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International Society for NeuroVirology

Editor: Dianne Langford, Ph.D.
Associate Editor: Michael Nonnemacher, Ph.D.

Hilary Koprowski, M.D. (1916-2013)

Hilary Koprowski, M.D., the internationally renowned researcher, died at the age of 96 on April 11, 2013 from complications associated with a series of strokes. He was born in Poland and received his M.D. from Warsaw University. Although best known for his scientific accomplishments, he was a gifted classical pianist and composer. While in medical school, Dr. Koprowski married Irena Grasberg, also a physician, who had achieved a considerable level of acclaim for her groundbreaking work on the development of the "Pap" test. Hilary was of Jewish heritage although he did not have a religious upbringing. Following the Nazi occupation of Poland in the late 1930s, Hilary and Irena fled Europe for Rio de Janeiro, Brazil where Hilary began his virus research work on yellow fever at the Rockefeller Foundation. He arrived in the United States in 1944 where he became a research associate at the Lederle Laboratories in Pearl River, NY.

Hilary Koprowski, M.D.
2004 Pioneer in Neurovirology

He rose to prominence during the late 1940s and early 1950s for his trailblazing research on the development of a polio vaccine. Although eclipsed by the triumphs of his formidable competitors, Albert Sabin and Jonas Salk, Hilary was actually the first to develop a viable oral vaccine for polio. Like Sabin, Hilary worked with an attenuated virus to develop his vaccine. After successfully producing immunity in monkeys, Hilary administered the attenuated virus to himself by ingesting it, with no ill side effects. He then administered the vaccine to 20 children with no neurological side effects and all of the children showed antibodies to the poliovirus. He published his findings in a seminal paper in 1952, several years before the published and public acclaims of his competitors.

Hilary arrived at the Wistar Institute in Philadelphia in the 1950s where he served as the director for 35 years. Under his leadership, the Wistar Institute recruited talented scientists and trainees and flourished into a world class research and education organization. His work on virology, notably rabies, continued to flourish and led to the development a rabies vaccine for humans and animals.

Throughout his illustrious career, Hilary was the recipient of numerous prestigious awards and accolades including the Order of the Lion from the King of Belgium, the French Order of Merit for Research and Invention, and of course the Pioneer in NeuroVirology award from ISNV in 2004.

Hilary's wife, Irena died in 2012. He is survived by two sons, five grandchildren, and three great grandchildren.

The magnitude of his contributions to biomedical research as well as the arts is immeasurable. His presence, intellect, and personality will be greatly missed.

Kamel Khalili

Meeting Report

5th International Conference on Polyomaviruses and Human Diseases: Basic and Clinical Perspectives

Jennifer Gordon

Dr. Joseph Berger asking questions at the 5th International Conference on Polyomaviruses and Human Diseases: Basic and Clinical Perspectives

The 5th International Conference on Polyomaviruses and Human Diseases: Basic and Clinical Perspectives was held in May 2013 at the Grand Hotel Bristol in Stresa, Italy along the shores of Lake Maggiore. The meeting, organized by Dr. Pasquale Ferrante of the University of Milan and Dr. Kamel Khalili of Temple University in Philadelphia covered the major polyomaviruses, BKV, JCV, and SV40, as well as a rapidly expanding list of human polyomaviruses, which have been discovered over the last six years. These newly emerging viruses now bring the total number of human polyomaviruses to thirteen and counting, and include Merkel cell polyomavirus and *Trichodysplasia spinulosa*-associated polyomavirus, both of which have been shown to cause rare skin disorders. Though the majority of the newer viruses have yet to be associated with a specific human disease, such discoveries have fostered new interest in the polyomaviruses. The emergence of JCV-induced progressive multifocal leukoencephalopathy in individuals treated with monoclonal antibody therapies such as Tysabri, in addition to its persistence as an opportunistic infection in the HIV-1 population, is of significant concern and continues to pose diagnostic and therapeutic challenges for clinicians. Over 150 participants from the US and Europe attended the two and a half day conference. Presentations focused on molecular biology, pathogenesis, genetics and epigenetics, epidemiology, animal models, diagnosis, and treatment strategies of polyomavirus infections. The small size of the meeting and the dynamic mix of established polyoma- virologists with those more recently entering the field provided a unique forum for discussing the most recent discoveries and advances related to both basic and clinician aspects with a strong emphasis on translational research. Abstracts from the meeting will be published in the June issue of the *Journal of NeuroVirology*. The dates and location for the 6th meeting in the series will be announced shortly.

Science News

How Herpesviruses Hitch a Ride in Neurons

Fred Krebs

The pathogenesis of neurovirulent herpesviruses such as herpes simplex virus (HSV) and varicella zoster virus (VZV) is dependent not only the establishment of a latent infection in susceptible neurons, but also on the ability of the virus to efficiently and expeditiously travel to the body of the neuron via retrograde axonal transport. Until recently, the molecular events involved in herpesvirus transport using neuronal microtubules have not been well understood. Investigators led by Gregory Smith (an associate professor in Microbiology-Immunology at the Northwestern University Feinberg School of Medicine) have now uncovered the mechanism that herpesviruses use to "hitch a ride on the intracellular highway" (Zaichick *et al., Cell Host & Microbe*, 2013).

To model herpesvirus neuronal transport, Sofia Zaichick and colleagues used pseudorabies virus (PRV), an animal herpesvirus noted for its neurovirulence and neuroinvasion via axonal microtubules in neurons within the sensory ganglia. Consistent with previous indications that viral protein 1/2 (VP1/2) tegument protein is essential for PRV propagation and critical for viral transit through the cell to the nucleus, the authors demonstrated that VP1/2 alone mediated microtubule transport through associations with the dynein/dynactin microtubule motor complex. Furthermore, structure/function studies indicated that mutations in a proline-rich sequence in the C-terminal portion of VP1/2 decreased both viral propagation and virulence.

To specifically demonstrate that these effects were due to impaired retrograde axonal transport, the authors used a series of

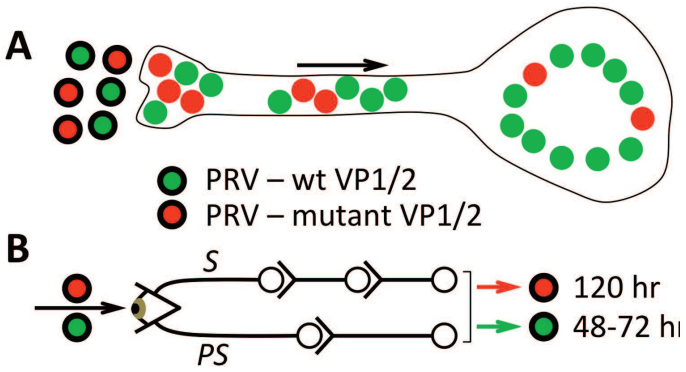

Figure 1. PRV VP1/2 is an important effector of axonal transport and neuroinvasion. (A) After neuronal infection, capsids containing mutated VP1/2 (red) are outpaced by faster, wild type capsids (green). (B) The time required for neuroinvasion after ocular infection is significantly greater for viruses containing mutated VP1/2 (red) relative to wild type viruses (green). S, sympathetic circuit; PS, parasympathetic circuit. (Adapted from Zaichick *et al., Cell Host & Microbe*, 2013)

elegant *ex vivo* and *in vivo* models to examine capsid transport and viral propagation in neurons. In experiments using primary chicken embryonic dorsal root ganglia (DRG) explants, mutations in the proline-rich portion of VP1/2 were sufficient to slow viral capsid transport to the nucleus when compared, in the same neuron, to the transport of capsids containing the wild-type VP1/2 (Panel A). Similarly, in a rat model of ocular infection, viruses

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ISNV Highlights - Cris Achim, MD, PhD

Pankaj Seth

Work from Dr. Cris Achim's laboratory has played an important part in our understanding of neuroinflammation and brain macrophage involvement in regulating neuronal homeostasis in chronic neurodegenerative diseases like HIV associated neurocognitive disorder (HAND). Dr. Achim completed his MD degree and residency training in General Medicine and Infectious Diseases at the in Bucharest, Romania. After completing PhD and postdoctoral studies at the University of California San Diego, Cris joined the University of Pittsburgh where he continued post-doctoral training in Behavioral Neurosciences and received a faculty appointment in the Department of Pathology in 1993, followed by tenure. His early studies described viral distribution, major histocompatibility complex expression and cellular distribution, alterations in neurotrophic homeostasis and BBB tight junction disruptions in the brains of HIVE patients. Cris also worked to develop an *in vivo* experimental model of HIVE in human neuroglia transplanted in SCID mouse brains. In 2007, Cris returned to UCSD where he is currently Professor of Psychiatry and Pathology (Neuropathology) and Deputy Director for Translational Research at Stein Institute for Research on Aging. More recent studies from his lab indicate disruption of immunophilin expression in HIVE (Soontornniyomkij *et al., JNV*, 2012), increased amyloid deposition (Soontornniyomkij *et al, AIDS*, 2012) and altered anti-oxidant response in HAND (Soontornniyomkij *et al., JNIP*, 2012). Dr. Achim's laboratory continues to conduct pioneering research in brain macrophage pathology in chronic neurodegenerative diseases, including HAND where he uses complex *in vitro* systems of human brain cell cultures to explore the contributions of co-morbid factors like methamphetamine and highly active antiretroviral therapy (HAART) neurotoxicity in the context of neuroglial immunophilin response to metabolic and oxidative stress and abnormal protein aggregation.

Dr. Achim has initiated a productive collaboration with AIDS investigators in Romania that has resulted in a series of research projects funded by NIMH/FIC R21 and R01 grants. With his colleagues in Romania, ongoing studies address HIV-1 clade F neurotropic molecular virology, host genetics and biomarkers as predictors of HAND in long-term survivors on HAART. The preliminary results suggest that the Romanian cohort has a high rate of neurologic complications and more than half suffer from HAND. Furthermore, a unique feature in this cohort is the prevalence of subacute myoclonic measles encephalitis (SMME). Based on these findings, Dr. Achim and collaborators at Victor Babes Hospital for Infectious Diseases in Bucharest have proposed SMME as an AIDS defining disease.

A major focus in the Achim lab continues to be CNS pathology in the post-HAART era studying the intersection of long-term survival with HIV and aging. Results suggest that aging on the background of the ApoE e4 genotype may result in significant β-amyloid deposition in the brain in HIV infected subjects (Figure 1). Furthermore, the amyloid plaques were associated with HAND in the e4 carriers. These findings suggest that detection of APOE ε4 genotype and markers of cerebral amyloid deposition may be useful in identifying living HAND subjects who could benefit from Aβ targeted therapies.

Dr. Achim's laboratory is actively involved in exploring the HIV associated co-morbidities including methamphetamine use *in vitro* (Tatro *et al., JNIP*, 2013) and in clinical and *in vivo* transgenic animal models through the Neuroscience and Animal Models Core, which he is directing, within the Translational Methamphetamine AIDS Research Center at UCSD.

Dr. Achim actively participates in training and early career investigator mentoring programs. He is currently involved with seminar series and Interdisciplinary Research Fellowship in NeuroAIDS. Cris has also been instrumental in initializing a few international societies and is founding member of the ISNV and the Stem Cell Society. ISNV wishes Dr. Achim and his research group the very best and hope to see more breakthroughs from their research endeavors.

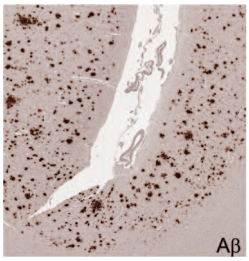


Figure 1: Immunohistochemical labeling with anti-Aβ antibody (clone 4G8) shows widespread plaques in the cortex of a 48 y.o. woman who died with HAND. Autopsy brain material obtained from the National NeuroAIDS Tissue Consortium.

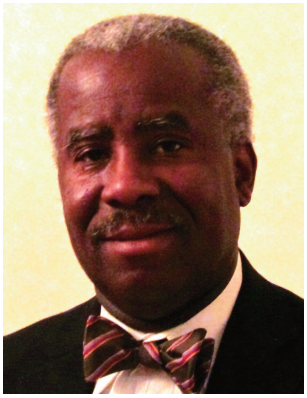
Science News - continued from page 2

containing the mutated VP1/2 tegument protein required up to five days for neuroinvasion along multi-neuron sympathetic and parasympathetic circuits. In contrast, viruses containing wild type VP1/2 protein propagated along those same circuits in 48-72 hours (Panel B). Both observations clearly demonstrate that VP1/2 is an important effector of long-distance capsid microtubule transport and viral neuroinvasion.

These results represent advances in herpesvirus research along several fronts. First, the demonstrated importance of VP1/2 in PRV retrograde axonal transport expands our basic understanding of herpesvirus neuroinvasion and neurovirulence. Second, recombinant viruses containing a wild type or variant copy of VP1/2 in combination with a traceable molecular marker may have utility in future brain mapping studies. Third, the central role of VP1/2 in retrograde axonal transport makes it a potential target for new therapeutic strategies that will effectively prevent the spread of herpesviruses from the site of infection to the nervous system. Finally, these mechanistic studies may also form the basis for recombinant herpesvirus vectors that deliver therapeutic genes deep into the nervous system along natural neuronal pathways. Each of these aspects is indicative of a new direction in the field of neurovirology.

ISNV Highlights – Walter Royal, MD

Kurt Hauser



Dr. Walter Royal III is the Director of the Maryland Center for Multiple Sclerosis Treatment and Research, a Professor of Neurology and Professor of Anatomy and Neurobiology at the University of Maryland School of Medicine, and Research Associate Director for the Veterans Administration (VA) Multiple Sclerosis Center of Excellence-East. Despite impressive clinical and teaching commitments, Dr. Royal maintains high profile research programs in both basic and clinical arenas as evidenced by over 70 peer-reviewed publications, and frequent authorship of reviews and book chapters.

Dr. Royal received A.B. and M.D. degrees, from Harvard College and Dartmouth University, respectively before pursuing residency training in internal medicine, and psychiatry and neurology. In addition to extensive medical training, he completed outstanding postdoctoral training with Dr. Opendra (Bill) Narayan at Johns Hopkins University. Dr. Royal is board certified in internal medicine and psychiatry and neurology. He has served on a number of scientific review panels, including being a regular member of the NIH NAED study section. He has also served on the editorial boards of numerous journals, including the *Journal of Neurovirology*, is on the board of directors of the ISNV, and has served on a number of ISNV committees.

His breadth of interests range from studying the effects of vitamin A deficiency and opioid abuse on parvalbumin-positive interneurons in the hippocampus and prefrontal cortex in HIV-1 transgenic rats to establishing global initiatives for managing and treating neuroAIDS worldwide. He maintains active collaborations with colleagues both nationally and internationally. One of Dr. Royal's many interests is to define the incidence and virologic correlates of HIV-associated neurocognitive impairment in populations that have not been previously characterized. In one example, Dr. Royal collaborates with colleagues in Abuja, Nigeria to assess the relative incidence of cognitive impairment and its impact on the populations there. This includes exploring the relation to viral load and unique HIV strains, such as subtype G virus, to neurocognitive dysfunction.

Recently, Dr. Royal has become interested in the deleterious effects of cigarette smoking in relation to several neurologic disorders including multiple sclerosis and neuroAIDS, as well as the effects of second-hand smoke on childhood development as a risk factor for increasing the likelihood of developing multiple sclerosis in adulthood. The exceptionally high incidence of cigarette smoking in HIV-1 infected individuals (some estimates 3-fold higher) compared to uninfected individuals suggests a causal link and likelihood of significant comorbidity and mortality. Importantly, Dr. Royal was one of the first investigators to tackle this problem by examining the effects of cigarette smoke exposure in the HIV-1 transgenic rat. His inevitable goal is to test novel antioxidant therapies in this model with the hope of allaying the deleterious effects of HIV and other insults on brain function. Despite pressing clinical demands, Dr. Royal has continued to maintain an outstanding program in basic biomedical research funded by NIH and the VA. When asked how he juggles a highly successful and dedicated clinical practice with an outstanding research program, he modestly acknowledges the tremendous support of colleagues at the Institute for Human Virology, the Veterans Administration, and University of Maryland Medical Center. When asked for advice to early-career scientists, he noted "Curiosity defines us". He cites the importance of allowing that inquisitiveness to foster the drive to keep learning while tempering that curiosity by always remaining focused on the "principal scientific questions that are the target of your research."

2013 Upcoming Conferences

CSH Neurogenetics & behaviour of nonhuman primates: September 6-9, Cold Spring Harbor, New York

European Brain and Behaviour Society: September 6-9, Munich, Germany

CSH Neurobiology of Drosophila: October 1-5, Cold Spring Harbor, New York

CSH Development, function and disease of neural circuits: October 21-25, Suzhou, China

Society for Neuroscience: Neuroscience 2013: November 9-13, San Diego, California

American College of Neuropsychoparmacology Annual Meeting: December 8-12, Hollywood, Florida

ISNV Highlights - Herve Perron, PhD

Eliseo Eugenia

While working on his PhD thesis in the Department of Virology from the University Hospital of Grenoble, France, Dr. Herve Perron became interested in the hypothesis of a link between multiple sclerosis and retroviruses earlier published in a paper co-signed by Hilary Koprowski and Robert Gallo (*Nature*, 1985). A search for reverse transcriptase (RT) activity in CSF from MS patients revealed RT-activity associated with the production of retrovirus-like particles likely from spontaneous outgrowth of leptomeningeal cells shed in the CSF (Perron, *Res. Virol.*, 1988). It was followed by a study showing the same virion particles and RT-activity in a majority of macrophage cultures from MS blood monocytes, but not from controls (*Lancet*, 1991) and surprisingly, similar observations from Sven Haahr's group in Denmark in EBV B-lymphoblatoid cells from MS pateints were published in the same issue. With grant funding from the Mérieux Foundation (Lyon, France) he pursued his research and collaborated with Jeremy Garson from the University College of London, with whom he published the first molecular characterization of this MS-associated retrovirus, MSRV (*Proc. Natl. Acad. Sci.* USA, 1994). MSRV proved to be a novel human retrovirus, but not a new HTLV as previously expected. Moreover, this discovery identified a previously unknown family of human endogenous retroviruses (HERV) now named HERV-W (*J. Virol.*, 1999).

Addressing the possible relationship between this HERV expression and immunological abnormalities or neuroglial impairment in neuroinflammatory diseases such as MS, he then pursued research in collaboration with Monique Lafon and Patrice Marche (Institut Pasteur and INSERM, Paris) with whom he evidenced the potent immunopathogenic effects of MSRV purified virions, reproduced by the corresponding HERV-W envelope protein, a Toll-like receptor 4 (TLR4) ligand (*Virology*, 2001; *J. Immunol.*, 2006). In collaboration with François Rieger (CNRS, Paris), his data provided evidence for MSRV virion-associated gliotoxicity (*FEBS Lett.*, 1999) that likely involves TLR4-mediated effects on the oligodendrocyte precursor cell differentiation blockade as seen in MS brain lesions (Kremer *et al. Ann. Neurol.* in press). Considering the successive independent studies published by different groups during the past decade that gradually implemented the concept of an association between HERV-W and MS (reviewed in *J. Neurol. Sci.*, 2009 together with *Mult. Scler.*, 2012), the pathogenic properties of HERV-W envelope protein were hypothesized to be a target for a novel therapeutic avenue in MS. In order to address this cutting-edge perspective Dr. Perron co-founded a biotech company, Geneuro SA, in Geneva, Switzerland and is presently Chief Scientific Officer. After having validated that the HERV-W envelope protein induced EAE in mouse models and having selected neutralizing monoclonal antibodies with pre-clinical efficiency, Geneuro has developed a humanized IgG4 antibody. Clinical trials with this antibody have provided very good safety results in Phase I (*Clin. Ther.*, 2012) and have now passed validation of phase IIa in patients with MS. This concept of a pathogenic involvement of HERV-W elements -as presented for MS in Figure 1- was not shown to be relevant for other neurological diseases tested today, except for cases with chronic demyelinating demyelinating polyneuropathy (*Mult. Scler.*, 2012). Nevertheless, recent studies revealed neuroinflammation (in particular, myelin inflammation of brain gray matter) in a significant proportion of psychotic patients with bipolar disorder (BD) or schizophrenia (SZ), the successive reports of an association with HERV-W abnormal expression in a significant proportion of patients with SZ or BD (reviewed in *World J. Biol. Psychiatry*, 2013, together with *Transl. Psychiatry*, 2012) also point to further research and therapeutic avenues.

This new domain of neurovirology may now prefigure an emerging change of paradigm in the conception of gene-environment interactions, as part of the aetiopathogenic processes involved in chronic, multifactorial diseases of the central nervous system. It remains to be seen if HERVs, as also shown with HERV-K elements in amyotrophic lateral sclerosis (*Ann. Neurol.*, 2011), represent a common "virogenetic" pathway from various environmental triggers to different neurological and other non-neurological diseases.

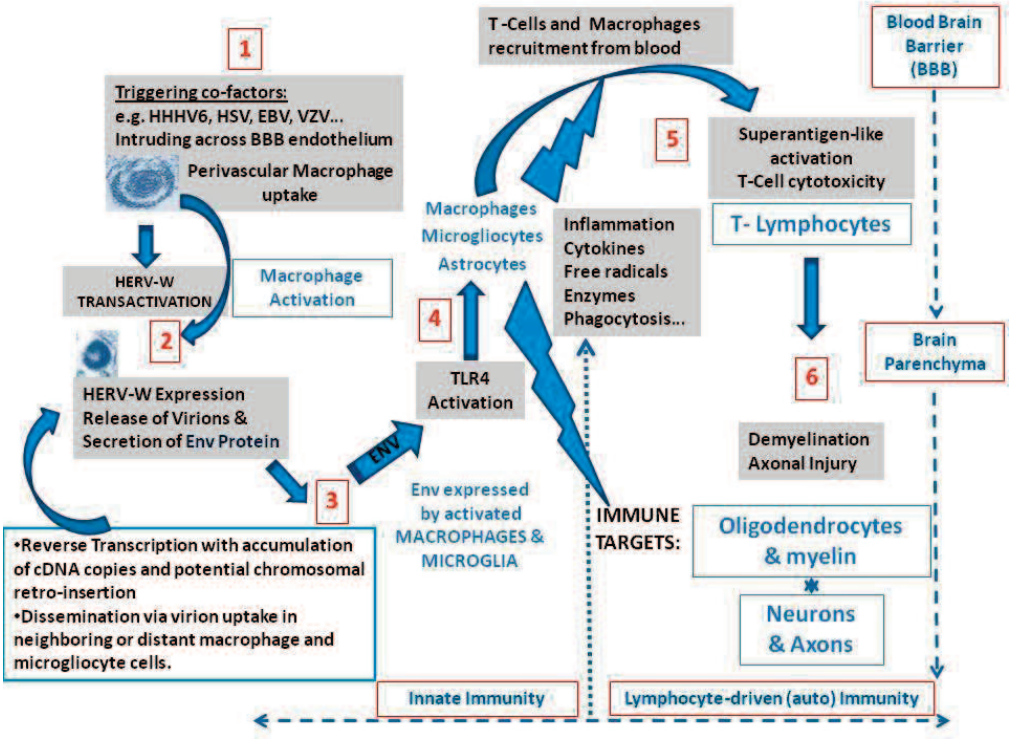
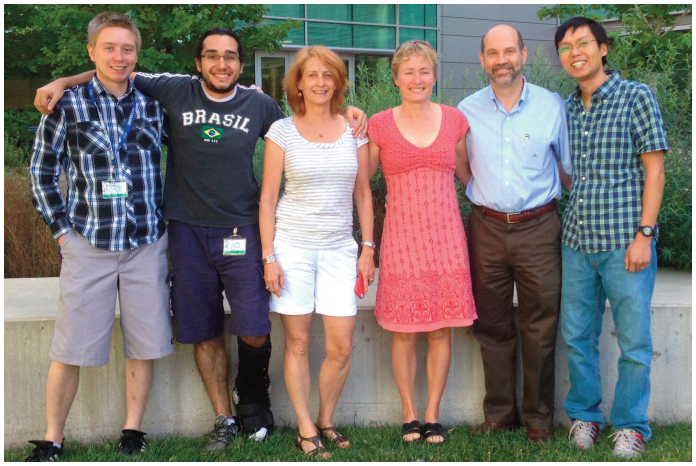


Figure 1. Global scenario of an immunopathogenic and neuroinflammatory pathway involving Human Endogenous Retroviral family 'W' (HERV-W) envelope (Env) expression as a pivotal element between infectious virus co-factors and the neuroimmune pathogenic cascade. (Perron et al. *Mult Scler.* 2012)

ISNV Highlights - Penny Clarke, PhD

Amanda Brown



Laboratory personnel (left to right): Scott Seitz, Eamon Quick, Smith Leser, Penny Clarke, Ph.D., Kenneth Tyler, M.D., and Yonghua Zhuang, Ph.D.

Dr. Penny Clarke is currently Professor of Neurology at the University of Colorado Anschutz Medical Campus in Aurora, Colorado. She earned her doctoral degree at the MRC Institute of Virology at the University of Glasgow, UK where she studied herpes simplex virus 2 and the role of viral ribonucleotide reductase in inducing mutations. Dr. Clarke then went on to postdoctoral studies under the mentorship of Dr. D. H. Gilden where she used Simian *varicella* as a model system to understand the molecular genetic mechanisms of human varicella virus latency in the nervous system. As a junior faculty member at the University of Colorado Health Sciences Center in Denver, Colorado, Dr. Clarke became interested in viral encephalitis, which causes significant mortality and morbidity worldwide. Her research expanded to focus on identifying the viral genes and molecular mechanisms involved in reovirus-induced neuronal apoptosis, viral encephalitis and, more recently, viral myelitis. Reoviruses are members of the Reoviridae family having an ability to infect humans and several other animals. Reoviruses lack a viral envelope and contain ten double-stranded RNA gene segments of approximately 1-4 kb in length, enclosed by two protein shells and an outer capsid. Reovirus has been shown to enter cells using receptors rich in carbohydrates such as sialic acid and junctional adhesion molecules and to replicate in the cytoplasm. Many early studies on reovirus infection contributed to our understanding the molecular determinants of neurotropism, however details of the signaling pathways involved in reovirus mediated neuronal injury remained to be discovered.

Using reovirus infection of neonatal mice, *ex vivo* organotypic slice cultures, and primary and immortalized cells as model systems, Dr. Clarke and colleagues have delineated many of the cellular signaling pathways that are important for virus-induced pathogenesis in the brain and spinal cord. These include apoptotic signaling which is required for reovirus-induced CNS disease and the death receptor and mitochondrial apoptotic signaling pathways implicated in reovirus pathogenesis. Her laboratory has also shown that c-Jun N-terminal kinase (JNK) signaling is activated in virus-infected neurons following infection of the brain with reovirus and that inhibition of JNK signaling results in decreased injury and increased survival of infected animals. Dr. Clarke and her group have delineated a complex role for nuclear factor kappa B (NF-κB) signaling following reovirus infection. In this regard, efficient apoptosis of reovirus-infected cells appears to require the early activation of NF-κB followed by a later inhibitory phase, which is associated with decreased expression of the apoptotic inhibitor cFLAR (CASP8 and FADD-like apoptosis regulator).

Dr. Clarke's research has also highlighted the role of innate immunity following reovirus infection of the brain. Her laboratory has shown that the interferon response is strongly activated in the reovirus-infected brain and restricts both virus growth and tropism. In addition, microglia and astrocytes are activated following reovirus infection and their specific role in reovirus-induced CNS disease is currently under investigation. Dr. Clarke plans future experiments to extend these studies that will include Japanese encephalitis virus (JEV), the most common cause of viral encephalitis in the world, West Nile virus (WNV), the most common cause of epidemic encephalitis in the U.S., and herpes simplex virus (HSV), the most common identified cause of acute sporadic viral encephalitis in the Western world. In this regard, Dr. Clarke's group has performed microarray analysis of gene expression changes following infection of the brain with JEV, WNV and reovirus and have identified individual genes and signaling pathways that are common to infection by all viruses. These genes and signaling pathways will be investigated as potential broad-spectrum therapeutic targets for virus infections of the CNS.

2014 Upcoming Conferences

Computational and Systems Neuroscience 2014: February 27-March 2, Salt Lake City, Utah

Conference on Retroviruses and Opportunistic Infections: March 3-6, Boston, Massachusetts

Cognitive Neuroscience Society Annual Meeting: April 5-9, Boston, Massachusetts

American Academy of Neurology Annual Meeting: April 26-May 3, Philadelphia, Pennsylvania

Psychoneuroimmunology Research Society: May 28-31, Philadelphia, Pennsylvania

Federation of European Neuroscience Societies: 8th FENS Forum of Neuroscience: July 5-9, Milan, Italy

ISNV Highlights - Michele Di Mascio, Ph.D.

Katherine Taylor

Since joining the National Institute of Allergy and Infectious Diseases in 2003, Dr. Michele Di Mascio has contributed to the establishment of two parallel programs: in vivo imaging of AIDS pathogenesis and mathematical biology. He is currently the Chief of the AIDS Imaging Research Section (AIRS) and Acting Chief of the Mathematical Biology Section (MBS) at the Division of Clinical Research of NIAID, NIH. Michele's primary research interests include the dynamics of residual viral replication and immune activation in HIV-1 infected antiretroviral-treated patients. The development of imaging technologies in non-human primate models to accelerate research in HIV pathogenesis and the search for a cure is central to AIRS and MBS mission.

Antiretroviral therapy can successfully reduce viral replication in HIV-1 infected patients by preventing new target cells from being infected, but cannot account for cells infected prior to initiation of therapy. Following interruption of therapy, residual virus rebounds within 2-4 weeks due to the persistence of viral reservoirs in the body. Non-mutually exclusive theories of viral persistence in the treated host suggest alternative strategies to HIV eradication or functional cure. Noninvasive in vivo imaging technologies and the non-human primates infected with simian immune deficiency virus (SIV models) can significantly accelerate scrutiny of candidate strategies capable of reducing the viral reservoir in treated hosts, and promptly test the effect of such perturbations following interruption of antiretroviral therapy, the ultimate intervention needed to prove the success of those strategies (Towards an HIV Cure: Global Scientific Strategy July 2012.). Following enhancement of the immune response through adoptive transfer of ex-vivo modified T-cells, whole-body non-invasive imaging reveals organ specific trafficking and persistence of these cells, otherwise requiring intensive and prohibitive longitudinal tissue sampling. Proof of concept studies have also shown the capability of these technologies to non-invasively image the penetration of antiviral compounds in anatomic compartments (Figure 1). By coupling ex-vivo viral reservoir measurements with imaging pharmacokinetics, the efficacy of therapeutics can be further estimated.

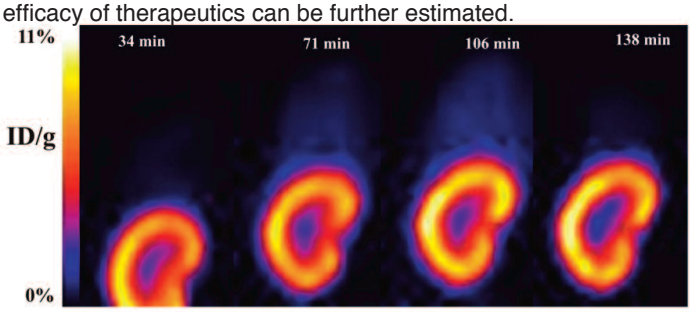


Figure 1. PET imaging reveals unexpected plateau kinetics of Tenofovir in the kidney (from Di Mascio *et al. AAC* 2009)

In 2009, following hematopoietic stem cells (HSC) transplantation from a healthy donor naturally resistant to HIV, an HIV-1 infected patient displayed evidence of a cure, and opened a series of questions that immunologists are trying to answer to identify the least invasive and most feasible strategy to reproduce the successful outcome. Non-invasive in vivo imaging and the SIV models of HIV-pathogenesis offer a unique opportunity to answer some of these questions in a shorter time period without the risk to patients withdrawing from HAART therapy. Ongoing studies in Dr. Di Mascio's program are focused on imaging of the whole-body Tell pool following total body irradiation and HSC transplantation. In addition, mild conditioning regimens specific to HIV disease are being explored as an alternative to total body irradiation to selectively deplete T cells and enhance host engraftment.

The same technology has been implemented to image the recovery of the immune system in SIV infected animals after initiation of HAART in a proof of concept study that allows to study anatomic specific repopulation of the T-cell pool during time without the use of invasive biopsies (Di Mascio et al. Blood 2009 and 19th International AIDS Conference, Abstract LBPE12, Washington DC, July 2012). These data allow also to highlight similarities in the dynamics of whole-body T cell repopulation between two independent perturbations of the steady-state (SIV infection followed by HAART, and, TBI followed by autologous HSC transplantation). The brain is a clear example of anatomic compartment hard to access without non-invasive in vivo imaging technologies. The program is also advancing studies to image SIV induced neuroinflammation by importing imaging systems of the central nervous system (CNS) from other models of pathogenesis. Such preclinical platforms have a unique potential to accelerate research in pharmacological strategies aimed to revert the HIV associated neurocognitive dysfunction comorbidity. Other imaging systems under development include in vivo imaging of cell death and viral replication through engineering of the immune system in the SIV model. Whole body models might help determine the etiological factors behind viral blips (transient increases in plasma viral load in the treated host) particularly since most of our knowledge on the dynamics of viral replication and immune depletion and activation in HIV infection relies on data obtained from the peripheral blood, which comprises less than 2% only of total lymphocytes in the body (Figure 2).

Much more can be learned by imaging insults of the virus to the immune system during time, through this bridge built between nuclear medicine imaging and HIV pathogenesis.

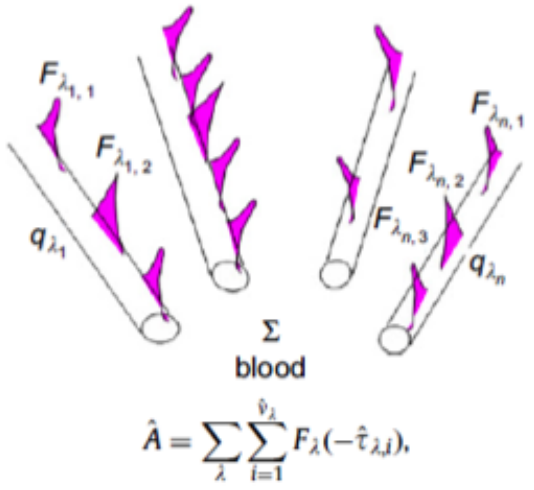


Figure 2. Viral blips can be thought, in part, as a discrete phenomenon resulting from the overlapping of elementary pulses of viremia, e.g. random release of virus and infected cells from unknown compartments, with sub-optimal drug concentrations and/or increased activation, into the blood compartment where they are more rapidly cleared. (from Percus et al. J.T.B. 2009)

Classifieds

Tenure-track Position In Microbiology & Neuroscience – Ohio Wesleyan University

The Department of Botany & Microbiology at Ohio Wesleyan University seeks an individual with training in both microbiology and cellular/molecular neurobiology for a new tenure-track position at the assistant professor level beginning with the 2014-2015 academic year. Candidates with a research focus on interactions between microbes and the nervous system are particularly encouraged to apply. The successful candidate will teach a course in introductory neuroscience, upper-level microbiology or molecular biology, and upper-level cellular and molecular neurobiology, contributing to both the major in microbiology and to building a modern and innovative undergraduate major in neuroscience at Ohio Wesleyan. Applicants should have previous undergraduate teaching experience and a research program amenable to participation by undergraduate students. Post-doctoral experience is preferred but not required. For complete job posting please visit http://jobs.owu.edu/. Send curriculum vitae, statement of teaching and research philosophy, undergraduate and graduate transcripts, and three letters of recommendation to hr@owu.edu. Direct inquiries about the position to David Johnson, Search Chair (dmjohnso@owu.edu, 740-368-3505). Review of applications will begin on 15 September 2013. Ohio Wesleyan University (www.owu.edu) is a selective, private, undergraduate liberal arts, residential institution founded in 1842 and is located just 20 miles north of Columbus. Ohio Wesleyan University is strongly committed to diversity within its community and encourages all interested applicants, including women and minorities, to apply (EEOE).

Non-tenure-track Position In Neuroscience – Temple University

Temple University School of Medicine has non-tenure track faculty positions in the Department of Neuroscience, a state-of-the-art multidisciplinary research and education basic science department. This is an opportunity to participate in a collaborative environment to perform comprehensive research toward understanding the mechanisms of disorders of the central nervous system in order to develop therapeutic strategies against relevant diseases and to provide an integrative graduate and postgraduate program to train first rate scientists in the field of neuroscience. Areas of research focus may include signal transduction, neural cell degeneration in diseases such as Alzheimer's and Parkinson's diseases, glial cell disorders including multiple sclerosis and brain tumors, vascular disorders and neuroimmunological disorders associated with viral infections including HIV-1 in AIDS and multiple sclerosis. Candidates must possess a Ph.D., M.D., D.V.M or equivalent degree and should have active NIH and/or other federal research funding. Candidates may visit the Department of Neuroscience at http://www.temple.edu/medicine/departments_centers/basic_science/neuroscience.htm. All applications must be made in hard copy. Rank commensurate with experience. Temple University offers a competitive compensation benefits package, including pension plan. Send curriculum vitae to: Kamel Khalili, Ph.D., Laura H. Carnell Professor and Chair, Department of Neuroscience, Temple University School of Medicine, 3500 N. Broad Street, 7th Floor, Philadelphia, PA 19140. Temple University is an EEO/AA employer and strongly encourages applications from women and minorities.

Research Opportunities in HIV-Associated Neurological Disorders (NeuroAIDS) - University of Texas

HIV-1 infection causes a spectrum of neurological/cognitive complications (NeuroAIDS), but the pathogenic mechanisms are poorly understood. NeuroAIDS presents a huge opportunity for young scientists who are enthusiastic about a career development in the field of infectious diseases in the nervous system. We are soliciting applications for research positions in NIH-funded projects that focus on the molecular and cellular mechanisms of NeuroAIDS. We will concentrate on the synaptic, glial, and neural circuitry pathogenic processes that contribute to the development of NeuroAIDS, in particular the HIV-associated pathological pain. The applicants must have enthusiasm on the research field, and have a strong research background, as recorded by publications, in at least one of the following aspects: molecular biology, developmental biology, neurobiology, HIV-1 biology, microscopic/confocal imaging, or electrophysiology (especially patch clamp in the spinal cord). Interested candidates can email their CV to Dr. Shao-Jun Tang, Associate Professor, Department of Neuroscience and Cell Biology, University of Texas Medical Branch, Galveston, TX 77573. Email: shtang@utmb.edu. Candidates whom are selected for further considerations will be notified.

Contact the ISNV Administrative office at:

Tel: (215) 707-9788 **@joinISNV**

Email: mail@isnv.org **www.isnv.org**

I&MM&ID Institute for Molecular Medicine & Infectious Disease

Center For Scientific Communication & Outreach

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