Fall 2013
Special Issue

ISNV

International Society for NeuroVirology

Editor: Dianne Langford, Ph.D.

Associate Editor: Michael Nonnemacher, Ph.D.

2013 Audrey Steinman Gilden Lectureship
Howard Lipton

Authored by Don Gilden

Dr. Howard Lipton, a graduate of the University of Nebraska School of Medicine, completed his neurology residency and a neurovirology fellowship at The Johns Hopkins University School of Medicine and Hospital. Appointed as Assistant Professor in the Department of Neurology at Northwestern University School of Medicine in 1972, he rose to the position of Ernest J. and Hattie H. Magerstadt Professor of Neurology and Professor of Microbiology and Immunology. After serving on the faculty of medicine as Professor of Neurology at the University of Colorado, he became the Henry P. and Georgette Goldschmidt Professor and Chair of the Department of Neurology at the Mount Sinai School of Medicine in New York City in 1991. Later, he returned to Northwestern University. Dr. Lipton is now Professor of Microbiology & Immunology and Neurology at the University of Illinois School of Medicine in Chicago. As a neurologist, Dr. Lipton's clinical and research focus centers on multiple sclerosis (MS) and its pathogenesis.

Having developed a strong interest in the possible viral etiology of MS during fellowship training, Dr. Lipton studied a viral model of demyelination rather than attempt to "isolate" a virus in MS, which his advisor, Richard T. Johnson, believed would surely be career-ending for academic research. Thus, Dr. Lipton revived studies of the 1930s, suggesting that Theiler's virus infection persisted in the central nervous system (CNS) in mice and might lead to a demyelinating pathology. Over the years, he and his laboratory have studied the molecular pathogenesis of this persistent CNS infection, making a number of sentinel observations, most representing initial discoveries in the field: (1) adaptation of brain-derived, low-neurovirulence Theiler's virus for growth in mammalian cells, which enabled quantification of viral infectivity by plaque assay and molecular studies; (2) infection of mice resulted in primary demyelination; (3) demyelination was primarily an immunopathology since disease could be reduced by immunosuppressive agents; (4) persistent infection in the mouse spinal cord was primarily maintained in infiltrating monocyte/macrophages; (5) host virus-specific Th1 CD4+ T lymphocytes played an essential role in the immunopathology (afferent limb); (6) class I H-2D genes influenced host susceptibility to demyelination; (7) analysis of the nucleotide sequence of high-(GDVII virus) and low-neurovirulence (BeAn virus) strains of Theiler's virus revealed

that Theiler's virus was a Cardiovirus (rather than an Enterovirus) in the Picornavirus family; (8) construction of infectious cDNA clones enabled generation of recombinant and mutant viruses for molecular pathogenetic studies indicating that the viral capsid played a role in viral persistence; (9) solution of the atomic structures of BeAn and GDVII viruses to 3Å; (10) persistent infections generated exceedingly high viral RNA copy numbers (108 copies/spinal cord) compared to low infectious virus titers; (11) infection induced apoptosis in macrophages in vitro through the intrinsic apoptotic pathway, restricting viral titers via caspase cleavage of assembled virions, a possible mechanism for viral persistence; and (12) infection in primary mouse oligodendrocyte precursors and mature oligodendrocytes in vitro also induced apoptosis.

Finally, Dr. Lipton's research has "come full circle," returning to a viral etiology of MS. Although the notion that MS is an autoimmune disease is widely accepted, an autoimmune mechanism remains unproven. Tissue damage in MS might also result from a viral infection in which the host immune response is directed at viral rather than self-proteins. However, efforts to identify a specific candidate virus in MS have not yielded conclusive evidence of causation. In the Lipton laboratory, an unbiased approach to specific viral discovery centers around the use of antibodies to detect long dsRNAs transcribed by RNA and DNA viruses. Since long dsRNAs are neither detected in normal or stressed cells nor produced by bacterial or other microbial infections (except fungi), these antibodies appear to be specific for virus infections. Dr. Lipton will present recent work-in-progress obtained with Dr. John Prineas' laboratory at the University of Sydney showing strong, specific dsRNA immunoreactivity in oligodendrocytes in newly-forming (pre-phagocytic) MS lesions from formalin-fixed, paraffin-embedded archival autopsy material of acute MS patients dying during or shortly after an acute exacerbation.

Dr. Lipton's contributions to the field of MS research have truly been revolutionary as he developed one of the few experimental animal models of virus infection that induce demyelination. He was elected to the American Association for the Advancement of Science in 2003. The ISNV is honored to have Dr. Howard Lipton present the 2013 Audrey Steinman Gilden Lectureship.

Audrey Steinman Gilden Lectureship

The Audrey Steinman Gilden Lectureship recognizes investigators whose cutting-edge research achievements have made important contributions to understanding the molecular pathogenesis of neurotropic virus infection. The lectureship was established by Dr. Don Gilden, who has contributed significantly to the disciplines of neuroscience and neurovirology through his groundbreaking work on lymphocytic choriomeningitis virus, varicella zoster virus, and multiple sclerosis. A 2007 recipient of the ISNV Pioneer in NeuroVirology award, Dr. Gilden established this lectureship in honor of his wife, Audrey.

International Society for NeuroVirology ISNV LectureShip Series

Contact the ISNV at:
(215) 707-9788
mail@isnv.org
www.isnv.org
@joinISNV

ISNV Newsletter printed by the Center for Scientific Communication & Outreach

DREXEL UNIVERSITY College of Medicine
Institute for Molecular Medicine & Infectious Disease