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Viral immunotherapy: Oncolytic approaches for solid tumors

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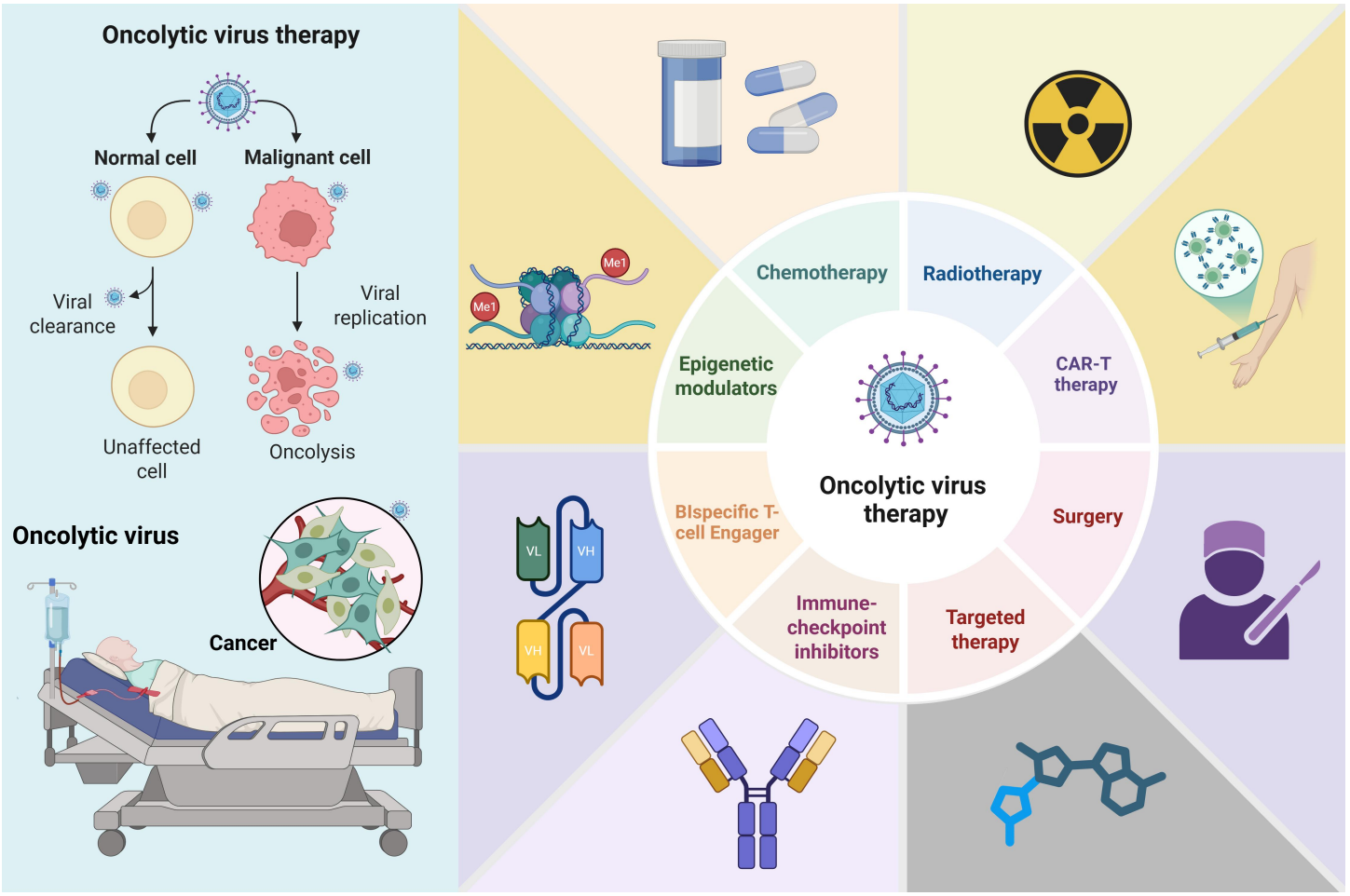
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Oncolytic virus therapy (OVT) displays considerable promise for treating solid cancers.
- Oncolytic viruses (OVs) enhance cancer therapy through diverse combination strategies.
- Provides insights into the rational design of next-generation OVs.

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Viral immunotherapy: Oncolytic approaches for solid tumors

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Despite advancements in oncology, a significant unmet need remains for therapies that effectively target and eradicate solid tumors while overcoming resistance mechanisms and minimizing damage to healthy tissues. Oncolytic virotherapy (OVT) has emerged as a promising approach to treating solid tumors by directly lysing cancer cells and simultaneously stimulating immune responses. A diverse range of viruses have been engineered to enhance their tumor-targeting capabilities. Preclinical studies show that these oncolytic viruses can induce immunogenic cell death, remodel the tumor microenvironment, and synergize with various established therapies. Their efficacy involves diverse mechanisms, including interferon signaling, metabolic reprogramming, and epigenetic regulation. While early clinical trials demonstrate promising safety and efficacy across multiple cancers, challenges such as systemic delivery and tumor heterogeneity persist. Ongoing optimization of viral engineering and combination strategies is crucial for unlocking the full clinical potential of this approach against solid tumors. This review summarizes the current landscape of OVT, highlighting its mechanistic basis, clinical progress, and the strategic innovations needed to overcome existing barriers and fully realize its potential in oncology.

INTRODUCTION

Cancer remains one of the leading causes of morbidity and mortality worldwide, and despite advances in surgery, radiotherapy, chemotherapy, and targeted therapies, durable responses are often limited, particularly in advanced or refractory disease. The search for novel therapeutic strategies has led to the development of oncolytic virotherapy (OVT), which harnesses the natural ability of viruses to infect and lyse malignant cells. Oncolytic viruses (OVs) are replication-competent viruses that selectively target tumor cells through exploitation of cancer-specific signaling pathways, defects in antiviral responses, or engineered genetic modifications.[1,2] Upon infection, OVs exert direct cytolytic effects and simultaneously stimulate antitumor immunity by releasing tumor-associated antigens, viral pathogen-associated molecular patterns, and danger signals, thereby converting immunologically "cold" tumors into "hot" tumors amenable to immune recognition.[3] The field of OVs has gained considerable attention following positive results from numerous clinical trials. To date, four OVs have been approved globally (Figure 1).

Over the past two decades, multiple viral backbones—including Herpes simplex virus (HSV), Vaccinia virus (VV), Parvovirus (H-1PV), Adeno-associated Virus (AAV), Adenovirus (ADV), Newcastle disease virus (NDV), Vesicular stomatitis virus (VSV), Reovirus (Reo), Measles virus (MV), M1 virus, Zika virus (ZIKA), Coxsackievirus A21 (CVA21), Varicella zoster virus (VZV) and Influenza A virus (IAV) have been explored for their oncolytic potential.[4-6] Among these, Talimogene laherparepvec (T-VEC), a genetically modified HSV-1 encoding GM-CSF, became the first OV approved for clinical use in 2015, establishing proof-of-concept for this therapeutic modality.[7] Despite this milestone, challenges remain, including limited systemic delivery, antiviral immunity that restricts viral spread, and heterogeneous responses across tumor types. Recent research has therefore focused on strategies to enhance OV efficacy, such as arming viruses with immunomodulatory transgenes, optimizing delivery methods, and combining OVs with immune checkpoint inhibitors (ICIs), targeted therapies, or radiotherapy.[8-10] These advances position OVs not only as direct cytolytic agents but also as potent immunotherapeutic platforms capable of reshaping the tumor microenvironment (TME) and synergizing with existing treatments.

OVT FOR SOLID TUMOR: PRECLINICAL AND CLINICAL EVIDENCE

DNA virus

HSV-1 has become a leading platform for OVT due to its rapid cell entry, efficient replication, broad receptor usage, and strong immunogenicity.[11] Engineered oncolytic HSV (oHSV) shows promise in treating gliomas and other malignancies. For instance, G47Δ-IL2 enhances glioblastoma survival by locally releasing IL-2 and activating $CD4^+$ T cells, while IL-27-armed oHSV boosts cytotoxic T Lymphocyte (CTL) function and immune memory.[12,13] oHSV also synergizes with mRNA vaccination to target HPV-related cancers, eliciting potent immune responses.[14] Besides, the research investigates the role of neutrophil extracellular traps (NETs) in glioma and oncolytic virotherapy. It shows that IGF2BP3 upregulation enhances MIB1 expression, leading to FTO degradation and increased m6A-mediated CSF3 release, promoting NET formation. NETosis is a specialized form of cell death in neutrophils, during which they release NETs. oHSV stimulates NETosis in glioma, while a BET inhibitor enhances oHSV activity by blocking IGF2BP3-induced NET formation.[15] PANoptosis, a newly discovered cell death pathway, is activated by oHSV, enhancing antitumor immunity, especially when combined with Fusobacterium nucleatum vesicles.[16] Clinical studies are beginning to translate preclinical findings into patient benefits. Seprehvir (HSV-1716) demonstrated favorable safety and antitumor activity without neurotoxicity, supporting further clinical development.[17] VG161 showed efficacy in checkpoint inhibitor–sensitive hepatocellular carcinoma, with gene expression–based stratification identifying patients with prolonged survival.[18] In recurrent glioblastoma, intratumoral CAN-3110 was well tolerated and achieved tumor-selective replication, with pre-existing HSV-1 immunity correlating with enhanced viral clearance, T cell activation, and survival.[19] Similarly, OH2 virotherapy was well tolerated without dose-limiting toxicities and showed durable efficacy in melanoma, particularly after anti-PD-1 failure, while T-VEC plus pembrolizumab was active and tolerable in PD-1-refractory melanoma, especially following recurrence on adjuvant anti-PD-1 therapy.[20,21] In a phase Ib trial (NCT04197882), 30 patients with resectable acral melanoma received neoadjuvant orienX010 plus toripalimab followed by adjuvant toripalimab. The regimen was safe and induced high pathological response rates with durable 2-year RFS and EFS. Pathological responses correlated with enriched lymphoid structures, TILs, and proinflammatory cytokine activation, supporting this combination as a promising strategy.[22] Together, these trials underscore the emerging clinical potential of oHSV across diverse tumor types.

VV is a cytoplasm-replicating DNA virus with high oncolytic potency and exceptional engineering capacity.[23] Engineered VV derivatives, such as OVV-aCD47nb, remodel the TME by recruiting immune cells like $CD8^+$ T cells and NK cells, and enhance the efficacy of immune checkpoint blockade.[24] A TGFβRII inhibitor-engineered VV, which overcomes TGFβ-mediated immunosuppression in resistant head and neck squamous cell carcinoma and synergizes with checkpoint inhibition.[25] Clinical trial results indicate that intrahepatic artery administration of TG6002 in combination with oral 5-FC is clinically feasible.[26] In metastatic colorectal cancer, PexaVec combined with durvalumab was well tolerated and increased circulating proliferative $CD8^+$ T cells, although progression-free survival was similar between cohorts.[27] Intrapleural administration of oncolytic vaccinia virus was likewise safe and elicited localized immune responses without systemic toxicity.[28] Together, these studies highlight the adaptability of vaccinia virus platforms for immune remodeling and durable therapeutic benefit.

Human adenovirus type 5 is the most extensively studied OVT platform, with a favorable safety profile, strong immunogenicity, transient gene expres-

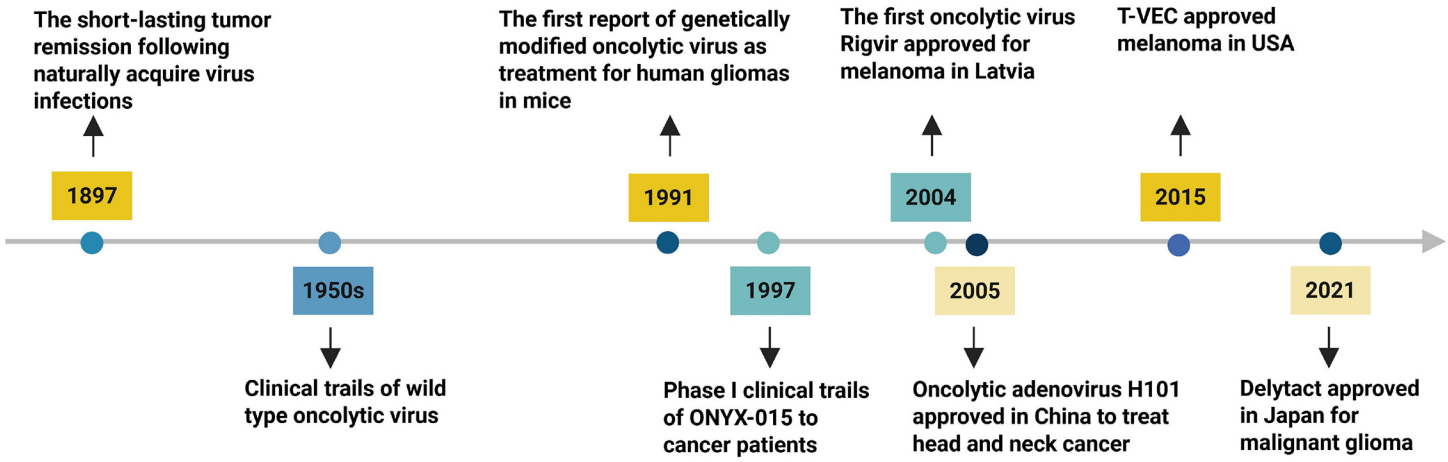


Figure 1. A timeline of key milestones in the development of oncolytic viruses as a cancer therapy.

sion, and lack of genomic integration.[29,30] Advances in viral engineering have substantially expanded its therapeutic scope. Recent engineering efforts have further expanded its potential, such as an ADV expressing a SIRPα/Siglec-10 fusion to block CD47 and CD24, enhancing macrophage phagocytosis and T-cell activation.[31] In HCC, Ad5-PC encoding a PD-1-CD137L fusion led to durable cures by sustaining $CD8^+$ T-cell responses.[32] Beyond immune modulation, ADV vectors can reprogram tumor metabolism, exemplified by ApoA1 delivery restoring cholesterol homeostasis and suppressing metastasis in triple-negative breast cancer.[33] Early-phase studies across multiple cancers highlight the safety and preliminary efficacy of oncolytic and immunotherapeutic agents. Ad-TD-nsIL12 was safe in recurrent high-grade glioma, with seizures defining the maximum tolerated dose and evidence of T cell infiltration.[34] TILT-123 showed systemic antitumor activity in both injected and non-injected lesions, supporting combination with checkpoint blockade or adoptive T cell therapy.[35] NG-350A demonstrated tumor-selective delivery and transgene expression after intravenous dosing without off-target toxicity.[36] In BCG-unresponsive non-muscle-invasive bladder cancer, cretostimogene plus pembrolizumab achieved durable complete responses with low-grade toxicity.[37] YSCH-01 and LOAd703 combinations were well tolerated and showed preliminary anticancer activity in advanced solid tumors and PDAC, respectively, supporting further development with synergistic regimens.[38,39]

AAV is primarily deployed as a gene delivery platform to induce immunogenic cell death or normalize tumor vasculature, thereby enhancing antitumor immunity and therapeutic efficacy. Recent advances demonstrate that rAAV-mediated delivery of cytotoxic effectors, including N-terminal gasdermin domains, can induce tumor pyroptosis, transiently disrupt the blood–brain barrier, promote immune infiltration, and synergize with immune checkpoint blockade in glioblastoma.[40] In parallel, AAV-based delivery of vascular-normalizing or antiangiogenic agents prolongs survival and enhances $CD8^+$ T-cell infiltration in ovarian cancer models.[41] Collectively, these studies position AAV as a flexible adjunct platform that potentiates oncolytic and immunotherapeutic strategies despite remaining production constraints.

H-1PV exhibits intrinsic oncolytic activity that can be enhanced by epigenetic modulation. Research show that combining H-1PV with histone deacetylase inhibitors such as valproic acid synergistically kills cervical and pancreatic carcinoma cells through oxidative stress, DNA damage, and apoptosis.[42] In the ParvOryx01 phase I/IIa trial, patients with recurrent glioblastoma received escalating doses of H-1PV via intratumoral or intravenous injection, followed by surgical resection and peri-cavity re-administration. The treatment was safe, with no maximum tolerated dose reached, and the virus successfully crossed the blood–brain/tumor barrier, spreading widely within tumors. H-1PV elicited antiviral antibodies, T-cell responses, and tumor infiltration by activated microglia/macrophages and cytotoxic T cells. Median survival exceeded that reported in meta-analyses, underscoring its clinical potential.[43] In a separate study of refractory pancreatic ductal adenocarcinoma (PDAC), ParvOryx was likewise well tolerated without dose-limiting toxicities. Two patients achieved partial responses with prolonged survival of 326 and 555 days. Pharmacokinetic and shedding analyses revealed dose-dependent distribution but no release of infectious particles. Viral genomes were detected in tumor samples, and all patients mounted T-cell responses, with immune activation most pronounced in responders.[6] Together, these early clinical studies demonstrate that H-1PV is safe, immunogenic, and capable of producing durable responses, warranting further development as a therapeutic platform.

RNA virus

Oncolytic NDV, an avian paramyxovirus, replicates efficiently in diverse tumor types and exerts potent cytotoxic effects through multiple mechanisms of cell death, including immunogenic cell death (ICD), apoptosis, autophagy-associated cell death, and necroptosis.[44-47] Recombinant NDVs have been engineered to enhance immune engagement. rNDV19 stably expresses CCL19, augmenting CAR T-cell infiltration and reprogramming the tumor microenvironment.[48] In melanoma, NDV combined with radiotherapy synergized with checkpoint inhibitors to enhance tumor clearance, while serving as a dose-sparing radiosensitizer and enabling localized anti-CTLA4 scFv expression with reduced systemic toxicity.[49] NDV-GT, a recombinant virus encoding porcine α1,3GT, eradicated tumors in HCC monkeys and achieved a 90% disease control rate with durable responses and minimal immunogenicity in clinical trials.[50] MEDI5395, an NDV expressing GM-CSF, was safe at doses up to 10^{11} FFU with durvalumab, with manageable toxicities and dose-dependent pharmacokinetics and shedding. Partial responses occurred in 10.3% of patients, associated with higher baseline PD-L1 and $CD8^+$ T-cell infiltration, while neutralizing antibodies did not compromise efficacy.[51] These findings highlight NDV-based oncolytic viruses as safe and immunologically active therapies with clinical potential.

VSV is a non-pathogenic, negative-strand RNA virus that preferentially replicates in tumors with defective interferon signaling, enabling selective oncolysis while sparing normal tissues.[52,53] Its low pre-existing immunity and rapid replication make VSV a versatile oncolytic and vaccine platform, further strengthened by cytokine and immunomodulatory engineering.[54,55] VSVΔ51, expressing truncated HER2 converted tumors into trastuzumab targets and, together with a HER2-directed VV, elicited curative $CD3^+$ T cell–mediated immunity. Notably, infection of both cancer and non-cancer cells by VSVΔM51 not only drove tumor regression but also promoted systemic cytokine release, dendritic cell activation, and $CD8^+$ T cell–mediated immunity.[56] Recent studies reveal strategies to overcome VSV resistance: 4-octyl itaconate enhances VSVΔ51 efficacy by suppressing antiviral immunity; recurrent CSDE1P5S mutations in VSV-IFNβ–escape tumors create neoepitopes, allowing viral adaptation and vaccine prevention of escape; CDK4/6 inhibition promotes MAVS degradation, boosting tumor-selective VSVΔ51 replication in GBM models.[57-59] Early-phase studies across refractory TCL highlight that a single IV dose of VSV-IFNβ-NIS is safe up to 1.7×10^{11} $TCID_{50}$ and shows dose-dependent efficacy. Ongoing expansion and combination cohorts further explore its therapeutic potential, highlighting VSV-IFNβ-NIS as a promising immune-oncolytic approach in relapsed hematologic malig-

nancies.[60] Together, these advances establish VSV as a versatile oncolytic platform with broad therapeutic promise, particularly when combined with immune modulation and rational design to circumvent antiviral resistance.

Reovirus, a ubiquitous non-enveloped double-stranded RNA virus, has been developed as an oncolytic platform based on the serotype 3 Dearing strain (RT3D), which enters tumor cells via junctional adhesion molecule-A.[61] Mechanistically, RT3D activates RIG-I–PARP-1 signaling to limit extrinsic apoptosis, whereas pharmacologic PARP-1 inhibition with talazoparib redirects cell fate toward inflammatory cell death, amplifying IFN/TNF responses and inducing curative, durable antitumor immunity in vivo.[62] Combination of RT3D with palbociclib further couples RNA sensing to ER stress, promoting cancer cell death, interferon release, innate immune activation, and HLA upregulation through epigenetic remodeling and endogenous retrovirus reactivation.[63] In HCC models, Reo not only stimulates immune cell degranulation but also suppresses HCV replication in vitro and in vivo, while retaining efficacy against HBV-associated HCC and EBV-associated lymphoma.[64] Clinically, Pelareorep was safe but did not improve progression-free survival when added to carboplatin/paclitaxel in metastatic pancreatic adenocarcinoma, regardless of KRAS status; immunologic analyses suggest that chemotherapy may enhance immune reconstitution and that targeting residual immunosuppressive pathways could improve OVT.[65] Bolus cyclophosphamide similarly does not reliably prevent Reo-neutralizing antibodies or alter Treg levels, yet Reo may retain antitumor efficacy through association with blood cells, evading immune complex formation despite high antibody titers.[66] Separately, an investigator-initiated trial evaluated PELA in combination with dexamethasone (Dex) and bortezomib (BZ) while characterizing the tumor immune microenvironment in multiple myeloma patients. PELA/BZ/Dex was well tolerated and induced anti-myeloma activity in a subset of patients, with responses linked to immune reprogramming, cytotoxic T-cell infiltration, and remodeling of the tumor immune microenvironment.[67] These studies underscore the potential of Reo to modulate immunity and achieve clinical benefit despite immune barriers.

MV, a negative-sense RNA virus with a ~16 kb genome, has emerged as a promising oncolytic platform due to its preferential replication in tumor cells with impaired IFN signaling.[68,69] For example, MV retargeted to the urokinase-type plasminogen activator receptor (uPAR) and armed with TLR2 agonists synergizes with PD-1 blockade to induce $CD8^+$ T cell-mediated clearance of glioblastoma.[70] Additionally, MV-BiKE variants, which recruit NK cells to CEA-expressing tumors, trigger cytokine release and selective cytotoxicity, while the recombinant rMV-Hu191 strain effectively targets gastric cancer via caspase-dependent apoptosis.[71,72] In a first-in-human trial of carcinoembryonic antigen-expressing oncolytic measles virus (MV-CEA) in recurrent glioblastoma, treatment was safe at the maximum feasible dose and achieved a median Overall survival (OS) of 11.6 months with 45.5% 1-year survival. Viral replication induced immune activation and $CD8^+$ T-cell infiltration, while a 22-gene ISG classifier inversely correlated with viral activity, supporting further development and biomarker-guided personalization of MV-based virotherapy.[73] Systemic administration of MV-NIS in myeloma patients enhanced T-cell responses to tumor-associated antigens, supporting the concept of OVT as an antigen-agnostic cancer vaccine.[74] These findings highlight measles virus derivatives as safe, immunologically active oncolytic agents with broad therapeutic potential.

M1 is a positive-sense RNA alphavirus with intrinsic tumor tropism and potent antitumor activity across multiple malignancies, with a unique ability to cross the blood–brain barrier.[75,76] Mechanistically, M1 exploits tumor-specific vulnerabilities by suppressing antiviral defenses, prolonging ER stress, and inducing apoptosis, effects that can be markedly amplified by pharmacologic sensitizers or small-molecule enhancers that promote cytokine-mediated bystander killing.[77] Engineering strategies have further expanded its therapeutic potential, including IL-18–armed variants that activate dendritic cells (DCs) and CTLs to drive systemic immunity and synergize with checkpoint blockade, as well as next-generation M1 strains evolved to enhance receptor engagement, evade innate immune restriction, and achieve orders-of-magnitude increases in oncolytic potency while maintaining safety.[78] Collectively, M1 represents a highly potent and adaptable oncolytic platform with exceptional translational promise. Encouragingly, in a phase I clinical trial (NCT04665362), M1-c6v1 combined with camrelizumab and apatinib was safe, well tolerated, and showed no viral shedding; among 10 evaluable patients with advanced HCC, the regimen achieved an objective response rate of 70% (all partial responses), with a median progression-free survival (PFS) of 8.9 months and OS of 15.4 months.[79] Overall, M1 and its engineered variants represent highly potent, safe, and immunologically active oncolytic agents with promising clinical efficacy.

ZIKV, a neurotropic flavivirus best known for its neuropathogenicity, has recently emerged as a highly selective oncolytic agent for glioblastoma and other central nervous system tumors. ZIKV preferentially infects and eliminates glioblastoma stem cells while sparing differentiated tumor cells and normal neurons, a specificity not shared by related flaviviruses.[80] Patient-derived models and in vivo studies demonstrate durable survival benefits, while genetic attenuation via microRNA-sensitive designs preserves oncolytic efficacy and enhances safety.[81] Tumor-intrinsic features, including reduced SLFN11 expression, further sensitize therapy-resistant glioma cells to ZIKV. Mechanistically, ZIKV targets tumor stem-like cells through a SOX2–integrin αvβ5 axis, and additional Wnt-dependent vulnerabilities have been identified in embryonal CNS tumors.[82] Together, these findings position ZIKV as a uniquely potent and selective oncolytic platform for refractory brain malignancies.

Coxsackievirus (COX) is a non-enveloped enterovirus with a positive-sense RNA genome, comprising COX-A serotypes linked to hand–foot–mouth disease and COX-B serotypes associated with myocarditis.[83,84] V937, an unmodified coxsackievirus A21, selectively targets $ICAM\text{-}1^+$ tumors and, in co-cultures with immune cells, triggers robust cytokine release and immune activation, revealing potent tumor-immune cross-talk.[85] In stage IIIB-D melanoma, neoadjuvant pembrolizumab with vibostolimab (anti-TIGIT) or gebasaxturev (coxsackievirus A21) showed manageable safety and pathologic responses comparable to pembrolizumab alone, with outcomes linked to tumor mutational burden and T cell–inflamed profiles.[86] Intravenous V937 plus pembrolizumab was safe but did not improve efficacy over pembrolizumab alone in NSCLC and urothelial cancer.[87] Overall, these findings highlight both the promise and the current limitations of V937 as an oncolytic immunotherapy.

IAV represents a promising oncolytic platform. To enhance its therapeutic potential, researchers engineered IAV to express antibody chains during infection, yielding viruses that replicate efficiently and secrete functional antibodies. An IAV variant encoding a CTLA4-blocking single-chain antibody (IAV-CTLA4 scFv) suppressed the growth of B16-F10 melanomas, induced abscopal effects, and prolonged survival in mice.[88] IAV holds promise as an oncolytic platform but poses risks in immunocompromised patients. A 4-hydroxytamoxifen (4-HT)-dependent H1N1 variant (S218) suppressed melanoma growth and lung metastasis in vivo, with 4-HT amplifying its efficacy. Folate-modified nanostructured lipid carriers enabled tumor-targeted 4-HT delivery, enhancing S218 activation and antitumor immunity. Combination with the STING agonist SR717 further potentiated metastatic regression.[89] Most patients respond poorly to ICIs, prompting exploration of oncolytic viruses as complementary therapies. Low-pathogenic IAVs not only induced direct oncolysis of NSCLCs in Raf-BxB mice but also reprogrammed tumor-associated macrophages (TAMs) toward an anti-tumor phenotype. NSCLCs and immune cells upregulated PD-L2/PD-1 and B7-H3 checkpoints, and combining IAV with a novel B7-H3 inhibitor markedly enhanced M1 macrophage polarization, T cell infiltration, and tumor clearance (~80%). By contrast, α-PD-1 treatment, alone or with IAV, showed no added benefit.[90] Collectively, these studies highlight IAV's versatility as an oncolytic agent, capable of being engineered for immune modulation, targeted activation, and synergy with checkpoint blockade.

Viruses share several common characteristics, including a genetic material composed of either single- or double-stranded DNA or RNA, and the ability to infect host cells and replicate under permissive conditions (Table 1). Relevant OVs and their clinical trials are shown in Table 2.

ONCOLYTIC VIRUS-BASED COMBINATION THERAPIES

Combined with CAR-T therapy

OVs are emerging as powerful allies to chimeric antigen receptor (CAR) T

Table 1. Classification of the oncolytic viruses.

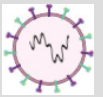
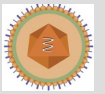
	Herpes Simplex Virus	Vaccinia Virus	Adenovirus	Adeno-ssociated Virus	Parvovirus	Reovirus	Newcastle Disease Virus	Vesicular Stomatitis Virus	Influenza A Virus	Measles Virus	M1 virus	Zika Virus	Coxackievirus
Model													
Genome	dsDNA 150 kb	dsDNA 190 kb	dsDNA 36 kb	dsDNA 4.7 kb	ssDNA 5 kb	dsRNA 123 kb	ss(-)RNA 36 kb	ss(-)RNA 11 kb	ss(-)RNA 13.6 kb	ss(-)RNA 16 kb	ss(+)RNA 12 kb	ss(+)RNA 10.8 kb	ss(+)RNA 28 kb
Capsid	Icosahedral	Complex	Icosahedral	Icosahedral	Icosahedral	Icosahedral	Helical	Helical	Helical	Icosahedral	Icosahedral	Icosahedral	Icosahedral
Virion	Enveloped	Complex coats	Naked	Naked	Naked	Naked	Enveloped	Enveloped	Enveloped	Enveloped	Enveloped	Naked	Naked
Methods of entry	HVEM, Nectin-1, Nectin-2	Receptor-mediated endocytosis	CAR, CD46	AAVR	SARs	JAM-A	Sialic acid	LDLR	Sialic acid	SLAM, CD46	MXRA8, TPRA1	TIM-1, AXL	DAF, CAR
Site of replication	Cytoplasm and Nucleus	Cytoplasm	Cytoplasm and Nucleus	Cytoplasm and Nucleus	Cytoplasm and Nucleus	Cytoplasm	Cytoplasm	Cytoplasm	Cytoplasm	Cytoplasm	Cytoplasm	Cytoplasm	Cytoplasm
Blood-brain barrier penetration	(-)	(-)	(-)	(-)	(-)	(+)	(+)	(-)	(-)	(-)	(+)	(+)	(-)
Transgene capacity	(+++)	(+++)	(++)	(+++)	(-)	(-)	(+)	(+)	(+)	(+)	(-)	(-)	(-)
Nuclear integration	(+)	(-)	(+)	(+)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Advantages	Large genome to insert large fragments and mulitipke transgenea	Efficient, fast spreading virus, up to 40kd large gene fragmen	High viral titlers,feasibility of manufacturing	Genomic stability	Easy to engineer genetically	Displaying no dose-limiting toxicity; good adaptability for intravenous injection	Nonpathogenic in human	High-speed life cycle; nonpathogenic in human	Easy to engineer and modify	Clinical trial experience	Nonpathogenic in human	Specific targeting of glioblastoma stem cells	Good adaptability for intraveous injection
Disadvantsges	Pathogenicity; ubiquitous nAbs	Pathogenecity	Extensive issue tropism	Low infection efficiency; Pre-existing immunity	Low infection efficiency	Rarely gene-editing	Rarely gene-editing	Clinicak trials were not entirely satisfactory	Pathogenecity	Rarely gene-editing	Rarely gene-editing	Pathogenecity	Pathogenicity; ubquitous nAbs

Table 2. Current research status of oncolytic viruses.

	Types of cancer	Combination	Trail phase	Trial number	Ref
HSV					
Seprehvir	Solid cancers	Alone	I	NCT00931931	(17)
VG161	HCC	Alone	I	NCT04806464	(18)
CAN-3110	Glioblastoma	Cyclophosphamide	I	NCT03152318	(19)
OH2	Melanoma	PD-1 therapy	I	NCT05868707	(20)
T-VEC	Melanoma	Pembrolizumab	II	NCT04068181	(21)
Orienx010	Melanoma	Toripalimab	I	NCT04197882	(22)
VV					
TG6002.	Colorectal Cancer	5-fluorouracil	I	Eudra-CT 2018-004103-39	(26)
PexaVec	Colorectal cancer	Durvalumab and tremelimumab	I/II	NCT03206073	(27)
Olvi-vec	Pleural mesothelioma	Alone	I	NCT01766739	(28)
ADV					
Ad-TD nsIL12	High-grade glioma	Alone	I	ChiCTR2000032402	(34)
TILT-123	Melanoma	TILs	I	NCT04217473	(35)
NG- 350A	Epithelial tumors	Pembrolizumab	I	NCT03852511	(36)
Cretostimogene	Invasive bladder cancer	Pembrolizumab	II	NCT04387461	(37)
YSCH-01	Advanced solid tumors	Alone	I	NCT05180851	(38)
LOAd703	Pancreatic cancer	Chemotherapy	I/ II	NCT02705196	(39)
H1-PV					
ParvOryx01	Glioblastoma	Alone	I/ II	NCT01301430	(43)
ParvOryx	Pancreatic ductal adenocarcinoma	gemcitabine	II	NCT02653313	(6)
NDV					
NDV-GT	Refractory metastatic cancer	Alone	I	ChiCTR2000031980	(50)
MEDI5395	Advanced solid tumors	Durvalumab	I	NCT03889275	(51)
VSV					
VSV-IFNb-NIS	T-cell lymphoma	Alone	I	NCT03017820	(60)
Reo					
Pelareorep	Metastatic Pancreatic ade nocarcinoma	Carboplatin and paclitaxe	II	NCT01280058	(65)
Reo	Solid tumors	Cyclophosphamide	I	EudraCT number 2007-001937-32	(66)
Reo	Multiple Myeloma	Alone	I	NCT02514382	(67)
MV					
MV-CEA	Recurrent glioblastoma	Alone	I/ II	NCT00390299	(73)
MV-NIS	Multiple myeloma	Alone	I	NCT00450814	(74)
M1					
M1-c6v1	Advanced HCC	Camrelizumab and apatinib	I	NCT04665362	(79)
CVA21					
Gebasaxturev	Melanoma	Pembrolizumab Plus vibostolimab	I/ II	NCT04303169	(86)
V937	Advanced solid tumors	Pembrolizumab	I	NCT02043665	(87)

cell therapy, particularly in solid tumors where limited infiltration and an immunosuppressive TME hinder efficacy. In glioblastoma, a CXCL11-armed oncolytic ADV enhanced CAR T cell therapy by promoting CAR T infiltration and reprogramming the TME, leading to durable antitumor responses with increased $CD8^+$ T cells, NK cells, and M1 macrophages, alongside reductions in MDSCs, Tregs, and M2 macrophages.[91] Beyond local modulation, systemic OV delivery has been shown to potentiate CAR T efficacy in melanoma and glioma by stimulating endogenous TCRs, driving dual-specific CAR T expansion, memory formation, and heightened antitumor activity. Preloading CAR T cells with VSV or Reo enabled homologous boosting, resulting in prolonged

survival in murine models and enhanced cytokine production in human CAR T cells.[92] To further broaden therapeutic potential, multifunctional OV platforms have been developed. The combinatorial adenoviral vector CAdTrio, encoding a cytokine, checkpoint inhibitor, and safety switch, expanded the potency and durability of HER2-CAR T cells against pancreatic cancer, enabling tumor trafficking, xenograft eradication, and systemic immune reprogramming in humanized models.[93] Similarly, mesenchymal stromal cells were employed to systemically deliver a CAd vector expressing IL-12 and a PD-L1 blocker, which boosted CAR T activity, cytokine secretion, and tumor clearance in orthotopic lung cancer and 3D spheroid models.[94] Tumor retargeting can also be achieved by OVs engineered to express artificial antigens: an oncolytic VV encoding truncated CD19 induced de novo CD19 expression, rendering solid tumors susceptible to CD19-CAR T cell killing and sustaining local immune activation with viral propagation across multiple models.[95] Nevertheless, OV-CAR T interactions can be context dependent. For instance, VSV-mIFNβ infection induced a proinflammatory chemokine shift in a B16EGFRvIII model but paradoxically caused attrition of EGFRvIII CAR T cells via IFN-driven apoptosis and upregulation of inhibitory receptors. Notably, interferon-insensitive CAR T cells circumvented this limitation and achieved superior efficacy in combination with VSV-mIFNβ.[96]

Combined with immune checkpoint inhibitors

Clinical and preclinical studies highlight the promise of next-generation oncolytic virotherapies engineered to modulate immune checkpoints and overcome TME-mediated resistance. Building on this, YST-OVH was designed to deliver localized PD-1 blockade, showing strong efficacy and safety while synergizing with CTLA-4 or TIM-3 inhibition.[97] Similarly, VV-scFv-TIGIT reprogrammed the TME from cold to hot and, in combination with PD-1 or LAG-3 inhibitors, induced complete responses in otherwise resistant tumors.[98] Moreover, although PD-1/PD-L1–based ICB shows promise, its efficacy is limited by low response rates and toxicity, partly due to an incomplete understanding of PD-L1 regulation. Recent integrative analyses—from chromatin architecture to extracellular secretion—reveal a remodeled TAD controlling coordinated transcription, multilayered post-transcriptional and post-translational regulation, and exosomal PD-L1 release, highlighting new strategies to improve ICB and combination therapies.[99] Concurrent targeting of PD-L1 and PD-L2 may further help overcome resistance to current PD-1/PD-L1 antibodies. Beyond immune checkpoint targeting, strategies addressing metabolic barriers within the TME are also emerging: the acidic milieu impairs mitochondrial metabolism in macrophages and T cells, driving resistance to oAd-αCD47 therapy. Oral NaBi counteracted acidosis by activating the CaMKII/CREB/PGC1α pathway, restoring immune cell metabolism and enhancing oAd-αCD47 efficacy.[100] Finally, rational engineering of rMVA (MVAΔE5R-Flt3L-OX40L) combined deletion of the cGAS inhibitor E5R with expression of Flt3L and OX40L. Intratumoral delivery elicited robust $CD8^+$ T cell- and cGAS/STING/IFN-dependent responses while selectively depleting $OX40^{hi}CCR8^{hi}$ Tregs, as confirmed by single-cell RNA-seq.[101]

Combined with bispecific T-cell engager

OVs armed with bispecific T cell engagers (BiTEs) represent a versatile strategy to redirect T cells toward tumors while simultaneously inflaming the tumor microenvironment. A B7H3-targeted BiTE-encoding OV achieved high local BiTE concentrations, converted tumors into T cell–inflamed niches, and redirected virus-specific T cells to $B7H3^+$ cancers, while a genome-edited HSV-1 expressing a camelid B7H3/CD3 engager enhanced intratumoral replication and antitumor efficacy.[102,103] Similarly, an NKG2D-BiTE–armed HSV activated T cells in an antigen-independent manner and synergized with radiation-induced NKG2DL upregulation to potentiate glioblastoma killing.[104] Other BiTE-armed OVs have expanded targeting to EpCAM (VV, ADV), MUC16 (ADV), CD19 (VV), and EphA2 (ADV), each demonstrating potent T cell redirection, tumor lysis, and reversal of local immunosuppression across solid and hematologic malignancies.[105-109] Notably, OVV-CD19BiTE outperformed systemic blinatumomab by enhancing intratumoral $CD8^+$ T cell responses and achieving durable tumor control without relapse,[110] while PD-L1 BiTE-armed OVs eradicated PD-L1-positive tumor cells and macrophage, reprogramming "cold" tumors into responsive ones without systemic toxicity.[108] Certainly, engineering oncolytic viruses to deliver tri-specific antibodies also holds significant potential. IMT030122, a tri-specific EpCAM×CD3×4-1BB antibody, elicits potent EpCAM-restricted T-cell activation and cytotoxicity. In colorectal cancer models, it promotes robust $CD8^+$ T-cell recruitment, expansion, and durable tumor control, maintaining efficacy even under lymphocyte-depleted conditions.[111] Together, these studies highlight BiTE-armed OVs as a modular platform for precision immunotherapy capable of overcoming tumor heterogeneity and immune resistance.

Combined with chemotherapy

Chemotherapy remains the most widely used cancer treatment due to its efficiency and broad-spectrum activity, primarily acting through DNA replication inhibition or microtubule disruption. However, chemo-resistant colorectal cancer exhibited reduced sensitivity to oncolytic viruses VSVΔ51 in vitro, in vivo, and in organoids, partly due to aberrant TBK1 activation, which triggers IFN signaling and limits viral replication. TBK1 inhibition restored VSVΔ51 replication, enhanced oncolysis, and amplified antitumor immunity, with NK cells identified as essential mediators of this synergy.[9] Clinically, ONCOS-102 combined with pemetrexed and cisplatin/carboplatin was well tolerated in malignant pleural mesothelioma and induced proinflammatory, T cell–rich tumor microenvironments, correlating with improved 18-month survival.[112] In a phase 2 trial (NCT02779855), neoadjuvant T-VEC plus chemotherapy in stage II-III triple-negative breast cancer achieved a 45.9% RCB0 rate and 65% RCB0–1 rate, with 89% 2-year disease-free survival and no recurrences in RCB0-1 patients; immune activation strongly correlated with response.[113] Similarly, LOAd703 combined with nab-paclitaxel and gemcitabine was safe and feasible in advanced pancreatic cancer, and an ongoing trial is evaluating the addition of atezolizumab.[39] Overall, combining oncolytic viruses with chemotherapy demonstrates synergistic potential by overcoming resistance pathways, enhancing immune activation, and improving clinical outcomes across multiple tumor types.

Combined radiotherapy

Ionizing radiation increases tumor cell permissivity and DNA damage, potentiating oncolytic virus replication, while viral oncolysis enhances radiotherapy (RT)-induced immunogenicity, providing a mechanistic basis for combination therapy. Delta-24-RGD synergizes with RT in pediatric high-grade glioma and diffuse intrinsic pontine gliomas by impairing DNA repair and boosting antitumor immunity, achieving superior therapeutic outcomes.[114] Similarly, combining NDV with RT and PD-1 or CTLA-4 blockade increased complete regression rates and abscopal effects in murine melanoma compared with either therapy alone, while local delivery of recombinant NDV expressing anti-CTLA-4 plus radiation matched the efficacy of systemic checkpoint inhibition.[49] Oncolytic ΔF4LΔJ2R VV replicated in and killed irradiated brain tumor–initiating cells in vitro, and in immune-competent orthotopic CT2A-luc mouse models, a single 10 Gy RT dose plus VACV markedly outperformed.[115] In murine models, high-dose hypofractionated stereotactic body radiotherapy (SBRT) combined with oncolytic VV enhanced antitumor efficacy, expanded splenic $CD4^+Ki\text{-}67^+$ helper and $CD8^+Ki\text{-}67^+$ cytotoxic T cells, increased tumor-infiltrating $CD4^+$ and $CD8^+$ T cells, and reduced intratumoral regulatory T cells.[116] However, OVs combined with RT are often limited by poor viral delivery and insufficient DNA damage. To overcome these barriers, a research team developed RadioOnco (AD@PSSP), an ADV coated with PEI-selenium-PEG, which enhances viral stability, tumor targeting, and infectivity, while suppressing DNA repair proteins (CHEK1, CDK1) to potentiate RT-induced damage.[117] Overall, combining oncolytic viruses with radiotherapy offers synergistic antitumor effects by amplifying DNA damage and immune activation, while novel delivery strategies such as RadioOnco further overcome barriers of viral stability and targeting, paving the way for more effective therapeutic applications.

Combined with small molecule inhibitors

OVT, which couples direct tumor lysis with immune activation, offers a conceptual blueprint for small-molecule inhibitors. $KRAS^{G12C}$ inhibitors synergize with IL-36γ-armed oncolytic virus, and further with PD-1 blockade, to achieve potent and durable tumor remission in $KRAS^{G12C}$-driven models.[118] An artificial microRNA, amiR-4, enhances VSVΔ51 replication by targeting ARID1A; ARID1A inhibition synergizes with EZH2 blockade to trigger synthetic

lethality, while extracellular vesicle-mediated transfer of amiR-4 enables bystander killing of uninfected tumor cells.[119] Forward-genetics–derived reassortant Reoes exhibit enhanced activity against TNBC, with topoisomerase inhibitors promoting viral replication via DNA damage responses; Reo-induced type III IFN is permissive, whereas type I IFN constrains TNBC growth, highlighting a combinatorial strategy to overcome resistance.[120] Reo type III Dearing synergizes with BRAF or MEK inhibition to trigger ER stress–driven apoptosis independently of viral replication, showing potent efficacy against BRAF-mutant tumors in vivo.[121] Proteasome inhibitors promote Reo replication in monocytes by suppressing NF-κB–mediated antiviral signaling, enhancing viral delivery and antimyeloma immunity independent of PI sensitivity.[122] Pevonedistat, a NEDD8-activating enzyme inhibitor, sensitizes tumors to VSVΔ51 by repressing ISGF3 and blocking NF-κB nuclear translocation, thereby inhibiting IFN-I signaling and augmenting oncolytic efficacy.[123] Coxsackievirus B5/Faulkner (CV-B5/F) induces ER stress–dependent apoptosis and autophagy in NSCLC, and DNA-PK or ATM inhibition amplifies DSBs and STING degradation, further enhancing viral replication and tumor cell killing without added toxicity.[124] Collectively, these studies demonstrate that rational combinations of oncolytic virotherapy with targeted small-molecule inhibitors can overcome resistance mechanisms, amplify viral replication, and trigger complementary cell-death and immune pathways, thereby broadening the therapeutic scope of OVT.

Combined with epigenetic modulators

Epigenetic reprogramming modulates antiviral pathways and tumor-intrinsic vulnerabilities, providing a mechanistic rationale for combining OVT with epigenetic agents to enhance therapeutic efficacy. HDAC/BRD4 dual inhibitors as promising agents against virus-associated lymphomas and reinforces the potential of oncolytic strategies to improve therapeutic outcomes.[125] CRISPR screens identify the ncBAF subunit BRD9 as a mediator of resistance to oHSV1. BRD9 loss or inhibition enhances oncolytic efficacy, boosts antitumor immunity, and correlates with improved outcomes in GBM models and clinical trials.[126] METTL3 supports oncolytic virus replication in pancreatic cancer cells with intact antiviral signaling, whereas its depletion triggers a RIG-I dependent antiviral state characterized by type III interferon secretion and upregulation of antiviral sensors, revealing METTL3 as a critical host factor for effective virotherapy.[127] Similarly, SIRT1 limits VSVΔM51 replication and oncolysis in prostate cancer, while HDAC inhibitors enhance viral permissivity via miR-34a mediated SIRT1 suppression, identifying SIRT1 as a key host restriction factor.[128] Together, these findings highlight epigenetic regulators as pivotal modulators of oncolytic virus activity and promising targets to optimize virotherapy.

Relevant OV-based combination therapies are shown in Table 3.

MODULATING OVS-MEDIATED HOST IMMUNE RESPONSES

Neutrophils in oncolytic virus therapy

Neutrophils play a dual role in shaping the tumor microenvironment, shifting between tumor-promoting and tumor-suppressing states in response to diverse cytokines, chemokines, and tumor-derived factors.[129] Neutrophils also play an important role in the therapeutic effects of OVs. Neutrophil depletion or pharmacologic inhibition of PI3Kδ with idelalisib impaired viral clearance, increased VV bioavailability and tumor deposition, and markedly enhanced antitumor efficacy, highlighting transient neutrophil blockade as a strategy to potentiate systemic OVT.[130] Mechanistically, IGF2BP3-driven m6A-dependent CSF3 release promotes neutrophil extracellular trap (NET) formation in glioma via MIB1 mediated FTO degradation. oHSV amplifies this NETosis program, limiting viral efficacy, whereas BET inhibition suppresses IGF2BP3-induced NETosis and enhances oHSV replication through BRD4-CDK9/RPB1 recruitment to viral promoters.[15] Neutrophils infiltrate tumors and foster an immunosuppressive microenvironment that limits OV efficacy. Here, a dual-functional conjugation strategy enables OVs to bind circulating neutrophils, using them as carriers to enhance tumor delivery. Infiltrated neutrophils subsequently undergo cell death, promoting T cell priming, alleviating exhaustion, and remodeling the tumor immune microenvironment, resulting in a 5.4-fold increase in intratumoral OV levels.[131] Conversely, systemic Orf virus therapy in a murine melanoma lung metastasis model triggered a robust influx of immature, activated, cytotoxic neutrophils that exerted TNF-α mediated tumoricidal activity and were essential for full therapeutic efficacy.[132] Together, these findings underscore the context-dependent dual role of neutrophils in oncolytic virotherapy, acting either as barriers that limit viral efficacy or as effectors that enhance antitumor responses.

Dendritic cells in oncolytic virus therapy

DCs are central orchestrators of antitumor immunity and a key determinant of OVT efficacy. Strategies that activate or expand DCs within tumors can enhance T-cell priming, overcome immunosuppressive microenvironments, and synergize with oncolytic viruses to achieve durable therapeutic responses. Intratumoral co-delivery of Delta-24-RGD and a CD40 agonist was well tolerated and elicited durable antitumor immunity, achieving complete responses in up to 40% of diffuse midline glioma models. This efficacy depended on cross-presenting DCs, with therapy promoting DC maturation, antigen uptake, and T-cell proliferation, highlighting DC activation as a key determinant of virotherapy success.[133] To overcome the limited efficacy of DC vaccines in immunosuppressive tumors, a nanohybrid complex combining an oncolytic ADV expressing IL-12 and GM-CSF with PEGylated paclitaxel polymer (oAd/APP) was developed. In glioma models, oAd/APP plus DCs synergistically enhanced intratumoral proinflammatory cytokines, increased DC infiltration and migration to lymphoid organs, expanded tumor-specific T cells, and reduced regulatory T cells, outperforming either monotherapy.[134] Similarly, oncolytic virus M1 (OVM) augments DC vaccine efficacy across multiple tumor models by enhancing $CD8^+$ T-cell infiltration and disrupting the SIRPα-CD47 checkpoint, a dominant suppressor of DC function. OVM downregulates SIRPα in DCs and CD47 in tumor cells while upregulating PD-L1, making PD-L1 blockade highly synergistic with OVM plus DC vaccination. These results position OVM as a potent adjuvant to overcome DC vaccine resistance in immunosuppressive tumor microenvironments.[135] Collectively, these studies highlight dendritic cells as pivotal mediators of oncolytic virotherapy efficacy, with strategies that activate or expand DCs markedly enhancing antitumor immune responses and overcoming tumor-induced immunosuppression.

Macrophages in oncolytic virus therapy

Macrophages are critical regulators of the tumor microenvironment, capable of both suppressing and promoting antitumor immunity. Oncolytic viruses can be engineered to harness or reprogram TAMs, enhancing phagocytosis, skewing macrophage polarization, and stimulating T-cell responses. Strategies that combine macrophage modulation with viral oncolysis or adjunct therapies can potentiate systemic antitumor immunity and improve therapeutic outcomes. An oncolytic VV armed with a CD47-blocking nanobody (OVV-hCD47nb-G1) selectively promoted macrophage phagocytosis of tumor cells while sparing red blood cells, outperforming the anti-CD47 antibody Hu5F9 in lymphoma models; both local and systemic delivery induced tumor regression and prolonged survival via immune remodeling of the tumor microenvironment.[136] Similarly, an ADV expressing a SIRPα/Siglec-10 fusion protein (AdV-mSS) simultaneously blocked CD47 and CD24, enhancing macrophage phagocytosis, skewing TAMs toward an immunostimulatory phenotype, upregulating MHC-I/II, and promoting $CD8^+$ T-cell proliferation and activation, resulting in potent, macrophage and T cell dependent antitumor efficacy.[31] In glioblastoma, dysregulated cholesterol metabolism impairs macrophage phagocytosis and fuels tumor progression; restoring cholesterol efflux with apolipoprotein A1 (ApoA1) reactivated macrophage-T cell immunity by remodeling lipid metabolism and alleviating 7-ketocholesterol–mediated suppression of TNF signaling. An ApoA1-armed oncolytic ADV reinstated antitumor immunity and established durable tumor-specific surveillance.[137] To overcome limited $CD8^+$ T-cell infiltration, oncolytic ADVes expressing neutrophil elastase (ADV^{NE}) or proteinase 3 (ADV^{PPE}) induced pyroptosis and HMGB1 release from colorectal cancer cells, activating TLR4-MyD88-NFκB-NLRP3 signaling in macrophages, driving M1 polarization, and enhancing effector T-cell infiltration and antitumor responses.[138] β-adrenergic blockade synergized with oHSV therapy by increasing $CD8^+$ T-cell infiltration and reshaping the myeloid compartment, reducing immunosuppressive perivascular macrophages ($VEGFA^+CD206^+CCL3^+CCL4^+$) and promoting inflammatory macrophage transition with expanded TCR clonotypes.[139] Conversely, type V ADV skews TAMs toward an M2 phenotype and promotes

Table 3. Key research findings in oncolytic virus therapy.

Classification	Virus	Modification	Combination therapy
CAR-T Therapy	ADV	CXCL11	CAR T therapy
	VSV	None	CAR T therapy
	ADV	None	HER2-CAR T therapy
	ADV	IL-12 and PD-L1Ab	CAR T therapy
	VV	CD19	CD19-CAR T therapy
	VSV	mIFNβ	EGFRvIII CAR T therapy
Immune checkpoint inhibitors	HSV	PD-1 Ab	CTLA-4/TIM-3 antibody
	VV	TIGIT scFv	PD-1/LAG-3 antibody
	VV	Hyal1	CD47 antibody
	VV	FIt3L/OX40L	None
Chemotherapy	VSV	None	TBK1 inhibitors
	HSV	GM-CSF	Chemotherapy
	ADV	GM-CSF	Cisplatin/carboplatin
	ADV	4-1BBL/CD40L	Gemcitabine
Small molecular inhibitors	VV	IL-36γ	KRASG12C inhibitors
	VSV	amiR-4	EZH2 blockade
	Reo	None	Topoisomerase inhibitors
	Reo	None	BRAK-and MEK-targeted inhibitors
	Reo	None	Proteasome inhibitors
	VSV	None	NEDD8 inhibitors
	CVB5	None	DNA-damage response inhibitors
	HSV	None	BRD9 inhibitors
	VSV	None	METTL3 inhibitors
	VSV	None	SIRT1 inhibitors
Radiotherapy	ADV	None	Radiotherapy
	NDV	None	Radiotherapy/PD-1 /CTLA-4 antibody
	VV	None	Radiotherapy
	ADV	None	Radiotherapy

Treg infiltration, dampening antitumor immunity. Thymosin α1 (Tα1) reprogrammed TAMs into an immunostimulatory state, and an ADV expressing Tα1 ($ADV^{Tα1}$) enhanced $CD8^+$ T-cell–mediated tumor control, offering a translational strategy.[140] Chemotherapy with oxaliplatin further potentiated OVT by suppressing IFNs to improve viral retention in injected tumors and reprogramming macrophages in distant lesions to recruit activated T cells, inducing systemic antitumor immunity.[141] Together, these studies demonstrate that macrophages are versatile modulators of oncolytic virotherapy, and strategies that reprogram or harness TAMs can potentiate antitumor immunity, enhance T-cell responses, and improve therapeutic outcomes.

T cells in oncolytic virus therapy

Tumor-specific T cells are often scarce and exhausted, whereas bystander T (TBYS) cells retain functional memory. An oncolytic virus encoding TBYS epitopes (OV-BYTE) redirected tumor recognition to pre-existing TBYS cells, achieving potent tumor control and antigen-spreading driven diversification of tumor-specific responses. Notably, OV-BYTE harnessing SARS-CoV-2 specific memory T cells suppressed tumor progression in xenograft models, highlighting a broadly applicable strategy for enhancing cancer immunotherapy in post-infection or vaccinated populations.[142] Tumor antigens often struggle to trigger strong immune responses. To overcome this, the researchers propose a groundbreaking solution—the H-TVAC system. This approach involves "grafting" highly immunogenic viral antigens onto tumor cells using oncolytic viruses, prompting the immune system to treat the tumor as a virus and mount an immune response to destroy it. The system leverages hepatitis B surface antigen (HBsAg) as a tag, offering a universal strategy for targeting solid tumors and enhancing immune activation.[143] Traditional strategies for engineering oncolytic viruses have focused primarily on activating exhausted intratumoral T cells. Recently, it has been recognized that oncolytic viruses can also activate tumor-irrelevant bystander T cells as well as virus-specific T cells to mediate tumor killing. This therapeutic approach holds great potential for clinical application.

Natural killer cells in oncolytic virus therapy

NK cells are critical effectors of antitumor immunity and can significantly influence the efficacy of OVT. OVs can be engineered to enhance NK cell recruitment, activation, and cytotoxicity, overcoming intrinsic antiviral restrictions and immunosuppressive tumor microenvironments. Strategies that combine viral oncolysis with NK cell targeted modulation offer a powerful approach to improve tumor clearance and therapeutic outcomes. Aberrant

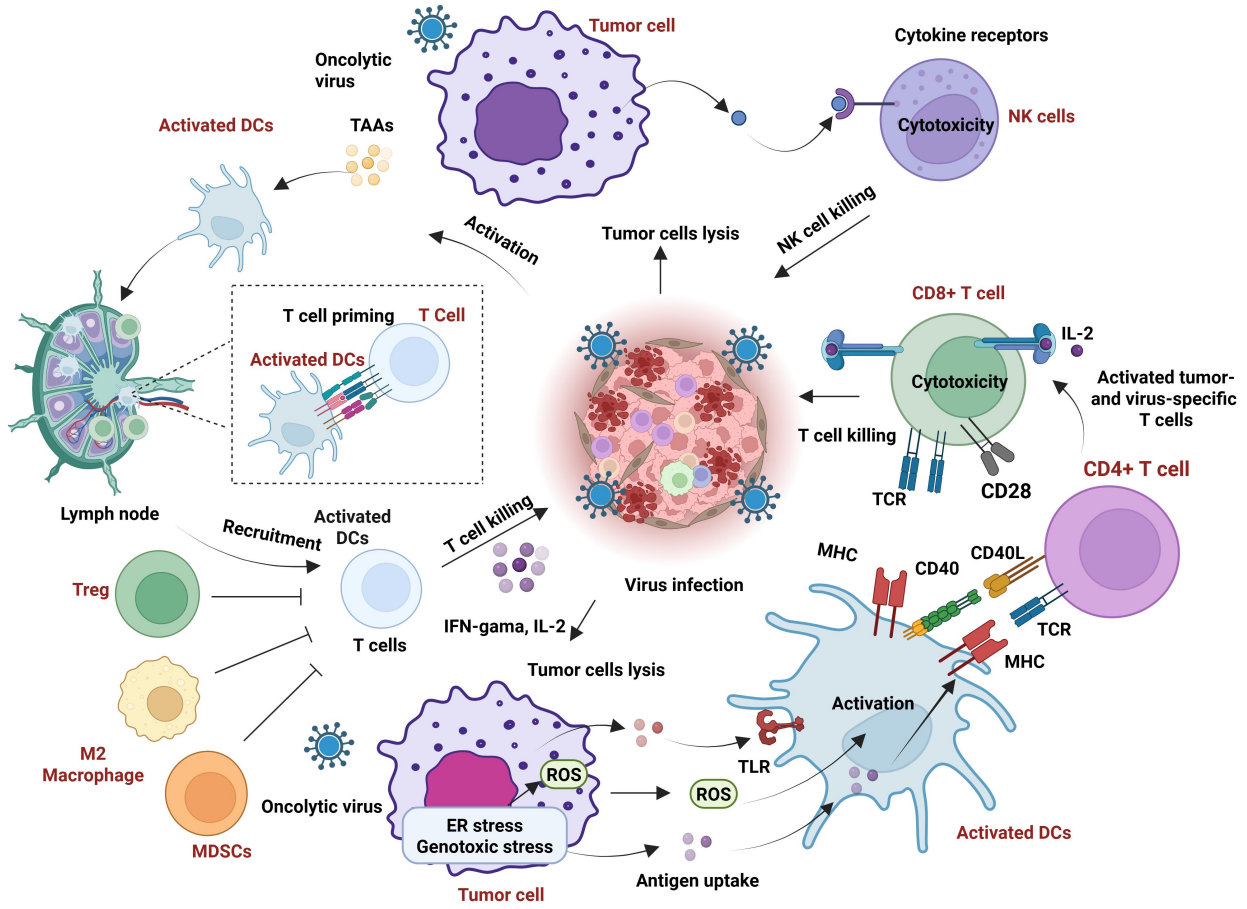


Figure 2. Oncolytic viruses reshape the tumor microenvironment.

TBK1 activation in chemoresistant colorectal cancer restricted OV replication via IFN signaling. TBK1 inhibition restored viral oncolysis, enhanced OV-induced antitumor immunity, and synergized with VSVΔ51 to drive NK cell dependent tumor clearance through RIPK1-mediated ICAM1 upregulation, establishing TBK1 blockade as a strategy to potentiate OV therapy.[9] An oncolytic ADV expressing Decorin (rAd.DCN) further amplified NK cell mediated antitumor activity, promoting NK proliferation, activation, cytotoxicity, perforin and IFN-γ expression, and tumor infiltration, resulting in superior colorectal cancer suppression in xenograft models.[144] Because measles virus activated NK cells exhibited limited direct tumor killing, MV-BiKE, an oncolytic measles virus encoding bispecific killer engagers targeting CD16A and carcinoembryonic antigen, was developed. MV-BiKE retained viral fitness, secreted functional engagers from infected tumor cells, and redirected NK cells to mediate cytokine release, degranulation, and antigen-specific cytotoxicity in colorectal and pancreatic cancer models, including patient-derived specimens.[72] Similarly, an HSV-based oncolytic virus secreting an IL15/IL15Rα fusion (OV-IL15C) enhanced NK and $CD8^+$ T-cell survival and cytotoxicity and, when combined with off-the-shelf EGFR-CAR NK cells, achieved synergistic tumor control in glioblastoma models via improved intracranial infiltration, activation, and persistence of effector lymphocytes.[145] Finally, a CCL5-expressing oncolytic VV retained infectivity while secreting functional CCL5 from infected tumor cells, enhancing $CCR5^+$ NK cell migration and accumulation within tumors without compromising function or viral resistance, outperforming the parental virus in vivo.[146] Together, these findings establish NK cells as pivotal effectors in oncolytic virotherapy, and strategies that enhance NK recruitment, activation, and cytotoxicity can overcome tumor immune evasion and substantially improve therapeutic efficacy.

The mechanism and remodeling strategies of OV remodels the TME is described in Figures 2-3.

CHALLENGES AND OPTIMIZATION STRATEGIES IN SOLID TUMOR OVT

Appropriate experimental animal model

The development of effective experimental animal models is crucial for translating OVT from preclinical to clinical stages. Syngeneic mouse models are essential for evaluating antitumor efficacy and immune responses, although viral replication may be limited by species-specific factors. Human tumor xenografts in immunodeficient mice allow direct testing of viral oncolysis but do not reflect host immunity. Humanized mouse models, which have human immune systems, offer an intermediate platform, though they face challenges like graft-versus-host disease (GvHD) around 40 days after transplantation, complicating the separation of immune responses from viral effects.[147] Large animal models, such as dogs and non-human primates, provide further insights into biodistribution, safety, and dosing. A strategic selection of these models is key for improving the translational relevance and predictive validity of OVT. In the future, the evaluation of the in vivo and in vitro efficacy of oncolytic viruses could be more appropriately conducted using the patient-derived tumor fragment (PDTF) platform and non-human primate tumor models.

Identification of biomarkers for oncolytic virus therapy

The identification of predictive biomarkers is critical for optimizing patient selection and enhancing therapeutic outcomes in OVT. Tumor-intrinsic determinants, including viral receptor expression, intracellular antiviral signaling pathways, and defects in interferon-mediated responses, play a central role in governing viral entry, replication, and direct oncolysis. For instance, differential expression of laminins, nectins, or ICAM-1 has been associated with susceptibility to specific oncolytic viruses.[148-150] Host epigenetic regulators, such as METTL3 and SIRT1, have also emerged as key modulators of viral replication and tumor permissivity.[127,128] Immune-related biomarkers are critical for understanding and optimizing OVT. In addition to direct tumor

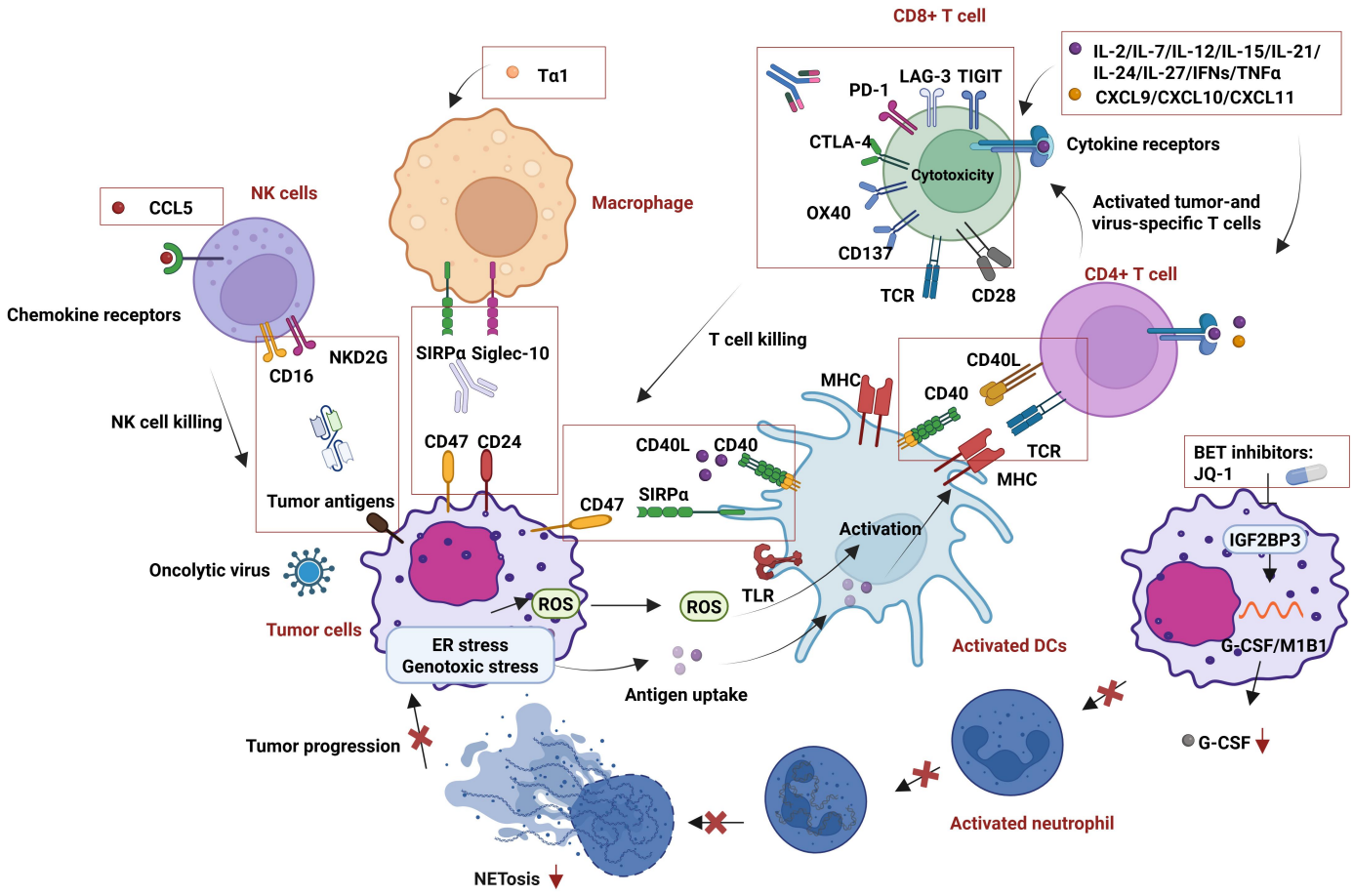


Figure 3. The remodeling strategies of oncolytic virus-induced immune activation and its synergistic effect with immunotherapy.

lysis, OVs reshape the tumor microenvironment and stimulate systemic immunity, making immunological indicators indispensable for evaluating therapeutic responses. Cytokines and chemokines, such as IFN-γ, IL-12, and CXCL10, provide insight into immune activation and T cell recruitment, while the abundance of $CD8^+$ T cells, NK cells, and dendritic cells, along with changes in Tregs and MDSCs, reflect both effector and suppressive dynamics. Immune checkpoint molecules (e.g., PD-1, PD-L1) further serve as predictive biomarkers and guide rational combination with checkpoint inhibitors. Moreover, viral gene expression and circulating viral nucleic acids offer direct evidence of replication and biodistribution. Integration of these biomarkers into OVT studies enables precise monitoring, patient stratification, and the design of synergistic treatment regimens, thereby enhancing translational relevance.

Immunosuppressive barriers of the tumor microenvironment

The immunosuppressive TME constitutes a major barrier to the efficacy of OVT. Although OVs can induce immunogenic cell death and stimulate antitumor immune responses, their therapeutic potential is often attenuated by multiple suppressive mechanisms within the TME. Principal barriers include the accumulation Tregs, MDSCs, and M2 macrophages, which collectively inhibit cytotoxic T lymphocyte (CTL) activation and effector function. Elevated expression of immune checkpoint molecules, such as PD-L1, B7-H3, and TIM-3, further diminishes antiviral and antitumor immunity. Physical and metabolic features of the TME, including hypoxia, nutrient depletion, and the accumulation of immunosuppressive metabolites such as adenosine and lactate, additionally restrict immune activation and limit viral dissemination. Moreover, stromal components and aberrant vasculature create structural barriers that impede immune cell infiltration and effective OV delivery. Strategies to overcome these immunosuppressive constraints-including viral engineering, immune checkpoint blockade, metabolic reprogramming, and modulation of myeloid cell phenotypes are essential to fully unleash the therapeutic potential of OVT.

Delivery inefficiency imposed by the structural barriers of solid tumors

Efficient delivery of OVs to solid tumors remains a formidable challenge due to the structural and physiological barriers intrinsic to the TME. Dense extracellular matrix (ECM) components, including collagen, laminin, and hyaluronic acid, impose a physical impediment that limits viral penetration and intratumoral dissemination. Aberrant tumor vasculature and elevated interstitial fluid pressure further constrain systemic delivery and uniform distribution of OVs, resulting in heterogeneous infection and suboptimal oncolysis. Additionally, hypoxia and metabolic gradients within tumors can impair viral replication and attenuate antiviral immune responses, thereby reducing therapeutic efficacy. Strategies to circumvent these barriers include enzymatic degradation of ECM components, co-administration of matrix-modulating agents, utilization of nanoparticle or cell-based carriers, and viral engineering to enhance tissue tropism and intratumoral diffusion. Overcoming these structural constraints is critical for improving viral delivery, maximizing oncolytic activity, and eliciting robust antitumor immune responses.

Safety Considerations in OVT

OVT holds remarkable promise as a therapeutic approach for cancer, offering the potential for targeted, selective tumor destruction with minimal side effects. However, the safety of these treatments is a complex issue that requires careful consideration of the host immune response, viral containment, genetic stability, and long-term outcomes. As clinical trials progress, rigorous safety monitoring and the development of advanced viral engineering techniques will be essential in ensuring the safe and effective use of OVs in cancer therapy. Given the rapid evolution of both viral engineering and cancer immunology, a multi-disciplinary approach will be critical to optimiz-

ing the therapeutic benefits while minimizing associated risks.

The clinical use of oncolytic viruses is increasingly widespread. T-VEC is generally well tolerated, with mostly mild adverse events. In a Phase I trial, the primary side effect was grade 1/2 fever, particularly in HSV-seronegative patients, along with fatigue, nausea, vomiting, and anorexia.[151] In a Phase II study, 85% of patients with advanced melanoma experienced grade 1/2 flu-like symptoms, and three responders developed vitiligo, a phenomenon also observed with other immunotherapies such as IL-2.[152] In the Phase III OPTiM trial, T-VEC demonstrated good overall tolerability; common adverse events included fatigue, chills, and fever, while grade 3/4 events were rare, with cellulitis reported in just over 2% of patients.[153] Overall, these findings underscore the favorable safety profile of T-VEC, supporting its continued clinical use in melanoma.

NEXT-GENERATION OVT STRATEGIES

Innovative aspects of recent OVT strategies

Recent breakthroughs in oncolytic virus therapy have opened new possibilities for cancer treatment. One such innovation involves creatively reverse-applying the harmful phenomenon of "hyperacute rejection" from organ transplantation to cancer therapy. This approach has been successfully demonstrated in both preclinical models and human trials, offering a novel strategy for cancer immunotherapy.[50] Besides, immunoglobulin E (IgE)-sensitized mast cells (IgE-MCs) acts like an "invisible cloak" for oncolytic viruses, protecting them and ensuring their smooth delivery to the tumor site. Once IgE-MC recognizes tumor-associated antigens, it rapidly releases the oncolytic virus it carries, enabling precise infection of tumor cells.[154] These innovative approaches provide new avenues for enhancing tumor-specific immunity and advancing cancer immunotherapy.

Future Directions for the Modification of OVT

The primary objectives of next-generation OV development are to balance potent oncolytic activity with safety, thereby facilitating the release of sufficient tumor antigens to promote antigen spread and elicit robust immune responses within an immune-activated environment. Given the transient presence of OVs within tumors, it is essential that they induce a localized "cytokine storm" within this limited time frame. This necessitates a careful evaluation of which exogenous factors, when delivered alongside the virus, can synergistically enhance the immune response triggered by viral infection. Moreover, conventional anti-cancer therapies, typically administered systemically, exert diverse effects on the immune system. While some may amplify the anti-tumor immune response initiated by OVs, others may potentially antagonize the therapeutic outcomes. Therefore, a critical avenue for future research lies in optimizing the integration of OV-induced changes in the tumor microenvironment with these therapeutic modalities to maximize clinical efficacy.

Besides, different tumor types have distinct TME and varying degrees of immune suppression. The differences in TME phenotypes across various solid tumors can significantly influence the efficacy of OVTs. The TME of each tumor type varies in terms of immune cell composition, hypoxia levels, extracellular matrix characteristics, and cytokine milieu, all of which can impact the virus's ability to infect, replicate, and kill tumor cells. For example, tumors with a highly immunosuppressive TME may hinder the activation of the immune system by OVTs, while those with a more immune-permissive environment may enhance the therapeutic effect. Certain OVs are engineered to exploit specific aspects of the TME, such as receptor expression or immune modulation, making them more effective in certain tumor types. In the future, it may be possible to design oncolytic viruses with specific immune-modulatory functions tailored to different tumor types, targeting epigenetic regulation and metabolic pathways.

CONCLUSIONS

OVT is rapidly emerging as a versatile cancer immunotherapy, combining tumor-selective cytolysis with potent activation of innate and adaptive immunity. Engineered viruses demonstrate efficacy across diverse solid tumors, while combination strategies with checkpoint inhibitors, CAR-T cells, and conventional therapies further amplify antitumor responses. Key challenges remain in systemic delivery, immune clearance, tumor heterogeneity, and intratumoral spread, but advances in viral engineering and immune modulation promise to overcome these barriers. Collectively, oncolytic viruses represent a multifaceted platform capable of durable tumor control and adaptive immunity, justifying continued clinical exploration and optimization.

Oncolytic viruses reshape the TME by infecting tumor cells, triggering the release of cytokines, chemokines, and DAMPs, which activate an innate immune response. These signals recruit immune cells—such as dendritic cells, natural killer cells, and T cells—to the tumor site. The viral-induced tumor cell lysis exposes TAAs and viral PAMPs, which are captured by dendritic cells and presented to T cells in the draining lymph nodes. This activates an adaptive immune response, further recruiting T cells to the tumor and overcoming immune suppression. The combined action of innate and adaptive immunity reshapes the TME, enhancing anti-tumor immunity.

OVs selectively infect tumor cells, inducing ER stress, genotoxic damage, and ROS production, which promote tumor antigen release and uptake by DCs. DCs present antigens via MHC to $CD8^+$ and $CD4^+$ T cells, providing co-stimulatory CD40–CD40L signals and driving tumor-specific cytotoxicity. NK cells are recruited by chemokines and recognize stressed tumor cells through NKG2D and CD16. Viral infection also disrupts tumor-associated macrophage "don't eat me" signals (CD47–SIRPα, CD24–Siglec-10), enhancing phagocytosis. Concurrently, BET inhibitors limit G-CSF/M1B1 signaling, restraining neutrophil activation and NETosis, and alleviating immunosuppressive effects. Collectively, OVs orchestrate direct oncolysis and reshape the tumor immune microenvironment to amplify anti-tumor immunity.

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AUTHOR CONTRIBUTIONS

C. Wu and Y. Xia drafted the manuscript and completed the figures and tables; C. Wu, T. Xing, X. Cheng and Y. Xia collected the references; C. Wu, T. Xing, X. Cheng and Y. Xia revised the manuscript; Y. Xia provided funding support. All authors have read and approved the final manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

No new data were created or analyzed in this study.