www.impactjournals.com/oncotarget/ Oncotarget, 2017, Vol. 8, (No. 60), pp: 102617-102639

Review

Review: Oncolytic virotherapy, updates and future directions

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Keywords: *oncolytic virus, immunotherapy, cytotoxicity*

Received: *April 19, 2017* ***Accepted:*** *May 03, 2017* ***Published:*** *May 31, 2017*

ABSTRACT

Oncolytic viruses (OVs) are viral strains that can infect and kill malignant cells while spare their normal counterparts. OVs can access cells through binding to receptors on their surface or through fusion with the plasma membrane and establish a lytic cycle in tumors, while leaving normal tissue essentially unharmed. Multiple viruses have been investigated in humans for the past century. IMLYGIC™ (T-VEC/ Talimogene Laherparepvec), a genetically engineered Herpes Simplex Virus, is the first OV approved for use in the United States and the European Union for patients with locally advanced or non-resectable melanoma.

Although OVs have a favorable toxicity profile and are impressively active anticancer agents *in vitro* and *in vivo* the majority of OVs have limited clinical efficacy as a single agent. While a virus-induced antitumor immune response can enhance oncolysis, when OVs are used systemically, the antiviral immune response can prevent the virus reaching the tumor tissue and having a therapeutic effect. Intratumoral administration can provide direct access to tumor tissue and be beneficial in reducing side effects.

Immune checkpoint stimulation in tumor tissue has been noted after OV therapy and can be a natural response to viral-induced oncolysis. Also for immune checkpoint inhibition to be effective in treating cancer, an immune response to tumor neoantigens and an inflamed tumor microenvironment are required, both of which treatment with an OV may provide. Therefore, direct and indirect mechanisms of tumor killing provide rationale for clinical trials investigating the combination of OVs other forms of cancer therapy, including immune checkpoint inhibition.

INTRODUCTION

Oncolytic viruses (OVs) are viral strains that can infect and kill malignant cells (oncolysis) while sparing their normal counterparts. Oncolysis can be either a natural property of the virus [naturally occurring OVs, e.g. reovirus] or a consequence of manipulation of the viral genome [genetically engineered OVs, e.g. adenovirus] and renders oncolytic virotherapy – the use of replication-competent virus for cancer treatment – a potential therapeutic modality in cancer treatment.

Oncolytic virotherapy has been studied for the last century. One of the first case reports of a dramatic regression of cervical cancer in a patient receiving the Pasteur-Roux live attenuated rabies vaccine was presented in 1910 [1]. In the 1940s, human studies with different types of viruses were launched [2]. The era of modern oncolytic virotherapy started in the early 1990s, when a genetically modified, live-attenuated, thymidine kinase (TK)-negative herpes simplex virus (HSV) strain was locally injected into human glioma xenograft models, showing promising results [3]. Today, IMLYGIC™ (T-VEC/Talimogene Laherparepvec), a genetically engineered HSV, is the first OV approved for use in the United States and the European Union for patients with locally advanced or non-resectable melanoma [4, 5].

In this review paper, we will discuss the general mechanisms of antitumor activity of OVs, limitations of oncolytic virotherapy, recent advances in clinical development for individual agents, and future prospects.

General mechanisms of oncolysis

OVs have been generally categorized into DNA and RNA viruses and further divided into double- and single-stranded. OVs can access cells through binding to receptors in their surface or through fusion with the plasma membrane. An essential characteristic of an OV is the ability to establish lytic cycle in malignant but not normal tissues, either by naturally exploiting inherent tumor weaknesses, such as RAS pathway activation [6–8] or by genetic modification. For example, knockdown of TK gene in HSV can lead to preferential killing of tumor cells, as TK-negative HSV can replicate only in dividing cells depending on their TK activity [3, 9, 10]. TK, an important enzyme involved in viral DNA synthesis and repair [11], is highly expressed in activated cells in G1 phase *in vitro* [12]. OVs have the ability to establish a niche of continuous viral replication within the tumor, recruit uninfected cells in proximity creating syncytia, infect dividing and non-dividing cells, and be stable *in vivo*, yet lack chromosomal integration and do not result in major disease [13]. OVs, like reovirus [14], HSV [15, 16] or vaccinia virus [17], can induce tumor-specific adaptive immune responses and indirectly cause malignant cell death. Adenovirus [18], Coxsackie B3 [19] and measles virus [20] can lead to endoplasmic reticulum (ER) stress and cause immunologic cell death – a type of cell death that leads to release of danger-association molecular patterns, like adenosine triphosphate, calreticulin and high-mobility group box-1, which attract immune cells [21].

OVs can also selectively target tumor neo-vasculature. Vesicular stomatitis virus (VSV) can selectively infect endothelial cells in the tumor microenvironment and cause thrombosis in the tumor vessels [22]. HSV and vaccinia virus can also selectively damage tumor endothelium [23, 24]; preferential replication in tumor vessels may be secondary to the dependence on high vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) levels for replication in normal endothelium [24]. OVs can be genetically engineered to express anti-angiogenic factors, like VEGF inhibitors [25, 26]. Vaccinia virus treatment can lead to a decrease in perfusion within the tumor and suppression of VEGF levels, which are restored after viral clearance, resulting in a synergistic antitumor activity with VEGF receptor (VEGFR) tyrosine kinase inhibitors (TKIs) [27]. Synergy with VEGFR TKIs may be a result of off-target inhibition of cellular antiviral defense proteins, like the double stranded RNA-dependent protein kinase (PKR) [28, 29].

Limitations of oncolytic virotherapy

OVs are not the 'magic bullet' for cancer therapy. Single agent activity is modest for most agents. The main limitation of oncolytic virotherapy is accurate delivery to the target. The ideal method of delivery is systemic, preferably intravenous (IV). In order for an OV to establish a niche within the tumor after systemic administration, the OV has to bypass the liver that may actively sequester a percentage of the administered dose [30]. Administering the virus directly within the tumor overcomes this limitation, mainly in the minority of tumors with easily accessible skin and subcutaneous lesions such as melanoma, with an abscopal effect and dissemination in distant sites [31–34]. For the majority of disseminated malignancies with visceral or osseous metastasis, the logistics of intralesional administration may prohibit its use. Further, as most OVs are ubiquitously present in nature and humans are infected at an early age or vaccinated against some, most patients have neutralizing antibodies that can bind the virus and limit target delivery [35]. For example, 50–80% of humans possess neutralizing antibodies against HSV and almost 90% against reovirus [36, 37]. Finally, the adaptive immune system may be a double edge sword, playing a role in both tumor killing and early elimination of viral infection through humoral (e.g. antibody and complement binding) and cellular mechanisms [38]. Preclinical data can often be misleading, as in immunocompromised mouse xenograft models an immune response cannot be generated leading to under- or overestimation of the agent efficacy. Using syngeneic immunocompetent models has been proposed as a possible solution to this problem, but the agent activity in a human vs. animal cell may be different.

Direct and indirect mechanisms of tumor killing provide rationale for the combination of OVs with cytotoxic, anti-angiogenic and immune therapies in patients with cancer. We will discuss individual agents in subsequent sections. Tables 1A, 1B and 2A, 2B and Figure 1 summarize individual agent design, mechanisms of action, preclinical and clinical data.

DNA viruses

Herpes simplex virus (HSV)

T-VEC is a genetically engineered oncolytic HSV, with mutations in infectious cell proteins (ICP) 34.5 and 47, while expressing US11 and granulocyte macrophage-colony stimulating factor (GM-CSF) [31]. GM-CSF is an immunomodulator that enhances viral oncolysis [39]. ICP34.5 protein is necessary for viral replication, viral exit from cells, avoidance of the early shut-off of protein

Table 1A: Summary of DNA, double-strand virus design, mechanisms of action and clinical implications

Virus	Design	Clinical Implications
Herpes Simplex Virus (HSV)	• T-VEC: ICP34.5/ICP47 mutant and US11/GM-CSF expressing [31]	• Melanoma [32, 33].
	• G207: ICP34.5/RR mutant [43, 61–63]	• Glioma [68, 69].
	• NV1020: ICP34.5 mutant [70, 71].	• CRC [72, 73].
	• HFA10: RR mutant [75]	• Data for breast, head and neck, and pancreas cancer [74–76]
Vaccinia Virus	• vvDD: TK mutant strain. Viral protein VGF binding to EGFR in cell surface [185–187].	• Phase I: ITu administration safe; abscopal effect [188].
	• JX-594: TK mutant / GM-CSF expressing strain [189].	• HCC [84] • Other solid tumors including CRC [85, 86]
	• GL-ONC1: TK mutant / HA expressing [190].	• Malignant Effusions: Intrapleural injection safe; prolongs disease stability in malignant mesothelioma [191]. • Peritoneal Carcinomatosis: IP administration safe [192]. • Solid tumors: IV administration, 18% SD as best response (lasting >6 months) – IHC revealed delivery to the tumor [193, 194].
Adenovirus	• ONYX-015: E1B55 mutant [90]	• Head and Neck [92].
	• Adenovirus chimeras • Ad5-D24: serogroup 5, E1A-/Rb-binding site negative; selectively kills cells with an abnormal p16/Rb pathway [195] • CRAd: Ad5-D24 plus serogroup 3 knob [196] • DNX-2401: Ad5-D24 plus RDG (integrin receptor) [197] • Ad5/3-D24-GMCSF and CGTG-102: CRAd and DNX-2401 plus GM-CSF respectively [197, 198]. • ColoAd1: tumor selective Adenovirus 11/3 • Ad5/3, hTERT and CD40 ligand expressing strain has improved antitumor immunity/activity [18].	• Phase I: CRAd by IP safe, 60% SD [196]. • Phase I: DNX-2401 by ITu administration in glioma safe, 12% CR rate, 11 months OS [199] • Phase I: DX-2401 or Ad5-D24-RDG-GMCSF ITu in solid tumors safe, 27% with SD [197]. • Phase I: CGTG-102 ITu in sarcoma safe, 75% with SD [198]. CGTG-102 ITu in solid tumors plus oral low-dose cyclophosphamide safe, 40% with controlled disease at 3 months [172]. • ColoAd1 has low level of pre-existing host immunity [200] and potentially higher potency than ONYX-015 [201]. It is tested in a mechanism of action Phase I study [202].
	• CG0070: E1A gene is under the control of E2F, GM-CSF expressing [94].	• Urothelial carcinoma [96]
	• CV764 and CN706: E1A gene is under the regulation of PSA [203, 204].	• Potential role in prostate cancer
	• OBP-301: hTERT promoter regulates the expression of E1 genes [205].	• Preclinical activity in a CRC [206]

CR: complete response, CRC: colorectal cancer, DNA: deoxyribonucleotide nucleic acid, EGFR: epidermal growth factor receptor, GM-CSF: granulocyte macrophage-colony stimulating factor, HA: hemagglutinin, HCC: hepatocellular carcinoma, hTERT: human telomerase, ICP: infectious cell protein, IHC: immunohistochemistry, IP: intraperitoneal, ITu: intratumoral, IV: intravenous, RR: ribonucleotide reductase, SD: stable disease, TK: thymidine kinase, US11: HSV RNA binding protein, VGF: viral growth factor.

Table 1B: DNA, single-strand viruses design, mechanisms of action and clinical implications

Virus	Design	Clinical Implications
Parvovirus	• H-1PV: Selectivity for mutated or inactivated p53; transformed cells are more vulnerable to H-1PV than normal cells [101]. • H-1PV-infected melanoma cells can activate dendritic cells as well as cross-prime cytotoxic T-cells [207].	• Preclinical data in glioma: selective replication, prolonged remissions and increased survival observed with ITu+IV H-1PV [208]. • Can cause direct and indirect lysis of tumor cells through stimulation of the immune system against uninfected tumor cells [209]. • Clinical data in glioma [102, 103].
Chicken Anemia Virus	• Induction of apoptosis through viral proteins 2 and 3 [210]; viral protein 3 (Apoptin), causes p53-independent apoptosis specifically in tumor cells [211]. • Bcl-2 protein can stimulate its apoptotic activity [212–214].	• Preclinical data in HCC: systemic delivery can induce apoptosis [215]. • Viral protein 3 combined with chemotherapy *in vitro*, demonstrated increased cytotoxicity [216]; *in vivo* induced apoptosis and caused tumor regression after ITu delivery into Rous sarcoma virus-induced tumors [217]. • No clinical studies reported

DNA: deoxyribonucleotide nucleic acid, HCC: hepatocellular carcinoma, ITu: intratumoral, IV: intravenous.

synthesis, and neurovirulence [40–43]. In eukaryotic cells infected with HSV, PKR is activated and phosphorylates the eukaryotic translation initiation factor 2 (eIF-2) thus terminating protein synthesis; ICP34.5 activates the eIF-2 phosphatase to allow for reactivation of eIF-2 and continuation of protein synthesis [42]. In the absence of efficient ICP34.5 activity, the cellular PKR-induced inhibition of protein synthesis and viral replication cannot be reversed [42, 44]. Cellular growth arrest and DNA damage-inducible protein 34 (GADD34, also known as MyD116), has a carboxy-terminal domain homologous to the ICP34.5 corresponding region and can restore protein synthesis in infected cells [45]; non-functional GADD34 in tumor tissue [46] can be potentially responsible for the tumor selectivity of ICP34.5 mutant strains. ICP34.5-mutant HSV can specifically induce cell death in malignant cells either by enhanced replication or by early shut-off of protein synthesis [47] and is non-neurovirulent [48]. US11, a viral ribosome-associated protein, can decrease the levels of active PKR [49]. ICP47 is an inhibitor of transporter associated with antigen presentation (TAP), a protein responsible for transferring the antigen-major histocompatibility complex (MHC) type I complex to the plasma membrane, leading to impaired antigen presentation in HSV-infected cells [50, 51].

Hu et al. published the results of a Phase I trial of T-VEC administered by intratumoral (ITu) injection in patients with multiple tumor types with accessible lesions [31]. Twenty-six of the 30 patients enrolled were evaluable. The most common toxicities were constitutional and injection-site reactions, with grade 3/4 adverse events (AEs) only in HSV seronegative patients. Disease stabilized in three patients, with no difference based on serologic status. On-treatment biopsies revealed tumor necrosis, extensive in some cases, with no necrosis and very rare presence of HSV antigens by immunohistochemistry in normal tissue present in biopsy specimens.

In a phase II study of T-VEC in 50 patients with non-resectable stage III/IV melanoma with lesions amenable to injection, subjects were initially treated

Table 2A: RNA, double-strand virus design, mechanisms of action and clinical implications

Virus	Design	Clinical Implications
Reovirus	• RAS-induced inhibition of cellular PKR is responsible for preferential activity in RAS-activated cells, allowing viral translation, replication, oncolysis and cancer cell death [8]. • RAS activated JNK and NFkB can mediate reovirus- induced apoptosis [218, 219]. • Reovirus can induce antitumor immune responses [14]. • Reovirus can preferentially infect and kill pancreatic cancer cells [116, 117]	• Preclinical data: wild-type reovirus type 3 Dearing (Reolysin), has demonstrated synergy and/or additive effects with standard chemotherapies [107, 111–114]. • Preclinical data: the combination with immune-modulating chemotherapeutic drugs may enhance the antitumor effects by attenuating the antibody response, allowing enhanced viral replication and circulation for longer time periods, and enhancing the antitumor immune effect [168, 170]. Combination therapy with immunosuppressant agents has synergistic antitumor activity and appeared to overcome a pre-existing immunity without affecting metastatic tumor regression [115]. • Preclinical data in pancreas cancer: inhibition of the peritoneal dissemination of pancreatic cancer cells [118]; activity with intraportal administration [119]. • Phase I: IV Reolysin established as a safe therapy [220, 221]. • Phase I: ITu Reolysin in glioma [222] and advanced superficial malignancies safe [223]. • Phase I: Reolysin infused locally for 72 hours in patients with gliomas safe, 66% SD – one PR [224]. • Combinations with docetaxel [225], paclitaxel/ carboplatin [226] and gemcitabine [171] are well tolerated. • Clinical data for NSCLC, CRC, breast and pancreas cancers [120–122, 124, 227].

CRC: colorectal cancer, ITu: intratumoral, IV: intravenous, JNK: c-Jun N-terminal kinase, NFkB: nuclear transcription factor kappa B, NSCLC: non-small cell lung cancer, PKR: double-stranded RNA-dependent protein kinase, RNA: ribonucleotide nucleic acid, PR: partial response, SD: stable disease.

Table 2B: RNA, single-strand virus design, mechanisms of action and clinical implications

Virus	Design	Clinical Implications
Coxsackie Virus	• Coxsackie A21 (CVA21): ICAM-1 and DAF forms the cellular receptor for CAV21 resulting in specific viral attachment, cell internalization, and subsequent rapid cell lysis [129], DAF is upregulated on surfaces of many tumors [127, 128]. • Coxsackie B3 (CVB3): The receptors for CVB3 are DAF and CAR. Normal lung cell lines express low levels of CAR but moderate to high for NSCLC cells [19].	• Preclinical data in Melanoma: activity with ITu, IP or IV CVA21 [130]. • Preclinical data in breast cancer: IV CVA21 plus doxorubicin had synergistic effects [228]. • Preclinical data for NSCLC: CVB3 was found to be active and selective [19]; abscopal effect was noted. • Clinical data in melanoma for CVA21 [131].
Measles Virus (MV)	• MV vaccine affects only cells with a high density of CD46, and therefore, does not affect normal cells [137]. • MV-GFP-H(AA)-IL-13: human IL-13 displayed at the C-terminus of the H protein; CD46 and SLAM-ablating mutations in H protein. Intracerebral administration has shown efficacy as well as lack of neurotoxicity [229]. • MV-CEA: expresses the CEA gene [230] • MV-NIS: expresses NIS; distribution can be monitored by functional imaging [231, 232] and allows intracellular transfer of ^{131}I and potentiation of antitumor activity.	• Preclinical studies in solid tumors and hematologic malignancies have evaluated measles virus through different routes (ITu, IV, IP or intrapleural) and administration schedules [140–144]. Treated animal tumors demonstrate cytopathic effect with syncytia formation followed by apoptotic cell death of MV-infected tumor cells [145]. • No toxicity was observed in clinical or laboratory tests after IP, ITu or IV administration [229, 233-235].
Newcastle Disease Virus (NDV)	• NDV binds cells via HN and fuses using the F protein [151] • PV701 and MTH68/H are live attenuated oncolytic viral strains of NDV, which have the capacity to selectively replicate in and lyse tumor cells, and to be immunostimulatory [152] • NDV-HUJ: can overcome the anti-apoptotic effect of anti-apoptotic protein Livin [156]. • The ER stress is a key component of induction of antitumor immunity [236–238].	• Preclinical data show induction of apoptosis in different cell types [239-241] • Oncolytic strains given via IV, IP, and ITu routes, have been shown to have tumor selectivity [242].
Vesicular Stomatitis Virus (VSV)	• VSV-hINFb: express IFN-β, resulting in effective oncolytic activity with increased antitumor immune response [163, 164]. • Mutation of the matrix gene: unopposed mRNA export from the nucleus, resulting in the stimulation of robust innate immune responses and induces anticancer cytokines. [165, 166]	• A toxicology study in rats and rhesus macaques has shown that ITu injection of oncolytic VSV expressing human interferon-β (VSV-hIFNβ) did not have any observed AEs [167].
Seneca Valley Virus	• The selective tropism of virus replication may involve receptor-mediated internalization [158–160].	• Preclinical data in SCLC: complete and durable responses with systemic administration [161]; preexisting antibodies are rare. SVV-001 can readily penetrate solid tumors from the vascular system. • Solid tumors with neuroendocrine features [162].
ECHO	• ECHO and Coxsackie Virus share mechanisms of cytotoxicity. • ECHO-1: enter cells through binding to the integrin alpha 2 beta 1 [243, 244].	• Preclinical data in ovarian cancer cells [244] and ovariand and prostate cancer xenografts [245]. • In a retrospective, non-randomized comparison, ECHO-7 Rigvir by regional intramuscular administration of Rigvir for up to 3 years in patients with excised stage II, seemed to improve OS even though did not increase disease-free survival [246]. • Rigvir has been approved for treatment of melanoma in Latvia since 2009.

CAR: coxsackie and adenovirus receptor, CEA: carcinomebryonic antigen, CRC: colorectal cancer, DAF: decay accelerating factor, ER: endoplasmic reticulum, HA: hemagglutinin, HN: hemagglutinin neuraminidase , ICAM-1: intercellular adhesion molecule-1, INF-b: interferon beta, IP: intraperitoneal, ITu: intratumoral, IV: intravenous, NIS: sodium iodide symporter, NSCLC: non-small cell lung cancer, OS: overall survival, RNA: ribonucleotide nucleic acid, SCLC: small cell lung cancer, SLAM: signaling lymphocyte–activating molecule.

with a total ITu injection of up to 4×10^6 pfu (plaque-forming units) followed in 3 weeks later by injections up to 4×10^8 pfu repeated every 2 weeks until disease progression (maximum of 24 injections) [33]. Up to 10 lesions were treated per visit. The overall response rate (ORR) was 26%; eight patients attained a complete response (CR). Most of the responses were sustained for > 6 months and occurred after the first 2 injections; in 6 patients, transient, local or distant progression preceded the response. Again, the HSV serological status did not appear to affect response rate. Responses in non-injected sites were observed. The disease control rate was 50%, and the 1-year overall survival (OS) was 58% (> 90% with response). AEs were mostly constitutional, with grade 3/4 events infrequent.

This study led to a Phase III, multicenter, randomized-controlled trial comparing T-VEC using the previous dosing schema, to subcutaneous GM-CSF (control arm) in the same patient population (OPTiM) [32]. The primary outcome was durable disease response (DDR-lasting more than 6 months). At the time of study was designed there were no life-prolonging therapies approved for disseminated melanoma and as such using a modestly active agent like GM-CSF (or placebo) as the control arm was reasonable. Four hundred thirty-six patients were randomized, with two-thirds of the patients having stage

IV disease and 50% patients having received prior therapy. One-third of the patients were HSV seronegative. This trial reached its primary endpoint with DDR of 16.3% in the T-VEC arm compared with 2.1% in the GM-CSF arm (OR 8.9; $P < 0.001$). DRR was higher in treatment-naïve patients and patients with earlier stage disease; there was no difference based on the patients' HSV serological status. Median time to response was 4.1 months. The same percentage of patients in both arms went on to receive subsequent therapies. There was a trend for improved OS compared to the control arm (23.3 vs.18.9 months in GM-CSF arm, $P = 0.051$). T-VEC was tolerable.

T-VEC is now an approved therapy for non-resectable melanoma. Combination trials with immunotherapy are ongoing. In an ongoing phase I/II study, the combination of T-VEC and ipilimumab in 18 patients with unresectable melanoma resulted in a DDR of 44%, response rate (RR) by immune-related response criteria was 56% with a third of the patients attaining CR. The immune-related response criteria do account for the potential increase in tumor size and appearance of new lesions secondary to treatment-induced tumor inflammation and is probably a better tool for evaluating responses in trials evaluating agents such as OVs or immune checkpoint inhibitors [52, 53]. Grade 3/4 treatment-related AEs occurred in a third of the patients. Two patients developed grade 3/4 immune-related AEs. The median time to response and progression-free survival (PFS) were 5.3 and 10.6 months, respectively. Twelve-and 18-month OS were 72.2% and 67% [54, 55]. Long et al have reported early outcomes of a combination strategy with pembrolizumab (MASTERKEY-265) [56–58]. Thirty-three percent of the patients experienced grade 3/4 AEs attributed to therapy. One patient developed cytokine release syndrome secondary to study treatment. The RR by immune-related response criteria was 48% with 14% of the patients attaining a CR.

Phase I studies have shown HSV replication after ITu injection into malignant brain tumors is safe and efficacious, and therefore, possibly effective as adjuvant therapy [59, 60]. G207 is an ICP34.5- and ribonucleotide reductase (RR)-mutated HSV [43, 61–63]. RR levels are elevated in dividing tumor tissue while not in normal ones [64–66]. In Phase I studies, G207 was administered by ITu injection into gliomas [67]. No toxicity was observed; radiographic and neuropathologic evidence of anti-tumor activity was suggested [67]. Also, multiple ITu dose delivery of G207 is safe before and after resection of malignant glioma [68] as well as concurrently with radiotherapy for recurrent glioma [69].

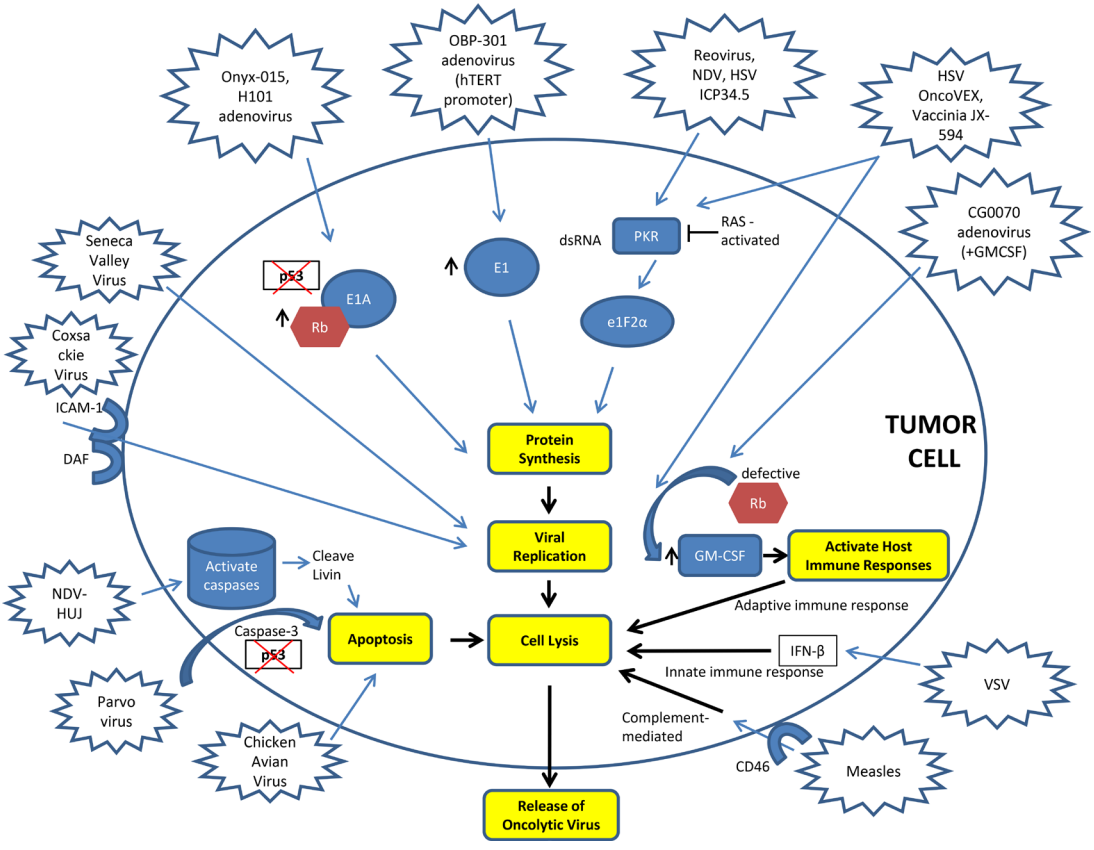

Figure 1: Mechanisms of action of oncolytic viruses. DAF – Decay Accelerating Factor, GM-CSF – Granulocyte Macrophage-Colony Stimulating Factor, HSV – Herpes Simplex Virus, hTERT – Human Telomerase, ICAM-1 – Intercellular Adhesion Molecule-1, ICP – Infectious Cell Protein, INF-β – Interferon beta, NDV – Newcastle Disease Virus, VSV – Vesicular Stomatitis Virus.

NV1020 is another HSV-1 strain, attenuated by ICP34.5 knockdown [70, 71]. NV1020 through hepatic artery infusion has been shown to be feasible, safe and potentially efficacious in the treatment of colorectal cancer liver metastasis [72, 73]. The ITu injection of HF10, a highly attenuated HSV-1, into metastatic head and neck cancer sites and recurrent breast cancer sites has shown to cause tumor cell death without any significant AEs [74, 75]. In another pilot study, six patients with non-resectable pancreatic cancer were treated with HF10 during laparotomy and through a catheter for three subsequent injections [76]. No subsequent treatment was administered in the next 30 days. No AEs were reported and 4 patients had clinical benefit (3 with stable disease (SD), 1 with partial response [76]. In a Phase I study, 24 patients with refractory, superficial cancers were treated with ITu administration of HF10 [77]. The treatment was safe; no efficacy data have been reported to date.

Vaccinia virus (VAC)

In early Phase I studies, ITu JX-594, a genetically engineered TK-mutant/GM-CSF expressing VAC, demonstrated highly promising results in patients with melanoma [78] and hepatocellular carcinoma (HCC) [79]. In a proof of principle study in patients with melanoma, 10 patients received ITu injections of JX-594 [80]. VAC replication was noted in non-injected lesions as well as intense perivascular lymphocytic infiltration. In another Phase I trial, direct injection of JX-594 into HCC was well tolerated and associated with viral replication, decreased tumor perfusion, and tumor necrosis [81]. In this study, the safety and efficacy of JX-594 followed by sorafenib was assessed in three patients. The sequential therapy regimen was well tolerated, associated with decreased tumor perfusion, and associated with objective tumor responses (using the Choi criteria [82, 83], a more appropriate response evaluation method for HCC that takes into account both target lesion size as well as perfusion), with tumor necrosis up to 100%. This study concluded that treatment of HCC with JX-594 followed by sorafenib has antitumor activity, and JX-594 may sensitize tumors to subsequent therapy with VEGFR TKIs.

In a randomized Phase II dose finding study, JX-594 was administered by ITu injection in 30 patients with unresectable HCC [84]. One severe treatment-related AE was recorded (nausea and vomiting), and all patients experienced grade 1/2 flu-like illness. One patient developed grade 1 pustular skin rash. The modified Choi RR was 62%, the disease control rate at week 8 was 46% overall (by modified RECIST). Responses were observed in injected as well as non-injected tumors. The OS was 14.1 months for the high-dose group (vs. 6.7 months in the low-dose). Of note, 25% of the patients in the high-dose group had disease refractory to sorafenib, whereas none in the low-dose group.

JX-594 has also demonstrated systemic delivery potential. The results of a Phase I dose-escalation trial of IV JX-594 in patients with metastatic tumors showed selective infectivity, replication, and expression of transgene products in cancer tissue in a dose-related fashion [85]. Normal tissues (adjacent normal tissues excised in on-treatment biopsies as well as blood mononuclear cells) were not affected [85].

JX-594 was tested in a Phase I dose-escalation trial in patients with metastatic, refractory colorectal cancer [86]. Fifteen patients were treated at three different dose levels IV every 2 weeks (total 4 doses). All AEs were grade 1/2 (no dose-limiting toxicity-DLT); most common were fever and chills (90%). One patient in the high dose group developed a pustular rash. Eighty-nine percent of the patients at the highest dose experienced disease stabilization. TRAVERSE, a Phase II study comparing intravenous and intratumoral JX-594 plus best supportive care to best supportive care alone in patients with advanced HCC who have progressed on sorafenib, is underway [87]. A randomized Phase III study of sorafenib vs. sorafenib following JX-594 in sorafenib-naïve patients is open to accrual (NCT02562755).

Adenovirus (Ad)

Oncolytic Adenoviruses are been genetically modified to take advantage of the altered tumor environment [88, 89]. ONYX-015 is an E1B55-mutant Ad that can cause oncolysis of cancer cells with mutant p53 [90]; although it has been shown to replicate independent of p53 [91]. In a phase II study of 37 patients with head and neck cancer, ONYX-015 by ITu injection was combined with chemotherapy. In this non-randomized trial, investigators compared RR and time to progression in injected vs. non-injected tumors with superior outcomes in injected tumors [92]. ONYX-015 was approved for human use in China in 2006, [93] but its clinical development in the United States and Europe has been halted since 2000 due to lack of efficacy.

CG0070 is a GM-CSF expressing Ad where the E1A gene is under the control of E2F, a retinoblastoma (Rb)-dependent transcription factor, providing selectivity for cells with abnormal p16/Rb pathway [94]. When Rb binding to E2F is lost, E2F remains transcriptionally active [95]. CG0070 has selective replication, cytotoxicity, production of GM-CSF and antitumor efficacy in urothelial carcinoma [94]. A first-in human Phase I trial of intravesical administration of CG0070 included 35 patients with non-muscle invasive urothelial cancer progressing after bacille Calmette-Guerin (BCG) therapy (4 different dose levels, single or multiple doses) [96]. Therapy was well tolerated with mostly grade 1 or 2 bladder AEs. Increased GM-CSF in urine and viral replication were observed. The RR was 48.6% and the median duration of response was 10.4 months. Increased expression of Rb by IHC was associated with higher RR (58 vs. 20%); however, the cohort of patients was too small for definitive conclusions.

Parvovirus (PV)

PV B19 can induce cell death through apoptosis in erythroid cells through non-structural proteins (NS1)-induced caspase-3 activation [97–100]. PV has selectivity for mutated or inactivated p53; transformed cells are more vulnerable to H-1PV than normal cells [101]. ParvOryx01 is a first in human, Phase I/IIa, dose-escalation study of H-1PV given locally and systemically in patients with recurrent glioma. The first part of the study (treatment of nine patients with ITu injection followed by tumor resection and virus injection in the tumor margin) has been completed without DLT [102]. Correlative studies in resected tumors showed the ability of H-1PV to cross the blood-brain barrier, spread and replicate in tumor tissue [103]. There was also evidence of induction of anti-tumor immunity, though clinical efficacy outcomes have not been reported.

RNA viruses

Reovirus (RV)

Reovirus preferentially targets cancer cells based on their higher rates of cell division, which differs from that of normal cells, reviewed by Gong and Mita [104]. An unmodified, nonpathogenic, type 3 Dearing reovirus strain (Reolysin) has been extensively evaluated in preclinical models and clinical studies. This RV has a dual mechanism of action including the selective lysis of tumor cells and induction of an anti-tumor immunity. The selective permissiveness of cancer cells to reovirus replication and lysis, not observed in normal cells, is dependent on a number of factors both, endogenous and exogenous. The former include: 1) defective PKR signaling; 2) RAS activation and/or mutations in upstream and downstream RAS-effector proteins that downregulate the IFN-induced antiviral response and 3) dysfunctional or deleted tumor suppressor-genes (e.g., p53 and ATM) [8, 104–106]. Exogenous factors include cellular stress resulting from chemo- and/or radiotherapy and reovirus modulation of interferon signaling [14, 107]. One or more of these factors allows for viral translation, replication, oncolysis and cancer cell death [8]. The presence of "infected" tumor cells and the release of viral- and tumor-associated antigens after tumor cell lysis, induce robust innate and adaptive antitumor immune responses [14, 108–110]. Therapy using a wild-type RV type 3 Dearing (Reolysin), has also demonstrated synergy and/or additive effects with standard chemotherapies [107, 111–114] and immunosuppressant agents [115]. Combination therapy can overcome pre-existing immunity to RV without affecting metastatic tumor regression. RV has been shown to preferentially infect, induce ER stress and kill RAS-activated pancreatic cancer cells [116, 117]. Furthermore, IP administration of RV inhibits the peritoneal dissemination of pancreatic cancer cells in a syngeneic immunocompetent animal model [118]. Intraportal administration of RV has decreased the number and size of treated tumors in the same model [119].

Reolysin is one of the best-studied OV and several Phase I and II studies have been completed. Over 1,000 patients have received single or multiple doses, IV or ITu, either as monotherapy or in combination with radiotherapy or chemotherapy (*Table 2A*). The most common AE related to Reolysin is a flu-like illness. It does not appear to increase toxicities in combinations with cytotoxic agents.

The Canadian Cancer Trials Group (CCTG) presented positive overall survival (OS) data from an open-label, randomized, phase 2 study assessing the therapeutic combination of intravenously-administered REOLYSIN given in combination with the chemotherapy agent paclitaxel versus paclitaxel alone, in patients with advanced or metastatic breast cancer (IND 213). The 74-patient study, powered to 90% and designed by the CCTG, reported that in the intention-to-treat patient population there was a statistically significant improvement in median OS from 10.4 months on the control arm to 17.4 months on the test arm (Hazard Ratio 0.65, 80% CI 0.46–0.91, $p = 0.1$) [120].

In a phase II, single arm study in 37 patients with metastatic KRAS- or EGFR-mutated, treatment-naïve non-small cell lung cancer (NSCLC), Reolysin was administered IV with paclitaxel and carboplatin [121]. No new safety concerns were observed. Thirty-one of the 35 evaluable patients had clinical benefit; the ORR was 31% (90% 1-sided lower CI) in comparison with the assumed historical response rate for paclitaxel and carboplatin alone of 20%. The median PFS and OS were 4 and 13.1 months respectively and 7 patients (20%) were still alive after a median follow-up of 34.2 months (range 26.9–71.5 months). Thus, it has been suggested that the effects in OS may be the result of the immunogenicity induced by Reolysin against the tumor cells.

REO 017 was a single arm Phase II study of Reolysin with gemcitabine in chemotherapy-naïve patients with advanced pancreatic adenocarcinoma [122]. With a median follow up of 2 years, the median PFS and OS were 4 months and 10.2 months, respectively [122]. Half of patients received chemotherapy after progression, including 12% nab-paclitaxel. On-treatment biopsies revealed virus localization in malignant cells, caspase-3 activation and increased PD-L1 expression in malignant cells [122, 123]. In a randomized Phase II study in a similar patient population, paclitaxel and carboplatin were administered alone (37 patients) or in combination with Reolysin (36 patients) [124, 125]. The median OS time in the test arm was median was 7.3 months (95% CI: 4.8–11.2 months) and in the control arm was 8.8 months (95% CI: 6.6–11.8, ($p = 0.68$). The median PFS time was 4.9 months (95% CI: 3.0–6.3 months) in the test arm versus 5.2 months (95% CI: 2.3–6.2 months) in the control arm ($p = 0.6$). Despite the fact that Noonan et al.

did not find any differences in response rate, PFS or OS between the two arms, the mature data showed a possible delayed effect on OS, with a divergence of survival curves occurring around year 1, and the strongest efficacy signal for improvement in OS occurring around year 2 in the Reolysin-containing arms in comparison to control arms. In fact, the estimated 2-year survival probability in the study with Reolysin and gemcitabine is 24% (95% CI 11–39%), consistent with estimated 2-year survival probability of 20% (95% CI 8–36%) in the randomized arm receiving Reolysin and in the NCI-8601 study.

The addition of Reolysin to chemotherapy has given mixed results depending on the tumor studied. What is becoming clear is that Reolysin works more like an immune-therapy agent with a major delayed effect in survival rather than as a cytotoxic that controls response rate and/or progression free survival.

The safety of ITu Reolysin with palliative radiotherapy was evaluated in a phase I study of patients with advanced cancer [126]. Among 23 patients, no DLT was observed, and the most common AEs were fever, flu-like symptoms, vomiting, asymptomatic lymphopenia and neutropenia.

To date, the AEs associated with Reolysin have been mild to moderate in severity and predominantly flu-like in nature (fever, chills, headache, fatigue, rhinorrhea, cough, myalgia, arthralgia, nausea, vomiting and diarrhea). Moderate and transient alterations in hepatic function tests and hematological investigations have also been observed.

Coxsackie virus (CXV)

Decay-accelerating factor (DAF) is highly expressed on surfaces of many tumors, including melanoma [127, 128]. A combination of surface-expressed intercellular adhesion molecule-1 (ICAM-1) and DAF forms the cellular receptor complex for CXV A21 (CAV21), resulting in specific viral attachment, cell internalization, and subsequent rapid cell lysis [129]. ITu, IP or IV administration of CVA21 were equally effective in reducing the tumor volume in melanoma xenografts [130]. CAV21 (CAVATAK) has been tested in humans. A phase II study in patients with advanced melanoma (CALM) has been completed [131]. The primary outcome of this study was PFS of more than 16% in 6 months (using the immure-related response criteria). CVA21 was administered by ITu injection in 57 patients. Almost 40% of the patients were alive and progression-free at 6 months, and the study reached its primary endpoint. The ORR using the immune-related response criteria was 28.1% with durable responses in 19.3% of the patients. Treatment was well tolerated with no grade 3/4 agent-related AEs. The most common AEs were grade 1 local injection reactions and flu-like illness.

Measles virus (MV)

MV enters cells through interaction of its H protein and cellular CD46 (membrane cofactor protein) and signaling lymphocyte–activating molecule (SLAM) [132–134]. The wild-type MV enter cells more effectively through SLAM; however, the MV vaccine strains enter more effectively via the CD46 receptors [135]. CD46 is overexpressed on tumor cells [136]. MV vaccine affects only cells with a high density of CD46, and therefore, does not affect normal cells [137]. MV kills tumor cells by inducing cell-to-cell fusion through F protein, formation of syncytia and subsequent apoptotic death [137–139]. Several preclinical studies in animal models, including both solid tumors and hematologic malignancies, have evaluated MV through different routes (ITu, IV, IP or intrapleural) and administration schedules [140–144]. Treated animal tumors demonstrate cytopathic effect with syncytia formation followed by apoptotic cell death of MV-infected tumor cells [145].

A phase I study of IP MV-CEA, a carcinoembryonic antigen expressing MV, to patients with recurrent ovarian cancer has been completed [146]. A total of 21 patients with measles immunity and platinum-refractory recurrent ovarian cancer were treated. No DLT was observed; the most common AEs were fever and abdominal pain. The best objective response was SD in 14 patients with a median duration of 92.5 days; clinical outcome was dose-dependent. All patients with viremia or CEA elevation had SD. In another phase I study, MV-NIS – a sodium-iodide symporter (NIS) expressing MV – was administered by IP injection every 4 weeks in patients with platinum-resistant ovarian cancer [147]. Therapy was well tolerated and no DLT was observed in 16 patients treated at high-dose levels. Viral accumulation was confirmed by ^{123}I uptake on functional imaging and was associated with long PFS. There was evidence of induction of anti-tumor immunity, as anti-tumor effector T cells recognizing tumor antigens were increased post-treatment. The median OS was 26.5 months. Early reports from a Phase I trial of systemically administered MV-NIS support selective replication within tumor tissue and potential efficacy in multiple myeloma [148]. Both patients in this report were seronegative for measles; decrease in tumor burden was seen in both and was maintained for 9 months in one patient.

Newcastle disease virus (NDV)

NDV is not pathogenic to humans and has been extensively studied as an oncolytic agent in several different human tumor cell lines and tumor models [149–150]. NDV binds cells via the hemagglutinin neuraminidase (HN) protein [151]. PV701 and MTH68/H are live attenuated oncolytic viral strains of NDV, which have the capacity to selectively replicate in and lyse tumor cells and to cause immunostimulation [152].

In three Phase I studies, PV701 has been given IV and shown to replicate in tumor cells, resulting in lysis of different tumor types [153]. In a phase I study evaluating four dosing regimens, 79 patients with advanced solid cancers that were unresponsive to standard therapy received PV701 IV [154]. The most common AEs

were flu-like symptoms, occurring mostly after the first dose and decreasing in number and severity with each subsequent dose. Tumor site-specific AEs and acute dosing reactions were also observed, without cumulative toxicity. Objective responses occurred at higher dose levels, with PFS of up to 31 months. Electron microscopy of tumor tissue from one patient, 11 months after therapy, demonstrated PV701 particles budding from the tumor cell membrane.

MTH68/H has been given to patients with high-grade glioma although outside of a clinical trial setting. In a report of four cases of advanced high-grade glioma after failure of conventional treatments, treatment with MTH-68/H resulted in survival rates of 5–9 years [155]. NDV-HUJ is a unique strain that can overcome the anti-apoptotic effect of Livin [156]. The phase I/II trial of IV NDV-HUJ in recurrent GBM showed good tolerability and responses [157]. Eleven of 14 patients received treatment with minimal toxicity of grade 1/2 fever in five patients; MTD was not achieved. One patient had a complete response.

Seneca valley virus (SVV-001)

Upon infection, this agent replicates intracellularly, resulting in tumor cell lysis and reduced tumor cell proliferation; the selective tropism of virus replication may involve receptor-mediated internalization [158–160]. In small cell lung cancer (SCLC) xenografts, doses $\geq 10^8$ viral particles/kg resulted in complete and durable eradication of tumors in all mice treated [161]. In a Phase I clinical trial, 30 patients were treated with SVV-001, including six with SCLC [162]. SVV-001 was well tolerated, with no DLT observed in any dose cohort [162]. Viral clearance was documented in all subjects and related temporally with the development of antiviral antibodies. Evidence of *in vivo* intratumoral viral replication was observed among patients with small cell carcinoma. One patient with previously progressive chemorefractory SCLC remained progression-free for 10 months after SVV-001 administration and is alive over 3 years after treatment.

Vesicular stomatitis virus (VSV)

rVSVs that express cellular genes, which modulate immunity, such as beta interferon (IFN-β) genes, result in effective oncolytic activity with increased antitumor immune response [163, 164]. VSVs with a mutation of the matrix (M) gene create a protein incapable of blocking mRNA export from the nucleus, resulting in the stimulation of robust innate immune responses following the infection of cancer cells, which increases production IFN-β and interferon-stimulated gene (ISG) [165, 166]. The resultant innate immune response causes stimulates the antigen-presenting machinery, increases NK cell activity, and induces anticancer cytokines. A toxicology study in rats and rhesus macaques has shown that ITu injection of oncolytic VSV expressing human interferon-β (VSV-hIFNβ) did not have any observed AEs [167]. No clinical trial results have been reported as of yet.

Oncolytic virotherapy: combination therapy and future directions

The generation of an antitumor immune response is an indirect mechanism of malignant cell death for both OV-infected and non-infected cells [34]. There is a theoretical concern that tumor-infiltrating lymphocytes can suppress viral replication and finally eradicate the virus. Pre-existing antibodies can also bind IV administered OV and clear it from the circulation, minimizing viral penetration. Combination strategies of OV with chemotherapeutic agents can potentially overcome those obstacles. Cyclophosphamide has been shown in preclinical animal models to improve reovirus access to the tumor and preserve neutralizing antibody levels sufficient for prevention of severe toxicity [168] but did not appear to affect antibody levels and duration of viremia [169]. Gemcitabine appears to negatively impact late phases of reovirus replication; however, the net effect is synergistic as it accelerates antitumor immunity generation most likely by decreasing immunosuppressive cells within the tumor microenvironment [170]. In a Phase II study of Reolysin in combination with gemcitabine, combination treatment did not prevent viral entry in malignant cells and subsequent apoptosis [122, 123]. Antibody response to Reolysin also appears to be attenuated with this combination strategy [171]. Activation of the programmed death-1/programmed death-ligand 1 (PD-1/PD-L1) axis in tumor cells can be induced by oncolytic virotherapy [122, 172], a finding likely related to natural stimulation of checkpoint molecules in the setting of chronic viral infections in order to minimize tissue damage [173].

There are preclinical data for synergy between OVs and immune checkpoint inhibition. In melanoma xenografts, the combination of Reolysin and anti-PD1 antibody significantly prolonged mice survival compared to either agent alone [174]. There was evidence of enhanced antitumor cytotoxic T cell and natural killer (NK) cell activity with the combination therapy. Suppression of antitumor immunity by regulatory T cells (Treg) in Reolysin alone treated mice was ameliorated by anti-PD1 therapy. In an immunotherapy-resistant lung adenocarcinoma animal model, treatment with oncolytic adenovirus plus anti-PD-1 antibody, significantly increased antitumor immune responses to multiple neoantigens and decreased tumor growth, suggesting reversal of anti-PD-1 resistance with oncolytic virotherapy [175]. NDV combined with immune checkpoint inhibition in immunogenic and non-immunogenic tumor animal models led to increased antitumor immunity and efficacy compared to either agent alone [34]. VSV-mIFNβ-NIS, an oncolytic VSV encoding human murine IFNβ and NIS, it has been shown to be active in an acute myeloid leukemia model and its activity was increased with anti-PD1 antibody therapy [176]. Synergy of oncolytic VSV with anti-PD1 antibody therapy has been also demonstrated in glioma models [177]. An oncolytic measles virus armed with genes coding for antibodies

against inhibitory immune checkpoints has been shown to have improved antitumor activity compared to control virus [178]. It appears to be a synergistic effect between oncolytic measles virus and immune checkpoint inhibitors [178]. Synergy of ITu vaccinia virus with ITu immune checkpoint blockade and radiation had been established in a lymphoma xenograft model, with tumor shrinkage in both treated and untreated tumors [179]. The results of oncolytic virotherapy and immune checkpoint inhibition in a Phase I clinical trial are promising [55]. Enhanced viral clearance with checkpoint inhibition still remains a concern [180].

Small molecule inhibitors can potentially improve OV penetration and activity. As mentioned in previous sections, combination strategies of OV with agents targeting the VEGF/VEGFR pathway are based on the potential selective targeting of the tumor neovasculature. VEGFR TKIs can also have off-target effects on antiviral defense mechanisms [28, 29]. Reolysin has shown synergy with VEGFR TKIs *in vitro* and *in vivo* in NSCLC models, with decrease in tumor growth and increase in antitumor immunity [181]. Similar efficacy is observed with BRAF and MEK inhibitors in BRAF mutated melanoma cells through induction of ER stress when combined with BRAF inhibition [182].

Multiple ambiguities exist regarding the optimization of combination strategies. It is unclear when the OV should be administered in regards to other novel agents. For example, administration of checkpoint inhibitors with OV on the same day or subsequent days in clinical trials or preclinical models has been performed but not been compared in a single study. It is not known whether the combination of two different OV has better efficacy compared to single agent therapy. Most importantly, we lack biomarkers predictive of response. Mutations in RAS pathway for Reolysin, Rb pathway mutations for adenovirus, GADD34 mutations for HSV are potential biomarker candidates but to date, no single study has stratified patients based on biomarkers of response. Real-time evidence of enhanced antitumor immune response generation as well as dynamic imaging for tumor perfusion may be methods that predict the benefit from oncolytic virotherapy. For example, in patients treated with T-VEC who develop minimal increase in CD^{8+} T cells from baseline after 6 weeks of therapy, the risk of subsequent disease progression is high [183]. Changes in PD-L1 expression and tumor-infiltrating lymphocytes in tumor tissue over time as well as alterations in serum cytokine profile and gene expression studies are currently being evaluated as secondary outcomes in clinical trials (clinicaltrials.gov NCT02824965, NCT02272855, NCT02364713).

CONCLUSIONS

After more than 100 years of intense research as a cancer therapeutic, the first OV therapy obtained regulatory approval in 2015, a modest success when compared to multiple cytotoxic agents, small molecule and antibody drug development programs that have obtained approval for clinical use over the last three decades. Although impressively active as anticancer agents *in vitro* and *in vitro*, with a favorable toxicity profile, the effectiveness as single agent therapy with OVs is limited. Thus, the addition of other agents to enhance OV efficacy is necessary. The immune system can enhance viral-induced oncolysis yet decrease viral penetration after systemic administration. Combinations of OV with cytotoxic agents are feasible and safe, with the potential of transient immunosuppression of the host in order to increase viral access to the tumor and provide time for viral oncolysis to exceed the tumor's replicative potential. Despite pre-clinical synergy with anti-angiogenic agents, it still remains to be seen if the combinatory approach would be clinically effective in randomized studies. Excessive antiviral immune response can also potentially eradicate the virus before it reaches its peak effect. Immune checkpoint activation in tumor cells has been noted with oncolytic virotherapy, a finding similar to the observed effector T cell exhaustion during chronic viral infections [184], therefore, providing rationale for combination strategies with novel immunotherapies. The future success of OV is likely to be determined through identification of biomarkers for tumor response that is currently lacking, improvement of OV delivery to tumor and its surrounding microenvironment, and ultimately its ability to enhance anti-tumor immune response through combinatory therapeutic approaches.

CONFLICTS OF INTEREST

The authors report no conflicts of interest

FUNDING

The cost of the manuscript was paid by Oncolytics Inc. Dr. Christos Fountzilas has received a Cancer Research Training Award by the Cancer Prevention and Research Institute of Texas (RP140105). Dr. Sukeshi Patel is supported by San Antonio Claude D. Pepper Older Americans Independence Center KL2 Award. National Cancer Institute P30 Cancer Center Support Grant # CA054174.

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