

THERAPEUTIC POTENTIAL OF ONCOLYTIC VIROTHERAPY COMBINED WITH IMMUNOTHERAPY FOR THE TREATMENT OF CHEMORESISTANT GLIOBLASTOMA STEM CELLS

**POTENCIAL TERAPÊUTICO DA VIROTERAPIA COMBINADA À
IMUNOTERAPIA NO TRATAMENTO DE CÉLULAS-TRONCO TUMORAIS
QUIMIORRESISTENTES NO GLIOBLASTOMA**

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ABSTRACT

Glioblastoma is one of the most aggressive tumors of the central nervous system and is characterized by marked cellular heterogeneity, a high rate of recurrence, and limited responsiveness to conventional therapies. Glioblastoma stem cells (GSCs) exhibit substantial self-renewal capacity and cellular plasticity and contribute to therapeutic resistance, including chemoresistance, thereby hindering effective disease control. Consequently, novel therapeutic approaches have been investigated to overcome the mechanisms underlying treatment resistance. The present study consists of an integrative literature review addressing the therapeutic potential of oncolytic virotherapy combined with immunotherapy to target glioblastoma stem cells. Oncolytic virotherapy has emerged as a promising therapeutic strategy based on genetically engineered viruses designed to selectively infect and lyse tumor cells, while also modulating the tumor microenvironment and stimulating antitumor immune responses. When combined with immunotherapy, oncolytic viruses may enhance immune activation and facilitate the recognition and elimination of tumor cells. Thus, the integration of oncolytic virotherapy and immunotherapy represents a promising strategy for disrupting the biological mechanisms underlying glioblastoma, targeting therapy-resistant tumor stem cell populations and potentially reversing the immunosuppressive tumor microenvironment. However, further studies are needed to establish optimal routes of administration, treatment combinations, and safety profiles and to determine the clinical efficacy of these approaches.

Keywords: Glioblastoma; Chemoresistance; Oncolytic Viruses; Immunotherapy; Glioblastoma Stem Cells.

RESUMO

O glioblastoma é classificado como um dos tumores mais agressivos do sistema nervoso central, e apresenta alta diversidade celular, elevada taxa de recorrência e baixa resposta às terapias convencionais. Possui como característica, elevada capacidade de autorrenovação, plasticidade celular e quimiorresistência das células-tronco tumorais, fatores que prejudicam uma resposta terapêutica. Assim, com a finalidade de superar os mecanismos que causam resistência, novas abordagens têm sido investigadas. Assim, o presente trabalho consiste em uma revisão integrativa de literatura, abordando o potencial terapêutico da viroterapia combinada à imunoterapia visando às células-tronco do glioblastoma. A viroterapia oncolítica tem sido uma estratégia promissora, utilizando vírus geneticamente modificados capazes de infectar e lisar somente as células tumorais, além de modular o microambiente tumoral e estimular respostas antitumorais presentes no sistema imune. Quando associada à imunoterapia, a ativação do sistema imunológico é potencializada e o reconhecimento e a eliminação das células tumorais é mais favorável. Dessa forma, a integração entre a viroterapia oncolítica e a imunoterapia emerge como uma estratégia promissora para desestruturar a biologia do glioblastoma, neutralizando as células-tronco tumorais e revertendo o microambiente imunossupressor, embora ainda sejam necessários estudos mais aprofundados sobre as vias de administração e os perfis de segurança para consolidar sua aplicação clínica.

Palavras-chave: Neoplasia; Resistência à antitumorais; Vírus oncolíticos; Terapia imunológica.

1. INTRODUCTION

Glioblastoma (GBM) is the most common malignant primary brain tumor in adults. According to the fifth edition of the World Health Organization (WHO) Classification of Tumors of the Central Nervous System (WHO CNS5), glioblastoma is classified as a CNS WHO grade 4 diffuse astrocytic glioma and, under the current classification, is defined as an IDH-wildtype and H3-wildtype tumor that meets specific histological and/or molecular criteria (Ahmad *et al.*, 2023).

GBM is characterized by rapid growth, self-renewal capacity, extensive invasive potential, marked cellular and molecular heterogeneity, and the ability to adapt to hostile conditions, all of which contribute to its poor prognosis (Nunes *et al.*, 2025; Agosti *et al.*, 2024). Although the treatment of GBM remains challenging, the standard-of-care approach consists of maximal safe surgical resection followed by radiotherapy with concomitant and adjuvant temozolomide (Hamad *et al.*, 2023). Despite this multimodal therapeutic approach, tumor recurrence is common and reflects the persistence of mechanisms underlying therapeutic resistance (Sun; Kim, 2022). These mechanisms are associated with tumor heterogeneity, the immunosuppressive tumor microenvironment, and the presence of highly treatment-resistant cellular subpopulations (Chu *et al.*, 2024).

Therefore, understanding the biological, genetic, and molecular properties of GBM, as well as its interactions with the immune system, is essential for the development of more effective therapeutic strategies, including immunotherapy and oncolytic virotherapy (Tang *et al.*, 2021). While immunotherapy aims to stimulate the patient's immune system to recognize and eliminate tumor cells, oncolytic viruses (OVs) can preferentially infect tumor

cells, inducing direct tumor cell death and stimulating antitumor immune responses (Tang *et al.*, 2021; Hamad *et al.*, 2023).

Emerging studies suggest that combining these therapeutic approaches may produce synergistic effects, as OV_s can modulate the tumor microenvironment, promote immune-cell infiltration, and potentially enhance the activity of immunotherapeutic strategies (Liu *et al.*, 2023; Asija *et al.*, 2023). In this context, the combination of immunotherapy and oncolytic virotherapy has emerged as a promising strategy for targeting immune-evasion mechanisms and therapeutic resistance in glioblastoma. Accordingly, this study aims to investigate the therapeutic potential of combined immunotherapy and oncolytic virotherapy for the treatment of glioblastoma, with particular emphasis on their potential effects on the elimination of glioblastoma stem cells and on overcoming mechanisms of chemoresistance.

2. MATERIALS AND METHODS

This study consists of an integrative literature review aimed at investigating the role of tumor stem cells in glioblastoma and their relationship with mechanisms of chemoresistance.

2.1. Search Strategy And Eligibility Criteria

The literature search will be conducted using the Virtual Health Library (BVS), PubMed, and EBSCOhost databases, complemented by ResearchRabbit as a citation-discovery tool. The following keywords and related terms will be used: “glioblastoma,” “cancer stem cells,” “glioblastoma stem cells,” “chemotherapy resistance,” “chemoresistance,” “oncolytic viruses,” “oncolytic virotherapy,” “virotherapy,” and “immunotherapy.” These terms will be combined

using the Boolean operators “AND” and “OR,” according to the conceptual relationships among the main topics and their synonyms.

Studies meeting the following eligibility criteria will be included: (a) published between 2020 and 2025; (b) written in English or Portuguese; (c) with full-text availability; (d) directly addressing the research topic; and (e) employing relevant study designs, including controlled clinical trials, observational studies, etiological studies, diagnostic studies, prognostic studies, and systematic reviews. Studies will be excluded if they do not have full-text availability, are published in languages other than English or Portuguese, or do not address the proposed topic.

3. RESULTS AND DISCUSSION

Glioblastoma exhibits a tumor microenvironment characterized by the expression of immunosuppressive molecules, hypoxia, the production of cytokines such as IL-10 and TGF- β , and the recruitment of immunosuppressive cells, particularly tumor-associated macrophages (TAMs). These factors impair T-cell and NK-cell activity and contribute to tumor progression (Su *et al.*, 2025; Tang; Al Amin; Campian, 2025; Zhou *et al.*, 2025).

The low tumor mutational burden of glioblastoma limits the generation of neoantigens and the induction of effective antitumor immune responses, whereas pronounced spatial and temporal heterogeneity and the plasticity of glioma stem cells (GSCs) contribute to immune evasion and therapeutic resistance. Therefore, multitarget strategies and therapies capable of increasing tumor immunogenicity are being investigated as potential approaches to

overcome these mechanisms of immune evasion (Su *et al.*, 2025; Tang; Al Amin; Campian, 2025; Zhou *et al.*, 2025; Hu *et al.*, 2026).

The blood-brain barrier (BBB) and the blood-tumor barrier exhibit heterogeneous permeability and may remain partially intact in infiltrative and peritumoral regions. This heterogeneity can limit the delivery of immunotherapeutic agents to tumor sites and has motivated the development of innovative drug-delivery strategies, including intranasal administration, exosome-based delivery, mesenchymal stem cell (MSC)-mediated delivery, and other local delivery approaches (Santillán-Guaján; Shahi; Castresana, 2024; Wang; Li; Jiang, 2026; Su *et al.*, 2025; Li; Zhang; Du, 2026; Zhou *et al.*, 2025).

Among the viral platforms investigated for the treatment of GBM, PVSRIPO is a neuroattenuated recombinant poliovirus derived from the live attenuated type 1 Sabin poliovirus vaccine, in which the internal ribosomal entry site (IRES) of poliovirus has been replaced with the IRES of human rhinovirus type 2 (HRV2). PVSRIPO combines direct cytotoxicity against tumor cells with activation of antitumor immune responses (Liu *et al.*, 2025). The virus utilizes CD155, also known as the poliovirus receptor (PVR), which is widely expressed in glioblastoma cells and is also present on cells of the tumor microenvironment, facilitating viral entry (Khan, 2023). The replacement of the poliovirus IRES with the HRV2 IRES attenuates the virus and confers neuronal incompetence, thereby markedly reducing its ability to replicate in neurons (Brown *et al.*, 2017). Following infection, PVSRIPO induces tumor-cell death and activates antiviral responses, including type I interferon (IFN-I) signaling (Khan, 2023). In addition, the virus can establish a persistent, sublethal infection in antigen-presenting cells (APCs),

including dendritic cells and macrophages, stimulating sustained type I interferon-dominant inflammatory responses and activation of the myeloid compartment (Brown *et al.*, 2017). This response promotes the recruitment and activation of T cells and contributes to remodeling of the immunosuppressive GBM microenvironment. Thus, the mechanism of action of PVSRIPO combines direct oncolysis, activation of innate immunity, and remodeling of the tumor microenvironment, thereby promoting the recognition of and immune responses against tumor cells (Khan, 2023).

Oncolytic human orthoreovirus, in turn, acts through a combination of direct cytotoxicity and activation of innate and adaptive antitumor immune responses. Following intravenous administration, reovirus RNA has been detected in peripheral blood cell populations, including CD14⁺ monocytes, CD19⁺ B cells, and CD56⁺ NK/NKT cells, suggesting that these cells may contribute to systemic viral trafficking and delivery to brain tumors. In the tumor microenvironment, reovirus infection has been associated with highly proliferative tumor cells and with activation of apoptotic pathways, as indicated by increased levels of cleaved caspase-3. In addition to its direct cytotoxic effects, intracellular viral RNA activates pattern-recognition receptors and induces the production of systemic and intratumoral interferons (IFNs). This inflammatory response is associated with increased expression of the chemokines CCL3 and CCL4, which can promote the recruitment of CD8⁺ T cells and other leukocyte populations to the tumor. Reovirus treatment also increases the expression of PD-L1 in tumor and infiltrating immune cells and is associated with increased PD-1 expression. Thus, reovirus can remodel the tumor microenvironment and promote antitumor immune activation, providing a rationale for combining

reovirus with sequential PD-1/PD-L1 checkpoint blockade (Samson *et al.*, 2018).

The oncolytic reovirus (pelareorep) is naturally oncotropic and exhibits preferential replication in tumor cells with activated RAS signaling. Its activity involves infection and destruction of tumor cells, together with activation of innate immune responses and induction of inflammatory cytokine pathways, including type I interferon (IFN- α/β) signaling, as well as peripheral activation of NK cells (Phillips *et al.*, 2018). The antitumor activity of reovirus may be enhanced when combined with immunomodulatory agents such as granulocyte-macrophage colony-stimulating factor (GM-CSF), as well as with chemoradiotherapy and temozolomide in specific treatment settings. However, systemic administration may be limited by factors including antiviral neutralizing antibodies and the heterogeneous permeability of the blood-brain barrier (BBB). To overcome these barriers and improve viral delivery to tumor sites, innovative strategies such as focused ultrasound-mediated BBB opening and cell-based delivery systems are being investigated (Liu *et al.*, 2025).

The Delta24-RGD model (DNX-2401) acts through a combination of direct oncolysis and activation of antitumor immune responses (van Putten *et al.*, 2022). It is an oncolytic adenovirus containing a 24-base-pair deletion in the E1A gene, which restricts viral replication in many normal cells while allowing preferential replication in tumor cells with defects in the retinoblastoma (Rb) pathway, a commonly altered pathway in gliomas (Hu *et al.*, 2023; Kiyokawa; Wakimoto, 2019; Ene; Fueyo; Lang, 2021). In addition, insertion of the RGD-4C peptide alters viral tropism and enhances infection of glioma cells by promoting interactions with $\alpha\beta3$ and $\alpha\beta5$ integrins (van Putten *et*

al., 2022; Liu *et al.*, 2025). Following entry into tumor cells, active viral replication induces direct cell lysis (Lang *et al.*, 2018). This form of cell death can promote immunogenic responses through the release of tumor-associated antigens (TAAs) and damage-associated molecular patterns (DAMPs) (Liu *et al.*, 2025; Lang *et al.*, 2018). These signals can be recognized by antigen-presenting cells (APCs), including dendritic cells, thereby promoting the recruitment and infiltration of macrophages and CD4⁺ and CD8⁺ T cells into the tumor microenvironment (van Putten *et al.*, 2022; Liu *et al.*, 2025). The inflammatory response is accompanied by increased local expression of Th1-associated proinflammatory cytokines, including IFN- γ and TNF- α , which may contribute to remodeling of the immunosuppressive glioblastoma microenvironment toward a state more permissive to antitumor immune activity (van Putten *et al.*, 2022). This potential for immunogenic conversion provides a rationale for combining DNX-2401 with immunotherapies such as PD-1/PD-L1 pathway blockade. Clinical studies of DNX-2401 combined with pembrolizumab have reported objective responses and durable responses in a subset of patients, although the prespecified primary efficacy endpoint was not met (van Putten *et al.*, 2022; Liu *et al.*, 2025).

G47 Δ acts through two complementary mechanisms: direct oncolysis and induction of antitumor immune responses. Following intratumoral administration, the virus replicates in glioblastoma cells and promotes their direct destruction (Kardani *et al.*, 2023). G47 Δ is a triple-mutated oncolytic herpes simplex virus type 1 (HSV-1) derived from G207 and contains deletions in the γ 34.5, ICP6, and α 47 genes, which contribute to viral attenuation and tumor-selective replication (Hu *et al.*, 2023). Specifically, deletion of α 47 prevents the viral protein from downregulating major histocompatibility complex class I (MHC

class I) expression through interference with the transporter associated with antigen processing (TAP), thereby facilitating antigen presentation in infected cells. The $\alpha 47$ deletion also places the late US11 gene under the control of the immediate-early $\alpha 47$ promoter, partially restoring functions lost through $\gamma 34.5$ deletion and enhancing viral replication in tumor cells. Viral replication and tumor-cell destruction can promote the release and presentation of tumor-associated antigens, thereby contributing to activation of antitumor immune responses. Preclinical studies have shown that G47 Δ can target glioblastoma stem-like cells, while clinical studies have demonstrated immune activation following intratumoral administration (Bi *et al.*, 2026; Kohlhapp; Kaufman, 2016). Thus, the therapeutic effects of G47 Δ may extend beyond direct oncolysis through the induction of antitumor immunity.

NSC-CRAAd-S-pk7 is a genetically modified oncolytic adenovirus designed for delivery using neural stem cells (NSCs). Following surgical resection of the glioma, NSCs loaded with viral particles are injected into the resection cavity, where they can function as cellular carriers and migrate toward residual tumor sites, facilitating localized viral delivery (Fares *et al.*, 2021). The adenovirus was engineered to preferentially replicate in and lyse glioma cells, including tumor cell populations with treatment-resistant characteristics. In addition to its direct oncolytic activity, immunological and histopathological analyses from the first-in-human clinical trial demonstrated changes in the tumor immune microenvironment after treatment, including increased infiltration of CD8⁺ T cells and changes in populations of myeloid cells and PD-1-expressing cells (Fares *et al.*, 2021; Alonso *et al.*, 2012). These findings suggest that NSC-mediated delivery of NSC-CRAAd-S-pk7 may combine active tumor targeting by neural stem cells, localized viral

oncolysis, and modulation of antitumor cellular immunity (Fares *et al.*, 2021).

Other viral models include vaccinia virus (vVDD) and myxoma virus (vMyx), which can efficiently infect and lyse glioma cells, resulting in direct cytotoxicity and the subsequent release of tumor-associated antigens that can stimulate adaptive antitumor immune responses (Tang *et al.*, 2020; Lun *et al.*, 2005). In addition to their intrinsic oncolytic activity, these viruses have been genetically engineered as gene-delivery vectors to express the IL-15R α -IL-15 fusion protein locally within the tumor microenvironment (Kowalsky *et al.*, 2018; Tomic *et al.*, 2014). Local production of this IL-15 superagonist increases the recruitment and infiltration of NK cells and CD8⁺ T cells and enhances their antitumor activity in preclinical glioma models (Kowalsky *et al.*, 2018; Tomic *et al.*, 2014). In addition, viral infection induces a local inflammatory state that can facilitate immune-cell recruitment and infiltration into the tumor. This therapeutic effect was further enhanced in preclinical models by combining the oncolytic viruses with rapamycin, which can increase viral infection and replication, and celecoxib, a cyclooxygenase-2 (COX-2) inhibitor that reduces prostaglandin synthesis and may alleviate local immunosuppression, thereby promoting the activity of infiltrating T cells (Kowalsky *et al.*, 2018; Tomic *et al.*, 2014). In these experimental models, tumor control resulted from the combined effects of direct oncolysis, tumor-antigen release, immune stimulation, and modulation of the immunosuppressive tumor microenvironment (Tang *et al.*, 2020).

Liu *et al.* (2025) describe vaccinia virus as a promising oncolytic platform for glioblastoma because of its efficient infection and large genome, which provides substantial capacity for the incorporation of

therapeutic transgenes. These modifications can include immunomodulatory cytokines, such as GM-CSF, IL-2, IL-12, and IL-21, as well as bispecific molecules (Liu *et al.*, 2025; Lee *et al.*, 2023). Following infection of tumor cells, vaccinia virus can induce cytolysis, resulting in the release of tumor-associated antigens and the activation of antitumor immune responses. Virus-encoded therapeutic payloads may further enhance immune activation, promote the recruitment of effector cells, and contribute to remodeling of the tumor microenvironment, including changes in tumor vasculature (Liu *et al.*, 2025; Suryawanshi; Schulze, 2021). However, despite the potential of armed vaccinia virus platforms, their application in glioblastoma remains largely at the preclinical or early translational stage, and additional clinical studies are required to establish their safety and therapeutic efficacy (Liu *et al.*, 2025).

R-613 is an oncolytic herpes simplex virus (HSV) designed to specifically target the EGFRvIII receptor, a constitutively active mutant variant of the epidermal growth factor receptor that is frequently detected in glioblastoma (Menotti *et al.*, 2018; An *et al.*, 2018). To achieve this specificity, the virus was genetically engineered by inserting a single-chain variable fragment (scFv) directed against EGFRvIII into the viral envelope glycoprotein D (gD), together with deletions in gD that abolish its interaction with the natural HSV receptors nectin-1 and herpesvirus entry mediator (HVEM) (Menotti *et al.*, 2018). This combined detargeting/retargeting strategy restricts viral entry to cells expressing EGFRvIII and markedly reduces infection of cells that express the natural HSV receptors but lack the target receptor. Preclinical studies demonstrated that R-613 can infect EGFRvIII-positive glioblastoma cells, including glioblastoma stem-like cells, while showing limited infection of non-target cells (Menotti *et al.*, 2018; Appolloni *et al.*, 2021).

Following infection, R-613 replicates in susceptible tumor cells, leading to tumor-cell lysis and release of progeny virions capable of infecting adjacent malignant cells (Maroun *et al.*, 2017; Appolloni *et al.*, 2021). In addition to direct cytotoxicity, oncolysis can release tumor-associated antigens and inflammatory signals, potentially promoting systemic antitumor immune responses (Lemos de Matos *et al.*, 2020; Appolloni *et al.*, 2021). Nevertheless, the therapeutic activity of R-613 in preclinical models was not dependent on a fully functional adaptive immune system, as treatment delayed tumor progression in immunodeficient mice (Appolloni *et al.*, 2021). Appolloni *et al.* (2021) further showed that early treatment substantially prolonged survival, whereas treatment of well-established tumors was less effective when R-613 was administered alone. These findings suggest that repeated administration or combination with additional immunostimulatory strategies may warrant further investigation.

The antitumor activity of Zika virus (ZIKV) against glioblastoma (GBM) has been investigated as an oncolytic approach based on its preferential ability to infect and eliminate glioblastoma cells, including populations with stem-like characteristics associated with tumor progression, invasion, and therapeutic resistance (Francipane *et al.*, 2021; Victorio *et al.*, 2024). Recent studies of live-attenuated ZIKV vaccine strains (ZIKV-LAV) identified AXL and integrin $\alpha\beta 5$ as important cellular receptors involved in viral entry into GBM cells (Victorio *et al.*, 2024). Earlier work also implicated the SOX2–integrin $\alpha\beta 5$ axis in the preferential targeting of glioma stem-like cells, suggesting that SOX2-dependent regulation of $\alpha\beta 5$ contributes to ZIKV susceptibility in these cells (Kim *et al.*, 2024; Francipane *et al.*, 2021). Following cellular entry, ZIKV-LAV undergoes productive replication and can spread to neighboring susceptible tumor cells

(Victorio *et al.*, 2024). ZIKV-LAV infection induces both non-lytic cell death through apoptosis, including caspase-3 activation, and inflammatory lytic cell death through pyroptosis involving gasdermin D (GSDMD) cleavage, membrane pore formation, and IL-1 β release (Victorio *et al.*, 2024). These immunogenic effects may alter the tumor microenvironment and promote the recruitment of immune cells, including CD8⁺ T cells and myeloid cells. In addition, ZIKV infection has been associated with molecular changes involving miR-34c, which can reduce the levels of the antiapoptotic protein Bcl-2 and the Notch antagonist Numb, thereby impairing the survival, invasiveness, resistance, and clonogenic self-renewal capacity of GBM cells (Francipane *et al.*, 2021; Victorio *et al.*, 2024). Importantly, the attenuated DN-1 and DN-2 strains showed reduced productive replication and cytopathogenicity in differentiated human neurons and primary endothelial cells, including human umbilical vein endothelial cells (HUVECs) and human brain microvascular endothelial cells (HBMECs), supporting their potential safety profile relative to wild-type ZIKV (Victorio *et al.*, 2024).

Newcastle disease virus (NDV), particularly attenuated or fusogenic strains such as NDV-HUJ, exerts antitumor activity through direct oncolysis and activation of innate immune responses, including type I interferon (IFN-I) signaling (Liu *et al.*, 2025; Ginting *et al.*, 2019). Viral infection can induce transcriptional programs involving IFN-stimulated genes, stimulate chemokine production, and alter myeloid-cell populations within the tumor microenvironment, potentially promoting the recruitment and activation of effector immune cells (Liu *et al.*, 2025). In clinical studies of patients with glioblastoma and other malignant brain tumors, however, the available evidence remains limited, and early-phase studies have primarily established the feasibility and tolerability of NDV-based

approaches rather than definitive clinical efficacy (Abdullah *et al.*, 2014).

CAN-3110 (linoserpaturev) is a replication-competent oncolytic herpes simplex virus (oHSV) genetically engineered to restrict viral replication through a nestin-responsive regulatory element, thereby preferentially targeting nestin-expressing glioma cells (Ling *et al.*, 2023; Liu *et al.*, 2025). Tumor-cell destruction and the subsequent release of tumor-associated antigens can promote immune priming and diversification of the T-cell receptor (TCR) repertoire, contributing to a broader antitumor immune response (Ling *et al.*, 2023; Liu *et al.*, 2025). In a first-in-human phase I clinical study, pretreatment HSV-1 seropositivity was associated with significantly longer overall survival among treated patients. In patients with IDH-wild-type recurrent glioblastoma, median survival was 14.2 months among HSV-1-seropositive patients compared with 7.8 months among seronegative patients; however, these findings represent an association and do not by themselves establish a causal relationship between HSV-1 serostatus and treatment efficacy (Ling *et al.*, 2023).

EGFP-oHSV-1 is an oncolytic herpes simplex virus type 1 (HSV-1) genetically modified by deletions in the γ 34.5 and US12 genes and by insertion of the enhanced green fluorescent protein (EGFP) reporter gene (Liu *et al.*, 2003; Reale *et al.*, 2024). Its mechanism of action combines direct oncolysis with activation of antitumor immune responses. Following tumor-cell lysis, ATP, damage-associated molecular patterns (DAMPs), pathogen-associated molecular patterns (PAMPs), and tumor-associated antigens can be released into the tumor microenvironment (Reale *et al.*, 2019). Deletion of US12 facilitates antigen presentation by infected cells, whereas viral infection promotes the recruitment of CD4⁺ and CD8⁺ T cells and

activation of macrophages and microglia. Deletion of $\gamma 34.5$ contributes to viral attenuation and reduces neurovirulence (Liu *et al.*, 2003; Reale *et al.*, 2024).

The mechanism of action of genetically modified oncolytic Zika virus (oZIKV) is based on selective oncolytic virotherapy, using modifications of the viral genome to promote preferential replication in tumor cells while restricting viral replication in healthy neural tissues (Novaes *et al.*, 2024). One strategy involves the insertion of microRNA response elements (MREs) into the viral genome. These sequences are recognized by microRNAs such as miR-129-5p and miR-219a-2-3p, which are expressed in normal neural cells (Novaes *et al.*, 2024). In cells expressing these microRNAs, their binding to the MREs promotes degradation or suppression of viral RNA and restricts viral replication, thereby reducing potential toxicity to neural tissue. In contrast, reduced expression of these microRNAs in tumor cells permits greater viral replication and oncolysis. This strategy is also supported by the natural tropism of ZIKV for neural cells and cells with stem-like characteristics, including glioblastoma stem-like cells. The oZIKV_3' and oZIKV_2k constructs differ in the location of the MREs: oZIKV_3' contains the regulatory sequence in the 3' untranslated region (3'UTR), whereas oZIKV_2k contains the MRE within the coding region of the 2k peptide. In experimental models, the modified viruses also demonstrated the capacity to reach intracranial tumors following systemic administration, supporting their potential for systemic delivery (Novaes *et al.*, 2024). Thus, this approach combines tumor tropism, selective viral replication, and tumor-cell lysis, while microRNA-mediated regulation may restrict viral replication in healthy neural tissues (Novaes *et al.*, 2024).

Initial studies of oncolytic virotherapy have reported survival outcomes that warrant further investigation, although direct comparisons with conventional therapy are limited by differences in patient populations, disease stage, treatment setting, and study design. In the landmark study by Stupp *et al.* (2005), the median overall survival (OS) of patients with newly diagnosed glioblastoma treated with radiotherapy plus concomitant and adjuvant temozolomide was 14.6 months, compared with 12.1 months for radiotherapy alone. These results established the clinical benefit of adding temozolomide to radiotherapy in newly diagnosed glioblastoma (Stupp *et al.*, 2005). In recurrent glioblastoma, median survival is typically only 6 months, even with reirradiation, repeat surgery, or chemotherapy (Lang *et al.*, 2018; Wen; Kesari, 2008).

In patients with recurrent glioblastoma treated with DNX-2401 delivered by convection-enhanced delivery (CED), a phase I study reported a median overall survival of 4.3 months, with individual survival ranging from approximately 2.2 months to more than 7.5 years in the reported cohort (van Putten *et al.*, 2022). In a separate phase I study involving patients with recurrent malignant glioma, 89% of whom had glioblastoma at first, second, or third recurrence, DNX-2401 was evaluated in two treatment groups. In the group receiving intratumoral injection without subsequent tumor resection (Group A, n = 25), the median overall survival was 9.5 months. Tumor reduction was observed in 72% of patients, and three patients experienced a reduction of $\geq 95\%$ in tumor size and progression-free survival of at least 3 years; two additional patients experienced sustained stable disease after initial tumor regression. In the group receiving viral injection followed by tumor resection 14 days after treatment for biological analysis (Group B, n = 12), the median overall survival was 13.0 months (Lang *et al.*, 2018). These

findings should be interpreted as results from early-phase, non-randomized studies rather than as evidence of superiority over conventional therapy.

Patients with residual or recurrent supratentorial glioblastoma following radiotherapy and temozolomide were treated intratumorally with the oncolytic virus G47 Δ . The primary endpoint, defined as the 1-year survival rate after initiation of G47 Δ treatment, was 84.2% (95% confidence interval, 60.4–96.6; 16 of 19 patients). The prespecified endpoint was met, and the trial was terminated early. Regarding the secondary endpoints, median overall survival was 20.2 months after initiation of G47 Δ treatment and 28.8 months from the initial surgery (Todo *et al.*, 2022).

Patients with newly diagnosed high-grade glioma treated with the neural stem cell (NSC)-delivered oncolytic adenovirus NSC-CRAd-S-pk7 achieved a median overall survival of 18.4 months (Fares *et al.*, 2021).

In patients with recurrent glioblastoma previously treated with radiotherapy and temozolomide, sequential treatment with intratumorally administered DNX-2401 followed by intravenous administration of the anti-PD-1 antibody pembrolizumab resulted in a median overall survival of 12.5 months (Nassiri *et al.*, 2023).

In patients with recurrent glioblastoma treated with PVSRiPO, median overall survival was 12.5 months from the time of treatment (Desjardins *et al.*, 2019). In patients with recurrent high-grade glioma or brain metastases treated with intravenous oncolytic reovirus, median overall survival was 15.4 months from the day of reovirus treatment. The study reported that patients with brain metastases

receiving optimal treatment generally have a median survival of approximately 9–10 months, although this comparison should be interpreted cautiously because the study was not designed as a randomized comparison with a historical control group (Samson *et al.*, 2018).

The R-613 model was evaluated in immunodeficient NOD/SCID mice bearing orthotopic xenografts of human glioblastoma cells expressing EGFRvIII. R-613 is an EGFRvIII-retargeted oncolytic herpes simplex virus designed to preferentially infect EGFRvIII-expressing glioblastoma cells. Early treatment with R-613 significantly increased the median survival of tumor-bearing mice, whereas treatment initiated after the tumors were well established was less effective. Importantly, tumor cells that remained uninfected after treatment retained susceptibility to R-613 infection *ex vivo*, suggesting that repeated administration may warrant further investigation (Appolloni *et al.*, 2021).

Zika virus (ZIKV) has also been investigated as an oncolytic agent targeting glioblastoma stem cells (GSCs). Preclinical *in vitro* and *in vivo* studies demonstrated preferential infection and killing of GSCs compared with differentiated tumor cells and normal neuronal cells. ZIKV-mediated depletion of patient-derived GSCs was also demonstrated in organoid models, supporting the potential of ZIKV-based virotherapy for targeting stem-like tumor cell populations (Francipane *et al.*, 2021).

In a preclinical murine model of orthotopic patient-derived glioblastoma, the combination of the intratumorally administered IL-7-loaded oncolytic adenovirus oAD-IL7 with intravenous infusion of B7H3-targeted CAR-T cells produced enhanced antitumor activity

compared with either treatment alone. The combination prolonged survival and reduced tumor burden in tumor-bearing mice. In ex vivo analyses, oAD-IL7 enhanced the proliferation and persistence of tumor-infiltrating B7H3-CAR-T cells, although it did not completely reverse T-cell exhaustion (Huang *et al.*, 2021).

In preclinical studies using the immunocompetent murine GL261 intracranial glioma model, combining oncolytic virotherapy with immunotherapy and pharmacological modulation produced substantial long-term survival. A combination regimen consisting of the IL15R α -IL15-expressing vaccinia virus vDD-IL15R α -YFP, adoptive transfer of GARC-1 neoantigen-specific T cells, rapamycin, and celecoxib resulted in elimination of gliomas in a substantial proportion of treated mice. Substitution of vDD-IL15R α -YFP with the myxoma virus vMyx-IL15R α -tdTr under the same combination regimen resulted in glioma elimination in 83% of treated mice. In addition, vaccination with the GARC-1 peptide combined with vDD-IL15R α -YFP, rapamycin, and celecoxib, without adoptive T-cell transfer, also produced tumor elimination in a substantial proportion of mice. In contrast, vDD-IL15R α -YFP monotherapy produced a more modest therapeutic effect, increasing median survival to 42 days compared with 32 days in control animals (Tang *et al.*, 2020).

Kim *et al.* (2024) developed a mathematical model to investigate the effects of SOX2 expression levels on Zika virus virotherapy against glioblastoma stem cells. The model incorporated the experimentally described relationship between SOX2 expression and the $\alpha\beta5$ integrin axis involved in ZIKV infection of GSCs. The analysis indicated that therapeutic efficacy depends on the interaction between SOX2 expression and viral replication dynamics. In particular, successful reduction of the GSC population was

associated with conditions in which the basic reproduction number (R_0) exceeds 1. The model identified critical thresholds associated with transcritical and Hopf bifurcations, indicating transitions between different dynamical regimes as SOX2 expression and viral replication parameters changed. The analysis also revealed a relationship between SOX2 expression and viral burst size in determining system stability, with the greatest reduction in the GSC population occurring near the transition between stable and oscillatory regimes (Kim *et al.*, 2024).

In a preclinical murine model of an aggressive central nervous system tumor using BALB/c nude mice bearing xenografts, a microRNA-modified oncolytic Zika virus (oZIKV_2k) was evaluated using two routes of administration. Direct intracerebroventricular administration resulted in tumor remission in 83% of treated animals and complete remission of spinal metastases in 33%. Systemic administration by the intraperitoneal route, given in three doses, resulted in an 80% survival rate in mice bearing established tumors. These findings indicate that oZIKV_2k retained antitumor activity following systemic administration and reduced the severity of ZIKV-associated clinical manifestations compared with the wild-type virus. However, the study did not establish that the virus completely crosses the blood-brain barrier without infecting healthy neural tissue; therefore, such a conclusion should be interpreted cautiously (Novaes *et al.*, 2024).

Overall, further studies are required to characterize the mechanisms of action and safety profiles of these oncolytic viruses more precisely. The route of administration may substantially influence viral biodistribution, therapeutic efficacy, and safety, together with viral characteristics, host-related factors, and tumor-specific features,

including anatomical location, disease stage, and tumor microenvironment. Consequently, differences in therapeutic strategies and clinical or experimental conditions may influence treatment responses and the occurrence of adverse effects.

4. CONCLUSION

The integration of oncolytic virotherapy with immunotherapeutic approaches is emerging as one of the most promising strategies to disrupt the complex and aggressive biology of glioblastoma. The principal scientific merit of this combination lies in its ability to target and neutralize tumor stem cells, highly resistant subpopulations that orchestrate tumor recurrence, immune evasion, and conventional therapeutic failure.

Mechanistically, the action of oncolytic viruses (OVs) transcends mere lytic destruction of the tumor. By selectively infecting neoplastic cells, they induce a cell death response that triggers the release of damage-associated molecular patterns (DAMPs) and tumor antigens. This process acts as a potent biological signal that reverses the local immunosuppressive and tolerogenic profile, promoting the active infiltration of CD4⁺ T lymphocytes, CD8⁺ T lymphocytes, and NK cells.

Despite encouraging outcomes observed in vitro and in animal models, translating these combination regimens to clinical settings still faces complex biological and anatomical limitations.

Conflict of Interest

The authors declare no conflicts of interest.

REFERENCES

ABDULLAH, J. M.; MUSTAFA, Z.; IDERIS, A. Newcastle disease virus interaction in targeted therapy against proliferation and invasion pathways of glioblastoma multiforme. **BioMed Research International**, v. 2014, 386470, 2014.

AGOSTI, E. *et al.* Role of glioma stem cells in promoting tumor chemo- and radioresistance: A systematic review of potential targeted treatments. **World Journal of Stem Cells**, v. 16, n. 5, p. 604–614, 2024. DOI: 10.4252/wjsc.v16.i5.604.

AHMAD, Z. *et al.* Events in CNS tumor pathology post-2016 WHO CNS: cIMPACT-NOW updates and other advancements: a comprehensive review plus a summary of the salient features of 2021 WHO CNS 5. **International Journal of General Medicine**, v. 16, p. 107–127, 2023. DOI: <https://doi.org/10.2147/IJGM.S394872>.

ALONSO, M. M. *et al.* Targeting brain tumor stem cells with oncolytic adenoviruses. **Methods in Molecular Biology**, v. 797, p. 111–125, 2012. DOI: 10.1007/978-1-61779-340-0_9.

AN, Z. *et al.* Epidermal growth factor receptor and EGFRvIII in glioblastoma: signaling pathways and targeted therapies. **Oncogene**, v. 37, p. 1561–1575, 2018.

APPOLLONI, Irene *et al.* Specificity, safety, efficacy of EGFRvIII-retargeted oncolytic HSV for xenotransplanted human glioblastoma. **Viruses**, v. 13, n. 9, p. 1677, 2021. DOI: 10.3390/v13091677.

ASIJA, S. *et al.* Oncolytic immunovirotherapy for high-grade gliomas: a novel and an evolving therapeutic option. **Frontiers in**

Immunology, v. 14, p. 1118246, 2023. DOI: <https://doi.org/10.3389/fimmu.2023.1118246>.

BI, Shiwen *et al.* Advancements on the synergistic application of oncolytic viruses and molecularly targeted therapies for the treatment of solid tumors (Review). **International Journal of Oncology**, v. 68, n. 2, art. 25, 2026. DOI: 10.3892/ijo.2025.5838.

BROWN, Michael C. *et al.* Cancer immunotherapy with recombinant poliovirus induces IFN-dominant activation of dendritic cells and tumor antigen-specific CTLs. **Science Translational Medicine**, v. 9, n. 408, eaan4220, 2017. DOI: 10.1126/scitranslmed.aan4220.

CHU, Xianjing *et al.* Cancer stem cells: advances in knowledge and implications for cancer therapy. **Signal Transduction and Targeted Therapy**, v. 9, n. 1, art. 170, 2024. DOI: 10.1038/s41392-024-01851-y.

ENE, C. I.; FUEYO, J.; LANG, F. F. Delta-24 adenoviral therapy for glioblastoma: evolution from the bench to bedside and future considerations. **Neurosurgical Focus**, v. 50, n. 2, e6, 2021. DOI: 10.3171/2020.11.FOCUS20853.

FARES, J. *et al.* Neural stem cell delivery of an oncolytic adenovirus in newly diagnosed malignant glioma: a first-in-human, phase 1, dose-escalation trial. **The Lancet Oncology**, v. 22, n. 8, p. 1103-1114, 2021. DOI: 10.1016/S1470-2045(21)00245-X.

FRANCIPANE, Maria Giovanna *et al.* Zika virus: a new therapeutic candidate for glioblastoma treatment. **International Journal of Molecular Sciences**, v. 22, n. 20, p. 10996, 2021. DOI: 10.3390/ijms222010996.

GINTING, T. E. *et al.* Antiviral interferons induced by Newcastle disease virus (NDV) drive a tumor-selective apoptosis. **Scientific Reports**, v. 9, 15160, 2019.

HAMAD, A. *et al.* Recent developments in glioblastoma therapy: oncolytic viruses and emerging future strategies. **Viruses**, v. 15, n. 2, p. 547, 2023. DOI: <https://doi.org/10.3390/v15020547>.

HU, Mingming *et al.* Advances in oncolytic herpes simplex virus and adenovirus therapy for recurrent glioma. **Frontiers in Immunology**, v. 14, 1285113, 2023b. DOI: 10.3389/fimmu.2023.1285113.

HU, Z. *et al.* Reshaping the immunosuppressive glioma microenvironment: mechanisms, biomarkers, and emerging immunotherapies. **Frontiers in Immunology**, v. 17, art. 1819951, 2026. DOI: 10.3389/fimmu.2026.1819951.

HUANG, J. *et al.* Interleukin-7-loaded oncolytic adenovirus improves CAR-T cell therapy for glioblastoma. **Cancer Immunology, Immunotherapy**, v. 70, n. 9, p. 2453–2465, 2021. DOI: 10.1007/s00262-021-02856-0.

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC). **Global Cancer Observatory**. Lyon: IARC, 2024. Disponível em: <https://gco.iarc.who.int/en>. Acesso em: 26 maio 2026.

KARDANI, Kimia; SANCHEZ GIL, Judit; RABKIN, Samuel D. Oncolytic herpes simplex viruses for the treatment of glioma and targeting glioblastoma stem-like cells. **Frontiers in Cellular and Infection Microbiology**, v. 13, 1206111, 2023. DOI: 10.3389/fcimb.2023.1206111.

KAUFMAN, Howard L.; KOHLHAPP, Frederick J.; ZLOZA, Andrew. Oncolytic viruses: a new class of immunotherapy drugs. **Nature Reviews Drug Discovery**, v. 15, n. 9, p. 660, 2016. DOI: 10.1038/nrd.2016.178.

KHAN, Alishba. A review of PVSRIPO as a treatment for glioblastoma. **International Journal of High School Research**, v. 5, n. 5, p. 10–13, 2023. DOI: 10.36838/v5i5.2.

KIM, Dongwook *et al.* Optimization of SOX2 expression for enhanced glioblastoma stem cell virotherapy. **Symmetry**, v. 16, n. 9, p. 1186, 2024. DOI: 10.3390/sym16091186.

KIYOKAWA, Juri; WAKIMOTO, Hiroaki. Preclinical and clinical development of oncolytic adenovirus for the treatment of malignant glioma. **Oncolytic Virotherapy**, v. 8, p. 27-37, 2019. DOI: 10.2147/OV.S196403.

KOWALSKY, S. J. *et al.* Superagonist IL-15-armed oncolytic virus elicits potent antitumor immunity and therapy that are enhanced with PD-1 blockade. **Molecular Therapy**, v. 26, n. 10, p. 2476–2486, 2018.

LANG, Frederick F. *et al.* Phase I study of DNX-2401 (Delta-24-RGD) oncolytic adenovirus: replication and immunotherapeutic effects in recurrent malignant glioma. **Journal of Clinical Oncology**, v. 36, n. 14, p. 1419-1427, 2018. DOI: 10.1200/JCO.2017.75.8219.

LEE, N. *et al.* Generation of novel oncolytic vaccinia virus with improved intravenous efficacy through protection against complement-mediated lysis and evasion of neutralization by vaccinia virus-specific antibodies. **Journal for ImmunoTherapy of Cancer**, v. 11, e006024, 2023.

LEMOS DE MATOS, A.; FRANCO, L. S.; MCFADDEN, G. Oncolytic viruses and the immune system: the dynamic duo. **Molecular Therapy – Methods & Clinical Development**, v. 17, p. 349–358, 2020.

LI, Dongyang; ZHANG, Xinyue; DU, Yanwei. Macrophage-based therapeutic strategies in glioblastoma: advancements in drug delivery and immunotherapy. **Frontiers in Oncology**, v. 16, art. 1746344, 2026. DOI: 10.3389/fonc.2026.1746344.

LING, A. L. *et al.* Clinical trial links oncolytic immunoactivation to survival in glioblastoma. **Nature**, v. 623, p. 157–166, 2023.

LIU, B. L. *et al.* The herpes simplex virus deleted ICP34.5 with enhanced oncolytic, immunostimulatory and antitumour properties. **Gene Therapy**, v. 10, p. 292–303, 2003.

LIU, J. *et al.* Immunosuppressive cells in oncolytic virotherapy for glioma: challenges and solutions. **Frontiers in Cellular and Infection Microbiology**, v. 13, p. 1141034, 2023. DOI: <https://doi.org/10.3389/fcimb.2023.1141034>.

LIU, Jiayu *et al.* Oncolytic Viruses in Glioblastoma: Clinical Progress, Mechanistic Insights, and Future Therapeutic Directions. **Cancers**, v. 17, n. 24, p. 3948, 2025. DOI: 10.3390/cancers17243948.

LUN, Xueqing *et al.* Myxoma virus is a novel oncolytic virus with significant antitumor activity against experimental human gliomas. **Cancer Research**, v. 65, n. 21, p. 9982–9990, 2005. DOI: 10.1158/0008-5472.CAN-05-1201.

MAROUN, J. *et al.* Designing and building oncolytic viruses. **Future Virology**, v. 12, p. 193–213, 2017.

MENOTTI, L. *et al.* HSV as a platform for the generation of retargeted, armed, and reporter-expressing oncolytic viruses. **Viruses**, v. 10, n. 7, p. 352, 2018.

NASSIRI, Farshad *et al.* Oncolytic DNX-2401 virotherapy plus pembrolizumab in recurrent glioblastoma: a phase 1/2 trial. **Nature Medicine**, v. 29, n. 6, p. 1370–1378, 2023. DOI: 10.1038/s41591-023-02347-y.

NOVAES, G. M. *et al.* Genetically modified ZIKA virus as a microRNA-sensitive oncolytic virus against central nervous system tumors. **Molecular Therapy**, v. 32, n. 2, p. 440–456, 2024. DOI: 10.1016/j.ymthe.2024.01.006.

NUNES, P. R. *et al.* Glioblastoma multiforme: Recent therapeutic advances and the current role of surgery in integrated management. **Research, Society and Development**, v. 14, n. 3, e48572, 2025. Disponível em: <http://doi.org/10.33448/rsd-v14i3.48572>. Acesso em: 26 maio 2026.

PHILLIPS, Matthew B. *et al.* Current understanding of reovirus oncolysis mechanisms. **Oncolytic Virotherapy**, v. 7, p. 53-63, 2018. DOI: 10.2147/OV.S143808.

REALE, A. *et al.* An oncolytic HSV-1 vector induces a therapeutic adaptive immune response against glioblastoma. **Journal of Translational Medicine**, v. 22, n. 1, art. 862, 2024. DOI: 10.1186/s12967-024-05650-5.

REALE, A. *et al.* Perspectives on immunotherapy via oncolytic viruses. **Infectious Agents and Cancer**, v. 14, p. 5, 2019.

SAMSON, A. *et al.* Intravenous delivery of oncolytic reovirus to brain tumor patients immunologically primes for subsequent checkpoint blockade. **Science Translational Medicine**, v. 10, n. 422, 2018. DOI: 10.1126/scitranslmed.aam7577.

SANTILLÁN-GUAJÁN, S. M.; SHAHI, M. H.; CASTRESANA, J. S. Mesenchymal-stem-cell-based therapy against gliomas. **Cells**, v. 13, n. 7, art. 617, 2024. DOI: 10.3390/cells13070617.

STUPP, Roger *et al.* Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. **New England Journal of Medicine**, v. 352, n. 10, p. 987–996, 2005. DOI: 10.1056/NEJMoa043330.

SU, Hai *et al.* Overcoming immune evasion with innovative multi-target approaches for glioblastoma. **Frontiers in Immunology**, v. 16, art. 1541467, 2025. DOI: 10.3389/fimmu.2025.1541467.

SUN, Rui; KIM, Albert H. The multifaceted mechanisms of malignant glioblastoma progression and clinical implications. **CancerandMetastasis Reviews**, v. 41, n. 4, p. 871–898, 2022. DOI: 10.1007/s10555-022-10051-5.

SURYAWANSHI, Y. R.; SCHULZE, A. J. Oncolytic viruses for malignant glioma: on the verge of success? **Viruses**, v. 13, 1294, 2021.

TANG, Bingtao *et al.* Synergistic combination of oncolytic virotherapy and immunotherapy for glioma. **Clinical Cancer Research**, v. 26, n. 9, p. 2216–2230, 2020. DOI: 10.1158/1078-0432.CCR-18-3626.

TANG, Justin; AL AMIN, Md. Al; CAMPIAN, Jian. Glioblastoma stem cells at the nexus of tumor heterogeneity, immune evasion, and

therapeutic resistance. **Preprints**, 2025. DOI: 10.20944/preprints202503.1215.v1.

TANG, X. *et al.* Targeting glioblastoma stem cells: a review on biomarkers, signal pathways and targeted therapy. **Frontiers in Oncology**, v. 11, p. 701291, 2021. DOI: <https://doi.org/10.3389/fonc.2021.701291>.

TODO, T. *et al.* Intratumoral oncolytic herpes virus G47 Δ for residual or recurrent glioblastoma: a phase 2 trial. **Nature Medicine**, v. 28, p. 1630-1639, 2022. DOI: <https://doi.org/10.1038/s41591-022-01897-x>.

TOSIC, V.; THOMAS, D. L.; KRANZ, D. M.; *et al.* Myxoma virus expressing a fusion protein of interleukin-15 (IL15) and IL15 receptor alpha has enhanced antitumor activity. **PLoS ONE**, v. 9, n. 10, e109801, 2014.

VAN PUTTEN, Erik H. P. *et al.* Convection enhanced delivery of the oncolytic adenovirus Delta24-RGD in patients with recurrent GBM: a phase I clinical trial including correlative studies. **Clinical CancerResearch**, v. 28, n. 8, p. 1572-1585, 2022. DOI: 10.1158/1078-0432.CCR-21-3324.

VICTORIO, Carla Bianca Luena *et al.* Repurposing of Zika virus live-attenuated vaccine (ZIKV-LAV) strains as oncolytic viruses targeting human glioblastoma multiforme cells. **Journal of Translational Medicine**, v. 22, n. 1, p. 126, 2024. DOI: 10.1186/s12967-024-04930-4.

WANG, Xuan; LI, Xudong; JIANG, Xiaobing. Blood-brain barrier heterogeneity in NRG BN007: implications for immunotherapy delivery. **Journal of Clinical Oncology**, v. 44, n. 13, p. 1266, 2026. DOI: 10.1200/JCO-25-01988.

WEN, P. Y.; KESARI, S. Malignant gliomas in adults. **New England Journal of Medicine**, v. 359, n. 5, p. 492–507, 2008. DOI: 10.1056/NEJMra0708126.

ZHOU, Yichen *et al.* An update on the clinical trial research of immunotherapy for glioblastoma. **Frontiers in Immunology**, v. 16, 1582296, 2025. DOI: 10.3389/fimmu.2025.1582296.

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