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Joseph Glorioso Gives the 2010 Paradigm Builder Lectureship

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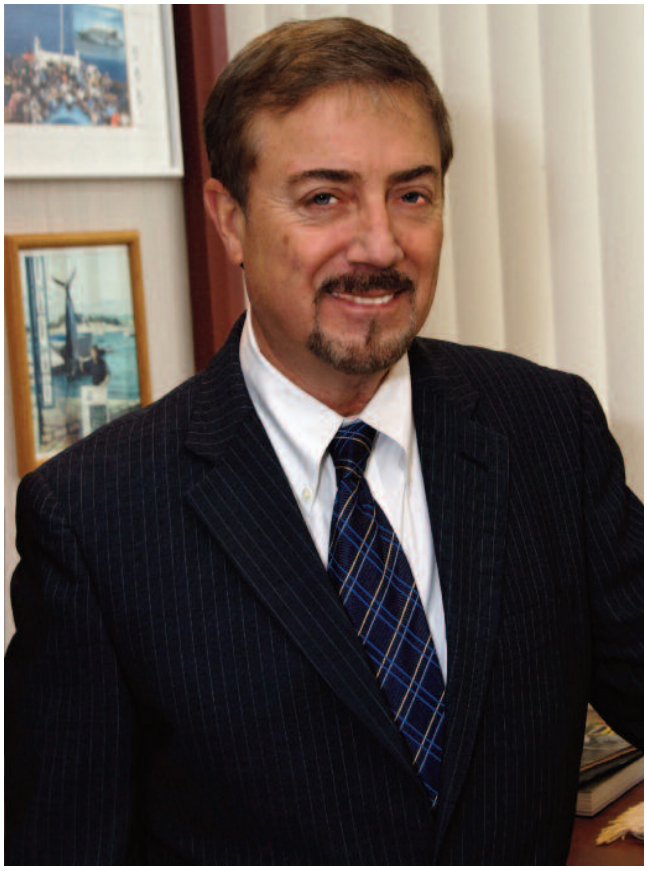

Dr. Glorioso's contributions to the field include defining antiviral immune responses to infection, the genetics of viral pathogenesis and latency, and mechanisms of viral infection. He is a pioneer in the design and application of HSV gene vectors for the treatment of nervous system diseases such as peripheral neuropathies, chronic pain, and brain tumors. In addition, Dr. Glorioso is a world leader in the HSV gene vector field through the construction of gene vectors and the development of manufacturing methods for Phase I and Phase II human clinical trials for gene therapy. Phase II trials using the enkephalin vector generated by his group will begin for treatment of intractable and chronic cancer related pain this fall.

Receptors for HSV infection are expressed on a very wide range of human cells and tissues and methods to limit infection disease targets are therefore desirable for the use of HSV as a gene delivery vehicle or lytic agent to destroy cancer cells. Over the years, Dr. Glorioso's group has studied the envelope glycoproteins of HSV that play a role in cell recognition and entry in order to acquire the knowledge to narrow and redirect the viral tropism by genetic manipulation of the key players.

Binding of the HSV glycoprotein gD to the cognate receptors HVEM or nectin-1 results in signaling events that activate the viral membrane fusion apparatus required for fusion of the viral envelope with cell membranes leading to release of the virus capsid into the cytoplasm. Because gD determines virus tropism, Dr. Glorioso's group has sought to identify and delete the receptor recognition domains (detargeting) and replace these with new ligands that will afford exclusive entry via novel receptors (full retargeting). Dr. Glorioso's laboratory detargeted the virus by N-terminal deletion abolishing HVEM binding and a point mutation that eliminated binding to nectin-1. A single chain antibody to the EGF receptor (EGFR) or carcinoembryonic antigen (CEA) were introduced into the N-terminal deletion. Viruses expressing either of these chimeric gD mole-

cules infect cells expressing EGFR or CEA, but not the cognate receptors. However, these mutant viruses demonstrate a much lower efficiency of entry than wild-type virus via nectin-1 or HVEM. To overcome this problem, a reiterative selection procedure yielded facilitating mutations in components of the HSV fusion apparatus, gB and gH, that could complement impaired gD-receptor binding, suggesting that the fusion apparatus was "sensitized" to receptor-dependent activation by gD. These mutations mediated greatly enhanced retargeted virus entry. Further study has shown that the altered specificity of the EGFR-retargeted virus prevents viral replication in normal brain, but allows efficient infectivity of tumors expressing EGFR, including glioblastomas.

Dr. Glorioso's most recent work focuses on the development of these "next" generation oncolytic HSV vectors for the treatment of glioblastoma. His laboratory has produced replication competent HSV vectors that will kill tumor cells by lytic replication, but are non-infectious for normal neurons and thus, nonpathogenic in the brain. These vectors do not recognize the normal virus receptors but rather are fully retargeted for infection via the tumor marker EGFR and its mutant derivative EGFRvIII. His team has also discovered viral glycoprotein mutations that greatly enhance the efficiency of tumor cell infection. Other modifications include the placement of essential viral replication functions under control of high abundance micro-RNAs that are differentially expressed in neurons and tumor cells. This combination of targeting methods provides a safe cancer treatment vector without compromising vigorous virus growth and intra-tumoral spread. This next generation vector is under study in preclinical models of human glioblastoma. Dr. Glorioso truly represents another great example of a Paradigm Builder. The Society congratulates Dr. Glorioso for his many outstanding scientific achievements.

Request for Nominations for The Paradigm Builder Lectureship

The 11th symposium will be held in New York, New York, 2012

International Society for NeuroVirology ISNV LectureShip Series

The International Society for NeuroVirology will accept nominations for the 11th International Symposium on NeuroVirology for the Sping of 2012. Please send all inquiries and nominations to mail@isnv.org

The Paradigm Builder Lectureship

International Society for NeuroVirology ISNV LectureShip Series

The Paradigm Builder Lectureship has been developed to recognize established investigators working in the area of neurovirology or a related discipline for their scientific achievements. More specifically, the lectureship has been developed to highlight the establishment of well-defined scientific frameworks within which theories, laws, generalizations, and the experiments performed in support of them, are formulated.

The International Society for NeuroVirology is seeking funding to endow this lectureship beyond those funds currently available to the Society to support this lectureship series. Interested parties should contact the ISNV Administrative Office at the address below.

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