

ISNV

International Society for NeuroVirology

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A Message from the President: 2012 ISNV Symposium Brief Summary



Our 11th International Symposium on NeuroVirology and 2012 Conference on HIV and the Nervous System in New York, NY in May/June was a tremendous success! We enjoyed a modern, cosmopolitan venue at the Grand Hyatt New York where our local chair David Volsky and organizing committee, Joan Berman, Susan Morgello and David Simpson, welcomed over 300 scientists and students from 13 different countries. The program included 4 1/2 days of 12 sessions, 12 plenary speakers, 81 total speakers, 5 Lectureship talks and 3 workshops (NIDA-sponsored 'Intersection of Substance Abuse and HIV in the CNS', 'Demyelinating disease pathogenesis including Multiple Sclerosis and polyomaviruses' and 'NeuroAIDS NRSA (T32) Trainee Workshop').

A Global NeuroAIDS Roundtable that was sponsored by the National Institute of Mental Health/NIH preceded the Symposia. The Roundtable featured research from Africa, Asia, Latin America, and Eastern Europe including several multi-site NeuroAIDS studies and focused on status updates for trends in the HIV epidemic regarding treatment regimens, response to treatments, and clinical patterns (for a brief summary see page 5).

A very successful evening poster session featured over 275 posters, which enabled attendees to network and seek common interests to expand their scope of research for future collaborations as well as meet and discuss young investigators research.

During the Pioneer in NeuroVirology Gala Dinner, Avi Nath was presented with the prestigious Pioneer Award. In keeping with our tradition, 10 Young Investigators-in-Training were honored for their work and presented with awards recognizing past Pioneer Award recipients (see page 3). Overall, the scientific program was cutting edge and all agreed that it was one of our most successful. We are already planning for the fall 2013 Symposium in Washington, D.C. Let us know your thoughts! Stay tuned for more updates in the next Newsletter.

Finally, as I approach the end of my 3-year tenure as the President of the Society, I offer my sincere thanks to the membership for allowing me to serve as your President. It has been a privilege to represent you and I am excited for the new President, Avi Nath, to take us to new heights.

Lynn Pulliam

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Science News

Nodding Syndrome in the News

Avindra Nath



Researchers in Kampala planning future studies on nodding syndrome. From left to right: Jeffrey Ratto, statistician for International Refugee Health Branch, Center for Global Health, CDC; Avi Nath, NIH; Eilene Farnon, CDC; James Sejvar, CDC.

Neurovirologists on the team in Uganda investigating Nodding Syndrome - A mysterious brain disorder seems to be spreading in the war torn regions of South Sudan and adjacent regions of Northern Uganda (Donnelly J, *Lancet*, 379: 299, 2012 and Wadman M, *Nature*, 475: 148-149, 2011). This disorder has been reported to affect up to 3000 children within the ages 5-15 years as estimated by the National Task Force of Uganda. This apparently new epileptic condition manifests as atonic seizures resulting in repetitive head flexion and hence called Nodding Syndrome (see photo below). The symptoms progress to cause persistent neuropsychiatric and cognitive problems, as well as development of additional seizure types; some children have died from trauma or accidents related to the seizures. Despite extensive investigations to date no cause has been found. A persistent but puzzling association with a parasite *Onchocerca volvulus* that generally infects the skin and eyes, but is not known to cause nervous system illness, and is endemic in this region, has been found. Vitamin B6 deficiency has also been identified as a possible contributory factor, although further investigation is needed (CDC, *MMWR* 61: 52-54, 2012). Several features of this epidemic suggest the possibility of a yet unidentified infectious agent.

Investigation of this population poses multiple challenges. The population resides in a remote region in Africa, which has been ravaged by war for several decades. Moreover, the population is largely uneducated, live under poor hygienic conditions and have high co-morbidities. To address these challenges and the urgent need for intervention, the World Health Organization (WHO) convened a team of scientists from the Center for Disease Control (CDC), the National Institutes of Health (NIH), European agencies and local researchers and officers of various levels of government, in Kampala from July 28-August 2, 2012 (see photo to the left). Neurovirologists James Sejvar (Neuroepidemiologist, Division of High-Consequence Pathogens and Pathology National Center for Emerging and Zoonotic Infectious Diseases at CDC) and Avindra Nath (Chief, Section of Infections of the Nervous System at the National Institute of Neurological Diseases and Stroke at NIH) were amongst the team of scientists. Dr. Sejvar and his team have been investigating this syndrome for the past two years. The meeting was successful in developing a working case definition of the syndrome, which can be used for prospective surveys of this population and other regions in Africa. This will also allow for initiation of clinical trials with anti-seizure medications, anti-parasitics and other symptomatic treatments. Further collaborative efforts are underway for investigation of the potential role of environmental toxins, *Onchocerca volvulus* infection, immune-mediated pathophysiology, genetic disorders and novel pathogens. However this will largely depend on the ability to collect appropriate biological samples which remains a daunting task.



NeuroAIDS NRSA T32 Trainee Workshop

Jay Rappaport and Brian Wigdahl



Clockwise from top: Kimberly Williams, Sarah Gheuens, Sarah Beltrami, Anna Abt

At the 11th International ISNV meeting in New York, the NeuroAIDS NRSA (T32) Trainee workshop was held for the third consecutive Symposium. This workshop has been highly successful and has been well attended by trainees and mentors at all levels. Dr. David M. Stoff, Division of AIDS Research, NIMH, gave the opening lecture of this session, describing historical trends in career development at the NIMH and NIH, various training approaches and mechanisms of support, as well as the broad mission and priority areas for NIMH. From the data presented, NIMH is highly committed to research training with over 10 percent of its budget directed toward

and comorbidities of HIV infection are the current emphasis on NeuroAIDS research and training supported by the NIMH. Dr. Stoff also discussed the future policy directions in NIMH training, with the goals of facilitating the temporal transition to independence and foster the successful first-time funding of new investigators.

Following the presentation by Dr. Stoff, trainees from four institutions presented their exciting and interesting work, including Sarah Gheuens (Postdoctoral Fellow, Beth Israel Deaconess Medical Center – Harvard Medical School, Boston, MA), Sarah Beltrami (Graduate Student, Temple University School of Medicine, Philadelphia, PA), Kimberly Williams (Graduate Student, The University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC) and Anna Abt (Graduate Student, Drexel University College of Medicine, Philadelphia, PA). For the complete agenda for this session, co-chaired by Jay Rappaport, Ph.D. (Temple University School of Medicine) and Brian Wigdahl, Ph.D. (Drexel University College of Medicine), please see <http://isnv.org/newyork12/06-01.php>. Based on the success and interest in this session, it is anticipated that this workshop will continue in future ISNV meetings.

training activities, with the T32 training grant mechanism being the most strongly supported. With improved treatments for HIV and longer life expectancies, the increased neurological complications

Investigator-in-Training Awardees

Dianne Langford

During the 11th International Symposium on NeuroVirology in New York, the ISNV was honored to present ten Investigator-in-Training Travel Awards to outstanding young investigators from top

neurovirology laboratories. Trainees presented their research at special sessions held at the 2012 New York meeting. Awardees included:



(A) Dionna Williams, (B) Manohar Mutnal, (C) Matthew Cusick, (D) Bradley Hollidge, (E) Camilla Carloni, (F) Sarah Berth, (G) Amrita Datta Chaudhuri, (H) Stephanie James, (I) Laura Ellis, and (J) Daniela Pajek

Awardee	Neurovirology Pioneer	University, Laboratory	Research Topic
Dionna Williams, Graduate Student	Diane Griffin	Albert Einstein College of Medicine, Joan Berman	HIV
Manohar Mutnal, Postdoctoral Fellow	Hilary Koprowski	University of Minnesota, James Lokensgard	CMV
Matthew Cusick, Postdoctoral Fellow	Michael B. Oldstone	University of Utah, Bob Fujinami	Theiler's Virus
Bradley Hollidge, Graduate Student	Neal Nathanson	University of Pennsylvania, Samantha Soldan	La Crosse Virus
Camilla Carloni, Graduate Student	Volker ter Muelen	University of Milan, Pasquale Ferrante	JCV
Sarah Berth, Graduate Student	Richard T. Johnson	University of Illinois, Scott Brady	HIV
Amrita Datta Chaudhuri, Graduate Student	Opendra Narayan	University of Nebraska, Howard Fox	HIV
Stephanie James, Postdoctoral Fellow	Don Gilden	University of Colorado School of Medicine, Don Gilden	VZV
Laura Ellis, Graduate Student	Kamel Khalili	Harvard University, Igor Koralnik	JCV
Daniela Pajek, Graduate Student	Avindra Nath	University of Glasgow, Gerard Graham	Semliki Forest Virus

ISNV Highlights – Rick Meeker, Ph.D.

Dianne Langford



Front row from left: Kimberley Williams, Lola Hudson, Rick Meeker, Bryan Yonish. Middle row, from left: Youmei Xie, Madison Savage, Gillian Clary. Back row from left: Snehla Rao, Xandi Hamilton, Barbara Sherman, Andrea Thompson, Margaret Gruen

Dr. Rick Meeker is a Professor in the Department of Neurology at the University of North Carolina (UNC) and a member of the Curriculum in Neurobiology. He also serves as Adjunct Professor in the Department of Molecular Biomedical Sciences at the North Carolina State University College of Veterinary Medicine (NCSU-CVM). Rick received his Ph.D. from Bowling Green State University in Ohio and completed post-doctoral training at Purdue University and UNC Chapel Hill in neurobiology and molecular pharmacology. Dr. Meeker joined the Neurology Faculty at UNC in 1982 as an Assistant Professor studying the role of glutamate receptors in neuroendocrine regulation.

Trained in neurobiology and pharmacology, Rick's interest in HIV grew from a desire to better understand the interactions of HIV with the nervous system. His current research activities are equally split between studies in his laboratory at UNC and *in vivo* studies at NCSU-CVM. Studies at UNC are largely focused on understanding the biology of HIV-associated neural damage using *in vitro* models. *In vivo* studies at the NCSU-CVM are focused on the neuropathogenesis of lentiviral infection using feline immunodeficiency virus (FIV) as the model. The overarching goal of these studies is to identify new therapeutic strategies, which can then be translated to an infectious animal model for preclinical evaluation.

Dr. Meeker's *in vitro* research efforts continue to explore the cellular mechanisms that underlie the development of neural damage. Early work focused on the development of tissue culture models for the investigation of FIV neuropathogenesis with an emphasis on the role of glutamate receptors. Parallel *in vivo* studies of FIV in collaboration with Dr. Lola Hudson and other FIV investigators at the NCSU-CVM were used to validate the model and to explore the potential contribution of macrophage trafficking across the blood-CSF barrier to infection and disease progression. A major goal of these collaborations was to improve CNS infection and neurovirulence of FIV to overcome the slow progression of CNS disease in FIV-infected cats. Dr. Meeker and collaborators were able to establish protocols that increased brain infectivity and viral burden resulting in more robust CNS disease in the feline model. This collaboration now includes a team of behavioral specialists at the NCSU CVM headed by Drs. Barbara Sherman and Margaret Gruen, who have developed new protocols for cognitive testing of the cats. These tests are designed to provide sensitive assessments of disease progression at various stages of FIV infection, which can then be used to evaluate efficacy of novel neuroprotective treatments.

The search for neuroprotective agents has employed a variety

of convergent approaches in cultures of neurons, microglia and macrophages including challenges with gp120, live and attenuated virus, macrophage supernatants and samples of HIV+ human CSF. The Meeker laboratory identified delayed calcium deregulation as a critical step in the development of neuronal pathology and verified that macrophage-conditioned medium had the most potent toxic activity. The actions of macrophage toxins that give rise to the pathology are not well understood and remain a focus of ongoing *in vitro* studies. Array studies of proteins in HIV+ CSF and in macrophage supernatants, designed to identify toxic factors, unexpectedly showed that changes in growth factors was a common finding. Subsequent studies were guided by the belief that pathogenesis may not only be

due to the secretion of toxic factors from macrophages, but also a failure to provide adequate trophic support. To explore this idea, the Meeker laboratory began collaborating with Dr. Frank Longo from Stanford who was just completing screens for non-peptide ligands that mimic the structure of neurotrophins. Studies investigating the prototype p75 neurotrophin receptor ligand, LM11A-31 showed strong neuroprotection and the capacity to suppress the delayed calcium dysregulation in neurons (Meeker et al., *J. of Neuroimmune Pharmacol.*, 7: 388-400, 2012). These experiments also revealed potential direct effects of neurotrophin ligands on macrophages and stimulated the recent characterization of p75 neurotrophin receptors (NTR) and the nerve growth factor receptor, TrkA, on human macrophages (Fig. 1). In light of these findings and the failure to protect neurons with numerous other strategies, his lab focused on studies needed for the translation of LM11A-31 to the FIV model and beyond. Dr. Meeker is "guardedly optimistic" that these efforts will lead to the clinical use of a new generation of potent compounds that protect neurons from damage due to HIV and possibly other neurodegenerative diseases.

Dr. Meeker's neuroprotection studies are now paralleled by studies at NCSU-CVM designed to assess the efficacy of novel antiretroviral compounds with a particular emphasis on substances that cross the blood-brain barrier and suppress virus replication in macrophages/microglia. Two compounds that target conserved proteins necessary for HIV and FIV replication are currently under investigation. These studies offer the hope that newer agents may be developed to reduce the CNS viral burden. It is Dr. Meeker's hope that together these efforts will provide new approaches that protect the brain against a variety of inflammatory challenges and also restore functions lost as a result of infection.

As a dedicated educator and mentor, Rick has trained numerous graduate and undergraduate students, post-doctoral fellows and junior faculty. He is an active member of several NIH study sections and journal review panels. His laboratory is supported by NIH and continues to publish cutting edge manuscripts in top-level peer reviewed scientific journals.

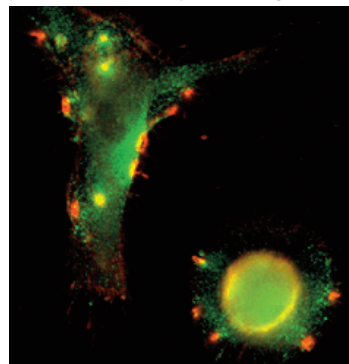


Figure 1. Expression of p75NTR (red) and TrkA (green) on human monocyte-derived macrophages.

ISNV Highlights - Lena Al-Harhi, Ph.D.

Dianne Langford

Dr. Lena Al-Harhi's laboratory focuses on cross talk between Wnt/ β -catenin signaling, inflammatory mediators, and HIV during regulation of HIV transcriptional activity and CNS pathogenesis. The Wnt/ β -catenin pathway is vital for proper CNS development and homeostasis and regulates hundreds of genes, including those involved in cell proliferation and survival via its interaction with TCF/LEF transcription factors. While considerable information exists on the role of Wnts in neuronal synaptic activity and plasticity, little is known about their role in astrocytes. Lena's laboratory has identified key contributions of the Wnt/ β -catenin signaling pathway on HIV replication in astrocytes. The Al-Harhi laboratory also showed that β -catenin interacts with TCF-4 on HIV's LTR to recruit the nuclear matrix protein SMAR (Henderson *et al.*, *J. Virology*, 86: 9495-9503, 2012). This interaction results in dissociation of HIV DNA from transcriptional machinery and repression of basal LTR activity. Moreover, her group showed that β -catenin's interaction with TCF-4 impairs Tat/TAR association and HIV replication (unpublished data). Her group also determined that this pathway exists in primary peripheral mononuclear cells (Kumar *et al.*, *J. Virology*, 82: 2813-2820, 2008). Dr. Al-Harhi proposes that factors that diminish β -catenin signaling will induce HIV productive replication and perturb astrocyte function. In this context, data from her lab showed that IFN- γ enhances HIV replication in astrocytes by inducing an antagonist of β -catenin signaling (DKK1) in a Stat-3 dependent manner (Li *et al.*, *J. Immunology*, 6: 597-607, 2011). Recently, studies from her laboratory reported that diminished β -catenin signaling in astrocytes impacts 128 genes involved in inflammation/immunity, uptake/transport, vesicular transport/exocytosis, apoptosis/cellular stress genes, and cytoskeletal/trafficking (Narasipura *et al.*, *J. Virology*, 86: 1911-1121, 2012). These findings suggest that diminished β -catenin signaling lead to enhanced HIV permissiveness in astrocytes and dysregulation of glutamate uptake (Fig. 1). Previously, the Al-Harhi laboratory studied the role of a unique subset of CD8+/CD4+ T cells called double positive (DP) T cells and showed that β -catenin signaling drives *de novo* expression of CD4 on CD8+ T cells (Schenkel *et al.*, *J. Immunology*, 185: 2013-2019, 2010). Two main findings from this research showed that DP T-cells are enriched in potent anti-HIV responses compared to CD8+ T cells (Zloza *et al.*, *Blood*, 114: 3841-3453, 2009) and that DP cells are present in the CNS of both infected and uninfected NOD/SCID/IL-2 γ ^{-/-} mouse reconstituted with human PBMCs. Whether these cells in the CNS are



Figure 1. Front row from left to right: Stephanie Min (Research tech), Erika Szotek, MS (Research tech), Lisa Henderson (PhD student), Lena Al-Harhi, PhD (PI), Srinivasa Narasipura, PhD (staff scientist); Back row from left to right: Amit Sharma, PhD (post doc), Maureen Richards, PhD (post doc)

neuroprotective or pathogenic is currently under investigation.

Dr. Al-Harhi received a Ph.D. in 1996 from George Washington University under the direction of Robert Gallo at Rush University where she enjoys mentoring postdoctoral fellows, graduate and undergraduate students. She serves on numerous committees, is a member of the editorial board of JNV, and has served as a reviewer for several NIH study sections and reviews manuscripts for numerous scientific journals. Her laboratory is supported by funds from NIH.

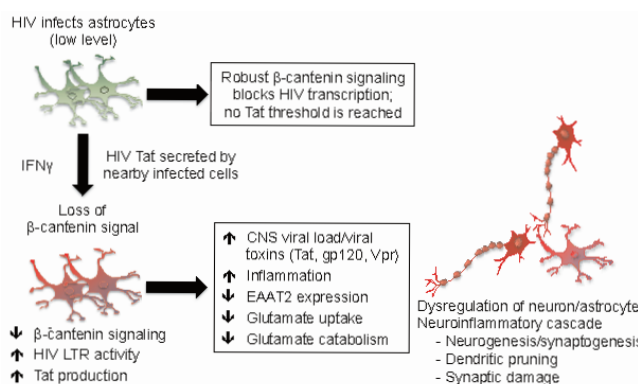


Figure 1. Model of β -catenin signaling in HIV-mediated neuropathogenesis based on extensive data from the Al-Harhi laboratory.

Global NeuroAIDS Round Table

Jeymohan Joseph



The Division of AIDS Research at the National Institute of Mental Health (NIMH) organized a satellite session entitled "Global NeuroAIDS Roundtable" on May 29th, 2012 in conjunction with the 11th International Symposium on NeuroVirology at the Grand Hyatt, New York, NY. This satellite session convened for the first time with NIMH funded investigators examining the impact of HIV on neuro-cognitive impairment from a global perspective. Four major sessions were conducted which included studies from the Africa Region (Uganda, Cameroon, Senegal, Gambia, Nigeria, South Africa, Zambia), Asia Region (India, China, Thailand) and several Multi-site projects (India, China, Peru, Brazil, Romania, South

Africa). A key goal of the meeting was to assess if global clade diversity had any impact on HIV-associated neurocognitive impairment. Data were presented from regions of the world where individuals were infected with Clades A, D, G, B, C, F, Recombinant CRF02_AG, AE_01, BF and BC and HIV-2. Preliminary studies presented showed that except for HIV-2 all clades of HIV-1 examined resulted in neurocognitive impairments. Studies in Uganda showed that in untreated HIV+ adults with advanced immunosuppression, HIV dementia may be more common among those patients with subtype D than those with subtype A. Conversely, HIV Subtype A was associated with poorer neuropsychological performance compared to subtype D in treatment-naïve Ugandan children. The Future Directions session examined several areas for follow-up relating global HIV-subtype diversity and neuropathogenesis.

ISNV Highlights - Valerie Wojna, Ph.D.

Shilpa Buch



The Wonja Laboratory from left to right: Rosa J. Rodriguez, Yamil Gerena, Valerie Wojna, Claribel Gonzalez, Joyce Velez, Rosa Hechavarria, and Miriam Matos. Not pictured: Tania Ginebra, Antonia Ortiz and Raul Mayo. Previous members of the laboratory that contributed significantly to the research are Tania De La Torre and Sharon Santiago.

Dr. Valerie Wojna is a Professor at the Neurology Division in the Department of Internal Medicine at the University of Puerto Rico, School of Medicine (UPR MSC). Valerie received her MD degree with a Neurology specialty, and Clinical Neurophysiology subspecialty at UPR MSC. In her capacity as a clinician-scientist, Valerie has taken on multifarious roles including patient service and education, mentoring & teaching of medical students and residents, as well as conducting translational research. All these are activities that she is very passionate about. As a clinical neurologist with a focus on women's health, she is committed to serving the underserved population and has established a unique cohort of Hispanic/Latino HIV-seropositive women to study HIV-associated neurocognitive disorders (HAND) with and without drug abuse.

Valerie's passion for helping her patients eventually led her to also embark on the career path of basic research. Her research interest is focused on examining the role of the soluble insulin receptor as a possible surrogate marker for HAND in the longitudinal cohort of Hispanic/Latino HIV-infected women (Gerena et al, *PLoS ONE* 7:e37358, 2012). Using this cohort, she has also investigated CSF for the presence of oxidative stress markers such as protein carbonyls, nitrosylated proteins, and antioxidant enzymes that could have potential value for development as disease biomarkers. She has played a lead role in the implementation of a Spanish Neuropsychological battery for determination of HAND, which is a Spanish validation of the HIV dementia scale.

Valerie's accomplishments include procurement of an extramural career development grant aimed at investigating the role of sex hormones in HAND in the cohort of Hispanic/Latino HIV-infected women. She attributes her success and achievement to the guidance and mentorship that she received from Dr. Avindra Nath, Clinical Director and Chief of the Section of Infections of the Nervous System of NINDS, NIH, and the support she received by the Special Neuroscience Research Program. She has since collaborated extensively with leaders in the field including Avi Nath, Justin McArthur, Norm Haughey, Ola Selnes, and Richard Skolasky.

Valerie has also been very active as an administrator serving as the Internal Advisor of the Puerto Rico Clinical & Translational Research Consortium (PRCTRC), Interim Editor-In-Chief of the *Puerto Rico Health Sciences Journal*, and Chair of Neurology Residency Research Committee. She has served as a member of various collaborative groups such as the NIH NINDS NIMH working group to define HAND, the Office of HIV/AIDS Network Coordination (HANC)-Behavioral Sciences Working Group (BSWG)-(NIMH/NIH) – for the consensus on neuropsychological assessment of patients with HIV/AIDS, and the NINDS Neuroscience Training Study Group. Currently, she serves on the Neurology Collaborative Science Group of the ACTG Network. Valerie is also a member of the Mind Exchange Program, an educational grant supported by Abbott International aimed at providing practical guidance for clinical management of HAND.

As a continuing educator, she participates in the Johns Hopkins NIMH Center for Novel Therapeutics (JHU R25), in the Master's in Clinical Research Program, and mentorship duties. The Hispanic/Latino HIV-infected women's cohort serves as a platform for teaching students of all levels ranging from high school, undergraduate, medical students, and young faculty at the UPR MSC and Rio Piedras, and other medical schools in PR, Universidad Central del Caribe and Ponce School of Medicine & Health Sciences, as well as the University of Nebraska Medical Center (UNMC). Valerie is an effective mentor and enjoys training students. Several of her students have received pilot and travel awards from NIH. Based on her passion for teaching and her accomplishments she was nominated both by the students and faculty for membership to the Alpha Omega Alpha Society.

Valerie sets a perfect example of having a balanced life. In addition to all her professional responsibilities, she also finds time for pursuing her hobbies that include flamenco dancing. She is a role model for women in science both at her Institute and outside.

ISNV Highlights - Fatah Kashanchi Ph.D.,

Dianne Langford

Dr. Fatah Kashanchi received his Ph.D. in 1990 from the University of Kansas in the laboratory of Dr. Charles Wood. He was further trained in Dr. John Brady's laboratory at NIH/NCI from 1991-1998 where he published over 30 papers. His research interests include Genomics and Proteomics of HIV-1 and HTLV-1-infected cells as well as transcription and epigenetic modulations. Research in the Kashanchi laboratory has been funded by private foundations and governmental organizations including DOE, DOD, and NIH. In total, he has obtained \$11.2 M in independent funding since his departure from NIH. He has 150 peer-reviewed publications in scientific journals, 9 book chapters, and is active in NIH study section review panels. He reviews for 12 journals and is on the editorial boards of *Retrovirology*, *JBC* and three *PLoS* journals. Dr. Kashanchi has trained 21 postdocs, 18 PhD, 26 MS, and 8 Research Assistant Professors. He recently joined the biodefense program at George Mason University and is Director of Research for the program.

Studies in the Kashanchi laboratory on HIV-1 latency and transcription have generated novel concepts regarding promoter-bound proteins that regulate mRNA biogenesis (including capping, elongation, termination, poly A addition, splicing), nuclear-cytoplasmic transport, and activation of nonsense mRNA degradation. His laboratory has mainly focused on HIV-1 Tat's control of fundamental signal transduction pathways in HIV-infected T-cells and macrophages. In this context, they discovered a GSK-3 protein complex in HIV-1-infected cells. In collaboration with the Kutsch laboratory at the University of Alabama Birmingham, they used a high throughput screening assay and discovered a new GSK-3 inhibitor, 6BIO. Through screening, they identified 6BIOder, which has a lower IC₅₀ in primary macrophages. Using primary cells, they also demonstrated that both 6BIO and 6BIOder have neuroprotective effects on Tat-induced cell death in rat mixed hippocampal cultures.

In collaboration with Dr. Aarthi Narayanan's lab at George Mason University, Fatah discovered exosomes as vehicles for intercellular communication. This important finding has opened new avenues of host-pathogen interactions, infection spread and viral modulation of host gene expression. While the concept of exosomes is well documented in the cancer field and viruses such as EBV, there are very few studies demonstrating exosomes as regulators of host-viral interaction and disease pathology in human retrovirus infections.

The broader interest of the laboratory is to understand the role of exosomes from virally infected cells in regulating host-virus interactions. Their hypothesis is that unique viral and host proteins and microRNAs in the exosomes of infected cells can serve as biomarkers reflective of disease progression and predictive of therapeutic efficacy. In support of this, Dr. Kashanchi's group has



Fatah Kashanchi (left) and Kylene Kehn-Hall (right) discuss ongoing collaborations.

detected virus-derived small, non-coding RNA species within exosomes from supernatants of HIV-infected PBMCs *in vitro* and from plasma clinical samples. The laboratory has carried out extensive proteomic analyses of exosomes using approaches such as LC-MS/MS and Reverse Phase protein microarray analyses and have identified approximately 100 host proteins and unique microRNAs in exosomes derived from HIV-1-infected cells, some of which are cytokines and kinases in disease relevant signaling cascades. These observations imply strong functionality from infected exosomes pertaining to cell-cell communication (Fig. 1).

The Kashanchi laboratory works closely with Dr. Kehn-Hall's laboratory at NCBID on a number of viruses related to CNS pathology, and have recently discovered a remarkable link between the neurotropic Venezuelan Equine Encephalitis Virus (VEEV) biology and the cellular microRNA. Arthropod-borne viruses are important causes of acute encephalitis and an emerging worldwide problem with significant risk for importation into new regions. The mosquito-borne encephalitic alphaviruses, VEEV, Eastern Equine Encephalitis Virus (EEEV), and Western Equine Encephalitis Virus (WEEV), are endemic in the Americas and cause outbreaks of encephalomyelitis. Despite being recognized as emerging threats, relatively little is known about the virulence mechanisms of these viruses, due to a significant knowledge gap regarding host-pathogen interactions important for their replication. Interference with critical host-pathogen interactions is an important area that can be utilized for therapeutic development. Recent studies implicate microRNA interactions in the pathogenesis of various viral diseases, and while many viruses down-regulate the microRNA pathway to facilitate replication, some viruses utilize specific microRNAs and the RNA interference machinery to enhance their replication. Based on this concept, the Kehn-Hall and Kashanchi laboratories have begun to study components of the microRNA machinery and processing in connection with VEEV replication. Their data indicate that knock-down of microRNA processing machinery significantly hinders VEEV replication. For instance, loss of microRNAs, Drosha and DGCR8 had the greatest effect on VEEV production (4 log), indicating the need for a nuclear processed microRNA for VEEV replication. Ago2 (a critical component of the miRNA machinery) null cells also demonstrated significantly reduced (50%) VEEV capsid production and VEEV-GFP expression driven from a duplicated subgenomic promoter. Importantly, of the 5 microRNAs predicted to have complementarity to the VEEV subgenomic promoter, inhibition of miR-3683 reduced VEEV replication. Ongoing studies will determine the influence of the host microRNAs on VEEV replication. Taken together, these studies will identify specific host microRNAs for therapeutic intervention and provide mechanistic details regarding how alphaviruses manipulate this pathway to facilitate replication.

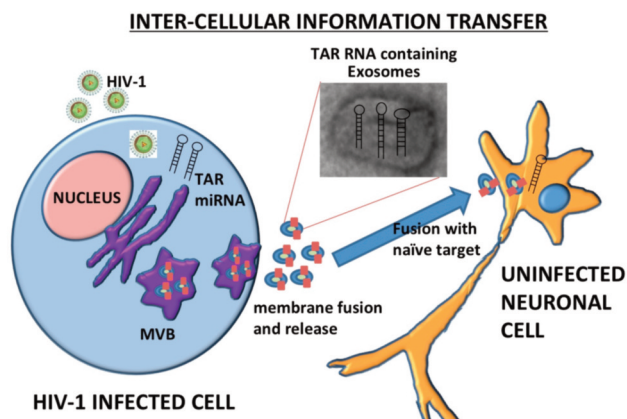


Figure 1. Overview of the effects of exosomes from HIV-1-infected cells on uninfected cells.

Classifieds

Postdoctoral position in drug abuse and NeuroAIDS research

Description: Several post-doctoral fellowship positions are available to join the laboratory of Dr. Lena Al-Harhi in the Department of Immunology/Microbiology at Rush University Medical Center (RUMC), Chicago, IL. The candidate will conduct NIH-funded studies to evaluate mechanisms of exacerbated drug abuse and HIV neuropathogenesis. Competitive applicants should have a Ph.D. degree in a relevant field (e.g. Virology and/or Neuroscience). Experience in NeuroAIDS research, drug abuse research, and working with primary neurons/astrocytes is highly desired.

Employer:

Department of Immunology/Microbiology/Al-Harhi Lab, Rush University. Rush University Medical Center is an institution of higher learning in the biomedical fields located in Chicago, IL. It is an equal opportunity employer.

Location:

Chicago, IL, United States

To apply:

Send resume to Lena_Al-Harhi@rush.edu

Postdoctoral position in HIV-elicited Neuronal Damage

Description: Postdoctoral position to participate in *in vitro* studies of HIV-elicited neuronal injury triggered by HIV/macrophage/neuronal interactions, and mechanisms of therapeutic intervention. HIV activates monocyte/macrophages via direct infection, through envelope gp120-chemokine receptor interactions, and by indirect TLR-mediated mechanisms. These pathways result in both activation of circulating monocytes, and activation of brain macrophages with production of neurotoxins. We are studying novel therapies to inhibit these processes. The project is focused on pathways involved in these processes that can be targeted therapeutically, and mechanisms responsible.

Qualifications:

PhD with a strong background in signal transduction, cell biology (particularly myeloid cell biology) and/or neurobiology (with *in vitro* neuronal cell model experience). Ability to carry out independent investigation. Strong written and oral communication skills.

Requirement:

Must be a U.S. Citizen or permanent resident.

Contact:

Please forward a cover letter, an updated C.V. including a list of your publications, and the names/addresses of 3 references to: collmanr@mail.med.upenn.edu

12TH INTERNATIONAL SYMPOSIUM ON

NEUROVIROLOGY

held jointly with

2013 Conference on HIV in the Nervous System

Coming Fall 2013
Washington D.C., USA

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