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REVIEW

Recent advances of oncolytic virus in cancer therapy

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ABSTRACT

Oncolytic viruses have been taking the front stage in biological therapy for cancer recently. The first and most potent virus to be used in oncolytic virotherapy is human adenovirus. Recently, ongoing extensive research has suggested that other viruses like herpes simplex virus (HSV) and measles virus can also be considered as potential candidates in cancer therapy. An HSV-based oncolytic virus, T-VEC, has completed phase Ш clinical trial and has been approved by the U.S. Food and Drug Administration (FDA) for use in biological cancer therapy. Moreover, the vaccine strain of the measles virus has shown impressive results in pre-clinical and clinical trials. Considering their therapeutic efficacy, safety, and reduced side effects, the use of such engineered viruses in biological cancer therapy has the potential to establish a milestone in cancer research. In this review, we summarize the recent clinical advances in the use of oncolytic viruses in biological therapy for cancer. Additionally, this review evaluates the potential viral candidates for their benefits and shortcomings and sheds light on the future prospects.

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Introduction

Oncolytic virotherapy, a revolutionary tool for cancer treatment has shown promising results for the last two decades.[1] More than a century ago it was first observed that cancer patients underwent cancer regression if they were infected with certain viruses.[2] Revolutions in recombinant DNA technology have provided important tools to study the biology of viruses, thereby advancing biological therapy for cancer, resulting in the new generation of cancer therapeutics. While chemo and radiation therapies continue to be the chosen cancer treatment options, the serious side effects are a major drawback of these therapies. Biological therapy for cancer, although relatively complex and challenging, is the preferred treatment option owing to good efficacy, limited side effects and being less painful to cancer patients. So far clinical trials report no deaths or clinically serious adverse events attributed to oncolytic virotherapy. In cancer treatment the patient's safety is of utmost importance and treatment, using oncolytic viruses seems to be the most promising in this aspect. Most of the oncolytic viruses chosen for cancer therapy are attenuated strains or strains that can infect and replicate in humans without causing any serious disease. It is also important that the viruses chosen must be capable of utilizing the host immune system to recognize and destroy the cancer cells.

Although oncolytic viruses are potentially powerful therapeutic agents for cancer treatment, a single type of oncolytic virus is not enough to destroy all the cancer cells due to the heterogeneity of cancer tissues and complexity of cancer cells. Some cancer cells and the non-transformed supporting cells may be resistant to certain oncolytic viruses, indicating that a single type of virotherapeutic agent may not be effective in all types of cancers. Therefore, the most challenging part of the oncolytic virotherapy is to identify the virus and the delivery method that best fits the patient's system and activates the immune system against the tumor cells. Currently, several viruses including vaccinia virus, coxsackievirus, adenovirus, reovirus, herpes simplex virus, and measles virus are being extensively investigated and are undergoing clinical trials for use in the treatment of various types of advanced cancers. The recognition of the genetically engineered herpes simplex virus-Talimogene Laherparepvec (T-VEC) by the U.S. Food and Drug Administration (FDA) and the European commission for oncolytic virotherapy is a major leap in the advancement of the application of viruses in cancer treatment. To achieve more stable and long-lasting results in cancer therapy, virotherapy has been combined with chemotherapy and/or immunotherapy recently.

In this review, we summarize the recent advances in biological therapy for cancer and also evaluate the potential viral candidates for their benefits and shortcomings while indicating the future prospects.

HSV-based oncolytic viruses

HSV has been considered and developed as an oncolytic virus for cancer therapy since 1991. There are seven HSV-based oncolytic viruses among which T-VEC (Commercial name Imlygic) has been approved by US-FDA and European Medicine Agency for clinical use after the successful phase I, II, and III clinical trials. This oncolytic virus is manufactured

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by Amgen Inc. (Thousand Oaks, USA), and was generated by deleting the ICP34.5 and ICP47 genes, and inserting two copies of human granulocyte-macrophage colony-stimulating factor (GM-CSF) gene in place of ICP34.5.[3] In normal cells, viral replication is blocked by protein kinase R (PKR) activation and subsequent phosphorylation of eukaryotic initiation factor 2 (eIF2). In cancer cells, the disrupted PKR-eIF2 pathway causes uncontrolled cell proliferation and unlimited permissiveness to viral replication as well.[4,5] ICP34.5 causes dephosphorylation of eIF2 and blocks PKR-induced disruption of protein synthesis. Deletion of ICP34.5 in T-VEC ensures abortive infection in normal cells thereby enabling its replication to be cancer cell-specific.[6] ICP47 decreases the immune destruction caused by the host cell thereby supporting HSV1 proliferation. Deleting ICP47 therefore allows immune destruction of the virus in normal cells while enhancing the cell surface expression of MHC1 in cancer cells and increasing the tumor antigen presentation by the infected cancer cells.[7]The GM-CSF engineered into T-VEC enhances T-cell priming by dendritic cells, thereby stimulating the immune system.

A phase I trial of T-VEC consisted of 30 patients all affected with different types of cancers, of whom 9 patients were diagnosed with refractory metastatic melanoma. Intratumoral T-VEC injection led to remission in two patients with no detectable adverse effects. This encouraged the researchers to perform phase II clinical trial on patients with stage IIIc or IV melanoma. Among the 50 patients treated intratumorally, 8 patients achieved a complete response (CR), while 5 patients achieved partial response (PR). This success led to a phase III clinical trial with the enrollment of 436 patients with stage IIIb, IIIc, and IV unresectable melanoma treated with T-VEC. This trial also compared T-VEC with recombinant GM-CSF. In the T-VEC group, the overall survival rate was higher than in the GM-CSF group. Among the 436 patients, the double response rate was higher in patients treated with T-VEC compared to those treated with GM-CSF alone. T-VEC treatment also showed profound efficacy in stage IIIB, IIIC, or IV M1a patients. Moreover, adverse effects related to T-VEC treatment except fatigue, chills, and pyrexia were not observed. This success of the phase III trial played a significant role in the US-FDA approval of T-VEC.[8] More T-VEC clinical trials are currently in progress. One single-arm, phase II, single-center study is being conducted on the low-risk squamous cell carcinoma patients, where 28 patients were injected with T-VEC at the target lesions. The second injection was administered 3 weeks after the first injection and the third and fourth injection were administered 2 weeks after the second and third injections, respectively (NCT03714828) (Table1). Another study currently in progress to evaluate the efficacy of T-VEC in squamous cell carcinoma patients is designed to test T-VEC alone and T-VEC combined with ipilimumab (NCT01740297) (Table 1). A phase I study is ongoing with 36 patients having a recurrent or metastatic head and neck squamous cell carcinomas to evaluate the dose-limiting toxicity of T-VEC in combination with pembrolizumab (NCT02626000) (Table 1). An ongoing phase II study comprising 112 patients with unresected stage IIIB to IV M1c melanoma is designed to evaluate the correlation between $CD8^+$ cell density and objective response rate in the patients (NCT02366195) (Table 1). Even though there is an overall success in the clinical trials using T-VEC as mentioned above such as in the treatment of stage IIIc and IV unresectable melanomas, one study has reported chronic granulomatous dermatitis at the T-VEC injection site in melanoma patients.[9] However, this is not of much concern as in most of the patients the granulomatous dermatitis did not relapse after treatment discontinuation and spontaneous regression of the nodules occurred over several months.[9]

HF-10, another HSV1-based oncolytic virus naturally lacks the expression of several genes of the virus such as *UL43, UL49.5, UL55, UL56*, and LAT (latency-associated transcripts). This oncolytic virus, produced by Takara Bio Inc., Japan[10] efficiently replicates in tumor cells and induces an increased number of $CD4^+$ and $CD8^+$ T-cells and NK cells within the tumor leading to a reduction in the tumor size. Like T-VEC, HF-10 has also been reported to have potent anti-tumor efficacy against a range of malignancies. It has been shown to effectively destroy colon carcinoma, peritoneal cancer, and melanoma in immune competent murine models when used alone or in combination.[11-13] Several clinical trials with HF-10 have either been completed, or are ongoing, or have been planned. Two studies have been conducted in melanoma patients (NCT02272855) (Table 1) in the USA: one is a monotherapy[14] and the other is a combination therapy with ipilimumab. Besides, a phase 2 study ongoing in Japan to treat resectable stage IIIB, IIIC, IV M1a melanomas has recruited seven patients treated with HF-10 in combination with nivolumab in a single-arm, open-label study (NCT03259425) (Table 1).[15] A combination therapy for 76 patients with unresectable pancreatic cancer is being evaluated in a phase I, open-label, multi-center study to determine the recommended dose of HF-10 (NCT03252808) (Table 1).[16] In February 2005, a study was carried out on HSV-seropositive patients with head and neck squamous cell carcinoma (HNSCC) to demonstrate the safety and efficacy of HF-10. These patients were treated with intratumoral injections of HF-10 with a dose of 1×10^5PFU for 3 days. However, no significant decrease in tumor size was observed, and patients reported low-grade fever after the injection. A new trial was then planned for testing higher doses of HF-10[15].

Although HF-10 and T-VEC originate from different strains, they have many similarities such as both their genomes consist of linear double-stranded DNA which has two unique inverted sequences and a unique long sequence flanked by terminally repeated long sequence and internally repeated long sequence.[17,18] T-VEC is obtained by modifying the JS1 strain to improve tumor-specific growth (deletion of ICP34.5 and ICP47) and immune response (insertion of hGM-CSF).[18] HF-10, on the other hand, has natural deletions of UL56 and LAT and increased expression of genes like UL53 which enhance its safety aspects.[19-21]

HSV1716 is an oncolytic HSV containing the deletion of only a specific determinant of virulence ICP34.5. This replication-defective mutant of HSV1 originates from the wild-type strain 17, and is produced by Virttu Biologics, Glasgow, UK. In a phase I study, HSV1716 has been administered in pediatric patients with relapsed or refractory extracranial cancer via an image-guided intratumoral injection. A total of nine patients has been treated; eight of them have been given single

Table 1. Clinical trials of the HSV-based oncolytic viruses.

Oncolytic Vector	Therapeutic agent	Cancer type	Phase, study type	Mode of therapy	Purpose of the study	Status	Clinical trial number
T-VEC	T-VEC	Squamous cell carcinoma	Phase 2, single-group study	Injection of T-VEC into target lesions	efficacy evaluation	Recruiting	NCT03714828
	T-VEC	Melanoma	Phase Ib, open-level, multicenter, single-arm study	Intra-tumoral injection of T-VEC in combination with intravenous ipilimumab	To evaluate safety of T-VEC in combination with ipilimumab	Active, not recruiting	NCT01740297
			Phase 2, open-label, multicenter, randomized study	Intra-tumoral injection of T-VEC in combination with intravenous ipilimumab; intravenous ipilimumab alone			
	T-VEC + pembrolizumab	Head and neck squamous cell carcinoma	Phase 1b, open-label, multicenter, randomized study	Intralesional injection of T-VEC followed by intravenous injection of pembrolizumab	Safety and efficacy evaluation in combination therapy	Active, not recruiting	NCT02626000
	T-VEC	Unresected melanoma, stage IIIb, IV M1c	Phase 2, multicenter, single-arm study	Intralesional injection of T-VEC	Safety and tolerability evaluation	Active, not recruiting	NCT02366195
HF-10	HF-10 + ipilimumab	Unresectable or metastatic melanoma	Phase 2, single-group assignment study	Intra-tumoral injection of T-VEC, intravenous infusion of ipilimumab	Efficacy and safety assessment	Completed	NCT02272855
	HF-10 in combination with neoadjuvant nivolumab	Resectable stage IIIb, IIIC, IV M1a melanoma	Phase 2, open-label, single-group assignment	Intra-tumoral injection of HF-10, infusion of nivolumab (subcutaneous or intravenous)	Evaluation of the safety and efficacy	Recruiting	NCT03259425
	HF-10 in combination with gemcitabine and Nab-paclitaxel or TS-1	Unresectable pancreatic cancer, stage III or IV	Phase 1, open label, multicenter study	Intra-tumoral injection of HF-10 and intravenous infusion of gemcitabine and Nab-paclitaxel for stage III patients; intra-tumoral injection of HF-10 in combination with oral TS-1 for stage IV patients	To determine the appropriate dose of HF-10 treatment in combination with chemotherapy	Active but not recruiting	NCT03252808
HSV-1716	HSV-1716	Non-central nervous system solid tumor, relapsed sarcoma and neuroblastoma	Phase 1, non-randomized, single-group assignment	Intra-tumoral	Dose-escalation study	Completed	NCT00931931
	HSV-1716	Malignant pleural mesothelioma	Phase 1/IIa single-group open-label study	Intra-pleural delivery of HSV-1716	To study the safety and tolerability and biological effects of the drug	Completed	NCT01721018
M03	M03	Recurrent malignant glioma	Phase I, single-group, open-label study	Intra-tumoral administration	To determine the safety and tolerability of the maximum dose	Recruiting	NCT02062827

doses while one has been given two doses. No dose-limiting toxicities have been observed, indicating that intratumoral HSV1716 is safe for children and young adults with late-stage aggressive cancers.[22] In a different phase I study, HSV1716 has been shown to be safe when injected at a dose of 10^5 PFU directly into human high-grade gliomas, and also when injected up to 10^6 PFU directly into brain tumors. A phase I dose-escalation study has recently been completed where HSV1716 was injected intratumoral or intravenous in patients with refractory non-central nervous system solid tumors (NCT00931931) (Table 1). In another phase I/II trial, patients with malignant pleural mesothelioma (MPM) were treated with an intra-pleural injection of HSV1716. This treatment was found to be safe and well tolerated by the patients. Adequate HSV1716 replication was seen resulting in an effective immune response in pleural fluid and blood (NCT01721018) (Table 1). Further studies indicating the use of HSV1716 in combination with immune checkpoint inhibitors in MPM patients have been suggested.[23]

G207 is an HSV1 resulting from the deletion of ICP34.5 and the substitution of ICP6 with LacZ. The deletion of ICP34.5 ensures the lack of neurovirulence while the ICP6 attenuation results in specificity for tumor cells with P16 tumor suppressor defects.[24] This clinically safe[25] oncolytic virus is manufactured by Medigene, Germany. Intratumoral injections of this oncolytic virus at high doses of 3×10^9 PFU were seen to be well tolerated among patients with tumors growing in important and sensitive organs. However, due to the lack of clinical efficacy evidence, cancer biotherapy using this oncolytic virus has not entered the phase II trial yet. In a study comprising six glioblastoma patients, two 1.15×10^9 PFU doses of G207 were injected stereotactically via a catheter into a resection cavity after 2–5 days of tumor removal. This was the maximum achievable dose that was tolerated when administered two times.[26] However, serious adverse events were experienced by all six patients due to their underlying disease. Even though some of the adverse events were thought to be related to G207 administration, no patients discontinued study participation. Also, the patient's saliva, serum, urine, and conjunctiva samples were tested and none of the samples showed pathogenic evidence of encephalitis caused by HSV.[26] Furthermore, in some patients, extensive distribution of the progeny virus in the treated tumors was not observed.

M032 is an HSV1-based second-generation oncolytic virus expressing IL-12, manufactured by Acttis Inc, Pennsylvania, USA. It causes the dying tumor cells to secrete IL-12 which promotes an anti-tumor immune response. Notably, IL-12 has anti-angiogenic effects, hence, preventing the tumor growth.[27] Currently, this HSV1-based oncolytic virus has entered phase I study for the treatment of recurrent malignant glioma (NCT02062827) (Table 1).

G47Δ, an HSV1-based third-generation oncolytic virus manufactured by Daiichi Sankyo Company, Tokyo Japan, is structurally quite similar to G207 except for an additional ICP47-deletion. One study showed that G47Δ can effectively kill different subtypes of breast cancer cells. It affected both paclitaxel-resistant cancer stem cells and non-cancer stem cells,[28] equally. In 2005, there was a report of G47Δ used in combination with androgen ablation for the treatment of human prostate cancer. The study done in vitro and in vivo xenograft tumor model using human prostate cancer cells demonstrated that G47Δ could be a good candidate for treating human prostate cancer.[29]

Adenovirus-based oncolytic viruses

Oncorine (also known as H101) is the first recombinant oncolytic adenovirus approved by China Food and Drug Administration Department (CFDA) to be used in combination with chemotherapy for the treatment of nasopharyngeal carcinoma in late 2005.[30-32] The modifications resulting in this oncolytic virus were E1B deletion and E3 partial deletion. A phase III study has been conducted successfully in patients with head and neck squamous cell carcinoma (HNSCC) and esophageal squamous cell carcinoma (ESCC). The intratumoral injection of H101 combined with cisplatin and 5-fluorouracil (PF) or adriamycin and 5-fluorouracil (AF) was compared with PF or AF treatment alone. The study indicated the safety and efficacy of the H101 intratumoral injection. This study was a milestone leading to CFDA's approval for the use of oncorine as combination therapy for combating cancer.[33] After it was launched in the market, clinical trials in China tested oncorine for four different types of cancers. The best results were observed for the oncorine-treated patients with malignant plural effusion, showing 38% complete recovery (Table 2).[34]

Almost at the same time, another adenovirus-based oncolytic virus, Onyx-015 was developed by Onyx Pharmaceutical, South San Francisco, USA, in which E1B (55 kDa) was completely deleted. Clinical trials involving Onyx-015 were done

Table 2. Oncorine's clinical trials.

Cancer type	Administration route	Groups	Patient Recovery					Adverse effects
			CR	PR	SD	PD	NC	
Hepatocellular carcinoma	Transartarial injection of Oncorine plus TACE	Oncorine + TACE	28.7%	32.2%	26.4%	12.6%	_	Not reported
		TACE	14.8%	21.6%	38.6%	25%	_	
Pancreatic cancer	Intratumoral (Oncorine), gemitabine (intratumoral)	Oncorine + gemitabine	_	15.8%	52.6%	_	_	Fever and diarrhea
Non-small-cell lung cancer (NSCLC)	Intratumoral (Oncorine), vinorelbine/cispaltin chemotherapy (NP)	Arm A (Oncorine +NP)	_	5 cases	10 cases	4 cases	_	Noninfectious fever, mild pneumothorax
		Arm B (NP)	_	3 cases	9 cases	5 cases	_	
Malignant pleural effusion	Intrathoracic injection of Oncorine/cisplatin	Oncorine group	10 cases	8 cases	_	3 cases	5 cases	Leukopenia
		Cisplatin group (Control)	8 cases	6 cases	_	5 cases	7 cases	

for the patients with HNSCC, pancreatic cancer, ovarian cancer, colorectal cancer, and premalignant oral dysplasia. Charles *et al.* have proved that the topical application of Onyx-015 as mouthwash therapy has significant efficacy against oral dysplasia.[35] For pancreatic cancer, phase I trial results ensured the safety of Onyx-015 for its use in combination therapy with gemcitabine. Among the 21 patients comprising the trial, six patients showed stable disease (SD), two showed partial response (PR), and two had minor regression (MR). However, the major challenge for Onyx-015 treatment is the preexisting neutralizing antibodies.[36]

DNX-2401 is another promising adenovirus-based oncolytic virus, produced by DNAtrix, Huston, USA. It consists of a deletion of 24 bps in the E1A region and the engineering of the RGD motif into the HI-loop of the fiber knob. While this insertion of the RGD-4C motif enhances the replication and infectivity of the adenovirus in cancer cells, it reduces the sequestration of adenovirus by CAR-expressing normal cells[37] thus emphasizing the potency and safety of DNX-2401. In a treatment regimen, two groups of patients with recurrent malignant glioma were treated with DNX-2401. One group (group A) received a single dose while the other group (group B) received 2 doses, first dose into multiple sites via implanted catheters and the second dose on day 14 after tumor regression. In group A, 5 among the 25 patients survived for more than 3 years of whom 3 patients showed more than 95% regression in tumor size. The results were promising, indicating that DNX-2401 could be used as a potential therapeutic agent in combination therapy for gliomas.[37,38] Currently, two phase I clinical trials is in progress for recurrent glioblastomas, one is in combination with temozolomide (NCT01956734) (Table 3) and the other is in combination with interferon-γ (NCT02197169) (Table 6). This success for glioblastoma patients has encouraged another ongoing clinical trial where the diffuse intrinsic pontine gliomas (DIPG) in children is being treated intratumorally with DNX-2401, 3–4 weeks prior to radiotherapy or chemotherapy (NCT03178032) (Table 3). The results of this study are unpublished. In another ongoing study for recurring glioblastoma or gliosarcoma, DNX-2401 is delivered directly to the tumor following intravenous administration of pembrolizumab (NCT02798406) (Table 3).

ONCOS-102, produced by Targovax, Oslo, Norway[39] is similar to DNX-2401 except that it is additionally armed with a potent immunological stimulator GM-CSF. A phase I study employing ONCOS-102 in combination with low-dose oral cyclophosphamide has been conducted to treat solid tumors in 12 patients.[40] The treatment was deemed safe, was well tolerated, and induced a tumor-specific immune response (NCT01598129) (Table 3). Another phase I/II study employing ONCOS-102 in combination with pemetrexed/cisplatin is ongoing in 30 patients with mesothelioma (NCT02879669) (Table 3). In another regimen, 12 patients with advanced melanoma have been treated with ONCOS-102 and pembrolizumab combination (NCT03003676) (Table 3). All these studies primarily indicate that ONCOS-102 is well tolerated and can induce an anti-tumor immune response.

VCN-01 is an Rb pathway selective- and hyaluronidase-armed oncolytic adenovirus, manufactured by VCN Biosciences SL, Barcelona, Spain. This oncolytic virus is being currently employed in several clinical trials, including a phase I dose-escalation study on advanced solid tumor treatment with intravenous VCN01 alone and in combination with gemcitabine and abraxane (NCT02045602) (Table 3), a phase I safety and VCN-01 activity evaluation study for patients with refractory retinoblastoma (RTB) (NCT03284268) (Table 3) and a phase I study assessing the safety, tolerability, and efficacy of VCN-01 in combination with durvalumab in patients with HNSCC (NCT03799744) (Table 3). VCN-01 has shown cytotoxic effects on glioma cells *in vitro* and *in vivo*.[41] Recently a team of researchers from SJD Barcelona children's hospital treated pediatric chemo-resistant retinoblastoma patients with intravitreous injection of VCN-01, and the results indicated enough viral replication in tumor cells to induce anti-tumor activity in retinoblastoma vitreous seeds and no systemic inflammation tumor.[42]

LOAd-703 is an oncolytic virus loaded with genes encoding CD40L and 4-1BBL, produced by Lokon pharma, Uppasala, Sweden. This oncolytic adenovirus is currently being evaluated for its safety in two Phase I/II clinical trials. One is for pancreatic cancer patients (NCT02705196) (Table 3) and the other where LOAd-703 is used together with the standard of care chemotherapy or gemcitabine for patients having various types of cancers (pancreatic, biliary, colorectal, or ovarian) (NCT03225989) (Table 3).

ICOVIR-7 and ICOVIR-5 are two types of oncolytic adenoviruses generated by the Targovax and Catalonia Institute of Oncology, respectively. ICOVIR −7 has been evaluated in a clinical trial for 21 patients with advanced and refractory solid tumors. Anti-tumor activity was observed in this clinical trial, showing stabilization or reduction in tumor size. The results were 1PR, 2MR, and 2SD, indicating its eligibility for further clinical trials.[43] A dose-escalation phase I clinical trial on metastatic melanoma patients showed that the virus could be used for successful systemic administration. However, it failed to induce tumor regression.[44]

Adenovirus-based oncolytic viruses have exploited the p53 inactivation in most cancer cells to continue replication. Oncorine and Onyx-015 contain a deletion of the E1B (55 kDa)[45] gene product which selectively binds to p53 protein causing disruption of apoptosis. The deletion of E1B (55 kDa) reduces the replication ability of adenovirus in normal cells. However, p53-deficient cancer cells are conducive for the replication of the reconstructed virus. The E1B (19 kDa) in both oncolytic viruses might prevent apoptosis by blocking the function of Bax. The oncolytic strategies of Onyx-015[46] and Oncorine are based on two factors, one is tumor cell-specific viral replication and the other is virus-induced cell death, while DNX-2401 emphasizes on improving the ability of infecting tumor cells. DNX-2401 has the RGD-4C motif inserted in the fiber which enables selective infectivity in cancer cells with Rb/p16 tumor suppressor pathway defects. Integrin specificity of the modified fiber causes receptor-independent infection of the cancer cells and the oncolysis resulting from viral replication. VCN-01 expresses hyaluronidase which degrades the extracellular matrix (ECM) that acts as a physical barrier for the tumor cells enabling viral spread within tumor cells.[47-49] This results in enhanced penetration and efficacy of chemotherapeutic agents.[50-52] LoAd703 was designed to modulate the tumor

Table 3. Clinical trials of the adenovirus-based oncolytic viruses.

Oncolytic vector	Therapeutic agent	Cancer type	Phase, study type	Mode of therapy	Purpose of the study	Status	Clinical trial number
DNX2401	DNX2401 in combination with temozolomide	Recurrent glioblastoma	Phase 1, open-label, single-group study	Intra-tumoral	Safety evaluation	Completed	NCT01956734
	DNX2401 with interferon gamma	Recurrent glioblastoma	Phase 1b, open-label, parallel assignment	Intra-tumoral	Efficacy evaluation of DNX-2401	Completed	NCT02197169
	DNX-2401	Diffuse pontine glioma	Phase 1, open-label, single-group study	Intra-tumoral	Safety evaluation and dose determination	Recruiting	NCT03178032
	DNX-2401 in combination with pembrolizumab	Recurrent glioblastoma or gliosarcoma	Phase 2, multicenter, open-label study	Intra-tumoral DNX-2401 with intravenous pembrolizumab	Single dose efficacy evaluation of DNX-2401	Active, not recruiting	NCT02798406
ONCOS-102	ONCOS-102 in combination with cyclophosphamide	Advance cancers, malignant solid tumor	Phase 1, open-label, single-group study	Intra-tumoral ONCOS-102 with intravenous cyclophosphamide	Safety and dosage determination	completed	NCT01598129
	ONCOS-102 in combination with pemetrexed/cisplatin or cyclophosphamide	Un-resectable malignant pleural mesothelioma	Randomized phase 1b or phase2 open-label, parallel group-study	Intra-tumoral ONCOS-102	Evaluation of safety, tolerability and efficacy of ONCOS-102 in combination with chemotherapy	Active, not recruiting	NCT02879669
	ONCOS-102 in combination with pembrolizumab or cyclophosphamide	Advanced or un-resectable melanoma	Phase1, open-label, single-group study	Intra-tumoral ONCOS-102 with intra-venous pembrolizumab	Safety evaluation of sequential treatment with ONCOS-102 in combination with pembrolizumab	Recruiting	NCT03003676
VCN-01	VCN-01 in combination with gemcitabine and Abraxane	Patients with advanced solid tumors	Phase1, open-label, single-group study	Intra-venous administration of VCN-01 with gemcitabine	Safety and tolerability evaluation of VCN-01 in combination therapy	Active, not recruiting	NCT02045602
	VCN-01	Refractory retinoblastoma	Phase 1, open-label, single-group study	Intra-vitreal injection of VCN-01	Safety and efficacy evaluation	Recruiting	NCT03284268
	VCN-01 in combination with durvalumab	Recurrent head and neck squamous cell carcinoma	Phase 1, multicenter, open-label, dose-escalation study	Intra-venous injection of VCN-01 and durvalumab	Safety, tolerability and efficacy evaluation	Recruiting	NCT03799744
LOAd703	LOAd703 in combination with gemcitabine and nab-paclitaxel	Pancreatic cancer	Open-label, single-group phase 1/2 trial	Ultra-sound guided percutaneas injection of LOAd703	Safety evaluation	Recruiting	NCT02705196
	LOAd703	Pancreatic, ovarian, biliary and colorectal cancer	Open-label, single-group, phase 1/2 study	Image-guided intra-tumoral injection of LoAd703	Evaluation of efficacy of LOAd703 in various cancers	Recruiting	NCT03225989
ColoAd1	ColoAd1	Resectable colon cancer, resectable non-small cell lung cancer, bladder cancer, renal cell carcinoma	Phase 1 study	Intra-tumoral injection or intravenous infusion of ColoAd1	Mechanism of action study	Completed	NCT02053220
	ColoAd1	Solid tumor of epithelial origin, colorectal cancer, bladder cancer	Phase I, Phase II study	Sub-acute fractionated intravenous injection	Dose escalation study	Completed	NCT02028442
OBP-301	Telomelysin (OBP-301)	Esophago gastric adenocarcinoma	Phase 2 study	Intra-tumoral	Safety and efficacy study	Recruiting	NCT03921021
	OBP-301 and pembrolizumab	Advanced solid tumor	Phase 1 study	Intra-tumoral	Safety and efficacy study	Recruiting	NCT03172819
	OBP-301	Hepatocellular carcinoma	Phase 1 study	Intra-tumoral	Safety and efficacy study	Recruiting	NCT02293850
	OBP-301	Melanoma Stage III/IV	Phase 2 study	Intra-lesion	Safety, efficacy evaluation	Active but not recruiting	NCT03190824
CG0070	CG0070	Bladder cancer (BOND2)	Phase 2 study	Intra-vesical therapy	Safety and efficacy study	Completed	NCT02365818
	CG0070	Bladder cancer (ExBOND)	Phase 2 study	Intra-vesical therapy	Safety and efficacy study	Withdrawn	NCT02143804
	CG0070	Carcinoma, transitional cell bladder neoplasms	Phase 1 study	Intra-vesical therapy	Evaluation of safety and dosing of CG0070	Current recruitment status is unknown	NCT00109655

Table 4. Clinical trials of MV-NIS.

Therapeutic agent	Cancer type	Phase, study type	Mode of therapy	Purpose of the study	Status	Clinical trial number
MV-NIS	Ovarian, fallopian or peritoneal cancer	Phase 2, open-label, randomized parallel study	Intra-peritoneal administration of MV-NIS and intravenous administration of the drugs like paclitaxel or gemcitabine	Safety, tolerability and efficacy evaluation of MV-NIS in comparison with standard chemotherapy	Recruiting	NCT02364713
MV-NIS in combination with	cyclophosphamide	Recurrent or refractory multiple myeloma	Phase 1 and phase 2, open-label, non-randomized, parallel study	Intravenous administration of MV-NIS with cyclophosphamide		Determination of maximum tolerated dose of MV-NIS in combination with
cyclophosphamide	Active, not recruiting	NCT00450814				
MV-NIS in combination with	cyclophosphamide	Recurrent or refractory multiple myeloma	Phase 2 open-label single-group assignment	Intravenous administration of MV-NIS		Determination of the clinical efficacy of MV-NIS in combination therapy with
cyclophosphamide	Recruiting	NCT02192775				
MV-NIS	Malignant pleural mesothelioma	Phase 1, open-label, single-group study	Intra-pleural administration of the oncolytic virus	Dose determination and safety evaluation	Active, not recruiting	NCT01503177
MV-NIS	Head and Neck metastatic squamous cell carcinoma or metastatic breast cancer	Phase1, open-label, single-group study	Intra-tumoral administration of MV-NIS	Dose determination and safety evaluation	Suspended	NCT01846091
MV-NIS	Unresectable or recurrent malignant peripheral nerve sheath tumor	Phase 1, single-group, open-label study	Intra-tumoral administration of MV-NIS	Dose determination and safety evaluation	Recruiting	NCT02706230

Table 5. Clinical trials of reovirus.

Therapeutic agent	Cancer type	Phase, study type	Mode of therapy	Purpose of the study	Status	Clinical trial number
Wild-type reovirus	High grade relapsed or refractory brain tumor	Phase 1, open-label, single-group study	Intravenous injection	Dose determination and safety evaluation	Active, not recruiting	NCT02444546
Reolysin in combination with paclitaxel	Recurrent or persistent ovarian epithelial, fallopian tube or primary peritoneal cancer	Phase 2, open-label parallel study	Intravenous administration of reolysin and paclitaxel	Efficacy evaluation of reolysin in combination with paclitaxel	Active, not recruiting	NCT01199263
Reovirus in combination with carfilzomib, dexamethasone and nivolumab	Relapsed or refractory multiple myeloma	Phase 1, open-label, parallel assignment	Intravenous administration of the drugs and the virus	Dose determination of wild-type reovirus	Recruiting	NCT03605719

Table 6. Clinical trials of PVSRIPO.

Therapeutic agent	Cancer type	Phase, study type	Mode of therapy	Purpose of the study	Status	Clinical trial number
PVSRIPO	Recurrent glioblastoma	Phase 1, open-label, sequential assignment	Intra-tumoral infusion	Dose and safety determination	Active, not recruiting	NCT01491893
PVSRIPO	Malignant glioma	Phase 2, open-label, single-group study	Intra-tumoral administration by convection-enhanced delivery (CED)	Single dose efficacy assessment	Recruiting	NCT02986178
PVSRIPO	Recurrent malignant glioma	Phase1, open-label, single-group assignment	Intra-tumoral delivery by CED	Safety and dose determination	Recruiting	NCT03043391

microenvironment and to simultaneously activate the immune system against the tumor cells.[53] Recently, a new oncolytic vector ORCA-010 has been reported to show enhanced oncolytic efficacy and safety *in vivo*. This oncolytic vector has a novel mutation (T1) which contains a single adenine-base insertion at position 445 within the ER retention domain of the E3/19K gene. This mutation significantly increases the oncolytic potential of adenovirus human serotype 5 (AdHu5)-based vectors. These vectors are estimated to be more potent than the licensed ONYX015.[54,55]

CG0070, produced by Cold Genesys is a conditionally replicating oncolytic adenovirus that is armed with GM-CSF. In vitro and in vivo studies with bladder transitional cell carcinoma (Bladder-TCC) models have shown promising results, suggesting that CG0070 could be a potential therapeutic agent for bladder cancer.[56] Intravesical treatment with

CG0070 in patients with Bacille Calmette-Guerin (BCG) resistant high-grade non-muscle invasive bladder cancer (NMIBC) has also shown promising results. A phase II study has also been conducted with patients suffering from BCG-unresponsive NMIBC who refuse cystectomy (NCT02365818). A group of 45 patients with 24 pure carcinoma-in-situ (CIS) patients was treated with intravesical CG0070. Within 6 months of the treatment regimen, 47% of the total and 50% of the CIS patients showed complete response,[57] indicating that CG0700 could be a potential anticancer therapeutic agent. Recently, another clinical trial has been planned by Cold Genesys to evaluate the combination therapy of CG0070 with pembrolizumab in bladder cancer.

Most of the adenovirus-based oncolytic viruses showed success in clinical trials. However, the major drawback is the high levels of neutralizing antibodies to the vector itself that was observed in the patients, which may impair the therapeutic efficacy. It is reported that chimpanzee adenovirus-based oncolytic virus could overcome the problems of preexisting immunity to human adenovirus serotypes,[58,59] which implies that chimpanzee adenovirus has the potential to be applied clinically. Other strategies that have been considered to avoid the problem of preexisting immunity includes: (1) using less seroprevalent adenovirus serotypes. Adenovirus subgroup D[60] has decreased intrinsic hepato-tropism due to low affinity to FX,[61] and adenovirus type 9 was found to be the most appealing alternate serotype for cancer therapeutic application;[62] (2) capsid pseudotyping. The fiber knob or the fiber of the AdHu5 capsid could be modified or substituted by the corresponding part from the less seroprevalent or less immunogenic serotypes. For example, exchanging AdHu5 hexon HVR with a less seroprevalent Ad48 HVR resulted in altered vector immunogenicity;[63-66] (3) genetic masking. It is achieved by either short heterologous peptide insertion within the fiber[67,68] or by fiber deknobbing. In this strategy, artificial peptide structures are used to remove or replace the fiber knob domain;[69] (4) chemical shielding. The viral vector is shielded using distinct carriers such as PEGylated polymeric carriers.[70] The covalent attachment of PEG with hexon and the fiber reduces the chance of an immune attack. Another form of chemical shielding can be achieved by bio-reducible (cationic) polymers,[71] with liposomes or with bi-specific adaptor molecules.[72-75]

Measles-based oncolytic viruses

Measles virus (MV) belongs to the paramyxoviridae family which also consists of mumps and other viruses that cause respiratory tract infections.[76] The extremely safe live-attenuated MV vaccine was derived following multiple passages in human kidney cells, human amnion cells, and chicken embryos following its isolation from the Edmonstonstrain.[77,78] With respect to safety, the MV vaccine is very promising as the risk of reverting back of the non-segmented genome into the pathological form is very unlikely.[79] This feature of the MV vaccine is therefore very reliable when it comes to the matter of oncolytic viruses where safety is of utmost importance. MV-Edm-Zagreb (MV-EZ) vaccine strain is the genetically unmodified measles virus strain that has been tested in an open-label dose-escalation phase I clinical trial conducted in Switzerland. This strain was used in the intratumoral treatment of five measles immune patients with CTLC. To control the MV-EZ spread in the normal tissues these patients were subcutaneously injected with interferon alpha (IFN- α) 72 or 24 h before treatment. Complete recovery was observed in one patient while the remaining four patients showed partial recovery with the recovery of distant-noninjected lesions in two patients. Two variants of oncolytic measles virus have been constructed by genetically expressing human carcinoembryonic antigen (MV-CEA) and human sodium iodide symporter (MV-NIS). Currently, the clinical trials that are ongoing aim at treatment of ovarian cancer, glioblastoma, multiple myeloma, mesothelioma, head, and neck cancer, breast cancer, and malignant peripheral nerve sheath tumors. While one study uses the measles oncolytic virus alone, the other which is still ongoing is a comparative study using MV-NIS with chemotherapy for ovarian, fallopian, or peritoneal cancer (NCT02364713) (Table 4). In some other ongoing trials, 21 measles immune patients with recurrent ovarian cancer were treated by intraperitoneal administration of MV-CEA, while MV-NIS was tested to treat multiple myeloma (intravenous) (NCT00450814, NCT02192775) (Table 4), mesothelioma (intrapleural) (NCT01503177) (Table 4), HNSCC (intratumoral) (NCT01846091) (Table 4), and malignant peripheral nerve sheath tumors (intratumoral) (NCT02700230) (Table 4). Completed studies have not shown any dose-limiting toxicity. The main drawback of measles-based oncolytic virotherapy is the preexisting anti-measles antibodies which may hamper the systemic administration of the virus.[80] Several strategies are being considered to overcome this problem: (1) delivery of the virus to its target using a cellular vehicle;[81] (2) suppression of the intracellular pathways associated with innate immunity by encoding one or two immune-suppressing genes of the wild-type MV into MV-EDM. However, the safety of this approach is questionable; (3) replacement of the H and F glycoproteins on the MV envelop with immunologically unreactive but structurally similar glycoproteins of the related animal virus;[82] (4) combination of the MV-based oncolytic therapy with immune-suppressive drugs.

Other oncolytic viruses

Reovirus is one among the naturally occurring oncolytic viruses. The natural strain of reovirus is capable of recognizing the altered signaling pathways in cancers.[83] Reovirus oncolysis occurs mainly through apoptosis combined with autophagy. In HCV-associated hepatocellular carcinoma (HCC), reovirus induced pro-inflammatory response efficiently suppresses the multiplication of HCV in host cells, and reovirus-based immune responses are also effective against HBV-based HCC.[84]

Several clinical trials have demonstrated that reovirus type 3 is a promising therapeutic agent for cancer.[85-89] In one study 33 patients with advanced cancers received escalating-doses of reovirus for 4 weeks and no dose-limiting toxicity was observed.[89] Currently, several phase I and II trials are ongoing some among which are combination therapies. Wild-type reovirus has been used in combination with sargramostim to treat the patients with refractory brain tumors (NCT02444546) (Table 5). Pelareorep, a live replication-competent naturally occurring

reovirus type 3 (Dearing strain)[90] has been used in combination with paclitaxel to treat patients with recurrent fallopian tube carcinoma, recurrent ovarian carcinoma, and recurrent primary peritoneal carcinoma (NCT01199263) (Table 5). In a phase I clinical trial, relapsed or refractory multiple myeloma was treated with pelareorep in combination with dexamethasone, carfilzomib, and nivolumab (NCT03605719) (Table 5).

Other naturally occurring oncolytic viruses include Newcastle disease virus (NDV) and parvovirus H-1 (ParvOryx).[91] NDV has been widely used and promising results have been observed in several clinical trials against a variety of cancers such as leukemia, lymphoma, melanoma, neuroblastoma, fibrosarcoma, colon carcinoma, mesothelioma, and head and neck carcinoma.[92-116] Phase II clinical trials with NDV on various cancer types including stage II and III melanoma,[117-120] colorectal cancer with liver metastasis,[121-123] resectable colorectal cancer,[124,125] metastatic renal cell carcinoma[126] have shown improved overall survival. NDV has a natural specificity for the cancer cells that have defects in the activation of the antiviral signaling pathway,[127-129] type I IFN signaling pathway,[127,130] defects in apoptotic pathway[131,132] etc. NDV armed with pro-apoptotic protein, apoptonin[133] or cytokine,[96] immunoglobulin[134] or tumor-associated antigens (TAA),[135] etc., is a better oncolytic virus.

Cavatak is a naturally occurring picornavirus-based oncolytic virus,[136] manufactured by Viralytics, Australia. PVSRIPO is another picornavirus-modified oncolytic virus that is CD155/Nec15-dependent, because the internal ribosome entry site (IRES) of the virus has been replaced with the IRES of human rhinovirus type 2 (HRV2). A phase I clinical trial has been conducted in which 61 participants with recurrent glioblastoma were treated with PVSRIPO (NCT01491893) (Table 6). Other trials are ongoing for patients with grade IV malignant glioma (NCT02986178) and pediatric patients with recurrent malignant glioma (NCT03043391) (Table 6).

JX-594 (known as Pexa-Vec) is an oncolytic vaccinia virus armed with the GM-CSF gene, produced by a France-based company, Transgene. The vector was designed to activate the host immune system against tumor cells. Pexa-Vec has been tested in a phase I/II study against refractory metastatic colorectal cancer to evaluate its safety, tolerability, and feasibility in combination with immune checkpoint inhibition (NCT03206073). Recently, a phase III PHOCUS clinical trial (NCT02562755) on advanced hepatocellular carcinoma patients was conducted by Transgene in partnership with South Korean biotech company SillaJen. However, it has been discontinued because the study failed to meet the primary objectives and did not show any significant clinical benefit, which has been attributed to the complexity of hepatocellular carcinoma.[137]

GL-ONC1 is an oncolytic vaccinia virus equipped with the light-emitting fusion protein Renilla luciferase-Aequorea green fluorescent protein (RUC-GFP). It enables easy detection and monitoring of virus infected-tumor cells both *in vitro* and *in vivo*. While virus induced-cell lysis is responsible for the death of the cancer cells, the release of TAA activates the immune system against the tumor.[138] A clinical trial has been carried out on patients with advanced-stage cancers with no standard care options for treatment (NCT03420430); however, no further information has been released yet. A phase I/II study, with GL-ONC1 is currently ongoing consisting of patients with recurrent or refractory ovarian cancer (NCT02759588). The treatment was planned as a monotherapy using GL-ONC1 alone or in combination with chemotherapy with or without bevacizumab. vvDD-CDSR is a vaccinia virus-derived oncolytic virus with deletion of the thymidine kinase (TK) gene and the growth factor gene and addition of the cytosine deaminase (CD) gene and the somatostatin receptor (SR) gene. vvDD-CDSR shows potential oncolytic activity in treatment for refractory and metastatic pediatric solid tumor. A phase I study has been conducted in patients with refractory-advanced colorectal or other solid cancers. The observations showed no dose-limiting toxicity or other adverse events except grade ½ flu symptoms. A potent Th1-mediated immunity against the virus as well as the cancer cells were also reported.[139]

Alpha virus M1 has natural oncolytic properties. It significantly suppresses a variety of cancer cells that have zinc finger antiviral protein (ZAP) deficiency. The initial study was carried out in non-human primates (cynomolgus macaques) to evaluate the safety of intravenous administration of the virus for human trials in future.[140,141] As ZAP is commonly deficient in human cancers, the application prospects of M1 are very broad. It is reported that M1 kills cancer cells by inducing endoplasmic reticulum stress-mediated apoptosis.[141] However, the neutralizing antibodies are the major issues for *in vivo* treatment using M1. A recent study reported that liposome encapsulation of M1 can ensure the secure transportation of this virus and protect it from neutralizing antibodies.[142] Clinical trials for evaluation of M1 are awaiting the safety confirmation so far.[143]

Future prospects

Oncolytic viruses as therapeutic agents for cancer biotherapy emerged when Oncorine was first approved by CFDA for the treatment of nasopharyngeal carcinoma. The US-FDA approval of T-VEC in 2015 also created a lot of interest in oncolytic virotherapy. Several viruses including vaccinia virus, reovirus, parvovirus, picornavirus have been assessed as potential candidates for oncolytic virotherapy. The major challenge in this therapy is the targeted delivery of the virus into the tumor. In most cases, systemic administration does not work well due to preexisting immunity. Therefore, virus delivery needs to be improved for effective systemic administration since intratumoral administration is expensive and difficult especially in cases of malignant gliomas. Some of the novel approaches involve the use of nanoparticles, complex viral particle ligands, and immuno-modulatory agents. Delivery of the virus into the tumor via nanoparticles uses a technologically complex image-guided delivery system. Alternatively, to secure the delivery of the oncolytic viruses via the blood stream, carrier cells that possess inherent tumor tropism have also been considered.[144] Another challenge is the optimization of combination therapies using oncolytic viruses along with the chemotherapeutic or immunotherapeutic drugs to get better and stable results. Immune response induction by oncolytic viruses after infection suppresses the replication of the virus thereby posing a hindrance to the effective functioning of the biotherapy intended to treat cancer. Presently, many oncolytic viruses are

undergoing clinical trials for applications in single therapy or combination therapy, and most of them are safe and show almost no dose-limiting toxicities. Therefore, the use of oncolytic viruses in cancer biotherapy has the potential to be an ideal and painless therapeutic option for the cancer patients in future if the above-mentioned challenges are appropriately dealt with.

Disclosure of potential conflicts of interest

The authors declare no competing interests.

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Author contributions

D.Z. conceived the study. M.M. and G.J. searched the literature regarding oncolytic viruses in cancer therapy. M.M. wrote the draft. D.Z., G.J. and P. H. edited the manuscript. All authors read and approved the final manuscript.

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