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Oncolytic Measles Virus Strains as Novel Anticancer Agents

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Abstract

Introduction—Replication-competent oncolytic measles virus (MV) strains preferentially infect and destroy a wide variety of cancer tissues. Clinical translation of engineered attenuated MV vaccine derivatives is demonstrating the therapeutic potential and negligible pathogenicity of these strains in humans.

Areas covered—The present review summarizes the mechanisms of MV tumor selectivity and cytopathic activity as well as the current data on the oncolytic efficacy and preclinical testing of MV strains. Investigational strategies to reprogram MV selectivity, escape antiviral immunity and modulate the immune system to enhance viral delivery and tumor oncolysis are also discussed.

Expert Opinion—Clinical viral kinetic data derived from non-invasive monitoring of reporter transgene expression will guide future protocols to enhance oncolytic MV efficacy. Anti-measles immunity is a major challenge of measles-based therapeutics and various strategies are being investigated to modulate immunity. These include the combination of MV therapy with immunosuppressive drugs such as cyclophosphamide, the use of cell carriers and the introduction of immunomodulatory transgenes and wild-type virulence genes. Available MV retargeting technologies can address safety considerations that may arise as more potent oncolytic MV vectors are being developed.

Keywords

cancer gene therapy; cell carriers; measles virus; MV-NIS; oncolytic virotherapy

1. Introduction

Despite the considerable progress accomplished in recent years, most advanced cancers remain incurable prompting the need for novel, less toxic and more targeted therapies. Oncolytic virotherapy is a novel treatment approach that exploits the ability of certain viruses to selectively infect and destroy cancer cells [1]. Millenia of adaptive evolution have resulted in diverse natural mechanisms via which viruses can efficiently invade human cells, take control of the cellular biosynthetic apparatus and ultimately lyse the infected cells resulting in release of viral progeny and further spread of infection to neighboring cells. Thus, in contrast to other therapeutic strategies, the antineoplastic effect of replication-competent oncolytic vectors is self-amplified by viral propagation and spread within the cancerous tissues.

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A variety of oncolytic virus families including adenoviruses, herpes simplex virus (HSV), measles virus (MV), Newcastle disease virus (NDV), reovirus, vaccinia virus and vesicular stomatitis virus have undergone clinical translation [2]. The furthest developed oncolytic vector in the Western world is talimogene laherparepvec, an oncolytic HSV engineered to express granulocyte macrophage colony-stimulating factor (GM-CSF), which was tested in a recently completed pivotal phase 3 randomized clinical trial for metastatic melanoma. Engineered attenuated MV strains represent an oncolytic platform more recently introduced in cancer treatment. A number of published clinical reports throughout the 20th century have indicated the anticancer potential of wild type measles virus (MV) strains. The first such case was published in 1949 and reported Hodgkin's lymphoma regression following wild-type measles infection [3]. This was followed by multiple case reports describing significant regressions of hematological malignancies, including Burkitt's lymphoma, Hodgkin's disease and leukemias, occurring after natural infection with wild-type MV [3-10].

The aim of this review is to provide a concise update on the progress of measles-based cancer virotherapy strategies, to review mechanisms of tumor selectivity and preclinical and clinical experience with MV-Edm derivatives, and to discuss the current and future prospects and challenges of this emerging field.

2. Oncolytic measles virology, cytopathic activity and cancer selectivity

MV belongs to the *Paramyxoviridae* family of enveloped negative-strand RNA viruses and is the cause of the highly contagious respiratory viral infection that can sometimes cause serious and potentially fatal lung and brain complications. Conversely, MV vaccine strains derived from the Edmonston-B (MV-Edm) strain are both nonpathogenic and noncontagious and have been utilized as vaccines successfully conferring lifelong immunity against measles. MV-Edm was originally isolated in 1954 from the throat washings and blood of an 11-year old patient with measles named David Edmonston [11, 12] and was attenuated via multiple *in vitro* passages. MV strains enter cells predominantly via the signal lymphocyte-activation molecule (SLAM or CD150) primarily expressed on activated B- and T-lymphocytes, memory lymphocytes, dendritic cells and immature thymocytes [13-15]. On the other hand, MV-Edm vaccine strains predominantly use the membrane cofactor protein (MCP; commonly designated as CD46) as a cellular receptor [15, 16]. This ability was acquired by MV-Edm strains via serial propagation in cell cultures expressing CD46. Nectin-4, also known as Polio virus receptor-related 4 (PVRL4), was recently identified as the third MV receptor. This receptor is predominantly expressed in the respiratory epithelium and it can be utilized by both wild-type and MV-Edm vaccine strains for cellular entry [17, 18].

The MV genome contains a total of six genes that encode eight distinct proteins: the nucleocapsid (N), phospho- (P), matrix (M), fusion (F), hemagglutinin (H) and large (L) proteins and the two P-cistron-encoded accessory proteins C and V [19]. Viral attachment and entry into host cells is mediated by the measles envelope H and F glycoproteins. The H glycoprotein naturally interacts with the three MV receptors [15, 18-21]. More specifically, covalently linked H dimers bind to the measles receptors on the cell surface resulting in signal transmission to the F protein which then executes irreversible, pH-independent, membrane fusion [22]. Cells infected by MV will then express on the cell surface the viral H and F glycoproteins which may subsequently interact with MV receptors on the cell surface of neighboring infected or uninfected cells leading to cell-to-cell fusion [23]. This process results in the formation of giant multinucleated cell aggregates, termed "syncytia", followed by cell death, thus resulting in a significant bystander effect [24-28]. For example, it has been shown that transfection of the measles H and F glycoproteins in the glioblastoma multiforme cell line U87 results in syncytia formation that may involve and destroy up to 80

neighboring non-transfected cells [28]. The contribution of syncytia formation to improved oncolysis/cytopathic effect has also been demonstrated in animal models using naturally nonfusogenic oncolytic viruses, including adenovirus, HSV and vesicular stomatitis virus (VSV) strains, genetically modified to express a fusogenic membrane glycoprotein that promotes syncytial formation resulting in superior in vivo oncolytic activity [29-31].

The MV-Edm receptor CD46 is ubiquitously expressed on all nucleated primate cells and frequently overexpressed in tumor cells [21, 32, 33]. CD46 is a member of the membrane-associated complement regulatory family of proteins and can protect cells against autologous complement destruction by acting as a cofactor in the proteolytic inactivation of C3b and C4b complement products [21]; tumor cell overexpression of CD46 is therefore thought to protect cells from complement mediated lysis. Fortuitously, this allows MV-Edm strains to preferentially infect cancer cells expressing higher CD46 levels. Receptor level expression represents a key determinant of productive MV infection [34], and accordingly non-malignant human cells expressing lower CD46 levels, such as astrocytes, ovarian surface epithelial cells, mesothelial cells, hepatocytes, peripheral blood lymphocytes, dermal fibroblasts and coronary artery smooth muscle cells, are minimally affected by MV-Edm infection [26, 34-37].

The recently identified third measles receptor, Nectin-4, is an E-cadherin-based adherens junction protein that is mainly expressed during embryogenesis and only scarcely expressed in adult normal tissues, with the exception of the respiratory epithelium and, to a lesser extent, the tonsils and lung pneumocytes [38, 39]. On the other hand, high Nectin-4 levels are found in lung adeno- and squamous carcinomas [40], ovarian [41] and breast cancers [42]. Indeed, Nectin-4 was originally identified as a tumor biomarker [38]. Therefore, the natural tropism of MV-Edm derivatives for Nectin-4 may further facilitate the tumor selectivity of these strains against cancers overexpressing this receptor, a hypothesis we are currently testing in preclinical models and clinical trial specimens. In addition to the above mechanisms of oncolytic selectivity that are unique to MV strains, a number of other factors may also favor the preferential infection and lysis of tumor tissues by MV-Edm derivatives [34, 43, 44]. For example, it has been reported in many other oncolytic RNA viruses that defects in the innate antiviral responses that are frequently seen in malignant cells, but not in non-transformed cells, may facilitate the preferential propagation of oncolytic RNA vectors, including measles, in cancer tissues [45]. Viral infection of non-malignant cells triggers a cascade of immediate, innate immune responses including type I interferon gene expression (IFN-I) with activation antiviral proteins and pro-apoptotic signals leading to infected cell death and preventing viruses from taking over the intracellular protein synthetic machinery. On the other hand, cancer cells tend to exhibit a high baseline metabolic activity and resist signals, such as those derived from the IFN-I cascade, that can interfere with protein synthesis. Thus, the innate IFN-I-mediated antiviral defense system of cancer cells is compromised as compared to non-transformed cells providing a unique niche for the replication and spread of oncolytic viruses [2, 45].

Unlike other RNA viruses such as influenza and HIV, MV vaccine strains demonstrate exceptional genetic stability even after prolonged replication in human hosts [46]. Indeed, MV-Edm derivatives have been shown to be remarkably safe in practice, as they have been administered in millions of people for over 50 years with only minimal toxicities noted and no reversion of these strains to pathogenicity with subsequent human-to-human transmission has ever been conclusively reported [47]. Recombinant MV-Edm strains can contain large sizes (> 6 kb) of foreign, inserted genetic sequences and show considerable stability both *in vitro* and *in vivo* [24, 48, 49]. The MV vaccine strains have also been shown to be very stable even after prolonged replication in human hosts [46]. In addition, there has been no conclusive evidence to date of any genetic recombination events between MV vaccine and

wild-type strains in people co-infected with both viruses. Of note, approximately 80% of the Western population is immune to measles as a result of natural infection or vaccination. As a safety precaution in the first in human application of measles oncolytic virotherapy, confirmed anti-measles immunity has been a prerequisite in the majority of the MV virotherapy trials except for trials in patients with recurrent multiple myeloma. The lack of dose limiting toxicity to date in these trials, including the myeloma trial as discussed in this review, actually raises the possibility that protective immunity against MV can be safely waived as an eligibility criterion in future studies.

3. Oncolytic efficacy, transgene expression monitoring and preclinical testing of measles virus vaccine strains

The oncolytic potential of MV-Edm vaccine strains chosen for clinical development based on their excellent safety record in human vaccination approaches [47, 50] has been demonstrated in a wide variety of primary human cancer cells, tissues, cell lines and animal xenograft and syngeneic cancer models (Table 1). Translational efforts to exploit the oncolytic potential of MV have been greatly facilitated by the development of a reverse engineering system for the rescue and propagation of genetically modified MV-Edm strains from cloned cDNA [51]. This strategy utilizes the MV-Edm tag strain as the original backbone and it has been used for the construction of essentially all genetically engineered oncolytic MV-Edm derivatives that have thus far been reported in the literature. Transgene arming of MV-Edm strains has been achieved via the introduction of the foreign genetic material as additional transcriptional units upstream of the viral N gene [52-57] or downstream of the viral H gene [25]. Preclinical testing of these engineered strains has demonstrated that the location of transgenes inserted into the MV-Edm tag backbone may alter MV replication kinetics and viral yields. These preclinical studies have also established that the insertion and high level expression of transgenes upstream of the N or downstream of the H gene does not significantly interfere with replication and oncolytic potency of the recombinant viruses that are currently in translational development [25, 52-57].

The clinical testing and application of oncolytic viruses can be greatly assisted by the use of simple, non-invasive strategies to monitor the replication, spread and elimination of the viruses *in vivo* and over time. Accumulation of such data can help in optimizing the dosage and time intervals of oncolytic treatment modalities and may also facilitate the development of individualized therapeutic protocols. Thus, MV-Edm strains have been modified to express clinically relevant reporter proteins. The first such virus to be tested in humans was MV-CEA, an MV-Edm derivative engineered to express the soluble N-terminal domain of human Carcinoembryonic antigen (CEA) [53, 58]. CEA is a well characterized, biologically inert tumor marker with only minimal immunogenicity. It is commonly being used to monitor disease recurrence, most frequently in patients with colorectal cancer [59]. Validated CEA measurement assays are thus available in most hospitals. MV-CEA infection and propagation in cancer tissues results in CEA gene expression and secretion of the soluble marker protein into the extracellular space. CEA measurement in the serum of treated patients may thus provide crucial feedback on the gene expression profile and viral kinetics of MV-CEA during clinical testing. It should be noted that although CEA detection in the circulation indicates MV-CEA propagation in infected tissues, it does not distinguish between malignant versus non-malignant infected cells. In order to monitor cancer-specific infection of multiple myeloma cells, another MV-Edm derivative (named MV-lambda) has been engineered to express the human lambda light immunoglobulin chain [54]. MV-lambda infection of monoclonal multiple myeloma cells producing kappa light immunoglobulin chain results in the generation and secretion of a unique chimeric immunoglobulin consisting of one kappa and one lambda light chain that is not naturally found *in vivo*. On the other hand, viral propagation in non-myeloma cells will result only in the secretion of

free lambda light chains. Thus, detection of these unique kappa/lambda immunoglobulins is specific for infection of multiple myeloma cells. This strategy has been called “marker conversion” and can be utilized in generating unique markers of cancer-specific viral infection and propagation [54].

A limitation of oncolytic viruses secreting soluble marker peptides is that these reporter genes do not provide information with regards to the anatomical location of oncolytic virus infection and spread. Thus, an Oncolytic MV-Edm derivative designated as MV-NIS was constructed to express the sodium iodide symporter (NIS) gene [25]. NIS is a membrane ion channel that is normally expressed in the thyroid and salivary glands, stomach, intestine and breast and mediates intracellular iodide uptake [60, 61]. Radioisotopes such as ^{123}I, ^{124}I, ^{125}I, ^{131}I and ^{99m}Tc may also be transported via NIS [62, 63]. MV-NIS-infected cells express NIS on the cell membrane which then mediates intracellular radioisotope concentration that can be non-invasively imaged using a variety of available imaging systems including γ camera, positron emission tomography (PET) or single photon emission computed tomography combined with computed tomography (SPECT/CT). NIS may also be used as a therapeutic transgene capable of further increasing the oncolytic potency of MV-NIS by facilitating the intracellular entry of radioisotopes such as ^{131}I, an emitter of beta particles to an average tissue-path length of approximately 0.8 mm [63]. Beta particles can induce direct radiation damage to adjacent uninfected cells or even lyse tumor cells that are otherwise resistant to MV-NIS virotherapy [25]. This strategy of radioisotope-mediated cancer ablation via an oncolytic virus that additionally expresses a radiotherapeutic transgene is termed “radiovirotherapy”.

The first preclinical efficacy studies of MV-CEA demonstrated considerable oncolytic potency of the virus in murine xenograft models of ovarian cancer [53, 64] and glioblastoma multiforme [26]. These tumors are frequently confined to the peritoneal cavity or central nervous system respectively and were accordingly selected for targeted intratumoral viral delivery of MV-CEA. Prior to clinical translation, toxicology and biodistribution studies in appropriate animal models had to be performed [65-69]. The murine xenograft models often utilized for preclinical efficacy studies are unsuitable for toxicity and pharmacology preclinical analysis because, the MV receptors CD46 and SLAM are not expressed in rodents. Therefore, MV cannot infect the majority of murine cells. Three main animal models have been used to gather preclinical information required in support of the Phase I clinical trials: the IFN type I receptor deficient (IFNAR^{KO}) CD46 expressing Ge transgenic mouse strain (a transgenic mouse strain expressing CD46 in a tissue distribution pattern and expression levels comparable to the CD46 expression in humans [70]), rhesus macaques (Macaca mulatta; Old World monkeys) and squirrel monkeys (Saimiri sciureus; New World monkeys).

Intranasal inoculation of MV-Edm derivatives in IFNAR^{KO} CD46 Ge mice can cause respiratory infection and lung inflammation [71, 72]. In addition, intracerebral inoculation of these strains in measles-naive IFNAR^{KO} CD46 Ge mice can be lethal [73]. MV-CEA and MV-NIS were preclinically tested in toxicity studies that closely reflected the protocols of each respective clinical trial (Table 2). Thus, MV-CEA and MV-GFP (a measles derivative expressing green fluorescent protein) have been injected intraperitoneally in IFNAR^{KO} CD46 Ge mice with no significant toxicities noted [43]. In addition, MV-CEA has been administered intracranially in measles-immune IFNAR^{KO} CD46 Ge mice. As already noted above, MV-Edm derivatives show significant neuropathogenicity in measles-naive IFNAR^{KO} CD46 Ge mice. However, mice that had been pre-immunized with measles, thus reflecting the immune status of the target patient population, do not exhibit any clinical toxicity following intracerebral MV-Edm strain inoculation [73]. Furthermore, intravenous injection of MV-NIS with or without cyclophosphamide did not demonstrate any significant

virus-related toxicities [68]. Rhesus macaques are used in large primate animal models as the gold standard for assessing the neuropathogenicity of MV vaccine lots. Intracranial inoculation of MV-CEA in the central nervous system of measles-immune macaques does not result in any significant toxicity [67]. However, in contrast to humans, rhesus macaques express CD46 on the cell surface of red blood cells and this may cause erythrocyte agglutination [74]. Thus, this primate model cannot be used reliably for toxicity studies requiring intravenous administration of MV-Edm strains. However, the red blood cells of squirrel monkeys express a truncated CD46 variant which does not interact with measles glycoproteins [74]. In addition, the SLAM receptor is expressed in squirrel monkeys rendering them susceptible to wild-type MV infection resulting in a measles-like illness [75]. Thus, squirrel monkeys are an appropriate primate model for studying viral distribution and kinetics following intravenous MV administration. Preclinical safety and efficacy data were also required prior to clinical testing of oncolytic MV combination with cyclophosphamide, an immunosuppressive drug which has the potential to block humoral and innate immune response, thus increasing the efficacy of oncolytic virotherapy [58, 76-80]. The transgenic $IFNAR^{KO}$ CD46 Ge mice and the squirrel monkey animal model have accordingly been used to demonstrate that intravenous MV-NIS administration with and/or without cyclophosphamide does not result in significant animal toxicity [68]. Subsequently, the combination of intravenous MV-NIS with cyclophosphamide is currently being tested in a phase I clinical trial in recurrent multiple myeloma patients [81].

4. Current clinical experience with oncolytic measles virus strains

Many decades after the initial anecdotal case reports of cancer regression following natural MV infections [3-10], the unmodified MV-Edm-Zagreb (MV-EZ) vaccine strain was clinically tested in five measles-immune cutaneous T-cell lymphoma (CTCL) patients [82]. This was an open-label non-randomized dose-escalation phase I clinical trial in patients with resistant or relapsing ≥ stage IIb CTCL. A total of 16 intratumoral MV-EZ injections (2-4 injections in 1 or 2 treatment cycles) were administered. Interferon-alpha (INFα) was also subcutaneously administered 72 hours and 24 hours prior to viral treatment. Innate defects in IFN signaling pathways in CTCL cells would allow easier MV-EZ spread in these cells compared to normal tissues in the presence of IFNα. The minimum and maximum MV-EZ doses per injection used in the trial were 10^2 and 10^3 $TCID_{50}$ (50% tissue culture infective dose), which were well-tolerated. One CTCL tumor completely regressed in 1 patient after the 1^{st} treatment cycle and a 2^{nd} lesion was accordingly injected with MV-EZ in the subsequent treatment cycle. Four of the treated tumors partially regressed while only one tumor did not significantly respond to the treatment. Two distant, non-injected tumors in 2 separate patients also improved noticeably indicating a potential systemic effect of the virus and/or the IFNα treatment. These initial results were encouraging, especially after taking into account the low viral doses injected. Follow-up investigations should elucidate the long-term efficacy of MV-EZ virotherapy and the contribution of IFNα treatment in the observed tumor responses.

The genetically engineered MV-CEA and MV-NIS strains are being tested in five phase I clinical trials at the Mayo Clinic and the University of Minnesota [2, 83]. The final results of the first human trial testing an engineered MV strain were reported in 2010 [58]. This was a trial of intraperitoneal administration of MV-CEA, conducted in 21 measles-immune heavily pretreated patients with ovarian cancer refractory to platinum and paclitaxel and confined to the peritoneal cavity. Patients were required to have normal CEA at enrollment; serum CEA elevations during MV-CEA therapy would therefore only be attributable to MV-CEA gene expression. The patients received monthly intraperitoneal injections of 10^3–19^9 $TCID_{50}$ MV-CEA to a total of 6 doses per patient. No dose limiting toxicities were noted with only mild (grade 1-2) adverse reactions noted. MV-CEA treatment did not induce

immunosuppression, there were no significant increases in anti-measles antibody titers and no anti-CEA antibodies were detected. The virus did not shed into urine or saliva specimens while only low levels of MV-CEA genomes were found by quantitative RT-PCR in peripheral blood mononuclear cells (PBMCs) of four asymptomatic patients. Both CEA production and clinical outcome were dose-dependent. Elevated serum CEA levels were detected in all 3 patients who received the highest MV-CEA dose of 10^9 $TCID_{50}$. Increased CEA levels were found in the peritoneal fluid of 1 patient at the 10^8 $TCID_{50}$ dose group and 2 patients in the 10^9 $TCID_{50}$ group. The best objective response was stable disease by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria [84] noted in 9 of 9 patients in the higher dose groups (10^7-10^9 $TCID_{50}$) compared to only 5 of 12 patients in the 10^3-10^6 $TCID_{50}$ groups. Five patients also had considerable (>30%) decreases in cancer antigen-125 (CA-125) levels. In addition, the median overall survival of 12.15 months achieved by MV-CEA-treated patients was twice longer than the expected median survival of 6 months seen in historical controls in this patient population [85]. A second phase I trial utilizing MV-NIS as an intraperitoneal oncolytic vector in patients with recurrent ovarian cancer with a 10 patient expansion at MTD has been completed and patients are being followed [86]. This trial will assess the potential clinical benefits of utilizing the NIS gene as a more informative monitoring modality and as a potential therapeutic transgene. Detailed immunologic analysis that has been incorporated in this trial will investigate the hypothesis that oncolytic tumor cell death represents an effective means of inducing an antitumor immune response.

MV-CEA is also undergoing clinical testing in a phase I trial for recurrent glioblastoma multiforme [87]. The virus is intracranially injected at a dose range of 10^5 to 2×10^7 $TCID_{50}$ to measles-immune patients that will undergo total or subtotal tumor resection. The study is being conducted in two patients groups. MV-CEA is being administered directly into the resected tumor cavity in the first patient group. After dose escalation up to 10^7 $TCID_{50}$ has been completed in the first group, patient accrual into the second group will begin. Patients in the second group will first receive one dose of MV-CEA directly into the tumor prior to resection. Five days later, when MV-CEA reaches the maximum projected viral replication and spread, tumor resection will be performed and a second MV-CEA dose will be injected into the resected tumor cavity; we have treated thirteen patients in this trial without dose limited toxicity being observed. MV-NIS is also currently being clinically tested in a phase I trial of intravenous MV-NIS therapy in patients with recurrent or refractory multiple myeloma [81]. Following determination of the maximum single agent tolerated dose in this study, additional cohorts of patients are treated with a cyclophosphamide/MV-NIS administration with the goal of enhancing virus replication and oncolytic efficacy. An open label phase I clinical trial of intrapleural MV-NIS administration in patients with malignant pleural mesothelioma has also been recently activated [88]. In addition, clinical testing of MV-NIS in patients with head and neck cancer is currently being planned. The above studies with extensive associated correlative analysis to address viral distribution will provide a strong basis for the development of future protocols with the goal of achieving superior treatment outcomes.

5. Engineering tumor selectivity of oncolytic measles virus strains

The CD46-tropic oncolytic MV vectors naturally demonstrate preferential tumor selectivity that is mediated, in large part, by the elevated CD46 expression on cancer cells. MV tropism towards Nectin-4 may further facilitate the tumor specificity of oncolytic MV strains in certain tumor types such as breast and ovarian cancer. Although, the clinical tolerability of oncolytic MV-Edm strains in the ongoing phase I clinical trials has been excellent, engineering even higher tumor specificity may address potential safety concerns that can arise as more potent vectors and higher viral doses are being tested. Indeed, it has been

demonstrated that, in contrast to CD46-tropic strains, retargeted MV-Edm derivatives are not neurotoxic even following direct administration to the CNS of measles-naïve IFNAR^{KO} CD46 Ge transgenic mice [55, 89, 90]. Furthermore, receptor retargeting may address any potential variability in CD46 or Nectin-4 expression patterns in tumor tissues. Of note, Galanis *et al.* found low CD46 expression in 2 of 15 tumor specimens immunohistochemically tested during the MV-CEA against ovarian cancer clinical trial [58]. Retargeting the virus to distinct receptors expressed in these two specimens could have enhanced oncolytic efficacy. In addition, retargeting MV strains to targets expressed on the tumor blood vessel endothelium may facilitate transfer of the virus into the tumor parenchyma following intravenous administration [91-93].

The fact that viral attachment and fusion is mediated by two distinct viral glycoproteins, H and F respectively, considerably facilitates retargeting strategies which can focus on H protein reengineering without compromising the fusogenicity of the virus that is mediated by F. Thus, multiple studies have shown that MV-Edm receptor tropism can be fully modified without significant attenuation of oncolytic potency against tumors tissues expressing sufficient levels of the target receptor [89, 90, 93-97]. The aminoacid residues necessary for the interaction of H with CD46 and SLAM have been well defined [16]. MV-Edm strains can become CD46- and SLAM-blind via single amino-acid substitutions such as the substitution of tyrosine by alanine at position 481 (Y481A) and the substitution of arginine by alanine at position 533 (R533A) respectively [16, 48, 94, 98]. Of note, Leonard et al. have demonstrated that the substitution of tyrosine by alanine at position 543 (Y543A) of the wild-type H protein will render the MV selectively blind to the Nectin-4 receptor [99]. Targeting molecules such as single chain antibodies, cytokines and peptide ligands may be displayed on the C-terminus of the H protein (Table 1) [48, 100, 101].

A second MV retargeting strategy involves the engineering of F glycoproteins that can only achieve maturation in the tumor microenvironment [20, 102]. The unmodified MV F protein normally achieves maturation after a precursor protein (F0) is proteolytically cleaved into the large F1 and the smaller F2 subunits by the ubiquitous cellular protease furin. Thus, selective cleavage of mutated F proteins by more tissue-specific proteases can restrict the tissue tropism of MV strains [103]. Accordingly, tumor specificity can be achieved by the insertion into the F protein of aminoacid sequences sensitive only to cancer-specific proteases [102]. A third new strategy for engineering tumor selectivity involves the insertion of microRNA (miRNA) target elements into the MV genome [104]. Endogenous cellular miRNAs, present in normal cells but downregulated or absent in tumor cells, can recognize these target elements and restrict viral replication in normal tissues. miRNA-7 is preferentially expressed in normal neuronal tissues but is notably downregulated in glioblastoma multiforme cells [105, 106]. Thus, a miRNA-7-sensitive MV-Edm derivative was constructed and has been shown to retain full oncolytic activity in glioblastoma xenograft models while lacking neuropathogenicity in measles-naïve IFNAR^{KO} CD46 Ge mice [104]. This virus was also strongly attenuated with regards to viral transduction and spread during infection of primary human brain explants [104]. The above targeting approaches can potentially be used simultaneously to develop highly specific oncolytic MV strains. MV is therefore now one of the most versatile retargetable oncolytic vectors. Dual or triple targeting of MV vectors may allow the development and safe clinical testing of highly potent vectors carrying wild-type virulence genes.

6. Evasion of antiviral immunity and triggering of antitumor immunity

Data from the clinical trials of oncolytic measles virus strains confirm the safety and minimal toxicity of oncolytic MV vaccine strains. Current efforts should thus concentrate more on enhancing the efficacy of these oncolytic vectors. Although, higher potency

oncolytic MV strains may indeed produce more side effects, the viral retargeting technologies described above can be utilized to ensure that safety is not compromised. A crucial challenge of measles-based therapeutics is the complex interplay between the host immune system and viral vectors. Notably, most patient candidates for measles-based oncolytics are immune to the measles infection and this may compromise treatment efficacy, particularly when measles vectors are administered intravenously. Systemic oncolytic MV delivery is required for treatment of metastatic or hematologic cancers. However, therapeutic viruses inoculated into the bloodstream may be scavenged by the mononuclear phagocytic system in the liver and spleen [107] or be neutralized by antibodies and serum complement [108, 109]. In order to reduce MV sequestration by the mononuclear phagocytic system, macrophage scavenger receptors can be saturated by ligands such as polyinosinic acid [107].

To circumvent anti-measles immunity, oncolytic MV strains can also be “hidden” inside cell carriers that will then safely deliver the viruses into the tumor tissues. The ideal cell carriers should also serve as viral “factories” capable of producing high viral loads that will not destroy the carriers themselves prior to tumor delivery. Cell carriers should specifically traffic to tumor deposits where the oncolytic cargo will be delivered. These cells should additionally be safe, non-tumorigenic and easy to mass produce and to genetically modify. An advantage of MV-based vectors with regards to cell carrier application is the fact that the MV natural life cycle includes a cell-associated viremia step that can protect the virus from immune neutralization [110, 111]. In addition, MV strains are naturally fusogenic thus allowing direct cell-to-cell transfer of viral progeny from carrier to target cells without exposure of naked virions to neutralizing factors in the extracellular environment. A wide variety of different cell types have shown promise as cell carriers for oncolytic MV strains including the U-937 monocytic cell line [108, 112], immature and mature primary dendritic cells [112], PMBCs [108], activated T cells [113], primary CD14+ cells [114], mesenchymal progenitor cells [115], the multiple myeloma MM1 cell line [109] and blood outgrowth endothelial cells [108, 116]. A clinical trial testing intraperitoneal delivery of MV-NIS infected adipose tissue derived mesenchymal stem cells is being planned. Another recently tested approach to circumvent anti-measles immunity targeted to the MV envelope H and F glycoproteins involves exchanging these glycoproteins with the closely related, but not immunologically cross-reactive, glycoproteins of the canine distemper virus (CDV) thus essentially generating a new MV serotype capable of escaping antibody neutralization [117]. Antibody escape by this envelope-chimeric virus is unlikely to represent a safety issue as all components of the virus are derived from non-pathogenic parental strains, i.e. the MV-Edm vaccine strain and the Onderstepoort CDV vaccine strain [117]. In addition, the chimeric virus is SLAM-blind and is thus unable to effectively infect lymphoid organs and tissues, which is a critical component of measles pathogenesis [118].

Anti-measles immunity can be attenuated by cyclophosphamide, an immunosuppressive drug that has been shown to decrease humoral immune response and delay viral clearance in measles-naïve squirrel monkeys intravenously inoculated with MV-NIS [68]. A recent study demonstrated in the IFNAR^{KO} CD46 Ge mouse model that antiviral antibody responses to MV-Edm strains can be suppressed using clinically approved oral or systemic cyclophosphamide regimens [79]. Preclinical studies have also indicated that combining MV virotherapy with cyclophosphamide can significantly enhance the therapeutic efficacy of the viruses [56, 76]. The effectiveness of this approach is currently being explored in the ongoing phase I clinical trial of intravenous MV-NIS treatment in refractory multiple myeloma patients.

As the excellent toxicity profiles of current attenuated MV-Edm vaccine derivatives are being established in clinical trials, the arming of these strains with wild-type MV genes is

being explored in order to enhance the oncolytic power of these agents [119, 120]. The MV P cistron additionally encodes the two accessory proteins C and V via overlapping open reading frames. The P, C and V proteins can suppress type I IFN-induced intracellular pathways [121-123]. On the other hand, mutational defects in the vaccine strain P cistron result in considerably higher type I IFN induction in tissues infected by MV-Edm derivatives. Activation of type I interferon intracellular pathways is a crucial component of antiviral immunity. It has thus been shown that replacing the vaccine strain P with a wild-type counterpart derived from the MV IC-B strain can significantly retard, but not nullify, type I IFN production in infected multiple myeloma xenografts and augment the antitumor potency of the chimeric virus [119]. Oncolytic activity may further be enhanced by also replacing the vaccine strain N, P and L genes counterparts with their wild-type measles counterparts (MV-NPL virus) [120]. The mechanism of MV vaccine strain attenuation is multifactorial. The ability of MV-Edm strains to inhibit interferon pathways is certainly a key factor. However, other important differences between vaccine and wild-type strains include preferential use of different receptors for entry as well as M protein substitutions that affect interactions with the viral nucleocapsid. Indeed, amino-acid substitutions in the MV-encoded proteins (with the possible exception of protein F) have been shown to be associated in the attenuation of MV vaccine strains as compared to their wild-type counterparts [124]. Careful reintroduction of a few selected wild-type genes in the oncolytic MV vaccine genome could theoretically lead to enhanced therapeutic benefit without compromising safety. Additional carefully designed safety studies are certainly warranted prior to clinical testing of such viruses to rule out unexpected toxicities. These constructs may also benefit by more stringent tumor targeting, via the retargeting technologies discussed above, to further ensure clinical safety.

Although, suppression of immunity may facilitate systemic viral delivery and intratumoral spread, activation of the immune system via the infection of cancer tissues may facilitate recognition of tumor-specific antigens and thus result in a primed antitumor immune response [125]. Data derived from *in vitro* experiments on mesothelioma cell lines have indicated that infection by an MV-Edm (Schwarz) strain may activate dendritic cells and prime autologous tumor-specific T cells [126]. A more recent study indicated that neutrophil infection by an MV vaccine strain prolonged the *ex vivo* life span and induced potential tumoricidal properties on these cells [127]. GM-CSF is an immunostimulatory cytokine that can recruit neutrophils, NK and dendritic cells and trigger a localized inflammatory reaction that can facilitate antitumor immunity [128-132]. Thus, an MV-Edm derivative genetically engineered to express murine GM-CSF (MV-GM-CSF virus) significantly enhanced oncolysis in a non-Hodgkin lymphoma xenograft model compared to the parent virus [130]. Interferon-beta (IFNβ) is an important immune regulator that has been shown to induce antitumor immune responses [133]. Recombinant MV-Edm derivatives modified to express mouse IFNβ have accordingly demonstrated enhanced therapeutic activity against mesothelioma by facilitating the recruitment of CD68+ immune cells and by inhibiting tumor neoangiogenesis [57]. The *Helicobacter pylori* (*H. pylori*) neutrophil-activating protein (NAP) is an immunomodulatory protein involved in mucosal inflammation during *H. pylori* infection [134, 135]. MV-Edm derivatives engineered to express NAP showed enhanced antitumor efficacy and significantly prolonged survival, as compared to other MV-Edm strains, in xenograft models of malignant breast cancer pleural effusion and lung metastasis [136]. This effect was shown to be in part mediated by the induction of proinflammatory cytokines and triggering of nonspecific inflammatory responses within the tumor tissues. This information becomes particularly relevant in the context of clinical trials, combining oncolytic viruses with immunosuppressive agents such as cyclophosphamide, which can be associated with the theoretical disadvantage of suppressing not only antiviral immune response but also antitumor immune response. This effect is, however, frequently dependent on the employed dose and schedule of the immunosuppressive agent. For

example, metronomic cyclophosphamide schedules in combination with other oncolytic viral platforms have been tested as a means of increasing antitumor immune response [77]. Emerging clinical data deriving from virotherapy trials incorporating immunosuppressive agents such as cyclophosphamide will be critical in allowing us to determine doses and schedules of immunosuppressive agents that can be used to optimize the oncolytic effect.

7. Other combinatorial treatment approaches

Oncolytic viruses are a unique class of therapeutic agents with mechanisms of action that could be additive or synergistic with other therapeutic modalities. Accordingly, cancer resistance to conventional treatments is not expected to result in cross-resistance to oncolytic agents, which can accordingly be used as last-line therapies when all other treatments fail. Furthermore, a rapidly growing wealth of data is showing that oncolytic MV-Edm therapeutics combined with other treatments demonstrate more potent anticancer effects. The beneficial effects of cyclophosphamide co-treatment have already been discussed above. Combination treatment of MV-Edm derivatives with external radiotherapy has also demonstrated a strong synergistic effect against both radiation-sensitive and radiation-resistant glioblastoma cells [137].

NIS expression on the surface of cancer cells infected by MV-NIS facilitates the intracellular accumulation of radioisotopes such as ^{131}I. Radioactive decaying of ^{131}I results in emission of beta particles which can induce direct radiation damage and cell death over distances averaging 0.8mm [63] which is approximately 80 times the diameter of the average cancer cell [138]. This allows cytotoxic radiation delivery to both infected and surrounding uninfected tumor cells resulting in a considerable bystander effect. Indeed, MV-NIS-mediated radiovirotherapy has demonstrated significant enhancement of oncolytic activity in xenograft models of multiple myeloma [25], prostate cancer [139], glioblastoma [140], head and neck cancer [141] and anaplastic thyroid cancer [142]. Synergy, at least in the glioblastoma model, was mediated via increased viral propagation in irradiated cells [140]. In addition, a clear synergistic effect of radiovirotherapy combination has been demonstrated even in tumors that are refractory to MV virotherapy. More specifically, systemic administration of ^{131}I resulted in complete regression of MV-NIS-infected MM1 multiple myeloma xenografts, a tumor model, which is normally resistant to MV-Edm oncolysis [25]. On the other hand, it should be noted that MV-NIS radiovirotherapy did not significantly prolong survival in a pancreatic cancer xenograft model compared to single-agent MV-NIS treatment [143]. This lack of synergy may have been due to the nonuniform intratumoral distribution of MV-NIS infection. Future efforts should concentrate on achieving a more homogenous intratumoral spread and on minimizing isotope efflux and enhancing NIS-mediated intracellular isotope concentration and retainment.

Efficient combination treatments of targeted oncolytic MV strains with potent prodrugs can be achieved via the insertion of prodrug convertase therapeutic transgenes (chemovirotherapy). The prodrug convertase purine nucleotide phosphorylase (PNP) can locally convert the prodrugs fludarabine phosphate and 6-methylpurine-2’-deoxyriboside into the highly cytotoxic 2-fluoroadenine and 6-methylpurine respectively. Thus, targeted MV-Edm derivatives additionally armed with the PNP gene have demonstrated significantly improved antitumor potency against human lymphoma xenograft and syngeneic murine colon adenocarcinoma models following administration of fludarabine phosphate or 6-methylpurine-2’-deoxyriboside respectively [55, 56]. Triple combination of chemovirotherapy with cyclophosphamide has further demonstrated enhanced anticancer efficacy in a lymphoma xenograft model [144].

Another combination tactic aims to augment MV fusogenicity via the co-treatment with certain small molecule drugs. Heat shock protein 90 (HSP90) inhibitors represent a novel anticancer drug class that has been shown to enhance the cytopathic activity of MV-CEA by increasing the susceptibility of cancer cells to MV-mediated fusion [37]. The exact mechanism of this effect remains to be elucidated but it may involve RhoA-mediated cytoskeletal modulation, a hypothesis further supported by the synergistic effect deriving from the combination of MV strains with RhoA inhibitors [145]. It should be noted that another study failed to demonstrate improvement in oncolytic efficacy of MV-Edm derivatives genetically modified to express heat shock protein 72 [146].

8. Conclusion

Replication-competent oncolytic MV strains are promising and extensively studied oncolytic vectors that preferentially infect and kill tumor cells. These agents have demonstrated strong preclinical *in vitro* and *in vivo* efficacy against very diverse hematological and solid cancers. Biotechnology advancements have allowed the extensive modification of oncolytic MV-Edm vaccine strains. Thus, MV-Edm strains have been equipped with reporter transgenes such as CEA and NIS, armed with therapeutic transgenes including NIS and PNP and fully targeted to specific tumor and neovascular antigens and tissues using different targeting strategies. Clinical translation of MV-CEA and MV-NIS is confirming the negligible pathogenicity of these strains in humans and is providing initial evidence of promising oncolytic activity. Pharmacokinetic clinical data provided by CEA and NIS transgene expression will facilitate the development of more complex treatment protocols and vectors. Immunomodulatory, immune evasion and combinational strategies are being explored to facilitate systemic delivery of the virus to tumor sites and to increase the oncolytic efficacy of MV strains.

9. Expert opinion

Clinical experience to date supports the promise of oncolytic MV strains as anticancer agents. Their full potential, however, has yet to be realized. Non-invasive monitoring of viral kinetics and gene expression is expected to become standard practice in the modern era of oncolytic virotherapy. Pharmacokinetic data provided by non-invasive reporter gene expression will facilitate early stage clinical development of oncolytic vectors and help define the optimal timing for combination treatment protocols. In addition, non-invasive transgene monitoring may ultimately allow tailoring of individualized treatment protocols based on the spread and elimination of the oncolytic virus in each patient. Accordingly, reporter gene data derived from completed and ongoing MV clinical trials will guide future strategies to improve viral delivery and intratumoral spread. NIS has thus far shown to be the most promising reporter transgene in measles-based therapeutics. However, further work might be required to improve NIS sensitivity, possibly by increasing intracellular radioisotope concentration and retention. NIS would also have limited utility in tumors located in organs with high background radioisotope activity such as the bladder and stomach. In these situations, other novel non-invasive reporter gene systems can be more appealing. Reporter gene strategies are also frequently incapable of distinguishing between infected malignant and non-transformed cells and novel approaches such as the “marker conversion” concept could address this issue. Synergistic combinatorial strategies of oncolytic measles strains with therapeutic modalities such as radiation therapy, chemotherapy, small molecule cell cycle inhibitors represent future steps in the clinical development of this oncolytic platform.

Potential advantages of measles virus as an oncolytic platform include the natural fusogenicity of MV strains which can induce a potent bystander antitumor effect and may

also facilitate the use of cell carriers for immune evasion. MV vaccine strains have a very extensive record of proven safety after administration in millions of individuals worldwide. MV is an RNA virus that does not generate intermediate DNA molecules, strictly replicates in the cytoplasm and does not interact with the host genome. MV vectors are also remarkably stable genetically and the chance of recombination or emergence of vaccine-escape mutants are extremely low. Therefore, oncolytic MV vectors cannot cause insertional DNA mutagenesis to the patients' chromosomes. In addition, the currently established reverse genetics system for engineering MV derivatives is very powerful and versatile and fully retargeted MV-Edm derivatives can be produced against a very wide variety of target molecules. A robust manufacturing system has also been developed to produce and purify high concentrations of clinical grade oncolytic MV strains using good manufacturing practices [147].

As improvements in manufacturing technology allow the generation of high titer stocks that can produce high-level viremia following intravenous administration, the ultimate challenge for systemic virotherapy will be anti-measles immunity. The immune system can be both a friend and foe to measles-based therapeutics as anti-measles immunity may neutralize the oncolytic vectors while cross-priming of anti-tumor immunity may induce cancer regression. Advances in our understanding of these processes may set the stage for the harmonization of the immune response to enhance oncolytic efficacy. Towards this goal, diverse strategies are being explored including the combination of oncolytic MV therapies with immunosuppressive drugs, the use of cell carriers to conceal measles virions and optimize MV delivery, the generation of new MV serotypes, the introduction of immunomodulatory transgenes that can enhance anti-tumor immunity and the arming of MV-Edm vectors with wild-type genes that can inhibit antiviral immune responses. Combinations of oncolytic measles strains with immunosuppressive agents, such as cyclophosphamide, are currently tested in the clinic and will help us determine the dose and schedule of this immunosuppressive agent that can augment viral replication without blocking induction of an antitumor immune response, as a result of oncolytic cell death. It is recognized, however, that this represents a therapeutic window that might be difficult to define clinically and its parameters are likely tumor type dependent.

Safety considerations may however arise as engineered MV-Edm derivatives are becoming more potent, particularly when wild-type genes are reintroduced into the MV-Edm genome. In such cases, more stringent tumor targeting may be warranted and towards this goal, and a number of different retargeting strategies have been successfully developed. A thorough understanding of the interactions between oncolytic MV strains and the recently discovered third measles receptor Nectin-4 might further enhance our understanding of the tumor-selective properties of these viruses and allow optimization of tumor targeting.

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highlights

- Attenuated MV vaccine strains are highly safe viral agents that have shown significant oncolytic efficacy and specificity against cancer tissues
- Two Phase I clinical trials of MV derivatives have been completed and four more are currently ongoing
- Engineering strategies have allowed genetic modification of MV strains, including the insertion of reporter and therapeutic transgenes as well as the tumor-specific retargeting of MV vectors
- A number of strategies are being developed to circumvent anti-measles immunity and to trigger anti-tumor immune responses during MV virotherapy

Table 1

Summary of *in vitro* and *in vivo* oncolytic measles virotherapy studies. All recombinant MV strains used are derived from the Edmonston-B attenuated vaccine strain (MV-Edm) unless otherwise indicated

Tumor type	MV strain	Genetic Modification	Tumor models used	References
Leukemias/lymphomas	MV-Edm	Unmodified	Human lymphoma/ leukemi a cell lines and xenografts; murine EL4 T-lymphoma cell line; completed clinical trial against CTLC	[55, 82, 119, 130, 144, 148-153]
	MV-EZ	Unmodified MV-Edm Zagreb vaccine strain		
	MV-lacZ	B-gal reporter gene		
	MVHαCD20	Retargeted to CD20		
	MV-GM-CSF	GM-CSF gene		
	MV-PNP H^{blind}CD20	PNP prodrug convertase; retargeted to CD20		
	MV-HSP72	HSP72 heat shock protein		
	MV-EGFP	EGFP reporter gene		
	MV-EGFP-T7	Retargeted via T7 scTCR display; EGFP reporter gene		
	MV-EGFP-m33	Retargeted via m33 scTCR display; EGFP reporter gene		
	MV-eGFP-Pwt	Armed with IC-B wild type MV P gene;EGFP reporter gene		
Multiple myeloma	MV-Edm	Unmodified	Human multiple myeloma primary cells, cell lines and xenografts; ongoing clinical trial	[25, 27, 35, 44, 68, 81, 91, 92, 107-109, 113, 114, 119]
	MV-EGFP-aCD38	Retargeted to CD38; EGFP reporter gene		
	MV-NIS	NIS reporter and therapeutic gene		
	MV-Luc	Firefly luciferase reporter gene		
	MV-EGFP-ERV	Retargeted via M28L echistatin display; EGFP reporter gene		
	MV-EGFP-Ecs	Retargeted via unmodified echistatin display; EGFP reporter gene		
	MV-EGFP-Wue	Retargeted to the Wue-1 ligand; EGFP reporter gene		
	MV-eGFP-Pwt	Armed with IC-B wild type MV P gene;EGFP reporter gene		
Ovarian cancer	MV-Edm	Unmodified	Human ovarian cancer primary cells, cell lines and xenografts; completed and ongoing clinical trial	[37, 53, 58, 64, 86, 95, 96, 107, 108, 115, 154]
	MV-EGFP	EGFP reporter gene		
	MV-RFP	RFP reporter gene		
	MV-Luc	Firefly luciferase reporter gene		
	MV-CEA	CEA reporter gene		
	MV-NIS	NIS reporter and therapeutic gene		
	MV-EGFP-alphaFR	Retargeted to the alpha folate receptor; EGFP reporter gene		
	MV-EGFP-αHER	Retargeted to Her-2/neu; EGFP reporter gene		
Glioblastoma multiforme	MV-Edm	Unmodified	Human glioblastoma primary cells, cell lines and xenografts; infection primary human	[26, 87, 89, 90, 94, 104, 116, 137, 140]
	MV-CEA	CEA reporter gene		
	MV-EGFP	eGFP reporter gene		
	MV-EGFP-H^{blind}αEGFRvIII	Retargeted to EGFRvIII; EGFP reporter gene		

Tumor type	MV strain	Genetic Modification	Tumor models used	References
		Retargeted to EGFR; EGFP reporter gene	brain tissues; ongoing clinical trial	
	MV-EGFP-H^{blind}αEGFR	Retargeted to IL-13 receptor via IL-13 display; EGFP reporter gene		
	MV-EGFP-H^{blind}IL-13			
	MV-EGFP-F^{miR7}	Retargeted via introduction of microRNA-7 sensitivity; EGFP reporter gene		
	MV-NIS	NIS reporter and therapeutic gene		
Breast cancer	MV-Edm	Umodified	Human breast cancer cell lines and xenografts including malignant pleural effuction and lung metastasis models; murine mammary tumors (MV-m-uPA)	[37, 93, 112, 136, 155, 156]
	MV-CEA	CEA reporter gene		
	MV-EGFP	EGFP reporter gene		
	MV-Luc	Firefly luciferase reporter gene		
	MV-EGFP-h-uPA	Retargeted to human uPAR; EGFP reporter gene		
	MV-EGFP-m-uPA	Retargeted to murine uPAR; EGFP reporter gene		
	MV-lambda-NAP	Chimeric secretory form of the NAP gene		
	MV-s-NAP	Chimeric secretory form of the NAP gene		
	rMV	MV HL wild-type strain		
	rMV-EGFP	Wild-type MV HL encoding EGFP reporter gene		
	rMV-SLAM^{blind}	Wild-type SLAM blind MV HL		
	rMV-EGFP-SLAM^{blind}	Wild-type SLAM blind MV HL; EGFP reporter gene		
	rMV-Luc-SLAM^{blind}	Wild-type SLAM blind MV HL; Firefly luciferase reporter gene		
Hepatocellular cancer	MV-EGFP	EGFP reporter gene	Human hepatocellular cancer primary cells, cell lines and xenografts; Infection of human tumor tissues slices	[20, 36, 108, 157]
	MV-CEA	CEA reporter gene		
	MV-NIS	NIS reporter and therapeutic transgene		
	MV- Mérieux	Mérieux/Schwarz unmodified vaccine strain		
	MV- Moraten	Moraten/Edmonston Zagreb unmodified vaccine strain		
	MV-L-16	Leningrad-16 strain unmodified vaccine strain		
	MV- AIK-C	AIK-C unmodified vaccine strain		
	MV-EGFP-MMPA1	MMP-activatable virus; EGFP reporter gene		
Cholangio-carcinoma	MV-EGFP-MMPA1	MMP-activatable virus; EGFP reporter gene	Infection of human tumor tissues slices	[20]
	MV-EGFP	EGFP reporter gene		
Colorectal cancer	MV-antiCEA	Retargeted to human CEA	*In vitro* and syngeneic tumor models using murine colon adenocarcinoma cells expressing human CEA;	[56, 117, 158]
	MV-PNP-antiCEA	PNP prodrug convertase; Retargeted to human CEA;		

Tumor type	MV strain	Genetic Modification	Tumor models used	References
	MV-PNP-CDV^{env}-antiCEA	CDV envelope proteins; PNP prodrug convertase; Retargeted to human CEA;		
Prostate cancer	MV-EGFP	EGFP reporter gene	Human prostate cancer cell lines and xenografts	[139, 159, 160]
	MV-CEA	CEA reporter gene		
	MV-NIS	NIS reporter and therapeutic gene		
	MV-Luc	Firefly luciferase reporter gene		
	MV-EGFP-αPSMA	Retargeted to PSMA; EGFP reporter gene		
Pancreatic cancer	MV-NIS	NIS reporter and therapeutic gene	Human pancreatic cancer cell lines and xenografts	[143, 161-164]
	MV-EGFP	EGFP reporter gene		
	MV-EGFP-anti-PSCA	Retargeted to PSCA; EGFP reporter gene		
	MV-PNP-anti-PSCA	Retargeted to PSCA; PNP prodrug convertase		
Mesothelioma	MV-Schwarz	Schwarz unmodified vaccine strain	Human mesothelioma cell lines and xenografts	[57, 126]
	MV-EGFP	EGFP reporter gene		
	MV-EGFP-NIS	EGFP reporter gene; NIS reporter and therapeutic gene		
	MV- mIFNβ	mIFNβ immunomodulatory gene		
	MV- mIFNβ-NIS	mIFNβ immunomodulatory gene; NIS reporter and therapeutic gene		
Renal cell carcinoma	MV-Edm	unmodified vaccine tag strain	Human renal cell carcinoma primary cells, cell lines and xenografts	[120]
	MV-P	Armed with IC-B wild type MV P gene		
	MV-NPL	Armed with IC-B wild type MV N, P and L genes		
Anaplastic thyroid cancer	MV-NIS	NIS reporter and therapeutic gene	Human anaplastic thyroid cancer cell lines and xenografts	[142]
Melanoma	MV-Edm	Unmodified vaccine strain	Human melanoma primary cells, cell lines and xenografts	[165]
	MV-EGFP	EGFP reporter gene		
Medulloblastoma	MV-EGFP	EGFP reporter gene	Human medulloblastoma cell lines and xenografts including a model of CSF dissemination	[166, 167]
Head and neck squamous cancer	MV-NIS	NIS reporter and therapeutic gene	Human head and neck squamous cancer cell lines and xenografts	[141]
	MV-EGFP	EGFP reporter gene		
	MV-EGFP-antiCD20	Retargeted to CD20; EGFP reporter gene		
	MV-EGFP-antiEGFR	Retargeted to EGFR; EGFP reporter gene		
	MV-CD-antiEGFR	Retargeted to EGFR; CD/UPRT prodrug convertase		
Fibrosarcoma	MV-Edm	Umodified	HT1080 human fibrosarcoma cell cultures and xenografts	[20, 102, 149]
	MVHαCD20	Retargeted to CD20		
	MV-EGFP	EGFP reporter gene		

Tumor type	MV strain	Genetic Modification	Tumor models used	References
	MV-EGFP- MMPA	MMP-activatable virus; EGFP reporter gene		
	MV-EGFP- MMPA1	MMP-activatable virus; EGFP reporter gene		
Rhabdomyo-sarcoma	MV-CEA	CEA reporter gene	TE671 human rhabdomyosarcoma cell cultures	[37]
Liver metastases from colorectal cancer, pancreatic cancer, B-cell non–Hodgkin's lymphoma, uveal melanoma and renal cell carcinoma	MV-EGFP-MMPA1	MMP-activatable virus; EGFP reporter gene	Infection of human tumor tissues slices	[20]
	MV-EGFP	EGFP reporter gene		

CD/UPRT: cytosine deaminase/uracil phosphoribosyltransferase; CDV: canine distemper virus; CEA: carcinoembryonic antigen; CTCL: Cutaneous T-cell lymphoma; EGFP: enhanced green fluorescent protein; mIFNβ: murine interferon β; L: measles virus large protein; MV: measles virus; N: measles virus nucleocapsid; NAP: neutrophil-activating protein; NIS: Sodium iodide symporter; P: measles virus phosphoprotein; PNP: purine nucleoside phosphorylase; PSCA: prostate stem cell antigen; PSMA: prostate-specific membrane antigen; RFP: red fluorescent protein; scTCR: single-chain T-cell receptor; SLAM: Signaling lymphocyte activation molecule; uPAR: urokinase-type plasminogen activator receptor

Table 2

Phase I clinical trials of oncolytic attenuated measles vaccine (MV-Edm) derivatives.

MV Strain	Genetic Modification	Type of Cancer	Patient population	Route of administration	Combination treatment	Current status
MV-Edm Zagreb vaccine strain (MV-EZ)	Commercially available measles vaccine (genetically unmodified)	CTLC	Five measles immune patients with ≥ stage IIb refractory or recurrent CTCL	Intratumoral	Subcutaneous interferon-alpha administration 72 hours and 24 hours before viral treatment.	Completed study [82]; No dose-limiting toxicity. Complete regression of 1 injected lesion, partial regression of 4 treated lesions and no response of 1 injected lesion.
MV-CEA	MV-Edm derivative engineered to express the soluble extracellular domain of human CEA	Ovarian cancer	Twenty-one measles immune patients with recurrent ovarian cancer confined to the peritoneal cavity	Intraperitoneal	No	Completed study [58]. No dose-limiting toxicity. Dose-dependent CEA detection. Stable disease in 14 patients (best objective response). Increased median overall survival compared to historical controls.
		Glioblastoma multiforme	Recruiting measles immune patients who are candidates for gross total or subtotal tumor resection.	Intracranial.	No	Recruiting [87].
MV-NIS	MV-Edm derivative engineered to express NIS	Multiple myeloma	Recruiting patients with recurrent or refractory multiple myeloma	Intravenous	With or without cyclophosphamide pretreatment 48 hours before viral treatment	Recruiting [81].
		Ovarian cancer	Recruiting measles immune patients with recurrent or refractory ovarian cancer confined to the peritoneal cavity	Intraperitoneal	No	Recruiting [86]
		Mesothelioma	Recruiting patients with malignant mesothelioma confined to single pleural cavity	Intrapleural	No	Recruiting [88]

CEA: carcinoembryonic antigen; CTCL: Cutaneous T-cell lymphoma; MTD: Maximum tolerated dose; NIS: Sodium iodide symporter; $TCID_{50}$: 50% tissue culture infective dose