

## Nebraska Center for Substance Abuse Research



## Satellite Symposium on HIV, NeuroAIDS, Drug Abuse and EVs

A morning satellite symposium on "HIV, NeuroAids, Drug Abuse, and Extracellular Vesicles" preceded the official opening of the fourth annual International Society for Extracellular Vesicles (ISEV) meeting in Bethesda, Maryland on Thursday, April 23rd 2015.

The symposium was organized by Dr. Shilpa Buch and NIH officials- Drs. Jeymohan Joseph (NIMH) and John Satterlee (NIDA). The general theme of the symposium was based on the role of EVs in HIV pathogenesis and drug abuse co-morbidity.

Within the past decade, extracellular vesicles have emerged as important

mediators of intercellular communication, with their involvement in transmission of biological signals between cells, thereby regulating myriad of biological processes. The field of EVs has seen a sudden explosion as evidenced by a quick glance at the literature: while only about 20 PubMed-referenced papers containing the word "exosomes" were published in 2003, and just over 60 in 2007, over 3000 exosome studies have been published since.

Recognition of the novel roles of EVs in pathophysiological processes such as cancer, infectious diseases, addiction and neurodegenerative disorders,

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### Center Recruit

Dr. Siddappa (Sid) Byrareddy was recruited as an Associate Professor in the Nebraska Center for Substance Abuse Research in the Department of Pharmacology & Experimental Neuroscience at UNMC in August 2015. Dr. Byrareddy completed his doctoral training at the premier Jawaharlal Nehru Center for Advanced Scientific Research and the National Institute of Mental Health and Neurosciences in Bangalore India. He completed his postdoctoral training at the Dana-Farber Cancer Institute in Harvard Medical School and was promoted to Instructor within two years. Dr. Byrareddy began his independent career track as an Assistant Professor at the Emory University School of Medicine. Dr. Byrareddy has a strong background in molecular retrovirology, lentiviral evolution, active and passive immunization and mucosal transmission using primate models. He has over 15 years of research experience and over 50 peer-reviewed publications in the field. Dr. Byrareddy has made significant contributions to his research interests. As a graduate student, he for the first time, showed that tat protein from HIV-1 subtype C is a defective chemokine and provided a model of pathogenesis to explain low levels of dementia in Indians infected with HIV. Furthermore.

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# Welcome message from the Director

Greetings everyone! It is with much enthusiasm that I welcome all of you to the official inauguration of the NCSAR. The Center was officially launched on July 1st 2015 with approval from the University of Nebraska Board of Regents.

Addiction caused by abused substances such as alcohol, opiates, cocaine and methamphetamine continues to be a serious public health problem affecting the health, social, and economic fabric of all societies in the United States and globally- it has no borders. Importantly, many of the nation's top health problems including cancer, cardiovascular and infectious diseases such as HIV/AIDS & Hepatitis, are directly linked to substance abuse. Furthermore, addiction also goes hand in hand with mental health. This is of special concern in the aging population who face increased incidences of mental illnesses such as Alzheimer's & Parkinson's diseases and depression.

The underlying pathways for addiction and the ability of these drugs to synergize with infectious agents, thereby eliciting exacerbated disease pathogenesis, is an area that warrants investigation. Moreover, effective treatment modalities for preventing and treating addiction are limited. This necessitates an urgent need in the field to focus on disease mechanisms underlying the biological processes of drug addiction and/or infection.

The vision of NCSAR is to promote multidisciplinary neuroscience research activities at the University of Nebraska to prevent, treat and diagnose degenerative, inflammatory and infectious neurologic disorders in the context of substance abuse. The Center will provide leadership, mentoring and infrastructure necessary to build upon established research excellence to impact its next stage development through early career faculty development and high-impact discoveries. The overarching goal of NCSAR is to serve as a nexus for enhancing research capacity while building bridges with clinical departments to promote benefits of academic medicine at UNMC. Ongoing collaborations with Departments of Anesthesiology and Psychiatry are a testament to this vision. Understanding that addiction is a chronic, often relapsing brain disease, is a first step in eliminating this debilitating condition. Together we can!

Sincerely, Shilpa Buch, Ph.D.



Ernest (right) receiving the award of NIDA-IAS-ANRS Research Fellowship in HIV and Drug Use from Prof. Françoise Barré-Sinoussi (left) President of the International AIDS Society and Dr. Jacques Normand (centre), NIDA AIDS Research Program Director at the 20th International AIDS conference (AIDS 2014) held in Melbourne, Australia.

## Mentored Fellowship

#### Ernest Chivero awarded NIDA-IAS-ANRS Research Fellowship in HIV and Drug Abuse

Ernest, a native of Zimbabwe and Fulbright Scholar recently graduated with a PhD from the University of Iowa where he was studying the delay in HIV disease progression in people infected with both GBV-C (a benign virus) and HIV. He was recently awarded the prestigious postdoctoral research fellowship in HIV & Drug abuse jointly by National Institute on Drug Abuse (NIH-NIDA), International AIDS Society (IAS) & French Research Agency (ANRS) under the mentorship of Dr. Shilpa Buch to perform research in the area of HIV & drug abuse synergy in the context of CNS disease. Despite the successes of antiretroviral therapy in improving the health of millions of people living with HIV-1, paradoxically as these individuals continue to enjoy increased longevity, the prevalence of HIV-associated neurological disorders (HAND) also continues to rise. Ernest's research is focused on understanding the mechanisms(s) by which residual HIV protein Tat and psychostimulants such as cocaine, co-operative to potentiate inflammatory pathways in the brain microglia, thereby exacerbating symptoms of HAND. His research will contribute to our understanding of the novel molecular pathway(s) critical for neuro-inflammation observed in HIV-infected cocaine addicts, thus providing leads into the development of novel adjunctive therapies for the treatment of HAND and cocaine abuse.

### SYMPOSIUM continued from pg 1

has highlighted novel targets for therapeutic intervention. In fact, both unmodified and engineered EVs are making headway in macromolecular drug delivery approaches.

Role of EVs in HIV, NeuroAIDS and Drug abuse co-morbidity is also gaining momentum. In conversations with NIH officials, it was agreed to organize a satellite symposium at the ISEV. The meeting kicked off with brief introductions of NIH priorities on exosomes by both Drs. Jospeh and Satterlee. This was followed by keynote lectures from experts from Johns Hopkins, Morehouse School of Medicince, George Mason University, University of California at San Francisco. Temple University and UNMC including Drs. Witwer, Haughey, Bond, Kashanchi, Pulliam, Dutta and Buch. The symposium highlighted the emerging trends in the field and this was followed by stimulating panel discussion by the experts with participation from the audience.

## Cocaine-mediated microglial activation involves the ER stress-autophagy axis

Gurudutt Pendyala, Ph.D.

Dr. Minglei Guo obtained his Ph.D. in molecular biology from Fudan University, China in 2006. Then, as a post-doctoral fellow in the laboratory of Drs. Yvonne Wan in University of Kansas Medical Center and later John Wang in the University of Missouri-Kansas City (UMKC), Dr. Guo focused on understanding the mechanisms involved in cocaine addiction. One of Dr. Guo's key research achievements involved identifying a novel role for Ca2+/ calmodulin-dependent protein kinase and dissecting the mechanisms critical for its binding and phosphorylation of the muscarinic receptor 4 which can be linked with cocaine addiction. In addition to this, his key findings on proteinprotein interaction have been critical in our understanding of cocaine-mediated neuronal excitability and behavioral changes. This work was published in the prestigious EMBO Journal in 2010 and importantly, marked his transition into a Research Assistant Professor. Since drug abuse and HIV go hand in hand, in 2013 Dr. Guo joined Dr. Buch's lab at UNMC and extended his research efforts on exploring HIV-associated neurological complications. Dr. Guo's recent findings on the role of

autophagy, a process critical for maintenance of cellular homeostasis, in mediating cocainemediated neuroinflammation, has recently been published in the prestigious *Autophagy Journal* (2015;11:



Minglei Guo Ph.D.

995-1009). These findings highlighted that cocaine-mediated induction of autophagy involved upstream activation of two ER stress pathways (EIF2AK3 & ERN1-dependent), which culminated into activation of microglia. Targeting autophagic proteins could thus be considered as a therapeutic strategy for the treatment of cocaine-related neuroinflammatory diseases. Dr. Guo's current studies are aimed at exploring the role of micro RNAs (miR-124) in drug/HIVinduced addiction/inflammation.



## MiR-9 promotes microglial activation by targeting MCPIP1

Shilpa Buch, Ph.D.



Lu Yang, Yeonhee Kook, Guoku Hu, Ke Liao

In this study, the authors (Yao H, Yang L, Hu GK, Liao K, Kook YH, Niu F, Liao K, Buch S) demonstrated induction of microglial microRNA-9, a highly conserved microRNA abundantly expressed in the CNS of the developing embryo, following exposure to inflammatory stimuli such as LPS and HIV protein Tat. Our findings implicate miR-9 as a regulator of microglial activation via its suppression of the target anti-inflammatory gene MCPIP1. MCPIP1, a novel anti-inflammatory molecule, was a target of miR-9mediated microglial activation. Using both pharmacological and genetic approaches, we demonstrated that the role of NF-ĸB activation in miR-9mediated microglia activation. These findings were also validated in vivo using the genetic approach of injecting mice with lentivirus (anti miR-9) into the

hippocampus/substantia nigra of mice followed by LPS injection. This resulted in restoration of microglial activation thus validating the role of miR-9 in microglial activation. MiR-9/MCPIP1 axis mediates a regulatory pathway critical for eliciting innate immune responses in microglia. Specific blocking of the miR-9 could thus be considered as a potential therapeutic target for treating neuroinflammatory conditions involving microgliosis.



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he has been instrumental in constructing and directing the complete characterization of a number of clade C SHIVs, and has conducted a series of active and passive immunization (involving HIV broadly neutralizing monoclonal/polyclonal antibodies) studies involving mucosal transmission. More recently, his research has focused on understanding gut homing molecules and the development of strategies to protect the gastrointestinal mucosa during HIV/SIV infection. Using anti- $\alpha 4\beta 7$  antibody Dr. Byrareddy's group has shown that this antibody protects against SIV mucosal transmission. This work was recently published in Nature Medicine. He is currently evaluating

interventions aimed at eliminating viral reservoirs from other tissues including the CNS. Dr. Byrareddy is a member of the International AIDS Society, NIH early career investigators group and the global young academy. Dr. Byrareddy has mentored several graduate students, trainees and postdoctoral fellows and has served as PI and co-Investigator on several NIH-funded grants. His ongoing work on opiates and HIV infection makes him ideally suited in understanding the emergence of novel viral variants in Clade C dominant areas of the world. We are thrilled to have Dr. Byrareddy be a part of the NCSAR!

## **Center Members**

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Lu Yang, Ph.D. Department of Pharmacology and Experimental Neuroscience University of Nebraska Medical Center

## What others are saying



"The interdisciplinary capabilities and approaches that will come together in the center will make UNMC a leader in combatting the plaque of substance abuse that brings pain and suffering to so many."

> Bradley Britigan, M.D. Dean, College of Medicine, UNMC



"Substance abuse continues to be a problem both in the region, nationally and around the world. We hope this center will bring together a broad array of expertise needed to understand and better address the consequences of drug abuse as we work together toward better treatments and prevention."

> Jennifer Larsen, M.D. Vice Chancellor for Research. UNMC



Prem Paul, D.V.M., Ph.D. Vice Chancellor for Research and Economic Development University of Nebraska-Lincoln





"I am enthusiastic that the new center will help the state address binge drinking and drug deaths, two behaviors that count towards becoming the healthiest state in the union by 2020."

> Ali S. Khan, M.D., M.P.H. Dean, College of Public Health, UNMC



"As a department we are more than thrilled to support and partner in this effort in the strongest manner possible. Shilpa is the right person to bring this important problem to center stage for our state and nation. The mechanisms, the treatment and prevention of substance abuse is an extension of

all the outstanding work currently being done by the Buch laboratory. This center is a natural next step in its evolution. The impact to our university and its mission is boundless."

> Howard Gendelman, M.D. Chairman, Department of Pharmacology and Experimental Neuroscience, UNMC





"Substance abuse disorders are rampant in society and produce devastating consequences and I'm enthusiastic about the center and its promise to help us understand these disorders better."

> Steve Wengel, M.D. Chair, Department of Psychiatry, UNMC

"We at the Department of Pharmaceutical Sciences will be happy to work with basic scientists and clinicians for Nebraska Center for Substance Abuse Research to accelerate innovative drug discovery for treating drug or alcohol addiction. Our expertise in pharmaceutics and drug delivery will be of great help for

preclinical characterization, pharmacokinetic, toxicity, and scale up of drug candidates, which are essential for drug development and early stage clinical trials. We are very enthusiastic about this Center and look forward to a positive collaboration."

> Ram I. Mahato, Ph.D. Chair, Department of Pharmaceutical Sciences, UNMC



"Substance abuse is a disease and it is important to treat it as one rather than as a behavioral problem. I am enthusiastic that this Center will focus on disease pathogenesis of addiction while also bringing awareness of this much stigmatized disorder."

> Surinder Batra, Ph.D. Chair, Department of Biochemistry and Molecular Biology, UNMC







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