls viral replication in the periphery, the expression of viral proteins and HIV replication still occurs in the brain. Aim: Determine if HIV-1 Nef expression in the rat hippocampus increases small intestine permeability. Methods: Astrocytes expressing Nef or GFP (control) were infused into the right hippocampus of 30 day-old Sprague Dawley rats. Two days after recovery rats were euthanized to harvest the ileum, and changes in short circuit current in response to acetylcholine were measured in vitro to quantify changes in ion transport. Occludin immunofluorescence was performed on paraffin embedded ileum tissue to determine changes in tight junction protein expression. Results: Nef-treated rats showed increased short circuit current levels when compared to the GFP controls ($p=0.0048$). Immunofluorescence analysis shows that occludin levels were lower in the Nef animals ($p<0.0001$). Conclusion: Nef expression in the rat hippocampus increases ion transport and down-regulation of tight junction proteins. These findings suggest that Nef expression in the hippocampus may be involved in the continued GI pathology observed in HIV patients on cART. **Supported by G12RR003050, G12MD007579, R25GM082406.**

DAMAGE CONTROL IN VIVO: NEUROPROTECTIVE LIPOCALIN-2 IS UPREGULATED IN BRAINS OF HIV-1/GP120-TRANSGENIC MICE. Hoefer MM, Maung R, De Rozieres CM, Dowling CC, Catalan IC, Sanchez AB, Kaul M; Infectious and Inflammatory Disease Center, Sanford-Burnham Medical Research Institute, La Jolla, CA 92037.

HIV-1 infection causes a progressive decline of the immune system, eventually leading to AIDS. Even in times of combination antiretroviral therapy, up to 50% of the AIDS patients develop a variety of neurological disorders. In our mouse model, expression of the HIV-1 envelope protein gp120 alone can elicit neuronal damage and astrocytosis that is surprisingly similar to the pathology observed in human AIDS brains. Knocking out the HIV-1 co-receptor CCR5 protects the animals from gp120-induced neuronal damage, but does not prevent astrocytosis. An extensive microarray analysis of brains from gp120+ and CCR5 knockout/gp120+ animals demonstrated that the secreted acute phase protein Lipocalin-2 (Lcn2) was one of the most highly upregulated genes. Lcn2 is an autocrine mediator of reactive astrocytosis and further analysis revealed Lcn2 expression in astrocytes in gp120+ animals. Interestingly, the inducible Lcn2 receptor megalin/Lrp2 was also upregulated in those animals, whereas the expression of the other known Lcn2 receptor, 24p3R/Slc22a17, remained unaffected. We thus hypothesized that megalin/Lrp2 signaling may play a role in neuroprotection and conducted in vitro experiments using mixed rat cortical cultures treated with Lcn2 and gp120 derived from different HIV-1 strains. Preliminary data indicate that Lcn2 might have a protective effect on gp120-treated neurons. Our current results suggest that Lcn2 and megalin/Lrp2 may play a role in neuroprotection and thus attenuate neuronal injury inflicted by HIV-1/gp120. **Supported by R01 MH087332 to MK, P30 MH062512 (NIMH, CSPAR) and IRFN Fellowship to MMH.**

HCV INFECTION AND HEROIN USE DYSREGULATE THE CIRCULATING MIRNA EXPRESSION. Zhou Y, Wang X, Sun L, Zhou L, Liu MQ, Wang F, Peng JS, Wang YZ, Li JL, Zhou DJ, Ho WZ; Department of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140; ABSL-III 3 Laboratory, Center for Animal Experiment, Wuhan University, Wuhan, 430071; Virology, Wuhan Center for Disease Prevention & Control, Wuhan, 430015.

Hepatitis C virus (HCV) causes a global public health problem. Injection drug users (IDUs) are the largest group at risk for HCV infection. Cell-free circulating microRNAs (miR) hold great promise as a new group of disease biomarkers. Recent studies have suggested that circulating miRNAs are associated with HCV infection and disease progression. Yet little is known about the impact of drug abuse on the expression of circulating miRNAs in HCV infected/uninfected IDUs. Thus, we investigated the impact of HCV infection and/or heroin use on the expression of circulating miRNAs in vivo. We examined a total of 15 miRNAs that have been identified to be related to host innate immunity and HCV infection, and found these circulating miRNAs were differentially regulated by heroin use. Among the 15 miRNAs examined, miRs-29a, 29c, 122, 212 and 431 were found to be significantly upregulated in heroin users, regardless of HCV infection. In contrast, miRs-351, 141 and 196b, which were reported to possess inhibitory effect on HCV replication, were significantly down-regulated in heroin users. The up-regulation of miR-212, and the down-regulation of miRs-141 and 351 in IDUs despite of HCV infection were confirmed by in vitro studies where the hepatic cell line Huh7.5.1 were experimentally exposed to morphine and/or HCV infection. These findings provide in vivo and in vitro evidence showing that HCV infection and/or heroin use dysregulate the expression of circulating miRNAs, which may account for the dysfunction of innate antiviral immunity and HCV infection/ persistence among IDUs. **Supported by DA012815 and DA022177 to WH**

URMC-099: A MIXED-LINEAGE KINASE-3 (MLK3) INHIBITOR WITH THE POTENTIAL TO ERADICATE HUMAN IMMUNODEFICIENCY VIRUS INFECTION.

Zhang G, Dash PK, Wiederin JL, Ciborowski PS, Goodfellow VS, McMillan JM, Smith NA, Gorantla AS, Gelbard, HA, Gendelman HE; University of Nebraska Medical Center, School of Medicine, Omaha, NE 68198; Califia Bio., Inc, San Diego, CA 92121; University of Rochester Medical Center, School of Medicine and Dentistry, Rochester, NY 14642.

Background: Although effectiveness of antiretroviral therapy in restricting human immunodeficiency virus (HIV) infection is profound, co-morbid conditions continue. With such therapeutic limitations adjunctive therapies are needed to facilitate improved clinical responses. Methods: Twenty two week old humanized NOD/scid-IL-2RÎ³cnull mice were infected with 104 TCID50 of HIV-1ADA for 10 weeks. URMC-099 (10mg/kg) was administered daily after 13 weeks by intraperitoneal injection of nanoformulated atazanavir and ritonavir (nanoART). Levels of HIV-1 infection, immune and disease-associated pathologies, in lymphoid and brain tissues were investigated. Proteomic tests, virus-associated antiretroviral and immune restorative responses were performed. Results: CD4+ T lymphocyte numbers were restored by nanoART when used with URMC-099. Plasma viral load (VL) was not detected. NanoART and URMC-099 were effective alone but showed synergy together. Histopathological tests of lymphoid tissues showed significantly decreases in IgM, IgG, and HIV-1p24 cells by either drug with viral attenuation when both drugs were applied. Brain tissue examinations showed morphologic preservation of synaptic and neural pathways. Tandem mass spectrometry and Western blot demonstrated alterations in endosomal pathways linked to the viral replication cycle and including modulations of Rab7 and 8 for HIV-1 infected MDM. Conclusions: Combinations URMC-099 with nanoART act in synergy to remove HIV-1 infection while protecting against CD4+ T lymphocyte depletion. **Supported by 5P01MH064570-11.**

ROLE OF IL-1 SIGNALING IN REGULATION OF BEHAVIORAL EFFECTS OF ETHANOL AND BENZODIAZEPINES. Blednov YB, Harris RA; Waggoner Center for Alcohol and Addiction Research, University of Texas, Austin, TX 78712.

Based on gene expression studies, IL-1 signaling is one of the pathways associated with genetic predisposition to high alcohol consumption in mice (Mulligan et al., 2006). Previously we showed that lack of the endogenous IL-1r antagonist (IL-1rn or IL-1ra) strongly reduces alcohol intake in several tests (Blednov et al., 2011). In this study we compared several ethanol-related behaviors in mice lacking either IL-1rn or the IL-1 receptor (IL-1r). We found that deletion of IL-1rn increases sensitivity to sedative/hypnotic effects (LORR) of ethanol (3.6 g/kg) and a GABA-receptor allosteric modulator (flurazepam, 225 mg/kg) and reduces severity of acute ethanol withdrawal (ACW). Conversely, mice lacking IL-1r demonstrated reduced LORR sensitivity to ethanol and flurazepam, increased severity of ACW as well as increased ethanol intake and preference. The increased LORR phenotypes (for ethanol and flurazepam) observed in IL-1rn knockout mice were rescued by administration of IL-1ra (Anakinra, 100 mg/kg, i.p.). Deletion of either IL-1r or IL-1rn produced faster recovery from acute ethanol-induced (2 g/kg) motor incoordination (rotarod) and this behavioral phenotype was not rescued in IL1rn null mice by administration of anakinra. These data show that several ethanol behaviors (consumption, sedation, withdrawal severity) are regulated by IL-1r signaling. This system also affects sensitivity to sedation from a benzodiazepine suggesting that at least some of these changes may be due to IL-1r perturbation of GABAergic neurotransmission. **Supported by AA U01 13520; INIA Project AA06399.**

HIV-1 INDUCED AMYLOID BETA ACCUMULATION IN BRAIN ENDOTHELIAL CELLS. Andras IE, Toborek M; Department of Biochemistry and Molecular Biology, University of Miami School of Medicine, Miami, FL 33136.

Following the introduction of antiretroviral therapy (ART), many HIV-1-infected patients have survived the disease for more than 20 years, leading to a change in HIV-1 epidemiology. Amyloid beta (Aβ) levels are increased in HIV-1 infected brains due to not yet fully understood mechanisms. While the introduction of ART has reduced the occurrence of HIV-associated dementia, the prevalence of minor HIV-1-associated neurocognitive disorders is increasing. Brain vascular dysfunction and the blood–brain barrier may be critical in Aβ homeostasis thus playing a role in Aβ accumulation in the brain. Our experiments suggest that Aβ accumulation in the brain endothelium involves a complex interaction between transport systems, lipid rafts/caveolae and the early endosomes. **Supported by MH63022, MH072567, NS39254, DA027569 and University of Miami Developmental Center for AIDS Research - P30A1073961.**

PACAP27 IS A NEW NEUROPROTECTIVE COMPOUND AGAINST TAT-MEDIATED NEUROTOXICITY. Rozzi SJ, Borelli G, Ryan K, Steiner J, Palchik G, Avdoshina V, Mocchetti I; Department of Neuroscience, and the Department of Pharmacology & Physiology, Georgetown University, Washington, DC 20007; National Institute of Neurological Disorders and Stroke NINDS), National Institutes of Health, Bethesda, MD 20892.

HIV infects the central nervous system and promotes neuronal injury that culminates in a neurocognitive disorder. Viral proteins, such as transactivator of transcription (Tat), have emerged as leading candidates to explain HIV-mediated neurotoxicity. Therefore, discovering new compounds that prevent Tat neurotoxicity may lead to a new therapy. We investigated the neuroprotective activity of the pituitary adenylate cyclase-activating polypeptide 27 (PACAP27) against cardinal features of Tat-induced neurodegeneration, such as the production of reactive oxygen species (ROS), as well as elevation in cytochrome c protein expression. PACAP27 (100nM) inhibited Tat (100nM) toxicity in rat primary cortical neurons. Exposure of neurons to Tat resulted in mitochondrial destabilization and significantly decreased cell viability, as measured by MTT. PACAP27 prevented mitochondrial membrane destabilization as well as ROS and cytochrome-c accumulation altered by Tat. In addition, we investigated DNA double strand breaks (DSBs) as a potential new mechanism of Tat-mediated neurotoxicity. PACAP27 diminished DNA DSBs induced by Tat in cortical neurons. Our data support a mechanism of Tat neurotoxicity in which Tat induces mitochondrial destabilization, thus increasing the release of ROS, which causes DNA DSBs leading to cell death. PACAP27 mitigates the effects of Tat-induced neuronal dysfunction, suggesting that PACAP27 could be a new strategy for an adjunct therapy against HIV-associated neurocognitive disorder.
Supported by R21 NS074916.

DYSREGULATION OF IL-33 AND ST2 IN HIV1 B AND C CLADES. Yndart A, Agudelo M, Munoz-Caamano K, Raymond A, Nair M; Immunology Department, College of Medicine, Florida International University, Miami, FL 33199.

IL-33, is an inflammatory cytokine expressed in the CNS, it activates microglia cells, functions intracellularly as a transcription factor and plays a role as an inflammatory mediator in CNS, suggesting effects in neuroimmune inflammatory processes. ST2 gene produces a trans-membrane form (ST2L), a receptor for IL-33, and a secreted soluble form (sST2). sST2 associated with IL-33 blocks ST2L-dependent signaling as well as the immunological effects of IL-33. We hypothesize that IL-33 cytokine and ST2 are dysregulated by HIV1 B and C clades, which correlates with different manifestations of HIV-associated disorders between clades. Human Astrocytes and SKNMC cells (human neuronal cell line) were separately infected with HIV1 B and C viruses. Same level of infection between clades was achieved and tested by p24 ELISA. The RNA was extracted and quantified for IL-33 and ST2 by q-RT-PCR, whereas secreted IL-33 and sST2 were measured by ELISA using culture supernatants and plasma from HIV positive non drug (HPND) and HIV negative non drug (HNND) human samples. Intracellular IL-33 and ST2 protein production were tested by Western Blot and flow cytometry. Our results indicated that infection with HIV1B showed a higher level of intra and extracellular IL-33 compared to HIV1C infection. No significant results were found for sST2. Higher values of secreted IL-33 than sST2 were found for human plasma from HPND. Similar results were obtained when compared with HNND. These results suggest that IL-33 and ST2 may play a role in differential neuropathogenesis induced by HIV-1B and C infection. **Supported by NIH/1RO1MH085259.**

MECHANISMS OF CEREBRAL HEMORRHAGIC LESIONS IN DRUG ABUSE NEUROAIDS. Haorah J, Abdul Muneer PM, Szlachetka A; University of Nebraska Medical Center, Omaha, NE , Neurovascular Oxidative Injury Laboratory, Dept. of Pharmacology and Experimental Neuroscience, Omaha, NE 68198-5215.

Recent epidemiological study concluded a strong association of HIV transmission/infection and the use of highly psycho-stimulant addictive drug, methamphetamine (Meth). Sexual habit and needle sharing are linked to Meth-induced HIV-1 transmission. But the mechanisms of accelerated HIV-1 viral entry to host cell and ingression of these infected cells across the blood-brain barrier (BBB) by Meth remains elusive. Thus, understanding of these promoting mechanisms by Meth is important in neuroAIDS progression and prevention. Our study uncovers that cerebral hemorrhagic lesion caused by Meth-induced oxidative injury plays a vital role in neuroAIDS progression and fast ageing. We observed that daily ip injection of Meth (15 mg/kg) in mice causes cerebral perivascular oxidative injury, inflammation, and impairs vascular angiogenesis that leads to hemorrhagic lesion via the TJ protein-MMP-VEGFR2 interactive VEGF-signaling loop. We found that induction of oxidative stress and matrix metalloproteinases (MMPs) by Meth led to degradation of BBB tight junction proteins and vascular endothelial growth factor receptor-2 (VEGFR2), thereby impairing the angiogenic repair activity of VEGFR2. Reduction of VEGFR2 elevated the intracellular VEGF-A level, which in turn activated caspase-1 to release IL-1² for further induction of oxidative stress and MMPs activation through the VEGF-signaling loop. Thus, Meth exposure aggravated vascular wound injury and hemorrhagic lesions (due to defective angiogenesis) to promote BBB leakage, cell infiltration, and neuroinflammation in neuroAIDS progression. **Supported by: NIH/NIAAA.**

HIV-TAT AND COCAINE MEDIATED DOWN-REGULATION OF BMP RECEPTOR AXIS IN PULMONARY ARTERIAL SMOOTH MUSCLE CELLS: IMPLICATIONS FOR HIV-PAH. Dhillon NK, Dalvi P, O'Brien-Ladner A; Internal Medicine, University of Kansas Medical Center, Kansas City, KS 66160.

Both human immunodeficiency virus and intravenous drug use (IVDU) have been identified as common independent risk factors of pulmonary hypertension. However, HIV-associated pulmonary arterial hypertension (PAH) appears more prevalent in patients with the concomitant history of intravenous drug abuse, indicating a possible "multiple-hit" phenomenon. We earlier reported that cocaine synergizes with HIV-Tat to promote pulmonary smooth muscle cell (pSMC) proliferation. Given that bone morphogenetic protein (BMP)/BMP-receptor (BMPR) signaling negatively regulates pSMC proliferation; we show here the effect of HIV-protein, Tat and/or cocaine on the BMPR axis. Combined treatment of human pulmonary arterial smooth muscle cells (HPASMCs) with cocaine (1µM) and Tat (25ng/ml) significantly reduced the levels of BMP-2, -4 and -7 in the cell supernatants collected at days 3, 6, 9 and 12 compared to the cocaine or Tat treatment alone. Significant increase in mRNA levels of BMPRII, BMPRIA and BMPRIB was observed with cocaine and Tat treatment compared to either treatment alone. On the contrary, protein levels of all three BMPR chains were significantly reduced after combined exposure to Tat and cocaine. Increase in the proliferation of HPASMCs in response to cocaine and Tat treatment was found to be diminished in cells over-expressing BMPRII. This observation was supported by an increase in anti-proliferative ID1 and a decrease in proliferative IL6 mRNA expressions in response to cocaine and Tat in cells over-expressing BMPRII, contrasting the effect of cocaine and Tat on these downstream BMP targets. **Supported by NIH 1R03DA031589-01, NIH 1R01DA034542-01, AHA11SDG7500016.**

HIV-1 TAT PROTEIN INCREASES MICROGLIAL OUTWARD K CURRENT AND RESULTANT NEUROTOXIC ACTIVITY. Liu J, Collins C, Xu P, Chen L, Xiong H; Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198-5880.

Microglia (MG) play a crucial role in the pathogenesis of HIV-1-associated neurocognitive disorders (HAND). HIV-1 infection leads to MG activation resulting in production of neurotoxins including, but not limited to, proinflammatory cytokines, nitric oxide (NO), reactive oxygen species (ROS), and viral protein Tat, which can injure neurons and contribute to HAND pathogenesis. To suppress MG production of neurotoxins, it is critical to identify potential targets to control MG activation. Increasing evidence suggest that KV channels play an important role in regulation of MG functionality. We hypothesize that HIV-1 brain infection triggers MG neurotoxic activity by increasing Kv1.3 conductivity, resulting in MG activation and consequent neuronal injury. To test this hypothesis, we investigated the role of KV channels in MG responsiveness to Tat. Treatment of rat MG with Tat (200ng/ml) enhanced KV1.3 channel expression and outward K currents, accompanied by an increased production of TNF-±, IL-1², NO and ROS. Blockage of MG KV1.3 by channel blockers Margatoxin (MgTx), 5-(4-Phenoxybutoxy) psoralen (PAP), 4-Aminopyridine (4AP) or knockdown of KV1.3 gene by transfection of MG with KV1.3-siRNA abrogated Tat-associated MG neurotoxic activity. Pretreatment of MG with KV blockers attenuated neurotoxic activity induced by Tat-treated MG. Further studies revealed an involvement of Erk1/2 mitogen-activated protein kinase in Tat-KV1.3-associated MG neurotoxic activity. Our data suggest that KV1.3 may be a potential target for development of therapeutic control of MG activation. **Supported by NIH NINDS R01 NS077873.**

SELECTIVE ACTIVATION OF CANNABINOID RECEPTOR 2 (CB2) IN LEUKOCYTES SUPPRESSES THEIR ENGAGEMENT OF THE BRAIN ENDOTHELIUM AND PROTECTS THE BLOOD BRAIN BARRIER (BBB). Rom S, Zuluaga-Ramirez V, Dykstra H, Reichenbach NL, Persidsky Y; Department of Pathology & Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140.

CB2 are highly expressed in cells of the immune system and their stimulation decreases inflammatory responses. We tested the idea that selective CB2 activation in human monocytes (Mo) will regulate their ability to engage the brain endothelium and migrate across the BBB. TNF-± stimulation of human brain microvascular endothelial cells (BMVEC) and application of relevant chemokine in vitro BBB models increased Mo adhesion/migration (1.8-4-fold). CB2 activation in Mo reduced adhesion (100%) and migration (60%). Mo interactions with BMVEC diminished barrier integrity in vitro and CB2 activation in Mo attenuated BBB injury. Next, we studied up-regulation of the active form of very late antigen, playing a key role in Mo rolling/adhesion. Peptide stimulation (mimicking Mo engagement by VCAM-1) resulted in 20-fold up-regulation of the active integrin form in Mo and CB2 agonists suppressed it 25-45%. CB2 agonists showed suppression of active Rac1 and RhoA (controlling Mo cytoskeleton). Cells treated with CB2 agonists showed increased levels of inhibitory sites of actin-binding proteins, cofilin and VASP, upstream regulators of conformational integrin changes. Next, we tested CB2 activation in LPS-induced neuroinflammation in vivo. Leukocytes were isolated, ex-vivo treated with CB2 agonists and injected into mice. Mice treated with LPS showed a 20-fold increase in adhesion of ex vivo labeled cells; CB2 agonists decreased leukocyte adhesion (91-96%). These results indicate that CB2 activation in Mo decreases key steps in Mo-BBB engagement suppressing inflammatory leukocyte responses. **Supported by NIAAA/AA015913RO1, NIMH/MH065151RO1.**

INTERPLAY OF HIV-1 GP120 AND OPIATES DURING THE PATHOGENESIS OF HIV-ASSOCIATED CHRONIC PAIN. Tang S-J, Shi Y, Yuan S; Department of Neuroscience and Cell Biology, University of Texas Medical Branch, Galveston, TX 77555.

Opiates are common analgesics for pain relief in HIV-1/AIDS patients. Paradoxically, clinical data indicate that repeated opioid treatment causes even heightened chronic pain (hyperalgesia). This side effect presents a compelling need to understand how chronic opioid use causes hyperalgesia in HIV patients. Using a mouse model that develops extensive similarities to the pain-related pathologies seen in HIV-1 human patients, we observed that repeated-morphine administration potentiates gp120-induced pain. Concomitant with the development of hyperalgesia, repeated morphine administration synergizes the effect of gp120 on astrocyte activation in the spinal cord dorsal horn (SDH), the first pain processing center in the CNS. This finding is relevant in light of our recent work revealing that astrocyte activation is specifically associated with pain pathogenesis in the HIV-1 patients. The chronic morphine-enhanced astrocyte activation is likely a pathogenically critical step to the potentiation of HIV-related hyperalgesia. We are interested in understanding the mechanism of the HIV gp120-morphine interaction in astrocyte activation in the SDH. Our data show that chronic administration of gp120 and morphine synergistically increased the expression of Wnt5a, a secreted signaling protein that specifically activates astrocytes but not microglia in the SDH. Based on our findings, we propose the novel hypothesis that the interaction of gp120 and morphine elicits astrocyte activation by synergistically stimulating Wnt5a signaling. The activated astrocytes can promote gp120-induction. **Supported by NINDS/NIH 1 R01 NS079166.**

INTERMOLECULAR INTERACTION BETWEEN HIV-1 TAT PROTEIN AND DOPAMINE TRANSPORTER DISRUPTS THE PHYSIOLOGICAL FUNCTION OF DOPAMINE SYSTEM. Zhu J, Midde NM, Huang X, Gomez AM, Booze RM>, Zhan, CG; South Carolina College of Pharmacy, University of South Carolina, Columbia, SC 29208;Psychology, University of South Carolina, Columbia, SC 29208; College of Pharmacy, University of Kentucky, Lexington, KY 40536.

HIV-1 Tat protein plays a crucial role in perturbations of the dopamine (DA) system by inhibiting DA transporter (DAT) function. We have demonstrated that Tat1-86 decreases DA uptake, and allosterically modulates DAT function in rat striatal synaptosomes (Zhu et al., 2009, 2011). In this study, we demonstrated that Tat protein interacts biophysically and biochemically with DAT. Through three-dimensional computational modeling, the recognition binding sites of human DAT (hDAT) for Tat were predicted. We then investigated pharmacological profiles of three residues in hDAT using site mutagenesis for Y88F, K92M, and Y470H. Compared to WT hDAT, the Vmax for DA uptake in CHO cells transfected with these mutants was differentially decreased: Y470H > K92M > Y88F without changes in Km values. No differences were found in IC50 values for unlabeled DA inhibiting DA uptake between each mutant and WT hDAT, suggesting that the identified residues in hDAT do not overlap with the binding sites of the substrate DA or influence the affinity for DA uptake. Exposure to Tat1-86 decreased Vmax by 38% in WT hDAT and by 18% in Y88F and K92M; however, no effect of Tat on Vmax was observed in Y470H. In addition, Y470H mutation led to outward-facing to inward-facing conformational transition in DA transport. Therefore, Y470H plays a critical role in intermolecular interaction between Tat and DAT. These results provide mechanistic insights into identifying targets on the DAT for developing compounds that specifically block Tat binding site(s) in hDAT, thereby stabilizing physiological DA system. **Supported by DA024275, DA026721 (JZ); DA025100, DA032910, DA013930 (CGZ); DA013137 and HD043680 (RMB).**

ASTROCYTES AND NEUROAIDS: THE WNT/B-CATENIN CONNECTION IN VIRUS/HOST INTERACTION AND NEUROPATHOGENESIS. Al-Harthi L; Dept of Immunology/Microbiology and Center for AIDS Research, Rush University Medical Center, Chicago, IL 60612.

Mechanisms driving HAND are multifaceted and involve many cellular players. We demonstrated that astrocytes express robust level of Wnt/b-catenin with a specific profile of Wnt ligands. Wnt/b-catenin down regulates HIV transcription by creating a multi-protein inhibitory complex, formed by b-catenin, TCF-4, and SMAR-1, that tethers on the HIV LTR to inhibit HIV transcription. Inflammatory cues, such as IFNg or methamphetamine, which diminish Wnt/b-catenin signaling lead to a higher level of HIV productive replication in astrocytes. As a counter balance, Tat down regulates b-catenin and it does so through its core and cysteine-rich domains. Without signals that repress Wnt/b-catenin signaling, astrocytes are latently infected and HIV latency is regulated by class 1 HDACs and methyl transferases. Wnt/b-catenin also positively regulates EAAT2 and glutamine synthatase expression in astrocytes. A model therefore emerges where down regulation of b-catenin by environmental cues lead to deregulation of a key function of astrocytes as a scavenger for excess glutamate. Lastly, secretion of Wnt ligands by astrocytes regulates CD8+ T cell differentiation, to generate a CD4+CD8+ T cell population, which is HIV-specific and found in NSG-HuPBL mouse brain. These findings demonstrate the significance of Wnt/b-catenin expression in regulating HIV, controlling key functions of astrocytes, and in promoting talk between astrocytes and CNS CD8 T cells. Understanding these complex interactions will better define the role of Wnt/b-catenin in astrocytes in health and in HAND. **Supported by R01 NS060632, R01 DA033966.**

ANTIRETROVIRAL THERAPY REVERSES HIV-MEDIATED SUPPRESSION OF ANTIVIRAL CELLULAR FACTORS. Liu MQ, Zhao M, Zhou W, Peng JS, Wang X, Wang F, Zhou DJ, Ho WZ; Department of Virology, Wuhan Centers for Disease Prevention & Control, Wuhan, 430015; Wuhan AIDS Care Center, Wuhan Municipal Institute of Dermatosis, Wuhan, 430030; Department of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19104.

Recent studies have identified a number of HIV restriction factors. Thus, we examined the expression of several key antiviral cellular factors (OAS-1, MxA, A3G, PKR and Tetherin) in PBMCs from HIV-infected patients before and during the course of antiretroviral therapy. Compared with uninfected control subjects, age-matched HIV-infected individuals have lower levels of the antiviral factors in PBMCs prior to the antiretroviral therapy. The treatment of subjects with antiretroviral drugs significantly suppressed viral load and increased CD4 counts, which was followed by a remarkable increase in the expression of the antiviral cellular factors, particularly OAS-1, A3G, and MxA at 3 months after the treatment. The expression of the antiviral cellular factors remained significant higher than that prior to the therapy. These findings indicate that antiretroviral therapy can reverse HIV infection-mediated suppression of host innate immunity, providing additional benefit for individuals infected with the virus. **Supported by NSFC: 81001303) (MQL); NIH DA12815, DA22177, and DA27550 (WZH).**

IMMUNOPATHOGENIC MECHANISMS OF HIV-1 CLADE B AND C: ROLE OF DOPAMINERGIC SYSTEM. Thangavel S, Rao KVK, Raymond A, Ding H, Atluri VSR, Nair MP; Institute of NeuroImmune Pharmacology (NIP), College of Medicine, Florida International University, Miami, FL 33199.

Aim: Previous studies have demonstrated that infections with HIV-1 B- and C-clades differentially contribute to the neuropathogenesis of HIV-associated neurocognitive disorder (HAND). Dopaminergic dysfunctions are known to play a significant role in neuropathogenesis of HAND. We hypothesize that clade-B and -C HIV infection exert differential effects on monocytes by down regulation of dopamine receptor-2 (DRD-2) and Ca2+/CaM-dependent protein kinases (CaMKs), the CaMK II gene and protein expression, and levels of the rate-limiting enzyme tyrosine hydroxylase (TH). Methods: RNA extracted from monocytes infected with HIV-1 clade-B and -C was reverse transcribed and analyzed by quantitative real-time PCR to determine DRD-2 and CaMK II gene expression. Cell lysates were analyzed by western blotting to determine protein expression. The enzymatic activity of TH was measured in cell lysates. Results: Our results indicate that HIV-1 clade-B significantly down regulated DRD-2, CaMK II gene and their protein expression, and the level of TH enzyme activity compared to HIV-1 clade-C. Conclusions: Our studies for the first time demonstrate that HIV-1 clade-B significantly down regulates DRD-2 and CaMK II as compared to HIV-1 clade-C. This differential effect may contribute to the increased neuropathogenecity associated with clade-B infection. **Supported by grants from the National Institute of Mental Health (NIMH); MH096640.**

CLASS I HISTONE DEACETYLASES AND A LYSINE-SPECIFIC HISTONE METHYLTRANSFERASE, SUV39H1, PROMOTE HIV LATENCY IN ASTROCYTES.

Narasipura SD, Min S, Al-Harthi L; Department of Immunology/Microbiology, Rush University, Chicago, IL 60612.

Identifying and understanding HIV-1 latent reservoirs is crucial for eradicating HIV-1 infection. We evaluated the role of astrocytes in HIV latency. We show that treatment of astrocytoma cell lines (U87MG and U251MG) containing stably integrated HIV LTR linked to luciferase with potent global histone deacetylase (HDAC) inhibitors induced LTR activity by 60-150 folds; while episomally transfected LTR under similar conditions showed a modest 2-3 fold induction. Treating these cells with class II or class III HDACs inhibitors did not impact HIV LTR activity, implicating class I HDACs as a significant contributor to LTR silencing. HDACs 1, 2 and 4 were abundantly expressed (HDAC 2>1>4) while HDACs 3, 5 and 7 were undetectable in U87MG and primary human fetal astrocytes. In addition, treatment of these cells with a lysine specific histone methyltransferase (HMT) inhibitor (SUV39H1) significantly induced LTR activity; while inhibitors of histone acetyltransferase (HAT) or a DNA methyltransferase (DNMT) did not affect LTR activity. Global potent HDAC inhibitors and SUV39H1 inhibitor also inhibited HIV transcripts in HIV infected primary human fetal astrocytes and an astrocytoma cell line harboring the HIV provirus. These studies implicate epigenetic modification of HIV LTR via class I HDACs and lysine-specific HMT in driving HIV latency in astrocytes, implicating astrocytes as a reservoir for HIV. **Supported by NIH/ R01 NS060632 and PO1 A1082971.**

ILLUMINATING HIV-1 VIROLOGICAL SYNAPSES. Chen BK; Division of Infectious Disease, Department of Medicine, Mount Sinai School of Medicine, New York, NY 10029.

The chronic infection by human immunodeficiency virus type 1 (HIV-1) depletes CD4+ T lymphocytes and leads to acquired immune deficiency syndrome (AIDS). We have been studying how specialized infectious cell-cell contacts formed between infected and uninfected CD4+ T cells, called virological synapses (VS), enhance the spread of HIV. VS are formed when the viral envelope protein on the surface of an infected cell engages CD4 on an uninfected T cell, inducing stable cell-cell adhesion. Live imaging studies of VS formation reveal the active recruitment of viral assembly to the cell-cell interface, and an endocytic uptake of the nascent virus by the target cell. We find that this route of transmission is more difficult to inhibit with neutralizing antibodies, indicating that it may support immune evasion and viral persistence. Multiple copies of HIV are transmitted through a single synapse, providing a mechanism by which HIV may tolerate high levels of genetic diversity. Ongoing studies are examining the role of VS during initial infection via parenteral routes using humanized mouse models. By studying the mechanisms of the HIV VS, we are learning how the virus persists in the face of vigorous immune responses and can use this knowledge to identify more effective strategies for vaccines and drugs. **Supported by NIH/NIDA DP1DA028866; NIH/NIAID R01AI074420; Burroughs Wellcome Fund.**

MECHANISM FOR ACCELERATED NEUROPATHOGENESIS IN DRUG ABUSE/HIV MODEL: ROLE OF SYSTEMIC INFECTION AND TOLL-LIKE RECEPTORS. Dutta Raini, Roy S; Department of Surgery, University of Minnesota, Minneapolis, MN 55455.

The role of inflammatory mediators in the context of persistent systemic infection in the etiology of HIV associated neurocognitive disorders (HAND) is warranted. We recently reported an accelerated neuronal apoptosis in a murine model of opioid addiction in the presence of HIV-1 Tat and co-infection with S. pneumoniae (Sp). In addition, we also observed lack of bacterial clearance and their subsequent dissemination into the brain. As a consequence, differential leukocyte migration into the CNS was observed in the same group of mice compared to the uninfected ones, with a greater infiltration of CD3, Ly6C and F4/80 immune cells. We next investigated if differential chemokine induction is a causal factor in this differential leukocyte trafficking. We observed significant induction of CCL5 following HIV-1 Tat treatment; however, infection with Sp led to preferential induction of CXCL12. Morphine potentiated both Tat and Sp mediated chemokine induction. Our previously published data demonstrate that MS treatment potentiates TLR expression in microglia. Therefore, the role of TLR in chemokine-ligand induction was further investigated. Our present data showed a significant role of TLR2 in CD3+CCR5+ migration. Activation of both, TLR-2 and -4 was necessary for migration of monocyte subtypes with chemokine receptors (CCR5 and CXCR4). This study shows for the first time that systemic infection in a drug abuse/HIV model leads to significant monocyte infiltration resulting in CNS inflammation, and, thus, contributing to neuropathogensis associated with HAND. **Supported by RO1 DA12104, RO1 DA022935, RO1 DA031202, K05 DA033881, P50 DA011806, 1R01 DA034582.**

MIR-9 PROMOTES MICROGLIAL ACTIVATION BY TARGETING MCPIP: IMPLICATIONS FOR HAND. Ma R, Yao H, Buch S; Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198.

In keeping with the emerging interest in the molecular mechanisms controlling the magnitude of microglia-mediated inflammatory responses in the CNS, a new and exciting aspect of gene regulation has been discovered in recent years--the mammalian microRNAs (miRNA). The highly conserved microRNA-9 (miR-9) plays a critical role in neuronal precursors as well as in axonal extension. Its role in inflammatory responses mediated by microglia, however, remains poorly understood. The present study was undertaken to identify the role of miR-9 in microglial activation in the CNS. Herein we have identified unique roles of miR-9 in mediating both the microglial inflammatory response as well as microglial migration through distinct signaling pathways. MiR-9-mediated regulation of both these processes involved down-regulated expression of a key target protein, macrophage-chemoattractant protein inducible peptide (MCPIP) that has been implicated in controlling inflammation. Our studies using rat primary microglia indicate that cellular activation mediated by miR-9 involves activation of the NF-kB pathway. Intriguingly, miR-9 mediated control of microglial migration also involved the Î²-catenin pathway. In vivo administration of lentivurus-premiR-9 resulted in increased microglial activation and migration, thus validating our cell culture findings. These findings highlight the role of miR-9 regulated MCPIP as a molecular switch determining microglial activation and migration, which has implications for various neurodegenerative disorders including HAND. **Supported by NIMH/5R01 MH068212.**

HIV-1 ENVELOPE GLYCOPROTEIN GP120 TRIGGERS A SENESCENCE PHENOTYPE IN CULTURED HUMAN ASTROCYTES. Crowe EP, Sell C, Torres C; Department of Pathology and Laboratory Medicine, Drexel University College of Medicine, Philadelphia, PA 19102.

Senescence is an irreversible proliferative growth arrest that is telomere-based, but can also be induced by stress. In addition to growth arrest, senescent cells signal to the immune system through a secreted profile known as the senescence-associated secretory phenotype (SASP) producing pro-inflammatory cytokines and chemotactic factors. Astrocytes undergo stress-induced senescence and this response could be physiologically-relevant since we are able to detect senescent astrocytes in aged brain tissue and in Alzheimer's disease. HIV-1 infection of astrocytes or acute exposure to gp120 results in gene expression changes and the release of inflammatory mediators, yet the role of gp120 as an inducer of astrocyte senescence is undefined. We investigated the effect of gp120 on induction of the senescence phenotype through senescence-associated beta-galactosidase staining and by measuring the expression of senescence biomarkers p16INK4a and activated p38MAPK. We observed a significant increase in SA Î²-gal activity, increased expression of p16INK4a and activation of p38MAPK. We profiled the secretion pattern of senescent astrocytes using an antibody array for pro-inflammatory factors and found that senescent astrocytes produce a number of inflammatory cytokines including interleukin-6 (IL-6) indicative of a SASP, which may be regulated by p38MAPK. Taken together, our results suggest HIV-1 viral products induce the senescence program in human astrocytes in vitro and establish the basis for further studies to determine the physiological significance of this finding. Supported by National Institute on Aging/NRSA F30.

THE PROINFLAMMATORY HYPOTHESIS OF ADDICTION: CLINICAL AND PRECLINICAL EVIDENCE. Hutchinson MR; School of Medical Sciences, University of Adelaide, Adelaide, 5005.

In the past two decades a trickle of manuscripts examining the non-neuronal central nervous system immune consequences of the drugs of abuse has now swollen to a significant body of work. Initially, these studies reported associative evidence of central nervous system proinflammation resulting from exposure to the drugs of abuse demonstrating key implications for neurotoxicity and disease progression associated with, for example, HIV infection. However, more recently this drug-induced activation of central immune signaling is now understood to contribute substantially to the pharmacodynamic actions of the drugs of abuse, by enhancing the engagement of classical mesolimbic dopamine reward pathways and withdrawal centers. This presentation will highlight the key in vivo preclinical and clinical evidence of these central immune signaling actions of two example drugs of abuse, opioids and alcohol. Moreover, the key molecular signaling events and activation of innate pattern recognition receptors that mediate the central immune involvement will be discussed. Excitingly, this new appreciation of central immune signaling activity of drugs of abuse provides novel therapeutic interventions and opportunities to identify 'at risk' individuals through the use of immunogenetics. **Supported by ARC Research Fellowship DP110100297.**

ADOLESCENT BINGE DRINKING PERSISTENTLY INCREASES NEUROIMMUNE SIGNAL EXPRESSION IN THE ADULT PREFRONTAL CORTEX. Vetreno RP, Qin L, Crews FT; Bowles Center for Alcohol Studies, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599.

Adolescence is characterized by increased social interaction and risk-taking that coincides with brain maturation. Adolescent humans engage in high levels of alcohol binge drinking that might alter adult neurocognitive functioning due to heightened frontal cortex neuroplasticity associated with adolescent brain maturation. We previously found that ethanol persistently increases mouse brain neuroimmune gene expression prompting studies in post-mortem human alcoholic brain. Human alcoholic frontal cortex had increased levels of several neuroimmune genes, including high-mobility group box 1 (HMGB1) and its receptors, receptor for advanced glycation end product (RAGE) and Toll-like receptor (TLR) 3 and 4. Brain expression correlated with lifetime alcohol consumption and age of drinking onset, consistent with adolescent drinking initiating neuroimmune gene expression. To investigate this hypothesis, we used an animal model of adolescent intermittent ethanol (AIE; [5 g/kg, i.g., 2-day on/2-day off) from postnatal day (P) 25 to 55, assessed as adults (P80). At P55, frontal cortex had increased TLR4 and HMGB1 expression, but not RAGE. At P80, long after the last ethanol treatment, RAGE/TLR/HMGB1 were increased, as were other neuroimmune genes in AIE animals. On the Barnes maze, AIE induced long-term reversal learning-perseveration deficits in adult rats, which correlated with neuroimmune signal expression. These findings suggest that ethanol increases neuroimmune gene expression that persists and accumulates, contributing to long-term adult neurocognitive dysfunction. **Supported by NADIA of the NIAAA.**

POLY(ADP-RIBOSE) POLYMERASE-1 (PARP) INHIBITION DECREASES HIV-1 REPLICATION IN PRIMARY HUMAN MONOCYTE-DERIVED MACROPHAGES (MDM).

Rom S, Reichenbach NL, Persidsky Y; Department of Pathology & Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19046.

The transcription of HIV-1 (HIV) is regulated by complex regulatory mechanisms involving various cellular factors and virus-encoded transactivators. PARP inhibition emerged recently as a potent anti-inflammatory tool, since PARP is involved in the regulation of some genes through its interaction with various transcription factors. We propose a novel approach to ameliorate HIV-associated dementia (HAD) via PARP inhibition using primary MDM as an in vitro system. TNFα-treatment of monocytes led to an increase in PARP activity (2-fold), which was reduced by PARP inhibitors, AIQ and PJ34 (40-50%). PARP inhibitors were able to reduce HIV replication in MDM by 60-70% after 3-5 days of infection. Long Terminal Repeat (LTR) acts as a switch in virus replication and can be triggered by several agents such as: Tat, TNFα, phorbol 12-myristate 13-acetate (PMA). Over-expression of Tat in MDM transfected with a LTR-reporter plasmid led to LTR activation by 4-4.5-fold; PARP inhibition in MDM led to 70% reduction. PMA or TNFα treatment resulted in a 3-fold increase in LTR activity. PARP inhibitors reduced it by 80-90%. MDM treated with PARP inhibitors showed 90% reduction in NFkB activity (known to mediate PMA- and TNFα-induced LTR HIV activation). These findings suggest that HIV replication in MDM could be suppressed by PARP inhibition via NFkB suppression and diminution of LTR activation. We suggest that PARP is essential to HIV replication and may provide a potent approach to HAD treatment. **Supported by R01 MH65151 (NIMH),awarded to YP.**

SELENOGLYCOPROTEINS SUPPRESS ADHESION OF BREAST CANCER CELLS TO HUMAN BRAIN ENDOTHELIUM VIA A MECHANISM INVOLVING NF-KB. Wrobel JK, Choi JJ, Xiao R, Kwiatkowski S, Power R, Toborek M; Department of Biochemistry and Molecular Biology, University of Miami Miller School of Medicine, Miami, FL 33136; Nutrigenomics Research Centre, Alltech, Nicholasville, KY 40356.

Feeding mice with selenium (Se) enriched yeast for 20 weeks markedly decreased growth of brain metastatic tumors. In order to identify components responsible for this protective effect soluble selenoglycoproteins (SGP) were extracted from Se-enriched yeast at pH 4.0 (SGP40) and 6.5 (SGP65). Co-cultures of brain endothelial cells (hCMEC/D3) with lung (A549) or breast (MDA-MB231) cancer cells were treated with SGP40 or SGP65. SGP40, but not SGP65 inhibited adhesion and migration of tested tumor cell lines through endothelial cell monolayers compared to the vehicle-treated control. We then employed electrophoretic mobility shift assay to determine the influence of the SGPs on NF-κB activation. SGP40 effectively suppressed TNFα-stimulated NF-κB activation in brain endothelial cells. While SPG65 also inhibited NF-κB DNA binding activity, these effects were less robust than those of SGP40. Surprisingly, pretreatment with SGP40 or SGP65 did not affect TNFα-induced expression of ICAM-1 and VCAM-1, suggesting involvement of another adhesion mechanism. To further evaluate the active components responsible for the unique properties of SGP40, experiments were performed using compounds identified as present in Se-enriched yeast. Several of the compounds showed high activity, decreasing adhesion of cancer cells to brain endothelium and suppressing NF-κB activation. These findings indicate that specific selenium compounds have the ability to inhibit adhesion and transendothelial migration of tumor cells via a process, which is likely to involve NF-κB activation. **Supported by Alltech, NIH/NCI R0CA133257, and NIH/NIEHS P42 ES07380.**

COMORBIDITY OF ALCOHOLISM, HIV INFECTION AND HEPATITIS C: IN VIVO BRAIN IMAGING. Pfefferbaum A, Zahr NM, Sullivan EV; Center for Health Science, SRI International, Menlo Park, CA 94025; Department of Psychiatry, Stanford University School of Medicine, Stanford, CA 94305.

HIV infected individuals who also exhibit heavy alcohol consumption are at substantial risk of reduced survival compared with moderate social drinkers. HIV infection and alcoholism (ALC) each have deleterious effects on the brain demonstrated with MR imaging and diffusion tensor imaging (DTI); these effects can be more pronounced in HIV+ALC. Longitudinal analysis of brain deficits in older HIV+ALC revealed accelerated volume loss in medial frontal and anterior cingulate cortex and central white matter (WM) predictive of processing speed impairment. Slopes of thalamus and hippocampus indicated a graded effect: volume declines were faster in HIV than controls and yet faster in HIV+AIDS. HIV+hepatitis C (HCV) coinfection resulted in steeper decreases than HIV alone in medial frontal, anterior cingulate, and limbic volumes. HIV+HCV was a significant factor in hastening degrading effects of aging on callosal, pontine, and central WM microstructure. History of alcoholism exerted an additional burden to HIV+HCV coinfection with faster WM anisotropy decline and diffusivity increase with advancing age. Even though all patient groups showed faster aging rates of increasing radial diffusivity trajectories than controls, HIV+ALC rates were faster than ALC alone. HIV+ALC with cognitive scores indicating impairment had steeper age trajectory effects on central WM than HIV alone. These data present novel evidence for accelerated aging in HIV infection and compounded effects of ALC and HCV on white matter microstructure, and are suggestive of neural substrates of functional decline. **Supported by NIAAA AA017347, AA017168.**

THC-INDUCED DYSREGULATION IN MICRORNA TRIGGERS MYELOID-DERIVED SUPPRESSOR CELLS AND CONSEQUENT SUPPRESSION OF T CELL RESPONSES TO GP120 OF HIV. Nagarkatti M, Hegde V, Nagarkatti P; Dept. of Pathology, Microbiology and Immunology, University of South Carolina School of Medicine, Columbia, SC 29209.

Marijuana use is known to increase susceptibility to infections such as HIV. Delta-9-tetrahydrocannabinol (THC), the active ingredient of marijuana, exhibits immunosuppressive properties, although the precise mechanisms remain unclear. Our studies have demonstrated that THC administration triggers induction of CD11b+Gr1+ myeloid-derived suppressor cells (MDSCs). In the current study, we tested the role of microRNA (miR) dysregulation in induction and functions of THC-induced MDSCs that mediate immunosuppression. To this end, we administered vehicle or 20mg/kg THC i.p. into C57BL/6 mice and 12 hours later, harvested the MDSCs from peritoneal exudates. Our studies demonstrated that these MDSCs produced arginase and nitric oxide, and suppressed polyclonal T cell activation. Furthermore, THC treatment of gp120-administered mice led to decreased Ag-specific T cell responses and lower serum titers of gp120-specific IgG Abs. We next performed a high-throughput miR array with MDSC isolated from bone marrow, spleen and THC-induced MDSC. We found that miR232 was significantly downregulated in THC-induced MDSCs which may be responsible for preventing granulocyte differentiation and arrest at the MDSC stage. We also observed downregulation of miR455 which targets iNOS and upregulation of miR22 directed against caveolin, an inhibitor of arginase. In summary, our studies demonstrated that select miR may be responsible for the generation and functions of the THC-induced MDSC that may result in immunosuppression. **Supported by NIH grants P01AT003961, R01AT006888, R01ES019313, R01MH094755, P20RR032684 and VA Merit Award BX001357.**

T-CELL RECONSTITUTION DURING MURINE ACQUIRED IMMUNODEFICIENCY SYNDROME (MAIDS) PRODUCES NEUROINFLAMMATION AND MORTALITY IN ANIMALS HARBORING OPPORTUNISTIC VIRAL BRAIN INFECTION. Mutnal MB, Schachtele SJ, Hu S, Lokensgard JR; Neuroimmunology Laboratory, Center for Infectious Diseases and Microbiology Translational Research, Uinversity of Minnesota , Minneapolis, MN 55455.

Infection with the LP-BM5 retroviral mixture was found to confer susceptibility to herpes simplex virus (HSV)-1 brain infection to normally-resistant C57BL/6 mice. Increased susceptibility to brain infection was due to severe immunodeficiency at 8 wks p.i. and a marked increase in programmed death-1 (PD-1) expression on CD4+ and CD8+ T-cells. Both T-cell loss and opportunistic brain infection were associated with high level PD-1 expression because PD-1-knockout mice infected with LP-BM5 did not exhibit lymphopenia and retained resistance to HSV-1. In addition, HSV-infection of MAIDS mice stimulated peripheral immune cell infiltration into the brain and its ensuing microglial activation. Interestingly, while opportunistic herpesvirus brain infection of C57BL/6 MAIDS mice was not itself lethal, when T-cell immunity was reconstituted through adoptive transfer of virus-specific CD3+ T-cells, it resulted in significant mortality among the recipients. This immune reconstitution-induced mortality was associated with exacerbated neuroinflammation as determined by MHC class II expression on resident microglia and elevated levels of Th1 cytokines in the brain. Taken together, these results indicate development of an immune reconstitution disease within the central nervous system (CNS-IRD). Experimental immune reconstitution disease of the CNS using T-cell repopulation of lymphopenic murine hosts harboring opportunistic brain infections may help elucidate neuroimmunoregulatory networks that produce CNS-IRIS in patients initiating cART. **Supported by MH-066703.**

ACTIVATION OF MACROPHAGE DOPAMINE RECEPTORS MAY EXACERBATE HAND BY INCREASING HIV ENTRY INTO MACROPHAGES AND ALTERING MACROPHAGE FUNCTIONS. Gaskill PJ, Berman JW; Department of Pathology, Albert Einstein College of Medicine, Bronx, NY 10461.

HIV infection of the CNS is a major public health issue despite the advent of cART. HIV infected individuals who abuse drugs show changes in the pathogenesis of HIV-associated neurological disorders (HAND). These changes may be due to elevated CNS dopamine levels, which mediate the addictive and reinforcing effects of many drugs of abuse. We hypothesize that the increase in CNS dopamine activates dopamine receptors (DR) on CNS macrophages, exacerbating HIV associated neurological damage. We showed previously that treatment of primary human monocyte derived macrophages (MDM) with dopamine increased HIV replication. We now show that the increased replication is due, at least in part, to increased HIV entry into MDM. The increased entry was induced by treatment with either dopamine or DR agonists, although not by the dopamine metabolites DOPAC or HVA. The increase in entry was also reduced by the DR antagonist flupentixol, demonstrating that it is specifically mediated by DR activation. In addition, DR activation increased MDM production of the inflammatory mediators IL-6, IL-8 and CCL2, with the changes in IL-6 and CCL2 being greater in HIV infected cells. Dopamine also reduced MDM phagocytosis. Thus, activation of macrophage DR by elevated dopamine may increase HIV infection of CNS macrophages, promote development of neuroinflammation and interfere with anti-microbial responses. These effects suggest that dopamine may be a common mechanism by which drugs of abuse exacerbate HAND. **Supported by NIDA.**

MORPHINE ATTENUATION OF LPS TOLERANCE-ROLE OF MIRNA. Banerjee S, Meng J, Das S, Krishnan A, Haworth, J, Charboneau R, Zeng Y, Ramakrishnan S, Roy S; Department of Surgery and Department of Pharmacology, University of Minnesota, Minneapolis, MN 55455; Immunology, Veteran Affairs Medical Center, Minneapolis, MN 55417.

Sustained hyper-inflammation during systemic infections is prevented by the development of tolerance to endotoxin. Here we report for the first time that chronic morphine treatment tempers endotoxin tolerance resulting in persistent inflammation, septicemia and septic shock. Our studies show that the attenuation of LPS tolerance by morphine in vitro, in vivo and ex vivo, in mice, and in vitro in human cells. To determine the role of miRNA, in LPS tolerance total RNA was isolated and subjected to miRNA array analysis. Among the screened miRNAs, miR-155 and miR-146a showed the highest induction at 48hr following LPS treatment, consistent with their perceived role in regulating inflammation and tolerance. Chronic morphine treatment in WT mice significantly decreased LPS induced mir-155 and mir-146. Next, we used lentivirus-mediated neutralization and over-expression of miR-146a and mir-155 both in vitro and in vivo. Antagonizing miR-146a resulted in complete abrogation of LPS tolerance within 48hours similar to morphine treatment with significant induction in IL6. Over-expression of miR-146a, as expected, significantly reduced LPS induced IL6 production in both placebo and morphine treated animals. Antagonizing miR-155 resulted in greater than basal expression of IL6 which was similar in morphine treatment. Surprisingly, over-expression of miR-155 also augmented LPS induced IL6. However morphine effects were abolished. These results suggest that induction of miR-146a acts as a molecular switch controlling hyper-inflammation in clinical and/or recreational use of morphine. **Supported by NIH grants RO1 DA 12104, RO1 DA 022935, RO1 DA031202, K05DA033881, P50 DA 011806 and 1R01DA034582 to Sabita Roy.**

PROTEOMIC FINGERPRINTS OF PRIMARY HUMAN ASTROCYTES TREATED WITH HIV-1 CLADE B AND C: IMPLICATIONS OF ER STRESS IN NEURO-AIDS.
López SN, Rodríguez M, Cubano L, Alves J, Boukli N; Universidad Central del Caribe, Bayamón, PR 00690.

One of the consequences of HIV-1 infection among patients is the HIV-associated neurocognitive disorder (HAND). It is suggested that the degree of neuro-AIDS vary according to the HIV-1 clade. The mechanisms underlying HIV-1 neuropathogenesis is complex and poorly understood. Exploiting proteomics, we hypothesize that clade B and C induce differential protein expression profiles on primary human astrocytes (PHA). In this study, we used a differential proteomic analysis of primary human astrocytes treated with HIV-clade B and C by two-dimensional gel electrophoresis (2DE), followed by liquid chromatography-tandem mass spectrometry to establish homologies and dissimilarities in protein expression. A total of 69 and 72 proteins were modulated by HIV-1 clade B and clade C respectively as analyzed on 2DE maps by PD Quest software. Among the proteins significantly upregulated by HIV-1 clade B are Annexin A5 and Cyclophilin A (pro-apoptotic factors), Protein Disulfide Isomerase, Elongation factor 2, quinone oxidoreductase Endoplasmic Reticulum and oxidative stress markers. In addition, HIV-1 clade C significantly upregulated a 14-3-3 protein signature characteristic of anti-apoptotic response as well as chaperones such as HSP60 and hTRiC5 as compared to HIV-1 clade B. These data suggest that HIV-1 clade B and C induce a differential protein profile in PHA. Further, our findings demonstrate that HIV-1 clade B appears to induce pro-apoptotic and ER and oxidative stress markers while HIV-1 clade C seems to be associated with generation of anti-apoptotic mechanisms in PHA. **Supported by Supported by NIH-RCMI Biomedical Proteomics Facility 2G12RR03035.**

NEUROTOXIC EFFECTS OF HIV-1 VPR EXPRESSION IN ASTROCYTES. Torres-Negron L, Noel Jr, RJ; Biochemistry Department, Ponce School of Medicine and Health Sciences, Ponce, PR 00732.

HIV infected individuals are at an increased risk of developing neurological abnormalities. HIV induces neurotoxicity by host cellular factors and individual viral proteins. Some of these proteins including Viral Protein R (Vpr) promote activation of cellular pathways including apoptosis and immune activation. Viral neurotoxins cause neuronal damage and may play a role in hippocampal loss of function. We have shown that Vpr causes learning impairment when expressed from astrocytes implanted into the hippocampus of rats. We propose that Vpr is involved in the dysfunction of hippocampal-dependent learning by disrupting neuronal integrity. Neurotoxic effects of Vpr were measured by co-culture of primary hippocampal neurons and primary rat astrocytes expressing Vpr. Cell lysates were analyzed for the expression of pro-inflammatory cytokines by real time RT-PCR. The effect of Vpr on neuronal apoptosis was examined by Annexin-V and Caspase Glo 3/7 assays. Cell viability and cytotoxicity were analyzed by MultiTox Cytotoxicity assay. Finally, hippocampal neurons of Vpr treated rats were assessed by nissl staining. Results showed that astrocytes expressing Vpr exhibit up-regulation of IP10 and RANTES at 24hr. Induction of neuronal death was detected at 48hr in presence of Vpr. Patterns of nissl staining in Vpr treated rats were distinct from GFP controls. These results show the ability of Vpr to induce pro-inflammatory cytokines in primary astrocytes and to induce apoptosis in primary hippocampal neurons which suggests a cause for the learning deficiencies in live rats. **Supported by R03DA026722 and G12RR003050.**

FORMATION OF D1/NMDA RECEPTOR COMPLEXES MEDIATES HIV-1 PROTEINS+METH SYNAPTODENDRITIC INJURY. Aksenova MV, Mactutus CF, Booze RM; Psychology Department, University of South Carolina, Columbia, SC 29208.

HIV-1 and methamphetamine (METH) act synergistically to produce neural and behavioral alterations, although little is known regarding the exact mechanism(s) of this interaction. D1 and NMDA receptors (NR1 subunit) localize to dendritic spines, are critical to memory processes, and may interact to produce synaptic (dys)function. Using rat midbrain cell cultures, we found that low dose HIV-1 protein Tat (10 nM) and METH (20 mkM) produced no change in D1 or NR1 protein expression, whereas the combination of low dose Tat+METH resulted in a moderate decrease in D1 and NR1 receptors and a decrease in dendritic spine density. However, an immunosorbent assay for detection of D1/NR1 complexes found a significant increase (253%) in cultures treated with Tat+METH. These in vitro data suggest that HIV-1 Tat+METH increases formation of D1/NR1 complexes. In order to test the generality of this interaction, in vivo studies were conducted with adolescent HIV-1 Tg (n=7) and F344 control rats (n=7) injected with either saline or METH (2.5 mg/kg) daily for 10 days, and midbrain tissue samples analyzed. We found that METH treatment decreased D1 and NR1 levels in both HIV-1 Tg and control animals. In contrast, D1/NR1 complexes increased significantly (HIV-1 Tg 182%; control 143%). Collectively, our in vitro and in vivo results indicate that the formation of excess D1/NMDA receptor complexes may be an early step in HIV-1 + METH synaptodendritic injury. **Supported by NIH Grant# DA013137, DA031604, HD043680.**

NICOTINIC ACETYLCHOLINE RECEPTORS: TARGETS OF NICOTINE AND AUTOANTIBODIES. Lindstrom JM; Department of Neuroscience, Medical School of the University of Pennsylvania, Philadelphia, PA 19104-6074.

AChRs are formed from 5 homologous subunits. They exist in many subtypes defined by their subunit composition. AChRs have been found in many tissues. Their distant relations have been found in bacteria. Homomeric AChRs are found both centrally and peripherally. Muscle heteromeric AChRs with low affinity for nicotine mediate neuromuscular transmission and are the target of autoantibodies which cause myasthenia gravis. They are also targets of snake venom toxins and muscle relaxant drugs. Neuronal presynaptic heteromeric AChRs of several subtypes with high affinity for nicotine mediate addiction to tobacco and are the targets of drugs for smoking cessation. Neonicotinoids are potent insecticides. In the future a range of drug types directed at a range of AChR subtypes in various tissues and organisms may be important therapeutics for a wide range of indications including pain, mood disorders, and Parkinson's disease. **Supported by NIH NS11323, DA 030929, MDA 186874.**

COCAINE REGULATES NEURONAL EXPRESSION OF RXR-Γ: IMPLICATIONS FOR RETINOIC ACID RESPONSIVE GENES AND NEURONAL PLASTICITY.
Kovalevich J, Corley G, Ozdemir AY, Yen W, Kim JK, Rawls S, Langford D; Neuroscience, Temple University School of Medicine, Philadelphia, PA 19140.

Cocaine abuse leads to widespread changes in gene expression and can ultimately result in neuronal loss and dysfunction. We have found that chronic cocaine exposure in adult mice leads to significantly decreased levels of retinoid X receptor-gamma (RXR-γ) in discrete brain regions. Retinoid X receptors serve as ligand-activated transcription factors which heterodimerize with other nuclear receptors to induce transcription of target genes in the presence of their respective ligands. Thus, loss of RXR following cocaine exposure resulted in a concomitant decrease in hippocampal synaptic plasticity markers regulated by cellular RA including neurogranin (Ng) and GAP-43. In vitro, SH-SY5Y neuroblastoma cells treated with a physiological dose of cocaine exhibited decreased protein RXR-γ protein levels, which could be attenuated by treatment with the 26 S-proteosomal inhibitor, Bortezomib. Furthermore, cocaine-induced decreases in RXR-γ levels resulted in decreased Ng expression after 24 hours of cocaine exposure. As decreases in both protein and mRNA levels of RXR-γ were observed following cocaine treatment in vivo, studies investigating how cocaine exposure results in transcriptional inhibition of RXR-γ are currently underway. Overall, results from our studies provide insight into the cocaine-mediated disruption of a master transcriptional regulator in neurons, and may provide clues into mechanisms of cocaine-induced neuronal damage. **Supported by NIDA.**

PINCH IN THE CELLULAR STRESS RESPONSE TO TAU-HYPERPHOSPHORYLATION. Langford D, Ozdemir AY, Rom I, Kovalevich J, Yen W, Adiga R, Dave R; Neuroscience, Temple University School of Medicine, Philadelphia, PA 19140.

Particularly interesting new cysteine- histidine- rich protein (PINCH) is an adaptor protein that our data have shown is required for neurite extension under stressful conditions in neurons. Our previous studies also report that PINCH is recalled by neurons showing decreased levels of synaptodendritic signaling proteins such as MAP2 or synaptophysin in the brains of human immunodeficiency virus (HIV) patients. The current study addressed potential role(s) for PINCH in neurodegenerative diseases. Mass spectrometry predicted the interaction of PINCH with Tau and with members of the heat shock response. Our in vitro data confirmed that PINCH binds to hyperphosphorylated (hp) Tau and to E3 ubiquitin ligase, carboxy-terminus of heat shock-70 interacting protein, CHIP. Silencing PINCH prior to induction of hp-Tau resulted in more efficient clearance of accumulating hp-Tau, suggesting that PINCH may be stabilizing hp-Tau. Accumulation of hp-Tau is implicated in more than 20 neuropathological diseases including Alzheimer’s disease (AD), frontotemporal dementia (FTD), and human immunodeficiency virus encephalitis (HIVE). Analyses of brain tissues from HIVE, AD and FTD patients showed that PINCH is increased and binds to hp-Tau. These studies address a new mechanism by which AD and HIV may intersect and identify PINCH as a contributing factor to the accumulation of hyperphosphorylated Tau. **Supported by NIMH.**

INTERPLAY OF COCAINE ABUSE AND HIV-1 TAT PROTEIN ON OLIGODENDROCYTE FUNCTION: IMPLICATIONS FOR HIPPOCAMPAL DEMYELINATION AND PROGRESSION OF HAND. Kovalevich J, Yen W, Ozdemir AY, Langford D; Neuroscience, Temple University School of Medicine, Philadelphia, PA 19140.

Both cocaine abuse and HIV-1 infection of the CNS are associated with altered myelin gene expression and loss of white matter (WM) proteins in patients. Cocaine potentiates disease severity and intensifies CNS damage from HIV infection, though underlying mechanisms remain largely unknown. We demonstrate for the first time that chronic cocaine administration in adult mice results in a significant loss of WM. Furthermore, cocaine exposure enhances lipid peroxidation, as evidenced by increased detection of 4-HNE protein adducts and elevated MDA levels in hippocampal tissue sections. Caspase activation specific to oligodendrocytes is also observed. Increased lipid peroxidation and loss of WM parallel a decrease in numerous synaptic plasticity markers, as well as in levels of RXR-Î³, a nuclear receptor critical to the myelination capacity of mature oligodendrocytes. In vitro, exposure of OPCs grown in conditioned media from cocaine-treated neurons to HIV-1 Tat results in elevated levels of 4-HNE and the pro-apoptotic protein, Bax. This effect is partially blocked by treatment with the RXR ligand 9-cis-retinoic acid. Taken together, our data provide evidence that cocaine exposure may compromise the anti-oxidant capacity of oligodendrocytes, leading to increased cell death and demyelination in response to subsequent insult by HIV toxic factors, including Tat. These findings have numerous implications for the role(s) of cocaine in HIV-associated neurocognitive disorders and CNS damage, and highlight avenues for potential therapeutic intervention.

ROLE OF HIV TAT PROTEIN IN THE REGULATION OF GENE EXPRESSION IN MACROPHAGE. POSSIBLE MECHANISM IN DRUG ABUSERS. Carvallo L, Fajardo JE, Berman JW; Department of Pathology, Department of Microbiology and Immunology, Department of Systems and Computational Biology, Albert Einstein College of Medicine, Bronx, NY 10461

Despite the success of cART, greater than 50% of HIV-infected people develop cognitive and motor deficits termed HIV-associated neurocognitive disorders (HAND). Macrophages are the major cell type infected in the CNS. They produce cytokines/chemokines and viral proteins that promote inflammation and neuronal damage, playing a key role in the progression of HAND. Many HIV-infected drug abusers have elevated CNS dopamine as a result of substance abuse as compared to non-drug abusers, and have increased inflammation that contributes to HAND. Our laboratory showed that treatment of cultured human macrophages with dopamine increased HIV infection, suggesting that drug abusers may have increased CNS HIV infection that may exacerbate HAND. In this study we are examining the role of the HIV tat protein, a viral protein essential for replication and transcriptional regulation of HIV, in the regulation of gene expression in human macrophages. Using THP-1 cells, a human monocyte/macrophage cell line, we generated stable cells that express Tat-Flag by infection with lentivirus. We performed ChIP-seq analysis of these cells and found 73 association sites of tat in promoters or genes. Among these were neurocan, BDNF, APBA1, SMAD4, IL-17RD and PLXNB2. We are confirming the association of tat with these sequences by ChIP assay and the expression of these genes identified by ChIP-seq in our THP-1 cell lines and in human brain tissue sections from people with HAND who abused drugs. Our data will indicate mechanisms by which tat may accelerate the development of NeuroAIDS in drug abusers. **Supported by Pilot Funding from Einstein (Epigenomics Shared Facility for massively-parallel sequencing assays) and NIMH MH090958.**

HIV INTERACTS WITH NEURONAL TUBULIN: A MECHANISM FOR MICROTUBULAR NETWORK IMPAIRMENT? Avdoshina V, Sahab ZJ, Rozzi SJ, Lim ST, Mocchetti I; Department of Neuroscience, Department of Molecular Oncology, and the Interdisciplinary Program in Neuroscience Georgetown University Medical Center, Washington, DC 20057

HIV-associated neurocognitive disorder (HAND) is a progressive disease characterized by neuronal loss and deteriorating CNS function. However, the molecular mechanisms underlying the pathogenesis of HAND are still debated. We have found that both HIVIIIB and gp120IIIB reduce the length of neurites in rat cortical neurons in vitro. This event is preceded by neuronal endocytosis of gp120IIIB and its binding to microtubules, the main structural component responsible for intracellular transport. We examined the interaction of gp120IIIB with the C-terminal tails of different tubulin isoforms and found that gp120IIIB binds 2. Indeed Δ-1A/1B-α3 and β exclusively to neuron-specific tubulin variants: gp120IIIB did not exhibit association with tubulin isoforms that are expressed by astrocytes. On the contrary, gp120BaL did not show interaction with neuron-specific tubulin. The interaction of both gp120s with tubulin was confirmed by mass spectrometry. These data provide evidence that neuronal loss, that accompanies HAND, is mediated by gp120IIIB, and may explain the neuron-specific toxic effect of gp120IIIB. Future studies will reveal whether this mechanism reduces trafficking of mitochondria or other cargo molecules crucial for axonal function. **Supported by 1R21 NS074916.**

HIV NEUROPATHOGENESIS: ROLE OF NEF+ EXOSOMES (EXNEF), METHAMPHETAMINE AND OPIATES. Raymonsd AD, Yndart-Arias A, Agudelo M, Munoz K, Atluri VS, Pilakka S, Thangavel S, Nair MP; Department of Immunology, Florida International University, Herbert Wertheim College of Medicine, Miami, FL 33199.

Methamphetamine(MA) and heroin are implicated in exacerbating HIV infection and progression to NeuroAIDS. HIV-1 Nef release from nef-transfected or HIV-infected cells in exosome-like vesicles was shown. However, the impact of exNef on HIV replication and the interplay with MA or opioids on neuropathogenesis are unknown. Using an in vitro model of the blood brain barrier (BBB), we show that exNef, MA and heroin disrupt the BBB and increase its permeability. MA and exNef lowered BBB resistance and increased permeability 4-fold compared to MA or exNef alone. We examined the effect of drugs of abuse on exNef release within the central nervous system (CNS) by infecting microglia with HIV-1(NLAD8) in the presence/absence of MA or Heroin. MA and heroin induced an upsurge of exNef in HIV-infected microglia. To find potential mechanism(s) of exNef-mediated up-regulation of HIV replication, a LTR-CAT reporter assay was used to assess the impact of exNef and MA on HIV LTR transcription. Neither MA nor exNef alone induced LTR transcription but together exNef and MA increased LTR transcription 3-fold. Taken together, results show that exNef is released by HIV-infected microglia; MA and heroin increase exNef released from HIV-infected microglia and that exNef regulates transcription of the HIV LTR. Our study shows a potential role for exNef in HIV neuropathogenesis and indicates that drugs of abuse such as MA and heroin can increase exNef levels in the CNS thereby exacerbating HIV-induced neurotoxicity. Thus, exNef may be a novel therapeutic target in HIV infected drug users. **Supported by NIDA, 3R01 DA027049-04S1.**

EFFECT OF HIV-1 GP120 ON THE GLUTAMIC ACID METABOLIC SYSTEM IN HUMAN ASTROCYTES. Vázquez-Santiago FJ, Meléndez LM, Wojna V, Noel RJ, Rivera-Amill V; Microbiology Department, Ponce School of Medicine and Health Sciences, Ponce, PR 00716; Microbiology and Medical Zoology Department, and Specialized Neuroscience Research Program, University of Puerto Rico Medical Science Campus, San Juan, PR 00936.

HIV-1 infected subjects on antiretroviral therapy may present with HIV-1 associated neurocognitive disorders (HAND). HIV-1 envelope (env) diversity within HAND subjects contributes to neuropathology. Previous studies in our lab have shown genetically distinct populations of env within one infected individual with HAND. Sequencing data have demonstrated that most of these isolates have a CCR5-tropic phenotype similar to HIV BaL. The extent whereby env influences its neurotoxic potency remains unclear. Using a variety of env strains and an in vitro approach, we examined whether HIV env exhibits broaden neurotoxicity in glial cells. Astrocytes are key metabolic regulators of glutamate in the brain and are susceptible to env-mediated damage. Glutamate regulatory components such as glutamate transporter 1 and 2 (EAAT-1 & 2), glutaminase, and glutamate synthetase and glutamate dehydrogenase (GDH) were tested. We hypothesize that HIV env from lab-adapted isolates exhibit enhanced in vitro neurotoxicity upon the glutamate cycle components. U87Mg astrocytes were transiently transfected with pcDNA3.1D HIV env BaL and pSYNgp120 JRFL. Protein and RNA were examined by western blot and RT-PCR, respectively. HIV env BaL expression in U87MG astrocytes resulted in disrupted excitatory EAAT-1 expression and enhanced GDH. Our findings suggest that env variability is key for HAND neuropathology by disrupting some of these components. Transfection with HIV env strains supports our conclusion that regulatory components of glutamate are altered contributing to a worsened disease outcome. **Supported by NCRR-RR003050; NIMHD-G12-MD007579, R01-MH08316-01, SNRP U54 NS43011, and RISE R25GM082406.**

MAGNETIC-NANOFORMULATION OF MU-OPIOID RECEPTOR ANTAGONIST (CTOP) FOR TREATMENT OF MORPHINE-INDUCED NEUROPATHOGENESIS IN HIV INFECTION. Sagar V, Pilakka-Kanthikeel, SK, Priestap H, Atluri VSR, Ding H, Guduru R, Khizroev S, Nair MP; Center for Personalized Nanomedicine, Institute of NeuroImmune Pharmacology, Department of Immunology, Herbert Wertheim College of Medicine, and Department of Biological Sciences, College of Arts and Sciences, Florida International University, Miami, FL 33199.

Recreational drug-addicted patients account for one-tenth of the HIV-infected population. Opiates such as morphine, heroin, etc., share common target-areas in the brain with HIV, causing increased neuropathogenesis of HIV infection. Supplementation of anti-opioid agents with ARV drugs in treatment of the opioid-addicted HIV population may prevent opioid-induced pathogenesis. However, current treatments to alleviate the action of opioids are less effective at the CNS level, basically, due to impermeability of therapeutic molecules across the blood-brain barrier (BBB). Emergence of nanotechnology in medicine has shown exciting prospects for development of novel delivery systems to administer desirable levels of therapeutic drugs in the CNS. We report herein that D-Pen-Cys-Tyr-D-Trp-Orn-Thr-Pen-Thr-NH2 (CTOP, a highly selective mu-opioid receptor antagonist incapable of penetrating the BBB) can be immobilized on the surface of magnetite nanoparticles (MNPs) as determined by FTIR spectroscopy. Cytfluorometric analysis shows that the biological efficacy of the MNP-CTOP complexes, in prevention of morphine-induced apoptosis in PBMCs, remains equivalent to that of free CTOP. Confocal microscopy also reveals that free and MNP-CTOP have comparable efficacy in protecting against changes in morphine-induced dendrite and spine morphology. The MNP-CTOP nanoformulation is being further examined for its ability to transmigrate across the BBB and reverse morphine-induced neurodegenerative processes in an HIV-infected model system.

DISRUPTION OF THE CHOLINERGIC ANTI-INFLAMMATORY RESPONSE IN THE HIV CONTEXT. Delgado-Velez M, Baez-Pagan, C, Gerena Y, Quesada O, Santiago-Perez, L, Wojna, V, Melendez L, Silva W, Lasalde-Dominicci J; Department of Biology, Department of Chemistry Department of Physical Sciences, University of Puerto Rico, Río Piedras Campus, San Juan, PR 00931; Department of Microbiology and Medical Zoology, Internal Medicine, Department of Pharmaceutical Sciences, School of Pharmacy, and the Department of Physiology, University of Puerto Rico, Medical Sciences Campus, San Juan, PR 00936.

Human immunodeficiency virus (HIV) remains a public health threat. The introduction of combined antiretroviral treatments (cART) has markedly increase life expectancy but two problems remain unsolved: persistence and inflammation. Recent studies linked macrophage's alpha7 nicotinic acetylcholine receptor (α7-nAChR) activation with anti-inflammatory responses to maintain homeostasis through the cholinergic anti-inflammatory pathway (CAP). Nonetheless, little is known about the effectiveness of this neuroimmune regulation in the HIV context. Here we examined whether CAP is disrupted in the setting of HIV-induced inflammation. We found that α7-nAChR is up-regulated in immune cells from HIV+ individuals and that gp120 may contribute to such alteration, as assessed in uninfected cells. Furthermore, this up-regulation, unexpectedly, confers a pro-inflammatory phenotype to macrophages. These results suggest that HIV tempering is a natural strategy to control inflammation by up-regulation of a key player in the CAP. Elucidation of the mechanism by which gp120 disrupts CAP while up-regulating the α7-nAChR is likely to be critical towards development of effective therapeutic strategies to reduce HIV-related chronic inflammation. **Supported by NIH/2U54NS43011, NIH/G12RR03051, PRCTRC/8U54MD007587-03, NIH/2R25GM061151-5A1.**

HIV PROTEASE INHIBITORS PROMOTE AMYLOIDOGENIC APP PROCESSING VIA PHOSPHO-EIF2-DEPENDENT TRANSLATIONAL UPREGULATION OF BACE1.

Gannon P, Akay C, Yee A, Odeleye A, Clements J, Mankowski J, Zink C, Jordan-Sciutto K; School of Dental Medicine, University of Pennsylvania, Philadelphia, PA 19104; School of Medicine, Johns Hopkins University, Baltimore, MD 21205.

The advent of antiretroviral therapy (ART) as the mainstay for HIV treatment has led to a significant reduction in the incidence of HIV-associated dementia (HAD). However, the prevalence of more mild forms of HIV-associated neurocognitive disorders (HAND) has persisted in the post-ART era. In addition, HAND neuropathology has evolved from a subacute, encephalitic condition to a prolonged, neurodegenerative disease. While increased longevity of HIV(+) populations is thought to contribute to alterations in HAND pathology, other risk factors, such as peripheral toxicities of ART and potential central effects, linked to accelerated aging, remain unexplored. Previous work has shown that ART is toxic to the PNS in vivo as well as DRG neurons in vitro. To explore ART-mediated neuronal toxicity we treated primary rat neuroglial cultures with commonly prescribed NRTIs, and HIV protease inhibitors (PI). Over the course of 8 days of treatment we found that PIs led to a significant MAP2 loss, indicating neuronal damage and death. Given the known role of PIs in activating ER stress, we explored the unfolded protein response in neurons. We found that therapeutically relevant concentrations of ART induce ER stress in neuroglial cultures leading to PERK-dependent phosphorylation of eIF2 and enhanced translation of ATF4 and BACE1. Additionally, we observed PI-mediated amyloidogenic APP processing and increased Ab secretion in CHO cells expressing human APP. Finally, ART administered to rats or SIV-infected macaques resulted in CNS damage and activation of ER stress.

E2F1 AT THE SYNAPSE: NOVEL FUNCTIONS FOR A CELL CYCLE TRANSCRIPTION FACTOR IN A NON-CELL CYCLE CONTEXT. Jordan-Sciutto KL, Ting JH, Schleidt S, Wu J, Marks, DR; Department of Pathology/Dental Medicine, University of Pennsylvania, Philadelphia, PA 19104.

Aberrant activation of the cell cycle machinery in neurons has been implicated in several neurodegenerative diseases. Specifically, expression of E2F1, a transcription factor know for its regulation of G1 to S phase progression, is increased in HIV associated Dementia, Alzheimer disease, and Parkinson disease. Despite reported roles in cell death, little is known regarding the role of E2F1 in healthy neurons. To investigate the physiologic role of E2F1 neurons, we examined its localization in neurons and found that E2F1 was enriched in neuronal process and synaptoneurosomes, localizations inconsistent with its known role as a transcription factor. Further fractionation of the synaptoneurosomes demonstrated that E2F1 is present in the postsynaptic densities (PSD) but mostly enriched in the fraction containing synaptic vesicles. Interestingly, we found that transgenic mice lacking functional E2F1 have significantly less synaptic proteins, including PSD95 and NMDA receptor 1, in hippocampus and olfactory bulb compared to wildtype littermates indicating synaptic loss. Cortical cultures derived from mice lacking functional E2F1 show a significant decrease in neuritic processes. These findings suggest E2F1 contributes to formation and or maintenance of synapses. We propose that E2F1 has a novel role in the synapse of postmitotic neurons and disruption of its physiologic function may contribute to the neurodegeneration observed in HAND and other diseases. **Supported by NIH R01 NS41202.**

THE ROLE OF CELL CYCLE PROTEIN E2F1 IN HIV-INDUCED NEUROTOXICITY. Jordan-Sciutto KL, Zyskind JW, Wang Y, Akay C, Kolson DL; Department of Pathology/Dental Medicine, and Department of Neurology/Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104.

Inflammatory factors released into the extracellular milieu by HIV-infected macrophages in the brain, are a major contributor to HIV Associated Neurocognitive disorder (HAND). We have previously shown that the transcription factor E2F1, which is known to activate gene targets required for G1 to S phase progression as well as for apoptosis, exhibits increased neuronal expression in HAND. However, classic E2F1 target genes are unchanged by HIV-induced neuronal damage in vitro suggesting E2F1 may be contributing to neuronal death via an alternative and less well-defined transcription-independent mechanism via activation of the calcium-sensitive cysteine protease calpain. Using an in vitro model of HIV-mediated neuronal loss, we have demonstrated that neuronal E2F1 is upregulated following insult and is cleaved to a lower molecular weight product by calpain. Further, increased levels of E2F1 in this model are due to altered stability of lower molecular weight E2F1 protein. Interestingly, we have found that the stabilization of the E2F1 cleavage product occurs exclusively in neuronal cell types in contrast to a more complete degradation observed in dividing cells. Given that pharmacological inhibition of calpain activation and genetic deletion of E2F1 attenuates neuronal death from the HIV insult, our data suggest that calpain cleavage of E2F1 contributes to HIV-induced neurotoxicity. We hope that by defining the role of E2F1 cleavage in HIV-induced neurotoxicity, therapeutic strategies to treat neuronal damage in HAND can be developed. **Supported by NIH R01 NS41202 and F31-NS-07492.**

INTEGRATED BEHAVIORAL CARE REDUCES DEPRESSIVE SYMPTOMS AND IMPROVES PSYCHOLOGICAL AND PHYSICAL HEALTH IN HIV PATIENTS.
Rivera-Amill V; Department of Microbiology, Ponce School of Medicine and Health Sciences, Ponce, PR 00716.

Human Immunodeficiency Virus (HIV) is one of the leading causes of death for people from 20-54 years old. Depression is a common comorbidity in HIV/AIDS and plays a crucial role in disease progression and health status. The goal of our work is to promote mental health in Puerto Ricans diagnosed with HIV/AIDS in order to positively influence overall health and the maintenance of an effective antiretroviral treatment. The objective of this study is to determine the impact of integrated behavioral health care on reducing levels of depression, increasing adherence to antiretroviral therapy (ART), and restoring immunological function to HIV/AIDS patients in Puerto Rico. Preliminary observations from a retrospective study revealed that levels of depression following psychological intervention were lower than those prior to intervention, and that these lower levels correlated with increased ART adherence, decreased viral load, and an increase in the CD4+ T cell count. In this study, we examined the clinical markers in HIV+ patients with and without depression who received an integrated behavioral care intervention. Results show that HIV+ individuals with depressive symptoms had increased levels of proinflammatory cytokines and lower antioxidant levels when compared with patients without depressive symptoms. The severity of depression tended to conform to the degree of inflammation and oxidative imbalance. These findings suggest that HIV+ individuals with depressive symptoms are at a greater risk for worsened disease-outcome and highlight the importance of managing both diseases.
Supported by Ponce School of Medicine and Health Sciences, and NIMHD-G12-MD007579.

HEROIN USE INHIBITS ANTI-HIV MICRO-RNA EXPRESSION IN CD4+ T CELLS. Wang X, Peng JS, Liu MQ, Zhou Y, Wang F, Zhou W, Zhou DJ, Ho WZ; Department of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140; Department of Virology, Wuhan Centers for Disease Prevention & Control, WUHAN, CHINA 430015.

Recent studies have demonstrated the anti-HIV role of some microRNAs (miR-28, 29, 125b, 150, 198, 223 and 382) in the primary target cells of HIV infection. Decrease or inhibition of the activity of these miRNAs can enhance replication of latent HIV in resting CD4+ T cells and in monocytes. As a commonly used drug, heroin has been implicated in the immunopathogenesis of HIV disease. Our in vitro investigation showed that morphine, the nociceptively active component of heroin, could inhibit expression of anti-HIV miRNAs in cultured human monocytes. This effect of morphine was mediated via activation of mu-opioid receptors. We examined the clinical effect of heroin on expression of anti-HIV miRNAs in heroin abusers with HIV and/or HCV infection. Compared with normal healthy control subjects, age-matched HIV+ heroin users have lower levels of the anti-HIV miRNA (miR-29a, miR-125b and miR-150) in their CD4+ T cells. These data indicate that heroin use impairs intracellular innate immunity against HIV, which may affect host susceptibility to HIV infection. (WX and PJS Contributed equally to this study). **Supported by NIDA (DA12815 and DA27550).**

COCAINE SELF-ADMINISTRATION POTENTIATES EXCITATORY RESPONSES OF RAT CORTICAL NEURONS TO HIV-1 TAT PROTEIN. Wayman WN, Napier, TC, Hu X-T; Department of Pharmacology and the Center for Compulsive Behavior and Addiction, Rush University Medical Center, Chicago, IL 60612.

Chronic cocaine (COC) exposure dysregulates the medial prefrontal cortex (mPFC) of the mammalian brain, which contributes to craving, drug-seeking and relapse in the abstinent individual. mPFC pathology also occurs in neuroAIDS. We hold that the exaggerated decline in mental and neurological health reported for the HIV+ COC abuser likely reflects convergent dysregulation within mPFC neurons. In support of this hypothesis, we show that COC self-administration (SA) followed by a protracted COC withdrawal results in the following: (1) Drug-seeking behavior (assessed by re-exposure to the COC-paired cues; termed cue reactivity, CR). (2) Abnormally increased reactivity of mPFC neurons to excitatory stimuli, and (3) exacerbated susceptibility/vulnerability of mPFC neurons to HIV-1 protein, Tat. Studies were conducted in male adult rats trained to SA COC for 14 days and saline yoked controls. CR was tested 1 day (CR1) and 18-22 days (CR2) after the last COC SA session. Only COC-exposed rats exhibited CR (i.e., CR2>CR1). The mPFC was harvested 1 day after the CR2 test (at the age of ~16 weeks), and whole-cell patch-clamp recordings were conducted from pyramidal neurons. Resting membrane potential was depolarized and firing was increased significantly in neurons from COC SA rats compared to saline-yoked rats. Bath-applied Tat facilitated membrane depolarization and neuronal firing in both COC SA and saline-yoked rats, but Tat-induced changes were more robust after COC SA. These findings in adult rats will be compared to our prior work with COC-exposed juveniles. **Supported by USPHSGs F31DA033206, DA033882, P30AI082151 and Daniel F & Ada L Rice Foundation, and Chicago DCFAR.**

CHRONIC MORPHINE PREVENTS GP120-MEDIATED CELL DEATH BY ALTERING THE PRO-BDNF PROCESSING. Campbell L, Passeri E, Mocchetti I, Bachis A; Department of Neuroscience, Georgetown University, Washington, DC 20057.

Opioids have been shown to exacerbate gp120 and Tat toxicity. However, morphine protects cortical cultures against the toxic effect of M-tropic gp120BaL. Using rat primary neurons we have observed that repeated exposures to morphine prevent gp120IIIB-mediated apoptosis. Thus, further research is required to determine whether opioids exhibit neuroprotective or neurotoxic activity in the presence of viral proteins. HIV and gp120IIIB have been shown to reduce the levels of BDNF by altering the cleavage of its precursor proBDNF. Chronic morphine in vivo has been shown to increase levels of tissue plasminogen activator (tPA), the activator of plasmin, that converts proBDNF into BDNF. Thus, opioids may prevent the neurotoxic effect of gp120 by augmenting the enzymatic processing of proBDNF. To test this hypothesis we used rat cortical neurons. We observed that morphine increases the levels and release of BDNF while at the same time decreases proBDNF. A similar imbalance in the ratio proBDNF/mature BDNF was confirmed in the cortex of rats chronically injected with morphine. The neuroprotective effect of morphine (through BDNF) was confirmed by results showing increased levels and activity of tPA in morphine-treated cells as well as by reduced neuroprotection in the presence of PAI-1, a tPA inhibitor. These data suggest that morphine’s ability to increase BDNF synthesis as well as alter proBDNF processing though tPA might be crucial to its neuroprotective effect against gp120. Our studies identify a new mechanism of interaction between morphine and HIV proteins. **Supported by NIH/DA026174; NIH/DA032282; Georgetown University Music for the Mind Award.**

CANNABINOIDS DAMPEN HUMAN MONOCYTE CYTOKINE RESPONSE TO HIV GP120. Jamerson M, Cabral GA; Department of Microbiology and Immunology, Virginia Commonwealth University, School of Medicine, Richmond, VA 23298.

Monocyte-derived macrophages (MDMs) release inflammatory factors in response to HIV infection including cytokines, chemokines, neurotoxic factors, and the virus-specified envelope glycoprotein, gp120. Gp120 induces production of cytokines and chemokines from monocytes and other immunocytes. Using 2-dimensional in-gel electrophoresis (2-DIGE), we have shown that the cannabinoids delta-9-tetrahydrocannabinol (THC) and CP55940 ablate the proteome profile generated by MDMs in response to gp120. Monocytes were isolated from human blood negative for markers of *Treponema pallidum*, hepatitis B virus, hepatitis C virus, HIV-1, HIV-2, West Nile Virus, Cytomegalovirus, and Parvovirus B-19. They were purified by plastic adherence, and matured for 7 days. These MDMs were co-exposed to gp120 (20 or 40 nM) and 10^{-6} M THC or CP55940 for 8h. Pathway-focused real-time RT-PCR revealed that THC and CP55940 exerted a decrease in gp120-induced mRNA levels for MCP-1, MCP-2, MCP-3, MIP-3alpha, CCL-22, IP9, IP10, CXCL5, IL-1beta, IL-1RN, IL-23alpha, IL-7, IL-8, LIF, and TNF-alpha. Cytokine antibody array performed on culture supernatants demonstrated that these cannabinoids also decreased protein levels for a subset of cytokines and chemokines. These results indicate that cannabinoids dampen expression of a diverse array of cytokines and chemokines that are elicited in response to gp120. However, whether disparate modalities in expression of select cyokines and chemokines are affected, and whether the cannabinoid-mediated inhibition is linked to cognate receptors remain to be defined. **Supported by NIDA R01 DA005832 and RO1 DA029532.**

REPEATED COCAINE ADMINISTRATION EXACERBATED HIV-1 TAT-MEDIATED CORTICAL EXCITABILITY VIA OVER-ACTIVATING L-TYPE CALCIUM CHANNELS. Chen L, Napier TC, Hu X-T; Department of Pharmacology and Center for Compulsive Behavior and Addiction, Rush University Medical Center, Chicago, IL 60612.

Cocaine (COC) abuse enhances deleterious effects of HIV on neurons. HIV-infected cells secret pathogenic proteins, including the HIV-1 transactivator of transcription (Tat), which can elevate cytosolic calcium (Ca) to excitotoxic levels. The structure and function of the medial prefrontal cortex (mPFC) are altered in both COC-abusing, and HIV+ individuals. We show here that chronic COC exposure enhances Tat-mediated excitation of mPFC pyramidal neurons via over-activating L-type Ca channels. This finding was electrophysiologically determined in forebrain slices from two rat models, young rats (4-5 weeks) treated with 15mg/kg/day ip COC for 5 days followed by a 3-day withdrawal, and adult rats (~16 weeks) that self-administered COC for 14 days with a 3-week withdrawal (see Wayman WN et al. in this meeting). In vitro application of Tat facilitated firing and Ca influx via diltiazem-sensitive L-channels in pyramidal neurons from saline-treated rats of both ages. Baseline firing and Ca influx were elevated in pyramidal neurons from COC-treated rats of both ages. The ability of Tat to promote firing and Ca influx was enhanced in COC-exposed rats of both ages. Tat-enhanced mPFC neuronal excitability (firing) appeared to be greater in adult rats than young rats after chronic COC exposure. The Tat-mediated Ca influx was independent of NMDA receptors. These findings demonstrate an involvement of L channels in the exaggerated effects of Tat on mPFC after chronic exposure to COC. Such dysregulation may also occur in the brain of chronic COC abusers comorbid with neuroAIDS. **Supported by USPHSGs DA026746, DA033882, the Chicago D-CFAR P30A1082151, the McManus Foundation, and Daniel F & Ada L Rice Foundation.**

ALCOHOL MEDITATED INDUCTION OF PROINFLAMMATORY CYTOKINES IN HUMAN ASTROCYTES. Nookala A, Gangwani M, Rey JP, Shah A, Kumar, S, Kumar, A; Pharmacology and Toxicology, UMKC-School of Pharmacy, Kansas City, MO 64108.

Alcohol is known to be toxic to the central nervous system (CNS), however, the mechanism contributing to neurotoxicity has not been fully elucidated. In this study, we measured the induction of the pro-inflammatory cytokines IL-6 and IL-8 in an SVGA astrocytes as well as primary fetal astrocytes after treatment with ethanol. Both IL-6 and IL-8 mRNA levels increased in a time-dependent manner after treatment with a single dose of 50mM ethanol. Peak induction of both cytokines (21.55 ± 2.93 fold for IL-6 and 42.76 ± 3.02 fold for IL-8) was observed after 3h of ethanol treatment in both cell line as well as primary cells. To determine the mechanism underlying the induction of IL-6 and IL-8, the translocation of NFκB was studied. The level of p50 was found to be higher in the nucleus as compared to cytoplasm after ethanol treatment and maximum translocation was observed at 1h post-treatment. Pre-treatment with IκBK inhibitor SC-514 abrogated the ethanol-mediated up-regulation of IL-6 and IL-8 in a concentration-dependent manner. These results were further confirmed using siRNA targeted against NFκB. To ascertain whether alcohol metabolism in astrocytes is responsible for production of these cytokines, the cells were pre-treated with Disulfiram (ALDH inhibitor). Disulfiram treatment abrogated induction of IL-6 and IL-8 by ethanol. These results demonstrate that NFκB and alcohol metabolism play key roles in ethanol-mediated up-regulation of inflammatory cytokines in the brain, which could serve as a better therapeutic target for the treatment of ethanol-induced neuroinflammation. **Supported by NIAAA AA020806.**

DOPAMINE INCREASES CD14+CD16+ MONOCYTE TRANSMIGRATION ACROSS THE BBB. Calderon TM, Lopez L, Williams DW, Gaskill PJ, Eugenin EA, Berman JW; Department of Pathology, Albert Einstein College of Medicine, Bronx, NY 10461; Public Health Research Institute and Department of Immunology and Molecular Genetics, University of Medicine and Dentistry of New Jersey, Newark, NJ 07103.

Drugs of abuse increase extracellular dopamine (Dop) in the CNS, a common mechanism of action that may contribute to more severe and accelerated HIV associated neurocognitive disorders (HAND) in infected drug abusers. An increase in a small subpopulation of circulating monocytes (Mo) expressing CD14 and CD16 is associated with HIV infection. CD14+CD16+ Mo are preferentially infected with HIV and expansion of this mature subpopulation correlates with CNS disease pathogenesis. The transmigration of infected and uninfected CD14+CD16+ Mo across the blood brain barrier (BBB) mediates HIV entry into the CNS and contributes to neuroinflammation. To study Mo transmigration into the CNS, our laboratory developed a human BBB model and a system of non-adherent culture of human peripheral blood Mo to expand the CD14+CD16+ subpopulation. Dop significantly increased CD14+CD16+ Mo transmigration across the BBB and also increased Mo pseudopodia, a component of cellular polarization involved in directed cell movement. Dop receptor 1 (D1R) and D5R were minimally expressed on freshly isolated Mo but were detected by FACS in cultures enriched for CD14+CD16+ Mo. The D1R/D5R agonist SKF38393 significantly increased CD14+CD16+ Mo transmigration, suggesting a role for D1R/D5R in Dop induced transmigration. Even though Dop does not cross the BBB, CD14+CD16+ Mo transmigration may be increased by Dop mediated effects on BBB cells and/or on the transmigration process once Mo have penetrated the BBB. Thus, Dop may increase CNS inflammation in HIV infected drug abusers, augmenting HAND. **Supported by NIDA DA025567; NIMH MH075679 and MH090958.**

UPREGULATION OF THE ALPHA7-NICOTINIC ACETYLCHOLINE RECEPTOR IN A TRANSGENIC MOUSE MODEL THAT EXPRESSES THE HIV COAT PROTEIN GP120. Capó-Vélez CM, Morales B, Melendez R, Lasalde-Dominicci JA; Department of Biology, University of Puerto Rico, Rio Piedras Campus, San Juan, PR 00931; Department of Anatomy and Neurobiology, University of Puerto Rico, Medical Sciences Campus, San Juan, 00936.

Cognitive and motor dysfunction can arise as a consequence of HIV-1 infection and are known as HIV-associated neurocognitive disorders (HAND). Advances in treatment of HIV-1, have led to improved survival rates, however, HAND still presents a significant health problem. To identify molecular and pharmacological targets for treatment of HAND, it is required to understand the events leading to neuronal damage in the central nervous system (CNS). A key protein associated with the neurological complications of HIV, gp120, forms part of the viral envelope and can interact with several receptors including CD4, CXCR4, and nicotinic acetylcholine receptors (nAChRs). In the present study, we investigated the link between the nAChR subtype α7 (α7-nAChR), gp120, and HIV/HAND pathogenesis. Using a transgenic mouse model that expresses the coat protein gp120, we have shown that the α7-nicotinic acetylcholine receptor (α7-nAChR) is up-regulated in lung, spleen, and peritoneal macrophages of these transgenic mice. Moreover, quantitative RT-PCR and western blot experiments on the brains of transgenic mice demonstrate a significant increase in α7-nAChRs mRNA and protein levels in the striatum, a region shown to be affected in HAND, which suggests a role for this receptor in HAND development. Understanding the role of α7-nAChRs in HIV disease progression could lead to novel therapeutic strategies that would increase life expectancy and overall quality of life in people living with HIV/AIDS.

THE INTERACTIVE ROLE OF ALCOHOL AND CANNABINOIDS ON DENDRITIC CELL FUNCTION. Agudelo M, Yndart A, Morrison M, MuÃoz K, Raymond A, Nair MP; Department of Immunology/Institute of NeuroImmune Pharmacology, Herbert Wertheim College of Medicine, Miami, FL 33190.

According to the National Survey on Drug Use and Health (NSDUH), after alcohol, marijuana has the highest rate of dependence and abuse among all drugs. Both of these psychoactive substances are well known to affect neuroimmune responses, and previous studies have focused mostly on their psychoactive effects. However, the immunological effects of alcohol and cannabinoids and their interactive role on antigen presenting cells such as monocyte-derived dendritic cells (MDDCs) have not been clearly elucidated. Therefore, it is hypothesized that alcohol and cannabinoids can exert their effects on MDDCs by altering expression of surface markers and co-stimulatory molecules, and by modulating MDDCs function such as antigen presentation. The ability of EtOH, THC and synthetic cannabinoids to modulate MDDCs surface markers and co-stimulatory molecules (CD11c, CD40, DC-SIGN, CD80, CD83, and CD86) was tested by qRT-PCR and flow cytometry. MDDCs from alcoholics showed higher levels of DC-SIGN and CD86. These findings were further confirmed in vitro using MDDCs treated with EtOH (0.05, 0.1 and 0.2%). MDDCs surface markers and co-stimulatory molecules were also shown to be regulated by cannabinoids. Furthermore, there were modulations in antigen presentation when HIV-infected MDDCs treated with EtOH and cannabinoids were co-cultured with T cells. Our results provide insights into the interactive role of alcohol and cannabinoids and their effects on dendritic cell function. **Supported by National Institute on Drug Abuse.**

UNRAVELING THE IMPACT OF CANNABINOIDS ON HIV DISEASE PROCESSES; A SYSTEM-WIDE APPROACH. LeCapitaine NJ, Amedee A, Zabaleta J, Voloshenyuk T, Mohan M, Winsauer P, Vande Stouwe C, Molina P; Department of Physiology, LSU Health Sciences Center, New Orleans, LA 70112; Division of Comparative Pathology, Tulane University, Covington, LA 70433.

Data from our studies in macaques show chronic Δ-9-tetrahydrocannabinol (THC) administration prior to and during simian immunodeficiency virus (SIV) infection ameliorates disease progression, attenuates viral load and tissue inflammation, leading to significantly reduced morbidity and mortality. Using a system-wide approach, we investigated molecular mechanisms mediating protective effects of THC in lymphoid organs during SIV infection. Chronic b.i.d. THC given 15-18 mo prior to SIV inoculation resulted in decreased viral replication and IFN-γ and IL-6 protein expression in lymph nodes and spleen at necropsy. Both proviral and 2-LTR DNA in the spleen were significantly reduced in THC/SIV. Duodenal tissue viral load was modestly suppressed and showed significantly increased Th2 cytokine protein levels. THC/SIV animals had differential regulation of duodenal CD4+ central memory (CM), integrin β7+CD4+ CM, and CD8+ CM cells. These findings suggest CD4+ T cell homeostasis may be preserved in THC/SIV animals improving control of viral replication. THC also produces changes in gene expression in the duodenum of SIV-infected macaques. Pathway analysis revealed differential expression patterns of relevant signaling pathways involved in host response to infection (immune/stress responses; cell-adhesion/ tight-junctions), raising the possibility that THC modulates inflammation and SIV infectivity. Thus, the data suggest that THC may modify host-pathogen interaction at various levels, including regulation of host immunity, inflammatory response, and viral integration and replication. **Supported by NIDA DA020419 & DA020419-051.**

NEUROINFLAMMATION IN YOUNG ADULT HIV-1 TRANSGENIC RATS. Persons AL, Chen L, Wayman WN, Hu X-T, Napier TC; Department of Pharmacology and Center for Compulsive Behavior and Addiction, Rush University Medical Center, Chicago, IL 60612.

HIV-1 infection in humans is associated with neurological and psychological impairments that endure during highly active antiretroviral therapy (HAART), and progress with age. To enhance understanding of the brain/behavior consequences of HIV/AIDS, we are studying a rodent model of human HIV infection with HAART, the HIV-1 transgenic (Tg) rats. These rats have elevated brain concentrations of mRNA for HIV proteins (i.e., Tat, gp120, nef and vif) as early as 2-3 months of age (Peng et al., J Neuroimmunol 218:94, 2012). We studied the effects of expressed HIV proteins on inflammation in the brain using immunohistochemistry to measure GFAP (an astrocyte marker), Iba1 (a microglia marker), and CD68/ED-1 (a marker for reactive/phagocytic microglia and macrophages) in 13-14 week old male Tg rats and age-matched Fisher 344 controls. Thus far, we have observed higher levels of GFAP and Iba-1 in the lateral septum of Tg rats as compared to controls. Levels of CD68/ED-1 were also increased in the choroid plexus of the adjacent lateral ventricles of Tg rats, indicating an infiltration of macrophages from the periphery (blood). No overt changes in the expression of these markers were observed in the hippocampus. As septal-hippocampal projections are involved in working memory, it is plausible that inflammation of the lateral septum at the age measured here is an early manifestation of neuropathology that could eventually progress to mnemonic dysregulation. These are ongoing studies, and additional markers and brain regions will be discussed in the poster. **Supported by USPHSG DA033882, the Chicago D-CFAR P30A1082151, and Center for Compulsive Behavior and Addiction.**

CANNABINOID BLOCKADE OF HIV-1 GP120-INDUCED EFFECTS ON HUMAN FETAL NEURAL PRECURSOR CELLS. Sheng, WS, Hu S, Rock RB; CIDMTR, Department of Medicine, University of Minnesota, Minneapolis, MN 55455.

Neural precursor cells (NPCs) are a self-renewing, multipotent population of cells that are capable of differentiating into neurons, astrocytes, and oligodendrocytes. Previously we have shown that hNPCs express high level of CXCR4, a binding site for HIV-1 gp120. We also found that hNPCs express a high level of cannabinoid receptor 1 (CB1). In this study we sought to investigate: 1) proliferation of hNPCs exposed to gp120 in the presence and absence of cannobinoids in vitro; 2) effect of gp120 on mNPCs in vivo. As activated microglia may also have impact on NPC survival and functions, we decided to study proliferation of hNPCs in the presence and absence of microglia under gp120 exposure, with and without cannabinoids. We found that proliferation of hNPCs declined in a dose-dependent fashion to gp120 exposure. Cannabinoids alone induced hNPC proliferation and blunted the inhibitory effect of gp120. Reduced numbers of BrdU-positive mNPCs were found on gp120- versus saline-injected animals. In the presence of microglia, proliferation of hNPCs was further suppressed during gp120 exposure. Pretreatment with cannabinoids CP55,940 or JWH015 reversed the synergistic inhibition of microglia on hNPC proliferation exposed to gp120. These findings demonstrate that cannabinoids can be beneficial in dampening HIV-1 gp120-induced and/or activated microglia-potentiated hNPC damage. Currently we are using in vitro and in vivo models to investigate the involvement of CB1/CB2 in gp120-microglia-NPC interaction in the presence of selective cannabinoid agonists. **Supported by NIDA.**

MORPHINE DISRUPTS LEUKOCYTE ENDOTHELIAL TRANS-CELLULAR MIGRATION. Koodie L, Roy S; Dentistry, Pharmacology, University of Minnesota, School of Medicine, Minneapolis, MN 55455; Division of Basic Translational Research, Department of Surgery, University of Minnesota, Minneapolis, MN 55446.

Tumor infiltrating leukocytes enhance tumor progression by modulating angiogenesis. Chronic morphine inhibits angiogenesis associated with tumor growth through inhibition of tumor infiltrating leukocytes. In these studies we investigated the effect of morphine, on leukocyte-trans-cellular-migration using an electric-cell impedance sensing system that measures trans-cellular resistance (TER). Our results show vehicle-treated endothelial cells lose TER upon interaction with human PLB985 cells (monocytes, granulocytic cells), which is an indication of successful trans-cellular migration. In contrast, morphine pretreated (100nM - 1.0µM) increased human umbilical-vein and foreskin-microvascular derived endothelial cell TER in the presence of leukocytes. Further, live imaging and co-culture studies of HUVECs and leukocytes showed that morphine prevented inflammation-induced structural changes of HUVECs (100ng/ml human TNFα/2hrs) necessary for leukocyte TEM. Finally, assessment of endothelial adhesion molecules (ICAM-1, VE cadherin) and leukocyte adhesion molecules (CD18/ß2 integrin) using Flow Cytometry show that morphine alters tumor necrosis-α or lipopolysaccaride-induced expression, potentially providing a cellular mechanism for the observed reduction in leukocyte recruitment. Taken together, these studies suggest that morphine treatment potentially decreases leukocyte transmigration to reduce angiogenesis associated with tumor growth.

DOPAMINE MEDIATED NEUROINFLAMMATION AND CNS DAMAGE IN THE CONTEXT OF HIV INFECTION: A COMMON MECHANISM OF DRUGS OF ABUSE.

Berma JW, Calderon TM, Lopez L, Williams DW, Coley J, Gaskill PJ, Eugenin EA; Department of Pathology, Albert Einstein College of Medicine, Bronx, NY 10461; Public Health Research Institute, and Department of Immunology and Molecular Genetics, University of Medicine and Dentistry of New Jersey, Newark, NJ 07103.

Our laboratory examines mechanisms that mediate HIV infection and neuroinflammation in the context of substance abuse. As drugs of abuse cause increased CNS dopamine, we use treatment with this neurotransmitter as a model of substance abuse. We and others showed that the mature CD14+CD16+ monocyte population is the cell type vulnerable to HIV infection and that crosses our model of the human blood brain barrier (BBB) and enters the CNS. We demonstrated that dopamine by itself is chemotactic for CD14+CD16+ monocytes as well as induces their transmigration across the BBB. As dopamine does not cross the BBB, we hypothesize that monocytes encounter dopamine once chemotaxis has begun and/or that dopamine affects the cells of the barrier. Dopamine also increases chemokine mediated transmigration of CD14+CD16+ monocytes. While dopamine alone is not chemotactic for T cells, it increases chemokine-mediated T cell transmigration. Thus, dopamine mediates increased neuroinflammation often characteristic of drug abuse. Once within the CNS, CD14+CD16+ monocytes elaborate neuroinflammatory and toxic mediators, and differentiate into perivascular macrophages. We showed that dopamine increases HIV infection of macrophages. Dopamine also alters cytokine production by infected and uninfected macrophages, as well as their phagocytic properties. In concert with chemokines, dopamine may alter junctional proteins that mediate BBB integrity. We propose that CNS dopamine, elevated with ongoing drug abuse, contributes to increased neuropathogenesis in HIV infected people. **Supported by NIDA DA025567; NIMH MH075679 and MH090958.**

ROLE OF ANTIGEN PRESENTING CELLS AND THE CANNABINOID RECEPTORS (CB) 1 AND 2 IN DELTA 9-TETRAHYDROCANNABINOL IMPAIRMENT OF THE INFLAMMATORY RESPONSE TO INFLUENZA INFECTION. Kaminski NE, Karmaus WF, Chen W, Crawford RB, Kaplan BL; the Cell and Molecular Biology Program, the Center for Integrative Toxicology, the Department of Microbiology and Molecular Genetics, the Department of Pharmacology and Toxicology, Michigan State University, East Lansing, MI 48824.

Delta 9-tetrahydrocannabinol (THC) has potent immune modulatory properties and can impair pathogen-induced immune defenses, which in part have been attributed to ligation of the CB1 and CB2. Here dendritic cells (DC) were identified for their potential to enhance influenza-induced immunopathology in mice lacking CB1 and CB2 (CB1-/-CB2-/-). The present study focused on modulation of the inflammatory immune response to influenza by THC and the role of CB1 and/or CB2 as receptor targets for THC. C57Bl/6 (WT) and CB1-/-CB2-/- mice were administered THC (75 mg/kg) surrounding the intranasal instillation of A/PR/8/34 influenza virus. Three days post infection (dpi), THC broadly decreased expression levels of mRNA induced by the innate immune response to influenza, suppressed the percentage of IFN-g-producing CD4+ and IL-17-producing NK1.1+ cells, and reduced the influx of antigen presenting cells (APC), into the lung in a CB1- and/or CB2-dependent manner. THC had little effect on expression of CD86, MHC I, and MHC II by APC isolated from the lung. In vitro studies demonstrated that lipopolysaccharide-induced maturation was suppressed by THC in bone marrow-derived DC (bmDC). Furthermore, antigen-specific IFNg production by CD8+ T cells after co-culture was reduced by THC-treatment of bmDC in a CB1- and/or CB2-dependent manner. Collectively, these studies suggest that THC potently suppresses myeloid cell immune function, in a manner involving CB1- and/or CB2, thereby impairing immune responses to influenza infection. **Supported, in part, by the NIDA DA007908.**

ROLE OF DEPRESSION ON PRO-INFLAMMATORY AND OXIDATIVE STRESS RESPONSES IN HIV-INFECTED PUERTO RICANS. Rivera-Rivera Y, Toro-Rodriguez V, Cappas-Ortiz N, Rivera-Amill V; Department of Microbiology, and Department of Clinical Psychology Ponce School of Medicine and Health Sciences, Ponce, PR 00716.

Depression is the most common psychiatric diagnosis in the HIV/AIDS population and represents a risk factor for poor disease outcomes. We want to study effects of depression on different components related to pro-inflammatory and oxidative-stress markers, which remain unknown in HIV-infected individuals. We hypothesize that depression will lead to increased pro-inflammatory cytokine levels and decreased antioxidant activity. We included males and females, aged 21 years, that were HIV sero-positive with a predetermined plasma viral load, and that were undergoing antiretroviral treatment. Patients completed the participation consent, socio-demographic information, and PHQ-9 (Patient Health Questionnaire-9) for depression assessment. We collected blood samples from participants for analyses of total viral load and T cell counts by RT-PCR. Flow cytometry was used for analysis of pro-inflammatory cytokine levels. We also performed assays for catalase and superoxide dismutase antioxidant activity using commercial kits (Cayman chemicals). According to the socio-demographic data, heterosexual and IDU (injection drug use) was the most common method of HIV infection among men, while heterosexual transmission was the most common method of HIV infection among women; according to the PHQ-9, 3 men and 5 women were depressed and 15 men and 5 women were non-depressed; HIV+ individuals with depression have increased levels of pro-inflammatory cytokines; and HIV+ patients with depression have lower catalase and superoxide dismutase levels when compared with those patients without depression. **Supported by NCRR-P20RR016470, -RCMI/RR003050, PSM&HS Institutional Funds.**

POST-TRANSLATIONAL MODIFICATIONS OF HISTONE H4 IN HUMAN IMMUNODEFICIENCY VIRUS-1 INFECTED HUMAN MACROPHAGES EXPOSED TO METHAMPHETAMINE AND ANTIRETROVIRAL DRUGS. Ciborowski P, Burns A, Olszowy PP; Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198-5800.

Histones play an important role in maintaining and remodeling of chromatin and have positive (activation) as well as negative (repression) effects on transcription regulation. These epigenetic effects of histones are regulated by differential post-translational modifications (PTM), which collectively are called the histone code. Therefore, characterization of the histone code is crucial for understanding cellular processes. In this study we used mass spectrometry to profile PTMs of Histone H4 isolated from human primary monocyte-derived macrophages (MDM) which were infected with HIV-1ADA. Three days after infection, cells were treated with methamphetamine (Meth) at a concentration of 100 µM. Two days after exposure to Meth, cells were treated with combinational antiretroviral therapy (cART – atazanavir, tenofovir, emtricitabine), all at a concentration of 5 µM. Five days later cells were harvested, histones were isolated to quantify changes in Histone H4 acetylation, mono-, di- and trimethylation and phosphorylation in these cells. Using proteomic approach we identified all reported biologically relevant acetylations in the N-terminal tail of Histone H4. We also found acetylation of asparagine at position 25 (25NAc), which until now has not been reported. Using a spectral-count approach, we have shown that exposure of macrophages to Meth and HIV infection led to significant decrease of 25NAc modification. Our results show that epigenetic regulation of MDM function may involve much more diverse mechanisms than previously postulated. This is the first systematic profiling of Histones in this context.

DUAL MECHANISM ENHANCED BBB CROSSING BY TRANSFERRIN CONJUGATED FLUORESCENT MAGNETIC LIPOSOME. Ding H, Agudelo M, Kanthikeel SP, Guduru R, Sagar V, Atluri V, Thangavel S, Nair MN; Department of Immunology, Florida International University, Miami, FL 33199.

Nanotechnology may bring a revolution for controlled CNS delivery. In our study, the dual mechanisms of receptor mediation and outer magnetic force were incorporated into fluorescent stealth liposomal iron oxide nanocarriers for BBB transmission enhancement. The ultra-small iron oxide magnetic nanoparticles were synthesized within ~7.0 nm by TEM. With the XRD assay, the dynamic scattering laser (DSL) illustrated the unique mono-dispersion in aqueous solution and narrow size-distribution of magnetic particles after they were encapsulated in liposomes, ~130±5.5 nm by extrusion. The optimized fluorescent magnetic liposomal formulation can keep luminescent stability and hydrodynamic size for over 2 months. The simulated capillary pressure experiment confirmed the physical colloid stability of magnetic liposome through at least 120 rounds. With a satisfied biocompatibility assay, the fluorescent magnetic liposome was conjugated with Transferrin and applied for BBB crossing studies. Using an in vitro BBB model, the dual mechanism transmigration of Transferrin mediation and outer magnetic force had significant advantage comparing with only Transferrin conjugates or liposome (2.2 and 2.8 times higher, respectively, after 2h of treatment) without affecting BBB integrity. The cellular iron-concentration in BBB also had a higher uptake from synergic dual mechanism treatment (2.4±0.4, 1.8±0.08 and 1.0±0.3 pg Fe/cell, for dual treatment, Transferrin mediation and only magnetic liposome, respectively, $P<0.05$). The fluorescent confocal and in vitro MRI images also confirmed this dual synergic effect. **Supported by NIH/1R01DA027049.**

BRAIN CELLS MODULATE ENCEPHALITOGENIC T-CELL RESPONSES VIA PD-1: PD-L1. Hu S, Schachtele SJ, Mutnal MB, Sheng WS, Lokensgard JR; Center for Infectious Diseases and Microbiology Translational Research, University of Minnesota, Minneapolis, MN 55455.

Engagement of programmed death (PD)-1 on activated cells by its ligand (PD-L1 [B7-H1] or PDL-2) has been shown to be a mechanism which suppresses T-cell responses, commonly referred to as T-cell exhaustion. In this study, we investigated the role of this second-signal pathway in controlling encephalitogenic T lymphocytes which infiltrate the brain to manage infection with murine cytomegalovirus, but which may also drive bystander neurotoxicity. Our data demonstrated that the PD-1 molecule was highly expressed on CD8+ T lymphocytes isolated from the brain at 30 d p.i. and that PD-L1 was up-regulated on approximately 86% of microglial cells isolated from these same animals. In addition, immunohistochemical analysis of infected brain tissue demonstrated a marked up-regulation of PD-L1 on both microglia and astrocytes. Correspondingly, primary murine microglial cell and astrocyte cultures expressed very low levels of PD-L1 mRNA under basal conditions which was up-regulated >250-fold following treatment with IFN-r. Most interestingly, blockade of this pathway using antibodies to either PD-1 or PD-L1 stimulated IFN-r production in primary murine astrocyte: CD8+ T-cell co-cultures. These data demonstrate that brain cells use this second-signal pathway to control T-cell responses and suggest a therapeutic potential of PD1: i.e., PD-L1 modulation to manage the deleterious consequences of uncontrolled immunity within the brain. **Supported by MH-066703, NS-038836.**

FEASIBILITY OF THE CONDITIONAL DEPLETION OF MOUSE MICROGLIA: IMPLICATION FOR HUMANIZED MOUSE MODEL IMPROVEMENT. Knibbe J, Gutti T, Akhter S, Bade A, Liu Y, Gorantla S, Poluektova L; University of Nebraska Medical Center, College Of Medicine / PEN Department, Omaha, NE 68114.

The modeling of human microglial development represents an attractive goal for improvement of a humanized mouse model for HIV-1 research. The depletion of mouse microglia is one of the prerequisites for the transplantation and expansion of human microglial cells in the mouse brain. To test this, immune competent mice carrying a transgene encoding simian diphtheria toxin receptor (DTR) under control of a CD11b promoter were utilized. Newborns were injected intraventricularly with DT, and the dose-dependent survival and mouse microglial depletion (Iba-1+, CD11b+ cells) were analyzed by immunohistology (24h, 3 and 6 days) and real-time PCR (1, 2 and 4-6 weeks) post injection. Survival rate was from 50-70%. The injection of DT induced a uni- and partial bilateral decrease of microglia cell number, and by 1 month, CD11b expression in the brains was not restored to the control levels in transgenic mice. Nine transgenic microglia-depleted mice were observed up to 6 months of age and the later consequences of depletion (reduced brain volume and neuronal abnormalities) were analyzed by manganese enhanced MRI. These studies confirm that mouse microglia can be partially depleted at birth and such depletion affects brain development. The transfer of a CD11b-driven DTR transgene on an immunocompromised NSG background will allow us to combine the humanization of mouse bone marrow and immune system with an efficient repopulation of the brain by human cells. **Supported by the University of Nebraska Medical Center.**

OPIATES DEACTIVATE REDOX-SENSITIVE STRESS RESPONSE PROGRAM IN T CELLS. Husain M, Rehman S, Chandel N, Lan X, Malhotra A, Singhal PC; Department of Biotechnology, Jamia Millia Islamia, New Delhi, 110025; Feinstein Institute for Medical Research, Hofstra North Shore LIJ Medical School, Great Neck, NY 11021.

Patients with opiate addiction have been reported to develop loss of T cells. Recently, a pivotal role of p66ShcA protein has been identified in generation of oxidative stress and induction of T cell apoptosis. We hypothesized that morphine would stimulate the p66ShcA pathway which would deactivate the redox-sensitive stress response program (RSSRP). In the present study, we examined the effect of morphine on activation of the RSSRP in T cells, both *in vitro* and *in vivo*. Morphine promoted ROS generation, which was associated with T cell apoptosis. This effect of morphine was attenuated in T cells lacking p66ShcA as well as cells pre-treated by antioxidants such as SOD and catalase. Moreover, morphine enhanced T cell expression of phspho-p66ShcA and phospho-Foxo3A. Morphine also enhanced expression of proapoptotic molecules by T cells such as BIM1 and FASL. In *in vivo* studies, mice receiving morphine not only showed enhanced splenic tissue ROS generation, apoptosis, and expression of phospho-p66ShcA and phospho-Foxo3A, but, also, displayed diminished production of antioxidants such as SOD and catalase. These findings indicate that morphine stimulated the p66ShcA pathway which deactivated RSSRP and resulted in accumulation of ROS by attenuating antioxidant generation. Accordingly, these processes facilitated T cells to assume an apoptotic phenotype.

METHAMPHETAMINE ALTERS GAP JUNCTIONAL COMMUNICATION BETWEEN NEURONS AND ASTROCYTES: POTENTIAL ROLE IN CNS COMPROMISE AND DRUG DEPENDENCY. Eugenin E, Nosanchuck J, Martinez L, Castellano P; Microbiology and Molecular Genetics, and the Public Health Research Institute, UMDNJ, Newark, NJ 07103; Department of Biomedical Sciences, Albert Einstein College of Medicine (Long Island University-Post, Brookville, NY) Bronx, NY 10461.

Methamphetamine (Meth) is an extremely addictive central nervous system stimulant abused by individuals worldwide. The intoxicating effects of METH alter judgment and reduce inhibitions, leading people to engage in unsafe activities that put them at risk for acquiring transmissible diseases, including HIV and others pathogens. These alterations in judgments and susceptibilities to infection are associated with mental and physiological alterations in the brain. However, the mechanisms that alter central nervous system (CNS) physiology in response to Meth treatment are not fully explored. Gap junction channels are crucial in coordination of electrical and chemical synapses by providing direct intracellular communication between connected cells. Loss of gap junctional communication is associated with cellular damage and inflammation that compromise CNS function. Our data demonstrated that Meth treatment of mice as well as human primary cultures of astrocytes and neurons result in disruption and loss of gap junctional communication. Thus, our data provide an additional mechanism by which Meth alters CNS function and toxicity by regulating trafficking of Cx43 and Cx3. **Supported by NIMH (MH096625 and MH076679); and a CFAR pilot project.**

HIV INFECTION OF ASTROCYTES INCREASED RELEASE OF DICKKOF-1 (DKK1) PROTEIN BY A HEMICHANNEL-DEPENDENT MECHANISM. Eugenin E, Orellana JA, Saez JC, Bennett M, Berman J, Morgello S; Microbiology and Molecular Genetics, Public Health Research Institute (PHRI)/UMDNJ, Newark, NJ 07103; Departamento de Fisiología, Pontificia Universidad Católica de Chile, Santiago, Chile; Centro Interdisciplinario de Neurociencias de Valparaíso, Valparaíso, Chile; Neuroscience, Pathology, and Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, NY 10461; Neurology, Mount Sinai Medical Center, NY, NY 10010.

Human immunodeficiency virus-1 (HIV) is a major public health issue often complicated by NeuroAIDS. In *vivo*, microglia/ macrophages are the main cells infected. However, a low but significant number of HIV-infected astrocytes also has been detected, but their role in the pathogenesis of NeuroAIDS is not well understood. Our previous data indicate that gap junction channels play a key role in amplifying toxicity from infected astrocytes. Now, we demonstrate that HIV infection of astrocytes results in opening of connexin43 hemichannels (Cx43 HCs). Opening of Cx43 HCs led to expression and secretion of dickkopf-1 protein (DKK1, a soluble wnt pathway inhibitor) resulting in neuronal compromise and damage. **Supported by NIMH MH096625 to EAE.**

HUMAN NEUROGENESIS IN NSG MICE FOR HAND PATHOGENESIS STUDIES.
Akhter SA, Knibbe J, Wu L, Li Y, Peng H, Gorantla, S, Poluektova LY; University of Nebraska Medical Center, Department of Pharmacology and Experimental Neuroscience, Omaha, NE 68198.

To study the direct influence of chronic HIV-1 infection on human neurogenesis, astrocyte, and microglia development we tested approaches to engraft human neuronal progenitor cells (NPC), fetal neurons, astrocytes and microglia into the brain of NOD/scid IL-2R common gamma chain knockout (NSG) mice, at birth. Transplantation of *in vitro* expanded NPC in irradiated NSG mice, at birth, into the lateral ventricle resulted in stable engraftment and enrollment of human neuroblasts in the ventriculo-olfactory neurogenic system, minimal integration in the hippocampal neurogenic niche, and absence of caudal migration (reproding results of Uchida et al., 2000). We also assessed efficacy of the engraftment of three different human fetal brain cellular populations derived from one-week-old brain cell cultures. The microglial progenitors were cultured in an M-CSF-containing medium, astroglia were cultured in a serum-containing medium, and neuronal progenitors (NP) were cultured in aserum-free medium. By 3 months of age, efficient engraftment in 15 of 19 mice was found. Mice had different patterns of repopulation and cells were found mainly in periventricular regions and meninges. Human cell aggregates in mouse brain contained at least three types of cells depending on transplanted cells: neurons, astrocytes and microglia/macrophages. We concluded that both approaches can be combined with transplantation of syngeneic human hematopoietic stem cells, at birth, and HIV-1 infection of blood/brain humanized mice. **Supported by NIH 5P01 NS043985-08.**

ANKYRIN-RICH MEMBRANE SPANNING PROTEIN (ARMS) PLAYS A CRUCIAL ROLE IN HIV-1 TAT-INDUCED ACTIVATION OF MICROGLIAL CELLS. Wooten AK, Jackson J, Kiebala M, Maggirwar SB; Department of Microbiology and Immunology, University of Rochester School of Medicine and Dentistry, Rochester, NY 14642.

Long-term consequences of HIV-1 infection in patients involve a wide range of cognitive dysfunctions, known collectively as HIV-1 Associated Neurocognitive Disorders (HAND). Microglia, which are the resident immune cells in the brain, can be directly infected by HIV-1, and can also secrete multiple proinflammatory molecules upon their activation, which contribute to the pathogenesis of HAND. Indeed, the number of activated macrophage and microglia in the brain is more highly correlated with cognitive impairment than the amount of neuronal apoptosis, suggesting that inflammation by immune cells significantly contributes to HAND. ARMS/Kidins220 is a transmembrane protein that is involved with neurotrophin signaling in the CNS. ARMS is important for neuronal survival through its involvement in signaling pathways such as MAPK and NF-KB. In addition to neurons, multiple immune cell types such as T-cells and dendritic cells have recently been shown to express ARMS. Using immunoblot analysis, we show that BV-2 cells, a mouse microglia cell line, and primary human microglia express ARMS. We investigated the role of ARMS in microglial cells upon exposure to HIV-1 proteins. In BV-2 cells transduced with a lentivirus encoding ARMS shRNA, we noted loss of ARMS expression, followed by a marked reduction in HIV-1 Tat-induced proinflammatory responses, such as TNF-alpha production and NF-KB signaling. Our results implicate ARMS in microglial activation by viral proteins and warrant additional studies to better understand the molecular mechanisms underlying progression of HAND. **Supported by NIH grant R01 NS066801.**

LPS INDUCES IMMUNE ACTIVATION AND SIV REPLICATION IN CHINESE RHESUS MACAQUES. Li J-L, Bao R, Guo M, Ye L, Zhang J, Dai M, Rao Y, Wang Y, Xian Q-Y, Huang Z-X, Tang Z-J, Persidsky Y, Ho W-Z; The Center for Animal Experiment/Animal Biosafety Level III Laboratory, Wuhan University School of Medicine, Hubei, 430071; State Key Laboratory of Virology, Wuhan University School of Medicine, Wuhan, PA 430071; Department of Pathology and Laboratory Medicine, Temple University School of Medicine , Philadelphia, PA 19140.

Chronic immune activation is a hallmark of progressive HIV infection and a major factor of disease progression. Bacterial lipopolysaccharide (LPS) in the circulation has been implicated as a key factor in HIV-related systemic immune activation. We thus investigated the impact of LPS on systemic immune activation in simian immunodeficiency virus (SIV) infected Chinese rhesus macaques (CRMs). Animals inoculated with either SIVmac239 or SIVmac251 became infected as evidenced by the increased plasma SIV RNA and decreased CD4/CD8 ratio. The plasma viral loads reached peak levels at week-2 post-infection and then declined to stable levels that occasionally fluctuated during the course of infection. The CD4/CD8 ratios had a ~50% drop at the early stage of infection (20 days post-infection) and subsequently recovered to stable levels that were still lower than those prior to infection. Intravenous administration of LPS induced a transient immune activation, which was indicated by elevated expression of IL-6, IL-8, IFN-alpha, TNF-alpha, and TLR4 in PBMC from treated animals. LPS treatment of infected animals also resulted in a transient and significant increase of viral load in both plasma and cerebrospinal fluid (CSF). These data demonstrated that LPS induced immune-activation and SIV-replication in CRMs suggesting that LPS may affect immunopathogenesis of HIV disease. **Supported by NIH/NIDA DA012815, DA027550, DA022177 to WZH.**

ETHANOL DOWN REGULATES T CELL VITAMIN D RECEPTOR THROUGH MODULATION OF EPIGENETIC FACTORS. Lan X, Chandel N, Lederman R, Valecha G, Malhotra A, Singhal PC; Feinstein Institute for Medical Research, Hofstra North Shore LIJ Medical School, Great Neck, NY 11021.

Alcoholics are prone to recurrent bacterial infections. This effect of ethanol has been attributed to occurrence of lymphopenia in this population. We have recently reported that ethanol stimulates T cell apoptosis through down-regulation of T cell vitamin D receptor (VDR) and associated activation of the renin angiotensin system. In the present study, we evaluated the role of epigenetic factors in ethanol-induced attenuated T cell VDR expression. RNA was extracted from T cells treated with ethanol (25 and 50 mM) and probed for HDAC (histone deacetylase) 1-6, DNMT (DNA methyl transferase) 1, DNMT2, DNMT3a, and DNMT3b. Also, Protein was extracted and probed for CYP24 (metabolizes vitamin D3 [VDR agonist]). The results showed that ethanol down-regulated T cell VDR expression in a dose dependent manner while promoting expression of both DNMT3a and DNMT3b. Ethanol also down-regulated expression of HDAC1, HDAC2, and HDAC3. It appears that ethanol-induced activation of DNA methyl transferases and simultaneous inhibition of deacetylation of histones contributed to down-regulation of T cell VDR expression. Interestingly, ethanol enhanced T cell expression of CYP24. It is likely that CYP24-induced reduction of vitamin D3 might also have contributed to down-regulation of VDR expression in T cells. These findings suggest that ethanol down-regulatess T cell VDR expression by modulation of epigenetic factors while enhancing expression of CYP24.

CYTOKINE PROFILES IN ANTIRETROVIRAL TREATED MACROPHAGES AND ASTROCYTES. King J, Chan J, Jordan-Sciutto K; Department of Pathology, University of Pennsylvania, Philadelphia, PA 19104.

Cytokines are important orchestrators of host defenses including immune and inflammatory responses and are strongly correlated in HIV neuropathogenesis. Recent studies have linked sequestration of replication-competent HIV in latently infected cells with a burst of inflammatory cytokines in the acute stages of infection. Following the acute phase of infection, a robust anti-inflammatory response ensues which could be a factor in development of long-lived latently infected cells. This is critical for the chronically infected HIV population in which HIV persists in tissue resevoirs despite suppression of replication by antiretroviral (ARV) therapy. Thus, we hypothesized that ARV drugs may alter cytokine profiles contributing to the persistence of HIV-infection in patients. Using the fluorescent based Luminex cytokine analysis, we quantified both anti-inflammatory and pro-inflammatory cytokines in human monocyte derived macrophages (MDMs) and primary rat astrocytes treated with ARVs: ritonavir, lopinavir and nevirapine. Our data demonstrated a time-dependent increase in pro-inflammatory cytokines, IFN-γ, TNF-α, IFN-α and IL-6 from MDM treated with these ARVs compared with vehicle-treated controls. There was also a concomitant, sustained increase in IL-10 whose anti-inflammatory properties have been associated with viral persistence. These findings provide new insight into the possible expression profiles of cytokines in ARV-treated patients as well as the implications of these factors on viral production and HIV latency. **Supported by NIH 1R01 MH098742-01, 2K12 GM081259-06.**

HIV-1 VIRAL PROTEINS DISRUPT NEURON AUTOPHAGY FUNCTION AND AUTOPHAGOSOME FORMATION: MECHANISMS IN HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS. Fields J, Dumaop W, Adame A, Masliah E; Department of Pathology, University of San Diego, California, La Jolla, CA 92093.

HIV-1 infection persists in the era of effective antiretroviral therapy, including over 1 million infected in the United States. The increasingly large portion of infected individuals over the age of 50 is particularly susceptible to HIV-1 associated neurocognitive disorders (HAND). Despite recent advances, new therapies are needed to prevent and treat HAND. Our group reported altered autophagy protein levels in postmortem brains of persons with HIVE; autophagy proteins were increased in young HIVE patients but decreased in aged HIVE patients. Since, studies have shown that HIV-1 proteins directly bind and block autophagy-protein function in monocyte derived cells. The mechanisms by which HIV-1 infection leads to dysregulated autophagy in the CNS, and the effects on neurons remain unknown. In the current studies we sought to determine if HIV-1 recombinant proteins affect neuronal autophagy. Neuronal cells were treated with recombinant HIV-1 proteins (gp120, nef and tat) with or without autophagy inducers and inhibitors for variable time periods and concentrations. Of the three proteins tested, Tat significantly reduced LC3-II and p62. Bafilomycin treatment increased LC3-II and p62 levels, but this increase was partially blocked by tat treatment. Tat-treated B103 cells showed altered autophagosome structure compared to untreated cells. These data suggest tat protein may initially induce autophagy and LC3-II degradation, and explain, in part, increased autophagy markers in young HIVE patients. These findings may lead to preventative treatments for young HIV patients. **Supported by NIMH (MH062962, MH5974, MH83506) and NIA (AG043384).**

CALPAIN-MEDIATED DEGRADATION OF MDMX/MDM4 EXPRESSION CONTRIBUTES TO HIV-INDUCED NEURONAL DAMAGE. Akay C, Colacurcio D, Daniels M, Kolson DL, Jordan-Sciutto KL; Department of Pathology, School of Dental Medicine, and the Department of Neurology, The Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104.

Neuronal damage in HIV-associated Neurocognitive Disorders (HAND) has been linked to inflammation induced by soluble factors released by HIV-infected, and non-infected, activated macrophages/microglia (HIVM/M) in the brain. It has been suggested that aberrant neuronal cell-cycle activation determines cell fate in response to these toxic factors. We have previously shown increased expression of cell cycle proteins such as E2F1 and phosphorylated pRb in HAND midfrontal cortex in vivo and in primary neurons exposed to HIVM/M supernatants in vitro. Here, we demonstrate that MDMx/MDM4, a cell cycle regulatory protein, is significantly reduced in HAND brains. Additionally, HIVM/M treatment of primary rat neuroglial cultures led to a calpain-dependent degradation of MDMx and decreased neuronal survival, while over-expression of MDMx conferred partial restoration of neuronal survival. Further, blocking MDMx activity led to neuronal death *in vitro* in the absence of toxic stimulus, which was reversed by calpain inhibition. Finally, pRb bound to, and directly blocked calpain-mediated MDMx degradation *in vitro*. Our results demonstrate that MDMx is a novel and direct calpain substrate. Further, MDMx plays a pro-survival role in neurons, and strategies to stabilize and/or induce MDMx by pharmacological or genetic approaches can provide neuroprotection in HAND and in other neurodegenerative diseases where calpain activation contributes to neuropathogenesis. **Supported by NS41202 (KJS) and MH095671 (DLK).**

ASHWAGANDHA (WITHANIA SOMNIFERA) REVERSES B-AMYLOID INDUCED NEURONAL TOXICITY: IMPLICATIONS IN HAND. Kurapati VKR, Atluri VSR, Samikkannu T, Yndart AA, Nair MPN; Immunology, Florida International University, College of Medicine, Miami, FL 33199.

Alzheimer's disease (AD) is characterized by progressive dysfunction of memory and higher cognitive functions with abnormal accumulation of extracellular amyloid plaques and intracellular neurofibrillary tangles throughout cortical and limbic brain regions. At present no curative treatment is available, and research focuses on drugs for slowing disease progression or providing prophylaxis. *Withania somnifera* also known as 'ashwagandha' is used widely in Ayurvedic medicine as a nerve tonic and memory enhancer. However, there is a paucity of data on the potential neuroprotective effects of *W. somnifera* against β-Amyloid(1–42)-induced neuropathogenesis. In the present study, we have tested the neuroprotective effects of ashwagandha against β-Amyloid induced toxicity using a human neuronal SK-N-MC cell line. First, Methanol:Chloroform (3:1) extract was prepared from the dried roots of *W. somnifera* and subjected for LC-MS analysis. The LC-MS fingerprint showed the presence of alkaloids and steroidal lactones, the most prominent being Withanolide A. This extract was used for all studies. The cultures stained with Giemsa as well as Sulphorhodamine showed clearly that β-amyloid induced cytotoxic effects in SK-N-MC cells with decreased cell growth when tested individually. However, when ashwagandha was added to β-amyloid treated samples, the cytotoxic effects of β-amyloid were neutralized. The MTT cell viability assays and confocal studies supported these findings showing the chemopreventive or protective effects of ashwagandha against β-amyloid induced toxicity. **Supported by NIH.**

CHARACTERIZATION OF SINGLE NUCLEOTIDE POLYMORPHISMS OF THE HUMAN ALPHA7 NICOTINIC RECEPTOR REVEALS ALTERATIONS IN FUNCTIONALITY AND RESPONSE TO BUPROPION: POTENTIAL IMPLICATIONS TO THE PATHOGENESIS AND TREATMENT OF HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS. Báez-Pagán CA, Aviles-Pagán E., Aponte-Santiago NA, Holder-Viera M, Lasalde-Dominicci JA; Department of Biology, University of Puerto Rico, Río Piedras Campus, San Juan, PR 00931.

The α7 nicotinic acetylcholine receptor (nAChR), a ligand-gated ion channel characterized by its high calcium permeability, was shown to be up-regulated in SH-SY5Y cells exposed to HIV-1 glycoprotein gp120 leading to Ca2+ overloading and cell death. These results suggest that HIV-associated neurocognitive disorders (HAND) could be related to increased neuronal death as result of excessive Ca2+ influx through the up-regulated α7 nAChR. They also suggest that α7 nAChR antagonists, such as bupropion, can be exploited for neuroprotection in HIV-1 seropositive patients. The rationale for using antagonists is that by interfering with up-regulated α7 nAChR activity, antagonists should reduce Ca2+ overloading and concomitant cell death. Genetic variants of the CHRNA7 gene (encodes α7 nAChR) that result in ion channels with increased expression and/or functionality could thus underlie increased risk of HAND. In addition, CHRNA7 genetic variants could also result in receptors with diminished response to antagonists. The hypothesis of this study is that non-synonymous single nucleotide polymorphisms (SNPs) located in the CHRNA7 gene could result in α7 nAChRs with enhanced functionality and/or expression levels, and with altered responses to drugs aimed at interfering with the excessive Ca2+ flow. Bupropion was studied as a model α7 nAChR antagonist. Herein we present data demonstrating that genetic variants of the CHRNA7 gene may result in α7 nAChRs with altered functionality and response to bupropion. **Supported by NIMH P30MH075673-07 and NIMHD 8U54MD007587-03.**

GENOMIC SIGNATURE OF PPAR AGONISTS IN BRAIN AND LIVER: ROLE IN ALCOHOL CONSUMPTION. Ferguson LB, Blednov YA, Harris RA; Waggoner Center for Alcohol and Addiction Research, University of Texas at Austin, Austin, TX 78712.

Accumulating evidence supports a neuroimmune hypothesis of addiction (Blednov and Harris, this meeting). Although originally prescribed for hyperlipidemia and diabetes, PPAR agonists are anti-inflammatory and neuroprotective and also decrease alcohol and nicotine self-administration (Ridder and Schwaninger, 2012, Panlilio et al., 2012, and Stopponi et al., 2011). We showed that PPAR agonists Tesaglitazar, Fenofibrate, and Bezafibrate decreased ethanol consumption with high, moderate, and low efficacy, respectively. In this study we gave daily oral injections of these three PPAR agonists to male C57BL/6 mice for 8 consecutive days and collected liver, prefrontal cortex, and amygdala 24h after the last injection. RNA was isolated and amplified cRNA was hybridized to Illumina MouseWG-6 v2.0 Expression microarrays. Expression profiles showed, for the first time, that PPAR agonists affect brain gene expression. Functional annotation showed lipid metabolism and immune genes were up-regulated in liver and genes for synaptic plasticity and transmission regulation were up-regulated in PFC and Tesa-treated AMY. Our results show that three different PPAR agonists produce changes in brain and liver gene expression with clear and unexpected specificity that may be related to their ability to decrease ethanol consumption. **Supported by NIAAA (AA U01 13520 - INIA Project; AA06399).**

MORPHINE IMPAIRS LYSOSOMAL ACIDIFICATION LEADING TO COMPROMISED BACTERIAL KILLING. Anand V, Koodie L, Banerjee S, Roy S; Division of BTR/Department of Surgery, University of Minnesota, Minneapolis, MN 55455; Dentistry, Pharmacology, University of Minnesota, Minneapolis, MN 55455.

We have shown in previous studies that morphine increases susceptibility to opportunistic infections. In the current study, we determined if the underlying mechanisms may be due to compromised bacterial killing and clearance. Furthermore, we also investigated if decreased bacterial uptake, defective phagolysosomal formation, impaired lysosomal acidification, decreased proteolytic activity of enzymes or impaired reactive oxygen intermediates formation also contributes in morphine's defect. We propose that defective bacterial clearance occurs because of a defect in lysosomal acidification in macrophages mediated by inhibition of CFTR chloride channels. We observed a significant decrease in lysotracker red fluorescence in morphine-treated J774.16 and RAW 264.7 macrophage lines compared to saline following infection with GFP tagged E.coli at 45 min. TRITC/DAPI fluorescence per cell of confocal images was significantly ($p < 0.05$) lower in the morphine group compared to saline. The results were confirmed by flow cytometry. These results suggest that impaired lysosomal acidification may be a major contributing factor underlying morphine's effect on bacterial clearance. The role of TLR in mediating morphine induced changes in lysosomal pH is currently under investigation. **Supported by RO1 DA12104, RO1 DA022935, RO1 DA031202, K05DA033881, P50 DA011806, R01 DA034582.**

HIV-1 CLADE B EXPRESS NEURONAL APOPTOTIC PROTEOMIC FINGERPRINTS.

Alves JM, Carrero RJ, Rodriguez M, Lopez SN, Cubano L, Boukli N M; Biomedical Proteomics Facility - Department of Microbiology and Immunology, Universidad Central del Caribe, Bayaman, PR 00960.

In the current study, we hypothesize that HIV-1 clade B and C induce differential protein expression in a human neuronal cell line leading to significant differences implicated in neuroAIDS. By a combination of 2D gel electrophoresis, which separated hundreds of proteins from neurons treated with HIV-1 clade B and C for quantitative comparison, with mass spectrometry (MS), we could identify proteins showing altered expression mainly in oxidative stress, protein folding, modification proliferation, apoptosis and anti-apoptosis. Proteins of relevance were further verified with RT-PCR. In this study, 164 and 214 proteins were differently modulated with treatments using HIV-1 clade B and C strains respectively, when compared to control. Among these regulated proteins, HIV-1 clade B, significantly up-regulates BRDA1 and oligodenylate synthetase. BRDA1 is an upstream regulator of oligoadenylate synthase, which activates the downstream RNAse L leading to apoptosis. HIV-clade C up-regulates ankyrin repeat and SOCS which use a classical negative feedback to inhibit JAK-STAT signal transduction and inhibit apoptosis. Thus, our results suggest that HIV-1 clade B and C differentially modulate expression of apoptotic molecules that may be correlated with differences in neuroAIDS manifestation induced by clade-specific infections. **Supported by NIMHD 8G12MD007583.**

LONGITUDINAL STUDY OF HIV-1 INDUCED NEUROPATHOGENESIS IN HUMANIZED NOD/SCID-IL 2RECEPTOR GAMMA CHAIN-NULL (NSG) MOUSE MODEL. Potula R, Zuluaga-Ramirez V, Reichenbach N, Cenna JM, Persidsky Y; Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140.

Small animal models of HIV-1 infection were used to study HIV-1 induced pathogenesis. However, longitudinal studies in humanized NSG mice are limited. In this ongoing study, NSG mice engrafted with CD34+ stem cells demonstrated a high percentage of the human cell chimerism indicating continued persistence of engraftment 6 months post transplantation. After intravenous (i.v.) inoculation with HIV-1, virus was detected in plasma by 1-week post infection (p.i.). CD8+ cell depletion was carried out 3 weeks p.i. in half of the HIV+ NSG mice. Although the set-point viral loads of CD8-HIV+ mice were significantly higher prior to CD8 depletion, immediately following it, virus replication (plasma viral load) plateaued, although virus titers subsequently increased at later time points. The humanized NSG mice showed long-lasting viremia after 3 months p.i. with gradual decline of the CD4+T cells and up-regulation of activation marker, CD69. At 62 days p.i., neuropathological analyses demonstrated more prominent microglial reaction in HIV+ animals compared to controls, and few microglial cells were p24+. HLA-DR+ cells were found in perivascular spaces and meningeal microvessels, while there was no CD8+ infiltration in brain parenchyma. Spleens demonstrated germinal center formation, expected distribution of CD3+ lymphocytes and CD68+ macrophages, but no evidence of CD21 follicular dendritic cells. Spleens of HIV-infected animals featured p24+ cells. In summary, humanized i.v. infected NSG mice are a reliable and relevant model to preform longitudinal studies in HIV-1 infection. **Supported by NIMH/R01 MH065151, NAED/R01 DA025566, NEAD/R01 DA031064.**

METHAMPHETAMINE (METH) MEDIATED IMMUNE DYSREGULATION IN AN ANIMAL MODEL OF CHRONIC VIRAL INFECTION. Haldar B, Cenna JM, Gofman L, Potula R; Department of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140.

A general characteristic of the adaptive immune response is its ability to mount a robust response to infection. Lymphocytic choriomeningitis virus (LCMV), as a model pathogen for the study of virus-induced immunopathology, enables investigation of mechanisms underlying T cell dysfunction during infection. Given the lack of understanding of putative mechanisms of immune dysfunctions in the setting of METH abuse and chronic viral infection, the present study investigated the combined effects of METH and chronic viral infection on T cell homeostasis and immune functions. C57BL/6 mice were administered a gradual escalating METH dose from 0.45 - 10 mg/kg over 6 days, followed by a single dose of 10 mg/kg/day until the mice were killed. When intravenously injected with LCMV clone 13 (2x106 PFU), both LCMV control and LCMV/METH mice (7 days post exposure) developed persistent viral infection as assessed by plasma viral load. Chronically-infected LCMV mice that were exposed to METH showed a reduced MHC class-I restricted LCMV-specific CD8 T cell response. Furthermore, METH exposure altered: levels of T cell activation and differentiation markers (CD44, CD25, EGF, CD62L, CD27, CXCR3, CCR7, PD1 and CD69); T cell cytotoxic functions (perforin, CD107a and granzyme B); markers of regulatory function of Th-1 (IL-2, IFN-γ, TNF-α), and Th-2 cytokines (TGF-β). Our study provides evidence that METH abuse results in phenotypic and functional changes in the T cell population which are crucial to elicit an antiviral immune response, thereby contributing to immune dysfunction of the host. **Supported by NIH grant R01 DA031064 to RP.**

NEONATAL ETHANOL EXPOSURE CAUSES LONG-TERM ALTERATION IN MICROGLIA SENSITIVITY AND RESPONSE TO STRESS. Franklin T, Sarkar DK; Endocrine Program, Rutgers University, New Brunswick, NJ 08901.

Fetal alcohol exposure has many detrimental effects on the developing brain and has been known to cause fetal alcohol spectrum disorder. Many of these patients show lifelong stress response abnormalities. Microglia, which are long-lived self-replenishing CNS immune cells, can initiate and perpetuate stress activation by releasing pro-inflammatory cytokine. It has been shown that microglia stimulation and activation can alter their responses to subsequent stimuli. We hypothesized that ethanol exposure during early development programs hypothalamic microglia to become more sensitize to subsequent stimuli in adulthood. Using the postnatal rat model, which is equivalent to the human third trimester, we treated newborn male pups to ethanol or control diet for 5 days from postnatal day (PD)2-6 and paired the alcohol group with another which received the microglia blocker minocycline. The pups were left to grow into adulthood and exposed to a single lipopolysaccharide (LPS) challenge at PD90. We found that neonatal ethanol exposure causes a hyper stress response to LPS, as determined by elevated plasma levels of corticosterone and adrenocorticotropin. Minocycline treatment reduces the hyper stress response in fetal alcohol exposed animals. Minocycline also reduces a fetal alcohol-induced increase in the levels of TNF-alpha and activated microglia in the paraventricular nucleus of the hypothalamus. These data suggest that ethanol exposure the during developmental period results in long-term alterations in stress response that may partially be due to over-sensitized microglia. **Supported by NIH R37AA08757.**

EFFECT OF HIV-1 SUBTYPE C INFECTION ON IMMUNE AND NERVOUS SYSTEM FUNCTION AND BIOLOGY IN A HUMANIZED MOUSE MODEL OF HIV/AIDS.

Makarov E, Adem S, Wood C, Poluektova L, Gendelman HE, Gorantla, S; Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198; Nebraska Center for Virology, University of Nebraska at Lincoln, Lincoln, NE 68583.

The role that different HIV-1 clades play in viral transmission and disease pathobiology remains incompletely understood. To this end, we used our novel humanized mouse model of NeuroAIDS to assess immune and central nervous system (CNS) pathologies linked to clade-specificity. Differences in clade-specific virulence, cytopathicity and neurotoxicity were monitored. NOD/scid-IL-2R cnull (NSG) mice reconstituted with functional human immune system allows for chronic HIV-1 infection. NSG mice reconstituted at birth with human CD34+ stem cells were infected at 22wk of age either with clade B (HIV-1ADA) or C (C1157) viruses. Blood was collected at 2,4,6,8 wk to determine viral load (VL), human CD4+ T cells, and levels of immune activation. At endpoint, brains were collected for quantitative immunohistology. We show that rates of CD4+ T cell depletion were reduced in clade C compared to B infections. T cell activation (percentage of CD4+CD38+ cells) was higher in clade C, with lower T cell exhaustion (CD4+PD-1+). The latter correlated to a higher number of splenic CD4+Ki67+ cells. Increased meningeal infiltration with immune cells was seen in clade C-infected mice. We conclude that higher immune activation and T cell turnover in clade C infection might be contributing to both a slower rate of CD4+ T cell depletion and immune cell infiltration into the nervous system. Humanized mice provide novel insights into clade-specific pathobiology of HIV-1 disease. **Supported by 5P01 NS043985-07, 5R01 NS076386-01.**

SERUM DETECTION OF SHED EXTRACELLULAR MICROVESICLES FROM BRAIN ENDOTHELIAL CELLS: SEROLOGICAL INDICATORS OF BLOOD BRAIN BARRIER (BBB) DISRUPTION DURING NEUROINFLAMMATION. Ramirez SH, Persidsky Y, Rom S, Dykstra H; Department of Pathology and Laboratory Medicine, Temple University School of Medicine, Philadelphia, PA 19140.

BBB dysfunction during HIV-1 neuropathogenesis is a well-known phenomenon with consequences on neurological function. There is a need for serological biomarkers that could indicate the development of neurological deficits associated with HIV-1 infection. As a result of inflammation and remodeling of the brain endothelium, shed extracelluar microvesicles (EVs) may offer a new source of biomarkers for evaluating the status of the BBB. Since structural proteins identify the cell-origin of the EV, BBB breach could also provide insight into the integrity of the neurovascular unit. Here we present results on the discovery that primary human brain endothelial cells (BMVECs) release EVs containing endothelial structural proteins, exosomal markers and proteins enriched on brain endothelial cells (such as Pgp, BCRP and tight junction proteins [TJP], claudin-5 and occludin). Importantly, this is the first demonstration that shed TJP can be detected in activated BMVECs. This biological process also occurs in mouse-brain endothelium and is measurable in the serum from animals with neuroinflammation. To allow for rapid detection and analytic quantitation of BMVEC EVs, we have constructed prototype assays using the platform available from MSD Inc. The use of a ruthenium (II) tris-bipyridine NHS ester Ru(bpy)32 tag (MSD tag) provides sub-picogram detection limits and up to five logs of linear dynamic range. Using these assays we present results from analysis of serum from 30 HIV-1 positive patients and 5 HIV-1 negative individuals. **Supported by MH065151, DA025566, AA015913, Temple University seed grant.**

VOLUNTARY EXERCISE REDUCES THE EFFECTS OF METHAMPHETAMINE ON THE EXPRESSION OF MULTIDRUG REGISTANCE TRANSPORTERS IN BRAIN ENDOTHELIUM. Kim HJ, Zhang B, Park M, Toborek M; Biochemistry and Molecular Biology, University of Miami, Miami, FL 33136.

Regular physical activity has many long-term benefits for healthy people and can help improve outcomes for those suffering from disease or addiction. Indeed, people struggling with substance abuse have been shown to benefit from regularly scheduled exercise. P-glycoprotein (P-gp) and multidrug resistance-associated protein (MRP)-1 are multidrug resistance transporters, involved in drug clearance and/or resistance. We investigated the effect of methamphetamine (METH) on the expression of P-gp and MRP-1 in isolated brain microvessels from sedentary and voluntarily exercised mice. Male C57BL/6J mice (12-week-old) were subjected to either 5wk of voluntary running or housed in cages with locked wheels. Then both groups were injected i.p. with escalating doses of METH (0.2 -2.4 mg/kg) or vehicle, 3 times daily for 4 days. Voluntary exercise significantly decreased METH-induced increases in P-gp expression in brain microvessels as compared to the METH-treated sedentary group. Interestingly, the protein expression of MRP-1 was significantly increased in the METH-injected sedentary group, but not in the METH-treated exercise group. Since P-gp and MRP-1 have crucial roles in the development of drug resistance, our observations suggest that exercise may improve drug efficiency in the CNS. **Supported by NIH DA027569, MH063022, MH072567, and MH098891.**

METHAMPHETAMINE-INDUCED OCCLUDIN ENDOCYTOSIS IS MEDIATED BY THE ARP2/3 COMPLEX-REGULATED ACTIN REARRANGEMENT. Park M, Kim HJ, Toborek M; Department of Biochemistry and Molecular Biology, University of Miami School of Medicine, Miami, FL 33136.

Methamphetamine (METH) is a drug of abuse with neurotoxic and neuroinflammatory effects, which include disruption of the blood-brain barrier (BBB). Tight junction proteins are critical structural and functional elements responsible for BBB integrity; however, the precise mechanisms regulating expression of these proteins are not fully understood. The present study focused on the actin cytoskeletal rearrangement as a modulator of METH-induced redistribution of tight junction protein occludin in brain endothelial cells. Exposure to METH resulted in a shift of occludin localization from plasma membranes to endosomes. These changes were accompanied by activation of the actin-related protein 2/3 (Arp2/3) complex, which stimulates actin polymerization by promoting actin nucleation. In addition, METH induced coronin-1b phosphorylation which deters the inhibitory effect of non-phosphorylated coronin-1b on actin nucleation. Blocking actin nucleation with CK-666, a specific inhibitor of the Arp2/3 complex, protected against METH-induced occludin internalization and increased transendothelial monocyte migration. Importantly, treatment with CK-666 attenuated a decrease in occludin levels in brain microvessels of METH-injected mice. The present findings indicate that actin cytoskeletal dynamics are detrimental to METH-induced BBB dysfunction by increasing internalization of occludin. **Supported by NIH DA027569, MH072567, MH098891, and MH63022.**

INSOMNIA CORRELATES WITH IMMUNE DYSREGULATION BUT NOT WITH HCT/OX SYSTEM DYSFUNCTION IN HIV-INFECTED WOMEN. Menéndez-Delmestre R, López R, Matos M, Skolasky RL, Vélez J, Ginebra T, Wojna V; NeuroAIDS, and the Division of Neurology, University of Puerto Rico, Medical Sciences Campus, San Juan, PR 00935; Department of Orthopaedics, Johns Hopkins University, Baltimore, MD 21287.

Insomnia is a frequent sleep disturbance in HIV-infected people. It is associated with dysfunction of the hypocretin/orexin (hcrt/ox) system and immune dysregulation. Previously, we demonstrated that a dysregulation of the hcrt/ox system is present in HIV-infected women. Our objective was to determine the correlation between CSF cytokine and hcrt/ox levels and insomnia in HIV-infected women. Retrospective study nested in the Hispanic Longitudinal cohort using stored data and CSF samples of 24 HIV-infected women and stored CSF of 4 controls. Insomnia was determined with the ATHENA scale. We determined CSF cytokines (IL-2, IL-4, IL-6, IL-10, TNF, and IFN-gamma; BD Biosciences) with flow cytometry and hcrt/ox with a fluorescent immunoassay kit (Phoenix Pharmaceuticals). Parametric and non parametric statistics were used, $p<.05$ as significant. CSF hcrt/ox levels were significantly higher in HIV-infected women when compared with controls. No difference was observed in CSF cytokine levels among groups. In the HIV-infected women a positive correlation was observed between ATHENA score and CSF IL-4, IL-10, and TNF levels. Presence of insomnia correlated with increased CD4 cell count. No association was found between CSF cytokine and hcrt/ox levels. CSF hcrt/ox levels correlated with increased age. Interestingly, a significant correlation between IL-6 levels and intake of protease inhibitors was observed. Findings sustain that insomnia in HIV-infected women correlated with immune dysregulation but not with hct/ox system dysfunction. Further studies are needed to corroborate these data. **Supported by R21MH095524, S11NS046278, U54NS043011, U54RR026139, 8U54MD007587, 2G12RR003051, 8G12MD007600, R25MH080661.**

SPECTRUM OF AUTOPSY HIV NEUROPATHOLOGY IN THE POST ANTI-RETROVIRAL THERAPY (ART) ERA: EXPERIENCE IN A SINGLE URBAN TERTIARY TEACHING HOSPITAL. Potula R, Zhang M, Ramirez SH, Persidsky Y, Mukherjee A; Pathology and Laboratory Medicine, Temple University Hospital and School of Medicine, Philadelphia, PA 19140.

Almost 71% of the newly diagnosed cases of HIV infection in 2010 belong to racial and ethnic minorities. While ART has changed the incidence and severity of HIV associated neurocognitive disorder (HAND), it is still prevalent in its milder form. Particularly intriguing are communities where treatment disparities may lead to greater complexity in understanding HAND evolution. We retrospectively assessed neuropathological findings in 20 HIV+ autopsy cases (4.8% of total adult autopsy) with (9) or without ART therapy (11). The systematic neuropathological examination included: categorization of the histopathologic changes (primary parenchymal HIV associated changes), neuroinflammation, and evaluation for Alzheimer type changes. Primary HIV related parenchymal histopathologic abnormality was detected in 25% of cases, more prevalent in the ART naïve. A higher percentage of ART naïve cases had microglial nodules and CD8 infiltrate in neuropil, although classic HIV encephalitis with pericapillary multinucleated giant cells was not detected in our cohort. Furthermore, secondary pathology attributable to infection (Cryptococcus, Aspergillous, and PML) was present in 30% of the cases, mostly in the ART naïve. Both groups showed similar degree of microglial activation (semi-quantitative assessment by Iba-1 and HLA-DR). This urban population with HIV infection continues to have a high proportion of untreated cases characterized by a high prevalence of both primary parenchymal HIV associated neuropathology, secondary opportunistic infections as well as significant microglial activation. **Supported by NIMH/R01 MH065151, NIDA/R01 DA031064 and R01 DA025566.**

ADAPTATION OF NMDA RECEPTORS FOLLOWING HIV-1 TAT-INDUCED POTENTIATION. Krogh KA, Thayer SA; Department of Pharmacology, University of Minnesota, Minneapolis, MN 55403.

HIV-associated neurocognitive disorders (HAND) afflict approximately 30% of HIV-infected patients despite antiretroviral treatment. Synaptodendritic changes correlate with cognitive impairment in patients with HAND. HIV-infected cells of the brain shed viral proteins, such as the transactivator of transcription (Tat), which causes synapse loss via an NMDA receptor (NMDAR) dependent mechanism. Here, we provide evidence that Tat causes a time-dependent, bi-phasic change in NMDAR-mediated Ca+2 influx. Tat-induced changes in NMDAR function were measured using fura-2-based Ca+2 imaging of rat hippocampal neurons in culture. Ca+2 influx was triggered by the transient application of NMDA (10μM) following 0 to 48h exposure to Tat (50 ng/mL). Exposure to Tat for 1h potentiated NMDAR-mediated Ca+2 influx. Potentiation persisted for 8h then adapted. NMDAR-mediated Ca+2 influx returned to basal levels after 24h exposure to Tat and dropped below baseline after 48h. Tat-induced NMDAR potentiation was prevented and reversed by inhibitors of lipoprotein receptors (RAP, 50 nM) and Src-family kinases (PP2, 10 μM), but was unaffected by a nNOS inhibitor (L-NAME, 100 μM). However, L-NAME prevented adaptation. Together, these findings indicate that Tat potentiates NMDARs via a Src-family kinase and this potentiation adapts via a nNOS-mediated pathway. This adaptation might be a neuroprotective mechanism to prevent excessive Ca+2 influx through NMDARs. Enhancing our understanding of such mechanisms could reveal targets for the treatment of HAND. **Supported by NIDA T32DA007097, R37DAO7304.**

TAT-MEDIATED CHANGES OF MALAT1 LONG NON-CODING RNA AFFECTS THE STRUCTURE AND FUNCTION OF SC35 NUCLEAR SPECKLES DOMAINS IN NEURONS. Pacifici M, Kadri F, Jeansonne D, Peruzzi F; LCRC, LSUHSC School of Medicine, New Orleans, LA 70112.

Nearly 70 % of HIV/AIDS patients are affected by neurocognitive impairments despite combined antiretroviral therapy. One of the viral proteins that have been shown to play a role in neuronal damage and dysfunction is the transactivating factor, Tat. Localized in various subcellular compartments, it binds to a variety of host factors altering their activity and function. While neurons are not permissive to the viral entry, they are permeable to Tat, which enters freely into the cytoplasm and nucleus of these cells. Recent new technologies allowed the discovery in mammalian cells of thousands of long transcripts that have no significant protein-coding capacity and have been named long non-coding RNAs (lncRNAs). Among the identified functions of these RNA species is the regulation of gene expression, nuclear organization, mRNA splicing, and nucleus-cytoplasm trafficking. The nuclear lncRNA MALAT1 is associated with the splicing factor SC35 in nuclear speckles and regulates alternative splicing of neuronal mRNAs. Here, we show that Tat treatment determines changes in MALAT1 expression and promotes dispersion of SC35 from nuclear speckles domains into small scattered dots. In addition, Tat determines cycles of RNA Pol II phosphorylation and dephosphorylation. Since MALAT1 associates with SC35 and P-TEFb/RNA Polymerase II complex, our findings may impact upon RNA Pol II mediated transcription/elongation and alternative splicing. **Supported by NIMH MH079751.**

NEUROPROTECTIVE ROLE OF PHOSPHODIESTERASE INHIBITOR IBUDILAST ON NEURONAL CELL DEATH INDUCED BY HIV-1 AND MORPHINE ACTIVATED GLIA. El-Hage N, Zou S, Snyder S, Podhaizer EM, Beardsley PM, Knapp PE, Hauser KF; Department of Pharmacology and Toxicology, Department of Anatomy and Neurobiology, Virginia Commonwealth University, Richmond, VA 23298.

Opiate abuse and HIV-1 have been described as interrelated epidemics, and even in the advent of combined anti-retroviral therapy, the additional abuse of opiates appears to result in greater neurologic and cognitive deficits. Neuronal damage is a hallmark feature of HIV-associated neurological disorders (HAND). Opiates such as morphine enhance HIV Tat-mediated toxicity in part because of the unique responses of microglia and astroglia. Given the need for novel adjunctive therapies for HAND, we examined the neuroprotective role of ibudilast, a non-selective cyclic AMP phosphodiesterase inhibitor with varied anti-inflammatory activity, in neuron and microglia exposed to Tat ± morphine. Ibudilast significantly suppressed neuronal cell death induced by Tat ± morphine. To examine ibudilast neuroprotection, the production of pro-inflammatory and anti-inflammatory mediators was examined. Ibudilast suppressed the production of Tat ± morphine mediated macrophage migration inhibitory factor (MIF) and inhibited microglial migration, as detected by a decrease in cell migration, and enhanced the production of the anti-inflammatory cytokine, IL-10. Interestingly, ibudilast reduced Tat ± morphine mediated transcription of MIF, via modulation of NF-κB signaling, as shown by p65 nuclear trans-migration, and analysis of inhibitor of IκBα stability. These results suggest that ibudilast may be a useful neuroprotective agent counteracting neurotoxicity in activated glial and may implicate ibudilast as a potential novel adjunctive therapy for the management of HAND. **Supported by NIDA DA018633, DA019398 (KFH); DA003203 (EMP).**

LONG-TERM HIV-1 INFECTION OF HUMANIZED MICE LEADS TO BEHAVIORAL ABNORMALITIES. Akhter S, Epstein A, Poluektova L, Gendelman HE, Gorantla S; Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198.

We have successfully mirrored the virologic and immune abnormalities in mice that follow chronic progressive HIV-1 infection in humans. Recently we demonstrated that virus-infected humanized mice show neuropathological deficits that reflect the motor, behavioral and cognitive abnormalities in HIV-1 associated neurocognitive disorders (HAND). NOD/scid-IL-2R cnull (NSG) mice transplanted at birth with CD34+ human hematopoietic stem cells (HSC) obtained from cord blood reconstitute the immune system of mice. These mice are infected with HIV-1ADA at 22wk of age. Animals were evaluated 1wk prior to, and 4 and 8 wk following viral infection by open field activity (OFA) as a measure of habituation in new environments, motor function and field exploratory behavior. OFA measurements are diminished during repeated tests in control-uninfected animals. This behavior reflects recognition of a new environment by the animal. In stark contrast, HIV-infected NSG animals failed to habituate to a new environment and paradoxically increased searching and exploratory behavior. This occurred despite repeated exposure and consecutive trials to a new environment. This finding was significant after 8wk of viral infection and the third trial. We conclude that chronic viral infection leads to behavioral abnormalities and as such reflects prior histopathological abnormalities that we previously demonstrated (Dash et al., J. Neuroscience 2011). We posit that this murine model of viral infection is a useful probe to mirror HAND as it reflects an infected human host. **Supported by 5 P01 NS043985-07.**

GLIAL P2X4 RECEPTORS MEDIATE OPIOID AND HIV-1 ASSOCIATED NEURODEGENERATION. Sorrell ME, Zou S, Knapp PE, Hauser KF; Department of Pharmacology and Toxicology, Department of Anatomy and Neurobiology, Virginia Commonwealth University, Richmond, VA 23298

Individuals who abuse opiates can have an increased incidence of HIV-1-associated neurocognitive disorders (HAND). Microglia play a significant role in HIV-1 neuropathogenesis by producing inflammatory molecules that lead to neuronal injury and death. Extracellular purines also increase microglial activation and/or neuronal injury. Morphine has been reported to increase microglial motility by modifying P2X4 signaling. This is important because Âμ opioid receptor agonists can increase HIV-1 replication, potentiate the release of oxyradicals and glutamate, and increase cytokine production in HIV-1 Tat-exposed microglia. To test that HIV-1 and opioid-induced neurotoxicity are mediated via purinergic signaling, co-cultures of primary neurons and mixed glia were treated with combinations of Tat, morphine, and TNP-ATP, a non-selective P2X antagonist. Individual neurons were repeatedly tracked and neuron survival versus time was assessed. Tat/morphine neurotoxicity was reversible by treatment with TNP-ATP. Next we investigated sub-lethal neuronal injury by measuring dendritic length and changes in intracellular Ca2+ ([Ca2+]i) levels. In both assays, TNP-ATP was able to prevent the effects of Tat/morphine. To investigate P2X4 receptor involvement, selective antagonists against the P2X1, P2X3, and P2X7 receptor subtypes were screened. Findings showed that these receptor subtypes were not involved in Tat + morphine neurotoxicity. Finally, cells from P2X4 null mice confirmed that the activation of P2X4 receptors on glia is necessary for opioid and/or Tat neurotoxicity. **Supported by NIDA DA018633, DA028741, DA007027.**

HIV-1 CLADE B ACTIVATES PRO-APOPTOTIC PROTEIN SIGNATURES IN HUMAN MICROGLIA. Rodriguez M, Escobales H, Lopez SN, Alves JM, Cubano L, Boukli NM; Biomedical Proteomic Facility, Universidad Central del Caribe, Bayamon, PR 00956.

HIV associated neurocognitive disorders (HAND) continue to be a consequence of HIV-1 infection, by the secretion of soluble viral proteins from perivascular macrophages and microglia. Although the incidence of severe neurological impairment is lower among HIV-1 clade C-infected patients. It has been suggested that the degree of HAND vary according to HIV clade, the molecular mechanisms behind differences in neuropathogenesis of subtypes still remain to be elucidated. In this study, we hypothesize that HIV-1 clade B and C induce a significant differential protein expression on a human microglia cell line. By means of 2D gel electrophoresis and Mass Spectrometry, hundreds of differentially expressed proteins from microglia treated with HIV-1 clade B and C were separated and identified, having altered expression mainly in oxidative stress, protein folding, apoptosis and anti-apoptosis. Relevant proteins were verified with RT-PCR. HIV-1 clade B upregulated both the mRNA and protein expression levels of Annexin A2 and Hsp60, which play a role in p53 induced apoptosis and Fas-mediated apoptotic pathway. Among other proteins, Pyruvate Kinase Isozyme M1/M2 was found to be down-regulated as compared to HIV-1 clade C, which could potentially protect the cell from apoptosis. Our findings show that apoptotic and oxidative protein signatures were up-regulated in cells treated with HIV-1 clade B and validated by RT-PCR and western blots. Further analysis will be run to confirm pro and anti-apoptotic roles of these proteins in terms of HIV-1 Clades B and C differential protein expression. **Supported by NIMHD 8G12MD007583.**

NEURAL STEM CELL PROLIFERATION IS MODULATED BY DIFFERENTIAL FGF-2 EXPRESSION DURING EXPERIMENTAL HERPES SIMPLEX ENCEPHALITIS.

Cheeran M C-J, Rotschafer JH, Hu S, Low WC; Veterinary Population Medicine, University of Minnesota, St. Paul, MN 55108; Center for Infectious Diseases and Microbiology Translational Research, Department of Medicine, and Department of Neurosurgery and Stem Cell Institute, University of Minnesota, Minneapolis, MN 55455.

Neural stem/progenitor cells (NSC) respond to inflammatory cues produced by the injured brain. The neuroimmune response to Herpes Simplex virus (HSV)-1 infection changes over time in cellular composition and soluble mediators, culminating in the accumulation of T cells and activated microglia in the brain. Little is known about the impact of persistent inflammation on NSC functions in the adult mammalian brain during viral encephalitis. The present study evaluated the proliferative response of NSCs in the context of HSV-1 brain infection. While there was an initial increase in NSC proliferation denoted by increases in numbers of nestin(+) cells and Sox2(+)Ki67/PCNA(+) cells, this surge in proliferative response decreased significantly at 15 and 30d p.i. to levels below that normally observed in uninfected brains. Both phenotypic and temporal changes in NSC proliferative response were demonstrated during the course of HSE. These changes in NSC proliferation were associated with concomitant modulation of FGF-2 expression in the brain, suggesting a possible mechanism by which HSV-1 brain infection alters neurogenesis. In further support of these findings, FGF-2 supplementation at 15d p.i showed increased numbers of proliferating cells in the brain. Studies are currently underway to determine the impact of immune cells and their products in modulating neurogenesis during HSE, with the goal to identify points of intervention that may enhance the reparative processes in an injured brain during viral encephalitis. **Supported by RO1 NS065817 and T32 DA007097.**

EXPOSURE TO FLAME RETARDANT BDE-47 INDUCES OCCLUDIN DISRUPTION AND VCAM-1 EXPRESSION IN HUMAN BRAIN ENDOTHELIAL CELLS. Eum SY, Choi JJ, Andra IE, Park M, Toborek M; Department of Biochemistry and Molecular Biology, University of Miami Miller School of Medicine, Miami, FL 33136.

Polybrominated diphenyl ether (PBDE) congeners are bioaccumulative, persistent, and toxic flame retardants that exhibit adverse biological effects including neurotoxicity, endocrine disruption, and carcinogenesis. However, information on the effects PBDEs have on cerebrovascular system is limited. The blood-brain barrier (BBB) is a physical and metabolic barrier separating the brain microenvironment from peripheral circulation. It is mainly composed of endothelial cells connected by tight junctions. We examined whether exposure to 2,2',4,4;'-tetrabromodiphenyl ether (BDE-47), the most abundant PBDE in human samples, can disrupt barrier functions of human brain microvascular endothelial cells (HBMECs). Occludin levels of HBMEC were dose-dependently decreased after exposure to BDE-47 at 1-10uM for 24h. This effect was markedly blocked by pre-treatment of methyl-beta cyclodextrin or Filipin III, which disrupts the lipid rafts/caveolae domain structure of the cell plasma membrane. In addition, exposure to BDE-47 up-regulated expression of vascular cell adhesion molecule 1 (VCAM-1) and increased adhesion of leukocytes to HBMEC monolayer. The treatment of lipid rafts/caveolae disruptors significantly reduced the up-regulation of VCAM-1 and cell adhesion. These data suggest that lipid rafts/caveolae and related signaling mechanisms may be involved in PBDE-induced brain endothelial activation and thus contribute to the cerebrovascular toxicity of PBDEs. **Supported by NIH grants (P42 ES07380, MH072567, and CA133257) and the American Heart Association (09SDG2300037).**

EFFECT OF GP120 IN CATHEPSIN B AND CYSTATIN B EXPRESSION IN HIV PATIENTS. Colon K, Delgado G, Melendez LM; Microbiology Department, University of Puerto Rico, Medical Sciences Campus, San Juan, PR 00935; Biology Deparment, University of Puerto Rico, Rio Piedras Campus, San Juan, PR 00931.

HIV-1 infected cells generate large amount of ROS accompanied by deregulation of antioxidant enzymes. An increase in antioxidants, increases the release of Cystatin B (CatB) from lysosomes. HIV infection upregulates CatB secretion and decreases interaction with its inhibitor, Cystatin B (CysB). Previous studies showed that CatB is neurotoxic. We hypothesize that viruses with different co-receptor tropism will have differences in CatB and CysB secretion. To test this hypothesis THP-1 cells, differentiated into macrophages, were exposed to 1ug/ml of R5 or X4 gp120 and supernatant collected at 1 4 and 24h post exposure, in triplicate. Supernatants were used to measure total antioxidant capacity and for western blotting. Results were analyzed by One-way or Two-Way ANOVA. The TAC was significantly decreased for HIV X4-tropic ($p>0.001$) and X4/R5-tropic viruses ($p>0.05$) compared to R5-tropic viruses from PBMCs supernatant. THP-1 exposed to X4 or R5 gp120 showed that as early as 1h both gp120s were able to significantly decrease TAC compared to negative controls; but at 24h, the X4 gp120 had lower TAC levels than cells exposed to the R5 gp120. No significant changes were observed in secretion of CatB or CysB. These results suggest that gp120 alone is not enough to deregulate the CysB/CatB system in macrophages. Further studies using pseudotyped viruses for envelope are needed to corroborate this conclusion. **Supported by R01-MH08316-01, R25-GM061838, G12RR03050, G12RR03051 and SNRP-NINDS-1-U54NS431.**

CLINICAL CORRELATION WITH CD4 COUNT AND MENTAL DIAGNOSIS AMONG HIV INFECTED DRUG USERS. Munoz-Caamano K, Raymond A, Yndart A, Pilakka-Kanthikeel S, Nair MPN; Dept. of Immunology, Institute of NeuroImmune Pharmacology, Herbert Wertheim College of Medicine, Florida International University, Miami, FL 33199.

Mental disorders (mdo) and drug use among HIV infected adults may impact quality of life. Although HIV infected adults on HAART therapy live longer, they have a risk of developing mdo. CD4 counts are used as a clinical correlate of HIV disease progression. There are no known correlates with CD4 count, mdo and drug use. In this study, we have performed a retrospective analysis of a group of HIV infected adults. Here, we show an association with CD4 count, mdo and drug use. We hypothesized that CD4 count can be associated with mdo, gender and drug use. We analyzed the CD4 count of HIV infected adults that have been diagnosed with a mdo and have reported the use of drugs. Adults diagnosed with depression exhibited >500 cells/mm^3 than those diagnosed with more than one mdo (Psych-do) who showed CD4 <500 cells/mm^3. Females diagnosed with Psych-do, showed a CD4 count <500 cells/mm^3 vs. males with the same diagnosis. Among females there is a difference in CD4 count and their mdo (Bipolar-do <500 and Psych-do >500). With respect to drug use, there is an incidence of mdo based on drug use. Adults that use more than one drug exhibit a higher percentage of Bipolar-do, and adults who use one drug exhibit a high percentage of Psych-do. Of this analysis, female non-drug users have higher CD4 counts than drug users among adults; however, females that use drugs experience a greater impact on their CD4 count than males. These results suggest that CD4 can be used as a correlate to identify mdo and drug use trends. **Supported by 5R01DA021537.**

HAND AND HOST FACTORS IN WOMEN ON CART: EXPERIENCE OF OUR HIV-SEROPOSIVIE WOMEN COHORT. Wojna V, Gerena Y, Bandaru VVR, Haughey N, Curry T, Raber J, Mayo R, Skolasky RL, Nath A; Neurology Division/NeuroAIDS SNRP, Pharmaceutical Sciences Department, University of Puerto Rico, Medical Sciences Campus, San Juan, PR 00936-5067; Department of Neurology, Department of Orthopeadic Surgery, Johns Hopkins University, Baltimore, MD 21287; Department of Obstetrics and Gynecology, University of Kentucky, Lexington, KY 40506; Division of Neuroscience, Oregon Health and Science University, Portland, OR 97239; Section of Infections of the Nervous System, National Institute of Neurology Disorders and Stroke, National Institute of Health, Bethesda, MD 20892.

In the post-CART era, HIV-infected individuals are enjoying longer life expectancies and reduced morbidity. However, HAND remains prevalent, even with adequate viremia control, and continues to afflict 50% of HIV patients. Several factors have been associated with HAND such as co-infection with Hepatitis C virus, depression, traumatic brain injury, substance abuse, gonadal dysregulation, and metabolic syndrome (mostly insulin resistance). As the HIV-infected population ages, other age-related factors such as neurodegenerative disorders and cerebrovascular accidents may synergize to increase the prevalence of HAND in the aging HIV-seropositive population. Using the experience of our Hispanic-Latino Longitudinal Cohort of HIV-seropositive Hispanic Women we will discuss the associations between gonadal hormones dysfunction, insulin resistance, and CSF oxidative stress markers with HAND and how they may have an adding effect with aging and neurodegenerative disorders. Age-related degenerative processes may interact with ongoing HIV infection to generate a unique spectrum of neuropathological and neurocognitive changes, which in turn will require novel prevention and treatment strategies. Understanding the risk factors for HAND in older HIV-infected individuals will be critical for developing diagnostic tools and therapeutics targeting this growing population. **Supported by R21MH095524, S11NS046278, U54NS043011, U54RR026139, 8U54MD007587, 2G12RR003051, 8G12MD007600, R25MH080661, P30MH075673, P20RR15592.**

EFFECT OF COCAINE IN THE PLASMA OF HIV SEROPOSITIVE WOMEN BY 18O ISOTOPIC LABELLING. Zenon F, Cruz A, Melendez L, Segarra A, Jorge I, Vazquez J, Serrano H; University of Puerto Rico Medical Sciences Campus, School of Medicine/UPR-RCM, San Juan, PR 00936; Cardiovascular Proteomics Laboratory, Centro Nacional de Investigaciones Cardiovasculares/Centro de Biología Molecular "Severo Ochoa", Madrid, E-28029.

Human immunodeficiency virus (HIV) infection is now being driven by drug-abusing populations. Epidemiological studies on drug abusers with AIDS link abuse of cocaine, even more than other drugs, to increase incidence of HIV seroprevalence and progression to AIDS. 18O-stable isotope labeling is a promising approach due to its general applicability, absence of secondary by products and low cost. This approach including: optimized 18O-labeling protocol suitable for all kind of samples; an improved algorithm and a refined method to calculate false discovery rates (FDR) for automated peptide identification; labeling efficiency control of each one of the quantified peptides; a software platform (QuiXoT) for quantification and statistical analysis. We aimed to identify proteins and metabolic pathways that are associated with the effect of cocaine use in the plasma of HIV seropositive women as compared to non-cocaine users. Hypothesis is that additional protein pathways are activated in cocaine users that may accelerate disease progression. Results of this method on 2 out of 12 plasma samples from HIV seropositive women with and without cocaine indicate that a total of 802 proteins were identified (FDR<0.05) and 252 proteins were quantified using a lower FDR<0.01. Around 20% proteins changed their abundance levels in plasma from HIV female using cocaine. Systems biology approaches revealed alterations in proteins involved in cytoskeleton, lipid metabolic process, and immune response. Differentially expressed proteins will be validated and correlated with viral-immune parameters. **Supported by SNRP: U54NS043011 and NCRR-2G12-RR003051/NIMHHD: 8G12-MD007600, PRCTRC: U54 RR026139-01A1, U54 MDA/UPR CA96300, 8U54MD 007587-03.**

ROLE OF EPIGENETICS IN ASTROCYTIC EAAT2 GENE EXPRESSION BY IL-1 BETA. Datta P; Neuroscience, Temple University School of Medicine, Philadelphia, PA 19140.

The high-affinity glutamate transporter subtype, EAAT2/GLT-1 located on the astrocytes clears extracellular glutamate in the brain. However, the expression of the astrocytic EAAT2/GLT-1 is perturbed in numerous neurodegenerative diseases including NeuroAIDS. Our studies demonstrate that HIV-1 induced pro-inflammatory cytokine, IL-1 beta inhibits EAAT2 expression in human fetal brain astrocytes. In the present study, we investigated whether epigenetic modifications at the chromatin level are involved in the regulation of the EAAT2 gene by IL-1 beta in astrocytes. Our studies demonstrate that overexpression of Brahma-related gene-1 (BRG-1), a protein contained in an ATP-dependent chromatin remodeling complex, and histone acetyltransferase (HAT), p300, induces not only basal EAAT2 promoter activity but also reactivates EAAT2 promoter activity in IL-1beta treated primary human fetal astrocytes and H4 astroglioma cells. On the contrary, over-expression of mutant form of BRG-1 (K798R, mutation in ATP binding site) inhibited not only basal EAAT2 promoter activity but also failed to reactivate EAAT2 promoter activity in IL-1beta treated cells. Together, these data suggest that epigenetic modifications of the chromatin in EAAT2 gene are involved in the transcriptional regulation of the gene in response to IL-1beta. These observations demonstrate that molecules targeting chromatin modifiers may have potential as novel therapeutic interventions for upregulation of astrocytic EAAT2 expression. **Supported by NIH/NIDA.**

CCR5-EXPRESSING NEURONS AND GLIA AS SITES OF CONVERGENCE FOR HIV-1 TAT AND OPIOID INTERACTIONS. Podhaizer EM, Zhang Y, Knapp PE, Hauser KF; Department of Pharmacology and Toxicology, Department of Medicinal Chemistry, Department of Anatomy and Neurobiology, Virginia Commonwealth University, Richmond, VA 23298.

In spite of cART's effects on patient survival, neurocognitive impairments are sustained in HIV-1 patients, while those who also abuse injection drugs (i.e. opioids) show more severe effects. We showed previously that morphine acts synergistically with HIV-1 Tat's neurotoxic effects. To examine the mechanisms of this interaction, we chose to study CCR5, which appears to be involved in both Tat-mediated glial inflammation and in regulating opioid signaling through heteromer formation or the convergence of downstream events. We hypothesized that disruption of CCR5 activity would abolish morphine + Tat interactive neurodegeneration. To determine if CCR5 inhibition or use of CCR5-/- cells affected neuronal endpoints, we assessed neuronal survival using repeated measures time-lapse microscopy, and sublethal changes to dendritic length with Sholl analysis over 72h. The CCR5 antagonist, maraviroc, prevented the morphine-Tat interaction, while use of CCR5-/- neurons or glia abolished the toxicity/dendrite length reductions from combined treatment. Use of CCR5-/- neurons and glia resulted in enhanced basal toxicity/dendritic shortening, with no treatment effect. Examination of inflammatory mechanisms found that cytokine/chemokine release as well as NF-κB p65 activation was affected by CCR5 inhibition suggesting potential mechanisms for the observed effects. These data suggest that CCR5 mediates key aspects of neuronal injury independently in neurons and glia, and the inclusion of CCR5 inhibitors may be helpful in preventing neurocognitive impairment in HIV-1 infected patients. **Supported by R01 DA019398 (KFH), T32 DA007027 (WLD), F31 DA003203 (EMP).**

IMPACT OF SUBSTANCE ABUSE ON HIV-1 LTR SINGLE NUCLEOTIDE POLYMORPHISMS (SNPS) AND DISEASE PROGRESSION IN A CLINICAL COHORT. Dampier W, Nonnemacher M, Pirrone V, Williams J, Aiamkitsumrit B, Wojno, A, Passic S, Blakey B, Zhong W, Moldover B, Feng R, Downie D, Lewis S, Jacobson J, Wigdahl B; Department of Microbiology and Immunology, Division of Infectious Disease and HIV Medicine, Department of Medicine, Drexel University College of Medicine, Philadelphia, PA 19102; B-Tech Consulting, LTD, B-Tech Consulting, LTD, Philadelphia, PA 19130; Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, PA 19104.

The current clinical studies focus on the identification of LTR SNPs derived from peripheral blood (PB) of patients enrolled in the HIV/AIDS Genetic Analysis Cohort in Philadelphia to identify HIV-1-infected individuals more prone to developing advanced disease and/or neurologic impairment. Patient demographics and clinical parameters including drug use, CD4/CD8 T cell count, and viral load are performed at every visit. Drug abuse is common within this cohort with cocaine use being favored. The cohort can be categorized into non-users (PN), preferential cocaine (PC), and multidrug users (MDU). SNPs have been identified that associated with CD4 T-cell count and viral load. SNPs were also identified that are unique to each drug abuse category. Using an in silico sensitivity analysis, we were able to determine significant differences for TF footprints at the Lef-1 site with a variation from an A to a G at position 321 to be significantly different between the PN and PC and PN and MDU subcohorts. Additionally, an A-to-G variation at position 286 within C/EBP site II was found to be significant in both the psychomotor and constructive neuropsychologically impaired patients. In previous studies, we have shown this position to have an increased affinity for C/EBP beta, increased HIV-1 basal LTR activity, a decreased prevalence in PB-derived LTRs from patients with increased disease progression, but an increased prevalence in brain-derived LTRs. These results suggest that cocaine may be applying selective pressure at these sites. **Supported by NINDS R01 NS32092; NIDA R01 DA19807.**

HIV-1 LTR SINGLE NUCLEOTIDE POLYMORPHISMS (SNPS) CORRELATE WITH CLINICAL DISEASE PARAMETERS. Nonnemacher M, Pirrone V, Dampier W, Aiamkitsumrit B, Williams J, Shah S, Wojno A, Passic S, Blakey B, Zhong W, Moldover B, Feng R, Downie D, Lewis S, Jacobson J, Wigdahl B; Department of Microbiology and Immunology, Division of Infectious Disease and HIV Medicine, Department of Medicine, Drexel University College of Medicine, Philadelphia, PA 19102; B-Tech Consulting, LTD, Philadelphia, PA 19130; Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, PA 19104.

The long terminal repeat (LTR) regulates HIV-1 gene expression by interacting with multiple host and viral factors. Cross-sectional studies in the pre-HAART era demonstrated that SNPs in C/EBP site I and Sp site III from peripheral blood-derived LTRs increased in frequency as disease severity increased and correlated with HIV-1-associated dementia. Current studies focus on the identification of LTR signatures derived from peripheral blood virus that can be used as molecular markers to identify HIV-1-infected individuals more prone to developing advanced stage disease and/or neurologic impairment. A prospective, longitudinal study was conducted on 504 HIV-1 seropositive patients currently enrolled in the DREXELMED HIV/AIDS Genetic Analysis Cohort in Philadelphia, PA. History of clinical parameters and comorbities were collected approximately every 6 months. The collection of extensive clinical parameters on these patients have allowed for cross-sectional and longitudinal analyses of the impact of these parameters on the development of SNPs during the course of disease. To date, SNPs have been identified that associated with CD4 T-cell count and viral load. Of the SNPs identified, SNPs at position 108 were the most significant and correlated with a gain in transcription factor binding. These results suggest that the HIV-1 genomic swarm may evolve during the course of disease in response to selective pressures that lead to changes in prevalence of LTR SNPs that may be predictive of more advanced stage HIV disease and that may result in alterations in viral function. **Supported by NINDS R01 NS32092; NIDA R01 DA19807.**

ANGIOTENSIN II AND IV IN GLUCOSE TOLERANCE AND OXIDATIVE STRESS OF HUMAN NEURONAL CELLS. Gerena Y, Sierra J, Sánchez-Courtney Y, Méndez J, Pérez S, Hilera C, Wojna V; Pharmaceutical Sciences Department, and the Neurology Division, University of Puerto Rico, Medical Sciences Campus, San Juan, PR 00936; Rio Piedras Campus, University of Puerto Rico, Rio Piedras, PR 00931; Medicine, San Juan Bautista, Caguas, PR 00725; Earth Institute, Columbia University, New York, NY 10027.

Angiotensin II Receptor Blockers (ARBs) are associated with reduction in dementia and glucose intolerance in neurodegenerative disorders. However, the recently discovered angiotensin IV/AT4 receptor system has become a novel therapeutic target for enhanced neuronal glucose uptake and cognition. The objective of our study was to determine the potential effect of Ang II type 1(AT1) or type 2 (AT2) receptor blockers and Ang IV to improve glucose uptake (GU) induced by Ang II in neuronal cells and investigate the role of Ang II in activation of neuronal oxidative stress (OS). Human SH-SY5Y neuronal cells were cultured in the presence of Ang II, Ang II plus Valsartan (AT1 blocker), Ang II plus PD123177 (AT2 blocker) or Ang IV for 24h. GU was assessed using a fluorescent glucose (2-NBDG) and flow cytometry (FC). The ability of Ang IV to antagonize Ang II on GU was evaluated by incubating the cells with Ang II plus increasing concentrations of Ang IV (200-1000nM). OS activation in cells exposed to Ang II was measured using ROS detection fluorescent reagent and FC. Valsartan inhibited significantly ($p<0.001$) the glucose uptake decrease induced by Ang II, finding not observed with PD123177. Ang IV (600nM) was able to antagonize effects of Ang II in GU. Ang II significantly increased OS in neuronal cells. This study indicates that detrimental effects of Ang II on GU by neuronal cells are mediated through AT1 receptors and counteracted by Ang IV. The enhanced OS activation by Ang II in neuronal cells may help to clarify the benefits of ARBs in neurodegenerative disorders. **Supported by R21MH095524, S11NS046278, U54NS043011, U54RR026139, 8U54MD007587, 2G12RR003051, 8G12MD007600, R25MH080661.**

HIV-1 LTR SINGLE NUCLEOTIDE POLYMORPHISMS (SNPS) THAT CORRELATE WITH CLINICAL DISEASE PARAMETERS ARE FOUND IN BOTH THE PERIPHERAL BLOOD AND BRAIN COMPARTMENTS. Antell G, Nonnemacher M, Pirrone V, Dampier W, Aiamkitsumrit B, Williams J, Shah S, Wojno A, Passic S, Blakey B, Zhong W, Moldover B, Feng R, Downie D, Lewis S, Jacobson J, Wigdahl B; School of Biomedical Engineering and Health Sciences, Department of Microbiology and Immunology, Division of Infectious Disease and HIV Medicine, Department of Medicine, Drexel University, Philadelphia, PA 19102; B-Tech Consulting, LTD, Philadelphia, PA 19130; Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, PA 19104.

The current clinical studies focus on the identification of long-terminal repeat (LTR) single nucleotide polymorphisms (SNPs) derived from peripheral blood (PB) of subtype B patients enrolled in the HIV/AIDS Genetic Analysis Cohort in Philadelphia to identify HIV-1-infected individuals more prone to developing advanced disease and/or neurologic dysfunction. The HIV-1 LTR serves a number of critical functions in viral replication, one of which involves regulating the transcriptional activity of the integrated provirus. Current studies focus on the identification of LTR signatures derived from PB virus that can be used as molecular markers to identify HIV-1-infected individuals more prone to developing advanced stage disease and/or neurologic impairment. To date, 8 SNPs have been identified that associated with CD4 T-cell count and/or viral load. In addition to analyzing integrated provirus from cells of the PB compartment, brain samples procured from the NNTC were also analyzed. LTR sequence derived from provirus extracted from multiple brain regions demonstrated the presence of all 8 SNPs, which independently associated with neurocognitive status at the time of death. These results suggest that the HIV-1 genomic swarm may evolve during the course of disease and these SNPs may be predictive of a more advanced stage HIV disease that may result in alterations in viral function. Given that these SNPs were found in the PB as well as the CNS, future studies will be conducted to determine whether they can predict patients that will succumb to neurocognitive impairment. **Supported by NINDS R01 NS32092; NIDA R01 DA19807.**

PROTEOMIC FINGERPRINTS OF PRIMARY HUMAN ASTROCYTES TREATED WITH HIV-1 CLADE B AND C: IMPLICATIONS OF ER STRESS IN NEURO-AIDS.

Lopez-Acevedo SN, Rodriguez-Valentin M, Cubano LA, Alves J, Boukli NM; Biomedical Proteomics Facility, Universidad Central del Caribe, Bayamon, PR 00956.

One of the consequences of HIV-1 infection among patients is the HIV-associated neurocognitive disorder (HAND). It is suggested that the degree of neuro-AIDS varies according to the HIV-1 clade. The mechanisms underlying HIV-1 neuropathogenesis is complex and poorly understood. Exploiting proteomics, we hypothesize that clade B and C induce differential protein expression profiles on primary human astrocytes (PHA). In this study, we used a differential proteomic analysis of primary human astrocytes treated with HIV-1 clade B and C, respectively, by two-dimensional gel electrophoresis (2DE), followed by liquid chromatography-tandem mass spectrometry to establish homologies and dissimilarities in protein expression. A total of 69 and 72 proteins were modulated by HIV-1 clade B and C, respectively, as analyzed on 2DE maps by PD Quest software. Among the proteins significantly up-regulated by HIV-1 clade B are Annexin A5 and Cyclophilin A (pro-apoptotic factors), Protein Disulfide Isomerase, Elongation factor-2, quinone oxidoreductase Endoplasmic Reticulum and oxidative stress markers. In addition, HIV-1 clade C significantly upregulated a 14-3-3 protein signature characteristic of anti-apoptotic response as well as chaperones such as HSP60 and hTRiC5 as compared to HIV-1 clade B. These data suggest that HIV-1 clade B and C induce a differential protein profile in PHA. Further, our findings demonstrate that HIV-1 clade B appears to induce pro-apoptotic, ER and oxidative stress markers, while HIV-1 clade C seems to be associated with generation of anti-apoptotic mechanisms in PHA. **Supported by NIH-RCMI Biomedical Proteomics Facility, NIMHD 8G12MD007583.**

HIV AND MORPHINE MEDIATED REGULATION OF NEURONAL DYSFUNCTION: BLAMING THE MESSENGER. Buch S, Hu G, Yao H, Fox H; Department of Pharmacology and Experimental Neuroscience, Univ of Nebraska Med Center, Omaha, NE 68198.

Neuronal damage is a hallmark feature of HIV-associated neurological disorders (HAND). Opiate drug abuse accelerates the incidence and progression of HAND; however, the mechanisms underlying the potentiation of neuropathogenesis by these drugs remain elusive. Opiates such as morphine have been shown to enhance HIV transactivation protein Tat-mediated toxicity in both human neurons and neuroblastoma cells. In the present study, we demonstrate reduced expression of the tropic factor platelet-derived growth factor (PDGF)-B with a concomitant increase in miR-29b in the basal ganglia region of the brains of morphine-dependent simian immunodeficiency virus (SIV)-infected macaques compared with the SIV-infected controls. In vitro relevance of these findings was corroborated in cultures of astrocytes exposed to morphine and HIV Tat that led to increased release of miR-29b in exosomes. Subsequent treatment of neuronal SH-SY5Y cell line with exosomes from treated astrocytes resulted in decreased expression of PDGF-B, with a concomitant decrease in viability of neurons. Furthermore, it was shown that PDGF-B was a target for miR-29b as evidenced by the fact that binding of miR-29 to the 3'-untranslated region of PDGF-B mRNA resulted in its translational repression in SH-SY5Y cells. Understanding the regulation of PDGF-B expression may provide insights into the development of potential therapeutic targets for neuronal loss in HIV-1-infected opiate abusers. **Supported by NIDA.**

CATHEPSIN B AND CYSTATIN B IN HIV INFECTION AND NEUROCOGNITIVE DISORDERS. Melendez LM; Department of Microbiology and SNRP-NeuroAIDS, Medicine, San Juan,PR 00935.

Chronic HIV infection leads to a spectrum of neurological and cognitive abnormalities, known collectively as HIV-associated neurocognitive disorders (HAND). These occur frequently during advanced HIV-1 infection and despite effective combination antiretroviral therapy (cART). The pathogenesis of HAND is thought to involve HIV-1 infected perivascular macrophages and microglia, whose activation leads to the release of pro-inflammatory cytokines and other soluble factors toxic to neurons. One factor that may be involved in macrophage-mediated HIV neurotoxicity is cathepsin B, a member of the cysteine protease family. We recently demonstrated that cathepsin B is upregulated in HIV-1 infected macrophages, and secreted in a form that causes neuronal apoptosis in vitro (Rodriguez-Franco et al., 2012). Our central hypothesis is that increased secretion of neurotoxic cathepsin B by HIV-infected macrophages causes neuronal dysfunction and death, and contributes to the pathogenesis of HAND. In preliminary studies of post-mortem tissue, we found cathepsin B was upregulated in the hippocampus and basal ganglia of patients with HAND. In addition, studies of Hispanic women with HAND demonstrated increased cathepsin B and cystatin B expression in plasma and monocytes, and decreased cathepsin B activity in the CSF (Cantres et al., 2013). This research is significant because it is expected to advance the understanding of the mechanisms of macrophage-derived products in neurotoxicity and to find additional targets for therapy. **Supported by NIH R01-MH08316-01, NCRR (2G12-RR003051) NIMHH (8G12-MD00760), SNRP-NINDS-1-U54NS43011.**

ERADICATION OF HIV RESERVOIRS FROM THE BRAIN. Nath A; Section of Infections of the Nervous System, NINDS, National Institutes of Health, Bethesda, MD 20892.

The successful eradication of HIV from a single patient and recent advances in genetic engineering as well as advances in our understanding of HIV pathogenesis have raised the possibility of developing therapeutic approaches for HIV eradication from tissue reservoirs. Thus several approaches are currently under various stages of development. However, their impact on brain reservoirs is not clear. Concern has been raised about approaches that require reactivation of the virus in the reservoirs due the possibility of cerebral injury from an inflammatory response in the brain, Before such strategies for cure can be implemented, several fundamental questions about the HIV reservoirs in the brain need to be answered. It remains unknown as to when the virus infects the brain and what host factors influence establishment of the reservoir. While HIV infects macrophages/microglia, the role of infection of other cell types in the brain is less clear. The rate of turnover of these cell types will determine if infected cells can be replaced with genetically engineered cells. For such strategies to be effective, it will be critically important to develop technology to measure the tissue reservoirs *in vivo*. In patients with high viral burden, the option of long-term viral suppression resulting in a functional cure may need to be considered. **Supported by NINDS.**

SEX STEROID MODULATION OF THE BEHAVIORAL RESPONSE TO COCAINE.

Segarra AC; University of Puerto Rico, Physiology Department, School of Medicine, San Juan, Puerto Rico 00936-5067. annabell.segarra@upr.edu

Sex hormones, such as estradiol and testosterone, regulate many motivated behaviors, such as eating, sexual behavior and drug intake. Our laboratory has studied the role of estradiol in cocaine sensitization and conditioned place preference (CPP) in male and female rats. In ovariectomized females, estradiol exacerbates sensitization and CPP to cocaine. Blocking estrogen receptors in the CNS of gonadally intact females by icv administration of the antiestrogen ICI 182,780 blocks sensitization and CPP to cocaine. In orchidectomized males, testosterone and estradiol, but not dihydrotestosterone, can restore sensitization to cocaine as observed in gonadally intact males. The interaction of sex steroids with D2 receptors in the nucleus accumbens of male and female rats will be discussed.

Supported by NIDDK, U54NS39405, and R25Gm061838.

HIV-RELATED PAIN AND GP120 IN THE BRAIN[1]Jonathan Palma, [1]Ellen B. Geller, [1]Martin W. Adler, [1,2]Toby K. Eisenstein and [1]Khalid Benamar.[1]Center for Substance Abuse Research, Temple University School of Medicine, Philadelphia, Pennsylvania, USA. [2] Department of Microbiology and Immunology, Temple University School of Medicine, Philadelphia, Pennsylvania, USA

Pain is part of the clinical picture associated with HIV and AIDS. Pain occurs at all stages of HIV-1 infection, although its severity and frequency are correlated with disease progression. HIV-infected individuals experience various pain syndromes (e.g. peripheral neuropathy, bone pain, headache etc), and they can have two or three different types of pain at any one time. Pain in patients with HIV disease may arise from various sources, including the effects of HIV by itself. Gp120, the surface envelope protein used by the virus to gain access into immune cells, has been implicated as a neurotoxic factor in HIV-infected individuals, and can mimic many of the behavioral and physiological dysfunctions that are characteristic of HIV infection, including peripheral neuropathy. In the present study sought to examine the supraspinal contribution of gp120 to HIV-related pain. Adult male Sprague-Dawley rats weighing 200-250 g were used, 8-10 rats per group. A sterilized stainless steel C313G cannula guide (Plastics One Inc., Roanoke) was implanted into the periaqueductal grey (PAG), and the hot-plate test was used to measure the nociceptive response. Gp120 (100-250 ng) microinjected into the PAG evoked a dose-related nociception. Pretreatment with the CXCR4 receptor antagonist AMD 3100 attenuated gp120-induced nociception. These results show the presence of gp120 in the PAG has a nociceptive effect. Furthermore, the fact that AMD 3100 reverses this effect indicates that this antagonist appears to have antinociceptive -like properties. Thus, targeting CXCR4 may have a potential therapeutic application in interventions seeking to prevent or control HIV-related pain.

Financial Support: DA 360682 and DA13429

MORPHINE ADMINISTRATION INCREASES SYSTEMIC INFLAMMATION DURING ACUTE PANCREATITIS. Barlass, U[1] , Dutta, R[1] , Kumar, S[1], Dawra, R[1], Roy, S[1], Saluja, AK[1]; [1]Division of BTR/ Department of Surgery, University of Minnesota, Minneapolis, MN 55455.

Analgesia, supportive care, and the treatment of systemic complications are the cornerstones of the treatment of acute pancreatitis. Opioids such as Morphine (MS) or its derivatives are widely used for pain management. The aim of this study was to evaluate the effect of MS on acute pancreatitis severity, gut permeability and systemic inflammation in experimental mouse model. Pancreatitis was induced using Cerulein(50ug/kg, hourly x 12), followed by implantation of subcutaneous pellet of MS (25mg) or placebo. Mice were sacrificed 48h after start of experiment. Gut permeability was significantly increased in animals with acute pancreatitis treated with MS as compared to acute pancreatitis alone. Subsequently an increase in bacterial translocation was observed in different organs(Lungs, Liver, Spleen, Mesenteric lymph nodes) in the same group. The severity of Pancreatitis and its systemic complications were also assessed. Myeloperoxidase activity in the lungs and pancreas, a measure of systemic inflammation (neutrophil infiltration) was significantly increased in the pancreatitis + MS group compared to pancreatitis alone, suggesting a persistence of inflammation. Histopathological evaluation of the pancreas again confirmed continuation of inflammation in MS treated group. MS increases intestinal permeability in mice with acute pancreatitis and causes a persistence of systemic inflammation compared to those with placebo. Our findings suggest that morphine should be cautiously used as analgesia in patients with acute pancreatitis. Supported by NIH grants DK093047,DK058694(AKS).

FUNCTIONAL ADAPTATION OF NMDA RECEPTORS FOLLOWING HIV-1 TAT-INDUCED POTENTIATION. Krogh, KA[1], Thayer, SA [1]; Department of Pharmacology, University of Minnesota Medical School, Minneapolis, MN 55455

HIV-associated neurocognitive disorders (HAND) afflict approximately 30% of HIV-infected patients despite antiretroviral treatment. Synaptodendrictic changes correlate with cognitive impairment in patients with HAND. HIV-infected cells in the brain shed viral proteins, such as the transactivator of transcription (Tat), which causes synapse loss via an NMDA receptor (NMDAR) dependent mechanism. Here, I provide evidence that Tat causes a time-dependent, bi-phasic change in NMDAR-mediated Ca^{+2} influx. Tat-induced changes in NMDAR function were measured using fura-2-based Ca^{+2} imaging of rat hippocampal neurons in culture. Ca^{+2} influx was triggered by the transient application NMDA (10 µM) following 0 to 48 h exposure to Tat (50 ng/mL). Exposure to Tat for 1 h potentiated NMDAR-mediated Ca^{+2} influx. Potentiation persisted for 8 h then adapted. NMDAR-mediated Ca^{+2} influx returned to basal levels after 24 h exposure Tat and dropped below baseline after 48 h. Tat-induced NMDAR potentiation was prevented and reversed by inhibitors of lipoprotein (LRP) receptors (RAP, 50 nM) and Src-family kinases (PP2, 10 µM), but was unaffected by a nNOS inhibitor (L-NAME, 100µM). However, L-NAME prevented adaptation. Together, these findings indicate that Tat potentiates NMDARs via the LRP receptor and a Src-family kinase and this potentiation adapts via a nNOS-mediated pathway. This adaptation might be a neuroprotective mechanism to prevent excessive Ca^{+2} influx through NMDARs. Enhancing our understanding of such mechanisms could reveal targets for the treatment of HAND.

Supported by NIH NIDA / T32DA007097 R37DA07304

Correlating SIV phylodynamic patterns and pathogenesis in the CD8-depleted Rhesus macaque model of neuroAIDS.

Marco Salemi
Department of Pathology, Immunology and laboratory Medicine & Emerging Pathogens Institute, University of Florida, Gainesville, FL, USA.

SIV infection of CD8-depleted rhesus macaques is a well-established rapid disease model of neuroAIDS. Six animals were intravenously inoculated with the SIVmac251 viral swarm and followed longitudinally until the onset of SIV associated encephalitis (SIVE) or meningitis to investigate the relationship between intra-host viral evolution and neuropathogenesis.

Approximately 1200 SIV gp120 sequences were sampled at three different time points from peripheral blood, multiple lymphoid tissues (including lung lymph nodes and bone marrow), as well as *post mortem* brain tissues. Bayesian phylodynamic analysis was performed to deduce the mode of transmission, the tempo of the appearance, and the spatial distribution of the virus in the brain. In addition, a novel algorithm was implemented to infer intra-host viral gene flow and transition times between different tissues.

Multiple brain-seeding events were detected throughout the infection, the initial one occurring as early as seven days post infection (dpi). The tissue of origin of each brain-seeding event appeared to follow a consistent order in each primate. Early in infection, SIV strains entering the brain mostly originated from plasma or peripheral blood, while the last migration wave was driven by viral strains from bone marrow, with a median transition time from periphery to brain of 50 dpi. Experiments with BrdU labeling also showed a significant increase in the export of monocytes from bone marrow at around the same time. Finally, all primates showed a peak in the effective viral population size (*Ne*), which represents the number of effectively infectious genomes contributing to the next generation, between 50 and 85 dpi.

Overall, the data indicate a specific phylodynamic pattern characterized by early SIV entry into the brain followed by a later brain re-infection with SIV strains from monocytes originated in the bone marrow, which coincided with an increase in viral *Ne* and the development of SIVE or meningitis in all animals. Further characterization of SIV infected monocytes in the bone marrow and their relationship with the onset of neuropathogenesis may ultimately provide the key to develop effective markers for HIV-associated neurological diseases, as well as novel targets for therapeutic intervention.

PROTEOMICS APPROACH OF ALCOHOL INDUCED ER STRESS IN HUMAN MICROGLIA CELLS

Ricardo J Carrero, Yanilda Ramos, Sheila Lopez, Janaina Alves, Hiram Escobales, Madeline Rodríguez, and Nawal Boukli. Universidad Central del Caribe

Microglia cells (MC) are the only line of defense, acting as Macrophages, antigen presenters T cells after the Brain-Blood-Barrier, Brain, and Spinal Cord. We hypothesize that Alcohol triggers a UPR endoplasmic reticulum (ER) stress driven response in human microglia cell line. This process typically protects cells from the toxic effects of accumulated misfolded proteins causing ER-stress. Although much is known about ER stress, much less is understood about the consequences of the disruption of these interactions due to alcohol treatment. In the present study, we investigated alterations in MC's viability, with variable concentration of alcohol, using MTT cytotoxic assay, Proteins were analyzed with 2D gel electrophoresis, protein identification using peptide mass fingerprinting, quantitative proteomics, and confirmation at the gene expression level by qRT-PCR. Preliminary results have shown that treated microglia at 2% of alcohol—were not able to show a significant decrease on cell viability when compared to control, whereas treated microglia cells with 3% of alcohol were able to decrease cell viability to almost 50%. MC's proteome induced with alcohol, demonstrated 23 differentially expressed proteins Alcohol significantly changed the expression of key components of the UPR-ER stress induced pathway that include chaperones, ER stress antioxidant enzymes, protein degradation proteins, and enzymes related to alcohol metabolism. qRT-PCR analyses highlighted enhance expression of important UPR and antioxidant genes that increased rapidly with alcohol treatment. Results of these analyses provide insights into alcohol mechanisms of regulating MC, and may suggest that alcohol induced a UPR transcriptional program in MC. We speculate that activation of a UPR by alcohol may protect the MC from oxidant injury that may lead to the development of alcohol-related diseases.

Supported by Supported by NIH-RCMI Biomedical Proteomics Facility 2G12RR03035.

EXOSOME-MEDIATED SHUTTLING OF MICRORNA-29 REGULATES HIV TAT AND MORPHINE-MEDIATED NEURONAL DYSFUNCTION.

Hegde R[1], Callen S[2], Hu G[2],Yao H[2], Chaudhuri AD[2], Duan M[2], Yelamanchili SV[2], Wen H[2], Cheney PD[1], Fox HS[2],Buch S[1,2].
[1]Department of Molecular and Integrative Physiology, University of Kansas Medical Center, Kansas City, Kansas 66160, USA; [2]Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198.

Neuronal damage is a hallmark feature of HIV-associated neurological disorders (HANDs). Opiate drug abuse accelerates the incidence and progression of HAND; however, the mechanisms underlying the potentiation of neuropathogenesis by these drugs remain elusive. Opiates such as morphine have been shown to enhance HIV transactivation protein Tat-mediated toxicity in both human neurons and neuroblastoma cells. In the present study, we demonstrate reduced expression of the tropic factor platelet-derived growth factor (PDGF)-B with a concomitant increase in miR-29b in the basal ganglia region of the brains of morphine-dependent simian immunodeficiency virus (SIV)-infected macaques compared with the SIV-infected controls. In vitro relevance of these findings was corroborated in cultures of astrocytes exposed to morphine and HIV Tat that led to increased release of miR-29b in exosomes. Subsequent treatment of neuronal SH-SY5Y cell line with exosomes from treated astrocytes resulted in decreased expression of PDGF-B, with a concomitant decrease in viability of neurons. Furthermore, it was shown that PDGF-B was a target for miR-29b as evidenced by the fact that binding of miR-29 to the 3'-untranslated region of PDGF-B mRNA resulted in its translational repression in SH-SY5Y cells. Understanding the regulation of PDGF-B expression may provide insights into the development of potential therapeutic targets for neuronal loss in HIV-1-infected opiate abusers.

Funding Agency/Grant: This work was supported by grants, DA020392, DA023397 and DA024442 (SB) from the National Institutes of Health.

IN VITRO AND IN VIVO EXPOSURE TO COCAINE ENHANCES HIV INFECTION IN QUIESCENT T CELLS.

Kim SG[1], Dixit D[2], Jung J[2], Rovner RJ[2], Zack JA[1,2], Baldwin GC[1], Vatakis DN[1]; [1]Department of Medicine, Division of Hematology and Oncology, [2]Department of Microbiology, Immunology and Molecular Genetics, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095.

Stimulant use such as cocaine has been shown to impact the human immune system. In regards to the human immunodeficiency virus (HIV) infection, a number of studies have indicated that cocaine users are at an increased risk for infection and display more rapid disease progression and morbidity. However due to many variables such as adherence to antiretroviral therapy, use of multiple classes of drugs and co-infections among others, it is difficult to fully appreciate the impact drug abuse has on HIV disease. We hypothesize that cocaine will influence the kinetics of HIV infection in quiescent cells by increasing their permissiveness to infection. To this end, quiescent cells were exposed to cocaine for three days. Based on our data, 3-day exposure, when compared to quiescent cells, resulted in increased reverse transcription kinetics, higher levels of viral cDNA, increased viral RNA and protein synthesis. In addition, the 3-day treated cells progressed to the G1b phase of the cell cycle and displayed a marked increase in the levels of CCR5. The patterns of enhanced HIV infection were also observed in vivo using the BLT humanized mice. Exposure of mice to cocaine resulted in accelerated and increased HIV infection. Therefore, cocaine exposure increases the permissiveness of quiescent cells to HIV infection through minor changes in their cell state.
Supported by National Institute of Drug Abuse/R21 DA031036-01A1.