Journal of NeuroVirology
2013 Impact Factor Climbs to 3.323!

We are happy to report that the new impact factor for Journal of NeuroVirology is 3.323, which has moved the journal ahead of several other well known virology journals. The impact factor (IF) for a given year is calculated by combining the number of citations to articles in the journal during the previous two years divided by the total number of articles published, i.e. 2013 IF = citations from 2011 + 2012 / total articles from 2011 + 2012. As you may recall, JNV began publishing under the Springer label in 2011, so this year represents the first impact factor since the move. We hope our partnership with Springer will see our impact factor continue to rise in the coming years. During this time, JNV published special issues on Alpha Herpes Viruses, edited by Don Gilden, and HIV and Aging, edited by Avi Nath, which were both well received and have certainly contributed to our new IF. This is truly a testament to the hard work and dedication of the journal's editorial board and the senior associate editors, as well as the authors and reviewers for JNV who have kept our journal doing so well over the last 20 years. We look forward to serving as a platform for the neurovirology community in the years to come.

Kamel Khalili
Improving on HSV as an agent for brain tumor therapy

Fred Krebs

Glioblastoma multiforme (GBM), which is classified as a WHO grade IV astrocytoma, is the most common and aggressively malignant brain tumor that occurs in adult humans (particularly in males). One novel approach to treating GBM is the use of oncolytic herpes simplex virus (oHSV) as an adjunct to tumor resection, which is the standard of care for GBM patients. In a paper published this year [Duebgen et al., J Natl Cancer Inst (2014) 106(6): dju090], investigators at the Massachusetts General Hospital provide evidence that oHSV treatment can be improved through key changes in oHSV delivery.

Oncolytic herpes simplex viruses are examples of therapeutic oncolytic viruses (virotherapeutics) under development as anticancer agents effective against solid tumors. Virotherapeutic agents have evolved from non-engineered, passaged strains of oncolytic viruses to recombinant viruses engineered to enhance their selectivity and/or express cytotoxic transgenes. The goal of virotherapy is to deliver viruses that selectively replicate in and kill cancer cells, which then release oncolytic progeny viruses that can subsequently infect neighboring or distant cells in the tumor mass. This unique approach to cancer therapy can provide durable efficacy as the oncolytic virus infection spreads to cells throughout the tumor.

A number of oncolytic viruses based on HSV have already been assessed in clinical trials. Although antitumor activity was evident in phase I and Ib clinical trials of cell-free oHSV variants used in conjunction with GBM resection, clinical responses in these trials were limited, perhaps as a consequence of reduced viral titers in the resection cavity caused by local bleeding and the flow of cerebrospinal fluid. To address this limitation, follow-up studies have explored the use of oHSV-infected mesenchymal stem cells (MSC) and biodegradable synthetic extracellular matrices (sECM) to promote virus retention and increased anti-tumor efficacy.

In their recently published studies, Duebgen and colleagues used in vitro experiments and a mouse model of GBM resection to demonstrate the dynamics and therapeutic effectiveness of oHSV-infected MSCs (MSC-oHSV). They observed that MSC-oHSVs effectively killed GBM cell lines in vitro as well as GBMs established in vivo. When delivered as sECM-encapsulated cells in their mouse model of GBM resection, MSC-oHSV were more persistently expressed in the tumor resection cavity and provided greater anti-GBM efficacy relative to purified, cell-free oHSV introduced by direct injection. Their studies culminated in GBM resection mouse model experiments that involved the use of a recombinant oHSV that expresses secretable TRAIL. These in vivo experiments demonstrated even greater levels of tumor regression and prolonged mouse survival attributable to the combined effects of (i) MSC used to deliver virus, (ii) sECM encapsulation used to promote MSC retention, and (iii) an oHSV variant “armed” with a transgene encoding a proapoptotic molecule.

These studies illustrate the potential for oHSV treatment of GBM and highlight the benefits of cell-associated delivery, retention in the resection cavity by encapsulation, and the added efficacy of a cytotoxic transgene. These findings may also point the way to more effective therapeutic delivery systems used treat solid tumors in the liver, prostate, breast, and other parts of the body.
Dr. Chris Power's laboratory investigates the fundamental processes underlying the causes and progression of infection and inflammatory disease of the nervous system. His body of work exploring these mechanisms reflects a long-standing interest in neuroscience. "I was always interested in the brain-behavior link. And I knew after my first biology tutorial in college, I would be a neuroscientist," Dr. Power said.

Dr. Power currently works as a Professor in the Departments of Medicine, Division of Neurology; Medical Microbiology and Immunology; and Psychiatry, Faculty of Medicine and Dentistry at the University of Alberta. In addition, he acts as the attending neurologist for the Multiple Sclerosis Clinic at the University of Alberta and the Southern Alberta Clinic (HIV) in Calgary. He is an adjunct professor at the University of Calgary in the departments of clinical neurosciences, and microbiology and infectious diseases.

In 2013, he became a Fellow in the Canadian Academy of Health Sciences, and currently holds a Canada Research Chair in Neurological Infection and Immunity. Dr. Power has supported and continues to teach multiple trainees and has received teaching and research awards. With over 100 invited presentations and 150 peer-reviewed manuscripts, Dr. Power continues to advance the understanding of infectious and inflammatory disorders of the nervous system. In addition to his scientific accomplishments, he is also an avid back-country skier.

By elucidating fundamental neuropathogenic mechanisms, his laboratory aims to translate such findings into improved care including diagnostic tools and treatments, for people affected by these neuroinfectious and neuroinflammatory disorders. The laboratory's primary diseases of interest include neuroAIDS and multiple sclerosis. The overall strategy of his laboratory is to integrate clinical information and biospecimens with validated experimental in vitro and in vivo models to yield insights into disease mechanisms and eventual clinical applications.

A central theme within the laboratory is the interactions between neuroinflammation and neurodegeneration with the ensuing outcomes including both protective and pathogenic effects.

For example, the laboratory showed that HIV-1 infection of glial cells resulted in the induction and cleavage of CXCL12, which is neurotoxic by suppressing neuronal autophagy (Zhang et al., Nat Neurosci 2003; Vergote et al., PNAS, 2006; Zhu et al., FASEB J 2009). The laboratory also reported that expression of endogenized retroviral proteins (e.g., Syncytin-1) in astrocytes causes immune activation adverse effects on oligodendrocyte survival through a mechanism involving endoplasmic reticulum stress (Antony et al., Nat Neurosci 2004; Deslauriers et al., J Immunol 2011). More recently, the laboratory has focused on the roles of CNS inflammasomes in neurological disorders (Figure 1)(Walsh et al., Retrovirology 2014) and the treatment of neuroinflammation using neuroactive steroids (Noorbaksh et al., Brain 2011; Maingat et al., FASEB J 2011). The laboratory is closely linked to the Alberta NeuroAIDS Cohort and University of Alberta Multiple Sclerosis Centre and Clinic.

In Memoriam - Axel Rethwilm

Dianne Langford

It is with deep sadness that the retrovirus community learned of the passing of Axel Rethwilm, Professor of Virology in Würzburg, Germany and expert on foamy virus (FV) in September of 2014 at the age 54. As a committed member of ISNV for over a decade, Dr. Rethwilm will be missed. Dr. Rethwilm worked for over 30 years on FV and his research led to the discovery that FV was actually a variant of a chimpanzee foamy virus zoonotically transmitted to man as a dead-end infection, leading to the reclassification of FV from human FV to prototype FV and designating it as a “virus in search of a disease”. In the last review that Axel wrote before he died, he ended with the words “if I can stimulate one or more researches to pick up FV biology in their research repertoire, the mission of this review is accomplished”.

Figure 1. HIV activates the NLRP3 inflammasome in human microglia. Control human microglia show ASC nuclear localization (A) but HIV-activation results in ASC cytoplasmic translocation (B). NLRP3 expression is minimally detected in control microglia (C) although increased NLRP3 expression in cytoplasm is evident with HIV activation (D).
In Memoriam: Dan C. Duiculescu

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On March 14, 2014 Dan Duiculescu, M.D., Ph.D. passed away; he was 63. Dan was our colleague, friend, and gifted mentor. He was born in Piatra Neamt, Romania. After earning the medical degree he started working at “Dr. Stefan Nicolau” Institute of Virology in Bucharest where his initial focus was on viral hepatitis. Under the mentorship of Professor Dr. Nicolae Cajal it was here where he started his career as a medical researcher. In 1983 Dr. Duiculescu was recruited to “Dr. Victor Babes” Hospital for Infectious and Tropical Diseases in Bucharest where in addition to research he will do clinical work as well.

In the late 1980s, Romania became known for the largest HIV pediatric iatrogenic epidemic. Dr. Duiculescu was among the first to understand its gravity and dedicate all his efforts to fight it. He was a founder of the “Center for Fight Against AIDS” in Romania. He developed a system to monitor patients infected with HIV, children and adults, and developed a standardized medical chart which is still used today. He also established very early a large database for patients infected with HIV.

One of Dr. Duiculescu’s greatest accomplishments was founding the “Casa Doru”, a pavilion at Dr. Victor Babes Hospital, entirely dedicated to children infected with HIV. He was the head of Casa Doru inpatient unit and outpatient clinic where he worked every day until his untimely death. His efforts translated into a much-improved quality of life for his patients and in many cases saved their lives.

Dr. Duiculescu was constantly trying to enhance his knowledge on AIDS. In 1991 he was a visiting scholar in the Department of Infectious Diseases at Karolinska Institute in Sweden. During 1992-1993 he was a visiting scholar in the Department of Immunology and Infectious Diseases, at the School of Medicine in Miami, Florida. Here he worked with Professor Dr. Gwendolyn Scott whom he very much admired and considered his mentor in pediatric AIDS. This collaboration produced a paper “Clinical and immunological correlations of p24 HIV-1 detected in HIV infected patients” published in Journal AIDS. This was also the basis of his Ph.D. thesis.

Dr. Duiculescu was a member of many scientific societies and advisory boards, to name just a few: Romanian National Society for Infectious Diseases, National AIDS Committee, National Chamber of Health Experts Committee on HIV/AIDS, International Board for Harm Reduction, Open Society, New York, Steering Committee for the Pediatric European Network for Treatment of AIDS, Euro-AIDS Steering Committee, Romanian Representative at the European Union of Medical Specialties (Infectious Diseases).

Beside his clinical talent and dedication to medical practice, Dr. Duiculescu also excelled in research. He published more than eighty papers in medical journals and participated in numerous national and international scientific conferences. His awards include: Ferdinando Serri Award for the best presentation, Rome 1996; First Prize for best platform presentation “Multifocal Progressive Leuconecephalopathy- Presumed Diagnosis, at the 9th National Congress of Infectious Diseases, Craiova, Romania, 2004; First Prize for best paper “Unique Aspects of Measles in HIV-1 Infected Children”, National HIV/AIDS Congress, Bucharest, 2006; Prize for Excellence for the platform presentation “Cerebral Toxoplasmosis in HIV-1 Infected Children” at the “Toxoplasmosis” scientific meeting, Constanta, 2007; Prize for Excellence, UNAIDS for contribution to fighting HIV/AIDS, 2007; First Prize for the paper “Hepatitis B Virus in CNS in Patients Infected with HIV-1,” at the 10th National Congress of Infectious Diseases, Cluj, Romania, 2008.

Among the most important contributions to the field of pediatric neuroHIV, was his original idea that subacute myoclonic measles encephalitis is a distinct and important clinical complication of measles in HIV-1 patients. He also described for the first time the potential neurologic complications associated with the presence of hepatitis B virus in the CSF of HIV-1 infected children. Dr. Duiculescu was principal investigator on several clinical studies on the efficacy and side effects of antiretroviral drugs. His published contributions on these studies helped develop new antiretroviral treatments. He also participated in studies organized by Pediatric European Network for Treatment of AIDS. Dr. Duiculescu was active in projects funded by the Romanian Academy of Medical Sciences and the Ministry of Education. His work contributed to developing new methods for molecular diagnosis in CNS complications in HIV infected children. He also did seminal research work on latent and active tuberculosis.

In 2006, Dr. Duiculescu started a collaboration with Cristian Achim, M.D., Ph.D., from UC San Diego School of Medicine. Under the auspices of the International Core at the UCSD HIV Neurobehavioral Research Center and funding from the NIMH the Romania-US collaboration evolved at a fast pace leading to a growing set of scientific aims while recruiting new collaborators; Dr. Duiculescu was at the center of this effort. Today, these research projects include a complementary set of topics like: the neuropathogenesis of HIV infection in a cohort of long term survivors, an international multi-site study of the association between various HIV sub-types and neurocognitive impairment, and long term effects of HIV subtype F on the developing brain.

Most defining, Dr. Duiculescu was a visionary regarding the need to develop a national framework that will integrate medical, psychological and social services for the HIV-infected children and young adults in Romania. Above all, his goal after providing the best medical care was to preserve human dignity, and that’s a message that he made clear to all his young disciples and could be his legacy. Dan was a generous and honest colleague, a loyal friend, a compassionate physician, a dedicated clinician with a keen scientific mind, a true pioneer, a beloved mentor with a good sense of humor and patience and understanding for the human character, and until the end, a gracious human being. He is survived by his wife, two sons, and countless of friends who will miss him.
Dr. Anirban Basu’s laboratory is located at the National Brain Center, Manesar, India. Dr. Basu received a Ph.D. at the Indian Institute of Chemical Biology in Kolkata in 1998. He then completed postdoctoral training under the mentorship of Dr. Steven Levinson at Pennsylvania State University, College of Medicine, Hershey, PA in Neural Behavioral Sciences where he studied neuroinflammation and neurodegeneration. Anirban then returned to India where he accepted a faculty position at the National Brain Research Institute, where he is currently a Professor.

The main focus of Dr. Basu’s research is to understand the role of neuroinflammation in the pathogenesis of Japanese encephalitis virus (JEV) and Chandipura virus (CHPV), both of which are currently leading causes of viral encephalitis and fatalities in India and the entire Asia-Pacific region. Dr. Basu’s laboratory has discovered that minocycline, a second-generation tetracycline, may have therapeutic potential to treat Japanese encephalitis (JE). Based on results from basic research conducted in Dr. Basu’s laboratory, a clinical trial was recently completed assessing the efficacy of minocycline for the treatment of JE. In the field of CHPV, Dr. Basu’s laboratory described a Fas-mediated mechanism of CHPV-induced neuronal death using both in vitro and in vivo models. They have identified key players in the cell that induce extrinsic apoptosis following CHPV infection. Moreover, they have suggested a potential target gene, CHPV phosphoprotein, the knock down of which attenuates neurodegeneration (Ghosh, Dutta & Basu, J. Virology, 87: 12398, 2013).

Dr. Basu’s work highlights the importance of the neuroimmune response in regulating viral infection of the brain, and has been instrumental in bridging the gap between translational and basic research for JEV and CHPV-mediated encephalitis (Figure 1).

Dr. Basu’s work addresses new principles that potentially contribute towards a cure for neuroinflammatory diseases that include infection of the CNS, but also other neurodegenerative disorders that affect millions of people worldwide. In addition to his studies on JEV and CHPV, Dr. Basu serves on the editorial boards of numerous scientific journals and is the recipient of several awards including being elected to the National Academy of Sciences in India in 2011.
Herpes simplex virus type 1 (HSV-1) is a common human pathogen that establishes a lifelong infection. HSV infections can be subclinical or can result in serious cases of encephalitis, meningitis, or blindness. As is the case with all herpesviruses, HSV establishes a latent infection that is characterized by very limited viral gene expression, and in the case of HSV latency this takes place in neuronal tissues. HSV can reactivate from latency to cause recurring disease, such as cold sores or genital herpes. Dr. Nigel Fraser’s research career has focused on the molecular biology of HSV-1 latency as well as applications of HSV-1 to treat brain tumors and neurogenetic diseases.

Early work in Dr. Fraser’s laboratory demonstrated that HSV-1 DNA is detectable in human brain tissue (PNAS, 78:6461-5, 1981) and in the trigeminal ganglia (J Virol., 62:3493-6, 1988). Work from his lab was instrumental in developing animal models of HSV latency, including demonstrating that a mouse model showed persistence of the virus in the central nervous system (CNS) (Nature, 302:523-5, 1983) and that the viral genome is maintained as an extrachromosomal episome in neuronal tissues (Virol., 158:265-75, 1987). Latent infection in the murine CNS is accompanied by detection of latency-associated RNA transcripts (LATs) (J Virol., 61:3841-47, 1987), and the latent viral genome is in a chromatin structure (J Virol., 63:943-7, 1989). The major LAT RNA is a highly stable intron that has anti-apoptotic effects (J Virol., 76:717-29, 2002) that may serve to promote viral persistence during latency.

The development of a mouse model of HSV-1 latency allowed for the testing of HSV-1 as a gene therapy vector to potentially treat neurogenetic diseases. This approach was first shown to be feasible in 1992, when a monogenic lysosomal storage disease was targeted and latent-phase gene expression of the missing enzyme was achieved (Nat Genet., 1:379-84, 1992). Subsequent work developed an optimal site to insert foreign genes, and they later showed HSV vector-mediated correction of lysosomal storage pathology in the mouse brain (Mol Ther., 13:859-69, 2006). HSV has a natural tendency to replicate in and to lyse tumor cells, and the development of mutant strains of HSV incapable of causing encephalitis allowed for the testing of HSV as an oncolytic agent that could potentially be used for human brain tumor therapy. Dr. Fraser’s work showed that attenuated HSV-1 can induce regression of human carcinoma tumors in the mouse brain (Laboratory Investigation, 73:636-48, 1995). This type of therapy also was beneficial for the treatment of murine melanoma in the brain (Virol., 211:94-101, 1995) and human mesothelioma in the brain (Canc Res., 57:466-71, 1997).

Dr. Nigel Fraser earned his Ph.D. in biochemistry from the University of Glasgow, Scotland. He went on to complete a post-doctoral fellowship at Rockefeller University, and in 1978 was hired as an assistant professor at the Wistar Institute in Philadelphia. He later moved to the department of microbiology at the University of Pennsylvania. He has trained about 50 graduate students and post-doctoral fellows during his career.
ISNV Highlights - Velpandi Ayyavoo, Ph.D.

Pankaj Seth and Dianne Langford

Dr. Velpandi Ayyavoo received her Ph.D. in microbiology from Madurai-Kamaraj University in Madurai, India in 1991 and then accepted a postdoctoral fellowship at the Wistar Institute in Philadelphia where she focused on molecular virology. After serving as a Research Associate for four years at the University of Pennsylvania (UPENN), she joined the Department of Pathology and Laboratory Medicine as a Research Assistant Professor. In 2000, Velpandi joined the University of Pittsburgh, where she continues to serve as Professor in the Department of Infectious Diseases and Microbiology, Graduate School of Public Health and Director of the Graduate Program.

Dr. Ayyavoo has been engaged in HIV biomedical research for nearly 25 years and findings from her studies have contributed significantly to understanding HIV-1 immunopathogenesis, disease progression and neuronal damage. In particular, she has uncovered novel functions of the viral protein Vpr. Her group was the first to report that HIV-1 Vpr suppresses immune activation and apoptosis through the regulation of nuclear factor k-B (NF-kB) and to reveal that leucine residues in Vpr mediate transactivation and viral replication. Results from her other studies demonstrated that Vpr impairs dendritic cell maturation, NK cell activation and T cell activation and may be important for immune escape of HIV-1. Realizing the importance of Vpr in HIV-1 pathogenesis, she further went on to develop a robust cell-based high-throughput screening assay to identify targets of HIV-1 Vpr dimerization (Zych et al., J. Drug Design Develop. Therapy 7:403-412, 2013). Other studies from Velpandi’s group have highlighted the important roles for microRNA-mRNA regulation by HIV-1 in neuropathogenesis using whole genome transcriptome analyses in brain, CSF, PBMCs and serum. Among these findings, new cellular mRNA including neurogranin, defensin and AIF were identified as potential targets of mRNA-miRNA regulation (Duskova et al, BMC Infect Dis. 13:250, 2013). Notably, Dr. Ayyavoo’s research identified distinct variations in sequences of alleles of Vpr that correspond to long term non-progressors compared to rapid progressors (Hadi et al., J Gen Virol., 95:700, 2014. Specifically, she reports that polymorphisms R36W and L68M are associated with rapid disease progression. Her efforts to identify early biomarkers for HIV associated diseases such as HAND led to findings that serum miRNAs can be used as pre-diagnostic markers for AIDS associated neurocognitive disorder. Ongoing studies in Velpandi’s lab are aimed at developing novel targets and to design new therapeutics against HIV-1 in the central nervous system.

Peter Kennedy is awarded 2014 RSE Sir James Black Medal

Sandy Weiss

Please join us in congratulating our former ISNV President, Dr. Peter Kennedy, as the 2014 winner of The RSE/Sir James Black Medal (Senior Prize) for his outstanding contribution to the field of tropical medicine through his pioneering work on human African trypanosomiasis (sleeping sickness) and Neurovirology. The RSE is the Royal Society of Edinburgh and Scotland’s National Academy of Science of which Dr. Kennedy has been a fellow since 1992.

Sir James Black (1924 – 2010) was a Scottish physician and pharmacologist who established the physiology department at the University of Glasgow. He became interested in the effects of adrenaline on the human heart and later developed two highly effective drugs in different fields. Sir James Black was a Fellow of the Royal Society of London and an Honorary Fellow of the Royal Society of Edinburgh (RSE). Dr. Black was awarded the Nobel Prize for Medicine in 1988, the Order of Merit in 2000, a Knighthood in 1981 and the RSE Royal Medal in 2001.

Professor Kennedy is the Burton Chair of Neurology at the University of Glasgow and a Commander of the Order of the British Empire (CBE) since 2010. Dr. Kennedy will receive the prestigious Sir James Black Medal in a ceremony scheduled for 2015.