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REVIEW ARTICLE

Complementing a pair of distinct engineered oncolytic viruses with functionalized magneto-nanoparticles for enhanced cancer targeting therapy: A revisit

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Abstract

Oncolytic viruses (OVs) are emerging as promising cancer immunotherapeutic agents due to their cancer-directed oncolysis and ability to induce potent and durable anticancer immune responses. They have shown encouraging results even in tumors that are resistant to conventional therapies. However, the therapeutic efficacy of OVs is hindered by antiviral immune responses that eliminate OVs before they reach their target site and the tumor stroma, limiting intratumoral virus spread in the tumor microenvironment (TME). To address these challenges, various strategies have been developed to shield OVs from immunosurveillance by loading viruses onto/into cellular carriers, extracellular vesicles, liposomes, and nanoparticles. Despite notable improvements in viral shielding and targeting strategies, inefficient intratumoral viral penetration remains a critical obstacle. In the TME, the tumor stroma accounts for 90% of the entire tumor mass, comprising non-cancerous cells and extracellular matrix. Since OVs are engineered to target only cancer cells, their cytolytic efficacy is counteracted by the tumor stroma. Therefore, innovative approaches are necessary to enhance the penetration of viruses within tumors, thereby increasing the efficacy of oncolytic virotherapy. This review aims to provide a comprehensive overview of OVs in terms of clinical applications, successes, and limitations, while also discussing future directions for enhancing the targeted delivery and intratumoral penetration of OVs.

Keywords: Virotherapy; Oncolytic viruses; Tumor microenvironment; Cancer immunotherapy; Targeted cancer therapy; Functionalized magneto-nanoparticles

1. Introduction

1.1. Introduction to oncolytic virus (OV) immunotherapy

Conventional cancer treatment methods, such as surgery, chemotherapy, and radiotherapy,[1,2] often produce satisfactory outcomes and are frequently associated with treatment-related side effects.[3,4] In contrast, cancer immunotherapy has evolved into a targeted cancer treatment approach that holds promise for enhancing patient outcomes while minimizing off-target toxicities. This method is now routinely utilized for both neoadjuvant and adjuvant therapies in various metastatic cases. Cancer immunotherapy functions by activating the patient's immune system to identify and eliminate cancer cells through strategies such as monoclonal antibodies, T-cell therapies, cancer vaccines, and OV immunotherapy (OVI).[5-7] Notably, OVI has shown encouraging results in pre-clinical and clinical trials due to its targeted antitumor activity.[8] OVs constitute a category of viruses that exhibit a natural preferential lytic infection of cancer cells and can be genetically engineered to selectively infect, replicate within, and lyse cancerous cells. The concept of exploiting viruses for cancer treatment originated in 1904, following a patient diagnosed with acute leukemia who went into remission after an influenza viral infection.[9,10] A similar clinical finding was also reported in a patient diagnosed with cervical cancer who had extensive tumor necrosis following a viral infection.[11]

The choice of viruses as potential OV candidates is contingent upon their capacity to specifically target and destroy cancer cells. Furthermore, these candidate viruses should possess a substantial genome size that allows for straightforward engineering to incorporate multiple therapeutic transgenes. They must also demonstrate the ability to replicate and disseminate across various tumor types while being incapable of inducing serious diseases.[12,13] Herpes simplex virus (HSV) serves as a notable example of an OV, with its large genome providing capacity for the insertion of multiple therapeutic genes.[14] HSV has an established safety profile, as it establishes latent infections that are manageable with antiviral therapy and can be engineered to infect a wide range of tumors.[15,16] Furthermore, transcriptional targeting of oncolytic HSV (oHSV) to cancer cells has been improved by deleting critical genes required for virus replication in non-dividing cells to limit off-target toxicity.[17]

1.2. Current status and clinical relevance of OV immunotherapy

OV immunotherapy has emerged as a promising new generation of cancer immunotherapy, which exerts its dual anticancer activity through cytolysis caused by intratumoral viral replication (Figure 1A) and the induction of an antitumor immune response.[18,19] Virus-based lysis of cancer cells results in the release of tumor-associated antigens that stimulate both innate and adoptive anticancer immune responses.[20] This dual anticancer activity of OVs has demonstrated better therapeutic outcomes in primary tumors, metastatic tumors, and tumors resistant to standard anticancer therapy.[21-23] Furthermore, the intratumoral replication of OVs that scale up viral load over time (dose amplification) makes OVI more efficient than conventional chemotherapy (Figure 1B), whose loading dose decreases over time due to hepatic drug metabolism, reducing the therapeutic lethal dose to the tumor.[24,25] Unlike chemotherapy, OVs are engineered to target different molecular pathways that promote cancer growth and metastasis by equipping them with different therapeutic transgenes. A good example is the oncolytic vaccinia viruses (VVs), which are armed with soluble vascular endothelial growth factor (VEGF) receptor-1 protein and granulocyte-macrophage colony-stimulating factor (GM-CSF) to target tumor vasculature and activate anticancer immune responses, respectively.[26-28]

As clinical trials of OVs generate encouraging outcomes, various therapeutic combination strategies involving OVs with other OVs, chemotherapy, radiotherapy, or immune checkpoint inhibitors (ICI) are being explored to identify the most efficient combination modality.[29] For instance, the evidence shows that combination therapy of OVs with either chemotherapy or ICI elicits a synergistic antitumor immune response that boosts the effectiveness of the treatment (Figure 1C). Similarly, the combination strategy of optimizing two viruses expressing either similar antigens or different therapeutic transgenes with synergistic activity to potentiate their oncolytic potency has also been investigated.[30] For instance, the benefit of synergistic activity has been demonstrated with the combination of a recombinant vesicular stomatitis virus (VSV) and VV, whereby the tumoricidal efficiency was superior in the combination modality than a single use of each virus alone, both in *ex vivo* and *in vivo* studies.[31] The possibility of sequentially using two antigenically different oncolytic adenoviruses (oAdV), followed by either VV or Newcastle disease (NDV) OV to treat solid tumors, such as pancreatic adenocarcinoma in animal models, has been demonstrated to boost oncolytic efficacy through activation of anticancer immune responses.[32,33]

1.3. Scope and objectives

In this review, we address the urgent challenges of immune clearance and stromal barriers that limit the efficacy of OVI in solid tumors. We also propose novel strategies

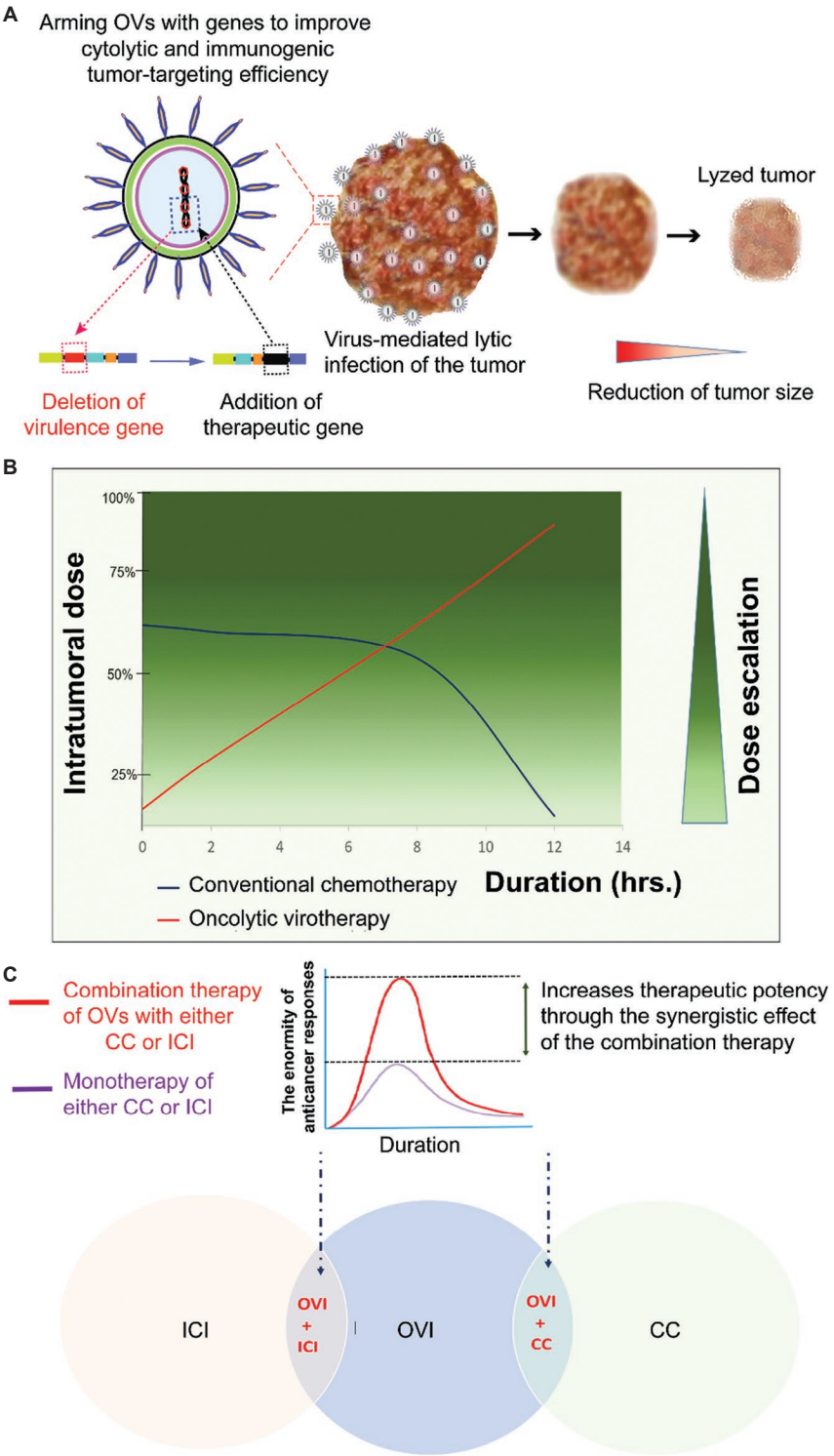

Figure 1. Development of OVs and their clinical application. (A) Schematic diagram showing genetic manipulation of OVs involving the removal of pathological genes and adding genes for improving oncolysis. (B) Oncolytic virotherapy has therapeutic benefits over chemotherapy, as viral replication enables intratumoral amplification, whereas chemotherapeutic drug concentrations are reduced by hepatic metabolism. (C) OVI makes "cold" (non-immunoresponsive) tumors "hot" (immunoresponsive), improving the effectiveness of conventional therapies by complementing the tumoricidal effect, particularly ICI.[34,35] Image created by the authors.

Abbreviations: CC: Cytotoxic chemotherapy; ICI: Immune checkpoint inhibitors; OVs: Oncolytic viruses; OVI: Oncolytic virus immunotherapy.

using functionalized magnetic nanoparticles (MNPs) to shield OVs from immune surveillance and disrupt stromal barriers, offering a new focused perspective on how these innovations could enhance OVI delivery, viral spread, and therapeutic efficacy in immune-refractory, stroma-dense cancers. We do not focus on specific OVs but rather provide an overview of the clinical application of OVs and highlight methods used to encapsulate OVs to improve OV targeting. We also discuss the success and limitations of OVI as well as suggest a promising strategy to complement the anticancer activity of OVs.

2. Clinical application of OVs

The tumor-targeting efficiency and restoration of antitumor immune response at the tumor microenvironment (TME) have prompted numerous studies evaluating the clinical utility of combining OVIs with other cancer therapies. OVs reverse "cold" TME (non-immunoresponsive) to "hot" (immunoresponsive), thereby improving the effectiveness of standard anticancer therapy.[34,35] For instance, the combination of OVIs with ICI has shown an improvement in therapeutic effect, mostly in a subgroup of patients who failed to respond to ICI due to immunosuppressive TME.[36,37] Similarly, recent studies have shown that the use of OVs with cytotoxic chemotherapies generates a synergistic tumoricidal activity that results in enhanced therapeutic effects not attained via the use of individual therapy alone.[38]

OV immunotherapies are in various stages of development, ranging from discovery and pre-clinical research to clinical trials (Phases I–III).[39,40] For instance, numerous clinical trials are currently underway to assess the therapeutic efficacy of teserpaturev/G47Δ (Delytact®), a triple-mutated strain of HSV-1 approved in Japan for the treatment of high-grade gliomas.[41] Ongoing clinical trials include Phase I trials in malignant mesothelioma and olfactory neuroblastoma, as well as a Phase III trial in prostate cancer treatment.[42] Other genetically modified OVs that have not yet been registered but demonstrate promising anticancer activities, including Pexa-Vec,[43] palareorep,[44] measles virus (MV),[45] parvovirus H-1,[46] and CG0070,[47] are summarized in Table 1.

For instance, ONCOS-102 is a genetically engineered adenovirus (AdV) that expresses human GM-CSF for selective replication in cancer cells. A pre-clinical study conducted by Kuryk *et al.*[67] showed that the combination of ONCOS-102 and anti-PD-1 pembrolizumab had an incredible therapeutic effect in treating melanoma in humanized mice. In a Phase I clinical study, ONCOS-102 was well-tolerated and demonstrated promising results in patients with solid tumors who did not respond to conventional therapy. Interestingly, ONCOS-102 has been reported to elicit both local and systemic antitumor immune responses.[54]

Another AdV 5-based OV, VCN-01, is used to treat osteosarcoma in children. Modified VCN-01 targets cancer cells that are dysfunctional in the retinoblastoma gene (Rb) pathway. Phases I and II clinical trial data have shown encouraging clinical results.[50] ICOVIR-7 is another AdV-based OVI used to treat refractory and late-stage solid tumors that replicate selectively in cancer cells that have a defective Rb-p16 pathway.[53] LOAd703 is an oAdV with TMZ-CD40L and 4-1BBL transgene insertions for triggering anticancer immune response.[51] DNX-2401 is an OVI designed with high potency and safety to counteract and kill devastating recurrent brain tumors (gliomas). The virus was engineered from a replication-competent oAdV by deleting the *E1A* gene, making it capable of replicating only in cancer cells with a deregulated Rb signaling pathway. This modification allowed DNX-2401 to attack only glioma cells by inducing cytolytic infection and enhancing the antitumor immune response. Additional improvement in the oncolytic potency was achieved by modifying the RGD-4C binding motif for targeting cancer cells via αvβ3 and αvβ5 integrins.[55]

Furthermore, some of the OVs are engineered to treat unresectable and aggressive tumors, such as glioblastoma multiforme and melanoma. For example, OVIs in clinical trials for the treatment of refractory brain tumors (glioma) and extracranial tumors include Seprehvir (HSV1716),[56] M032 (oHSV),[60] Canerpaturev,[62] and NDV.[66] On the other hand, OVs that are engineered to treat unresectable malignant melanoma via intraregional injection include OrienX010,[61] PVSRIPO,[63] Cavatak,[64] and LOAd.[52]

Although numerous clinical trials for OV-based cancer therapies are still ongoing, there are only four registered OVIs, including Rigvir, Oncorin, T-VEC, and teserpaturev, that are utilized to treat squamous cell carcinoma of the head and neck, malignant glioma, and melanoma.[68] Rigvir/ECHO-7 is a non-virulent, non-genetically engineered virus used to treat melanoma and was registered as an OVI in Latvia in 2004.[65] A retrospective analysis of the efficacy of Rigvir in early-stage melanoma patients demonstrated a significant reduction in mortality and prolonged survival without side effects, with mortality odds 4.39–6.57 times lower than those in the control group.[65] Another OVI is Oncorin (H101), the oAdV with deleted *E1A/E1B* genes. Oncorin was approved by China's State Food and Drug Administration in 2005 for the treatment of patients with nasopharyngeal cancer in combination with chemotherapy.[49] Furthermore, talimogene laherparepvec (T-VEC) is a registered OVI,

Table 1. A comprehensive summary of oncolytic viruses categorized into natural or genetically engineered DNA or RNA viruses

Viruses/OVI	Modifications	Target cancer types	Mechanism of action
Genetically engineered DNA viruses in OVI			
AdV			
ONYX-015[48] (dl1520)	Chimeric AdV serotypes 2 and 5 backbone attenuated by deleting the *E1B-55K* coding sequence	Head and neck cancers, NSCLC	Selective replication in p53-deficient cancer cells induces lysis by exploiting tumor cell defects.
Oncorine[49] (H101)	AdV vector serotype 5 with E1B-55kD and E3 partial deletion	Nasopharyngeal carcinoma	Targets p53-deficient cancer cells; enhances tumor lysis synergistically with chemotherapy.
CG0070[47]	Human GM-CSF cDNA insertion in the E3 region of AdV5 genome	Bladder cancer	Expresses GM-CSF to stimulate immune response; selectively replicates in pRb-deficient tumor cells.
VCN-01[50]	AdV5-based OV that is pRb-dependent and loaded with a transgene encoding human PH 20 hyaluronidase for tumor selectivity	Pancreatic cancer, retinoblastoma	Targets pRb-deficient tumors; PH 20 breaks down hyaluronan in stroma, improving viral spread.
LOAd700[51,52]	AdV serotype 5/35 with one anticancer immune stimulator inserted: *TMZ-CD40L*	Pancreatic cancer, solid tumors	Expresses CD40L to activate dendritic cells and stimulate T-cell-mediated antitumor immunity.
LOAd703[51,52]	AdV serotype 5/35 with two anticancer immune stimulators inserted: *TMZ-CD40L* and *4-1BBL*	Pancreatic cancer, ovarian cancer	Dual activation of CD40L (dendritic cells) and 4-1BBL (T-cell co-stimulation) to enhance immune attack.
ICOVIR-7[53]	pRb-dependent AdV5 modified by 24 bp deletion in *E1A* as well as insertion of *E2F-1* promoter modified with *E2F* binding hair-pins	Glioblastoma, solid tumors	Selectively replicates in pRb-deficient tumor cells, promoting targeted viral replication and lysis.
ONCOS-102[54] (CGTG-102)	AdV5 with chimeric capsid serotype 3-fiber knob (AdV5/3) armed with GM-CSF	Mesothelioma, melanoma, NSCLC	Targets tumor cells via integrins (αvβ3/αvβ5); GM-CSF promotes dendritic cell activation and immunity.
DNX-2401[55] (tasadenoturev)	AdV with *E1A* deleted gene and modification of RGD-4C binding motif for targeting OVs to cancer cells via αvβ3 and αvβ5 integrins	Glioblastoma, solid tumors	Selectively binds integrins (αvβ3, αvβ5) overexpressed in tumors; replicates in cancer cells to induce lysis.
HSV-1			
Seprehvir®[56] (HSV1716)	HSV-1 with *ICP34.5* gene deletion for selective replication in cancer cells	Glioblastoma, pediatric cancers	Targets and selectively replicates in cancer cells; avoids normal cells due to *ICP34.5* deletion.
Talimogene laherparepvec[57,58] (Imlygic®) (T-VEC)	Attenuated HSV engineered by deletion of *ICP34.5* and *ICP47* lethal genes and armed with human GM-CSF transgene	Melanoma	Direct lysis of tumor cells and GM-CSF-mediated recruitment of dendritic cells to activate immunity.
Teserpaturev/ G47Δ[59] (Delytact®)	Triple-mutated HSV-1, which has deleted γ*34.5*, α*47*, and *ICP6* viral genes, along with an insertion of the *Escherichia coli LacZ* gene	Glioblastoma, prostate cancer	Selectively replicates in cancer cells; induces immune responses while minimizing neurotoxicity.
G207[59]	HSV-1 with deleted *γ34.5* and *ICP6* genes and *LacZ* insertion	Glioblastoma, brain tumors	Selective replication in tumor cells; *LacZ* insertion serves as a reporter for viral distribution.
M032[60]	HSV modified by deleting the *ICP34.5* gene and inserting *IL12*	Glioblastoma, brain tumors	Selective replication in tumor cells; IL-12 promotes immune cell activation and antitumor response.
OrienX010[61]	Engineered HSV-1 with deletion of *ICP34.5* and *ICP47* genes, and insertion of human GM-CSF transgene	Solid tumors, melanoma	Selectively lyses tumor cells while GM-CSF stimulates dendritic cell activation and immune responses.
Canerpature[62] (C-REV/HF10)	HSV with natural deletion and insertion resulting in loss of expression of *UL43*, *UL49.5*, *UL55*, *UL56*, and *LAT*	Pancreatic cancer, breast cancer	Natural tumor selectivity; replicates preferentially in cancer cells, inducing direct lysis.

(Cont'd)

Table 1. ***(Continued)***

Viruses/OVI	Modifications	Target cancer types	Mechanism of action
VV			
Pexastimogene devacirepvec[43] (Pexa-Vec/ JX-594)	VV with deleted thymidine kinase and insertion of human GM-CSF transgene and β-galactosidase transgenes for immune stimulation	Liver cancer, solid tumors	Selective replication in TK-deficient tumor cells; GM-CSF enhances immune response against the tumor.
Natural and genetically engineered RNA viruses in OVI			
Picornaviruses			
PVSRIPO[63]	Live attenuated type-I poliovirus, where the IRES of the poliovirus receptor CD155 was replaced with IRES from human rhinovirus type 2	Glioblastoma, solid tumors	Targets cells expressing CD155 receptor (overexpressed in tumors); induces direct lysis and immunity.
Cavatak[64]	Coxsackievirus A21 is a natural virus	Melanoma, bladder cancer	Natural tumor tropism for ICAM-1-expressing cancer cells; triggers lysis and enhances immune response.
Echovirus group			
ECHO-7[65] (Rigvir®)	Natural OVs	Melanoma	Naturally targets and lyses tumor cells; no genetic modification.
Reovirus			
Palareorep[44] (Reolysin®)	Unmodified oncolytic reovirus type 3	Breast cancer, pancreatic cancer, NSCLC	Direct cytotoxic activity by selectively replicating in and lysing Ras-activated tumor cells.
Paramyxoviridae family			
MV[45]	Engineered to express human CEA by inserting the human *MV-CEA* gene and/or the human *NIS* gene to express human NIS (MV-NIS virus)	Ovarian cancer, multiple myeloma	Selectively infects tumor cells expressing CD46; human MV-CEA allows monitoring, while human NIS enables radiotherapy synergy.
Newcastle disease virus[66]	Natural virus	Glioblastoma, lung cancer	Natural tumor selectivity via defective IFN signaling in cancer cells induces apoptosis and immune activation.
Parvovirus			
Parvovirus H-1[46] (ParvOryx)	Natural virus	Glioblastoma, pancreatic cancer	Replicates in rapidly dividing tumor cells; induces lysis and stimulates innate immune responses.

Abbreviations: AdV: Adenovirus; CEA: Carcinoembryonic antigen; GM-CSF: Granulocyte-macrophage colony-stimulating factor; HSV: Herpes simplex virus; ICAM: Intercellular adhesion molecule; IL: Interleukin; IRES: Internal ribosomal entry site; MV: Measles virus; NIS: Sodium/iodide symporter; NSCLC: Non-small cell lung carcinoma; OVI: Oncolytic virus immunotherapy; OVs: Oncolytic viruses; pRB: Retinoblastoma protein; TK: Thymidine kinase; VVs: Vaccinia viruses.

which exploits the HSV-1 approved by the United States Food and Drug Administration to treat patients with recurrent melanoma.[57,58]

3. Methods for encapsulating OVs

The effectiveness of OVs is hindered by antiviral immune reactions, which involve neutralizing antibodies and circulating immune cells. To overcome this issue, various biocompatible viral shuttling tools (BVSTs) have been developed to protect OVs from neutralizing antibodies and innate immune surveillance (Figure 2A). Targeted BVSTs optimized for OVs to date include synthetic NPs, such as liposomes (LPOs), MNPs, and natural biological vectors, including cell-mediated vehicles and extracellular vesicles (EVs).[69] Biological vehicles are inherently capable of selectively homing in tumors, whereas synthetic vehicles are structurally decorated on their surface with specific tumor-binding ligands or manipulated by external magnetic fields (EMFd) to target the tumor.[70-73]

In particular, the cell-mediated vehicles model involves different types of cells, which include immune and cancer cells.[74-77] For instance, packaging either oncolytic VSV or reovirus in modulated T-cells with chimeric antigen receptor (CAR) T-cells has demonstrated an improved virus delivery to the tumor, thereby boosting the therapeutic potency of CAR T-cells in solid tumors.[74] Alternatively,

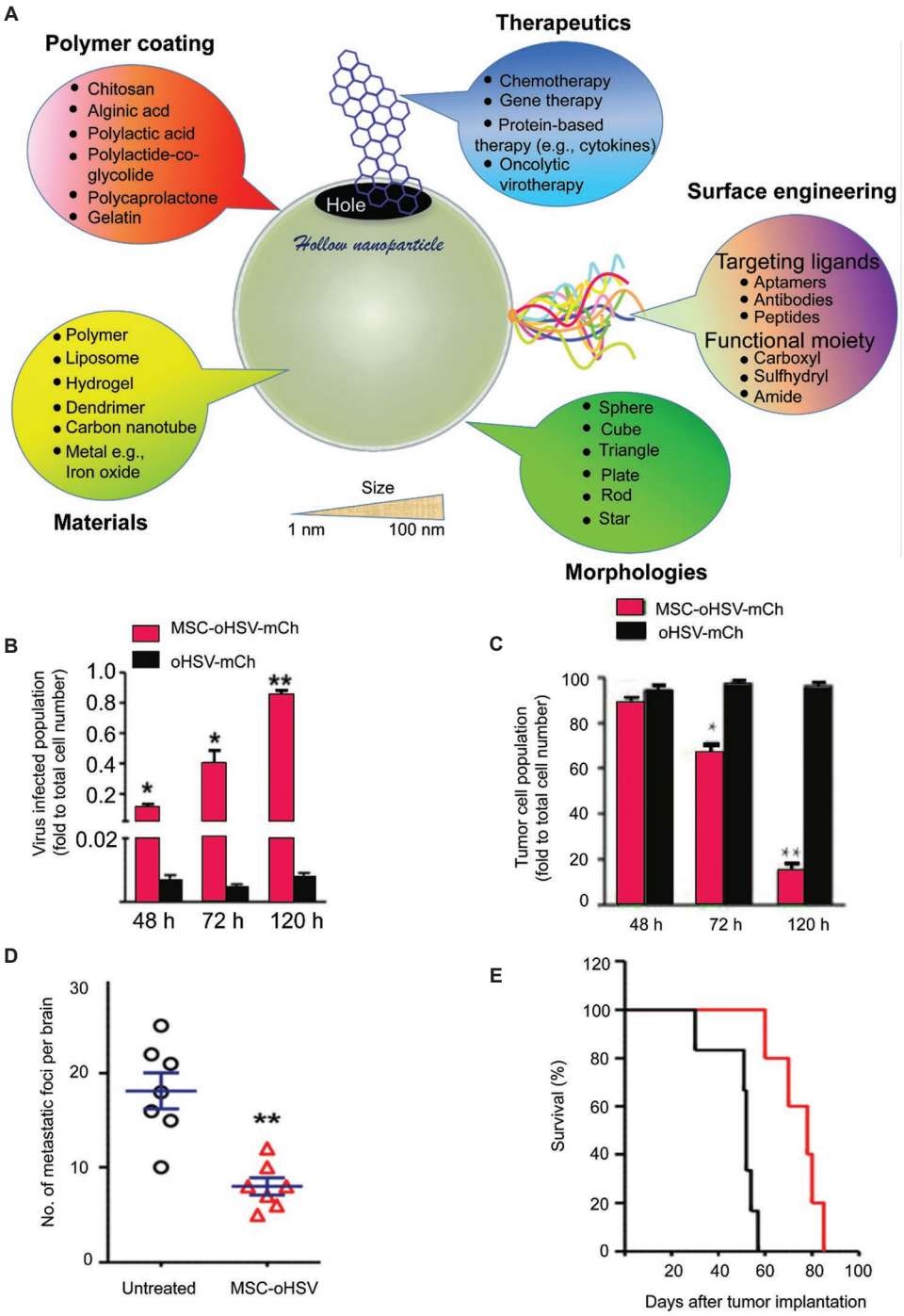

Figure 2. Functionalized hollow nanoparticles are used as a vehicle for targeted delivery, therapeutic, and diagnostic purposes. (A) Depending on the material used, nanoparticles are produced in different sizes, shapes, and types. (B) The populations of oHSV-mCh-infected cells. (C) The populations of tumor cells in the brains of mice at different time points after internal carotid artery injection of MSC-oHSV-mCh or purified oHSV-mCh versus the oHSV-mCh-injected group (n = 3 mice per group). (D) Number of pigmented metastatic foci in the brain of MSC-oHSV-treated and untreated mice 4 weeks after tumor cell implantation (n = 7 mice per group). (E) Kaplan–Meier survival curves of brain-tumor-bearing mice treated with MSC-oHSV or control MSCs, p=0.0014 in MSC-oHSV and control MSC comparison, log-rank test (n = 6 mice per group). Figure 2B–E reproduced with permission from Du *et al.*[7]

Notes: *p<0.05, **p<0.01.

Abbreviations: mCh: mCherry; MSC: Mesenchymal stem cells; oHSV: Oncolytic herpes simplex virus.

radio-sterilized multiple myeloma-derived cells represent another group of carrier cells used for the targeted delivery of OVs in disseminated multiple myeloma (DMM) disease. The choice of myeloma cancer cells as a carrier vehicle was considered the histological similarity between carrier cells and target cells, which ensures selective homing of OVs to DMM lesions, as well as the successful replication of OVs in carrier cells.[76] In addition, myeloma carrier cells overexpress the chemokine receptor type-4, which directs them to the bone marrow regions where DMM tumors grow. Apart from myeloma cells, mesenchymal progenitor cells have also been utilized to target OVs to DMM tumors.[76] Similar results have been reported, with mesenchymal stem cells (MSCs)-based encapsulation of oHSV shielding viral particles from the immune response. Systemic administration of oHSV-loaded MSCs targeted metastatic melanoma cancerous cells in the brain, thereby prolonging survival in mouse models (Figure 2B–E).[7]

Extracellular vesicles are intercellular messengers that specifically deliver biomolecular information to target cells.[78] Since they are accepted by immune cells, they are used to target OVs to tumors. The literature suggests that EVs secreted from cells infected with viruses carry viral components, such as proteins and nucleic acids.[79] For example, EVs derived from cytomegalovirus (CMV) infected fibroblasts have been reported to carry CMV-related glycoproteins.[79] The evidence suggests that OVs encapsulated in EVs are more infectious than non-encapsulated/naked viruses because EVs are better at shielding and targeting viruses to the tumor site.[80]

In vitro studies have shown that EVs loaded with oAdV induce cancer cell death significantly more than naked oAdV. Similar results have been reported in *in vivo* studies, justifying that the systemic administration of oAdV-loaded EVs potentially suppresses tumor growth compared to the use of naked oAdV.[81]

On the other hand, LPOs have also been used as BVSTs for the targeted delivery of OVs. For LPOs to transport their cargo to selected distant sites in the bloodstream, their synthesis requires adjustment of their size, shape, lipid configuration, and surface charge. Surface engineering is crucial in the synthesis of LPOs to improve their targeting efficiency.[82] For instance, sheathing OV M1 with LPOs (M1-LPOs) protected viral particles from neutralizing antibodies and improved the elimination of tumor cells defective with zinc finger antiviral protein.[83] Likewise, PEGylated LPOs have been reported to improve targeted delivery of oncolytic reovirus in mice bearing human pancreatic cancer. However, it has been found that the efficiency of targeted delivery is limited by the tumor stroma, which presents a physical barrier to OV spread.[84]

It is clearly evident that nanotechnology is a promising approach for the targeted delivery of therapeutics that include pharmacological drugs and OVs. Advances in nanotechnology have enabled the fabrication of NPs with high efficiency for targeted delivery via the amalgamation of nanocarriers with various target molecules, such as antibodies, aptamers, peptides, and cancer-specific ligands.[85] Therefore, ideal synthetic NPs should be precisely targeted to the tumor, be permeable, and exhibit increased bioavailability and half-life. It is also important for NPs to move across biological, physiological, and mechanical barriers such as enzymes, cell membranes, and epithelial and endothelial linings.[86] The delivery of therapeutics to target sites by synthetic NPs can be achieved using passive or active approaches. Passive targeting exploits the characteristics of solid tumors, which exhibit increased vascular permeability and an enhanced retention effect, whereas active targeting optimizes specific ligands that enhance selective uptake by the tumor.[87] An example of active targeting is the surface engineering of trans-ferritin modified polyethylene glycol (PEG)-phosphatidyl-ethanolamine NPs to target solid tumors that overexpress transferrin, such as ovarian cancer.[88,89]

Polymer-based synthetic NPs (polymersomes) are equipped with drug-release mechanisms that exploit endogenous features of the TME, such as pH, hypoxia, and temperature. Polymersomes constitute base polymers conjugated with release-triggering molecules that are sensitive to conditions of the TME, thereby inducing controlled release of payloads.[90-92] For example, a novel cancer-homing and penetrating peptide iRGD (CRGDK/RGPD/EC) is sensitive to hypoxia; thus, when incorporated in polymersomes, it generates hypoxia-sensitive iRGD-conjugated polymersomes that release their payload in hypoxic TME.[93,94] On the other hand, NPs with porous structures can be synthesized for the temporal storage and controlled release of drugs. For instance, silicate-based NPs (SNPs) are emerging as tools to target drugs to the tumor. SNPs possess porous constructs for loading poorly water-soluble medicines and protecting pore-entrapped drugs in the matrix from enzymatic degradation. Interestingly, the design of the pore gates prevents the premature release of drugs, and off-target toxicity is minimized by the incorporation of specific ligands into SNPs to selectively deliver the cargo into the tumor.[95] Despite the improved tumor targeting and controlled drug release provided by synthetic NPs, the tumor stroma impedes the intratumoral penetration of therapeutics. Therefore, a new strategy is needed to improve both the targeting and intratumoral penetration of therapeutics.

In addition, an increasing amount of research substantiates the application of high-intensity focused

ultrasound for the precise delivery and improved intratumoral distribution of nanotherapeutic agents, such as OVs. The synergistic use of microbubbles alongside ultrasound aids in achieving targeted delivery, evading immune clearance, and enhancing the penetration of OVs. Microbubbles serve to encapsulate the OVs, thereby preventing their elimination by the immune system, while the targeted release of these viruses within the tumor can be accomplished by destroying the microbubbles through high-intensity focused ultrasound.[96]

The application of ultrasound-assisted destruction of polymeric nanocups resulted in a marked enhancement of the intratumoral infiltration of oncolytic VV in xenograft models involving liver and colon tumors.[97] Comparably, the concurrent administration of a luciferase-expressing adenovirus (AdEHE2F-Lu) along with microbubbles succeeded in improving the delivery and intratumoral distribution of viruses in a murine model of breast cancer by exposure to high-intensity-focused ultrasound[98] (Figure 3).

Nanocarriers with various properties, including magnetism, can be engineered to produce a complex synthesis of OVs with MNPs that can potentiate intratumoral virus penetration by disrupting extracellular matrix deposition. To ensure targeted delivery, image-guided techniques for monitoring functionalized MNPs primed with OVs are employed.[99] In addition, various materials have been utilized in the fabrication of NPs, such as graphene oxide sheets (GOS), which are biocompatible and whose surface can be easily modified for the selective dispatch. For example, polyethyleneimine (PEI)-GOS-PEG-folic acid (FA) has demonstrated a shielding effect on the oncolytic MV (MVs-Edm) against neutralizing antibodies and immune cells. The MVs-Edm is encased with PEI-GOS-PEG-FA to create a complex that protects OVs, enhancing viral delivery to the tumor and consequently improving antitumor activity, which prolongs the survival of the experimental mice.[100]

A common illustration of employing MNPs to enhance the intratumoral infiltration of OVs is evidenced by the application of iron oxide (Fe_3O_4) MNPs, which support the penetration of oAdV in models of bladder cancer (Figure 4). The researchers adorned the surface of oAdv carrier cells aimed at bladder cancer cells and showcased their navigation within tumor models through the application of an EMFd, which also enhanced their retention within the tumor.[101] Notably, Fe_3O_4 MNPs have demonstrated significant efficacy in encapsulating chemotherapy agents and delivering them selectively to tumor sites. Furthermore, the targeted release of chemotherapy payload to the tumor by Fe_3O_4 MNPs was thermally mediated. Fast-spinning Fe_3O_4 MNPs are facilitated by an EMFd of high frequency, which causes a temperature rise in the TME (hyperthermia) and disrupts cancer cells.[102] It has been reported that the targeted delivery and intratumoral penetration of oAdVs are enhanced by cell robots generated by modifying oAdV-infected 293T cells with a cyclic arginine-glycine-aspartic acid tripeptide for selective latching to bladder tumor cells and subsequent immobilization of Fe_3O_4 MNPs on the surface of the cell.

Interestingly, coating cell robots with magnetic iron oxide enhanced their directional movement and tissue penetration through manipulating an EMFd in a 3D cell culture mouse bladder tumor model.[101] Another interesting work fabricated magnetic microbubbles (MMBs) by coating microbubbles with NPs for targeted delivery of gene therapy and pharmacological agents. The MMB shells were capable of releasing the NPs' payload upon ultrasonic stimulation. In addition, MMBs have shown in both *ex vivo* and *in vivo* studies that they can dislodge doxorubicin-containing poly(lactic-co-glycolic acid) NPs across physiological barriers. Consequently, MMBs were able to selectively deliver doxorubicin-containing NPs at an increasing amount of 18-fold to zebrafish heart tissue and 5-fold to mouse tumor tissue.[103]

In general, targeted BVSTs for OVs have improved the selective delivery of OVs to tumors. However, the challenge of a dense tumor stroma limits the intratumoral spread of OVs. Literature suggests that MNPs, with their ability to disrupt tumor stroma (Figure 5), have beneficial applications comparable to other OV-targeted delivery methods. It has been reported that the heterogeneity and dynamicity of the TME, which include physical barriers, exorbitant mutation load, hypoxic states, and abnormal vasculature, are the key causes of cancer immunotherapy being effective in a subset of patients or inducing resistance to conventional therapy.[104-106] Interestingly, NPs can selectively disrupt tumor stroma to remodel the immunosuppressive TME to immunocompetent, thereby sensitizing resistant tumor cells to immunotherapy and other conventional therapies.[107] The destruction of the tumor and its stromal components by MNPs involves mechanical and thermal strategies. Mechanically, once taken up by the tumor, MNPs induce damage to cancer and stromal cells in the TME through particle rotation influenced by an EMFd.[108,109]

Alternatively, intratumoral hyperthermia is generated by the penetrated MNPs when stimulated by an alternating EMFd. The intratumoral rise in temperature caused by alternating EMFd leads to the death of cancer cells and cancer-associated stromal cells, which consequently limits tumor growth.[110,111] For instance, pancreatic ductal

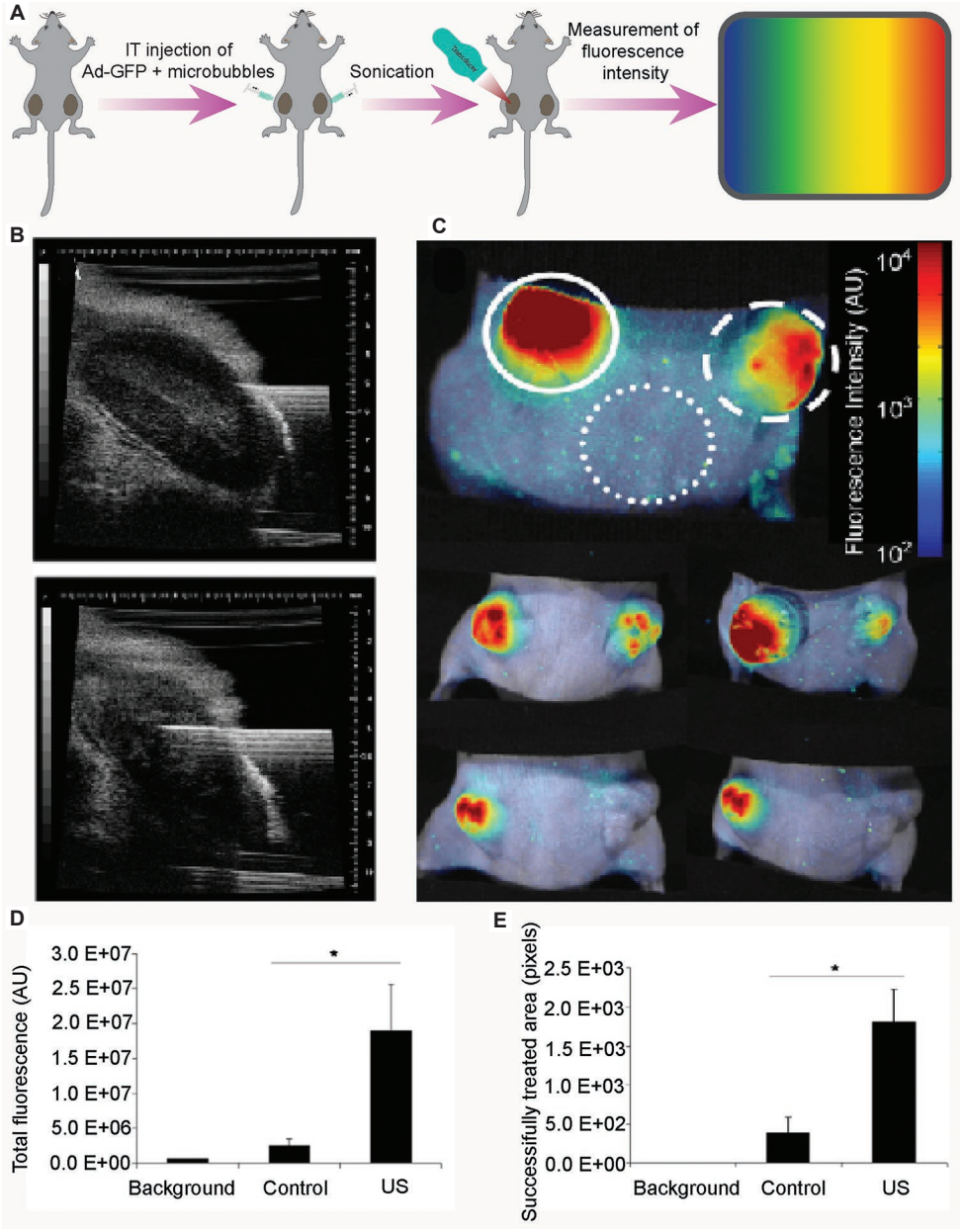

Figure 3. Enhancement of intratumoral penetration of oncolytic adenovirus using ultrasound-targeted microbubble destruction. (A) Schematic diagram illustrating the intratumoral co-injection of adenovirus vector (Ad-GFP) and microbubbles, followed by exposure to high-frequency-focused ultrasound at 500 kPa peak refractional focal pressure, 90% duty cycle, 10 Hz pulse repetition frequency, for 20 s on the left-sided tumors. (B) B-mode ultrasound images depicting the intratumoral administration process. Note that the injectate was localized to a limited area (approx. 3 mm) and was not homogeneously distributed. (C) Transgene expression 24 h post-treatment as a function of fluorescence intensity. Regions of interest for quantitative analysis are depicted by a solid line (sonicated), dashed line (control), and dotted line (background). (D) Quantitative GFP expression of background, control, and sonicated regions of interest. (E) Successfully treated tumor areas in the background, control, and sonicated regions. Reproduced with permission from Bazan-Peregrino *et al.*[98] Copyright © 2013 Elsevier B.V.
Abbreviations: GFP: Green fluorescent protein; IT: Intrathecal; US: Ultrasound.

adenocarcinoma (PDAC) is one of the deadliest cancers associated with poor prognosis due to its late diagnosis, tumor aggressiveness, and treatment resistance. PDAC disease progression and treatment failure are caused by a less-passable, dense tumor stroma that creates a physical barrier to therapeutic delivery.

The treatment of PDAC with the combination of chemotherapy and radiotherapy results in moderate survival benefits, whereas advanced-stage disease becomes resistant to chemoradiotherapy and responds poorly to immunotherapy. However, the treatment of PDAC is potentiated by multifunctional MNPs, which

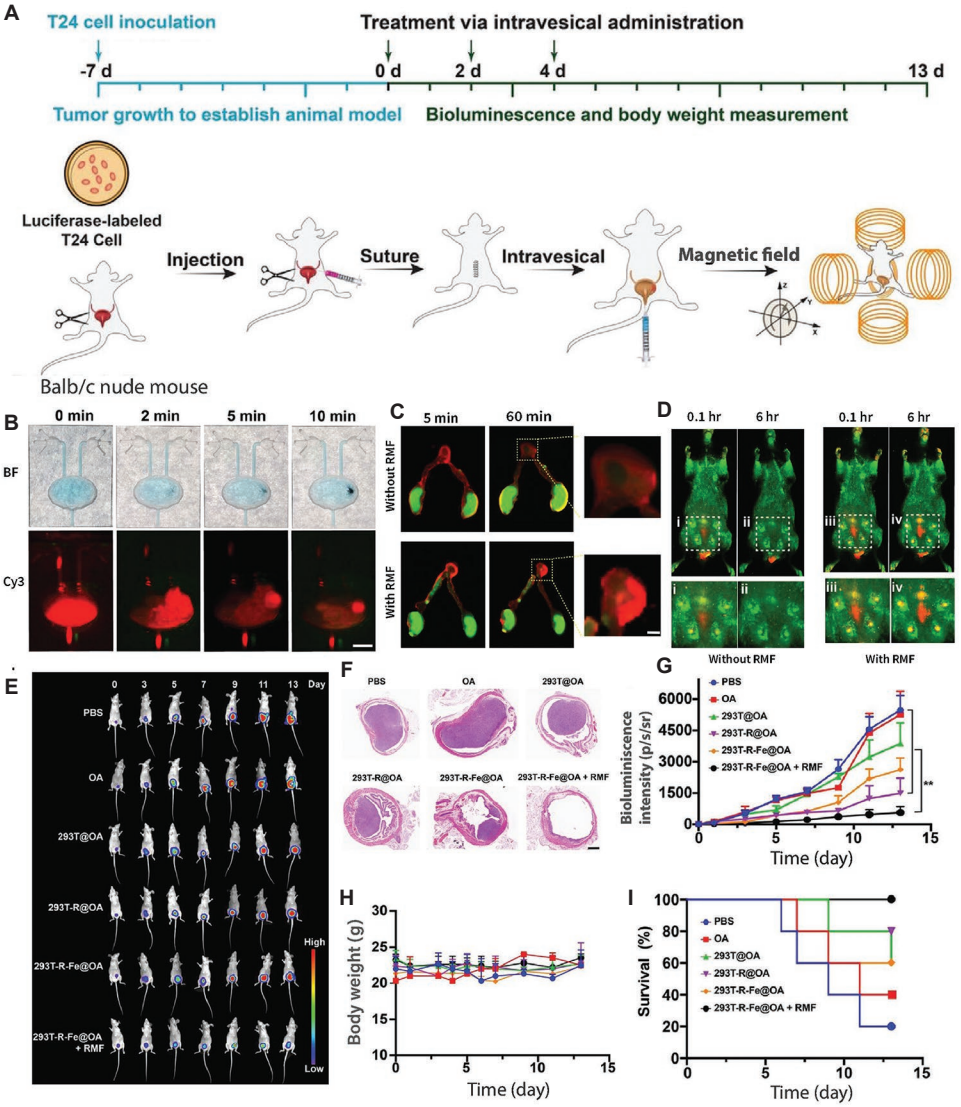

Figure 4. Enhancement of oncolytic adenovirus penetration of bladder cancer using MNP-coated carrier cells. (A) Schematic diagram illustrating the development of an orthotopic bladder tumor model and intravesical treatment with oncolytic adenovirus. (B) Bright-field and fluorescence images of MNP-decorated carrier cells in bladder mold under RMF control (10.3 mT, 17 Hz) at different time points. (C) Fluorescence images of MNP-decorated carrier cells with and without RMF control in the dissected urinary system of mice. (D) *In vivo* fluorescence images of MNP-decorated carrier cell distribution with and without RMF exposure. (E) Time series bioluminescence images of OA-treated mice under different carrier modifications. (F) Hematoxylin and eosin-stained bladder slices at the end of treatment (day 13) for different treatment conditions. (G) Quantitative analysis of *in vivo* bioluminescence intensities of mouse tumors under different treatment conditions. (H) Body weight of mice under different treatment conditions. (I) Survival rate of mice under different treatment conditions. Reproduced with permission from Cong *et al.*,[101] Copyright © 2022 Wiley-VCH GmbH.

Abbreviations: 293T@OA: Oncolytic adenovirus in 293T carrier cells; 293T-R@OA: 293@OA with surface-attached cRGD; 293T-R-Fe@OA: 293T-R@OA with surface MNPs; MNP: Magnetic nanoparticle; OA: Naked oncolytic adenovirus; PBS: Phosphate-buffered saline; RMF: Rotating magnetic field.

facilitate targeted delivery, disrupting stromal barriers of PDAC, and activating antitumor immune responses. Magnetic iron oxide NPs are optimized as theranostics in PDAC, serving both diagnostic and therapeutic purposes. Therapeutically, they induce tumor killing by magnetic hyperthermia.[113]

4. Common hurdles in OV immunotherapy and proposed solutions

4.1. Factors limiting OV immunotherapy efficiency

Cancer cells continually recruit and modulate immune cells, fibroblasts, mesenchymal stromal cells, and endothelial

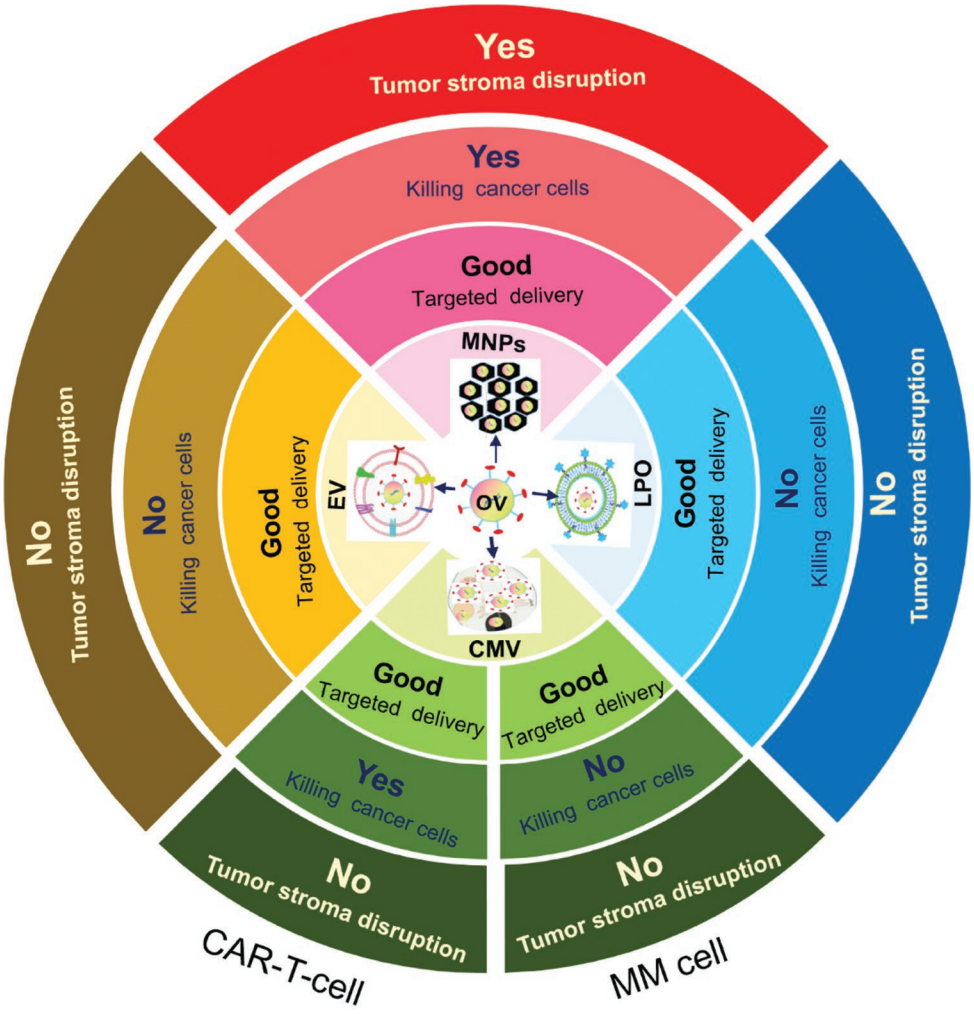

Figure 5. Methods used for encapsulation and targeting OVs to the tumor. The infographic shows that all encapsulation methods for OVs have good targeted-delivery efficiency. Aside from targeting OVs to the tumor, LPOs[83] and EVs in particular, tumor-derived exosomes[51] are unable to kill cancer cells or destroy tumor stroma. However, cell-mediated vehicles involving cancer cells (e.g., MM) and immune cells (e.g., CAR T-cells) indicated that only CAR T-cells[72] but not MM cells[76] have the ability to kill cancer cells. Interestingly, MNPs[108,112] have demonstrated beneficial applications comparable to other encapsulation methods for targeted delivery of OVs to tumors due to their ability to kill cancer cells and disrupt tumor stroma. Image created by the authors. Abbreviations: CAR: Chimeric antigen receptor; CMV: Cell-mediated vehicle; EV: Extracellular vesicle; LPO: Liposome; MM: Multiple myeloma; MNPs: Magnetic nanoparticles; OV: Oncolytic virus.

cells to create a tumor-promoting TME that stimulates tumor growth and metastasis.[114] Apparently, OVs only target cancer cells[115] and lack cytolytic activity against stromal cells[116] that make up the bulk of the tumor mass (90%) and also play a key role in cancer progression.[117-120] An increased population of modulated stromal cells in the TME consequently forms a denser tumor stroma, creating a physical barrier that enables OVs to infect cancer cells and spread within the tumor, inducing oncolysis.[20]

One of the approaches used to combat the dense tumor stroma is the engineering of OVs that target cancer cells and stromal cells. For instance, the development of oAdV that expresses fibroblast activation protein (FAP)-targeted bispecific T-cell engager to destroy cancer-associated fibroblasts (CAFs) expressing FAP, significantly decreased the number of CAFs and enhanced viral spread in the TME.[121] Since the tumor stroma consists of multiple components, such as tumor-associated macrophages (TAMs), MSCs, CAFs, and endothelial cells, targeting one component of the tumor stroma has so far failed to achieve desired therapeutic efficacy. For instance, various studies have utilized armed OVs with a therapeutic transgene to target one component of the tumor stroma, such as CAFs,[122] tumor vasculature,[123] or TAMs.[124] However, the results were suboptimal due to tumor-promoting activities of the neglected stromal components.

Another limitation of OVs is the host's antiviral immune response. The host's antiviral immunity-mediated clearance of OVs has been evaded using BVSTs. The BVSTs are engineered for the targeted delivery and shielding of OVs against neutralizing antibodies and immune cells. Carrier cells,[74,75] EVs,[51,81] LPOs,[83] and NPs[99,100] are examples of BVSTs that have been used to encapsulate OVs. Despite BVSTs improving the targeted delivery of OVs, tumor infectivity can be compromised by downregulation or lack of receptors required for viral uptake. For instance, the oncolytic activity of oAdV is efficient in tumors expressing coxsackie and AdV receptors but limited in tumors with reduced or no expression of these receptors.[125] Targeted-BVSTs have enhanced the shielding and dispatching of OVs to tumors; however, intratumoral viral spread and oncolytic potency will be compromised by dense tumor stroma if left untreated.

4.2. Proposed strategy to overcome OV immunotherapy hurdles

To overcome the aforementioned therapeutic limitations of OVs, a combination treatment strategy involving concurrent or sequential use of two different replication-competent OVs armed with two distinct therapeutic transgenes can be selected. The goal of using two genetically distinct OVs is to eliminate the risk of viral genetic recombination and complement their tumoricidal activities. For instance, Le Boeuf *et al.*[31] reported beneficial synergistic antitumor activity in combining VSV and VV to attack cancer cells. Interestingly, the VV complement oncolytic activity of VSV and VSV enhanced the spread of VV in the tumor, ultimately resulting in an improved treatment outcome observed in cell experiments and animal study models.[31,33] Furthermore, equipping different OVs with transgenes encoding different specific molecules to target various cancer pathways, such as anti-angiogenic factors and apoptosis-inducing ligands, has improved the efficiency of OVI.[126-128]

On the other side, functionalized MNPs can be engineered to target OVs to cancer cells. Numerous studies have demonstrated that MNPs, through their surface modification, are utilized as vehicles for the targeted delivery of drugs, nucleic acids, and virus particles in tumors.[128-130] In particular, Fe_3O_4 MNPs and magnetite are the most widely used NPs in the field of oncology because they are mechanically stable, biocompatible, reproducible, uniformly nanosized, and non-toxic.[112,131-133] Thus, functionalized MNPs target OVs to the tumor and enable mechanical destruction of the tumor stroma by manipulating the EMFd.[99,108,133,134] In addition to the EMFd-driven MNPs-mediated mechanical destruction of cancers, the transfection efficiency of OVs into cancer cells is also remarkably enhanced by EMFd.[73,108]

The antitumor activity of OVs is complemented using functionalized MNPs (Figure 6A), which serve as vehicles for the targeted delivery of OVs and therapeutics that target both cancer cells and the tumor stroma. The advantage of utilizing two different OVs equipped with two distinct therapeutic transgenes, such as anti-VEGF and GM-CSF (Figure 6B), is to synergize their selective antitumor activity, trigger lysis of cancer cells, disrupt tumor vasculature, and stimulate antitumor immune response.

5. Limitations of the proposed strategy

Several challenges should be addressed to realize the full potential of MNPs in enhancing the delivery and distribution of OVs in tumors. One of the biggest hurdles is the restricted penetration and targeting efficiency due to the rapid attenuation of magnetic fields with tissue depth. External magnets generate gradients that are only strong enough to effectively localize MNPs in superficial tumors.[135] For deep-seated tumors, the magnetic force becomes too weak to retain or concentrate sufficient therapeutic complexes. In the case of OVs coated with MNPs, this means that while the delivery to subcutaneous tumors may be feasible, localization in deep-seated tumors, such as pancreatic or liver cancers, remains highly inefficient. Consequently, much of the virus–NPC complex either circulates systemically or accumulates non-specifically in other organs, undermining therapeutic efficacy. Advances in magnet design to enhance field strength and tissue penetration will overcome this limitation, enabling the proposed strategy to be used for deep tumors. For instance, using arrays of permanent magnets, sufficient field gradients of up to 7 Tesla per meter can be generated, which is sufficient to propel MNP-coated OVs to deep-seated tumors.[136]

Another critical limitation is the immune recognition and rapid clearance of MNP-virus complexes in circulation. Following their injection into the bloodstream, MNPs readily adsorb plasma proteins, forming a protein corona that alters their surface properties.[137] This process promotes opsonization, activation of complement cascades, induction of an inflammatory response, and recognition by the reticuloendothelial system, particularly macrophages in the liver and spleen.[138,139] For OVs coated with MNPs, this results in accelerated clearance from circulation, thereby shortening the therapeutic window. Even with magnetic guidance, only a fraction of the complexes may reach the tumor before being sequestered by the immune system. This clearance also raises the risk of viral inactivation, as immune cells may degrade or neutralize the virus before it exerts its oncolytic effects. This limitation can be overcome by carefully selecting MNP coatings to slow down their sequestration and

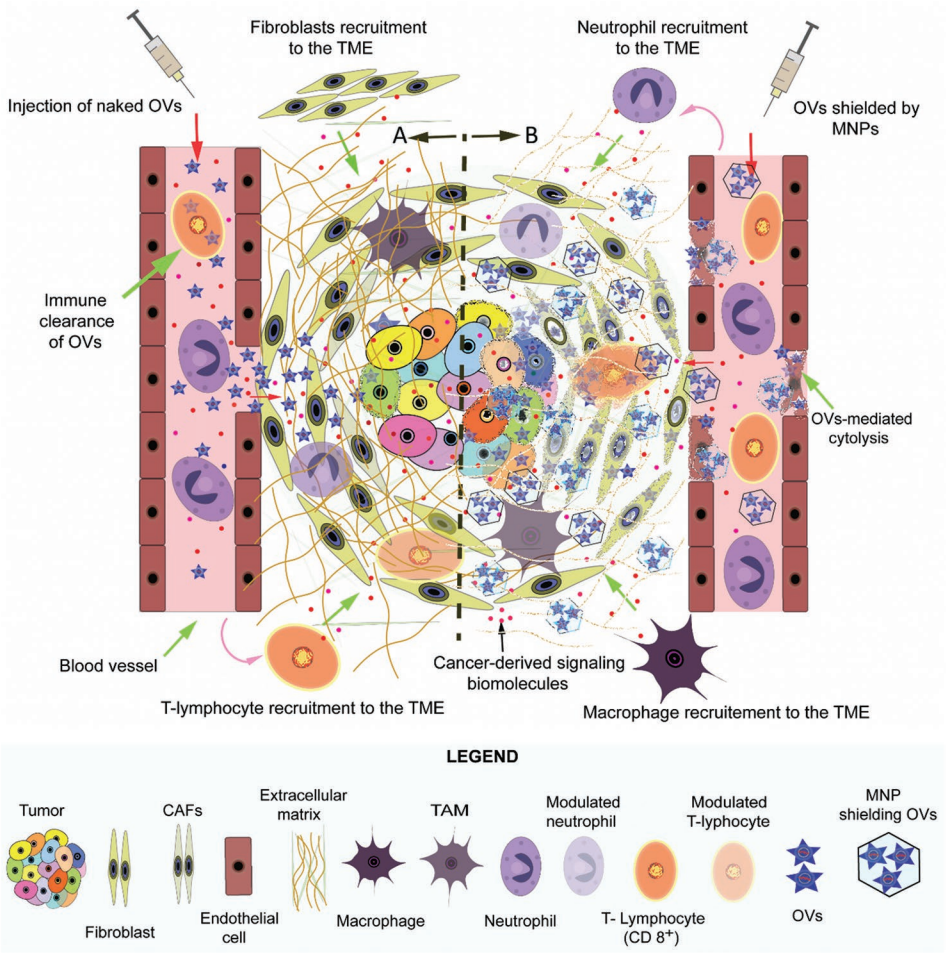

Figure 6. A hetero-dynamic TME involving the recruitment and modulation of stromal cells through the secretion of signaling molecules, such as cytokines and growth factors. The stromal cells recruited in the TME include immune cells and fibroblasts, which increase the density of the tumor stroma to limit the spread and cytolytic infection of OVs. In addition, through signaling molecules, cancer cells modulate fibroblasts and immune cells, such as macrophages, to CAFs and TAMs, respectively, both expressing a pro-tumor phenotype. Image created by the authors.

Notes: A: Antiviral immune response and tumor stroma that constitute stromal cells and extracellular matrix both impair anticancer activity of naked OVs; B: Targeted delivery of OVs with functionalized MNPs shields OVs from host antiviral immune response, and under the influence of EMFd, improves the efficiency of intratumor viral spread and cytolytic infection to destroy the tumor stroma.

Abbreviations: CAFs: Cancer-associated fibroblasts; EMFd: External magnetic field; MNPs: Magnetic nanoparticles; OVs: Oncolytic viruses; TAMs: Tumor-associated macrophages; TME: Tumor microenvironment.

degradation. For instance, 3-aminopropyl-triethoxysilane-coated MNPs preferentially accumulate in the spleen and are degraded at a slower rate than dimercaptosuccinic acid-coated MNPs that preferentially accumulate in the liver.[140]

Beyond these functional challenges, there are significant safety concerns regarding the use of MNPs in drug and virus delivery. Iron oxide-based MNPs, which are among the most studied and utilized, release free iron ions during degradation,[141] leading to oxidative stress and tissue damage.[142] Long-term accumulation of MNPs in non-target organs, such as the liver, spleen, and lungs, raises concerns about chronic toxicities resulting from inflammation and tissue fibrosis.[143] When combined with OVs, the risk of immune overstimulation becomes more pronounced, as both the viral component and the NPs may trigger innate immune responses. This dual activation could lead to excessive cytokine release, thereby increasing the likelihood of systemic side effects similar to those observed in cytokine release syndromes.[144] Furthermore, the aggregation of MNPs under physiological conditions can obstruct small blood vessels, impairing blood flow and contributing to local tissue damage.

6. Future directions

Looking ahead, this revisit highlights the critical need for precision-engineered viral platforms and next-generation

MNP designs tailored to specific tumor pathophysiology. However, the path to clinical adoption faces not only biological and safety challenges but also scalability barriers. Manufacturing replication-competent OVs with stable expression of complex therapeutic transgenes requires robust and standardized production pipelines, which remain difficult to scale up while maintaining viral potency and genomic stability.[145,146] Similarly, the reproducible synthesis of MNPs with uniform size, surface chemistry, and functionalization remains a bottleneck, particularly when transitioning from laboratory-scale synthesis to good manufacturing practice-compliant industrial production.[147] The requirement for dual quality control during manufacturing to ensure both viral infectivity and NPC performance adds further complexity and creates further regulatory and cost challenges for clinical translation.

Addressing these limitations will unlock the full potential of OVI as a transformative cancer therapy. By consolidating innovations from nanotechnology, cancer immunotherapy, and virotherapy, this conceptual model provides a blueprint for next-generation OVI-based combination regimens aimed at overcoming therapeutic resistance, side effects, and adverse events. With scalable platforms for both viral engineering and NPC production, such regimens could enhance tumor-specific treatment delivery and ultimately improve clinical outcomes for patients with solid tumors.

7. Conclusion

OV immunotherapy represents an emerging cancer-targeting immunotherapy characterized by its selective tumor-killing and immuno-oncolytic activities, while exhibiting minimal off-target toxicities. The clinical efficacy of OVI is limited by the rapid clearance of viral particles in the circulatory system as well as the limited intratumoral penetration due to barriers imposed by the tumor stroma. In this review, we provide a thorough review of the status of OVI to highlight the challenges that limit its clinical efficacy. We have also presented our proposed next-generation combination therapy strategies involving replication-competent distinct OVs equipped with different therapeutic transgenes and MNPs to address both penetration and oncolysis challenges. Our proposed dual-pronged strategy involving replication-competent OVs engineered with complementary transgenes, such as anti-VEGF, to disrupt tumor vasculature and GM-CSF to activate anticancer immunity, alongside the deployment of functionalized MNPs, has the potential to significantly enhance the efficacy of OVI.

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Conflict of interest

The authors declare that they have no competing interests.

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Ethics approval and consent to participate

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Consent for publication

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Availability of data

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