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Editorial Board: Walter Atwood, Ph.D., Fred Krebs, Ph.D.
Steven Jacobson, Ph.D., Ehud Lavi, M.D.

4th International Symposium on NeuroVirology

TO BE HELD CONJOINTLY WITH THE 10TH CONFERENCE ON NEUROSCIENCE OF HIV INFECTION

Gabriele Arendt, MD, Düsseldorf, Germany

On behalf of Drs. Joseph Berger, Kamel Khalili, Robert Levy, Volker ter Meulen, Thomas Weber and Brian Wigdahl, I would like to welcome you to the 4th International Symposium on NeuroVirology to be held conjointly with the 10th Conference on Neuroscience of HIV Infection in Düsseldorf from June 19th to June 22nd. The organizing committee for this year's conjoint symposium consists of myself and Drs. Detlev Riesner, Eva Neuen-Jacob, Heiner Schaal, Hans-Jürgen von Giesen, Thomas Weber, Mark Oette, Ortwin Adams, Ingo Husstedt, and Hubertus Köller. The welcoming reception on Tuesday, June 18th and the entire Congress will take place in the Rheinterrassen Convention Center on the banks of Rhine river. The official hotel for the Congress participants will be the Düsseldorf Hilton Hotel which is within walking distance. Shuttle services will also be provided between the conference center and the Hilton.

The Congress will combine basic and clinical science in the field of neurovirology including HIV infection, clinical neurology, neuropathology, molecular biology, neuroimmunology and prion disease. On the clinical side, the meeting will focus on the results of therapeutic trials in neurovirological disorders, especially in HIV-1-associated brain disease.

The Congress will include the presidential lecture given by the 1997 Nobel Prize winner Stanley Prusiner. The meeting will consist of ten plenary sessions with over forty invited speakers from around the world, a Young Investigator in Training Session, Clinical and Basic Science Workshops and Forums, as well as poster presentations. Over 260 abstracts have been accepted for oral and poster presentations. There will be more than twenty travel awards presented to young investigators in training.

The 2002 Pioneer in Neurovirology Award will be presented during a special forum at the medieval castle Schloss Burg. All accepted abstracts will be published in a supplement of the Journal of Neurovirology (JNV). A Conjoint Symposium Summary will also be published in JNV along with research summaries provided by the invited speakers. We are very glad to acknowledge the support provided by the United States National Institutes of Health, particularly the National Institute of Mental Health, National Institute of Neurological Disorders and Stroke, and the National Cancer Institute, and the Deutsche Forschungsgemeinschaft DFG, as well as the support of many industrial sponsors.

The Local and Conjoint International Organizing Committee want to welcome everybody who is interested in neurovirology and/or neuroscience of HIV infection. The social programme will reflect the open and friendly character of the people living near the Rhine and will consist of a river cruise and the castle banquet. Furthermore, delegates will have the opportunity to make new friends in the Düsseldorf old town "Altstadt", known to be the world's longest pub where the typical local beer "Altbier" can be enjoyed.

The Rheinterrasse convention center is located within close walking distance to the city center. Additionally, Düsseldorf can serve as the starting point to all the European trips you can imagine. For further information concerning the Congress please contact AKM Congress Service GmbH (phone: 49 7621 9833 – 0; email: fleischmann.c@akmcongress.com). Please mark your calendar for this exciting event. We are looking forward to seeing you in Düsseldorf.

Abstracts for the Conjoint ISNV/NS-HIV Symposium are available for viewing at http://www.jneurovirol.com/symposium.php

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ISNV Focus on Shohreh Amini, Ph.D., Temple University

Walter Atwood, Ph.D., Providence, RI, USA

Dr. Shohreh Amini received her Ph.D. in Molecular Biology from the University of Pennsylvania in 1983. In preparing her doctoral dissertation, a significant finding was reported. This important discovery on the membrane association of PP36, a target protein for the Rous sarcoma virus oncogene, src, was the subject of a paper published in PNAS. Dr. Amini continued to pursue the relationships between src and its target proteins in polyomavirus-transformed cells as a post-doctoral fellow in the Laboratory of Tumor Virus Biology at the National Cancer Institute. In 1987, Dr. Amini joined the faculty in the Department of Biochemistry and Molecular Biology at Thomas Jefferson University where she was also a member of the Jefferson Institute of Molecular Medicine. Currently, Dr. Amini is the principal investigator in the Laboratory of NeuroAIDS and Gene Therapy in the Center for Neurovirology and Cancer Biology at Temple University. Additionally, she holds the academic rank of Professor in the Department of Biology at Temple and serves as the Director of the Graduate Program in biology. Dr. Amini remains a consummate researcher in her pursuit of a greater understanding of the molecular events that lead to the development of neurological disorders associated with HIV-1 infection of the brain. The focus of her research is the investigation of the mechanism whereby viral gene expression and replication are regulated in brain cells and to identify the cellular factors that contribute to pathogenesis upon deregulation. In this regard, her research group was the first to identify a novel pathway in which the HIV-1 regulatory protein, Tat, modulates expression of the HIV-1 genome in brain cells such as astrocytes. Additionally, her research team demonstrated a new mechanism for Tat in enhancing production of several cellular proteins with known neurotoxic function whose presence may be deleterious to uninfected cells, such as neurons.

This research led to an investigation of the mechanisms involved in neuronal cell injury in HIV-1 infection and in the identification of several novel events that lead to neuronal cell death upon deregulation. This research is far-reaching in its scope, as these regulatory events may also be involved in other non-viral diseases that induce neuronal cell death, including Alzheimer's Disease. Dr. Amini, along with her research group, are involved in a major effort in the development of novel therapeutic strategies that use gene therapy and stem cell technology to block viral gene replication in brain cells. As a result of this research, a collaboration developed with other members of the Center for Neurovirology and Cancer Biology at Temple University which demonstrated that Vpr, the mutant variants of the viral regulatory protein have the ability to suppress viral gene transcription and replication. In addition to demonstrating the cooperation of cellular and viral effector molecules in the regulation of viral gene expression, her research group has confirmed that Tat and Vpr, two viral encoded proteins, physically interact and upregulate viral gene expression.

In collaboration with Dr. Bassel Sawaya, she has shown that a trans-dominant mutant of Vpr competes with its wild-type counterpart and also interferes with the potent transactivation effect of the Tat protein. They have further documented the efficacy of such a mutant in replication of the virus using a chimeric mutant derivative of HIV-1. Recently, the National Institute of Neurological Disorders and Stroke (NINDS) at the National Institutes of Health (NIH) has awarded Dr. Amini's program project entitled "Signaling pathways modulating HIV-1 induced injury in CNS". This multidisciplinary five-year program project is

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Eugene O. Major Appointed Acting NINDS Deputy Director

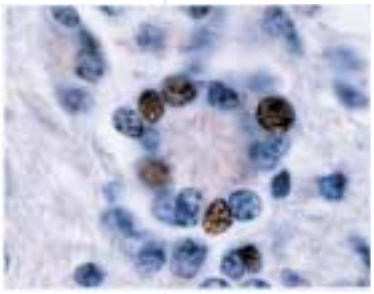
Steven Jacobson, Ph.D., Bethesda, MD, USA

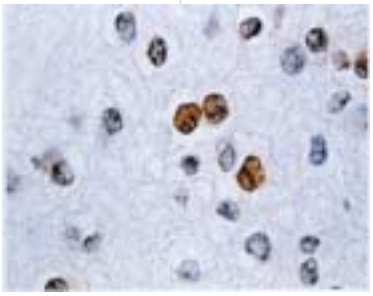
Dr. Eugene O. Major has recently been named acting Deputy Director of the National Institutes of Neurological Disorders and Stroke, NIH. He will be responsible for coordinating intramural and extramural activities that relate to the overall mission of the NINDS and the NIH. Dr. Major will provide leadership in the development of NINDS programs in the scientific and medical community, nationally and internationally. He will maintain liaisons with other government research programs, scientific societies, lay interest groups, and international health and research organizations with interests in the neurological sciences and disorders. Dr. Major will continue as Chief of the Laboratory of Molecular Medicine and Neuroscience. Dr. Major's investigations focus on the biology of virus infections in the nervous system and the molecular regulation which control cellular and viral gene expression. He has developed a basic research laboratory focusing on mechanisms of viral pathogenesis in the human nervous system, which includes JC Virus-induced demyelination, Progressive Multifocal Leukoencephalopathy, and HIV-1 associated encephalopathy. Dr. Major received his A.B. degree from Holy Cross College and his M.S. and Ph.D. degrees from the University of Illinois Medical Center. Following academic appointments as Associate Professor at the University of Illinois Medical School and the Loyola University Medical School in Chicago and Associate Dean of Graduate Programs at Loyola, Dr. Major joined the Neurology Institute in 1981.

Human polyomavirus JCV and CNS neoplasia – culprit or innocent bystander?

Joseph Berger, M.D., Lexington, KY, USA

Recent studies on the human neurotropic virus, JCV, have lead to the detection of this common virus in a broad range of human brain tumors. Though JCV is best known as the causative agent of the fatal demyelinating disease, Progressive Multifocal Leukoencephalopathy (PML), which currently strikes approximately 8% of AIDS patients, recent studies have pointed to its potential involvement in cancer. Through the use of PCR amplification followed by Southern blot hybridization with probes specific for JCV and parallel immunohistochemical staining using antibodies which recognize the viral regulatory protein, T-antigen, investigators working in Dr. Kamel Khalili's laboratory at Temple University have analyzed over 129 cases of paraffin embedded biopsy and autopsy specimens from individuals with CNS tumors. The samples analyzed to date include 43 cases of medulloblastoma, a common but devastating childhood tumor, and 86 cases of glial origin tumors including oligodendroglioma, astrocytoma, glioblastoma, as well as ependymoma. Their results demonstrate that sequences identical to a region of the viral genome that encodes JCV T-antigen can be amplified from 76.7% of human medulloblastomas and 69.4% of glial-origin tumors while JCV T-antigen protein is detected by immunohistochemistry in 36% of medulloblastomas. Of note, they found no evidence of the presence of the viral capsid proteins, whose genes reside in the late region of the viral genome, in CNS tumors. Their recent studies reported in the Journal of the National Cancer Institute, showed production of the viral late auxiliary protein, Agnoprotein, in 45% of 20 medulloblastoma samples analyzed. These are intriguing observations in light of earlier epidemiological data showing that 80% of the human population world-wide have been exposed to JCV. JC virus may be readily detected in the kidney where it remains latent and it may also linger in tonsilar stromal cells, the lower gastrointestinal tract, and circulating B lymphocytes. Thus far, several studies have failed to detect the JCV genome in normal human brain tissue analysis raising questions as to why the viral genome can be detected in such a high number of CNS tumors. It should be mentioned that JCV T-antigen has been shown to induce a broad range of neural-origin tumors in several in vivo animal models and, in fact, is the only human virus known to be oncogenic in non-human primates. Examination of tumor tissue from several of these models as well as detailed molecular studies on cell lines generated from the tumor tissue has revealed that JCV T-antigen is able to physically interact with a number of cellular reguatory proteins, including the tumor suppressor proteins p53 and pRb, which are involved in the control of cell growth and proliferation. In fact, expression of p53 has been correlated with that of JCV T-antigen by immunohistochemistry in some of the clinical samples. However, the functional consequence of T-antigen expression in human brain tumors remains to be demonstrated. More recent studies by Khalili's group as well as others have suggested the involvement of other regulatory pathways including Wnt and IGF-1 in the development of JCV-associated medulloblastoma in vitro and in animal models. At present, the role of Agnoprotein in the JCV life cycle remains unclear. Of note, a greater number of tumor samples contain the viral genomic sequences than express JC viral proteins, leading Khalili to hypothesize a "hit and run" mechanism wherein the viral proteins may contribute to tumor formation at an early stage of its development but may not be required to maintain the cells in a transformed state. In support of this notion, immunostaining in human CNS tumor samples has revealed a heterogeneous expression pattern of T-antigen. However, such a concept may be difficult to confirm in clinical samples while JCV may leave its fingerprint at the scene of the crime, the evidence pointing to JCV as a causative agent of these tumors remains circumstantial. Future in-depth studies on clinical samples for the presence of JCV in brain tumors and studying potential mechanisms by which JCV may induce tumor formation will help address these questions.





The "Featured Brief" section of the newsletter highlights an area of international importance that the editors feel deserves special attention. An update of current activity and information on a "featured" topic should help keep members aware of fast paced studies and new results. The Editors are always interested in your ideas for future articles and brief comments on its topics.

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built around her results pointing to the involvement of an indirect pathway in the neuropathogenesis of AIDS. Dr. Amini strongly believes that by dissecting the molecular mechanisms involved in the neuropathogenesis of AIDS, one would be able to design more effective therapeutic approaches to combat this disease. This is exceptionally significant because the current treatment regimens have not proven effective in ameliorating CNS disease. Her current effort incorporates gene transfer and stem cell technology to develop safe and effective therapeutic strategies toward HIV-1 induced CNS disease and identifying elements that are involved in the neuropathogenesis of AIDS.

Selected Publications

Darbinian N, Sawaya BE, Khalili K, Jaffe N, Wortman B, Giordano A, Amini S. 2001. Functional interaction between cyclin T1/cdk9 and Puralpha determines the level of TNFalpha promoter activation by Tat in glial cells. J Neuroimmunol. 121:3-11.

Sawaya BE, Khalili K, Gordon J, Taube R, Amini S. 2000. Cooperative interaction between HIV-1 regulatory proteins Tat and Vpr modulates transcription of the viral genome. J Biol Chem. 275:35209-14.

The Nebraska Center for Virology

Charles Wood, Ph.D., Lincoln, NE, USA

The Nebraska Center for Virology (NCV) was established by the NIH-NCRR "Center for Biomedical Research Excellence (COBRE)" program in the fall of 2000. It is a Center of Research Excellence as designated by the University of Nebraska-Lincoln (UNL) Board of Regents, and has created an infrastructure linking the virology programs of Nebraska's leading biomedical research institutions: UNL, the Medical Center, and Creighton University. The program consists of enhancing the research of current faculty, recruiting new talent, providing a mentoring environment for junior faculty, and providing state-of-the art core facilities to promote interaction and collaboration. The Center also strives to develop a strong mentoring environment to attract and promote the development of promising researchers.

NCV research projects focus on biomedically important areas of virology. They are developing partnerships between basic and clinical researchers working with human, animal, and potentially important plant systems, to unravel the mechanisms of viral pathogenesis and replication. Understanding these fundamental processes will enable the design of novel vaccines and therapeutic strategies to block disease. They are also conducting innovative research addressing questions about infectious agents and the host responses that may lead to pathological changes, especially neuropathogenesis and apoptosis. Visit their website at: http://www.unl.edu/virologycenter.

ISNV Highlight of the Research of Dennis L. Kolson, M.D., Ph.D., at the University of Pennsylvania, School of Medicine

Ehud Lavi, M.D., Philadelphia, PA

Dennis obtained his Ph.D. (1984) and M.D. (1985) from the University of Pittsburgh. He completed his Neurology residency at Duke University in 1989, and came to the University of Pennsylvania in Philadelphia for a fellowship in Neurovirology with Drs. Francisco Gonzalez-Scarano and Neal Nathanson. He was appointed Assistant Professor of Neurology at Penn in 1992, and was promoted to Associate Professor with tenure in 2001.

Dennis' interest is in the pathogenesis of HIV-induced neurodegeneration, both clinically and experimentally, in addition to his interest in other inflammatory, demyelinating and infectious diseases of the central nervous system (CNS). He sees patients at the Hospital of the University of Pennsylvania, and participates in clinical and radiological studies of HIV-associated dementia and Multiple Sclerosis. He serves on the Neurology Subcommitte of the AIDS Clinical Trials Group (ACTG), and is the University of Pennsylvania's site Principal Investigator for the NeuroAIDS Research Consortium (NARC).

Dennis' laboratory focuses on several aspects of the pathogenesis of CNS HIV infection. He has made important observations about the interaction between HIV and neuronal cells, and has worked to develop in vitro neuronal cell models for HIV-induced neuronal dysfunction. In his early studies, he described the trans-activating role of the HIV Tat protein in neurons, and the ability of Tat to alter adhesive properties of neurons and astrocytes. He has used the Ntera- 2 (NT2.N) human neuronal cell system for biochemical studies of acetylcholinesterase expression, neuronal chemokine receptor expression and function, and for development of a model system of HIV–induced neuronal apoptosis. Dennis is currently focused upon the pathways of HIV-induced neuronal apoptosis and how neuronal survival pathways may protect against such apoptosis. Dennis is the prinicipal investigator of several NIH grants, including a section in a program project under the directorship of Dr. Gonzalez-Scarano, investigating the cellular and molecular biology of HIV encephalopathy.

Selected publications:

1. Kolson, D.L., et al., HIV-1 Tat alters normal organization of neurons and astrocytes in primary rodent brain cell cultures: RGD sequence dependence. AIDS Res Hum Retroviruses, 1993. 9(7): p. 677-85.
2. Kolson, D.L., et al., Human immunodeficiency virus type 1 Tat activity in human neuronal cells: uptake and trans-activation. J Gen Virol, 1994. 75 (Pt 8): p. 1927-34.
3. Llanes, C., et al., Acetylcholinesterase expression in NTera 2 human neuronal cells: a model for developmental expression in the nervous system. J Neurosci Res, 1995. 42(6): p. 791-802.
4. Kolson,D.L., Lavi,E. and Gonzalez-Scarano,F. The effects of HIV in the central nervous system. Adv.Virus Res, 1998. 50: 1-47.
5. Coughlan, C.M., et al., Expression of multiple functional chemokine receptors and monocyte chemoattractant protein-1 in human neurons. Neuroscience, 2000. 97(3): p. 591-600.
6. Choe, W., et al., Functional expression of the seven-transmembrane HIV-1 co-receptor APJ in neural cells. J Neurovirol, 2000. 6 Suppl 1: p. S61-9.