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Prospect and progress of oncolytic viruses for treating peripheral nerve sheath tumors

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Abstract

Introduction—Peripheral nerve sheath tumors (PNSTs) are an assorted group of neoplasms originating from neuroectoderm and growing in peripheral nerves. Malignant transformation leads to a poor prognosis and is often lethal. Current treatment of PNSTs is predominantly surgical, which is often incomplete or accompanied by significant loss of function, in conjunction with radiotherapy and/or chemotherapy, for which the benefits are inconclusive. Oncolytic viruses (OVs) efficiently kill tumor cells while remaining safe for normal tissues, and are a novel antitumor therapy for patients with PNSTs.

Areas covered—Because of the low efficacy of current treatments, new therapies for PNSTs are needed. Pre-clinically, OVs have demonstrated efficacy in treating PNSTs and perineural tumor invasion, as well as safety. We will discuss the various PNSTs and their preclinical models, and the OVs being tested for their treatment, including oncolytic herpes simplex virus (HSV), adenovirus (Ad), and measles virus (MV). OVs can be ‘armed’ to express therapeutic transgenes or combined with other therapeutics to enhance their activity.

Expert opinion—Preclinical testing of OVs in PNST models has demonstrated their therapeutic potential and provided support for clinical translation. Clinical studies with other solid tumors have provided evidence that OVs are safe in patients and efficacious. The recent successful completion of a phase III clinical trial of oncolytic HSV paves the way for oncolytic virotherapy to enter clinical practice.

Keywords

virotherapy; MPNST; HSV; soft tissue sarcoma

1. Introduction To Peripheral Nerve Sheath Tumors And Oncolytic Viruses

Peripheral nerve sheath tumors (PNSTs) are relatively rare neoplasms originating from neuroectoderm and growing in the peripheral nerves, causing pain, reducing nerve function

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and leading to disability. PNSTs are typically benign, schwannomas and neurofibromas, and sporadic or caused by genetic disorders of the nervous system, such as neurofibromatosis, and are categorized as soft tissue tumors^{1, 2}. Malignant peripheral nerve sheath tumors (MPNST) are very aggressive and characterized by a high mortality rate^{3, 4}. Benign plexiform neurofibromas (PNF) can transform to a malignant form⁵. These are common tumors in patients with neurofibromatosis type 1 (NF1) and 2 (NF2)¹. The most recent classification of nerve sheath tumors is summarized in the WHO Classification of Tumors of Soft Tissue and Bone⁶. We will not discuss the rarer PNSTs, such as myxoma, perineurioma, and triton tumors. Carcinoma perineural invasion also involves tumor growth in peripheral nerves and thus has treatment issues that overlap with PNSTs.

Although the idea of using virus infection to induce tumor cell death, virotherapy, has been known more than 100 years⁷, the advances in genetic engineering provided new possibilities to modify viruses for safety and efficacy. Oncolytic viruses (OVs) selectively replicate in tumor cells without harming normal tissue, making new infectious virus that can then spread and kill additional tumor cells^{7, 8}. They can kill tumor cells not only by direct cytopathic effect, oncolysis, but also by indirect mechanisms, such as inducing anti-tumor immune responses or attacking the tumor vasculature⁹⁻¹¹. OVs include those viruses that: (i) have a natural propensity to replicate in tumor cells, i.e. myxoma and Newcastle disease viruses (NDV); (ii) are vaccine strains that have been attenuated, i.e. measles (MV), poliovirus (PV), and vaccinia virus (VV); or (iii) are genetically engineered with mutation/deletions in pathogenic genes, genes required for replication in normal cells, and/or retargeted to tumor cell receptors, i.e. adenovirus (Ad), herpes simplex virus (HSV), and vesicular stomatitis virus (VSV)¹². OVs can be 'armed' with therapeutic transgenes, including; immunomodulatory, anti-angiogenic, and cytotoxic genes, that are expressed in the tumor after infection^{13, 14}. Depending on the tumor type, OVs can be used: (i) as single agents, (ii) in combination with chemo- or/and radio-therapy, or (iii) expressing therapeutic transgenes. During the last two decades, numerous OVs have entered into clinical trials for a large variety of cancers^{7, 15}. However, there has been only one clinical trial to date reporting OV treatment for PNST, using oncolytic Ad¹⁶. Recently, the first oncolytic virus, talimogene laherparepvec, an oncolytic HSV, was approved by the FDA in the US for the treatment of advanced melanoma^{17, 18}. Because of this lack of completed clinical trials for PNST, we will focus on OVs that have been explored preclinically for the treatment of PNSTs (Table 1), strategies to improve OV efficacy in PNSTs, safety, and future virotherapy directions.

2. Peripheral Nerve Sheath Tumors (PNST) and Perineural Invasion in Cancer

2.1. Schwannoma

Normal Schwann cells form myelin, a protective sheath around peripheral nerves. Schwannomas, the most common PNST in adults and comprised of abnormal Schwann-like cells, are benign, slow-growing, circumscribed, encapsulated, solitary, and non-infiltrating tumors^{2, 19}. NF2 patients develop schwannomas, often multiple, in cranial, spinal, and peripheral nerves, with bilateral vestibular schwannomas a hallmark^{2, 19}. NF2 is an autosomal dominant disease (affects about 1:25000 births) caused by inactivating mutations

of the NF2 tumor suppressor gene located on chromosome 22q12, and characterized by the development of nervous system tumors, ocular abnormalities, and skin tumors²⁰. The NF2 gene, encoding merlin (moesin-ezrin-radixin-like protein), is also mutated or lost in most sporadic schwannomas^{21, 22}. Schwannomas are often asymptomatic, although vestibular schwannomas often lead to hearing loss, and can usually be treated with surgical resection^{2, 20}. A broader understanding of the molecular mechanism of NF2 pathogenesis should lead to new therapies, with a number of downstream effectors of merlin being tested in clinical trials, i.e.: erlotinib (Her-1/EGFR inhibitor), lapatinib (Her-2/EGFR inhibitor), and everolimus (mTOR inhibitor)^{23, 24}. While the targeted therapies are promising, they have not been curative, so virotherapy is an attractive approach.

2.2. Neurofibroma

Neurofibromas are benign PNSTs arising from Schwann cell precursors that include fibroblasts, mast cells, and distinct from schwannomas, a matrix of collagen fibers^{2, 5}. Typically they occur sporadically, however approximately 10% are associated with NF1, where they are a diagnostic criteria²⁵. NF1 is a frequently occurring autosomal dominant genetic disease (affects about 1:3500 births), caused by mutations in the NF1 gene located on chromosomal segment 17q11.2 and encoding neurofibromin²⁶. Neurofibromin contains a Ras-GTPase activating protein (Ras-GAP) domain that negatively regulates Ras activity, so that NF1 is a member of the RASopathy cancer predisposing syndromes²⁷. Unlike schwannoma, neurofibromas are not encapsulated and infiltrate between the nerve fascicles. There are three subtypes of neurofibroma based on their location and appearance: (i) localized cutaneous or dermal neurofibromas, which are the most common, appear at puberty and grow from small nerves in the skin or just under the skin. They have limited growth, remaining benign throughout life, and do not transform into malignant PNSTs⁵; (ii) diffuse or subcutaneous neurofibromas are typically located within the subcutaneous tissues of the head and neck, are often pigmented or with melanocytic differentiation^{25, 28}, and in NF1 are associated with internal neurofibroma tumor burden and mortality^{29, 30}; and (iii) plexiform neurofibromas (PNF) are usually congenital, occurring in about a third of NF1 patients, and present anywhere in the body but often internal where they can remain asymptomatic²⁶. They involve multiple nerve fascicle trunks and infiltrate surrounding tissue²⁵. Importantly, PNFs can undergo malignant transformation and progress to MPNST, which occurs in about 5-10% of cases^{5, 31, 32}. PNFs are typically debulked by surgery when indicated, but this can be associated with nerve damage and hemorrhage, and is often incomplete^{5, 33}. Based on our understanding of neurofibromin, a small phase II clinical trial examined imatinib mesylate (Gleevec), a kinase inhibitor, to treat PNF³⁴.

2.3. Malignant peripheral nerve sheath tumor (MPNST)

MPNST is a soft-tissue sarcoma arising from peripheral nerves or benign PNSTs that displays nerve sheath differentiation^{25, 35}. They account for about 10% of soft tissue sarcomas, but half arise in NF1 patients. There are histological and clinical differences between sporadic and NF1-associated MPNSTs^{33, 36}, although a recent meta-analysis suggested that the survival differences have been converging in the last decade³⁷. MPNST frequently occurs in the extremities, often in major nerve trunks like the sciatic nerve³⁵. Like other malignancies, metastasis may also occur, often to the lung, liver, brain, soft tissue,

bone, regional lymph nodes and retroperitoneum³². In NF1, loss-of-heterozygosity of NF1 occurs in over 90% of tumors³⁸, with tumors having constitutively activated RAS and downstream activation of the Akt and MAPK pathways³⁹. However, the complex karyotypes in MPNSTs suggests that additional genetic alterations, such as in p53, CDKN2A, CDK4, contribute to malignancy³⁵. Surgical resection is the main treatment option for MPNST, however it is often incomplete, with a local recurrences ranging up to 65% depending on the tumor location, and associated with potentially significant loss of function^{33, 40}. Radiotherapy is recommended for high-grade lesions when surgery is not possible or incomplete, but hasn't been shown to improve survival^{33, 40}. Adjuvant chemotherapy, ifosfamide and doxorubicin, may have some activity in pediatric patients and non-NF1 patients^{40, 41}. The long-term survival of MPNST patients is poor, around 50% at 5 years^{37, 40, 41}, so there is a critical need for novel therapeutic approaches.

2.4. Perineural invasion in cancer

Perineural invasion (PNI), the presence of tumor cells within any of the layers of the nerve sheath, is a route of metastasis distinct from vascular or lymphatic dissemination⁴². It is very common and often the typical route of metastasis in head and neck squamous cell carcinoma (~80%), prostate (~80%), gastric (~50%), and colorectal cancers (~30%), and almost all pancreatic tumors⁴²⁻⁴⁴. PNI is an independent prognostic factor in these tumors, with 5 year survival often decreased by half, and is also associated with severe pain, especially in pancreatic cancer^{42, 43, 45}. Understanding the molecular mechanisms of PNI is lagging and it is still unclear how tumor cells penetrate the nerve sheath and layers of collagen and basement membrane, or why some carcinomas have a penchant for PNI. The lack of targeted treatments and poor prognosis for PNI makes this an important target for novel therapies and potentially OV's.

3. Oncolytic Viruses

3.1. Herpes simplex virus (HSV)

HSV-1 is an enveloped virus with a 152 kb double-stranded DNA genome encoding about 84 genes⁴⁶. Viral glycoproteins in the envelope bind to host attachment factors on the cell surface (heparin sulfate, nectin-1 (PVRL1), PILR α , and HVEM (TNFRSF14)) and induce membrane fusion⁴⁶. This can impact cancer cell susceptibility, for example HVEM is not expressed on most MPNST cell lines, including sensitive cells, while the levels of nectin-1 expression correlate with virus yields⁴⁷. In permissive cells, the HSV replication cycle is usually completed in less than 24 hr, and cells release viral progeny ready to infect adjacent cells. HSV is a neurotropic virus that can invade the nervous system and infect neural cells. HSV can be genetically engineered to mutate/delete viral genes that confer selective replication in tumor cells and attenuate neurovirulence, make them oncolytic. For example: (i) the thymidine kinase (TK) and ribonucleotide reductase (ICP6) genes are involved in nucleotide metabolism and necessary for virus replication in nondividing cells, but not in tumor cells; and (ii) γ 34.5 is a major determinant of HSV pathogenicity, so that deletions of γ 34.5 significantly reduce neurovirulence permitting treatment of nervous system tumors⁴⁸.

3.2. Oncolytic HSV (oHSV)

A number of oHSVs with different mutations/deletions (ICP6, γ 34.5) have been tested in a variety of PNST models (Table 1). G47 Δ , a third generation oHSV (ICP6 Δ , γ 34.5 Δ , ICP47 Δ), was examined in a number of human xenograft and mouse transgenic schwannoma models^{49, 50}. In a NF2 transgenic model, spontaneous subcutaneous schwannomas were treated with a single intratumoral injection of G47 Δ after MR imaging to identify the tumors⁴⁹. This led to a decrease in tumor volume within 2 weeks in G47 Δ -treated tumors, however, in some cases control-treated tumors also regressed. This is an issue not only with the mouse models, but also in human patients⁵¹, and confounds both preclinical and clinical studies of benign tumors with variable growth rates. In addition, it took about 18 months for the transgenic schwannomas to become apparent, making treatment studies difficult. To get around this problem, human schwannoma xenografts were generated by subcutaneous implantation of schwannoma tissue from patients with NF2 or schwannomatosis in immunocompromised mice⁴⁹. These tumors were histologically schwannomas and susceptible to G47 Δ infection and replication⁴⁹. Treatment with two doses of G47 Δ resulted in a reduction in tumor volume, while the vehicle-treated tumors continued to grow⁴⁹. In a separate study, subcutaneous tumors were established in nude mice with a human immortalized schwannoma cell line HEI193 or a mouse line (NF2S-1), and treated two successive times with G47 Δ ⁵⁰. Both tumors showed significant inhibition of tumor growth or regression compared with control animals, however, the NF2S-1 tumors regrew at about 7 weeks after treatment⁵⁰. These positive results in a variety of schwannoma models strongly support the use of oHSV for the treatment of schwannomas.

MPNST is a lethal tumor and there are more MPNST cell lines available as models than for benign PNSTs, making it a more frequent target for OV therapy. Initial studies *in vitro*, showed that a set of human MPNST cell lines were sensitive to oHSV G207 and hrR3 (Table 1), regardless of Ras activation, whereas normal human Schwann cells were not permissive to virus replication⁵². In contrast, the susceptibility of mouse MPNST cells isolated from transgenic mouse tumors to G207 was dependent upon elevated levels of Ras activation⁵³. Both G207 and hrR3 were able to inhibit tumor growth and survival after intraperitoneal injection of mice bearing intraperitoneal xenografts of human STS26T MPNST⁵⁴. rQLuc, similar to G207, but expressing luciferase (Table 1), was efficacious in subcutaneous xenografts of STS26T and S462.TY after intratumoral injection⁵⁵. Luciferase expression permits non-invasive monitoring of virus spread using bioluminescence imaging.

Transcriptionally-targeting of oHSV is a way to drive replication selectively in tumor cells⁴⁸. Midkine (MDK) is overexpressed in MPNST cells compared to fibroblasts and Schwann cells⁵⁶ and thus the MDK promoter should drive MPNST-specific transcription. To enhance oHSV replication, γ 34.5 was placed under the MDK promoter, generating oHSV-MDK-34.5 (Table 1)⁵⁶. oHSV-MDK-34.5 had increased viral replication and cytotoxicity in human STS26T MPNST cells *in vitro*, and inhibited tumor growth and increased survival in subcutaneous xenografts compared with the control virus oHSV-MDK⁵⁶.

Recently, a new orthotopic MPNST model was developed by implantation of mouse NF1 transgenic MPNST cell lines or human NF1 MPNST stem-like cells (MSLCs) into the

sciatic nerves of immunocompetent and immunodeficient mice, respectively ⁵⁷. In this model, mice develop progressive hind limb deficits, which can be quantified to evaluate treatment efficacy. Neurologic deficits are apparent prior to palpable tumors, which provides an indication that the tumor is established and growing and thus suitable for treatment. MSLCs were isolated from an established human MPNST cell line, S462, which could self-renew, had increased expression of stem cell markers, could differentiate into cells from multiple lineages, and were more tumorigenic ⁵⁸. About a third of mice bearing human MSLC-derived tumors treated with a single low dose intratumoral injection of only 2×10^5 plaque forming units (pfu) of G47 were long-term survivors, with no evidence of tumor and limited neurologic deficit, in contrast to mock-treated mice which all succumbed to tumor growth ⁵⁷. In the immunocompetent mouse MPNST model, a single dose of G47 significantly delayed tumor growth, improved neurologic score, and significantly extended survival compared with control, with the 35% long-term survivors lacking macroscopically detectable tumor or ultrastructural abnormalities ⁵⁷. Therefore, oHSV has been shown to be very effective in treating PNSTs, both benign schwannomas and malignant MPNSTs.

PNI can be modeled by tumor cell implantation into sciatic nerves. The first description of oHSV treatment in such a model was the demonstration that a single intratumoral injection of G207 could extend the survival of mice bearing tumors after implantation of human neuroblastoma IMR32 cells into the sciatic nerve ⁵⁹. Tumors were similarly established in the sciatic nerve with human carcinoma cell lines from pancreatic (MiaPaCa2), squamous cell (QLL2), and prostate (PC3, DU145) cancers, and treated with oHSV NV1023 (Table 1) ^{60, 61}. While all saline-treated mice developed complete hindlimb paralysis, most NV1023-treated mice had preserved nerve function and significant tumor regression ^{60, 61}. A similar oHSV, NV1020, has been in clinical trial for metastatic colorectal carcinoma to the liver ⁶².

3.3. oHSV expressing therapeutic transgenes

While OV's are effective therapeutic agents, their activity can be enhanced by 'arming' them with therapeutic transgenes. Expression of transgenes in the tumor can target uninfected tumor cells and normal cells and extracellular matrix of the tumor microenvironment ^{14, 63}. A number of different transgenes have been inserted into oHSV and examined in MPNST models, including those encoding antiangiogenic factors, immunomodulatory cytokines, receptor decoys, and proteinase inhibitors ⁴⁸. rQT3 encodes human tissue inhibitor of metalloproteinase 3 (TIMP3) (Table 1), blocking the activity of matrix metalloproteinases, which promote tumor invasion and are expressed in MPNST cells ⁵⁵. rQT3 was much more effective than G207 or rQLuc at inhibiting MPNST STS26T and S462.TY tumor growth ⁵⁵. G47 expressing anti-angiogenic factors platelet factor 4 (PF4) and dominant-negative fibroblast growth receptor (dnFGFR) have been constructed ^{64, 65}. Mouse MPNST cell lines expressing dnFGFR or PF4 had reduced tumor growth and angiogenesis *in vivo* ^{64, 65}. Infection of human endothelial cells with G47 -dnFGFR or G47 -PF4 was more cytotoxic than control G47 -empty and conditioned media from infected tumor cells reduced endothelial migration *in vitro* ^{64, 65}. *In vivo*, G47 expressing dnFGFR or PF4 significantly inhibited subcutaneous mouse MPNST growth in nude mice and decreased vascular density compared with control G47 alone ^{64, 65}. The effects of PF4 and IL-12 expression on oHSV

efficacy in an immunocompetent setting were examined using the orthotopic sciatic nerve mouse MPNST implant model. G47 -PF4 was not as effective in immunocompetent mice and only significantly extended survival compared to G47 -empty⁵⁷. In contrast, G47 -IL12 was significantly better than G47 -empty at inhibiting neurologic deficit progression and tumor growth, and increasing survival⁵⁷.

3.4. oHSV in combination with drugs

MPNST is resistant to standard single agent chemotherapy^{41, 66}. Using oncolytic virotherapy in combination with existing chemotherapeutics may lead to synergistic interactions that increase therapeutic effects not achievable by either therapy alone⁶⁷. oHSV has been successfully combined with a number of chemotherapeutic and molecularly targeted drugs in a variety of solid tumors⁶⁷. So far this promising strategy has not been explored in PNST models, except for erlotinib (inhibitor of EGFR tyrosine kinase), and in the oncolytic Ad clinical trial. *In vitro*, erlotinib in combination with hrR3 or G207 was more cytotoxic to STS26T MPNST cells than either treatment alone⁵⁴. Unfortunately, combination treatment of the tumors did not enhance efficacy over oHSV alone⁵⁴.

3.5. oHSV safety

Wild type HSV is highly neuroinvasive in the peripheral and central nervous system and neuropathogenic⁴⁶. After footpad inoculation, HSV-1 invades the CNS via the sciatic nerve, causing paralysis and death⁶⁸. Direct injection of wild type HSV-1 into the sciatic nerve causes nerve demyelination, Wallerian degeneration, and inflammation at early times, followed by paralysis and lethal encephalitis^{59-61, 69}. In contrast, sciatic nerve injection of NV1023 at a 10-fold higher dose caused no significant toxicity, with only mild Wallerian degeneration⁶¹. Similarly, sciatic nerve injection of G47 was non-toxic, with mice gaining weight and exhibiting transient neurologic deficits no different than PBS-injected control mice⁵⁷. The G47 -injected sciatic nerves did not exhibit any ultrastructural abnormalities, with the exception of focal needle track damage that was also seen in the PBS-injected nerves⁵⁷.

3.6. Adenovirus

Oncolytic Ad ONYX-015 is a hybrid Ad2/Ad5 derived from mutant of Ad dl1520 containing a deletion of E1b-55K protein⁷⁰. E1b-55K protein together with the E4orf6 protein target p53 for degradation, so that ONYX-015 selectively replicates in tumor cells with mutated p53. More recent studies suggest that E1B-55K is also involved in blocking DNA damage responses and export of late viral RNAs⁷¹. ONYX -015 has been evaluated in a large number of clinical trials for a variety of cancers⁷². In 2005, Galanis et al.¹⁶ reported on completed results from the first clinical trial using ONYX-15 to treat patients with advanced sarcoma in combination with mitomycin-C, doxorubicin, and cisplatin chemotherapy. Among the six patients treated was one patient with metastatic MPNST (p53⁺, MDM2⁻), who received the highest ONYX-015 dose (10¹⁰ pfu)¹⁶. This was the only patient who achieved a partial response, in both the injected bulky tumor and 2 small uninjected lesions, which lasted 11 months. Unfortunately, clinical testing with ONYX-015 was halted during a pivotal phase III trial when Onyx divested the program. A similar oncolytic Ad, H101, has been approved in China for use in head and neck cancers in

combination with chemotherapy ⁷². Since then many new oncolytic Ad vectors have been constructed. Ad5/3-D24-GMCSF (CGTG-102) (Table 1) selectively replicates in p16/Rb-defective cells and has been evaluated in patients with advanced solid tumors ⁷³. Ad5/3-D24-GMCSF has been examined in an immunocompetent Syrian hamster soft-tissue sarcoma (STS) model in combination with doxorubicin and ifosfamide ⁷⁴. The combination drug/virus treatment was highly effective and resulted in synergistic antitumor efficacy compared with single agent treatments ⁷⁴. These studies suggest that oncolytic Ad in combination with chemotherapy may be an attractive strategy for PNST.

3.7. Measles virus (MV)

MV, a Morbillivirus in the family Paramyxoviridae, is an enveloped virus with a non-segmented, negative-strand RNA genome ⁷⁵. Several cases of spontaneous tumor regression in individuals with lymphoma after MV infection have been reported, suggesting that MV may have oncolytic properties ⁷⁵. Wild type MV uses the cellular receptor SLAM (signaling lymphocyte activation molecule) for cellular entry, which is not commonly expressed on tumor cells, however, attenuated vaccine MV strains like Edmonston are adapted for cellular entry using CD46, which is highly expressed on human tumor cells, including MPNST ^{76, 77}. The human sodium iodide symporter (NIS) has been inserted into MV-Edmonston (MV-NIS) (Table 1) to enable non-invasive monitoring of virus infection and spread using ¹²⁵I SPECT ⁷⁶. NIS expression can also facilitate radiotherapy with ¹³¹I administration ⁷⁶. MV-NIS is currently in clinical trials for multiple myeloma, ovarian cancer, and mesothelioma ⁷⁶. MPNST cell lines were very susceptible to MV-NIS cytotoxicity, while normal Schwann cells were not, despite high-level expression of CD46 ⁷⁷. *In vivo*, intratumoral injection of MV-NIS was efficacious in inhibiting the growth of subcutaneous MPNST ST88-14 and S462TY tumors ⁷⁷. NIS expression permitted the detection of MV-infected cells in mice bearing tumors ⁷⁷. MV is associated with a number of serious neurologic complications in the CNS, but there is no evidence that it invades or causes pathology in the PNS ⁷⁸.

3.8. Vestibular stomatitis virus (VSV)

VSV is a non-segmented negative-strand RNA virus from the Rhabdoviridae family ⁷⁹. VSV oncolytic selectivity is due to its extreme sensitivity to type 1 interferon (IFN) and innate antiviral responses, which are defective in most cancer cells ⁷⁹. VSV can be further attenuated by disrupting the gene order, as in VSV-G/GFP, which was used to isolate VSV-rp30a (Table 1) by positive selection on glioblastoma cells ⁸⁰. VSV-rp30a also grew and killed human MPNST cell lines S462-TY and STS-26T better than its parent VSV-G/GFP, and growth was not inhibited by pretreatment with INF- α ⁸¹. Primary fibroblasts and vascular endothelia cells were about 10-fold less sensitive to VSV-rp30a than the MPNST cells ⁸¹. In a human subcutaneous fibrosarcoma model, a single intravenous dose of VSV-rp30a completely inhibited tumor growth ⁸¹. A clinical trial is currently ongoing with VSV expressing IFN β in patients with refractory hepatocellular carcinoma (<http://clinicaltrials.gov/ct2/show/NCT01628640>).

4. Conclusions

OVs have multiple mechanisms of action, including; direct tumor cell killing, amplification *in situ*, and induction of anti-tumor immunity. This makes them powerful therapeutic agents. They have unique properties that derive from the biology of the viruses from which they were generated. The results we describe from preclinical studies demonstrate that OVs have robust anti-PNST activity and warrant clinical translation. Most of the studies have been conducted with oHSV, a neurotropic virus that can be genetically engineered to selectively replicate in tumor cells but not normal tissue. Safety studies with oHSV demonstrated no toxic effects or nerve damage after direct injection into the sciatic nerve. Arming oHSV with therapeutic transgenes enhances anti-tumor activity. Other OVs have also been armed, but so far none examined in PNST models. The availability of a number of MPNST preclinical models and the lack of targeted therapies or significant improvements in outcomes for this malignancy, make it a prime target for OV therapy, which has demonstrated impressive efficacy in preclinical models. Even benign PNSTs are highly susceptible to oHSV therapy. There have been fewer studies with other OVs, but oncolytic Ad ONYX-015 is the only OV to be administered to a patient with PNST. Preliminary studies with MV and VSV, suggest that they also have potential to treat PNST.

5. Expert Opinion

Despite the great progress in understanding the molecular mechanisms of pathogenesis of PNSTs, surgical resection of these tumors remains the main treatment paradigm. Due to size or location, these tumors are often inoperable or entail a risk of nerve damage. On the other hand, they are not very susceptible to chemotherapy or radiotherapy, and effective molecularly targeted drugs have not been identified. Therefore, new therapeutic strategies are necessary for both benign and malignant PNSTs. OVs are one new promising approach that has been underexplored. Unfortunately, the lack of preclinical animals models for benign PNSTs has hampered progress in developing and testing new therapies, including OVs. However, where models are available, OVs have demonstrated robust anti-tumor activity. The number and types of preclinical models has increased and improved dramatically over the past decade and include models more representative of the clinical situation, such as cancer stem cells, patient-derived xenografts (PDX), and transgenic mice. All models have limitations, but having multiple options improves the likelihood of successful clinical translation.

Advances in genetic engineering allows the construction of OVs that are safe and with specificity for the molecular diversity of tumors. Arming OVs with therapeutics transgenes can target the tumor microenvironment locally. The normal cells and stroma comprising the tumor are a critical component in tumorigenesis and an important target for therapy. The size of transgene to be inserted will vary depending on the virus, but for oHSV this can be between 10-30 kb, sufficient for even multiple transgenes. The choice of transgene is unlimited; be it reporter genes to monitor OV activity, cytotoxic agents or prodrug activating enzymes to kill cells, antiangiogenic factors to inhibit neovascularization, immune modulatory factors to enhance anti-tumor immunity, or extracellular matrix modifying agents to enhance OV spread or inhibit tumor cell migration. Importantly, expression is

regulated by the selectivity of the OV, so that it is typically expressed locally within the tumor, limiting systemic toxicity.

OVs derived from 12 different viruses have entered clinical trials for a large variety of cancers¹⁵. There is no obvious reason why OVs, in addition to those described here, should not also be effective in treating PNSTs. Talimogene laherparepvec, an oHSV similar to G47 Δ except expressing GM-CSF, was recently approved by the FDA for the treatment of advanced melanoma. This is the first OV approved for clinical use in the US and should significantly increase the interest of the pharmaceutical industry and clinicians in the use of OVs. This is an exciting time for the field of oncolytic virotherapy and PNST is an excellent target for this new therapeutic strategy.

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Article Highlights

- Oncolytic viruses efficiently kill tumor cells while remaining safe for normal tissues.
- Oncolytic viruses, especially oncolytic HSV, have demonstrated efficacy and safety in treating PNST and perineural invasion in cancer.
- ‘Arming’ oncolytic viruses with therapeutic transgenes or combining with other therapeutic agents enhances antitumor activity.
- A limited number of preclinical tumor models for PNST has slowed progress in the development of new therapeutic strategies.
- Preclinical studies with oncolytic HSV in MPNST and schwannoma support clinical translation.

Table 1

OVs used in PNST pre-clinical models

Abbreviations: GFP, enhanced green fluorescent protein; h, human; IL, interleukin; LacZ, β -galactosidase; NIS, sodium/iodide symporter; pro, promoter; TIMP3, tissue inhibitor of metalloproteinases 3; IE4/5, immediate-early gene 4/5.

Oncolytic Virus	Genetic Modifications	Transgene	Drug Combination	PNST Model	Ref.
oHSV					
G47	γ 34.5 , ICP6-, ICP47 , LacZ+			MPNST orthotopic sciatic nerve, Transgenic schwannoma, Subcutaneous schwannoma	49, 50, 57, 65
G207	γ 34.5 , ICP6-			Subcutaneous and intraperitoneal human MPNST in athymic mice	52, 54
NV1023	UL56 /1 copy of ICP0, ICP4 and γ 34.5			Perineural invasion model in sciatic nerve	60, 61
G207	γ 34.5 , ICP6-		Erlotinib	Subcutaneous and intraperitoneal: human MPNST in athymic mice	54
rQT3	γ 34.5 , ICP6-	IE4/5pro-TIMP3, ICP6-GFP fusion in ICP6		MPNST xenograft models	55
hrR3	ICP6-, LacZ+			Subcutaneous and intraperitoneal human MPNST in athymic mice	54
oHSV-MDK-34.5	Mdk pro- γ 34.5 and ICP6-GFP fusion in ICP6			Subcutaneous human MPNST in athymic mice	56
G47 -PF4	γ 34.5 , ICP6-, ICP47 , ICP47pro-Us11	PF4		Subcutaneous MPNST xenograft, MPNST orthotopic sciatic nerve in immunocompetent mice	57
G47 -dnFGFR	γ 34.5 , ICP6-, ICP47 , ICP47pro-Us11	dnFGFR		Subcutaneous MPNST xenograft, MPNST orthotopic sciatic nerve in immunocompetent mice	64
G47 -mIL12	γ 34.5 , ICP6	mIL-12		MPNST orthotopic sciatic nerve in immunocompetent mice	65
Other OVs					
Ad5/3-D24-GMCSF	Ad5/3 fiber, E1A 24-bp , E3	hGMCSF	doxorubicin, ifosfamide	leiomyosarcoma cells in Syrian hamster	74
MV-NIS	Edmonston vaccine strain	NIS		Subcutaneous human MPNST in athymic mice	77
VSV-rp30a	Disruption of gene order			In vitro human MPNST cell lines	81