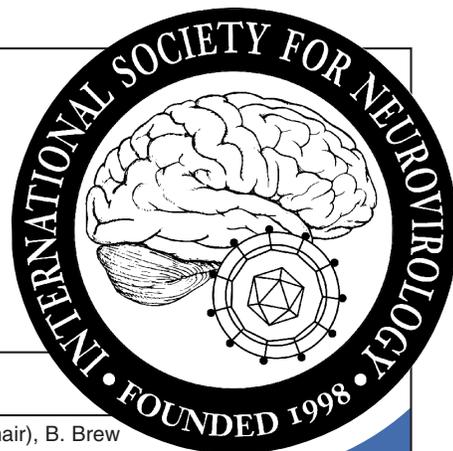


ISNV



International Society for NeuroVirology

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ISNV Publications Subcommittee: K. Khalili (Chair), B. Brew
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Message from the President

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

The Society has now been in existence for 7 years since its foundation, and I would like to mention some of the significant developments that have taken place since my term of office started in January, 2004. Following in the footsteps of the ISNV's first



president, Brian Wigdahl, was somewhat daunting to say the least, but I have been greatly helped by a number of people in the Society, particularly Brian, Kamel Khalili, Jennifer Gordon, Walter Atwood, and Alan Jackson. To all of these, and the many other Board and Society members who have given such valuable advice and assistance, I would like to express my gratitude. The Society's membership has remained pretty stable at approximately 225 members, although it did peak at over 300 in 2003 following the Baltimore NeuroVirology meeting. A major reason for the fluctuation in numbers is that many student and post-doctoral memberships lapse after they join the Society as part of their Symposium registration. But some memberships lapse for other reasons. Maintaining and, indeed, significantly increasing the Society's membership is of paramount importance to our ongoing activity. I would invite you to renew your

membership when it becomes due and also urge you to encourage as many of your colleagues as possible at all levels to join the Society. In addition, please remember that we maintain greatly reduced membership rates for students and post-doctoral fellows. We have also recently established a strategic alliance with the Society of Italian Virologists (SIV), which provides reduced membership dues for SIV members with reciprocity for ISNV members. We are also currently in contact with American and European virology organizations to explore potential interactions that could be of mutual benefit. What is clear is that the Society must increase its European membership as well as its overall membership numbers.

The 6th International Symposium on NeuroVirology, held in Sardinia, Italy, in September, 2004 was a great success, and I wish to thank the local organizers, Ninella Dolei and Pasquale Ferrante, for their superb organizational skills and efforts. Both the scientific excellence of the presentations and the ambience of the venue were memorable, and it was a great pleasure for me to present the 2004 Pioneer in NeuroVirology Award to Dr. Hilary Koprowski for his seminal contributions over many years in a range of areas, particularly, of course, rabies. He follows a distinguished line of past awardees, including Richard Johnson, Volker ter Meulen, Neal Nathanson, and

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Announcing the 7th International Symposium on NeuroVirology

Doubletree Hotel Philadelphia
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May 31st – June 3rd, 2006

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ISNV Highlight - Igor Koralnik, M.D.

Kamel Khalili, Ph.D. • Philadelphia, PA

Dr. Igor J. Koralnik is an associate professor of Neurology at Harvard Medical School, and the Director of the HIV/Neurology Center at Beth Israel Deaconess Medical Center, Boston, MA, where he treats HIV-infected people who have neurologic problems. The main focus of Dr. Koralnik's basic science and clinical research program is on JC virus and Progressive Multifocal Leukoencephalopathy (PML). His laboratory has pioneered the study of the cellular immune response against JCV and characterized epitopes of JCV VP1 protein recognized by CD8-positive cytotoxic T lymphocytes (CTLs). In a series of publications, they have shown that the presence of JCV-specific CTLs in the blood of PML patients is predictive of a favorable clinical outcome. These results suggest a potential for immune-based therapies for PML, which are now in development in his laboratory.



Because of the very narrow host range of JCV, there is no animal model of PML. Dr. Koralnik's lab has used the simian polyomavirus SV40, which has 69% homology with JCV, to develop a model of PML in nonhuman primates, and they have been able to induce a PML-like disease in immunosuppressed rhesus monkeys. Such a model may prove useful for understanding the pathogenesis of PML and devising interventions for this lethal disease.

One of the most enduring dogmas in polyomavirus biology was that JCV could only infect glial cells, and not neurons. Based on clinical and histopathological observations, Dr. Koralnik and collaborators at Mount Sinai Medical Center, NY, have identified a JCV variant with specific tropism for granule cell neurons of the cerebellum, causing cerebellar atrophy and disorders of gait and coordination. This is a novel clinical syndrome, distinct from PML, which they have called JCV granule cell neuronopathy (JCV GCN).

In addition to studies on JCV, Dr. Koralnik has also extended the scope of his research to the polyomavirus, BK. BKV has a high degree of homology with JCV, and can cause a nephropathy in renal transplant recipients that may lead to loss of the allograft. Dr. Koralnik has now initiated studies on the immune response to BKV in renal transplant recipients with BKV nephropathy in collaboration with Drs. Gordon and Khalili at Temple University, Dr. Trofe at the University of Pennsylvania, and Dr. Woodle at the University of Cincinnati.

ISNV Highlight - Hirofumi Sawa, M.D.

Kamel Khalili, Ph.D. • Philadelphia, PA

Dr. Sawa has been working with Dr. Kazuo Nagashima, who was a professor in the Department of Molecular & Cellular Pathology, Hokkaido University School of Medicine, Sapporo, Japan. He was the organizer of the Second International Conference on Polyomaviruses and Human Diseases that was held in Sapporo in June, 2004. Although Professor Nagashima retired in March, 2005, he is still active and contributing to both research and pathology.

Dr. Sawa has moved from the Department of Molecular & Cellular Pathology to the Department of Molecular Pathobiology, Hokkaido University Research Center for Zoonosis Control, which was built in April 1, 2005. The head of this research center is Professor Hiroshi Kida, who is a specialist in avian influenza.



Dr. Sawa's research efforts have concentrated on the interactions between human polyomavirus, JC virus (JCV), and infected cells, including the entry of JCV into cells, and the nuclear entry and egress of the virus. Dr. Sawa's research group is particularly interested in the small proteins of JCV, i.e., the agnoproteins that consist of 71 amino acids. Using the yeast two-hybrid assay, he has identified several cellular proteins that bind to agnoprotein. For example, he has found that agnoprotein binds to heterochromatin protein 1 alpha that is bound to the lamin B receptor (LBR). This process is thought to contribute to the reassembly of the nuclear envelope after cell division, to induce its dissociation from LBR resulting in destabilization of the nuclear envelope, and to promote the translocation of JCV virions out of the nucleus. In addition, Dr. Sawa has also found that agnoprotein interacts with fasciculation and elongation protein zeta 1 (FEZ1), which is a microtubule-binding protein. Agnoprotein facilitates JCV propagation by inducing the dissociation of FEZ1 from the microtubule. As a consequence of this work, Dr. Sawa believes that JCV agnoproteins play a role in intracellular trafficking of JCV.

Future investigations in Dr. Sawa's laboratory will continue to focus on the relationship between the virus and host cells. In addition, he has indicated his willingness to collaborate with other laboratories in this area and would be pleased to talk with other investigators about the prospect of collaborative research into diseases caused by these pathogenic viruses.

Drugs of abuse and their relevance to HIV progression

Toby Eisenstein, Ph.D. • Philadelphia, PA

One third of HIV infected patients in the United States are intravenous drug abusers. This statistically robust intersection raises the question of whether the drugs play a role in HIV progression, including to HIV dementia. Evidence gleaned from human epidemiological studies addressing this question has not shown an unequivocal link between drug abuse and faster progression of HIV infection, with some studies supporting a correlation and others not. Lack of robust and consistent correlations at the epidemiological level has led to the potentially false conclusion that there is no causal linkage. Factors that may confound the epidemiological approach include, first and foremost, poly-drug use by intravenous drug abusers (IVDUs), who combine alcohol, nicotine, cocaine, and marijuana with opioids such as heroin. There is no epidemiology study on HIV progression that has controlled for the type of drugs used or their frequency of use. This omission is a fatal flaw in the experimental design of these studies, and leaves the conclusions open to question.

In contrast, there is significant evidence from laboratory studies supporting the hypothesis that abused drugs can alter HIV replication. It has been shown that morphine up-regulates HIV added to cultures of peripheral blood mononuclear cells (PBMCs) obtained from uninfected volunteers (1) and also increases virus expression in latently infected PBMCs taken from infected patients (2). Further, methadone is reported to increase HIV replication in human fetal brain microglia and human monocyte-derived macrophages infected *in vitro* (3). (The major active metabolite of heroin is morphine, which binds to the mu opioid receptor. Methadone also binds to the mu opioid receptor). In co-cultures of chronically HIV-infected U1 cells, a promonocytic cell line, morphine treatment of LPS-stimulated human fetal brain cells up-regulated virus production (4). In these studies, opioid antagonists that act at the mu receptor have been shown to block the effects of the drug. Cocaine has also been reported to increase HIV replication in PBMCs (5,6), and has been shown to potentiate HIV infection in SCID mice implanted with human PBMCs infected with HIV (7). Taken together, these results clearly support the conclusion that these drugs upregulate HIV. Although the results are not consonant with the conclusions of the epidemiological studies, many investigators in the HIV field have tended to believe the epidemiological rather than the experimental results.

There are other types of experimental data that link drugs of abuse to alterations in HIV replication. Morphine and DAMGO, a highly selective, synthetic mu agonist, have been shown to up-regulate both CCR5 and CXCR4 in monocytes, activated T cells, astroglia, and a human lymphocytic cell line, which correlated with increased replication of HIV *in vitro* (8-11). Opioids also enhance chemokine expression (12). The consequences of enhanced chemokine levels may be accumulation of T cells or monocytes/macrophages at sites of HIV replication, or blockage of the HIV co-receptors. An intriguing

set of new observations shows that there is heterologous desensitization between opioid and chemokine receptors in human monocytes and also in CHO cells expressing cloned opioid and chemokine receptors (13-15). DAMGO can desensitize CCR5, and the chemokines, RANTES and SDF-1 alpha, can desensitize the mu opioid receptor (13). Opioids block chemotactic responses of lymphoid cells via this mechanism and can also block HIV infectivity via CCR5 (15). Evidence for *in vivo* heterologous sensitization comes from studies in which rats with cannulae in the periaqueductal gray region of the brain were pretreated with RANTES or SDF-1 alpha prior to receiving DAMGO. Chemokine infusion blocked the analgesic effect of DAMGO, suggesting that heterologous desensitization of the mu opioid receptor had occurred (13). This study lends support for interactions between opioid and chemokine receptors in the brain, with obvious implications for the potential to alter HIV progression in the neural compartment.

Finally, there is robust literature documenting the immunosuppressive effects of opioids and cannabinoids. Immunosuppression could potentiate HIV progression by reducing T cell immunity. It has been proposed that morphine and tetrahydrocannabinol (THC) bias the immune response toward a Th2 phenotype (16), which would be detrimental to control of HIV. However, other evidence indicates that morphine suppresses antibody responses (17). There are relatively few studies exploring the effects of drugs of abuse on resistance to infections, although it is well documented that IVDUs have an increased incidence of infection. Where they have been examined, opioids and cannabinoids have, in general, been shown to decrease host resistance to systemic or oral infection with bacteria, parasites, and viruses (18,19).

An important aspect of drug abuse that must be taken into consideration is that tolerance develops to many of the effects of opioids. The majority of the laboratory studies cited above have been carried out using acute drug administration. If tolerance develops to the immune effects, then under chronic usage, the immunomodulatory effects may dissipate. On the other hand, withdrawal from opioids may again affect immune responses. The few studies that have been published on the effects of withdrawal show immunosuppression (20). In monkeys, chronic morphine administration did not seem to have a marked effect on SIV progression, but withdrawal increased viral titers (21). Similar experiments in cats infected with FIV failed to show an alteration in disease progression (22).

Despite the enormous intersection between drug abusers and those infected with HIV, there are relatively few studies directly testing the hypothesis that drugs affect retroviral progression, and none examining HIV in the brain. Further studies are



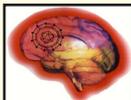
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Message from the President (continued)

Michael Oldstone. The next Pioneer Award will be announced at the 7th International Symposium on NeuroVirology, which is scheduled to take place at the end of May 2006 in Philadelphia, Pennsylvania, in the United States. We welcome nominations for this next award from our Society members. Our current view is that we will present this award at our international meetings, which will be held every 18 months.

I also want to mention some changes that have recently been made to the structure and operation of the ISNV Board of Directors. We recently appointed four new Board members, namely Walter Royal (US), Ruth Brack-Werner (Germany), Israel Steiner (Israel) and Ninella Dolei (Italy), all of whom

will make valuable contributions to the Society. I have also established six Board sub-committees, each of which has a Chair who reports back to myself and the Board of Directors. These committees will oversee membership, fundraising activities, meetings, Women in NeuroVirology (we call that WIN!), investigators-in-training, and publications. It is already clear that this new infrastructure will increase the Board's overall remit and activity, and will make the governance of the Society more productive and proactive. That can only be a good thing for all of our members. Without membership, we have no Society. In closing, I am very grateful to everyone within the Society for their inspiring enthusiasm and support.



2006 PIONEER IN NEUROVIROLOGY AWARD

REQUEST FOR NOMINATIONS

Awardee to be announced at the

7th International Symposium on NeuroVirology

to be held in

Philadelphia, PA, USA, May 2006

Nominations should be forwarded to:

Peter G. E. Kennedy, M.D., Ph.D.

President, International Society for NeuroVirology
University of Glasgow Institute of Neurological Science
Southern General Hospital
Glasgow, Scotland G51 4TF, UNITED KINGDOM

For additional information and/or questions:

Tel: 44-141-201-2474 • Fax: 44-141-201-2993

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Investigators-in-Training recognized in Sardinia

Lectureship awards were given to five of the ten Investigators-in-Training who presented at the 6th International Symposium on NeuroVirology, Sardinia, Italy, in September, 2004. Awards were given to the following individuals in honor of past Pioneers in NeuroVirology: Essia Bouzamondo-Bernstein (Richard Johnson, 1999), Jennifer Clarke (Volker ter Meulen, 2000), Satish Pillai (Neal Nathanson, 2002), Diane Lawrence (Michael Oldstone, 2003), and Armine Darbinyan (Hilary Koprowski, 2004).



L to R: Armine Darbinyan; Diane Lawrence; Michael Oldstone, MD (2003 Pioneer); Hilary Koprowski, MD (2004 Pioneer); Richard T. Johnson, MD (1999 Pioneer); Essia Bouzamondo-Bernstein; Jennifer Clarke; and Satish Pillai.

JNV Announces On-line Manuscript Submission

The Journal of NeuroVirology will soon begin accepting manuscripts via ScholarOne, a web-based interface hosted by Manuscript Central. On-line manuscript submission will streamline the submission process, manuscript review, and

production, all of which will reduce the amount of time from submission to publication. Visit JNV at www.jneurovirol.com for more information.

Drugs of abuse (continued)

clearly warranted to examine more closely whether a causal relationship exists between drug usage and HIV progression, especially in the neural compartment.

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