HHS Public Access

Author manuscript

Expert Opin Biol Ther. Author manuscript; available in PMC 2018 March 01.

Published in final edited form as:

Expert Opin Biol Ther. 2017 March ; 17(3): 353–363. doi:10.1080/14712598.2017.1288713.

Potential and clinical translation of oncolytic measles viruses

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Abstract

Introduction—Oncolytic viruses represent a novel treatment modality that is unencumbered by the standard resistance mechanisms limiting the therapeutic efficacy of conventional antineoplastic agents. Attenuated engineered measles virus strains derived from the Edmonston vaccine lineage have undergone extensive preclinical evaluation with significant antitumor activity observed in a broad range of preclinical tumoral models. These have laid the foundation for several clinical trials in both solid and hematologic malignancies, which have demonstrated safety, biologic activity and the ability to elicit antitumor immune responses.

Areas covered—This review examines the published preclinical data which supported the clinical translation of this therapeutic platform, reviews the available clinical trial data and expands on ongoing phase II testing. It also looks at approaches to optimize clinical applicability and offers future perspectives.

Expert opinion—Reverse genetic engineering has allowed the generation of oncolytic MV strains retargeted to increase viral tumor specificity, or armed with therapeutic and immunomodulatory genes in order to enhance anti-tumor efficacy. Continuous efforts focusing on exploring methods to overcome resistance pathways and determining optimal combinatorial strategies will facilitate further development of this encouraging antitumor strategy.

Keywords

Virotherapy; measles; MV-CEA; MV-NIS; oncolytic; Edmonston

1. Introduction

Early reports of tumor regression in the setting of acute viral infections have served as an impetus for investigators to attempt utilizing viruses as novel antineoplastic agents [1]. The ability of oncolytic viruses to exploit the replication machinery of rapidly proliferating tumor cells makes the latter a preferential target (versus normal cells). In addition, viruses are able to exploit defects of the interferon response pathway and take advantage of overexpression of oncolytic virus receptors in tumor cells [2–4]. To date, there have only been two oncolytic viruses that have achieved regulatory approval worldwide, based on

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Declaration of interest

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phase III data; both involved intratumorally injected attenuated viruses. H101, an E1B attenuated adenovirus, was approved in 2005 in China after demonstrating superior response rates in combination with chemotherapy over chemotherapy alone in patients with squamous cell cancer of the head and neck or esophagus [5,6]. Similarly, talimogene laherparepvec (T-VEC), an oncolytic herpes virus (HSV1) engineered to produce granulocyte macrophage colony-stimulating factor (GM-CSF), demonstrated a superior durable response rate and promising overall survival in patients with melanoma, becoming the first oncolytic virus approved in the USA and Europe in 2015 [7].

Early reports documenting an oncolytic effect in the setting of natural measles virus (MV) infections were published between 1971 and 1981 in Burkitt's lymphoma, Hodgkin's disease and leukemia [8–12]. Table 1 summarizes the completed, ongoing, or soon to be activated oncolytic measles virotherapy trials. This review will focus on the rationale for utilizing modified MV strains as oncolytic viral therapeutics. We will explore the preclinical data that justified the aforementioned trials, as well as expand upon approaches aimed at enhancing the therapeutic efficacy as well as exploring solutions for overcoming possible limitations.

2. Biological structure

Wild-type MV is an extremely contagious negative single-strand RNA paramyxovirus that can cause infection of up to 90% of non-immunized contacts exposed to an infected individual [24]. Improvements within available healthcare systems in developed countries and increased immunization in children have been credited with reducing the fatality rate in infected individuals from 30% to 0.5% in developed countries, and nearly a 75% fall in measles related deaths in children under 5 years of age, respectively [24]. John Enders isolated the wild-type MV strain from which all vaccine strains are derived, by inoculating chick embryo fibroblast cultures with throat samples obtained from an afflicted student, David Edmonston [25]. Passing the virus through tissue culture systems has allowed for the creation of vaccine strains, via the development of mutations which significantly reduced their virulence without impacting their ability to induce immunity [26–28].

Understanding the structural biology of the MV and its function is essential in order to allow development of strategies which can result in enhanced activity without compromising viral specificity. MV is a negative-strand RNA virus that belongs to the family of Paramyxoviridae. There are six genes within the MV genome encoding eight proteins [29]. The nucleocapsid (N) protein encapsidates genomic RNA and it thus plays a central role in the replication of viral genomic RNA. The phosphoprotein (P) and large (L) protein are associated with ribonucleotide protein (RNP) and are involved in the enzymatic activity of the RNA polymerase complex respectively. The matrix (M) protein regulates transcription. The V and C protein block interferon-induced transcriptional response and signaling [30]. The hemagglutinin (H) glycoprotein facilitates viral attachment to the target host cell. The fusion (F) glycoprotein, through its interaction with the host cell membrane, induces fusion and thus mediates viral entry into the host cell [31]. There are three known receptors for the MV. Signaling lymphocyte-activation molecule (SLAM or CDw150) is a membrane glycoprotein expressed on T and B cells, and is the cellular receptor for the wild-type MV

[32,33]. In contrast, the laboratory generated and attenuated vaccine strains of the MV utilize predominantly CD46, a membrane cofactor protein involved in complement regulation [34,35]. More recently, nectin-4 (poliovirus-receptor-like-4, PVRL4), the adherens junction protein found mainly on epithelial cells (but also tumors), has been identified as a third receptor for both wild-type and engineered MV strains [36–40]. The viral H and F proteins, through their interaction with CD46, facilitate intercellular fusion with subsequent syncytia formation, the characteristic cytopathic effect of MV. This formation of syncytia provides the added advantage of enhancing viral replication unencumbered by exposure to the host's neutralizing antibodies, and potentiates the immunogenicity of malignant cell death [41]. The differential expression of CD46 in tumors, compared with normal tissues, has been shown to account for tumor selectivity and further justified the use of the MV Edmonston strain (MV-Edm) as a viral oncolytic [42].

3. Noninvasive monitoring

Recognition of the need to develop noninvasive methods to monitor the spread, elimination and viral gene expression variation prompted the development of trackable viruses that were engineered to express inert soluble markers [43]. One of the earliest markers used in preclinical, as well as clinical, testing was the soluble extracellular domain of the human carcinoembryonic antigen (CEA). Several studies demonstrated that MV strains encoding CEA retained their oncolytic efficacy [44–46], while providing a noninvasive means of determining viral gene expression through the measurement of serum CEA levels. This mode of monitoring, however, does not allow localization of infected cells. This created the impetus to engineer MV strains enabling tracking of viral localization. MV strains expressing the human thyroidal iodide symporter (NIS) can serve this function [47]. NIS expression in infected cells results in uptake of radioiodide isotopes or Tc99 m and thus facilitates *in vitro* and *in vivo* localization of infected cells [48–52]. In addition to permitting anatomic localization of the infected tumor cells, NIS can also function as a therapeutic transgene, allowing uptake of therapeutic radioiodine isotopes, with resultant improved tumor regression, as well as local bystander effect [47,53–57]. Attempts at maximizing therapy and monitoring with multiple transgenes have produced mixed results. An attempt at combining NIS and CEA transgenes yielded poor replication kinetics compared to single transgene expressing strains [52].

4. Improving the oncolytic efficacy and safety of MV strains

Preclinical testing of oncolytic MV strains has been performed in multiple solid and hematologic tumor models. These include: adult acute lymphoblastic leukemia and chronic lymphocytic leukemia [58,59], adult T cell leukemia/lymphoma [60], atypical teratoid rhabdoid tumor [61], breast cancer [44,62], cholangiocarcinoma [63], colorectal cancer [64], cutaneous T cell lymphoma [65], gliomas [66], head and neck squamous cell cancer [67], hepatoblastoma [68], hepatocellular cancer [51], lung cancer [64,69,70], malignant peripheral nerve sheath tumor [71], mantle cell lymphoma [72], medulloblastoma [53,73,74], melanoma [75,76], mesothelioma [77,78], multiple myeloma [47,79], non-Hodgkin's lymphoma [80], osteosarcoma [81], ovarian cancer [52,82,83], pancreatic cancer

[49,50,84], prostate cancer [45,85], renal cell carcinoma [86], rhabdomyosarcoma [87], and splenic marginal zone lymphoma [88].

Different approaches have been employed to further amplify oncolytic efficacy or enhance specificity. These include viral-specific modifications such as targeting, arming, and shielding [89]. Targeting strategies are genetic modifications aimed at enhancing cancer specific tropism. Arming of the MV strains involves the insertion of genes to enhance therapeutic potency via prodrug convertases or production of therapeutic proteins. Shielding protects the virus from the host innate and cellular immune response. Conversely, combinatorial approaches could be used to augment the oncolytic efficacy of the virus. In most of the approaches discussed here, the NSe strain of the Edmonston vaccine lineage was employed as the backbone for the modifications.

4.1. Viral targeting

Targeting aims to enhance the specificity of the virus against tumor cells. This can improve the efficacy and limits potential harm to normal cells. Viral targeting of the viruses can be accomplished by enhancing the entry of oncolytic strains through receptors specific to the cancer cells. Conversely, one may employ a post-entry strategy, where the cytopathic effect of the oncolytic virus is exerted only in an environment of tumor cells overexpressing the desired trigger.

A pivotal accomplishment early in the development of oncolytic MV strains was the ability to improve viral target specificity by modifying the H glycoprotein required for attachment, without compromising the ability of the virus to induce cellular fusion [90]. Retargeted viruses, via single-chain antibodies, have been developed, thus far, against tumor cell specific targets including: CD38, epidermal growth factor (EGFR), EGFR mutant vIII, alpha folate receptor [91–93], CD133 [94], insulin-like growth factor receptor 1 [93], CEA [95], CD20 [80], prostate-specific antigen [85], and the urokinase receptor [96,97]. MV strains displaying cytokines, such as IL-13 and thus targeting the glioma specific interleukin-13 receptor alpha2, were also successfully created [98].

To overcome the potential development of resistance against oncolytic MV strains retargeted against a single receptor, Friedrich et al. evaluated the use of designed ankyrin repeat proteins (DARPins) [99]. They demonstrated enhanced cytolytic efficacy *in vitro* as well as increased oncolytic effect *in vivo* of the DARPin-MV as compared to the single chain antibody displaying MV. Additionally, the investigators successfully used the ability of DARPins to link to each other without adversely impacting their folding or expression in order to create a selective bispecific targeted oncolytic MV strain. This retargeted bispecific OV against HER2/*neu* and EpCAM was able to infect cells via both receptors and retained its cytolytic potential [99].

In addition to targeting receptors specific to the tumor cells, it has been shown that the MV can be engineered to target the endothelium of newly formed tumor vessels via integrin binding peptides [100]. Incorporating target sites for microRNA-7 in the viral fusion gene allowed for glioblastoma-specific tropism, given the relative differential expression of

neuron-specific microRNA-7 between glioma cells and normal brain tissue, without negatively impacting oncolytic efficacy [101].

In addition to approaches targeting viral entry, MV strains can be engineered to selectively generate the active form of fusion F protein within the tumor microenvironment, by incorporating cleavage sites for enzymes preferentially expressed in this environment. For example, a recombinant MV strain encoding a matrix metalloproteinase (MMP) activated F protein lacked pathogenicity in MMP non-expressive cell lines, but demonstrated antitumor effect both in a mouse fibrosarcoma model, as well as *in vitro* studies of patient-derived primary and secondary liver cancer MMP expressing cells [102,103].

4.2. Arming of the MV

While the retargeting of the MV has the potential to enhance selectivity, the antitumor efficacy of MV can be further enhanced by modifying it to express prodrug converting enzymes or cytokines. In addition to being retargeted to enter CD20 positive non-Hodgkin lymphoma cells, Ungerechts and colleagues modified the virus to also express the fludarabine prodrug convertase, purine nucleoside phosphorylase (PNP). In a Burkitt's lymphoma xenograft model, treatment with the virus followed by administration of the prodrug resulted in increased therapeutic efficacy through a synergistic bystander effect [80]. In a pancreatic cancer xenograft model, treatment with a MV modified to express PNP, followed by intraperitoneal administration of fludarabine, significantly decreased tumor growth through a synergistic effect of oncolysis and activated drug killing [84]. Zaoui and colleagues utilized a combination approach with EGFR targeting and arming of the MV with a bifunctional enzyme that facilitates conversion of 5-fluorocytosine (5-FC) into 5-fluorouracil and cytosine deaminase/uracil phosphoribosyltransferase. They showed superior oncolysis and increased bystander effect, greater tumor volume reduction and longer survival in a head and neck squamous cell cancer mouse xenograft model in the presence of 5-FC, as compared to treatments with an EGFR-retargeted MV, 5-FC or mock treatments alone [67]. Similarly, a retargeted MV engineered to enter melanoma cells via the high molecular-weight melanoma-associated antigen and armed with the FCU1 gene (facilitating conversion of 5-FC to 5-FU) showed superior cytotoxic effect and increased bystander killing in a human xenograft mouse model [76]. Subsequent evaluation of this 5-FC to 5-FU prodrug convertase arming approach has also demonstrated activity in cholangiocarcinoma [63], hepatocellular carcinoma [104] and ovarian carcinoma xenograft models [83].

In addition to prodrugs, MV strains can be armed with stromaspecific targeting genes. For example, engineered oncolytic MV strains expressing the angiogenesis inhibitors angiostatin and endostatin, resulted in reduced tumor-associated blood vessels, without compromising viral oncolytic activity in a medulloblastoma model, a highly vascular tumor [105].

MV engineering can be employed to enhance the immunostimulatory potential of the virus. Using MV strains expressing the interferon beta gene in a mesothelioma model resulted in increased expression of interferon and innate immune cellular infiltration in the tumor microenvironment [78]. Incorporating wild type measles N, P and L genes which antagonize the innate cellular immune response through the interferon alpha pathway resulted in an increased cytopathic effect, faster lysis and greater apoptosis in human renal cell carcinoma

cells [86]. MV expression of the neutrophil-activating protein (NAP) of helicobacter pylori, a potent toll-like receptor 2 agonist, resulted in increased levels of tumor necrosis factor-α, interleukins 6 and 12 with a resultant significant increase in the median survival in breast cancer pleural effusion and lung metastatic xenograft models [106]. In a colorectal tumor immunocompetent murine mouse model expressing CEA, treatment with a retargeted MV strain armed to express granulocyte colony stimulating factor (GM-CSF) resulted in tumor regression. In addition, one third of treated mice that demonstrated complete tumor response rejected subsequent tumor re-challenge [107].

4.3. Overcoming immune-mediated clearance

Most of the Western population is immune to the MV as a result of natural infection or immunization. Although this does not appear to impact efficacy and viral gene expression following intracavitary or intratumoral administration [108,109], it can impact efficacy and applicability of systemic administration of the virus [110]. A number of preclinical efforts aiming to overcome immunologic clearance of the virus have employed cell carriers. Multiple xenograft models have demonstrated increased MV delivery to tumor sites in the presence of neutralizing antibodies through cell carriers, as opposed to naked viral strains, via cell-to-cell transfer from the carrier cell through heterofusion and induced syncytia formation. Cell carriers successfully employed for this purpose include T cells, mesenchymal stem cells, bone marrow-derived mesenchymal stromal cells, tumor-associated macrophages, and lethally irradiated myeloma cells [111–118]. Combinatorial strategies with the alkylating agent cyclophosphamide have been explored in an attempt to capitalize on cyclophosphamide’s lymphocyte depleting effect in order to suppress humoral immunity. Pretreatment with cyclophosphamide resulted in decrease of the primary antibody response to MV treatment in susceptible mice. Additionally, retreatment with MV immune mice concurrently treated with cyclophosphamide displayed suppression of the anamnestic antibody response [110].

An attempt was also made at creating a chimeric virus capable of evading antibody neutralization by exchanging the viral envelope F and H proteins with the corresponding proteins of the morbillivirus canine distemper virus (CDV) [119]. This chimeric MV retained its oncolytic ability even in the presence of neutralizing antibodies when administered to MV-immune mice bearing MC38CEA tumors [119]. To avoid the eventual development of neutralizing antibodies which could occur with sequential treatment, other chimeric strains were created by exchanging the MV F and H glycoproteins with those of the Tupaia paramyxovirus. This yielded a suboptimal oncolytic product, which retained the ability to spread by cell-cell fusion, but it was limited in its ability to produce viral particles and was subsequently abandoned [120]. In another study, it was demonstrated that while modifications of the H glycoprotein in retargeted MV strains protected it from neutralizing antibodies targeting the receptor binding surface, it did not convey added protection over non-retargeted strains, presumably because additional epitopes were needed to accomplish such protection [121].

4.4. Combination approaches

Combining therapeutic modalities has the ability to yield an additive or synergistic effect exceeding either approach alone. The local and bystander ablative effect of combining MV strains encoded to express NIS with radioiodide administration has been explored as discussed above. Combining low-dose alkylating chemotherapy with cyclophosphamide has similarly been explored as a means of overcoming immune mediated clearance. Another combinatorial approach with cytotoxic chemotherapy, has demonstrated accelerated MV-induced oncolysis of senescent tumor cells in hepatoma, pancreatic cancer, and mammary gland carcinoma models following treatment with gemcitabine, doxorubicin, or paclitaxel [122]. In a mantle cell lymphoma xenograft model, a triple sequential combination approach of cyclophosphamide pretreatment, delivery of MV armed with a prodrug convertase, followed by delayed fludarabine administration (to maximize prodrug availability) resulted in complete tumor regression [72].

Additive studies with novel targeted agents have also proved synergistic. An enhancement of the MV cytopathic effect was seen when the heat shock protein 90 inhibitor geldanamycin, was combined with the oncolytic MV-CEA strain in breast, ovarian and rhabdomyosarcoma cell lines with significant increase in apoptosis mediated via the extrinsic caspase pathway [87]. Inhibition of Rho-associated coiled-coil-forming kinase in combination with MV infection similarly enhanced the cytopathic effect in breast, glioblastoma and prostate cancer cell lines through disruption of the cytoskeleton and increased fusogenicity [123]. In addition to augmenting the cytopathic effect of MV, treatment with the histone deacylase inhibitor resminostat in a hepatocellular carcinoma model, also demonstrated improvement in tumor infection and prevented the induction of interferon stimulated genes [124]. Targeting the shift of glioblastoma cells to aerobic glycolysis following oncolytic MV infection with the glycolysis inhibitor dichloroacetate resulted in increased necrotic cell death and promoted viral replication in a xenograft model [125]. Similarly, the aurora A kinase inhibitor, alisertib, enhanced MV oncolysis and improved survival in breast cancer xenografts via enhanced viral gene expression and upregulation of IL-24 [126].

External beam irradiation has also been shown to be synergistic in combination with oncolytic measles virotherapy. In a glioblastoma model, the combination showed significant prolongation of survival compared to single modality treatment or controls, likely through increased viral replication and apoptotic cell death [127]. In a colorectal cancer xenograft model, the synergistic effect of external beam irradiation with MV-NIS therapy was further augmented by checkpoint kinase 1 (Chk1) inhibition [128].

4.5. Immunomodulation

An increasing number of studies have evaluated the impact of MV oncolytic therapy beyond the direct oncolytic effect. The immunostimulatory potential of oncolytic MV strains has become equally relevant, during a time of multiple regulatory approvals for cancer immunotherapeutics.

MV strains have been successfully engineered to express immunomodulatory genes. Grote and colleagues showed that treatment of a human lymphoma model in SCID mice with

oncolytic MV stimulates neutrophil response. A GM-CSF-armed MV strain resulted in augmented oncolytic effect, with greater neutrophilic infiltration [129]. Zhang et al. subsequently showed that while both wild-type and an oncolytic MV strain were able to infect human neutrophils, infection with the oncolytic strain resulted in increased antitumor cytokine release with neutrophil activation with potential tumoricidal properties [130]. Bacterial protective antigens such as NAP are potent immune activators. Iankov et al. successfully engineered an oncolytic MV strain to encode helicobacter pylori NAP and demonstrated its ability to elicit strong cellular and humoral mediated immunity against co-expressed poor immunogens [131]. As noted earlier, treatment of a lung metastatic breast cancer xenograft model with MV-NAP strains resulted in superior survival as compared with those treated with MV-NIS. In a breast cancer pleural effusion model, mice treated with MV-NAP showed significantly higher levels of inflammatory Th1 cytokines, IL-12/23, IL-6 and tumor necrosis factor-α (TNF-α) as compared to those treated with a MV-lambda control strain associated with improved outcome [106].

In a series of experiments with a Schwarz strain oncolytic MV, Guillerme and colleagues showed that infection of tumor cells with an oncolytic MV was able to activate the antigen-presenting plasmacytoid dendritic cells through TLR7, inducing type I interferon secretion [132]. In an immunocompetent mouse model of malignant melanoma, treatment with intratumoral injections of CD20 armed MV encoding the T cell inhibitory factors, cytotoxic T lymphocyte antigen 4 (CTLA-4) or programmed death-1 ligand 1 (PD-L1), led to decreased tumor volume and subgroups with partial tumor regression respectively when compared to controls [133]. Treatment with MV-aCTLA4 and MV-aPD-L1 both led to increased CD3 + T cells and decreased regulatory T cells in the tumor with increased survival over mock controls [133]. The ability of oncolytic MV strains to initiate antitumor immune responses following intratumoral treatment coupled with the immunosuppressive nature of tumors like glioblastoma, led to the development of combinatorial strategies with anti-PD1 checkpoint inhibition. [134]. Upregulation of PD-L1 as well as production of damage-associated molecular pattern molecules (DAMPs), such as high-mobility group protein 1 (HMG1) and heat shock protein 90 (hsp90) in human GBM cells infected with MV-NIS were demonstrated. As murine cells do not express natural MV receptors, retargeted MV against EGFR were used to evaluate the combinatorial strategy with anti-PD-1 therapy in the syngeneic model with the EGFR expressing glioma line, GL261. Mice treated with the combination of MV-EGFR and anti-PD-1 therapy had superior survival over either agent alone or in untreated mice. This was shown to be due to a T cell-mediated response, via predominantly CD8 + T cells [134].

5. Preclinical toxicology studies

Individuals infected with the wild-type MV tend to present with symptoms resembling a mild respiratory illness. However, as the disease progresses, multiple organ systems may be affected and this is facilitated in part by a clinically significant, albeit transient suppression of cell-mediated immunity. The symptoms may vary in severity from mild manifestations such as diarrhea, to more serious complications including but not limited to pneumonia, laryngotracheobronchitis and encephalitis, occasionally leading to death [24]. Despite the excellent safety record of vaccine strains, prior to the clinical translation of oncolytic MV

derivatives from requisite animal studies in measles permissive models, mimicking the clinical routes of administration, were essential in order to ensure patient safety.

Murine models used to typically test oncolytic efficacy are unsuitable for toxicology studies as rodents lack the receptors required for MV entry [35]. The prohibitive cost of limiting toxicology studies to primate models necessitated creation/use of a transgenic mouse model susceptible to infection by attenuated oncolytic MV strains. However, the generation of CD46-transgenic mice which highly expressed the required entry receptor could not replicate the pattern of MV dissemination seen in normal primate hosts [135]. The generation of an alpha/beta interferon receptor deficient ($IFNAR^{KO}$) CD46 Ge mouse strain overcame this barrier [136–138]. The $IFNAR^{KO}$ CD46 Ge transgenic mice, which express the MV CD46 receptor in a distribution similar to humans, were instrumental in toxicology studies prior to the clinical translation in recurrent ovarian cancer, glioblastoma and multiple myeloma [139–141]. In these studies, oncolytic MV strains were administered in a manner mirroring the proposed trials. Intraperitoneal administration was performed with MV-CEA, MV-Luc (encoding luciferase), and MV-GFP (encoding green fluorescent protein). There were no significant toxicities nor was there evidence of viral dissemination to the brain, skeletal muscle, or heart. The biodistribution was best demonstrated with MV-GFP, identifying the macrophages as the primary cell type of infection and the source of lymphatic trafficking of the virus [139]. In preparation for a trial in malignant gliomas, the $IFNAR^{KO}$ CD46 Ge transgenic mice were intracranially inoculated with MV-CEA. There was no evidence of clinical toxicity or neurotoxicity. There was no evidence of CNS infection or extracranial MV-CEA dissemination [140]. In contrast to the aforementioned studies with compartmentalized administration of the oncolytic MV strains, a toxicology study in preparation for the treatment of patients with multiple myeloma required intravenous administration of the virus [47,79]. In support of the proposed trial, $IFNAR^{KO}$ CD46 Ge transgenic mice were administered MV-NIS intravenously alone or following a single dose of cyclophosphamide (to delay the onset of antiviral immunity development) [141]. As anticipated, detectable levels of MV RNA were higher in the blood and spleen of the cyclophosphamide pretreated mice. Histological analysis at necropsy demonstrated variable lymphocyte depletion, hypocellularity in the bone marrow, inflammatory changes in the bladder and degenerative changes in the gonads all attributable to cyclophosphamide [141].

Prior to clinical translation, large animal studies were also required. The old-world primate species, Rhesus macaques, are the standard for studying the neurotoxic effects of measles. In support of the planned phase I/II clinical trial in patients with recurrent gliomas, immune adult male rhesus macaques were administered MV-CEA in a manner and schedule that mimicked the planned human administration. There were no clinical signs of neurotoxicity. Magnetic resonance imaging revealed no encephalitis. Similarly, there was no detection of MV-CEA in blood, buccal swabs, or cerebrospinal fluid [142]. Old-world primates express CD46 on the surface of their red blood cells (RBC) and hemagglutinate in the presence of the MV [143] as such, they were unsuitable for toxicology studies in support of the multiple myeloma trial The new world primate species squirrel monkeys do not express CD46 in their RBC and manifest a measles like illness when infected with the wild type virus [144]. Therefore, squirrel monkeys were used as the large animal model for the toxicology and

biodistribution studies to evaluate intravenous administration of MV-NIS in support of clinical protocol for patients with refractory multiple myeloma. There were no virus related toxicities in either the MV-NIS alone or MV-NIS in combination with cyclophosphamide-treated squirrel monkeys. As with the $IFNAR^{KO}$ CD46 Ge transgenic mice, cyclophosphamide pretreatment resulted in increased viral RNA copy numbers in buccal and cheek swabs as compared to those treated with MV-NIS alone [141].

6. Reported clinical trials

The first reported clinical trial was a single institution, open-label, phase I dose escalation study utilizing the unmodified attenuated MV-Edmonston Zagreb (MV-EZ) strain, conducted at the University Hospital Zurich in Switzerland [145]. A total of 5 patients (4 male and 1 female) received up to 16 intratumoral injections, at doses of 100, 500 and 1000 $TCID_{50}$, following interferon-α pretreatment. The treatment was well tolerated without dose-limiting toxicity. Five of 6 injected lesions showed a response to therapy. There was one lesion that displayed a complete response; two of 5 non-injected distant lesions showed response.

Data has also been published from Mayo Clinic led trials utilizing engineered oncolytic MV strains in ovarian cancer [108,109] and multiple myeloma [146]. A phase I dose escalating study was initially conducted in 21 heavily pretreated, platinum refractory women with recurrent ovarian cancer with intraperitoneally administered MV-CEA, who had normal pretreatment CEA levels [109]. There were no dose-limiting toxicities, up to a total of 10^9 $TCID_{50}$ at 4-weekly intervals up to a total of 6 cycles. Toxicities were predominantly grade 2 or less, with fever, fatigue and abdominal pain the most commonly reported. The best response was stable disease in 14 of the 21 evaluable patients for a median of 92.5 days (54–277), with a median overall survival of 12.15 months (1.3 – 38.4). High expression of the measles receptor CD46 was found in 13 of 15 patients with evaluable tissue. There was no evidence of viral shedding in evaluated saliva and urine specimen by quantitative RT-PCR [109].

The subsequent phase I/II study was conducted with MV-NIS given intraperitoneally to 16 women with taxane and platinum refractory recurrent or progressive ovarian carcinoma [108]. Like the aforementioned study, there were no dose-limiting toxicities. Unlike the prior study with MV-CEA which started with doses of 10^3 $TCID_{50}$, these women received 10^8 or 10^9 $TCID_{50}$. The most common adverse effects were abdominal discomfort, fatigue, fever, and neutropenia. The best response was stable disease in 13 of 16 patients, with a median duration of 67 days (54–277) and median overall survival of 26.6 months (16.3–37.3). Ten of 14 patients with evaluable tissue had high CD46 expression and 13 of 14 had high nectin 4 expression, with all 14 patients having high expression levels of at least one of the two MV receptors: this high receptor level expression in ovarian cancer patients supports use of measles-based therapeutics in the treatment of ovarian cancer. Similarly to the MV-CEA trial, there was no evidence of viral shedding in saliva or urine samples, nor was there evidence of viral genome in evaluated peripheral blood specimen. Utilization of MV-NIS facilitated noninvasive monitoring, and three patients treated at the higher level showed evidence of radiotracer uptake, despite pre-existing levels of neutralizing antibodies, with a

comparatively long progression-free survival. Pooled results of both trials showed a more prolonged survival in favor of the higher dose with a median overall survival of 29.3 months (7.0–83.5+ months) versus 10.6 months (1.3–79.9 months) for those treated with 10^8–10^9 $TCID_{50}$ as opposed to 10^3–10^7 $TCID_{50}$, respectively [108]. Given the fact that study patients were platinum resistant/refractory, and had received multiple prior chemotherapy regimens (median 3–4), the observed survival far exceeds the expected outcome of 6–12 months in historic controls.

In a preliminary report of an ongoing phase I clinical trial utilizing the MV-NIS with or without cyclophosphamide in patients with refractory multiple myeloma (NCT00450814), 2 prior heavily pretreated patients demonstrated evidence of treatment response [146] after receiving a very high single dose of the virus (10^{11} $TCID_{50}$) administered intravenously. Both patients were seronegative for prior measles exposure and demonstrated considerable reductions in the levels of their free light chains and complete resolution of their bone marrow plasmacytosis. The first patient exhibited a complete response that was durable for 9 months. The second had a partial response that lasted 6 weeks. Targeted infection of their known plasmacytomas was documented by SPECT-CT imaging. These results led to a phase II expansion of the trial targeting measles seronegative patients [146].

Presently at the Mayo Clinic, there are ongoing phase I/II clinical trials in squamous cell cancer of the head and neck and breast cancer(NCT01846091), malignant peripheral nerve sheath tumor (NCT02700230), glioblastoma (NCT00390299), ovarian cancer using adipose tissue mesenchymal stem cells for virus delivery (NCT02068794), and mesothelioma, comparing a single versus multiple viral doses (NCT01503177). In addition, a single-arm phase II trial is ongoing for seronegative patients with multiple myeloma (NCT00450814), as well as a randomized phase II trial in ovarian, fallopian or peritoneal cancer is comparing physician’s choice chemotherapy to MV-NIS (NCT02364713). Finally, a phase I/II trial combining MV-NIS with the anti-PD1 antibody nivolumab in advanced non-small cell lung cancer (NCT02919449) is due to be activated in early 2017. The University of Arkansas has also activated a study with the MV-NIS engineered strain in combination with cyclophosphamide in patients with recurrent or refractory multiple myeloma (NCT02192775).

7. Expert opinion

The early body of work on oncolytic MV strains are centered on documenting the preclinical efficacy in multiple malignancies. A reverse genetics system developed by Raedecke has allowed successful engineering of the virus including retargeting, which has been shown to increase specificity and arming with therapeutic transgenes including drug convertases and immunomodulatory genes such as NAP. This extensive body of preclinical work has culminated in ongoing and recently completed clinical trials in both hematologic and solid tumor malignancies. These have demonstrated early evidence of biologic activity, which will undergo prospective validation in ongoing randomized phase II trials. These clinical trials utilizing the oncolytic MV strains have offered encouragement to pursue and improve upon some of the observations, such as prolonged survival in the ovarian carcinoma patients treated with higher viral titers [108], pathologic complete responses in the same setting, as

well as complete responses in heavily pretreated measles seronegative multiple myeloma patients [146]. In addition, these trials have provided evidence for the immunostimulatory potential of oncolytic virotherapy with measles vaccine strains as indicated by the development of antitumor-specific Th1 response in ovarian cancer patients [108]. This clinical data, along with preclinical data demonstrating that measles infection results in the release of immunologic 'danger signals,' (DAMP molecules such as HMGB1), by the infected cells and data in syngeneic models demonstrating synergy with anti-PD1 antibodies [134] support the promise of combinatorial immunotherapeutic strategies. The soon to be activated clinical trial of MV-NIS with the anti-PD1 antibody nivolumab in non-small cell lung cancer represents such an example.

In parallel, efforts to help harness any preexisting antiviral immune response, which can impact the efficacy of systemic administration, are important to pursue. Viral shielding or creation of hybrid vectors such as vesicular stomatitis/MV strains or measles/mumps strains represent other possible directions to explore when systemic administration is contemplated [147–149]. In addition, understanding and characterizing the impact of innate immune response in viral replication could create opportunities for patient selection [150]. Enrichment for susceptible tumors can optimize virotherapy efficacy. For example, in an adult T cell leukemia/lymphoma model, type 1 interferon production deficient tumors were more susceptible to the oncolytic effect of the MV [151]. In a subsequent experiment evaluating the efficacy of MV infection and oncolysis in a mesothelioma model, defect in type I interferon response was more predictive of oncolytic benefit than CD46 expression [152]. It should be noted, however, that even limited viral replication appears to be adequate in generating an immunostimulatory signal that can be subsequently synergistically augmented via combinatorial strategies with immune enhancers, such as immune checkpoint inhibitors [134].

Continued efforts at elucidating underlying mechanisms of action of the oncolytic effect of the virus, coupled with vigorous pursuance of novel methods to overcome resistance pathways, explore immunostimulatory properties and optimize combinatorial strategies can foster our ability to capitalize on the potential of this novel antitumor strategy.

Acknowledgments

Funding

The work was in part funded by National Cancer Institute grants K12 CA090628, P50 CA108961, P50 CA116201, P50 CA136393, R01 CA154348, R01 CA136547.

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Article highlights

- Preclinical testing has demonstrated potent antitumor effect of oncolytic measles virus strains in a wide range of hematologic and solid tumor models.
- Retargeting of oncolytic measles virus strains by displaying single chain antibodies or cytokine ligands and ablating entry through natural receptors has been successfully accomplished.
- Oncolytic measles virus strains can be modified to express therapeutic transgenes such as prodrug converting enzymes or immunomodulatory cytokines.
- Reported and ongoing clinical trials have shown that oncolytic measles virus strains can be safely administered to patients and have yielded encouraging preliminary results.
- Measles virus induced oncolytic cell death is immunogenic. Combination of measles virotherapy with immune checkpoint inhibitors results in synergistic activity setting the stage for translational applications

This box summarizes key points contained in the article.

Table 1

Registered Oncolytic Measles Virotherapy Trials.

Therapeutic virus	Cancer	Phase	Route administered/Regimen	Clinicaltrials.gov identifier
MV-NIS	Non-small cell lung cancer	I	Single dose of MV-NIS followed by 2-weekly doses of nivolumab	NCT02919449[13]
MV-CEA or MV-NIS	Ovarian or primary peritoneal cancer	I	Intraperitoneal administration of MV-NIS or MV-CEA every 28 days up to 6 doses	NCT00408590[14]
MV-NIS	Ovarian cancer	I/II	Intraperitoneal administration of MV-NIS infected mesenchymal stem cells every 28 days up to 6 doses	NCT02068794[15]
MV-NIS	Squamous cell head and neck cancer or metastatic breast cancer	I	Intratumoral injection on day	NCT01846091[16]
MV-NIS	Ovarian, fallopian or peritoneal cancer	Randomized phase II	MV-NIS intraperitoneally every 28 days versus physician's choice chemotherapy	NCT02364713[17]
MV-NIS	Malignant peripheral nerve sheath tumor	I	Intratumoral injection on day 1	NCT02700230[18]
MV-CEA	Glioblastoma	I	Administered to the resection cavity following resection (arm A); intratumoral injection via catheter on day 1 followed by injection into resection bed following en bloc resection on day 5 (arm B)	NCT00390299[19]
MV-NIS	Multiple myeloma	I/II	Intravenous administration day 1 (stage 1). Intravenous administration on day 1, followed by cyclophosphamide on day 2 (stage 2)	NCT00450814[20]
MV-NIS	Malignant pleural mesothelioma	I	Intrapleural administration every 28 days up to 6 cycles	NCT01503177[21]
MV-NIS	Multiple myeloma	II	One intravenous dose of MV-NIS in conjunction with a 4 day course of cyclophosphamide	NCT02192775[22]
MV-NIS	Medulloblastoma or atypical rhabdoid tumor in children and young adults	I	Direct injection into tumor bed for local recurrences. Administration via lumbar puncture for patients with disseminated disease	NCT02962167[23]