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REVIEW

Optimizing Oncolytic Virotherapy for Malignant Glioma: From Bench to Bedside

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Abstract: Malignant glioma is a highly aggressive brain tumor characterized by frequent recurrence, poor prognosis, and limited responsiveness to standard therapies. Glioblastoma multiforme, the most common and aggressive subtype, further complicates treatment due to its infiltrative nature, genetic heterogeneity, the protective blood-brain barrier, and an immunosuppressive microenvironment. Despite aggressive treatment strategies such as surgical resection combined with chemoradiotherapy, the median survival for malignant glioma patients remains low, highlighting the urgent need for more effective therapeutic approaches. Oncolytic virotherapy (OVT), a dual-modality approach that combines immunotherapy and biotherapy, has emerged as a promising alternative. Oncolytic viruses (OVs) can replicate continuously, disseminate within the tumor, and stimulate anti-tumor immunity, offering distinct advantages in targeting invasive and immunologically "cold" malignant glioma. However, the efficacy of OVT in clinical trials remains unsatisfactory, particularly in single-agent regimens. This limitation is primarily attributed to the viruses' limited replication efficiency, suboptimal immune induction, premature clearance by antiviral immune responses, and the blood-brain barrier, which impedes effective intracranial delivery. Thus, further optimization of viral modifications, delivery systems, and treatment regimens is critical to enhancing therapeutic potency before OVT can become a standard therapy for malignant glioma. This review systematically summarizes current strategies for enhancing OVs, including genetic engineering, chemical functionalization, and carrier-based delivery. Furthermore, it highlights combination therapies that aim to synergistically enhance therapeutic efficacy through chemotherapy, radiotherapy, and immunotherapy. Finally, the review emphasizes recent clinical trials leveraging these enhancement strategies, aiming to offer novel insights for translating OVs from research to clinical practice.

Keywords: oncolytic viruses, glioma, genetic engineering, chemical modification, carrier delivery, combination therapy

Introduction

Malignant glioma is the most common primary malignant brain tumor in adults and is associated with a poor prognosis.[1] The standard treatment currently involves surgical resection, followed by radiotherapy and temozolomide (TMZ)-based chemotherapy.[2] Although surgery is the preferred initial treatment, complete removal is usually impossible because the tumor tends to infiltrate surrounding functional brain tissue, and its margins are poorly defined.[3] As a result, microscopic tumor cells are often left behind, leading to high local recurrence rates. For instance, in glioblastoma multiforme (GBM), a World Health Organization grade IV glioma, over 90% of patients experience recurrence within 2–3 cm of the original tumor margin.[4] Radiotherapy offers significant survival advantages and serves as the primary treatment modality for unresectable glioma.[5] However, its clinical application is constrained by the risks of radiation necrosis in healthy brain tissue and permanent neuronal damage.[6,7] To minimize toxicity, clinicians often restrict the radiation dose, which can compromise tumor control.[8] TMZ possesses demonstrated efficacy, but its benefits are constrained by the blood-brain barrier (BBB), which limits drug delivery into the brain, and by resistance mechanisms inherent to the tumor.[9]

Limitations in traditional delivery methods emphasize the urgent need for innovative therapies capable of overcoming these barriers. One promising approach is oncolytic virotherapy (OVT), which has gained significant research interest for treating malignant glioma.[10] Virus has affected glioma treatment and management by impacting multiple organ systems.[11] Oncolytic viruses (OVs) are genetically engineered or attenuated viruses designed to selectively target and

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kill cancer cells. They achieve this by exploiting virus-specific receptors on tumor cells, tumor-specific promoters, and vulnerabilities such as defective tumor suppressor pathways.[12,13] The effectiveness of OVs primarily relies on two mechanisms: direct oncolysis and the induction of antitumor immunity. Upon infection, OVs replicate continuously, ultimately triggering cell death through structural disruption and inhibition of host protein synthesis. Subsequent release of viral progeny facilitates infection of surrounding tumor cells, enabling progressive elimination. Concurrently, damage-associated molecular patterns (DAMPs) and tumor associated antigens (TAA) released from lysed tumor cells trigger antitumor immunity.[14,15] This dual mechanism is particularly advantageous for GBM, which often exhibits resistance to conventional therapies and profound immunosuppression.[16,17] Importantly, OVs tend to have a favorable safety profile, with most side effects being mild and self-limiting, supporting their clinical development and potential in combination or maintenance therapies.[18,19]

Despite these theoretical advantages, the clinical translation of OVT for malignant glioma faces challenges, primarily due to its insufficient efficacy. Current delivery strategies of OVs mainly involve intravenous administration and intratumor injection.[13] While intravenous delivery attracts considerable attention due to its minimally invasive nature, standardized protocols, and procedural simplicity, its effectiveness is severely constrained by antiviral immunity, such as preexisting neutralizing antibodies and innate immune cells.[20] Furthermore, the BBB further limits this approach by preventing OVs from effectively penetrating into the brain.[21] Intratumor injection circumvents BBB limitations and minimizes systemic immune interference, making it the dominant clinical approach, despite its high invasiveness, technical challenges, and poor repeatability. Nevertheless, elevated intratumor pressure and dense extracellular matrix barriers hinder the diffusion of the virus.[22,23] Importantly, the inherent therapeutic efficacy of OVs is suboptimal, with replication efficiencies insufficient to induce a robust antitumor immune response. The development of optimized intratumor and intravenous delivery platforms, along with enhancing the intrinsic therapeutic efficacy of OVs, represents a critical priority. Notably, individual variability and the heterogeneity of malignant gliomas frequently constrain the clinical applicability of single-agent virotherapies, manifesting as a limited beneficiary population and restricted long-term efficacy, thereby underscoring the critical need for synergistic approaches to comprehensively address these challenges.[24]

This review systematically summarizes strategies to improve the effectiveness of OVT, including genetic engineering, chemical modifications, carrier-based delivery, and combination therapies (Figure 1). We also review recent clinical trials and confirm the translational potential of these approaches. Future prospects and challenges are discussed to outline a translational roadmap for developing more effective OVT strategies against malignant glioma.

Genetic Engineering of OVs

Genetic engineering serves as a primary strategy for modifying OVs to enhance both safety and efficacy. Currently, extensive research has focused on optimizing OVs safety through several principal approaches, including deletion of viral virulence genes to generate attenuated strains, removal of genes essential for viral replication in normal cells, and incorporation of tumor-specific promoters to ensure selective replication within tumor cells.[25,26] These modifications have significantly improved the safety of OVT, with observed adverse effects typically being self-limiting and clinically manageable.[27,28] While safety has been well-established, the therapeutic efficacy of OVs in malignant glioma treatment remains limited due to the insufficient tumor targeting leading to non-specific dissemination, the inadequate oncolytic capacity to eliminate tumor cells, and the suboptimal induction to activate effective antitumor immunity. Apparently, enhancing therapeutic efficacy has emerged as the main objective in malignant glioma treatment. In the following sections, we outline fundamental genetic engineering strategies employed to address these key limitations and augment the antitumor efficacy of OVs, and discuss their effectiveness in preclinical studies.

Precise tumor targeting is the foundational requirement for optimizing OVT,[25] where genetic modifications aim to restrict viral tropism to cancer tissues while minimizing damage to adjacent normal tissues.[29] Receptor retargeting represents one of the primary approaches to enhance viral specificity and efficacy, achieved through structural modifications of viral surface proteins to redirect binding toward glioma-specific receptors.[30] Based on this strategy, Irene et al evaluated the efficacy of R-613, an oncolytic herpes simplex virus (oHSV) genetically engineered to express an EGFRvIII-targeting peptide.[31] EGFRvIII, a variant of the epidermal growth factor receptor (EGFR) containing a GBM-

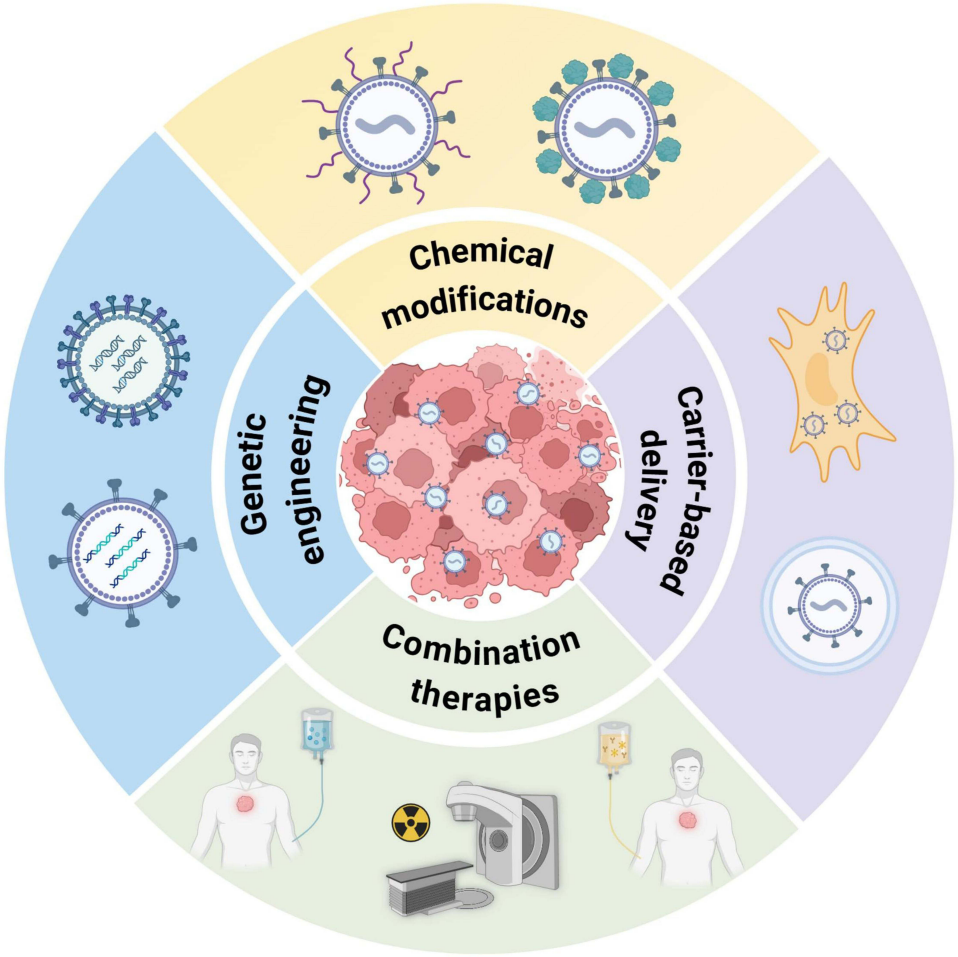

Figure 1 Strategies to enhance OVT efficacy: genetic engineering, chemical modifications, carrier-based delivery, and combination therapies. Created in BioRender. Xinbo, Y. (2025) https://BioRender.com/ml7a1va.

associated mutation,[32] confers R-613 with highly specific tropism toward EGFRvIII-expressing GBM cells. The experimental results revealed that R-613 achieved precise tumor-specific localization, with accumulation predominantly observed in tumor tissues while maintaining minimal off-target effects in normal tissues. Notably, neither viral encephalitis nor any trace of viral presence outside the injection site was detected. In terms of therapeutic efficacy, mice treated with R-613 demonstrated significantly delayed tumor progression compared to those receiving the wild-type virus. Moreover, the R-613 treatment group exhibited a median survival of 114 days, representing a substantial improvement over the 81 days observed in wild-type virus-treated controls.

While targeting ensures viral accumulation within tumors, therapeutic success relies on the development of multimodal cytotoxic mechanisms capable of effectively lysing tumor cells. To address the limited innate oncolytic capacity of wild viruses against highly heterogeneous glioma cells, arming OVs with exogenous cytotoxic gene has emerged as a predominant approach.[26,33] Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL), a member of the TNF superfamily, can selectively induce apoptosis in cancer cells by binding to death receptors (DR4/DR5) on their surface while sparing normal cells.[34,35] Based on this mechanism, He et al constructed a recombinant Newcastle disease virus (NDV) Anhinga strain by inserting the TRAIL gene (NDV/Anh-TRAIL), to enhance its cytotoxicity against glioma cells.[36] In vitro experiments demonstrated that NDV/Anh-TRAIL induced a total apoptosis rate in U251 glioma cells nearly 20% higher than that observed in wild-type NDV-treated cells. In addition, in vivo studies revealed that the average tumor volume in the NDV/Anh-TRAIL treatment group was significantly smaller than that in the wild NDV group. Notably, the wild-type NDV group exhibited an average tumor volume of 205.03 mm^3 compared to only

97.21 mm³ in the NDV/Anh-TRAIL group, suggesting the significantly enhanced cytotoxicity and therapeutic efficacy of NDV/Anh-TRAIL against glioma.

Enhancing targeting specificity and oncolytic capacity significantly improve local oncolysis efficacy.[37] However, the highly immunosuppressive microenvironment of gliomas restricts the activation of antitumor immunity following oncolysis, thereby limiting the potential for comprehensive and sustained therapeutic outcomes.[38] Engineered viruses incorporating diverse immunomodulatory genes have emerged as a promising solution to reprogram the tumor microenvironment (TME). Interleukin-12 (IL-12), a multifunctional cytokine capable of activating multiple immune effectors including natural killer (NK) cells and T lymphocytes, serves as a potent enhancer of antitumor immunity.[39,40] Hiroshi et al developed a HSV-1 G47Δ variant by integrating the human IL-12 gene as a fusion peptide (T-hIL12) to amplify antitumor immune responses (Figure 2A).[41] Compared to the control group treated with T-01 (a HSV-1 carrying an empty shuttle vector cassette), the T-hIL12 group demonstrated elevated IL-12 expression levels and enhanced infiltration of CD4+ and CD8+ cytotoxic T lymphocytes (CTLs) within tumor tissues (Figure 2B–D). Furthermore, the concurrent increase of interferon gamma levels in T-hIL12-treated mice suggested functional activation of these immune cells. As anticipated, the T-hIL12 group exhibited significantly reduced tumor volumes compared to the controls, with therapeutic effects observed both at the treated site and at distant, untreated tumor sites, thereby demonstrating the effective induction of localized and systemic antitumor immunity (Figure 2E).

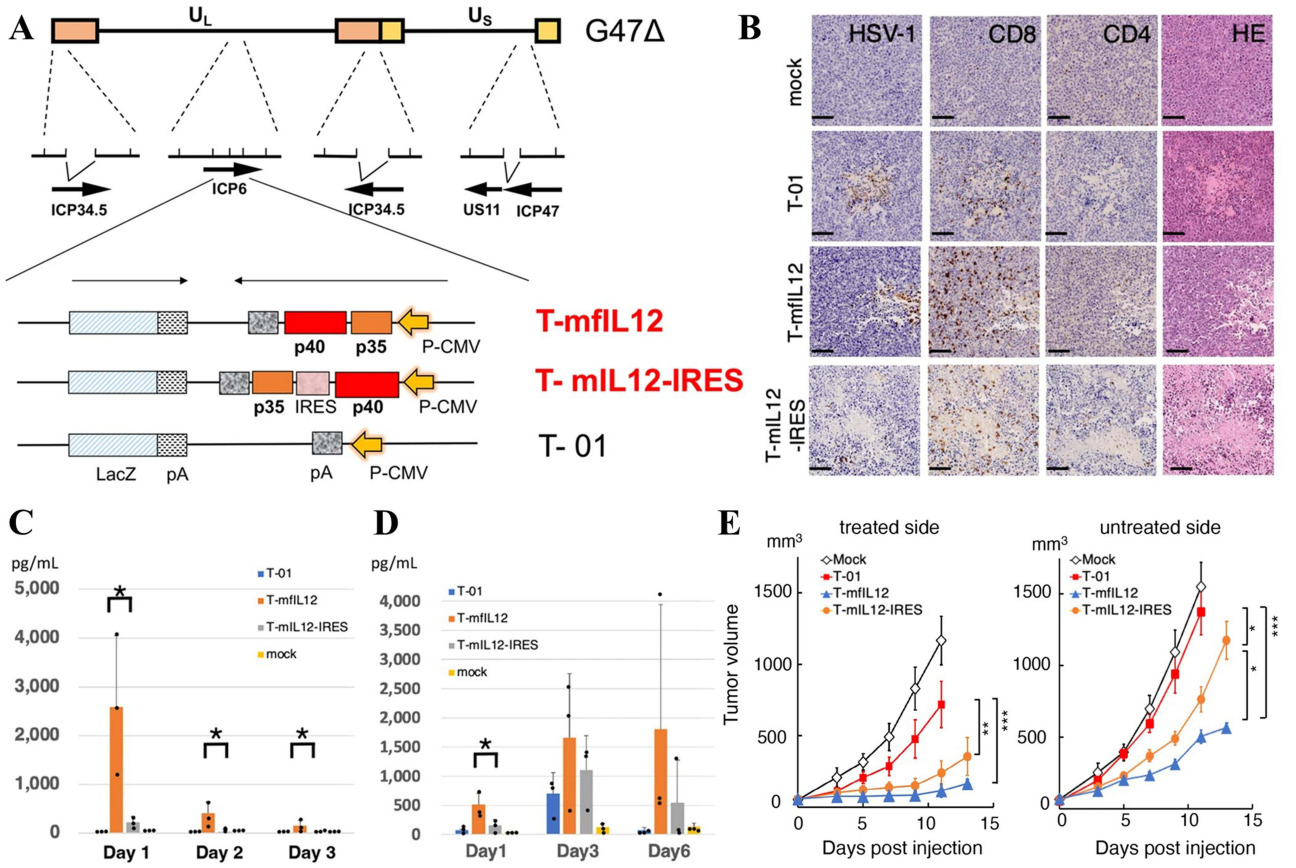

Figure 2 (**A**) Schematic of T-mfIL12 and T-mIL12-IRES structures. (**B**) H&E-stained GBM from mice under different treatments. The levels of IL-12 (**C**) and INF-γ (**D**) in tumor under different treatments. *p < 0.05; **p < 0.01; NS, not significant; one-way ANOVA with Tukey's multiple comparisons. (**E**) Tumor volume at the treated and untreated sites under different treatments.*p < 0.05; **p < 0.01; ***p < 0.001; Two-way ANOVA with Bonferroni's multiple comparisons test. Reproduced from Fukuhara H, Sato YT, Hou J, Iwai M, Todo T. Fusion peptide is superior to co-expressing subunits for arming oncolytic herpes virus with interleukin 12. Communicat Med. 2023;3(1):40. http://creativecommons.org/licenses/by/4.0/.[41]

Chemical Modifications of OVs

Chemical modification has recently emerged as a pivotal non-genetic engineering strategy to enhance the therapeutic efficacy of OVs. Through covalent or non-covalent conjugation, bioactive molecules, such as polymers, antibodies, peptides, or drug, are anchored to viral surfaces, thereby endowing OVs with augmented biological properties (Table 1).[42] These enhancements encompass improved circulatory stability, BBB penetrability, and antitumor efficacy from the loading drugs.[43,44] In the next sections, we provide a concise discussion of these chemical modification strategies, emphasizing the advantages they confer to OVs in glioma therapy.

Polyethylene glycol (PEG) is one of the most extensively utilized biocompatible polymers in biomedical engineering. Its conjugation significantly enhances the pharmacokinetic profile, optimizes pharmacodynamic behavior, and attenuates immunological clearance, ultimately contributing to enhanced therapeutic efficacy of OVs.[55] RVG29, a 29-amino acid peptide derived from rabies virus glycoprotein (RVG), can selectively bind to nicotinic acetylcholine receptors that are abundantly expressed on both cerebral microvascular endothelial cells and neurons.[56] This unique targeting property enables its efficient BBB penetration through receptor-associated transcytotic mechanisms. Building upon these, Chen et al engineered a dual-functionalized HSV-2 (OH2) through conjugation with both RVG29 and PEG, designated OH2-PEG-RVG, enabling enhanced BBB penetration and blood circulation.[43] As expected, OH2-PEG-RVG exhibited significantly prolonged blood circulation time and enhanced accumulation in tumor and brain compared to the control group (OH2). Importantly, OH2-PEG-RVG demonstrated superior antitumor efficacy, achieving a 60-day survival rate of

Table 1 Summary of Recent Chemical Modifications of OVs

Oncolytic Virus	Methods	Polymer	Efficacy	Ref.
OH2-PEG-RVG	Chemical conjugation	PEG-RVG	Improved circulatory stability; Improved BBB penetrability; Enhanced antitumor efficacy.	[43]
PD-1/Al@OV(Ad)	Electrostatic interaction	PD-1, Al	Improved circulatory stability; Improved BBB penetrability; Enhanced antitumor efficacy.	[44]
VSV–porphyrin	Chemical conjugation	Protoporphyrin IX	Improved circulatory stability; Improved BBB penetrability; Enhanced antitumor efficacy.	[45]
Ad/chitosan–PEG–FA	Electrostatic interaction	Chitosan-PEG-FA	Improved circulatory stability; Enhanced tumor targeting	[46]
YKL-1001-ABP	Chemical conjugation	ABP	Improved circulatory stability; Enhanced tumor targeting	[47]
RdB/shVEGF-PPCBA	Electrostatic interaction	PPCBA	Improved circulatory stability; Enhanced tumor targeting	[48]
DWP418-PEG-HER	Chemical conjugation	PEG-HER	Improved circulatory stability; Enhanced tumor targeting	[49]
ΔB7-U6shIL8-PNLG	Electrostatic interaction	PNLG	Improved circulatory stability; Enhanced antitumor efficacy	[50]
DWP418-PPSA	Electrostatic interaction	PPSA	Improved circulatory stability; Enhanced antitumor efficacy	[51]
Ad5-PAMAM-G2-PEG-GE11	Chemical conjugation	PAMAM-G2-PEG-GE11	Improved circulatory stability; Enhanced antitumor efficacy	[52]
oAd-PEG-PTX	Chemical conjugation	PEG-PTX	Improved circulatory stability; Enhanced antitumor efficacy	[53]
OVV-Luc@Ce6	Chemical conjugation	Chlorin e6	Improved circulatory stability; Enhanced antitumor efficacy.	[54]

Abbreviations: OH2, Oncolytic herpes simplex virus type 2; PEG, polyethylene glycol; RVG, rabies virus glycoprotein; Al, alendronate; OV, oncolytic virus; VSV, vesicular stomatitis virus; FA, folic acid; ABP, arginine-grafted bioreducible polymer; PPCBA, pH-sensitive and bio-reducible polymer; HER, Herceptin; PNLG, poly{N-[N-(2-aminoethyl)-2-aminoethyl]-l-glutamate; PPSA, mPEG-PEI-*g*-arginine-S-S-arginine-*g*-PEI-mPEG; PAMAM, polyamidoamine dendrimer; PTX, paclitaxel; OVV-Luc, oncolytic vaccinia virus; Ce6, Chlorin e6.

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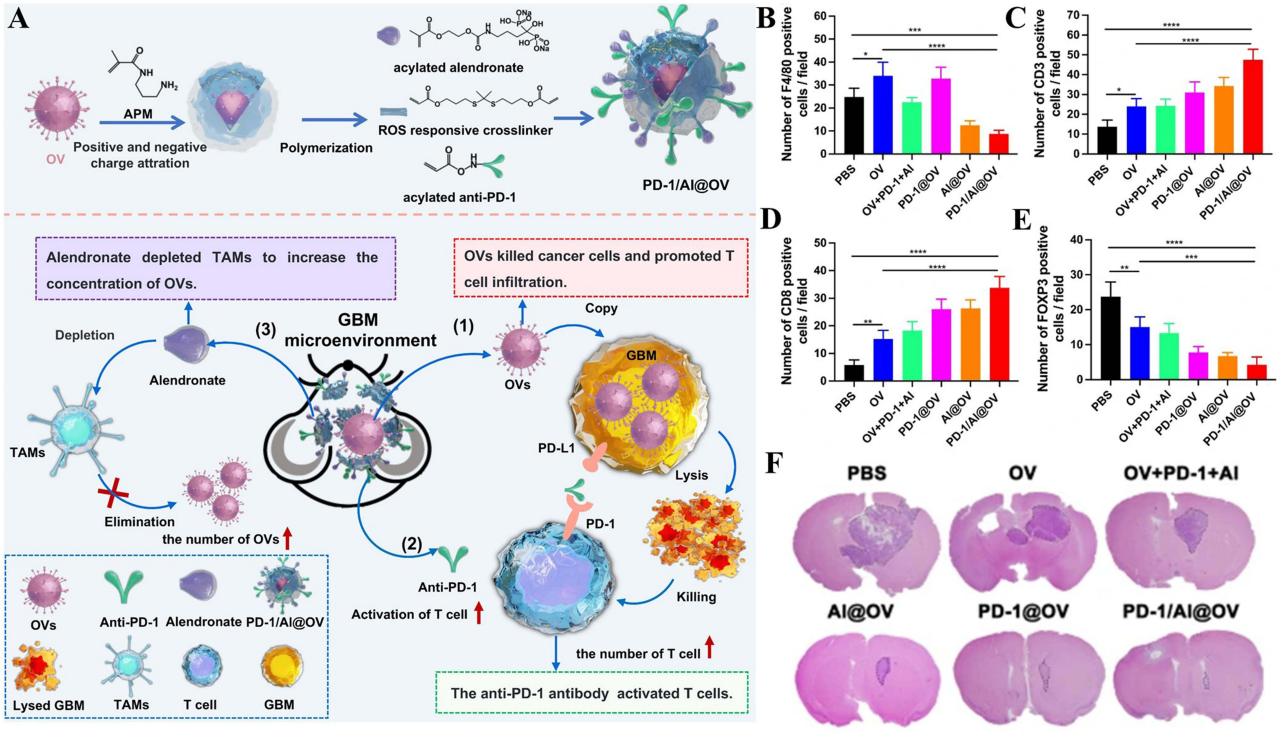

Figure 3 (**A**) Schematic of PD-1/Al@OV synthesis and its triple-modality antitumor mechanism. Quantitative analysis of F4/80-positive cells (**B**), CD3-positive cells (**C**), CD8-positive cells (**D**), FOXP3-positive cells (**E**) under different treatments. (**F**) H&E-stained coronal brain sections from mice with GBM under different treatments. *P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001; one-way ANOVA test. Reproduced from Zhu Y, Zhang X, Jin J, et al. Engineered oncolytic virus coated with anti-PD-1 and alendronate for ameliorating intratumoral T cell hypofunction. Exp Hematol Oncol. 2025;14(1):16. http://creativecommons.org/licenses/by/4.0/.[44] Copyright 2025, Springer Nature.

30% in treated mice, which exceeded the control group's maximum survival of approximately 40 days. The modified virus also maintained favorable biosafety and cerebral compatibility, without hematological abnormalities, histopathological organ damage, or behavioral alterations in treated mice.

In addition to enhancing efficacy through increased tumor accumulation, therapeutic agents can also be incorporated into OVs to achieve direct synergistic effects. In this context, Zhu et al coated OVs with anti-programmed cell death protein 1 (PD-1) antibodies (α-PD1) and alendronate using reactive oxygen species (ROS)-sensitive crosslinkers (PD-1/Al@OV) (Figure 3A).[44] The PD-1/Al@OV complex disassembles under high ROS conditions in tumors, releasing alendronate, OVs, and α-PD1. This triple combination strategy demonstrated remarkable therapeutic synergy. Specifically, alendronate suppressing the proliferation and function of tumor-associated macrophages (TAMs), increasing OVs concentration; OVs lyse tumor cells and promote T cells infiltration; and α-PD1 block the PD-1/PD-L1 pathway, enhancing the antitumor activity of T cells.[13,57,58] Results showed that compared to the control group (unmodified OVs), PD-1/Al@OV treatment significantly reduced the number of TAM (F4/80+ cells) and regulatory T cell (Treg, FOXP3+ cells), while increasing CD3+ T cell and CD8+ T cell infiltration in tumor (Figure 3B–E). Furthermore, PD-1/Al@OV exhibited superior therapeutic outcomes, achieving significant tumor growth inhibition (Figure 3F) and extending survival to 61 days versus 35 days in the control group. Importantly, the modified OVs maintained good biosafety profiles in vivo, without observable pathological damage or hematological abnormalities. Similarly, Nazarenko et al innovatively engineered a conjugation by covalently linking protoporphyrin IX with vesicular stomatitis virus, establishing a dual-modal oncolytic system combining photodynamic therapy and virotherapy.[45] Remarkably, this synergistic system achieved significant tumor cell death with a low viral titer (10^3-10^4 $TCID_{50}$/mL) and porphyrin concentration (0.5 μg/mL). This optimized combinatorial approach not only minimizes the required therapeutic doses compared to conventional OVT, but also enhances tumor cytotoxicity through the complementary mechanisms of viral replication and light-activated ROS generation.

Carrier-Based Delivery of OVs

The therapeutic potential of OVs is frequently limited by multiple biological barriers, including host immune clearance, inadequate tumor targeting, and inefficient BBB penetration and cerebral parenchymal diffusion.[13] To circumvent these critical limitations and enhance viral delivery precision, innovative carrier-based delivery systems have emerged as promising solutions. Recent preclinical studies have demonstrated that some vehicles, such as cell carriers and nanoparticles, can effectively encapsulate or conjugate OVs and achieve remarkable improvements in tumor-specific accumulation and therapeutic efficacy.[59,60] Cell carriers, primarily stem cells including neural stem cells (NSCs), mesenchymal stem cells (MSCs), and adipose-derived stem cells, are favored for their intrinsic tumor-tropic migratory capabilities, ability to cross the BBB, and immune-evasive properties. These cells naturally respond to tumor-associated signals, such as chemokines, enabling targeted delivery of OVs to glioma sites.[61,62] In contrast, nanoparticle-based carriers—such as nanocapsules and polymeric systems—offer an engineered approach, enhancing BBB penetration and facilitating tumor-specific release.[63,64] In the following sections, we review recent advances of carrier-based delivery of OVs for malignant glioma treatment.

Cell-based delivery systems have gained considerable attention due to their natural biocompatibility, tumor tropism, and immune-evasive properties.[65] Several promising cell carriers, including mesenchymal stem cells (MSCs), adipose-derived stem cells, and neural stem cells (NSCs), have been extensively investigated for their safety and delivery efficiency.[59,66,67] For instance, Wang et al developed mouse bone marrow-derived MSCs (BM-MSCs)-loaded Ad5 (MSC-Ad5) complexes to enhance oncolytic adenovirus (oAd) therapy in GBM. These MSCs demonstrate intrinsic tumor tropism while protecting the encapsulated oAd from host immune clearance.[68] Compared to previous attempts with high-dose intratumor virus injection, MSCs carrying reduced viral loads demonstrated significantly enhanced therapeutic efficacy. Notably, intratumor administration of MSC-Ad5 exhibited superior tumor growth suppression compared to equivalent Ad5 doses alone. Beyond whole-cell carriers, subcellular components like cell membranes have been strategically utilized. Both NSC membranes (NCM) and GBM cell membranes (GCM) possess BBB penetration ability, and tumor targeting specificity.[69,70] Based on these properties, Jia et al engineered oAd coated with either NCM or GCM, termed NCM-Ad and GCM-Ad, respectively (Figure 4A).[21] Results demonstrated that NCM-Ad and GCM-Ad effectively traversed the BBB and selectively infect GBM cells. Moreover, regardless of whether the administration was intratumor or intravenous, the membrane-coated oAd groups exhibited a markedly higher accumulation of viral particles at the tumor site compared to the control group (single Ad5) (Figure 4B and C).

Nanocarriers, owing to their tunable physicochemical properties and versatile modification potential, have emerged as crucial tools for delivering OVs.[72] He et al developed an innovative colloidal nanocarrier system incorporating matrix metalloproteinase-2 (MMP-2) substrate (MS) peptides and angiopep-2 (ANG) peptides, designed to encapsulate the recombinant enterovirus EV-A71-miR124T, named as EV71@AM (Figure 4D).[71] In the EV71@AM nanocapsule, ANG facilitates BBB penetration via transcytosis mediated by low-density lipoprotein receptor-related protein-1, a protein that is abundantly expressed in both the BBB and gliomas. Concurrently, the MMP-2 cleavage site in the MS peptide enables tumor-specific release of OVs through enzymatic cleavage by MMP-2, a protease overexpressed in the tumor microenvironment.[73,74] Additionally, since microRNA-124 (miR124) is abundantly expressed in normal brain tissue but markedly depleted in glioma, the modified EV-A71 was engineered with miR124 target sequences to further enhance its selective oncolytic capability.[75] In vivo studies demonstrated the therapeutic advantages of EV71@AM. Compared to the control group (EV-A71-miR124T), EV71@AM treatment led to increased viral accumulation in the brain, stronger tumor suppression, and improved survival rates (Figure 4E–G). Notably, EV71@AM displayed no hematologic toxicity or pathological organ injury, underscoring its excellent safety profile. In addition to colloidal nanocarrier, some nanoparticles exhibit unique advantages in viral delivery, as they not only encapsulate viruses to mask antigens but also leverage the enhanced permeability and retention effect to facilitate BBB penetration and tumor-targeted delivery of OVs.[76,77] Wang et al developed a tannic acid-ferric-based carrier for the systemic delivery of oAd (OA@TA-Fe^{3+}).[60] Beyond the fundamental roles of immune shielding and improved brain biodistribution, this system demonstrates TME-responsive therapeutic enhancement. Under acidic tumor conditions, Fe^{3+} is released and catalyze hydrogen peroxide decomposition via the Fenton reaction, generating ROS and oxygen.[77] This process not only amplifies oxidative stress

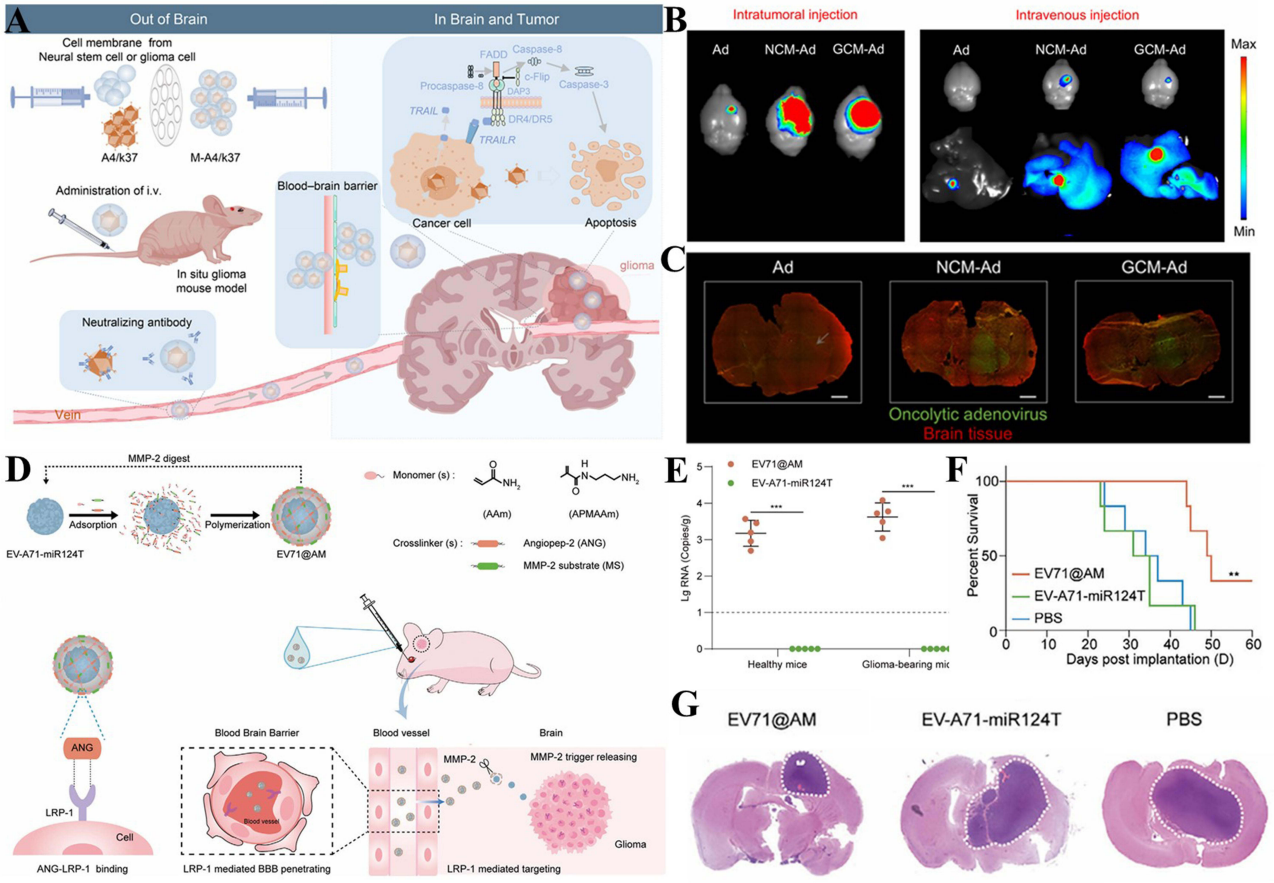

Figure 4 (**A**) Schematic of synthesis and antitumor mechanism of cell membrane-coated oAd. (**B**) Fluorescence imaging of different viruses 48 h after injection. (**C**) Immunofluorescence analysis of different viruses and tumor location. (**D**) Schematic of design and BBB penetration mechanism of EV71@AM. (**E**) Quantification of viral accumulation in brain tissue 48 h after injection of viruses under different treatments. (**F**) Survival curve of the glioma-bearing mice under different treatments. **p < 0.01; ***p < 0.001. (**G**) H&E-stained full-brain sections from the glioma-bearing mice under different treatments. Reproduced with permission from Jia X, Wang L, Feng X, et al. Cell membrane-coated oncolytic adenovirus for targeted treatment of Glioblastoma. Nano Lett. 2023;23(23):11120–11128.[21] Copyright 2023, American Chemical Society. Reproduced with permission from He Y, Li W, Zhang X, Cui Z. Oncolytic virus targeted therapy for Glioma via intravenous delivery. Adv Healthc Mater. 2025;14(7):e2404965. © 2025 Wiley-VCH GmbH.[71]

but also promotes oAd replication in the hypoxic TME, thereby reversing the immunosuppressive TME and enhancing antitumor efficacy. Results demonstrated that, compared to mice treated with naked oAd, intravenous administration of OA@TA-Fe^{3+} significantly inhibited GBM progression, consequently extending survival time.

Combination Treatment to Boost OVT Efficacy

Despite considerable progress in modification and delivery strategies to enhance the anti-tumor efficacy of OVs, their clinical benefits as monotherapies remain limited in malignant glioma.[78] This limitation stems from individual variations in immunological and genetic characteristics, tumor differences across subtypes and stages, and the highly heterogeneous nature of glioma itself. In contrast, combination therapies leverage synergistic effects to amplify antitumor efficacy while mitigating the inherent limitations of individual therapies. Such multimodal regimens have emerged as a foundational strategy to improve the efficacy of OVT for malignant glioma.[24] In the following sections, we discuss OVs-based combination strategies, including chemotherapy, radiotherapy, and immunotherapy, to outline a comprehensive and personalized therapeutic approach.

Currently, chemotherapy, particularly TMZ, remain a fundamental regimen in the treatment of malignant glioma.[9] While chemotherapy is theoretically capable of synergizing with OVT through inducing immunogenic cell death, a process whereby both chemotherapy and OVT damaged tumor cells release DAMPs and TAA to induce antitumor

immunity,[79] emerging evidence reveals complex interactions between these modalities. Contrary to expectations, Saha et al demonstrated that TMZ administration adversely affect the efficacy of immune-virotherapy in preclinical models.[80] Concurrent TMZ treatment with oHSV not only failed to improve survival in orthotopic GBM-bearing mice but also abrogated the therapeutic benefits of oHSV monotherapy. This adverse interaction was associated with TMZ-induced cytotoxic effect on locally activated immune cells, along with impaired viral replication efficiency potentially due to reduced efficiency of deoxyribonucleic acid (DNA) molecule production. Therefore, the optimal timing of combination therapy appears critical for achieving therapeutic synergy. Natalia et al found that most glioma cultures developed resistance when TMZ was administered 24 hours post-viral exposure, whereas delayed TMZ administration at 60 hours post-infection yielded a synergistic or additive effect.[81] This time-dependent interaction suggests that establishing an optimal therapeutic window, allowing sufficient viral replication and immune activation prior to chemotherapy, is essential for maximizing the efficacy of the combination therapy.

Radiotherapy remains a cornerstone in the management of malignant gliomas.[82] Beyond its direct cytotoxic effects through DNA strand breaks,[83] ionizing radiation induces immunogenic cell death characterized, thereby activating localized antitumor immune responses.[84,85] The therapeutic synergy between radiotherapy and OVs has emerged as a promising strategy to amplify these effects. OVs can inhibit various components of the DNA damage repair mechanism, such as the DNA repair proteins Rad50 and Mre11, thereby increasing radiation-induced DNA damage.[86] Concurrently, the immune-stimulating effects of OVs synergize with radiotherapy to enhance tumor infiltration of CD4+ helper T cells and CD8+ CTLs, effectively remodeling the immunosuppressive TME.[87,88] Storozynsky et al evaluated the effectiveness of vaccinia virus ΔF4LΔJ2R, engineered to depend on host cell dNTP synthesis for replication, in combination with radiotherapy for aggressive GBM.[89] The results showed the combination approach achieved a remarkable 66.7% cure rate in mice, significantly surpassing outcomes from radiotherapy alone (21.4%) or ΔF4LΔJ2R alone (13.3%). The dual-modality therapy not only improved local tumor control but also induced systemic antitumor immunity. Notably, 50% of cured mice (1/2) completely resisted secondary tumor implantation in the abdominal region, demonstrating the establishment of durable immunological memory.

Radiochemotherapy, leveraging the dual therapeutic mechanisms of radiotherapy-induced localized DNA damage and chemotherapy-induced systemic cytotoxicity, provides an optimal platform for synergistic combination with OVT. In a study on combination therapies for GBM, Alex et al demonstrated the therapeutic potential of recombinant oAd-loaded NSC (NSC-OV) in conjunction with radiotherapy and TMZ.[90] The results revealed that the multimodal approach achieved a significant 29% extension in median survival compared to radiotherapy-TMZ alone. Notably, temporal optimization of treatment sequencing emerged as a critical determinant of therapeutic outcomes. Preconditioning with NSC-OV 24 hours prior to radiotherapy-TMZ administration induced significantly higher levels of tumor cell apoptosis and cytotoxicity compared to reversed treatment sequences.

Current advances in glioma immunotherapy have highlighted the therapeutic potential of combining OVs with immune checkpoint inhibitors (ICIs) and chimeric antigen receptor (CAR)-T cell therapies.[91,92] While OVs lyse tumor cells to initiate antitumor immunity and enhance T-cell infiltration into the TME, they also induce the expression of PD-L1 on both cancer and immune cells within the TME, which suppresses T cell activation.[93] To overcome this challenge, combining OVs with ICIs such as α-PD1 have been explored. Sun et al utilized a recombinant vaccinia virus expressing IL-21 (VVΔTK-STCΔN1L-mIL21) in combination with α-PD1, achieving remarkable outcomes.[94] The engineered VV lysed GBM cells, promoted T cell infiltration, and leveraged IL-21 to enhance CD8+ T cell antigen affinity, suppress Treg differentiation, and activate NK cells. Furthermore, α-PD1 blocked the PD-1/PD-L1 pathway, enhancing T cell activity and further strengthening the antitumor immune response. As expected, the combination therapy exhibited robust therapeutic effects, with an 80% cure rate in mice and no recurrence observed for 180 days. In contrast, monotherapies with VV and α-PD1 achieved cure rates of only 40% and 30%, respectively. In addition, the combination of CAR-T therapy with OVs to enhance anti-tumor efficacy has also been demonstrated. Wang et al developed a novel oAd expressing CXCL11 (oAd-CXCL11), which serves as a chemotactic factor for CAR-T cells by binding to the CXCR3 receptor (Figure 5A).[95] The results revealed that the oAd-CXCL11/CAR-T combination achieved near-complete tumor regression, with four out of five mice surviving beyond 70 days, whereas monotherapy (oAd-CXCL11 or CAR-T alone) exhibited tumor progression and survival limited to 40 days (Figure 5B and C).

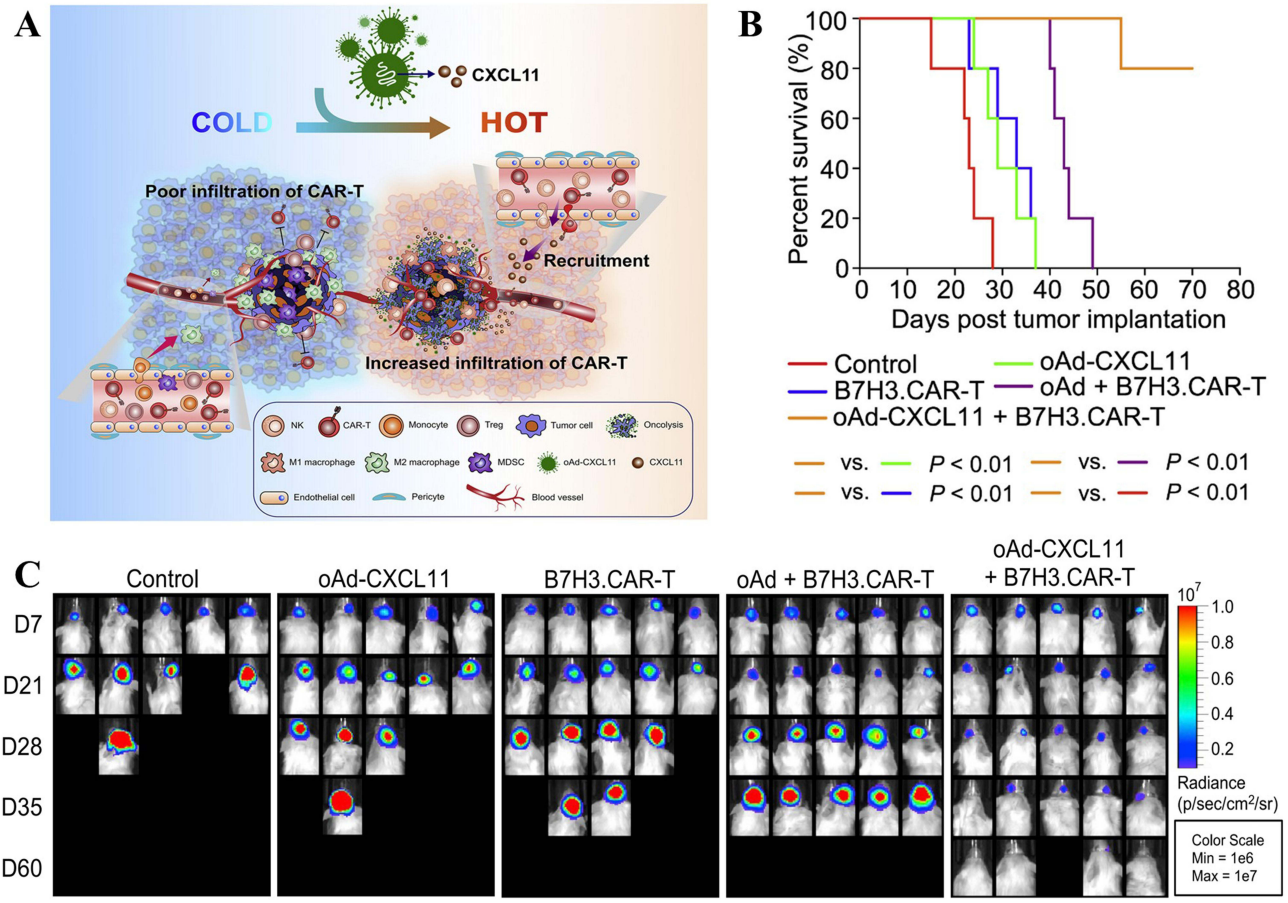

Figure 5 (**A**) Schematic diagram of synergistic anti-tumor mechanism of oAd-CXCL11 combined with CAR-T therapy. (**B**) Survival times of tumor-bearing mice after different treatments. (**C**) Fluorescence imaging of GBM growth in mice after different treatments. Reproduced with permission from Wang G, Zhang Z, Zhong K, et al. CXCL11-armed oncolytic adenoviruses enhance CAR-T cell therapeutic efficacy and reprogram tumor microenvironment in glioblastoma. Mol Ther. 2023;31(1):134–153.[95]

Clinical Translation of OVT in Malignant Glioma

In recent years, various OVs targeting malignant glioma, such as Ad, measles virus, have progressed to clinical trials (Table 2).[96,97] Several studies have completed Phase II/III clinical investigations, demonstrating encouraging efficacy and safety profiles. Notably, a third-generation genetically engineered HSV-1, teserpaturev (G47delta, G47Δ), has been approved in Japan for the treatment of malignant glioma. Furthermore, the US Food and Drug Administration has granted Fast Track designation to several investigational OVs including genetically engineered poliovirus (PVS-RIPO), Ad (DNX-2401), and HSV (CAN-3110)[98,99] The clinical development of OVT for malignant glioma has evolved from proof-of-concept studies to efficacy optimization phases, with diverse strategies, including genetic engineering, vector delivery, and combination therapies, being extensively explored.[100–102] The following sections will summarize the optimization approaches and key findings from recently completed clinical trials, providing insights for further OVT development in neuro-oncology.

Through modulating the expression of key functional genes to enhance replication efficiency, safety profile, immune activation, and tumor selectivity, engineered OVs have demonstrated substantial therapeutic potential in clinical trials. As the first government-approved OVT for malignant glioma, the triple-mutated oncolytic HSV-1 G47Δ is derived from the gamma34.5 (γ34.5)-deficient HSV-1 vector G207, with additional deletions of the alpha47 (α47) gene and the promoter region of US11.[103,104] This synergistic engineering addresses critical limitations of earlier constructs. The γ34.5 gene serves as the primary neurovirulence determinant of HSV, and plays a critical role in blocking the host cell's shutdown of protein synthesis following viral infection. While γ34.5 deletion reduces neurotoxicity, it concurrently compromises replication capacity. The α47 gene, which inhibits the transporter associated with antigen presentation, has been removed

Table 2 Summary of Recent Clinical Trials with OVs for Malignant Glioma

OVs	Functional Modification	Combination	Phase	Cancer type	Status	Identifier
DNX2401 (Ad)	Genetic engineering (deletion of 24 base pairs in the E1A region; insertion in virus fiber with a RGD-4C motif)	TMZ	I	Recurrent glioblastoma	Completed	NCT01956734
DNX2401	Genetic engineering	Pembrolizumab	II	Glioblastoma or gliosarcoma	Completed	NCT02798406
DNX2401	Genetic engineering		I/II	Recurrent glioblastoma	Completed	NCT01582516
DNX2401	Genetic engineering	IFN-γ	I	Recurrent glioblastoma or gliosarcoma	Completed	NCT02197169
MSC-DNX-2401 (Ad)	Genetic engineering; nanocarrier-based delivery (BM-hMSCs)		I	Recurrent high-grade glioma	Recruiting	NCT03896568
NSC-CRAd-S-p7 (Ad)	Genetic engineering (incorporation of a survivin promoter for E1A gene expression and insertion in Ad5 fiber protein with a polylysine sequence (pk7); nanocarrier-based delivery (NSCs)	Radiotherapy, TMZ	I	Newly diagnosed malignant glioma	Completed	NCT03072134
CAN-2409 (Ad)	Genetic engineering (insertion of HSV thymidine kinase gene)	Radiotherapy, TMZ, valacyclovir	II	Malignant glioma	Completed	NCT00589875
TS-2021 (Ad)	Genetic engineering (insertion of Ki67 promoter, TGF-β_2 5'UTR, and IL-15 gene)		I	Recurrent malignant glioma	Recruiting	NCT06585527
Ad-TD-nsIL12 (Ad)	Genetic engineering (deletion of E1ACR2 gene, E1B19K gene and E3gp19K gene)		I	Recurrent high-grade glioma	Completed	ChiCTR2000032402
M032 (HSV-1)	Genetic engineering (insertion of IRS-1 gene; deletion of γ34.5 gene)		I	Recurrent malignant glioma	Active, not recruiting	NCT02062827
M032	Genetic engineering	Pembrolizumab	II	Recurrent malignant glioma	Recruiting	NCT05084430
C134 (HSV-1)	Genetic engineering (insertion of IL-12 gene; deletion of γ34.5 gene)		I	Recurrent glioblastoma	Active, not recruiting	NCT03657576
ON-01 (HSV-1)	Genetic engineering (insertion of cytosine deaminase gene; deletion of toxic genes and DNA synthetases)	Flucytosine	I/II	Recurrent malignant glioma	Completed	NCT06562621
CAN-3110 (HSV-1)	Genetic engineering (insertion of a nestin promoter)	Cyclophosphamide	I	Recurrent malignant glioma	Recruiting	NCT03152318
G47Δ (HSV-1)	Genetic engineering (deletion of γ34.5 gene, α47 gene and the promoter region of US11)		I/II	Progressive glioblastoma	Completed	UMIN000002661
G47Δ	Genetic engineering		II	Residual or recurrent glioblastoma	Completed	UMIN000015995
MV-CEA (measles virus)	Genetic engineering (insertion of CEA gene)		I	Recurrent glioblastoma	Completed	NCT00390299
PVSRIPO (poliovirus)	Genetic engineering (replacement of viral IRES element with that of HRV2)		I	Recurrent glioblastoma	Completed	NCT01491893

Abbreviations: OVs, Oncolytic viruses; Ad, adenovirus; HSV, herpes simplex virus; RGD, arginine -glycine-asparagic acid; BM-hMSCs, bone marrow-derived human MSCs; NSCs, neural stem cells; UTR, untranslated regions; IL, interleukin; DNA, deoxyribonucleic acid; CEA, carcinoembryonic antigen; IRES, internal ribosomal entry site; HRV2, human rhinovirus type 2; TMZ, temozolomide; IFN-γ, interferon gamma.

to increase major histocompatibility complex class I expression in infected cells, thereby enhancing antitumor immune responses. Moreover, because the transcripts encoding α47 and US11 overlap, the deletion of α47 strategically repositions the late-phase US11 gene under the control of the immediate-early α47 promoter, thereby enhancing the growth of

γ34.5-negative mutants by preventing the shutdown of protein synthesis and achieving an optimal balance between safety and replicative potency.

A Phase II single-arm trial evaluated repeated intratumor G47Δ administration in recurrent/progressive GBM patients following standard chemoradiation.[100] The regimen demonstrated remarkable survival benefits compared to historical controls from pooled analyses of 16 trials investigating chemotherapeutic regimens for recurrent GBM (median OS: 20.2 vs 5.0 months; median PFS: 4.7 vs 1.8 months). Treatment-emergent adverse events (TEAE) were generally manageable, with fever and headache being the most common, reflected expected antiviral immune responses without dose-limiting toxicities (DLT). Furthermore, histopathological analyses revealed enhanced antitumor immunity mediated by G47Δ, characterized by progressive infiltration of CD8+/CD4+ tumor-infiltrating lymphocytes and sustained suppression of Tregs (Foxp3+ cells).

Some exogenous genes, including therapeutic and immune regulatory genes, have been introduced to further enhance antitumor efficacy. IL-12, recognized as a potent cytokine for its dual capacity to activate antitumor immunity and suppress tumor angiogenesis, has been limited in clinical translation due to systemic toxicity.[105,106] A non-secreting form of IL-12 (nsIL12), which primarily exerts its effects intracellularly and within the local tumor microenvironment, retains its antitumor potency while avoiding systemic toxicity, making it an attractive option. Based on this concept, Ad-TD-nsIL12, an oAd expressing non-secreting IL-12, was developed to achieve a more robust oncolytic effect. This virus combines tumor-selective replication and enhanced antitumor immune activation through targeted deletions in E1A-CR2, E1B-19K, and E3-gp19K regions with localized immune stimulation via nsIL-12 expression.[107]

A Phase I trial was conducted to evaluate the safety and preliminary efficacy of Ad-TD-nsIL12, administered via intratumor stereotactic injection and injection through a pre-inserted Ommaya reservoir in patients with high-grade glioma.[108] The results demonstrated that within the maximum tolerated dose at 1 × 10^10 viral particles, TEAE were tolerable, with fever being the most common, followed by nausea, vomiting, and fatigue. Notably, among the three patients treated at this dose, one achieved a complete response (CR) and one achieved a partial response, suggesting the tremendous potential of Ad-TD-nsIL12 for therapeutic efficacy.

Tumor-specific promoters or tumor-targeting sequences have been investigated to enhance the selective replication and targeting capabilities of OVs. CAN-3110, an oHSV, exemplifies this approach under the regulation of a nestin promoter. Nestin is a transcriptional element selectively active in invasive tumors but silenced in normal tissue. Unlike conventional attenuation methods that compromise viral replication through gene deletion, this design leverages tumor-specific promoter activity to spatially restrict viral cytotoxicity while preserving γ34.5-driven replication potency.[109] A phase I trial of CAN-3110 confirmed the localized therapeutic effect, with all inflammatory responses confined to the injected tumors and absent in the surrounding brain tissue.[110] Notably, HSV1-seropositive patients achieved a median overall survival (OS) of 14.2 months, exceeding historical benchmarks of 6–9 months for recurrent GBM. Furthermore, CAN-3110 exhibited a favorable safety profile, demonstrating relative human safety at all tested doses.

To further enhance efficacy, the tumor-targeting peptide RGD motif was incorporated into an oAd DNX-2401, enabling integrin-mediated tumor targeting through αvβ3/αvβ5 receptors overexpressed in malignant cells. Moreover, a 24-base pair deletion in the E1A gene confers selective replication in Rb pathway-deficient tumors on DNX-2401.[111] A phase I clinical trial for recurrent malignant glioma showed that convection-enhanced delivery of DNX-2401 was well tolerated, with no DLT encountered.[112] Although the overall efficacy results may not seem impressive, with a median PFS of 82 days and a median OS of 129 days, it is noteworthy that 2 of 19 patients achieved long-term survival of 7.5 and 2.5 years, including one patient who experienced a CR and remains recurrence-free at last follow-up.

Building upon these engineering innovations, emerging delivery platforms and combination regimens are being clinically investigated to amplify therapeutic efficacy. A pioneering first-in-human phase I trial evaluated NSC-mediated delivery of CRAd-S-pk7, an engineered oAd.[113] By incorporating a survivin promoter to drive expression of the replication-essential E1A gene and modifying the Ad5 fiber protein with a polylysine sequence (pk7), CRAd-S-pk7 was engineered to enhance viral replication and targeting of glioma cells.[114] Meanwhile, leveraging NSCs' intrinsic tumor tropism and tissue-penetrating capacity, this delivery system achieved enhanced intratumor viral distribution while minimizing off-target effects.[115] When combined with standard radiotherapy and TMZ, the regimen demonstrated superior clinical outcomes compared to historical controls: median PFS improved from 6.9 to 9.05 months, and OS

increased from 14.6 to 18.4 months. Importantly, NSC-CRAd-S-pk7 exhibited a favorable safety profile, with no DLT observed. TEAE appeared to be attributable to concurrent chemoradiotherapy rather than the investigational agent. Additionally, the combination of OVs with ICIs has been explored. OVs can modulate the immune microenvironment, attracting immune cells that can be further activated by ICIs, thus synergistically enhancing antitumor efficacy.[93] A phase I/II trial tested the overall safety and efficacy in recurrent GBM through intratumor DNX-2401 administration followed by intravenous pembrolizumab.[102] The combination demonstrated acceptable safety with no DLT, and the full-dose combined treatment was well tolerated. Furthermore, a promising survival benefit was observed, with 12-month OS at 52.7% and median OS of 12.5 months. Remarkably, one patient survived beyond 60 months, and two patients achieved CR.

Discussion

OVs represent a promising frontier in malignant glioma therapeutics, offering sustained replication and immune induction capabilities. In recent years, preclinical studies with OVs like Ad and HSV have confirmed their efficacy and safety.[116] However, clinical trials reveal limited success with OV monotherapy.[82] This highlights the necessity of further optimizing and modifying OVs, as well as rational combination therapy strategies to synergize with OVs' inherent antitumor mechanisms.

Genetic engineering serves as a core strategy for enhancing the precision selectivity, therapeutic efficacy, and safety of OVs.[117] Recently, an increasing number of genetically engineered OVs have entered clinical trials for malignant gliomas, showing promising preliminary efficacy.[29] However, the marked heterogeneity characteristic of malignant glioma may lead to limitations in single-gene modifications, resulting in compromised long-term clinical responses in subsets of patients.[118] Exploring multi-target regulation is necessary to deal with the dynamic changes in the TME. Chemical modification strategies have demonstrated potential in enhancing circulation stability, targeting, and ability to induce immunity of OVs.[46,119] However, chemically modified OVs in glioma have been scarcely explored and warrant broader investigation. Moreover, future studies should take into account that excessive or imprecise chemical modifications can reduce viral invasion efficiency. It is essential to develop standardized production processes that accurately control the modification density to preserve viral bioactivity while achieving functional enhancement. Nanocarriers utilize physical adsorption or encapsulation to offer protective delivery systems against antiviral immunity. Some bioinspired carriers, such as cell membranes derived from NSCs and GBM, can also improve the tumor targeting and BBB penetration.[21] However, certain nanomaterials, such as polyamidoamine dendrimers, may introduce toxicity risks, requiring careful optimization of modification intensity and biocompatibility.[120] Current research on nanocarrier-mediated delivery of OVs remains limited, with only cell-based delivery system, such as NSC-carried OVs, entering clinical trials for malignant glioma.[113] Furthermore, research is mainly focused on improving targeting, stability, and BBB penetration. A broader range of carrier options and additional designs, such as responsive designs, should be developed to meet the needs of precision medicine.

Both preclinical and clinical investigations have explored OVs as monotherapies or in combination regimens. However, monotherapies fail to defeat malignant glioma due to the marked heterogeneity.[24] Rational combination strategies have demonstrated synergistic therapeutic potential. However, the complexity of combination therapies and the risk of cumulative toxicity from different regimens remain key challenges for clinical translation. Additionally, the mechanisms of interaction between different treatment modalities, optimal dosages, and timing of administration still need to be validated and optimized through extensive basic research and clinical trials.[121] Additionally, in terms of clinical translation, although OVT holds great promise, its deployment faces key challenges. Manufacturing requires complex genetic engineering and process optimization to ensure safety, efficacy, and scalability, which are costly and technically demanding. Regulatory hurdles further complicate translation, as strict safety assessments and environmental concerns prolong approval timelines. Furthermore, raw material costs—such as specialized cell lines and cold chain logistics—add to the economic burden. Overcoming these obstacles will require improved manufacturing efficiency and balanced regulatory frameworks to facilitate wider clinical use.

The advancement of OVT for malignant glioma from the laboratory to clinical settings requires interdisciplinary collaboration and continuous refinement of clinical practices. With the continuous optimization of viral genetic

engineering, chemical modifications, nanocarrier delivery, and combination therapy strategies, OVT is expected to play a crucial role in malignant glioma treatments, driving the realization of precision medicine and bringing new breakthroughs to the field of cancer therapy.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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