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Herpes simplex virus oncolytic vectors (oHSV) armed with the NKG2D ligand ULBP3 enhances treatment of gliomas

Joseph C Glorioso, Kohanbash G, Akula S, Bailey L, Hall B, Cohen, Goins W, Amankulor N and **Grandi P**
University of Pittsburgh School of Medicine, USA

Glioblastoma (GBM) is an incurable brain tumor for which the standard of care is not effective. Oncolytic viral therapies are under development to destroy GBM using engineered viral vectors that preferentially replicate in tumor cells. Although early phase trials have reported sporadic successes, improvements in vector design are needed to improve therapeutic efficacy. Effective viral therapy requires vectors that induce virolysis and promote anti-tumor immunity. This outcome is particularly challenging in GBM because glial malignancies are immunologically cold, and embedded in a profoundly immunosuppressive microenvironment. We have focused on the development of oHSV because these vectors (i) are highly virolytic for GBM, potentially releasing immunogenic cell debris, (ii) can be rendered safe without compromising virus lytic activity and (iii) can be engineered to express multiple immunomodulatory transgenes capable of activating innate and acquired anti-tumor responses. Here we describe an advanced oHSV vector armed with ULBP3, an activating NK cell (NKG2D) ligand that is often down-regulated as an immune escape mechanism in glioma. We tested the hypothesis that the expression of ULBP3 from an oHSV could activate NK cells and thereby improve the efficacy of GBM oncolytic virotherapy. Using human-derived glioma stem cells and a mouse glioma cell line, we demonstrated that infection of multiple cell lines with oHSV-ULBP3 significantly improves NK cell-mediated cytolysis *in vitro*. We then tested the therapeutic efficacy of an oncolytic vector armed with ULBP3 in a xenogeneic nude mouse model using the GBM-30 human glioma cell line. We observed that this new vector displayed an improved therapeutic profile compared to the parental unarmed vector (80% vs 40% long-term responders). Further studies using a GL261N-based orthotopic syngeneic model demonstrated that ULBP3 expression induced infiltration of cytotoxic CD8 T cells, suggesting that ULBP3 can be a potent inducer of both innate and acquired immunity. Our ongoing studies will determine whether a ULBP3 expression can enhance long-term animal survival in an NK cell or CD8 T cell-dependent manner.

Biography

Joseph C Glorioso began his career at the University Of Michigan School Of Medicine, Ann Arbor, MA, USA (1976–1989), where he became Professor of Microbiology and Immunology and Assistant Dean for Research and Graduate Studies. He subsequently moved to the University of Pittsburgh, School of Medicine, and Pittsburgh, USA, where he served as Chair and the McElroy Professor of Biochemistry until 2009. He is a former president of the American Society of Gene and Cell Therapy and serves as the American Editor of Gene Therapy. His research focuses on molecular genetic aspects of herpes simplex virus (HSV) pathogenesis and the development of HSV gene vectors for treatment of chronic pain, neuropathy, and cancer.

glorioso@pitt.edu

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