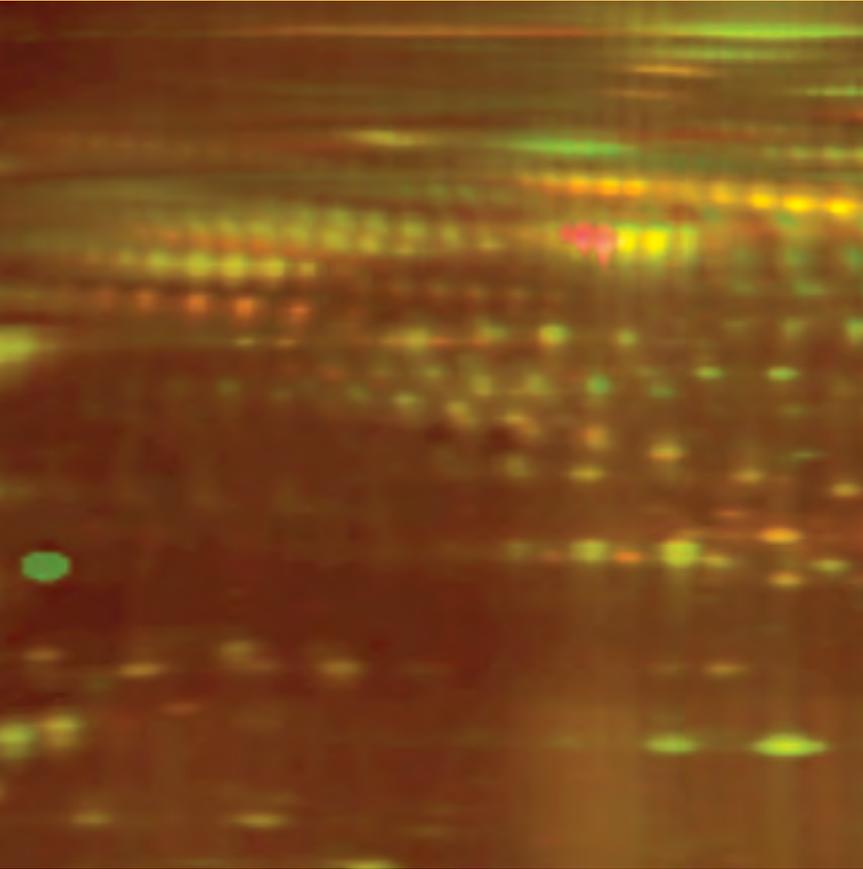




UNIVERSITY OF NEBRASKA MEDICAL CENTER unmc.edu

BIOMARKERS FOR NEUROAIDS



Recent Progress in the Field

Durham Research Center Auditorium
Omaha, Nebraska

June 5, 2012 | 8 a.m. - 3:00 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 as HIV-associated neurocognitive disorders (HAND, or neuroAIDS).

One critical gap in neuroAIDS research, similar to many other neuropsychiatric and neurodegenerative conditions, is the identification of reliable molecular biomarkers.

The day's talks and discussion will highlight the work of the NIMH neuroAIDS centers as well as that of other outstanding researchers in the field performing state-of-the-art research into the identification of clinically relevant biomarkers to aid in improving current diagnosis, developing new presymptomatic treatments, and identifying high-risk individuals and disease subgroups.

Program Sponsor

Chronic HIV infection and Aging in NeuroAIDS (CHAIN) Center

Howard S. Fox, MD, PhD

Professor

Department of Pharmacology and Experimental Neuroscience

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| 7:30 a.m. | BREAKFAST |
| 8 a.m. | Howard S. Fox, MD, PhD, University of Nebraska Medical Center
Welcome |
| 8:10 a.m. | Cristian L. Achim MD, PhD, University of California, San Diego
Studies of micro RNA and findings in the brain as potential biomarkers of HAND |
| 8:30 a.m. | Beau M. Ances, MD, PhD, Washington University, St. Louis
Neuroimaging Biomarkers of HAND - Are We There Yet? |
| 8:50 a.m. | Joan W. Berman, PhD, Albert Einstein College of Medicine
Prion protein as a biomarker: Clues in the pathogenesis of HAND |
| 9:10 a.m. | Pawel Ciborowski, PhD, University of Nebraska Medical Center
HAND, biomarkers and proteomics: What's next? |
| 9:30 a.m. | BREAK |
| 9:45 a.m. | Howard S. Fox, MD, PhD, University of Nebraska Medical Center
Proteomic studies for biomarkers in HAND |
| 10:05 a.m. | Howard E. Gendelman, MD, University of Nebraska Medical Center
Biomarkers for nanomedicine |
| 10:25 a.m. | Igor Grant, MD, FRCP(C), University of California, San Diego
Current status of HAND and Perspectives on Biomarkers |
| 10:45 a.m. | Norman Haughey, PhD, The Johns Hopkins School of Medicine
Lipidomic/metabolomic studies for biomarkers in HAND |
| 11:05 a.m. | Justin C. McArthur, MBBS, MPH, FAAN, The Johns Hopkins School of Medicine
Development of Biomarkers: Progress and Pitfalls |
| 11:30 a.m. | LUNCH |
| 12:30 p.m. | Avindra Nath, MD, National Institutes of Health
Biomarker studies on oxidative stress in HAND |
| 12:50 p.m. | Richard Price, MD, University of California, San Francisco
Strategies for CSF Biomarker Discovery and Evaluation in HIV Infection |
| 1:10 p.m. | Ronald Ellis, MD, PhD, University of California, San Diego
Biomarkers in the current era of HAND |
| 1:30 p.m. | BREAK |
| 1:45 p.m. | Panel Discussion - All presenters
Moderator: Shilpa Buch, PhD, University of Nebraska Medical Center |
| 2:45 p.m. | Summary |

Cristian L. Achim, MD, PhD
University of California, San Diego



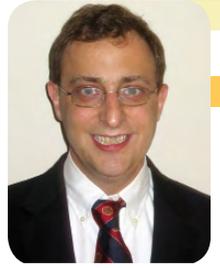
Dr. Cristian Achim is Associate Professor of Psychiatry/ Pathology, University of California, San Diego. He received his medical degree followed by clinical residency (general medicine and infectious diseases) and research training (neurovirology) in Bucharest, Romania. At UCSD, Dr. Achim completed a postdoctoral fellowship in NeuroAIDS and received a PhD in Experimental and Molecular Pathology. Dr. Achim was recruited for a faculty position at University of Pittsburgh School of Medicine where he reached the level of Associate Professor of Pathology and Neurology with tenure. At Pitt, in addition to continuing the work in NeuroAIDS, the research interests of Dr. Achim included experimental models of neurodegeneration, neuroprogenitor cells, neurotrophic factors, blood-brain barrier pathology and neuroimaging.

Upon his return to UCSD, Dr. Achim's experimental neuropathology laboratory has focused on the molecular mechanisms of disease in HIV associated neurocognitive disorders (HAND) and associated comorbidities, such as methamphetamine abuse and major depressive disorder. Areas of interest in these studies are: brain macrophages, neuroinflammation, chronic neuronal stress, axonal degeneration, abnormal protein aggregation, and neurotrophic response. Key molecules hypothesized to be involved in these processes are associated with glucocorticoid receptor and brain immunophilin signaling.

In collaboration with the HIV Neurobehavioral Research Center (HNRC), the Translational Methamphetamine AIDS Research Center (TMARC), the California NeuroAIDS Tissue Network (CNTN), and the NeuroPET Research Center, all at UCSD, Dr. Achim's laboratory has developed new research paradigms based on clinico-pathologic correlations in HIV subjects with HAND. In conjunction with the HNRC International Core, Dr. Achim has developed a collaboration with AIDS clinicians in Romania studying the long term effects of HIV on the developing brain in a cohort of young adults surviving with the infection since the first years of life. More recently, in collaboration with the Stein Institute for Research on Aging (SIRA), Dr. Achim's research group has begun studying the neurobiology of successful aging.

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Beau M. Ances, MD, PhD
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Dr. Beau Ances is Assistant Professor and Dana Foundation Brain Immuno-Imaging Scholar in the Departments of Neurology, Neurosciences, Biomedical Engineering, and Microbiology, Washington University, St. Louis. He is certified by the American Board of Psychiatry and Neurology in Adult Neurology.

Dr. Ances graduated magna cum laude from University of Pennsylvania in 1989 with a BA in International Relations and Biology. He received a Thouron Fellowship and obtained a MSc in Health Planning and Finance from the London School of Economics/ London School of Hygiene and Tropical Medicine in 1994. He returned to the United States and entered the University of Pennsylvania School of Medicine. In 2000, he obtained his PhD in neurosciences and a MD degree in 2001. In 2001, he received the Eric C. Raps Memorial Prize for excellence in Clinical Neurology at the University of Pennsylvania. From 2005-2008, Dr. Ances was a post-doctoral fellow in NeuroAIDS at the University of California, San Diego. For his cutting edge research in NeuroAIDS, he received the Universitywide AIDS Research Program of California Clinical Fellowship Award and American Federation for AIDS Research Fellowship. He has received multiple NIH awards.

His work looks at novel neuroimaging biomarkers of disease in HIV associated neurocognitive disorders (HAND) - impairments in neurocognition, slowed motor movements, and behavioral disturbances. HAND is quite difficult to detect using current diagnostic criteria such as neurological examination or pencil and paper tests. These methods are labor intensive and can be influenced by the state of the patient (i.e. a subject had a bad night's sleep or has been worrying about a family matter). Other biological markers of HAND need to be developed and validated. The aim of the Ances laboratory is to translate discoveries of the pathophysiological mechanisms of HAND into novel neuroimaging therapeutics. He also uses neuroimaging to assess the efficacy of various highly active anti-retroviral therapies (HAART) in the brain.

In addition, the Ances Laboratory is interested in discovering early neuroimaging biomarkers for Alzheimer's Disease and Rapidly Progressive Dementias such as Cruetzfeldt Jacob Disease.

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Joan W. Berman, PhD
Albert Einstein College of Medicine



Dr. Joan W. Berman is Professor of Pathology and of Microbiology and Immunology at the Albert Einstein College of Medicine, New York, New York. Her laboratory examines mechanisms that mediate the pathogenesis of NeuroAIDS. Her studies are specifically focused on understanding how HIV-infected monocytes and in some cases, T cells, cross the blood-brain barrier (BBB) and initiate and propagate neuroinflammation and BBB damage. She also examines tissues and fluids from HIV-infected individuals for biomarkers and predictors of HIV-associated neurocognitive impairment. In addition, her laboratory investigates mechanisms of CNS pathology in HIV infected substance abusers, as well as the impact of the therapeutic buprenorphine, given for opiate addiction, on CNS inflammation and the BBB in the context of HIV infection. Additionally, she investigates the interrelationship of cerebral malaria and HIV CNS disease. The laboratory studies epigenetic regulation of host-viral interactions, with a focus on identifying microRNAs that mediate macrophage response to HIV infection.

Dr. Berman is the Director of the Graduate Student Program in Experimental Pathology at Albert Einstein School of Medicine and is the Senior Faculty Advisor of Einstein's Biomedical Graduate Division. She is also the Director of Basic/Translational Research for the Medical School and the Co-Director of the Immunology and Pathology Core of Einstein's Center for AIDS Research. She is on the Editorial Board of the Journal of Neurovirology and is a member of the Executive Board of the International Society of Neurovirology, as well as the Chair of the Women in Neurovirology Committee for ISNV. She was selected to give the "Women in Neurobiology" 2012 lectureship at the International Society of Neurovirology meeting.

Dr. Berman has several NIH funded programs and is a reviewer for many high impact journals. She served on several study sections and review boards and is an advisor to the NIMH funded CHARTER, a six research center consortium studying diverse populations with NeuroAIDS. She also is the Co-Chair of the undergraduate women's mentoring program at Brown University.

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Pawel Ciborowski, PhD
University of Nebraska Medical Center



Dr. Pawel Ciborowski graduated from University of Warsaw, Warsaw, Poland and obtained his PhD 1984 from the National Institute of Hygiene, Warsaw, Poland. He is currently an Associate Professor in the Department of Pharmacology and Experimental Neuroscience and Director of Mass Spectrometry and Proteomics Core Facility at the University of Nebraska Medical Center.

The main focus of Dr. Ciborowski's research is to use proteomics and systems biology approaches to study the molecular mechanisms of pathogenesis of HIV infection of the brain with further focus on HIV Associated Neurocognitive Disorders (HAND). This consists of two parallel avenues. One is to study molecular mechanisms that define phenotype and function of HIV-infected mononuclear phagocytes. The second is the clinical translational study in the area of biomarker discovery. These avenues intertwine in such a way that results of biomarker discovery projects are used to build hypothesis driven projects and conversely, results from studies of molecular mechanisms of HIV infection of macrophage are verified (validated) as potential biomarkers. Both avenues are being extended to study the effects of drug of abuse and potential toxicity of cART on the function of macrophage during HIV infection.

Another logical extension and subsequent step in the proteomic research development is to use it as part of a systems biology approach. This part evolved into close collaboration with bioinformaticians at the University of Nebraska at Omaha whose expertise is in bioinformatics and modeling of systems biology. As Director of Mass Spectrometry and Proteomics Core Facility, Dr. Ciborowski is involved in multiple collaborative projects related to various aspects of HIV infection. He has published extensively on biomarkers in HIV including body fluids such as serum/plasma and CSF.

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Ronald J. Ellis, MD, PhD
University of California, San Diego



Dr. Ronald Ellis attended Boston University School of Medicine where he obtained his PhD and MD in 1989. He is board certified in Neurology and currently an Associate Professor in the Department of Neurosciences, University of California, San Diego.

Dr. Ellis's research is focused on the neurological manifestations of HIV infection and their pathogenesis and treatment, particularly dementia, neurocognitive disorders, and sensory polyneuropathy. Dr. Ellis serves as Co-Director of the NIMH-funded P03 HIV Neurobehavioral Research Programs (HNRP) and is the principal investigator of its Neuromedical Core, which is comprised of two interacting subunits, a Clinical Research Support Unit (CRSU) and a Laboratory, Pharmacology and Biomarker Unit (LPBU). He also serves as Co-Director of the multicenter CNS HIV AntiRetroviral Therapy Effects Research (CHARTER) study and the Translational Methamphetamine AIDS Research Center (TMARC) at UCSD.

TMARC comprises an integrated program of human clinical, neuroimaging, laboratory and animal model investigations being conducted at UCSD, The Sanford-Burnham Institute, and The Scripps Institute. He is the protocol neurologist for the AIDS Clinical Trials Group's Adult ACTG Longitudinal Linked Randomized Trials (ALLRT) study, and Principal Investigator of a 5-site trial to test a novel strategy for targeting antiretroviral therapies to the CNS to maximize neurocognitive outcomes in HIV. Since 1997, he has published extensively on CSF biomarkers in HIV, including viral load, immune markers, indicators of neuronal injury and proteomics.

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Howard S. Fox, MD, PhD
University of Nebraska Medical Center



Dr. Howard Fox received his BA and MA in Biophysics from The Johns Hopkins University and his MD and PhD 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.

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Howard E. Gendelman, MD
University of Nebraska Medical Center



Dr. Howard E. Gendelman is the Larson Professor of Internal Medicine and Infectious Diseases, Chairman of the Department of Pharmacology and Experimental Neuroscience at the University of Nebraska Medical Center. Under Dr. Gendelman's guidance, significant contributions have been 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. One of these rests in nanomedicines that were recently developed in the Gendelman laboratory for targeted drug delivery to sites of human immunodeficiency virus (HIV) infection and disease. These include, but are not limited to, the reticuloendothelial system and other tissue sites including the central nervous system. To realize the specific potential of bench to the patient bedside, nanoformulated antiretroviral therapy (nanoART) research activities have focused efforts on cell-based approaches for nanoART carriage. This has proven to positively affect outcomes in animal models of HIV disease.

The past half decade has seen significant development and use of mononuclear phagocyte lineage cells as Trojan horses for ART carriage. Biomarker profiling has elucidated the mechanisms of cell-based nanoART carriage, endosomal shuttling, redox biology, cytotoxicities, drug secretion and cytoskeletal network alterations that facilitate transmission across tissue barriers including the brain. The promise of this new technology and the perils in translating it for clinical use are developed through proteomic profiling performed in the differentiated and immune activated macrophage.

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Igor Grant, MD, FRCP(C)
University of California, San Diego



Dr. Igor Grant is Distinguished Professor and Executive Vice-Chair of the Department of Psychiatry at the University of California, San Diego School of Medicine and Director of the HIV Neurobehavioral Research Program at UCSD. Dr. Grant is a neuropsychiatrist who graduated from the University of British Columbia School of Medicine and received specialty training in psychiatry at the University of Pennsylvania, and additional training in neurology at the Institute of Neurology (Queen Square) London, U.K.

Dr. Grant's academic interests focus on the effects of various diseases on brain and behavior, with an emphasis on translational studies in HIV and drugs of abuse. He has contributed to approximately 500 scholarly publications and is principal investigator of several NIH studies, including a NIDA P50 (Translational Methamphetamine AIDS Research Center – TMARC) and NIMH funded California NeuroAIDS Tissue Network (CNTN), CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER), and co-director of the HIV Neurobehavioral Research Center (HNRC).

Dr. Grant is the founding Editor of the Journal of the International Neuropsychological Society and founding co-editor of the journal AIDS and Behavior.

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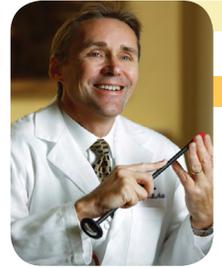
Dr. Norman Haughey received a PhD in Pharmacology from the University of Manitoba (Canada) in 1998. He then completed three years of post-doctoral training at the University of Kentucky's Center on Aging and the National Institutes of Health, National Institute on Aging before joining the Department of Neurology at Johns Hopkins in 2002. Now an Associate Professor, Dr. Haughey directs the Surrogate Marker Core for The Johns Hopkins NIMH Center for Novel Therapeutics of HIV-Associated Neurocognitive Disorders (HAND).

Dr. Haughey and his colleagues use a multidisciplinary approach for biomarker discovery that includes proteomic, lipidomic, and metabolomic platforms. Data obtained from clinical samples and from pre-clinical models are incorporated and interrogated using systems biology approaches to identify networks that are perturbed early in the pathogenesis of HAND. Diagnostic and prognostic indicators that are identified in these studies may be useful to identify HIV-infected individuals at risk for cognitive impairments, as surrogate markers to determine the effectiveness of therapeutic interventions, and to identify novel targets for neuroprotective drug development.

Dr. Haughey has been active with NIH Study Sections and grant review committees. He has served as an Ad-hoc reviewer for multiple journals including Journal of Neurochemistry, Journal of Neuroimmunology, Journal of Neuroscience, Journal of Neuroscience Research, Neuroscience, Neurobiology of Aging, Neuromolecular Medicine, Neurobiology of Disease, Biochemical Journal, Canadian Journal of Pharmacology and Physiology, Glia, Cell Death and Differentiation, Journal of Biological Chemistry and the Journal of Neuroimmune Pharmacology.

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Justin C. McArthur, MBBS, MPH, FAAN
The Johns Hopkins Hospital



Dr. Justin McArthur received his medical degree from Guys Hospital Medical School at the University of London. He then completed an internship and residency in Internal Medicine at The Johns Hopkins Hospital. Dr. McArthur stayed at Johns Hopkins to complete a second residency in neurology and to achieve a master's degree in public health.

Now a Professor of Neurology, Pathology, Medicine and Epidemiology, Dr. McArthur has become nationally and internationally recognized for his work in the epidemiology and treatment of HIV infection, multiple sclerosis, and other neurological infections and immune-mediated neurological disorders. He has been instrumental in the design and conduct of numerous clinical trials for these disorders. With Jack Griffin, he also developed a clinically-validated technique to use cutaneous nerves to study sensory neuropathies, including those associated with chemotherapy, HIV infection, and diabetes mellitus. He was recipient of the Department of Medicine Osler Housestaff Award in recognition of outstanding contributions to Housestaff teaching for four years, and the JHU Professor's Award for Distinction in Teaching in the Clinical Sciences.

Dr. McArthur is currently the Director of the Department of Neurology at Johns Hopkins and is also the Director of the Johns Hopkins/National Institute of Mental Health Research Center for Novel Therapeutics of HIV-associated Cognitive Disorders. The Center is comprised of an experienced interdisciplinary research team who have pooled their talents to study the nature of HIV-associated cognitive disorders. The aim is to translate discoveries of the pathophysiological mechanisms into novel therapeutics.

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Avindra Nath, MD
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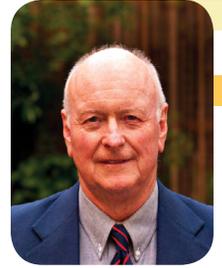
Dr. Avindra Nath received his medical degree from Christian Medical College in Ludhiana, India, did a residency in neurology followed by a fellowship in neuroimmunology at the University of Texas Health Science Center in Houston and a fellowship in Neuro-AIDS at the National Institute of Neurological Diseases and Stroke (NINDS). He previously held faculty positions at University of Manitoba, University of Kentucky, and Johns Hopkins University.

Currently, Dr. Nath is Chief of the Section of Infections of the Nervous System at National Institute of Neurological Disorders and Stroke in the National Institutes of Health. He is also the Clinical Director at NINDS, the Vice President of the International Society of Neurovirology, and the Chair of the Section of Neuro-infectious Diseases of the American Academy of Neurology. He is also an Associate Editor of the Journal of Neurovirology.

His major research interest is in the neuropathogenesis of HIV infection and endogenous retroviruses. His laboratory has previously shown how viral proteins can use novel mechanisms for causing neuronal injury. His current research interests are related to understanding the mechanisms by which HIV establishes a reservoir in the brain and how strategies for controlling viral replication and elimination impact the brain. Ongoing research includes the determination of the size of the HIV reservoir in the brain, how HIV-infected lymphocytes transmit the virus to glial cells, and how activated lymphocytes in the setting of immune reconstitution syndrome can cause neuronal damage. Dr. Nath also directs the Translational Neuroscience Center at NINDS, which is working towards developing new sensitive biochemical and radiological biomarkers of cerebral injury that can be used for monitoring patients in clinical trials. The Center is also developing new pharmacological and biological approaches for the treatment of HIV-associated neurocognitive disorders.

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Richard W. Price, MD
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Dr. Richard Price is Professor and Division Chief of Neurology at the San Francisco General Hospital, University of California, San Francisco. Dr. Price received his MD from Albany Medical College followed by an internship in medicine at Peter Bent Brigham Hospital and fellowships at Harvard Medical School and Cornell University Medical College. He completed his residency at Cornell University Medical College.

Dr. Price has had a long-term interest in the neurological complications of HIV infection dating back to the early years of infection. In recent years, he has focused on discovery and evaluation of cerebrospinal fluid biomarkers in a series of collaborative studies examining viral (quantitation, phenotype, and genotype), immune (cellular and soluble) and neural biomarkers and their use both in exploring pathogenesis and in clinical management.

Dr. Price has had NIH funding for over ten years; has been a member on a number of NIH review committees, served on numerous of editorial boards, and continues supervising and teaching neurology residents and medical students at SFGH. Currently, Dr. Price is Director of San Francisco General Hospital/University of California, San Francisco, HIV Neurology Research Program.

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