Oncolytic virus for high-grade glioma

- Impact of SPP1 and HMOX1 Genes in Glioma: Correlations With Oncolytic Virus Infection, Adverse Prognosis and Increased Cell Proliferation
- Oncolytic HSV-IL27 expression improves CD8 T cell function and therapeutic activity in syngeneic glioma models
- Unraveling the immunosuppressive microenvironment of glioblastoma and advancements in treatment
- An update on the clinical trial research of immunotherapy for glioblastoma
- Comparison of the L3-23K and L5-Fiber Regions for Arming the Oncolytic Adenovirus Ad5-Delta-24-RGD with Reporter and Therapeutic Transgenes
- IDH status dictates oHSV mediated metabolic reprogramming affecting anti-tumor immunity
- Oncolytic Virus Infection Modulates Lysine Acetyltransferase in Gliomas: Comprehensive Analysis and Experimental Validation of KAT8 in Glioma
- Therapeutic and prognostic values of ferroptosis signature in glioblastoma

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Oncolytic viruses represent a promising and innovative approach for the treatment of high-grade gliomas, which are aggressive and often difficult-to-treat brain tumors. These viruses are designed to selectively infect and destroy cancer cells, leaving healthy cells unharmed. Here are key points regarding oncolytic viruses for high-grade gliomas:

1. Selective Tumor Targeting:

Oncolytic viruses are engineered or naturally occurring viruses that can specifically target and infect cancer cells. For high-grade gliomas, this targeting is crucial to minimize damage to surrounding healthy brain tissue. 2. Replication and Cell Lysis:

After infecting cancer cells, oncolytic viruses replicate inside them, leading to the destruction of the cancer cells through various mechanisms such as direct cell lysis (rupture) or induction of apoptosis (programmed cell death). 3. Stimulation of Immune Response:

Oncolytic viruses can stimulate the immune system, contributing to a broader anti-cancer effect. The immune response triggered by the virus may extend beyond the initially infected cells, targeting additional cancer cells. 4. Potential Synergy with Standard Therapies:

Oncolytic virotherapy can be used alone or in combination with other standard treatments such as surgery, chemotherapy, and radiation therapy. Combining therapies may enhance overall treatment efficacy. 5. Overcoming Blood-Brain Barrier:

High-grade gliomas are often protected by the blood-brain barrier, which can limit the delivery of therapeutic agents. Some oncolytic viruses are designed to bypass or disrupt this barrier, allowing them to reach and infect cancer cells within the brain. 6. Types of Oncolytic Viruses:

Various viruses have been studied for their oncolytic potential in gliomas, including adenoviruses, herpes simplex viruses, measles viruses, and others. Each virus may have specific advantages and considerations. 7. Clinical Trials and Research:

Oncolytic virotherapy for high-grade gliomas is an active area of research and clinical trials. Researchers are exploring different viruses, delivery methods, and treatment combinations to

optimize outcomes for patients. 8. Challenges and Considerations:

Challenges in oncolytic virotherapy include potential development of resistance by cancer cells, overcoming the immune system response, and addressing safety concerns. Ongoing research aims to address these challenges. 9. Patient-Specific Approaches:

The use of oncolytic viruses may be tailored to individual patients based on the specific characteristics of their tumors. Personalized medicine approaches aim to optimize treatment outcomes. 10. Future Perspectives:

The field of oncolytic virotherapy for high-grade gliomas is evolving, and ongoing research may lead to the development of new and improved viral therapies. Future advancements may further enhance the effectiveness and safety of this treatment modality. In summary, oncolytic viruses show promise as a targeted and potentially effective treatment for high-grade gliomas. Ongoing research and clinical trials are crucial to advancing our understanding of their safety, efficacy, and potential integration into standard treatment protocols for patients with glioblastoma and other high-grade gliomas.

Data from a previous clinical trial using the oncolytic adenovirus Delta-24-RGD showed that generation of anti-viral neutralizing antibodies may affect the long-term survival of glioma patients. Past studies have examined the effects of neutralizing antibodies during systemic virus injections but largely overlooked their impact during local virus injections into the brain. We found that immunoglobulins colocalized with viral proteins upon local oncolytic virotherapy of brain tumors, warranting a strategy to prevent virus neutralization and maximize oncolysis. Thus, we generated a chimeric virus, Delta-24-RGD-H43m, by replacing the capsid protein hexon hypervariable regions from the serotype 5-based Delta-24-RGD with those from the rare serotype 43. Delta-24-RGD-H43m evaded neutralizing anti-adenovirus serotype 5 antibodies and conferred a higher rate of long-term survival than Delta-24-RGD in glioma-bearing mice. Importantly, Delta-24-RGD-H43m activity was significantly more resistant to neutralizing antibodies present in sera of glioma patients treated with Delta-24-RGD during a phase 1 clinical trial. These findings provide a framework for a novel treatment of glioma patients that have developed immunity against Delta-24-RGD [1)]

Preclinically, pediatric brain tumors are highly sensitive to oncolytic virotherapy with genetically engineered herpes simplex virus type 1 (HSV-1) G207, which lacks genes essential for replication in normal brain tissue.

Friedman et al. conducted a phase 1 trial of G207, which used a 3+3 design with four dose cohorts of children and adolescents with biopsy-confirmed recurrent or progressive supratentorial brain tumors. Patients underwent stereotactic placement of up to four intratumoral catheters. The following day, they received G207 (107 or 108 plaque-forming units) by controlled-rate infusion over a period of 6 hours. Cohorts 3 and 4 received radiation (5 Gy) to the gross tumor volume within 24 hours after G207 administration. Viral shedding from saliva, conjunctiva, and blood was assessed by culture and polymerase-chain-reaction assay. Matched pre-and post-treatment tissue samples were examined for tumor-infiltrating lymphocytes by immunohistologic analysis.

Twelve patients 7 to 18 years of age with high-grade glioma received G207. No dose-limiting toxic effects or serious adverse events were attributed to G207 by the investigators. Twenty grade 1 adverse events were possibly related to G207. No virus shedding was detected. Radiographic, neuropathological, or clinical responses were seen in 11 patients. The median overall survival was 12.2 months (95% confidence interval, 8.0 to 16.4); as of June 5, 2020, a total of 4 of 11 patients were still alive 18 months after G207 treatment. G207 markedly increased the number of tumor-infiltrating lymphocytes.

Intratumoral G207 alone and with radiation had an acceptable adverse-event profile with evidence of responses in patients with recurrent or progressive pediatric high-grade glioma. G207 converted immunologically “cold” tumors to “hot.” (Supported by the Food and Drug Administration and others; ClinicalTrials.gov number, NCT02457845.) [2)].

A set of six patient-derived glioblastoma cells treated ex-vivo with herpes simplex virus type 1 (HSV1) modeled a clinical setting of OV infection. The cellular transcriptome and secreted proteome (separated into extracellular vesicles (EV) and EV-depleted fractions) were analyzed by gene microarray and mass-spectroscopy, respectively. Data validation and in silico analysis measured and correlated the secretome content with the response to infection and patient survival. Glioblastoma cells reacted to the OV infection in a seemingly dissimilar fashion, but their transcriptomes changed in the same direction. Therefore, the upregulation of transcripts encoding for secreted proteins implies a common thread in the response of cancer cells to infection. Indeed, the OV-driven secretome is linked to the immune response. While these proteins have distinct membership in either EV or EV-depleted fractions, it is their co-secretion that augments the immune response and associates with favorable patient outcomes [3)].

Reviews

In a Review Raziye Piranlioglu *et al.* from

Affiliations	Harvey Cushing Neuro-oncology Laboratories, Dept. Neurosurgery, Brigham and Women's Hospital, Boston, MA, USA; Dana-Farber Cancer Institute, Boston, MA, USA

published in *Seminars in Immunology* with the **Purpose** to synthesize data from clinical trials of oncolytic viruses (OVs) in glioblastoma, evaluating immunomodulatory effects, delivery strategies, and challenges in assessing immune responses. They concluded that Oncolytic virus therapy is well tolerated in GBM trials and can convert the immunosuppressive microenvironment into an immunologically active state. However, limitations in post-treatment sampling and delivery methods impede full understanding of biological mechanisms.

This review is a rehash of well-known take-home messages, offering little in the way of novel synthesis or incisive critique. The authors lean heavily on canonical trials (e.g., oHSV, adenovirus) but fail to integrate preclinical correlates from myeloid-targeting strategies, such as macrophage polarization dynamics or MDSC modulation. There’s no fresh mechanism, no meta-analysis of response rates, and no exploration of why most trials remain phase I with limited impact. Sample-scarcity is once again highlighted as a blocker—but no alternative trial designs (e.g.,

neoadjuvant window cohorts, liquid biopsy) are proposed. In short, the review scratches the surface of challenges without pushing the field forward.

- **Methodology flaws**: Reliance on clinical trial summaries without critical assessment of sample sizes, endpoints, or confounders. - **Relevance**: Glioblastoma is the archetype of immunotherapy resistance—yet this review reiterates, rather than interrogates, that fact. - **Novelty**: Absent—this is a telescoped summary without new angles on delivery vectors, immune biomarker development, or pivot strategies after failure. - **Interpretation errors**: The authors imply “immune activation” equates to therapeutic efficacy, with no link to survival or functional endpoints. - **Weak conclusions**: Acknowledge limitations, but then offer safe, bland suggestions with zero disruptive insight.

Final Verdict

This review is perfunctory—a missed opportunity to provoke meaningful debate or propose technical advances. Strictly descriptive, minimally analytical, and intellectually unambitious.

Takeaway for Neurosurgeons

GBM oncolytic-virus trials confirm feasibility and safety, but therapeutic impact remains marginal, and mechanistic insights are too scant to change practice.

Bottom Line

Safe and well-tolerated, but clinically stagnant.

Score

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Publication date: June 23, 2025 *Corresponding author email*: rpiranlioglu@bwh.harvard.edu

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