ANIMAL MODELS FOR NEUROAIDS

A Research Symposium

DURHAM RESEARCH CENTER AUDITORIUM
OMAHA, NEBRASKA
MARCH 24, 2011 | 8 A.M. - 4 P.M.
Overview

As we enter the 4th decade of the HIV pandemic, investigations into the diagnosis, prevention and treatment of the virus’s effects on the nervous system continue to evolve.

Despite substantive positive outcomes seen in disease morbidity and mortality as a consequence of combination antiretroviral therapy, viral infection continues to affect the nervous system.

In addition to the neurocognitive, motor, behavioral and sensory deficits resulting from HIV itself, the now chronic nature of HIV infection can intersect with other comorbid infections as well as diseases influenced by aging, such as neurodegenerative disorders.

Animal models have contributed greatly to advances in knowledge about HIV pathobiology and its effects on the immune and nervous system.

This symposium will highlight the current issues in neuroAIDS research where animal models are critical in meeting gaps in our overall knowledge.

Program Sponsors

Department of Pharmacology and Experimental Neuroscience
University of Nebraska Medical Center

Howard S. Fox, M.D., Ph.D.
Professor

Howard E. Gendelman, M.D.
Professor and Chair

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Program

Breakfast

Howard S. Fox, M.D., Ph.D., University of Nebraska Medical Center
Welcome

Shilpa Buch, Ph.D., University of Nebraska Medical Center
“Delivering HIV proteins into the Rodent CNS Recapitulates Aspects of HAND”

Sulie Chang, Ph.D., Seton Hall University
“HIV-1 Transgenic Rat: Feedback Interaction Between Addictive Substance and HIV Viral Proteins”

Janice Clements, Ph.D., Johns Hopkins School of Medicine
“The SIV Model: Unraveling Mechanisms of HIV CNS Disease”

Howard S. Fox, M.D., Ph.D., University of Nebraska Medical Center
“Chronic SIV infection”

Break

Howard E. Gendelman, M.D., University of Nebraska Medical Center
“Rodent models for testing adjunctive HAND therapies”

Johnny He, Ph.D., Indiana University School of Medicine
“Inducible and brain-specific Tat transgenic mouse model for HIV/neuroAIDS research”

Marcus Kaul, Ph.D., Sanford Burnham Medical Research Institute
“HIV co-receptors in models of HIVgp120-induced brain injury”

Rick Meeker, Ph.D., University of North Carolina School of Medicine
“FIV infection”

Larisa Poluektova, M.D., Ph.D., University of Nebraska Medical Center
“HIV infection of humanized immunodeficient mice”

Lunch: On your own (Vendors available in Durham Research Center Commons)

Christopher Power, M.D., F.R.C.P(C), University of Alberta, Canada
“Use of transgenic mice in studies of HIV-associated neurologic disorders”

David J. Volsky, Ph.D., Columbia University
“Neurocognitive Disease in Mice Infected with Chimeric HIV”

Kenneth Williams, Ph.D., Boston College
“A CD8-lymphocyte depletion model of SIV neuropathogenesis”

Break

Panel Discussion - All presenters
Moderators: Howard S. Fox, M.D., Ph.D., and Howard E. Gendelman, M.D.

Howard E. Gendelman, M.D., University of Nebraska Medical Center
Summary
Dr. Shilpa Buch is currently a Professor and Vice Chair for Research in the Department of Pharmacology and Experimental Neuroscience at the University of Nebraska Medical Center in Omaha, Nebraska. She obtained her Ph.D. from M.S. University India in 1982 and then went to Canada to pursue her post-doctoral fellowship. In 1987, she moved to Hospital for Sick Children in Toronto as a research faculty to pursue work on hyperoxic lung injury. In 1995, she moved to Kansas University Medical Center. As an Assistant Professor at KUMC, she led work on neuroAIDS using the cell culture, rodent and macaque models of HIV infection. She has a long-standing interest in the interplay of drugs of abuse and HIV infection and the molecular signaling mechanisms involved in this synergy.

She runs an active program with students, post-docs and, in the past worked actively with clinical fellows. Dr. Buch is well funded from the National Institutes of Health, has published extensively, and continues to also broaden her research interest in the area of blood-brain barrier and its impairment with HIV-1 infection and/or drugs such as cocaine.

Dr. Buch is on the editorial board of several journals and holds administrative positions with various national and international societies. She is also a long-standing member of the NIH study section and contributes her services actively to mentoring.

sbuch@unmc.edu
Dr. Chang is a Professor and the Director of the Institute of NeuroImmune Pharmacology at Seton Hall University (SHU). After obtaining a B.A. in Sociology from National Chengchi University in Taiwan, she came to the US where she earned a M.A. in Social Psychology from State University of New York in Albany, a Ph.D. in Biochemistry from The Ohio State University, and completed a post-doctoral fellowship in cell biology at the National Institutes of Health (NIH). She then served on the faculty of Tulane Medical School and the Louisiana State University Medical Center in New Orleans, LA. Dr. Chang became an Assistant Professor of Biological Sciences at SHU in 1994 and rose thru the ranks to become a Professor of Biological Sciences and Neuroscience. Dr. Chang served as Chairperson of the Department of Biological Sciences in 1999-2005, during which time she developed and implemented the Ph.D. Program in Molecular Bioscience.

Dr. Chang has been funded continuously by the NIH since 1989. She is currently investigating (1) feedback interactions between substances of abuse and microbial infection in the central nervous system; (2) nicotine’s effects on learning behavior in the presence of HIV-1 viral proteins; (3) age-dependent developmental changes in neurotransmitter systems in the brain; and (4) alcohol related behavior disorders in adolescents. Dr. Chang is the principal investigator on two R01 grants [National Institute on Drug Abuse (NIDA)] and one RC2 grant (National Institute on Alcohol Abuse and Alcoholism), and holds a K02-Independent Scientist Career Award (NIDA).

Dr. Chang has been a member of two NIH Study Sections and currently is a member of the Innate Immunity and Inflammation (III) Study Section. She is on the Editorial Board of Journal of Neuroimmune Pharmacology and Journal of NeuroVirology, and has served as an ad hoc reviewer for various scientific journals.

sulie.chang@shu.edu
Janice Clements trained in Neurovirology with Richard T. Johnson and Bill Narayan in the Department of Neurology and joined the faculty of Johns Hopkins School of Medicine in 1978. She has led the Retrovirus Laboratory at JHU School of Medicine since 1992 and became Vice Dean for Faculty in 2000. She co-authored the studies demonstrating that HIV was a lentivirus and pioneered molecular pathogenesis studies using the simian immunodeficiency virus model. The research in the Retrovirus Laboratory focuses on the molecular virology and pathogenesis of lentivirus infections. In particular, the simian immunodeficiency virus (SIV) is used to examine the molecular basis for the pathogenesis of HIV CNS disease. Research includes studies of viral molecular genetics, host innate immune responses in the SIV-infected brain and the role of miRNAs in the host responses viral infection and CNS pathogenesis. SIV infection of macrophages and viral pathogenesis in the central nervous system and the lung have identified the viral genes that determine neurovirulence of SIV and development of CNS disease.

Clements laboratory was the first to identify the role of CD4-independent virus entry in the pathogenesis of CNS disease showing that neurovirulent SIV infects cells in a CD4-independent, CCR5 dependent manner in primary CNS endothelial cells. The Retrovirus Laboratory developed an accelerated, consistent SIV macaque model and demonstrated that replication of SIV in brain and viral load in the CSF but not the peripheral blood directly correlates with the development of CNS disease; and differential regulation of virus replication in the brain and the periphery is due to infection of in macrophages in brain. The SIV model was used to identify the mechanism of innate immune control of virus in the CNS and miRNA regulation of immune responses in macrophages and brain in the pathogenesis of HIV/SIV CNS disease. A SIV HAART model is currently being used to study HIV/SIV latency and eradication.
Dr. Fox received his B.A. and M.A. in Biophysics from Johns Hopkins University, and his M.D. and Ph.D. from the University of California, San Francisco (UCSF). Following post-doctoral work at Cold Spring Harbor Labs and anatomic pathology residency at UCSF, he began his independent research career in 1990 in the Department of Immunology at The Scripps Research Institute, moving to the Department of Neuropharmacology (later renamed Molecular and Integrative Neuroscience) to pursue his work on the effects of HIV on the brain. In 2008 he moved to the Department of Pharmacology and Experimental Neuroscience (PEN) at the University of Nebraska Medical Center (UNMC) to further expand the basic and translational aspects of this work.

He has completed a long-term chair of the Center for Scientific Review Study Section on NeuroAIDS and Co-morbidity Factors in AIDS, served on the University of California University-Wide Taskforce on AIDS, on multiple extramural NIH neuroAIDS grant external advisory boards, and leads the Scientific Advisory Group for the National NeuroAIDS Tissue Consortium. He is currently Professor and Executive Vice-Chair in the PEN Department and Senior Associate Dean for Research and Development for the School of Medicine at UNMC. He directs the Chronic HIV Infection and Aging in NeuroAIDS (CHAIN) Center (P30, NIMH) and the University of Nebraska Center for Integrative and Translational Neuroscience (CITN), as well as NIH R01 and P01 grants.

Dr. Fox’s work focuses on knowledge learned from the SIV/nonhuman primate model of neuroAIDS. In addition to functional, neuropathologic and neuroimmune findings, he has integrated high-density data acquisition and analysis through transcriptomic, proteomic and metabolomic technologies with a systems biology approach to better understand, prevent and treat these disorders resulting from brain infection by HIV.
Howard E. Gendelman, M.D.
University of Nebraska Medical Center

Dr. Gendelman is the Larson Professor of Internal Medicine and Infectious Diseases, and Chairman of the Department of Pharmacology and Experimental Neuroscience at the University of Nebraska Medical Center. Under Dr. Gendelman’s guidance, significant contributions were made in understanding how alterations in mononuclear phagocyte function induce metabolic changes in the brain and ultimately lead to neural cell damage. These discoveries have had broad implications in preventing, slowing or reversing infectious, metabolic and degenerative disorders of the nervous system. As a consequence, immunotherapy and nanomedicine strategies were developed for HIV-1 and Parkinson’s diseases. Dr. Gendelman obtained a Bachelor’s degree in Natural Sciences and Russian Studies with honors from Muhlenberg College and his M.D. from the Pennsylvania State University where he was the 1999 Distinguished Alumnus. He completed a residency in Internal Medicine at Montefiore Hospital, Albert Einstein College of Medicine and was a Clinical and Research Fellow in Neurology and Infectious Diseases at Johns Hopkins. He occupied senior faculty and research positions at Hopkins, the National Institute of Allergy and Infectious Diseases, the Uniformed Services University, the Walter Reed Army Institute of Research, and the Henry Jackson Foundation before joining UNMC in 1993.

Dr. Gendelman has authored over 350 peer-reviewed publications, edited nine books and monographs, holds eight patents and is Editor-In-Chief of the Journal of Neuroimmune Pharmacology. He also serves on numerous editorial boards, national and international scientific review and federal and state committees. He is included among a selective scientific group listed on highly cited.com as being among the top 0.5 percentile cited investigators in his field. His leadership is credited with the growth of the Department of Pharmacology and Experimental Neuroscience to be among the top ranked pharmacology departments (top ten).

hegendel@unmc.edu
Johnny He, Ph.D.
Indiana University School of Medicine

Dr. He trained at the Aaron Diamond AIDS Research Center of Rockefeller University and Dana Farber Cancer Institute of Harvard Medical School. He was recruited to join the Department of Microbiology and Immunology at Indiana University School of Medicine in 1997. He was promoted to Full Professor in 2007, as well as Director of the Indiana University Center for AIDS Research.

His research focuses on the molecular biology of host-virus interactions. His long-term goal is to understand how human cells interact with HIV/HCV viruses and to develop therapeutic strategies specifically targeted at these interactions. On basic studies, he is interested in determining what cells are infected by HIV/HCV, how these cells are infected by HIV/HCV, what host factors are needed to support virus replication, and how these infections alone or in combination ultimately lead to diseases. On translational studies, he is interested in development of therapeutics that are able to attack the viruses and/or prevent the diseases.

Dr. He has been collaborating with investigators in countries such as China with limited resources but rapidly increased HIV infected populations to determine how viral, host and socio-economical factors affect the nature and prevalence of HIV/HCV-associated diseases and their treatment. He has made extremely novel observations such as identifying the human mannose receptor as the HIV receptor for infection of CD4 negative astrocytes and in elucidating the mechanisms by which HIV1 Tat protein leads to neurotoxicity. His development of an HIV Tat transgenic mouse model has allowed numerous research laboratories across the world to make advances in HIV neuropathogenesis research. In addition, Dr. He has been a leader in studying the interactions between HIV and Hepatitis C virus and has developed important collaborations in China to study the impact of these diseases on public health.

jjhe@iupui.edu
Marcus Kaul, Ph.D.
Sanford Burnham Medical Research Institute

Marcus Kaul received his Ph.D. in the Departments of Medical Microbiology and Hygiene and Pharmaceutical Chemistry at the Johannes Gutenberg-University, Mainz, Germany. After postdoctoral work at Harvard Medical School, Boston, MA, and then Burnham Institute, La Jolla, CA, he was appointed as a Research Assistant Professor in the institute’s Center for Neuroscience and Aging Research in 2001. In June 2007, he was recruited as an Assistant Professor to the Infectious and Inflammatory Disease Center at Sanford-Burnham Medical Research Institute. In December 2006, he accepted a position as Assistant Adjunct Professor in the Department of Psychiatry at the University of California, San Diego and is now a faculty member and principal investigator in this department’s Translational Methamphetamine AIDS Research Center.

Dr. Kaul’s laboratory studies at the organism as well as cellular and molecular levels how infections and comorbidity factors, such as drug use, and the responding immune system can induce inflammation and degenerative diseases. A major focus is the role of chemokines and inflammatory cytokines and their receptors in the promotion or prevention of HIV-associated neurodegeneration and neurocognitive disorders using human cell types and rodent models. Dr. Kaul’s laboratory investigated the neuropathological and protective role of HIV chemokine coreceptors using genetic knockout models of the receptor proteins CCR5 and CXCR4. For in vivo experiments, his laboratory generated crosses of CCR5-deficient animals and transgenic mice that express HIV gp120 in the brain. More recently the Kaul laboratory characterized in collaboration with Dr. Amanda Roberts at The Scripps Research Institute, La Jolla, CA, alterations of the acute effects of methamphetamine on locomotor activity and stereotypic behaviors in HIV/gp120-transgenic mice in comparison to non-transgenic controls. These studies are embedded in an overall effort in the Kaul laboratory to better characterize available small animal models and to develop improved in vivo models for HIV and neuroAIDS research.

mkaul@sanfordburnham.org
Dr. Meeker graduated in 1976 from Bowling Green State University with a Ph.D. in physiological psychology. In subsequent postdoctoral training at Purdue University, he gained experience working with cats and macaques including aseptic large animal stereotaxic surgery. A second postdoctoral fellowship at the University of North Carolina provided training in the molecular pharmacology of cholinergic and glutamate receptors. He joined the Department of Neurology at the University of North Carolina as an Assistant Professor in 1983 where he remains as a full professor. In 2002, he was appointed an Adjunct Professor in the Department of Molecular Biomedical Sciences at the North Carolina State University College of Veterinary Medicine where he maintains strong collaborations for the study of feline immunodeficiency virus (FIV).

Current research includes studies done at UNC and the College of Veterinary Medicine that are focused on three major areas: improving the FIV model to facilitate the translation of research findings and therapeutic strategies to humans, exploration of the mechanisms that underlie the development of neural dysfunction in HIV infection and the development of novel therapeutic compounds that restore cellular homeostasis, prevent neuronal damage and reduce inflammation. A strong emphasis is on the development of a new p75 neurotrophin receptor ligand that has the potential to prevent CNS damage and suppress macrophage-associated inflammatory damage. Their hope is that this compound will provide a safe and potent therapy that will prevent neurodegeneration associated with HIV and other inflammatory diseases.

meekerr@neurology.unc.edu
Dr. Poluektova received her M.D. and Ph.D. from the Latvian Medical Academy and Latvian Center of Hepatology, Riga, Latvia. She began her research career as an infectious disease immunologist, then became involved in immunopharmacology/immunotoxicology and for 15 years led the Laboratory for Applied Immunopharmacology and Immunotoxicology. In 1993, she did post-doctoral work at the University of Quebec at Montreal, Montreal, Canada. In 1996, she immigrated to the United States from Latvia and did a postdoctoral fellowship at Creighton University, Omaha, Nebraska.

In 1998, she joined the Center for Neurovirology and Neurodegenerative Disorders at University of Nebraska Medical Center (UNMC), Omaha, Nebraska. Here, she was trained as a neuroimmunologist. As an associate professor in the Department of Pharmacology and Experimental Neuroscience at UNMC, Dr. Poluektova’s work focuses on the development, characterization and application of the “humanized” mouse models for HIV-1. The goal of this research is to better understand, prevent and treat viral disorders resulting from brain infection by HIV.

lpoluekt@unmc.edu.org
Dr. Power is Professor of Neurology at the University of Alberta, Edmonton Alberta and holds a Canada Research Chair in Neurologic Infection and Immunity. He received a B.Sc. from the University of Toronto and an M.D. from the University of Ottawa. He did subsequent postgraduate training in medicine and neurology at McMaster University and the University of Western Ontario, respectively, with postdoctoral fellowships in neurovirology at Johns Hopkins University and Rocky Mountain Laboratory, NIAID-NIH.

Dr. Power is an internationally recognized physician-scientist dedicated to investigating the disease mechanisms, diagnosis, treatment and prevention of neuroinflammatory diseases including multiple sclerosis and neuroAIDS. Aside from directing the Laboratory for Neurologic Infection and Immunity, he is also an attending consultant in the University of Alberta NeuroAIDS and MS Clinics. His laboratory, coupled with clinical activities, has focused on utilizing clinical samples to guide experimental inquiries using different models of disease including both in vitro models of primary neural cells complemented by in vivo models including models of viral infection and transgenic models for both diseases. Identification of pathogenic pathways in the above studies has lead to the development of ‘drug-able’ molecular targets as therapeutic strategies.

He is the author of over 125 peer-reviewed publications, multiple book chapters, and has edited two monographs on emerging and established viral infections of the nervous system.
David J. Volsky received a B.Sc. in Biology from Ben-Gurion University, Israel, and M.Sc. and Ph.D. in Biochemistry from Hebrew University in Jerusalem. Following postdoctoral research on Epstein-Barr virus receptors and cell transformation at the Karolinska Institute in Stockholm, Dr. Volsky was recruited by Dr. David Purtillo to join the Department of Pathology at the University of Nebraska Medical Center where he rose through the ranks to tenured professor. There, he established and directed the Molecular Biology/Diagnosis Laboratory and began his independent research career in virology. With the advent of the AIDS epidemic, Dr. Volsky began studying HIV, which remains the focus of his work.

In 1987, he moved to St. Luke’s-Roosevelt Hospital Center and Columbia University in New York and became Director of the Molecular Virology Division and Professor of Pathology and Cell Biology. Dr. Volsky’s HIV/AIDS research has expanded to include various aspects of HIV biology and viral pathogenesis including interaction of the virus with cellular receptors, mechanism of virus entry into cells and regulation of viral expression, and mechanisms of HIV infection in cells such as astrocytes. Dr. Volsky’s laboratory has a particular interest in HIV interactions with brain-derived cells and molecular mechanisms of viral neuropathogenesis. To facilitate this research, Dr. Volsky and collaborators recently developed a model of infection of mice with chimeric HIV and applied it to the study of experimental HIV neuropathogenesis including induction of neurocognitive deficits in mice.

Dr. Volsky is a member of several scientific societies and editorial boards of scientific journals; he is a founding and current board member of the International Society for NeuroVirology; he also serves on several institutional committees. He has served as peer-reviewer for NIH and AmFAR since 1985. Dr. Volsky has authored or co-authored over 200 peer-reviewed publications in scientific journals.
Kenneth Williams, Ph.D.
Boston College

Kenneth Williams is a Professor of Biology at Boston College, Chestnut Hill, MA. He received a B.S. from Northland College, and Ph.D. from McGill, where he studied in the Neuroimmunology group of Dr. Jack Antel. He did a post doctoral fellowship with Dr. William F. Hickey at Dartmouth Medical School and then took a position as Instructor in Pathology at Harvard Medical School. He was an Assistant and Associate Professor at Harvard Medical School and worked in Dr. Norm Levin’s group.

Dr. Williams studies brain macrophage populations in the normal and inflamed CNS with a focus on AIDS pathogenesis, CD8 T cell biology, and monkey models of neuroAIDS. His recent work has focused on monocyte turnover from bone marrow, expansion in blood, traffic to, turnover and exit from the CNS. He is interested in biomarkers of AIDS including sCD163 that correlated with viral replication, severity of histopathogenesis, and macrophage accumulation in the CNS and heart.

He is the author of over 60 peer-reviewed publications and book chapters on HIV and SIV infection of the CNS and monocyte/macrophage biology.