ISNV

International Society for NeuroVirology

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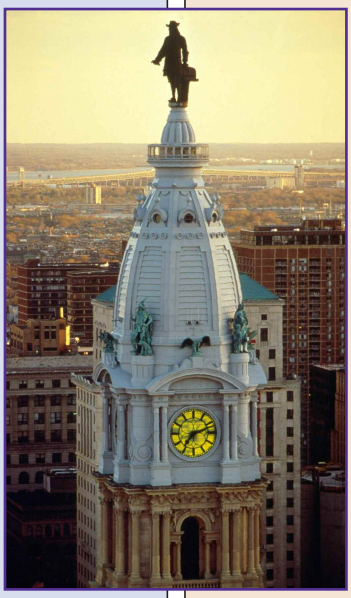
ISNV Publications Subcommittee: K. Khalili (Chair), B. Brew
J. Clements, P. Ferrante, E. Major

Welcome to the 7th International Symposium on NeuroVirology

Brian Wigdahl, Ph.D. • Philadelphia, PA

On behalf of the international organizing committee, welcome to the 7th International Symposium on NeuroVirology! This year, the symposium takes place in historic Philadelphia, birthplace of the International Society for NeuroVirology, home to the Journal of NeuroVirology, and site of the First International Symposium of NeuroVirology.



The primary goal of this year's symposium is to provide a forum where molecular mechanisms of virus-induced neurologic disease can be examined and understood. Special emphasis will be placed on the role of the immune response in controlling CNS infection and specific aspects of the inflammatory response to pathogenic agents that cause neurologic dysfunction subsequent to entry into the CNS. By bringing together international investigators in the fields of neurology, neuropathology, neuropathogenesis, neurobiology, neuroimmunology, neurochemistry, and molecular

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New Initiatives

Peter Kennedy, M.D., Ph.D. • Glasgow, UK

During the past two years, the ISNV has continued to work through the Board of Directors to implement a number of new initiatives that will continue to strengthen the Society and create an environment of inclusivity. These efforts have been facilitated by the establishment of a number of Board Subcommittees, including Fundraising (Chair, Kamel Khalili), Membership (Chair, Alan Jackson), Publications (Chair, Kamel Khalili), Women in NeuroVirology (Chair, Suzanne Gartner), Investigators-in-Training (Chair, Eugene O. Major), and Meetings (Chair, Brian Wigdahl). The current membership on these subcommittees is provided in the Program for the 7th International Symposium on NeuroVirology and the ISNV website at www.isnv.org.

The ISNV is especially proud to announce three new initiatives that will become cornerstones of future Symposia. The first, the Paradigm Builder Lectureship, will highlight investigations that have led to basic scientific concepts and new dogma in the field of neurovirology or related disciplines. The inaugural lecture, to be

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Contact the ISNV Administrative Office at:
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ISNV Highlight - Olimpia Meucci, M.D. Ph.D.

Kamel Khalili, Ph.D. • Philadelphia, PA

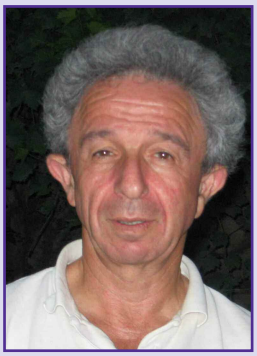
Research in Dr. Meucci's laboratory is focused on the intracellular mechanisms that regulate neuronal survival, and the events that underlie the neuropathogenesis of AIDS and neuroinflammatory diseases. A major goal is to determine the role of chemokines in CNS physiology (i.e. neuronal survival and development) and pathology (HIV-1-related neuropathology and neuro-inflammatory diseases). Current research efforts are determining the direct effects of chemokines on neurons, and identifing the molecular mechanisms that regulate the activity of neuronal chemokine receptors, including their interactions with major neurotransmitter and neuropeptide systems. These studies will also define the roles of chemokines as both neuroprotective and neurotoxic agents, demonstrate the impact of various cellular and environmental conditions on chemokine functions, and relate these effects to their role(s) in CNS physiology and pathology. To this end, her research group has recently analyzed the effect of chemokine receptor activation (by endogenous ligands or viral proteins) on neuronal cell cycle proteins implicated in neuronal survival and differentiation, namely the retinoblastoma protein Rb and some of its downstream targets, including the transcription factors E2F-1 and p53. These efforts have identified novel pathways potentially altered by HIV-1 infection in the brain. For instance, recently published results (Mol Cell Neurosci, 30:58-66, 2005) suggest that stimulation of different p53 targets is instrumental in determining the outcome of the activation of the chemokine receptor CXCR4 on neuronal survival.

In parallel studies, Dr. Meucci's research group is examining the interactions of CXCR4 with opioid receptors in neurons. Initial investigations have revealed an interesting coupling between these two classes of G protein coupled receptors that might have important implications for the physiological and pathological actions of chemokines in the CNS. In fact, modulation of the effect of SDF-1 alpha (the natural CXCR4 ligand) by neuropeptides may serve as a natural mechanism to adjust chemokine signaling to meet physiological demands (during development, for instance) and to contribute to the deleterious effects of SDF-1 alpha (or the HIV-1 protein gp120) under pathological conditions.

The long-term goal of her research is to foster the development of therapeutic molecules against neurodegenerative and neuroinflammatory conditions, including neuroAIDS.

ISNV Highlight - Israel Steiner, M.D.

Pasquale Ferrante, M.D. • Milan, Italy



The main thrust of the Laboratory of Neurovirology in the last decade has been the study of the molecular features of herpes simplex virus type 1 (HSV-1) latent infection in the nervous system. Following primary infection, the virus establishes latent infection in human peripheral sensory ganglia and is capable of reactivation associated with both peripheral muco-cutaneous disease and central nervous system complications and involvement. HSV-1 is transcriptionally active during latent infection to produce the latency-associated transcripts (LATs), 2.0 and 1.5 kb in size. This transcription has been linked to the ability of the virus to reactivate (Steiner et al., EMBO J. 1989;8:505-11), but its potential gene products and mechanisms of action are unknown. The group has generated a transgenic mouse and neuronal cell lines that constitutively express this gene, and used these systems and the mouse latency model to show the following: HSV-1 LATs are bound to polyribosomes during latency in vivo, as well as in neuronal cells in vitro, and therefore might be translated (J Virol, 71:2897-904, 1997); the relative LAT amounts associated with polyribosomes in mice brainstem and trigeminal ganglia (TG) are tissue specific and might have a role in the reactivation function of HSV-1 (J Neurovirol, 4:426-32, 1998); replication of HSV-1 was markedly repressed in LAT-expressing cells and associated with reduced steady-state levels of IE gene mRNAs, suggesting that the LATs may repress viral replication in neuronal cells by reducing IE gene mRNA levels and facilitate the establishment of latency (J Virol, 72:5067-75, 1998); the LATs interfere with HSV-1 superinfection of latently infected neurons, and may therefore protect the latent HSV-1 reservoir from cytopathic superinfections and at the same time the host is protected at the viral entry site from HSV-1 insults that may cause encephalitis (J Neurovirol, 8 Suppl 2:97-102, 2002); replication of HSV-1 was suppressed in primary embryonic fibroblasts obtained from LAT-expressing transgenic mice and reactivation of latent HSV-1 from TG of these mice was more efficient, confirming the in vitro results (J Virol, 77:12421-9, 2003). Recently, they have proposed that HSV-1 latency, like bacteriophage lambda lysogeny, is associated with protection from cell death and restriction to super-infection, and that viral reactivation from the latent state is triggered by exogenous stress signals that interfere with cellular viability and may eventually lead to cell death (J Theor Biol, 236:88-94. 2005).

Another avenue that the laboratory started to pursue in the last years is the usage of mice organotypic brain slices to study the neurotropism of HSV-1. Preliminary findings suggest that neonate brain tissue is much more permissive for HSV-1 infection, that the efficacy of infection is multiplicity of infection and cell type dependent, and that it does not follow the anatomic pattern present during herpes encephalitis (Brown et al., in preparation).

ISNV Highlight - Janice Clements, Ph.D.

Brian Wigdahl, Ph.D. • Philadelphia, PA

The Retrovirus Laboratory at Johns Hopkins Medicine is an interdisciplinary group of scientists studying the molecular pathogenesis of HIV-1 central nervous system (CNS), peripheral nervous system (PNS), and pulmonary disease. A major accomplishment of the lab has been the development of a novel SIV/macaque model that reproduces all of the stages and disease outcomes of HIV-1 infection in humans on a rapid, reproducible schedule. Scientific leadership is provided by four faculty – Janice Clements, Ph.D., M. Christine Zink, D.V.M., Ph.D., Joseph Mankowski, D.V.M., Ph.D. and Sheila Barber, Ph.D. – each with different but complementary expertise, including biochemistry and molecular virology (Clements), macrophage biology and neuropathology (Zink), genetics and pathology (Mankowski), and signal transduction, gene regulation and innate immunity (Barber). Research is supported by a primate colony with outstanding veterinary support directed by Dr. Robert Adams. Each faculty member has individual NIH grant funding and works collaboratively with other Retrovirus Laboratory faculty and with other leaders in the HIV-1 field, including Justin McArthur, M.B.B.S., M.P.H. (HIV-1 CNS and PNS disease), Avindra Nath, M.D. (HIV-1 CNS disease) and Robert Siliciano, M.D. (SIV and HIV-1 latency).

There is an exciting collaborative atmosphere in the Retrovirus Laboratory, which moved to 10,000 sq. ft. of custom-built research space in 2003. Research in the laboratory is kept new and stimulating by a constant influx of graduate students from diverse graduate programs in the School of Medicine, including Biochemistry, Cell and Molecular Biology, Human Genetics, Cellular and Molecular Medicine, and Pathobiology. Currently, there are 12 graduate students in the laboratory (Mathew Caples, Justyna Dudaronek, Michael Nicholson, Edward Wright, Kenneth Witwer, Gregory Szeto, Shruthi Rabimohan, Emily McVey, Susan Follstaedt, Victoria Laast, Kris Helke, and Angela Brice); the last three are also veterinarians. The laboratory is superbly managed by a molecular biologist, Lucio Gama, and research is made possible by a dedicated group of excellent technicians (Brandon Bullock, Ming Li, Tauni Voelker, John Anderson, Chante Austin, Chris Bartizal, Jamie Young, Christine Brennan, and Erin Shirk).

The Retrovirus Laboratory has been directed by Dr. Clements since 1993 and, in the last 12 years, the laboratory has published over 120 papers. A major contribution of the group has been the development of a novel, accelerated, and consistent model of SIV AIDS and CNS/PNS disease (J Neurovirol, 8 Suppl 2:42-48, 2002). In just 3 months, infected macaques recapitulate all stages of HIV-1 infection, from acute infection at 7-10 days post inoculation, to asymptomatic infection at 21-56 days, and finally to end-stage disease by 84 days, with all macaques developing AIDS and over 90 percent having CNS lesions typical of those seen in HIV-1-infected individuals. This rapid model has recently been shown to be an excellent model of HIV-1 peripheral neuropathy. The model has led to new insights into HIV-1 CNS pathogenesis, provided an efficient and rigorous model for the testing of new therapeutic approaches for HIV-1 CNS disease, and is being used to study the mechanisms of induction and reactivation of latent virus in tissue reservoirs (such as the brain) in macaques treated with a HAART-like regimen.

One of the most exciting discoveries facilitated by this model is the revelation that the antibiotic minocycline has potential as a therapeutic for controlling inflammatory responses in the brain to HIV-1/SIV infection, as well as the surprising finding that minocycline inhibits replication of HIV-1 and SIV in both lymphocytes and macrophages. These studies have provided the foundation for a human clinical trial, led by Ned Sacktor, M.D., in collaboration with M. Christine Zink, in which HIV-1-infected patients with mild cognitive impairment are treated with minocycline.

Another unexpected discovery made possible by the model was the finding that innate immune responses, particularly IFN-beta, control SIV replication in the CNS after acute infection (J Neurovirol, 10 Suppl 1:15-20, 2004). This finding led to the identification of transcriptional latency of virus in brain, most likely in resident CNS macrophages. This latency in the CNS has intriguing parallels to latency in resting CD4 lymphocytes in the blood since both forms of latency are attributed to host immune responses.

Research in the Retrovirus Laboratory has evolved from studying the virological and molecular aspects of the virus in vitro and in vivo to our current general understanding of the integral viral and host contributions to nervous system disease processes using lentiviruses as the "biological probe." The contribution of host genetics and epigenetics are being examined in the macaque model because of the close genetic relationship between macaque and human genes and the recent completion of the monkey genome.

The Retrovirus Laboratory also has a personality and spirit – the lab T-shirts sport the motto, "Work Hard, Play Hard" and this exemplifies the daily operation of the group. One laboratory tradition is to make Halloween an opportunity for hard work (annual clean up of cold rooms, freezers and other tasks that are routinely postponed) as well as play – all must come in costume for the day's activities. The lab's Friday Happy Hour is open to all, so if you are ever in Baltimore at 4 pm on Friday, stop in for some

If you would like to see a basic science researcher or clinical investigator featured in the ISNV newsletter, please forward his or her name along with a brief research description and curriculum vitae to Kamel Khalili (Chair, Publications Subcommittee) at isnv@jneurovirol.com.

Symposium (continued)

virology, the meeting will (i) enhance cross-fertilization of basic/clinical concepts concerning prevention and treatment of neurologic disease caused by HIV and other viral and non-viral pathogens, (ii) attract young investigators into these complementary and important multidisciplinary fields of investigation, and (iii) stimulate collaborations with an international scope. This Symposium will also emphasize the integration of basic, translational, and clinical research to develop new strategies to prevent, diagnose, and treat virus-associated neurologic disease.

Scientific sessions this year will cover a wide range of interests in the field of neurovirology, including multiple sclerosis, Alzheimer's disease, and prion-associated pathogenesis. Specifically, scientific sessions featuring 68 investigators from around the world will focus on (i) mechanisms of inflammatory disease, (ii) neuroAIDS, (iii) neurotropic viruses and multiple sclerosis, (iv) HAM/TSP, (v) drugs of abuse, inflammation, and CNS pathogens, (vi) host and viral genetics, (vii) co-morbidity pathogens, (viii) aging and its association with viral and non-viral pathogens, (ix) viral latency, reactivation, and molecular pathogenesis, (x) neurogenesis, hematopoiesis, and cellular therapy, and (xi) neuropathogenesis and animal models.

Of course, the highlight of the Symposium will again be the ISNV Pioneer in NeuroVirology Gala Dinner, which will take place on Friday evening. As in previous years, the evening will culminate in the presentation of the 2006 Pioneer in NeuroVirology Award to an individual who will join a growing list of accomplished investigators in the field of neurovirology, including Drs. Richard Johnson (1999), Volker ter Meulen (2000), Neal Nathanson (2002), Michael Oldstone (2003), and Hilary Koprowski (2004).

Our goal over the next several days is to provide you with the opportunity to gain a greater understanding of current issues in field of neurovirology, and to facilitate cross-talk between investigators and clinicians interested in virus-associated nervous system disease. We hope your trip to the City of Brotherly Love is both productive and enjoyable.

New initiatives (continued)

delivered by Dr. Charles Weissmann, is entitled the "Molecular Biology of Prions." Dr. Weissmann is a leading investigator in the field and is currently Professor and Chair of the Department of Infectology at Scripps Florida, in Jupiter, Florida, and a member of the National Academy of Sciences.

The second initiative, the Outstanding Women in Neuroscience Lectureship, is sponsored by the ISNV Women in NeuroVirology Subcommittee. This lectureship will emphasize the major contributions of basic science and clinician/scientist investigators in neuroscience and other related areas of biomedical science. For the 2006 ISNV Symposium, the subcommittee has selected Dr. Diane Griffin to deliver the Outstanding Women in Neuroscience Lectureship. The title of Dr. Griffin's lecture is "Alphavirus encephalomyelitis: Determinants of outcome." Dr. Griffin is currently Professor and Chair of the Department of Molecular Microbiology and Immunology at the Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland, and a member of the National Academy of Sciences.

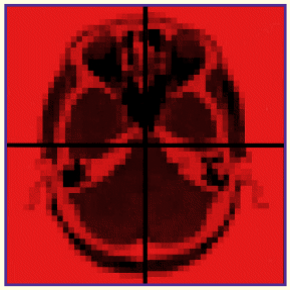
The third special initiative in development is the special ISNV scientific workshop. This year, the workshop will focus on multiple sclerosis. This workshop will be chaired by Dr. Antonina Dolei, Sassari, Italy. Dr. Dolei will also present a talk in the neurotropic viruses & multiple sclerosis session chaired by Drs. Dennis Kolson and Micheline McCarthy. Both the workshop and plenary session will highlight recent advances in defining the intricate molecular pathways that lead to the genesis of this progressive neurologic disease. Developing new strategies for treatment and prevention will also be a focal point.

An additional initiative that continues to expand is the provision for travel fellowships provided to predoctoral, postdoctoral, and clinical trainees in the name of recipients of the Pioneer in NeuroVirology Award. Funds for these travel fellowships have been provided by the National Institutes of Health and the Society. All trainees are invited to the Investigators-in-Training Pioneer Luncheon to be held on Friday, June 2. Again, this process will be one of the important aspects of the 7th Symposium as well as future Symposia.

JNV Online Submissions

Kamel Khalili, Ph.D. • Philadelphia, PA

The Journal of NeuroVirology is currently accepting manuscripts via ScholarOne, a web-based interface hosted by Manuscript Central. The online system streamlines manuscript submission, the review process, and manuscript production, all of which serves to reduce the amount of time from submission to publication. Visit the JNV web site at www.jneurovirol.com for more information.



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