Joseph C Glorioso, Virol Mycol 2018, Volume 7
DOI: 10.4172/2161-0517-C2-025

Joseph C Glorioso

University of Pittsburgh, USA

Development of retargeted oHSV vectors for systemic treatment of breast cancer

The development of safe, oncolytic (o) HSV vectors for systemic treatment of metastatic breast cancer provides an opportunity for combining virus lytic activity with the potential to induce anti-tumor immunity. Ideally oHSV should be engineered for selective infection of tumor cells and escape from neutralizing antibodies. Complete retargeting strategies both detarget the viral attachment/entry glycoprotein gD from recognition of its cognate receptors, HVEM and nectin-1, and provide gD with a novel ligand that recognizes a highly expressed tumor-associated receptors that are poorly or not expressed on non-tumor tissue. Here we present design strategies for engineered oHSV that preferentially infect and lyse breast cancer cells by recognition of GFRα1, a receptor highly expressed on a subset of estrogen receptor-positive breast cancers. We replaced the signal peptide and HVEM binding domain of gD with pre-pro-(pp)GDNF to create a GFRα1 targeting protein, gD(Y38)-GDNF, that can still bind nectin-1. Virus expressing gD(Y38)-GDNF was propagated on cells expressing nectin-1 and purified virus was shown to enter nectin-1/HVEM-deficient J1.1-2 and B78H1 cells in a GFRα1-dependent manner. U2OS cells engineered to express GFRα1 were found to support propagation of a fully retargeted derivative virus that no longer recognizes nectin-1 but selectively infects cells through recognition of GFRα1, resulting in MOI-dependent tumor cell death *in vitro*. Moreover, direct intratumoral injection in nude mice showed complete tumor destruction *in vivo*. We have discovered, however, that retargeting can reduce the efficiency of virus entry and increase sensitivity to neutralizing (VN) antibodies, both associated with reduced retargeted gD incorporation into the virus envelope. Efficient infectivity was partially restored by selective residue changes in the downstream fusogen gB. Current studies involve engineered and selected changes in the epitope structure of retargeted gD that allow escape from VN antibodies to permit efficient systemic application of oHSV for metastatic breast cancer therapy.

Recent Publications

1. Uchida H, Chan J, Goins W F, Grandi P, Kumagai I, Cohen J B and Glorioso J C (2010) A double mutation in gB compensates for ineffective gD-dependent initiation of HSV-1 infection. Journal of Virology 84(23):12200-9.
2. Uchida H, Marzulli M, Nakano K, Goins W F, Chan J, Hong C S, Mazzacurati L, Yoo, J Y, Haseley A, Nakashima H, Baek H, Kwon H, Kumagai I, Kuroki M, Kaur B, Chiocca E A, Grandi P, Cohen J B and Glorioso J C (2013) Effective treatment of an orthotopic xenograft model of human glioblastoma using an EGFR-retargeted oncolytic herpes simplex virus. Molecular Therapy 21(3):561-9.
3. Mazzacurati L, Marzulli M, Reinhart B, Miyagawa Y, Uchida H, Goins W F, Li A, Kaur B, Caligiuri M, Cripe T, Chiocca E A, Amankulor N, Cohen J B, Glorioso J C and Grandi P(2015) Use of miRNA response sequences to block off-target replication and increase the safety of an unattenuated, glioblastoma-targeted oncolytic HSV. Molecular Therapy 23(1):99-107.
4. Goins W F, Huang S, Cohen J B and Glorioso J C (2014) Engineering HSV-1 vectors for gene therapy. Methods in Molecular Biology 1144:63-79.
5. Shibata T, Uchida H, Shiroyama T, Okubo Y, Suzuki T, Ikeda H, Yamaguchi M, Miyagawa Y, Fukuhara T, Cohen J B, Glorioso J C, Watabe T, Hamada H and Tahara H (2016) Development of an oncolytic HSV vector fully retargeted specifically to cellular EpCAM for virus entry and cell-to-cell spread. Gene Therapy 23(6):479-88.

Biography

Dr. Glorioso began his career as a professor in the Microbiology and Immunology and Laboratory Animal Medicine at the University of Michigan School of Medicine in 1976 and later in 1989, he moved to the University of Pittsburgh School of Medicine as the W.S McEllroy Professor and Chair of the Department of Microbiology and Molecular Genetics. He has established a 40-year history of research related to the basic biology and genetics of herpes simplex virus. His contributions to the field include defining antiviral immune responses to infection, the genetics of viral pathogenesis and latency, and mechanisms of viral infection. He has been 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.

glorioso@pitt.edu

Notes: