German Journal of Veterinary Research

eISSN:2703-1322

Review

Oncolytic virotherapy and the current approaches in veterinary medicine

Bengü Bilgiç*, Banu Dokuzeylül and Mehmet E. Or

Department of Internal Medicine, Faculty of Veterinary Medicine, Istanbul University-Cerrahpasa, 34320 Avcılar, Istanbul, Turkey

Article History:
Received: 14-Feb-2022
Accepted: 10-Mar-2022
***Corresponding author:**
Bengü Bilgiç
bengubilgic90@gmail.com

Abstract

Cancer has an increasing incidence worldwide in humans and animals. In addition to traditional treatments such as surgery, radiotherapy, and chemotherapy, there is a search for new treatment strategies for cancer treatment. Oncolytic virotherapy arouses great interest in human medicine with the development of biotechnology and increasing knowledge about virus-cell interactions in recent years. Many *in-vivo* and *in-vitro* studies have led to the development of a United States Food and Drug Administration (FDA)-approved, genetically modified oncolytic viral therapy. Based on the studies in human medicine, some clinical trials have also been carried out with oncolytic virotherapy in veterinary medicine. But the studies in cats and dogs are very limited. This review aims to compare the development of oncolytic virotherapy in human and veterinary medicine with current studies and to draw attention to the fact that virotherapy can be used as a treatment option for various tumoral diseases in veterinary medicine in the future.

Keywords: Oncolytic viruses, Virotherapy, Veterinary medicine, Cancer

Citation: Bilgiç, B., Dokuzeylül, B. and Or, M. E. 2022. Oncolytic virotherapy and the current approaches in veterinary medicine. Ger. J. Vet. Res. 2 (2): 17-27. https://doi.org/10.51585/gjvr.2022.2.0032

Introduction

Cancer, which is increasing globally, is one of the most important causes of death in both humans and animals. Traditional treatment regimens include surgery, radiotherapy, and chemotherapy. Today, new treatment strategies are being developed in addition to conventional treatments. These include immunotherapy, hormone therapy, stem cell therapy, genetically modified lymphocytes, and virotherapy applications with oncolytic viruses (Cao et al., 2020; Rahman and McFadden, 2020).

Oncolytic viruses selectively replicate in tumor cells without harming normal cells (Stojdl et al., 2000; Adair et al., 2012). Furthermore, some cellular responses such as translation suppression and apoptosis in healthy cells are restricted in tumor cells to limit viral infections. In addition, tumor cells have several defense mechanisms against recognition and destruction by the immune system. These factors cause many viruses to form a tropism against tumor cells (Russell, 2002).

In this review, we shed light on the development of oncolytic virotherapy to emphasize the prospective use of oncolytic viruses in the treatment of cancers in veterinary medicine in the future.

A brief history of oncolytic virotherapy

The idea that viruses can destroy tumors dates back to 1912 when Italian clinician N. De Pace first observed regression of cervical carcinoma in a patient treated with Pasteur therapy for a dog bite and thought that rabies virus might cause oncolysis (Southam, 1960). The first *in-vitro* investigation on viral oncolysis took place in 1922 when Levaditi observed that the smallpox vaccine virus (vaccinia virus) spread and sometimes inhibited various tumor types in mice and rats (Levaditi and Nicolau, 1922). In 1950, the tick-borne encephalitis virus, family *Flaviviridae*, formerly known as Russian Spring-Summer encephalitis virus (RSS), was inoculated into experimentally induced lymphoid tumors in chickens, and it was reported that the virus had a high oncolytic effect on tumor areas (Sharpless et al., 1950).

In 1957, a study carried out by Koprowski and colleagues revealed that only some virus types were effective in malignant cells. However, it was observed that tissues that survived the oncolytic effect of the virus were more immune to the subsequent viral inoculation (Aptekman and Lewis, 1951; Koprowski et al., 1957). In the 1960s, the oncolytic activities of many viruses that caused various infections in animals but

did not affect humans were investigated in experimental animals (Hammon et al., 1963; Pond and Manuelidis, 1964). Viruses reported having oncolytic activities include Newcastle disease virus (family *Parmyxoviridae*), influenza virus (family *Orthomyxoviridae*), Vesicular Stomatitis virus (family *Rhabdoviridae*), and Bovine Enterovirus (family *Picornaviridae*) (Lindenmann, 1963; Cassel and Garrett, 1965; Lindenmann, 1970; Sedmak et al., 1972).

In a clinical study in 1952, the West Nile virus was administered to thirty-four patients with advanced neoplastic disease. Although no curative effect was obtained in the study, the virus had a transient inhibitory effect on tumor growth in nine patients (Southam and Moore, 1952). In a case report in 1964, in which oncolytic virotherapy was applied in humans, various animal viruses including Sendai virus (family *Paramyxoviridae*), Newcastle disease virus, influenza strains, Semliki forest (family *Togaviridae*) and Sindbis virus (family *Togaviridae*)] were continuously administered intravenously to a patient with leukemia at different times, and 95% change was observed in blastic cells (Wheelock and Dingle, 1964). In a similar study, the effect of the avian influenza virus on myeloblast cells in patients with leukemia was examined, and it was reported that significant hematological improvements were observed (Sauter et al., 1974). Asada and coworkers published many cases covering the years 1907-1928, in which they isolated the Mumps virus (family *Paramyxoviridae*) from the saliva of patients with epidemic parotitis and administered it to patients who had different tumor types (Asada, 1974).

While the clinical studies continued, significant progress in DNA technology was made in 1968, with the discovery of making changes in the viral genome by adding polynucleotides to the Tobacco mosaic virüs (Rogers and Pfuderer, 1968). Meanwhile, increased knowledge about virus-cell interactions has also shed light on the mechanisms of the natural viral tropism of some viruses to tumor cells (Alemany et al., 2000). The regression of the tumor after oncolytic virotherapy and the recurrence of the disease following clinical improvements have led to various biotechnological interventions for a more effective oncolysis to date (Kelly and Russell, 2007).

Oncolytic viruses

Only a limited number of viruses are naturally oncolytic. They selectively infect neoplastic cells and have a potent cytopathic effect. However, many factors such as high pathogenic potential, insufficient tropism to tumor cells, sensitivity to neutralization by the host immune system, and inability to develop a tumor-targeted immune response limit the effectiveness of natural oncolytic viruses (Pol et al., 2016).

The general mechanisms of oncolytic viruses are illustrated in Figure 1. Zeng and colleagues have summarized the mechanisms of oncolytic in the following points: i) Due to defective or suppressed antiviral innate immune mechanisms pathways (e.g., IFN pathway) in cancer cells, oncolytic viruses can selectively or preferentially replicate in cancer cells leading to oncolysis (Stojdl et al., 2000; Adair et al., 2012; Zeng et al., 2021). ii) As a result of cell lysis, tumor-associated antigens (TAAs), cell-derived damage-associated molecular patterns (DAMPs), and viral pathogen-associated molecular patterns (PAMPs) are released, which can recruit dendritic cells (DCs) and innate lymphoid cells (e.g., NK cells) for early clearance of virus-infected cells (Shi et al., 2020). iii) The release of TAAs, DAMPs, PAMPs, pro-inflammatory cytokines, and chemokines by lysed tumor cells and innate immune cells can promote antigen presentation and antigen-specific adaptive immune responses (Kanerva et al., 2013; Saha et al., 2016). iv) Oncolytic viruses can promote the recruitment of tumor-infiltrating lymphocytes into tumor sites, making the immunosuppressive microenvironment "hot" and suitable for other immunotherapies (Gujar et al., 2018).

Studies on the use of natural oncolytic viruses in cancer treatment began to decline in the 1970s due to insufficient data to control viral pathogenicity. With the development of modern genetic engineering and a better understanding of the structure and functions of viral genes, non-pathogenic, genetically engineered viruses have led to the advancement of oncolytic virus technology by making various changes in the viral genome (Fukuhara et al., 2016). In addition, factors such as the limited oncolytic effect seen in studies, dose-related toxicities, inhibition of viral replication by many cellular factors such as interferon release from healthy cells or protein kinase activation led these viruses to be reprogrammed to make them more cancer-specific and safer (Balachandran and Barber, 2004; Cattaneo et al., 2008). Over time, together with the biotechnological initiatives, many advances were made to increase the oncolytic effect of viruses. These can be listed as redesigning viral envelope or capsid proteins to redirect the virus through the receptors on the tumor cell surface, deactivating viral genes that counteract cellular responses, or adding additional structural genes to the viral genome that encode proteins that increase the killing potential of uninfected tumor cells (Russell, 2002).

Among the viruses used for oncolytic purposes, Newcastle disease virus, Vesicular Stomatitis virus, Parvovirus, Coxsackievirus, Reovirus, Sindbis virus, Adenovirus, Vaccinia virus, Herpes Simplex virus can be counted (Parato et al., 2005; Huang et al., 2012; Atherton and Lichty, 2013; Goshima et al., 2014). In 1991, a mutated herpes simplex virus was inoculated intraneoplastically to treat malignant brain tumors in humans, and tumor growth inhibition was observed (Martuza et al., 1991). However, many Herpesvirus vectors were developed to examine their effects on tumors (Varghese and Rabkin, 2002).

Some recently completed clinical phase studies for oncolytic viruses are shown in Table 1. The developed strain Pexa-Vec (pexastimogene devacirepvec, JX-594) belongs to the oncolytic and immunotherapeutic vaccinia virus designed to destroy cancer cells by viral lysis and granulocyte-macrophage colony-stimulating factor

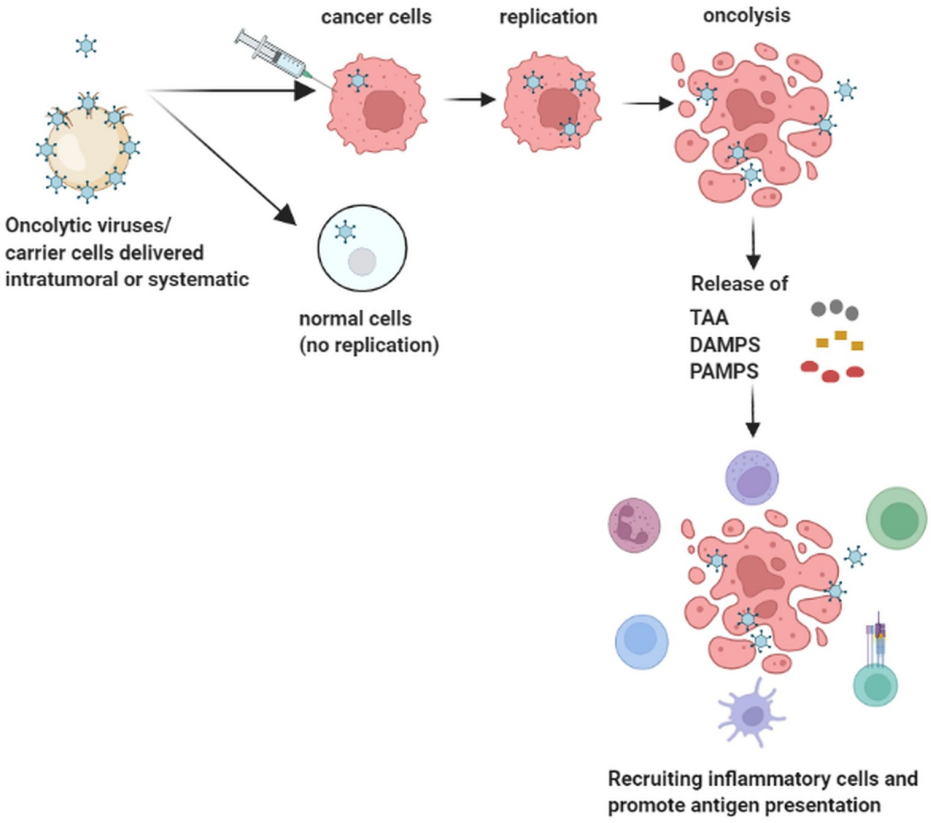

Figure 1: General mechanism of oncolytic viruses. Oncolytic viruses replicate in tumor cells leading to oncolysis, which in turn lead to the release of tumor-associated (TAAs), cell-derived damage-associated molecular patterns (DAMPs), and viral pathogen-associated molecular patterns (PAMPs) and recruiting of inflammatory cells.

(GM-CSF). Phase 1 and phase 2 studies were done in patients with both intratumoral and intravenous administration, alone or combined with other treatments (Parato et al., 2012; Cripe et al., 2015). In patients with malignant pleural mesothelioma, the replication-restricted oncolytic herpes simplex virus HSV1716 was administered intrapleurally, and the application was well tolerated in phase 1 and phase 2 studies (Danson et al., 2020).

Measles virus (MV-NIS) was used in phase 1 multiple myeloma treatment study in humans. It is selectively oncolytic and targets tumor cells through CD46, a membrane regulator of complement activation, which is known to be over expressed in many human malignancies (Dispenzieri et al., 2017). A phase 1 study was done by applying the improved adenovirus NSC-CRAd-S-pk7 strain to people diagnosed with malignant glioma in 2021. The study reported that treatment-related deaths were not observed, and the application was safe (Fares et al., 2021). Carcinoembryonic antigen, a marker peptide for the Measles virus, was developed to be expressed by the virus (MV CEA virus) for real-time monitoring of viral gene expression in tumors in the clinical setting and was inoculated to patients with ovarian cancer as part of a phase 1 study (Galanis et al., 2010).

In addition, MV-NIS recombinant created by adding the sodium-iodine symporter gene to Measles virus was administered intrapleurally to patients with malignant pleural mesothelioma, and its long-term potential therapeutic effects were observed (Peikert et al., 2017). A phase 1 study evaluated the maximum tolerable dose of oncolytic adenovirus ICOVIR-5 in patients with malignant melanoma (García et al., 2019). In humans with glioblastoma, oncolytic parvovirus H-1 (H-1PV) was administered within the scope of phase 1 and phase 2 studies and its cytotoxic and oncosuppressive effects were observed (Geletneky et al., 2012). In patients with malignant glioma, adenovirus DNX-2401 (Delta-24-RGD) was found to be a tumor-selective and competent replication-capable oncolytic agent (Lang et al., 2018).

Approved oncolytic viruses for cancer treatment

In humans, four oncoviruses, namely, Rigvir (picornavirus), Oncorine (adenovirus), Imlygic (herpes simplex virus, HSV-1), and DELYTACT (HSV-1), were approved in 2004, 2005, 2015, and 2021, respectively (Table 2).

Rigvir

Riga virus, inartificial Enteric Cytopathogenic Human Orphan type 7 (ECHO-7) picornavirus, has been approved to treat melanoma in Latvia, Georgia, and Armenia so far (Doniņa et al., 2015). Although it has gained regulatory approval, few articles described its

Table 1: Current clinical phase studies on oncolytic viruses.

Virus (Recombinant)	Family	Type of cancer	Reference
Measles virus (MV-CEA virus)	*Paramyxoviridae*	Ovarian tumor	Galanis et al. (2010)
Parvovirus (H-1PV)	*Parvoviridae*	Glioma	Geletneky et al. (2012)
Vaccinia virus (JX-594)	*Poxviridae*	Solid tumors	Cripe et al. (2015)
Herpes simplex virus (OncoVEXGM-CSF)	*Herpesviridae*	Malignant melanoma, gastrointestinal cancers, cutaneous masses	Hu et al. (2006)
Adenovirus (ONCOS-102)	*Adenoviridae*	Solid tumors	Ranki et al. (2016)
Herpes simplex virus (HSV1716)	*Herpesviridae*	Brain tumor	Streby et al. (2017)
Measles virus (MV-NIS)	*Herpesviridae*	Malignant pleural mesothelioma	Peikert et al. (2017)
Measles virus (Edmonston)	*Paramyxoviridae*	Multiple myeloma	Dispenzieri et al. (2017)
Adenovirus (CG0070)	*Adenoviridae*	Bladder tumor	Packiam et al. (2018)
Adenovirus (DNX-2401)	*Adenoviridae*	Malignant glioma	Lang et al. (2018)
Vaccinia virus (GL-ONC1)	*Poxviridae*	Peritoneal carcinomatosis	Lauer et al. (2018)
Adenovirus (ICOVIR-5)	*Adenoviridae*	Malignant melanoma	García et al. (2019)
Adenovirus (Ad5-DS)	*Adenoviridae*	Pancreas tumor	Lee et al. (2020)
Herpesvirus (HSV1716)	*Herpesviridae*	Malignant pleural mesothelioma	Danson et al. (2020)
Adenovirus (NSC-CRAd-S-pk7)	*Adenoviridae*	Malignant glioma	Fares et al. (2021)

biological characteristics and efficacy when used to treat malignant tumors.

Oncocrine

Oncocrine, adenovirus serotype 5, is the first recombinant developed oncovirus approved in China to treat patients with head and neck cancer (Alberts et al., 2016; Liang, 2018; Wei et al., 2018). Oncocrine is an attenuated serotype 5 adenoviral vector with a deletion in viral E1B-55k and four deletions in viral E3. Oncorine plus chemotherapy-treated head and neck cancer patients (78.8%) have a significantly higher response rate compared with chemotherapy-treated head and neck cancer patients (39.6%) (Cao et al., 2020).

Talimogene laherparepvec (T-Vec)

Talimogene laherparepvec (T-Vec) or Imlygic was approved by the United States Food and Drug Administration (FDA) in 2015 for the treatment of melanoma (Andtbacka et al., 2015). T-Vec is a recombinant human HSV1 with deleted ICP34.5 (neurovirulence factor) and attenuated ICP47 (Immun-evasions proteins) (Liu et al., 2003) that replicates almost exclusively in tumor cells. In tumor cells, the function of the cellular proteins eIF2α and Beclin-1 are impaired; thus, the ICP34.5 is not required to compensate for their antiviral functions. In non-cancer cells, replication of T-Vec is impaired by the absence of ICP34.5 (Aita et al., 1999; Liang et al., 1999; Farassati et al., 2001; Mohr, 2005).

An additional genetic modification of T-Vec is the insertion of the human granulocyte-macrophage colony-stimulating factor (hGM-CSF) gene, which is involved in the proliferation and differentiation of granulocyte and macrophage progenitor cells and is approved as a drug in the USA under the name Leukine® (Kaufman et al., 2014). The combination of T-VEC and PD-1 inhibitor pembrolizumab can have better efficacy and fewer side effects at the same time (Andtbacka et al., 2015).

DELYTACT® (teserpaturev/G47Δ)

The DELYTACT® (teserpaturev/G47Δ) is a genetically engineered oncolytic HSV-1 developed with triple mutations within the viral genome (Deletion of ICP34.5, ICP6, and α47 genes). The G47Δ (Delytact/Teserpaturev) has a strong induction of antitumor immunity, and it has been shown to kill cancer stem cells derived from human glioblastoma efficiently (Fukuhara et al., 2016). Moreover, in June 2021, G47Δ was approved to treat malignant gliomas in Japan (Harrington et al., 2019; Sugawara et al., 2021).

Oncolytic virotherapy in veterinary medicine

The traditional methods used for the treatment of cancer in pet animals are mainly surgery, chemotherapy, radiation, and hyperthermia. Advanced cancer patients often have a poor prognosis. Many cancer types seen in cats and dogs are similar to humans in many aspects, such as histological appearance, biological behavior, genetic tumoral structure, risk factors, pathological mechanism, and treatment response (Pinho et al., 2012). Although there are many ongoing clinical phase studies of oncolytic viruses in humans, clinical studies in cats and dogs are very limited (Demissie and Abda, 2020) (Table 3).

In a study in 2005, the possibility of cross-species replication of human adenovirus type 5 (Ad5) in canine cells was explored. As a result of the study, the canine models were suggested for preclinical analysis of recombinant adenovirus agents designed for human virotherapy (Ternovoi et al., 2005). In 2002, with the demonstration that Measles virus Edmonston-B strain could infect Myeloma cells in mice (Peng et al., 2001), an *in-vitro* study was performed to investigate whether the lymphoid tissue in dogs with lymphoma could cause apoptosis by Measles virus and Distemper virus, which

Table 2: Approved oncolytic viruses in humans.

Oncovirus	Virus	References
Rigvir	- Enteric Cytopathogenic Human Orphan type 7 (ECHO-7) picornavirus - Approved in Latvia, Georgia, and Armenia for treatment of melanoma	Alberts et al. (2016)
Oncorine	- Adenovirus serotype 5 - Deleted for viral E1B-55K and with four deletions in viral E3) - Approved in China for treatment of head and neck cancer	Wei et al. (2018)
Imlygic	- HSV-1 (deletion of ICP34.5 and ICP47; encoding two copies of human GMCSF) - Approved in the United States and Europe for treatment Metastatic melanoma	Raman et al. (2019)
DELYTACT	- HSV-1 (Triple mutation (Deletion of ICP34.5, ICP6, and α47 genes)) - Approved in Japan for treatment of malignant glioma or any primary brain cancer	Sugawara et al. (2021)

Table 3: Clinical studies on oncolytic virotherapy in cats and dogs.

Virus (Recombinant)	Family	Disease	Animal	Reference
Canarypoxvirus (ALVAC) Vaccinia virus (NYVAC)	*Poxviridae*	Fibrosarcoma	Cats	Jourdier et al. (2003)
Adenovirus (AdCD40L)	*Adenoviridae*	Malignant melanoma	Dogs	Westberg et al. (2013)
Newcastle disease virus (Lasota)	*Paramyxoviridae*	Cutaneous lymphoma	Dogs	Sanchez. et al. (2014)
Vesicular stomatitis virus (VSV-IFNb-NIS)	*Rhabdoviridae*	Anal adenosarcoma, multiple myeloma lymphoma	Dogs	Naik et al. (2018)
Myxoma virus (MYXVΔserp2)	*Poxviridae*	Soft tissue sarcoma	Dogs	MacNeill et al. (2018)
Herpes simplex virus (M032)	*Herpesviridae*	Glioma	Dogs	Chambers et al. (2021)
Herpes simplex virus (M032)	*Herpesviridae*	Glioma	Dogs	Omar et al. (2021)

belong to the same family (Suter et al., 2005).

Canarypoxvirus (ALVAC) and vaccinia virus (NYVAC) recombinants were administered intratumorally in cats with fibrosarcoma, and it was demonstrated a decrease in tumor recurrence rates from 61% in control animals to 39 and 28% in domestic cats receiving NYVAC or ALVAC, respectively, in addition to conventional therapy (Jourdier et al., 2003). Due to the limited *in-vivo* replication of human adenoviruses in animals, conditional replicative adenoviruses (CRAds) targeting osteosarcoma cells in dogs were developed and administered to healthy dogs and no toxicity was reported (Smith et al., 2006). To evaluate the efficacy of the oncolytic vaccinia virus strain GLV-1h68 as a therapeutic agent for treating mammary tumors in dogs, when administered to mice, the tumor size was significantly reduced with tumor growth restriction (Gentschev et al., 2009). In dogs, the effects of the oncolytic vaccinia virus GLV-1h109 strain on soft tissue sarcomas and prostate carcinomas were studied *in-vitro* (Patil et al., 2012).

The activities of reoviruses in mast cell tumors in dogs were investigated *in-vitro*; these viruses may have significant therapeutic potential in oncolytic virotherapy in the future (Hwang et al., 2013). Different Vaccina virus recombinants such as STSA-1 for soft tissue sarcoma, CHAS for melanoma, D-17 for osteosarcoma, and DT08/40 for prostate carcinoma developed against many types of cancer in dogs (Gentschev et al., 2013). While *in-vitro* studies on oncolytic viruses in cats and dogs continue, clinical studies on the oncolytic effect of viruses in dogs started in 2013. adenovirus AdCD40L was administered intratumorally to dogs with malignant melanoma, and the application was safe and effective with mild side effects after treatment (Westberg et al., 2013).

The Lasota strain of the Newcastle disease virus was administered intravenously and intratumorally to dogs with cutaneous lymphoma. Although new lesions were not observed in four-week follow-up, complete flattening and a decrease in the diameter of all lesions were observed (Sanchez. et al., 2014). Cytopathic effects of Semliki Forest virus strain VA7-EGFP on osteosarcoma cells in Beagle dogs were reported. In addition, a single dose of intravenous viral strain infusion was administered to two female dogs, and no side effects were reported (Autio et al., 2015). In another similar study, healthy Beagle dogs were safely injected with vaccinia virus TG6002 intravenously (Béguin et al., 2021).

A comprehensive study evaluating the intravenous administration of oncolytic virotherapy in animals was done in 2018. Accordingly, it was emphasized that both the application was safe after intravenous administration of the vesicular stomatitis virus VSV-IFNb-NIS to dogs diagnosed with anal adenosarcoma, multiple myeloma, and lymphoma lesions regressed (Naik et al., 2018). Similarly, the developed Myxoma virus strain MYXVΔserp2 was found safe after intratumor administration in dogs with soft tissue sarcoma (Mac-

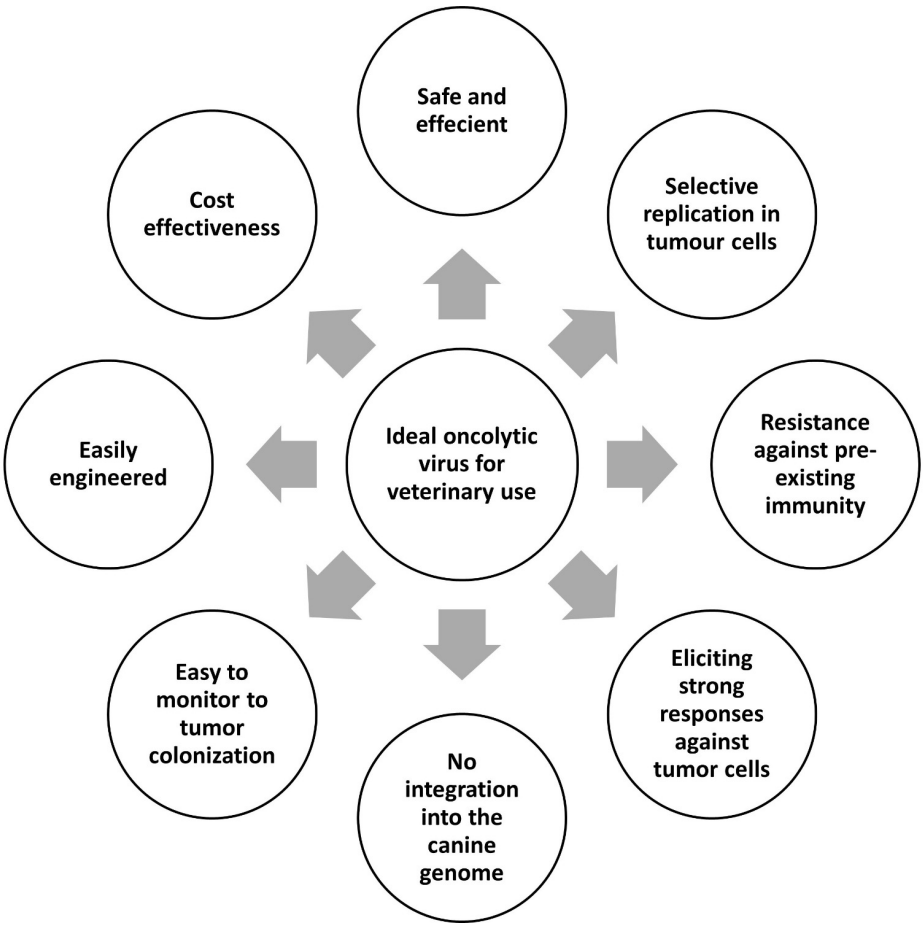

Figure 2: Ideal oncolytic viruses for veterinary use (Patil et al., 2012).

Neill et al., 2018). More recently, an oncolytic herpes simplex virus M032 was administered intratumorally in dogs with glioma, and 83% tumor-specific immune responses were observed, including interferon signaling, lymphoid and myeloid cell activation, and T and B cell activation (Chambers et al., 2021). In another recent study in 2021, herpes simplex virus strain M032 was inoculated intracranially to dogs with glioma, and the application did not have any harmful effects, and the oncolytic virotherapy with surgery could prolong the survival time (Omar et al., 2021).

Challenges and opportunities of oncolytic viruses in animals

The properties of the ideal oncolytic virus for canines are summarized by Patil and colleagues in 2012 (Figure 2). Although several oncolytic viruses provided promising results in preclinical trials, it is unlikely that the viruses will possess all the criteria of an 'ideal' oncolytic agent. Despite promising results of some oncolytic viruses, several limitations hinder the efficacy of oncolytic virotherapy. The delivery challenges and the upregulation of checkpoints following oncolytic virotherapy also mediate resistance to oncolytic viruses by diminishing immune responses.

Additionally, the localization of receptors of viruses in the tight junctions, interferon responses, and the aberrant expression of genes involved in the cell cycle of the virus, including their infection and replication, reduce the efficacy of oncolytic viruses (Blackham et al., 2014; Goradel et al., 2022). Factors such as viruses having to cross the endothelial barrier to reach the target cells, abnormal lymphatic networks and vascular hyperpermeability in tumors, interstitial hypertension caused by the dense extracellular matrix of solid tumors, weaken viral infiltration. In addition, oncolytic viruses induce a strong immune response because of the interaction between themselves and antigen presenting cells (Zheng et al., 2019). The heterogeneity of the tumor population due to the high mutation potential and rapid proliferation of cancer cells contributes to poor virion uptake and poor viral spread during virotherapy administration (Hong and Yun, 2019).

To minimize these limitations, many challenges and solutions such as production of formulations based on cationic liposomes capable of encapsulating the virus to avoid antibodies, modifying host range, improving the therapeutic effect of other oncolytic viruses with polymer-based delivery system, enhancing viral replication and gene transfer, enhancing tumor-specific accumulations have been proposed (Davis and Fang, 2005; Hong and Yun, 2019).

Patil et al. (2012) reported that some vaccinia virus and adenovirus strains possess several criteria of an ideal oncovirus and show the most promising results in preclinical studies. Many of the treatment options used

in veterinary medicine resemble protocols used to treat human cancer patients. Combining of recombinant oncolytic viruses with conventional anti-cancer therapies like chemotherapy and radiotherapy might be a promising strategy to improve the efficacy of viral oncolysis. Some *in-vitro* and *in-vivo*, either preclinical or clinical trials have indicated that combining oncolytic viruses with radiotherapy might yield extra or synergistic antitumor effects (Wennier et al., 2012; Touchefeu et al., 2011). Radiotherapy enhanced the replication and oncolysis within irradiated tumors. For instance, combining oncolytic virotherapy with chemotherapy has had synergistic effects in dogs (Patil et al., 2012).

Conclusions

Oncolytic virotherapy has attracted attention in both human and veterinary medicine as a new treatment strategy for many types of cancer in recent years. Various recombinant virus strains have been developed, and their efficacy has been observed for many years with many preclinical and clinical studies. With studies in human medicine, oncolytic virotherapy drugs were developed, and their safety and therapeutic effect were approved by the FDA, e.g., Imlygic®. In addition, many ongoing studies have pointed out new oncolytic agents such as Reolysin® for human cancers. However, most studies with oncolytic virotherapy in veterinary medicine are at the preclinical stages.

There are no studies of clinical evaluation of the efficacy of oncolytic virotherapy against cancer in horses, livestock, and poultry. The limited *in-vivo* clinical studies in cats and dogs primarily aimed at evaluating the safety of virotherapy applications. Considering the recent biotechnological developments, oncolytic virotherapy is extremely promising against various types of cancer. Therefore, we believe that oncolytic virotherapy can be used as an effective treatment strategy in the future against many cancer types with poor prognosis in cats and dogs. However, more clinical studies are needed to evaluate treatment efficacy in veterinary medicine.

Article Information

Funding. This research received no funds.

Conflict of Interest. The authors have no conflict of interest to declare.

References

Adair, R.A., Roulstone, V., Scott, K.J., Morgan, R., Nuovo, G.J., Fuller, M., Beirne, D., West, E.J., Jennings, V.A., Rose, A., Kyula, J., Fraser, S., Dave, R., Anthoney, D.A., Merrick, A., Prestwich, R., Aldouri, A., Donnelly, O., Pandha, H., Coffey, M., Selby, P., Vile, R., Toogood, G., Harrington, K., Melcher, A.A., 2012. Cell carriage, delivery, and selective replication of an oncolytic virus in tumor in patients. Science Translational Medicine 4, 138ra77. 10.1126/scitranslmed.3003578.

Aita, V.M., Liang, X.H., Murty, V.V., Pincus, D.L., Yu, W., Cayanis, E., Kalachikov, S., Gilliam, T.C., Levine, B., 1999. Cloning and genomic organization of Beclin 1, a candidate tumor suppressor gene on chromosome 17q21. Genomics 59, 59–65. 10.1006/geno.1999.5851.

Alberts, P., Olmane, E., Brokāne, L., Krastiņa, Z., Romanovska, M., Kupčs, K., Isajevs, S., Proboka, G., Erdmanis, R., Nazarovs, J., Venskus, D., 2016. Long-term treatment with the oncolytic ECHO-7 virus Rigvir of a melanoma stage IV M1c patient, a small cell lung cancer stage IIIA patient, and a histiocytic sarcoma stage IV patient-three case reports. Acta Pathologica, Microbiologica, et Immunologica Scandinavica 124, 896–904. 10.1111/apm.12576.

Alemany, R., Balagué, C., Curiel, D.T., 2000. Replicative adenoviruses for cancer therapy. Nature Biotechnology 18, 723–727. 10.1038/77283.

Andtbacka, R.H.I., Kaufman, H.L., Collichio, F., Amatruda, T., Senzer, N., Chesney, J., Delman, K.A., Spitler, L.E., Puzanov, I., Agarwala, S.S., Milhem, M., Cranmer, L., Curti, B., Lewis, K., Ross, M., Guthrie, T., Linette, G.P., Daniels, G.A., Harrington, K., Middleton, M.R., Miller, W.H., Zager, J.S., Ye, Y., Yao, B., Li, A., Doleman, S., VanderWalde, A., Gansert, J., Coffin, R.S., 2015. Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. Journal of Clinical Oncology 33, 2780–2788. 10.1200/JCO.2014.58.3377.

Aptekman, P.M., Lewis, M.R., 1951. Evidence of resistance to tumor graft in early stages of induced oncolysis. Journal of Immunology 66, 361–364.

Asada, T., 1974. Treatment of human cancer with mumps virus. Cancer 34, 1907–1928. 10.1002/1097-0142(197412)34:6<1907::aid-cncr2820340609>3.0.co;2-4.

Atherton, M.J., Lichty, B.D., 2013. Evolution of oncolytic viruses: novel strategies for cancer treatment. Immunotherapy 5, 1191–1206. 10.2217/imt.13.123.

Autio, K.P.M., Ruotsalainen, J.J., Anttila, M.O., Niittykoski, M., Waris, M., Hemminki, A., Vähä-Koskela, M.J.V., Hinkkanen, A.E., 2015. Attenuated Semliki Forest virus for cancer treatment in dogs: Safety assessment in two laboratory beagles. BMC Veterinary Research 11, 170. 10.1186/s12917-015-0498-2.

Balachandran, S., Barber, G.N., 2004. Defective translational control facilitates vesicular stomatitis virus oncolysis. Cancer Cell 5, 51–65. 10.1016/s1535-6108(03)00330-1.

Blackham, A.U., Northrup, S.A., Willingham, M., Sirintrapun, J., Russell, G.B., Lyles, D.S., Stewart, J.H., 2014. Molecular determinants of susceptibility to oncolytic vesicular stomatitis virus in pancreatic adenocarcinoma. The Journal of Surgical Research 187, 412–426. 10.1016/j.jss.2013.10.032.

Béguin, J., Gantzer, M., Farine, I., Foloppe, J., Klonjkowski, B., Maurey, C., Quéméneur, , Erbs, P., 2021. Safety, biodistribution and viral shedding of oncolytic vaccinia virus TG6002 administered intravenously in healthy beagle dogs. Scientific Reports 11, 2209. 10.1038/s41598-021-81831-2.

Cao, G.D., He, X.B., Sun, Q., Chen, S., Wan, K., Xu, X., Feng, X., Li, P.P., Chen, B., Xiong, M.M., 2020. The oncolytic virus in cancer diagnosis and treatment. Frontiers in Oncology 10, 1786. 10.3389/fonc.2020.01786.

Cassel, W.A., Garrett, R.E., 1965. Newcastle disease virus as an antineoplastic agent. Cancer 18, 863–868. 10.1002/1097-0142(196507)18:7<863::AID-CNCR2820180714>3.0.CO;2-V.

Cattaneo, R., Miest, T., Shashkova, E.V., Barry, M.A., 2008. Reprogrammed viruses as cancer therapeutics: targeted, armed and shielded. Nature Reviews. Microbiology 6, 529–540. 10.1038/nrmicro1927.

Chambers, M.R., Foote, J.B., Bentley, R.T., Botta, D., Crossman, D.K., Manna, D.L.D., Estevez-Ordonez, D., Koehler, J.W., Langford, C.P., Miller, M.A., Markert, J.M., Olivier, A.K., Omar, N.B., Platt, S.R., Rissi, D.R., Shores, A., Sorjonen, D.C., Yang, E.S., Yanke, A.B., Gillespie, G.Y., 2021. Evaluation of immunologic parameters in canine glioma patients treated with an oncolytic herpes virus. Journal of Translational Genetics and Genomics 10.20517/jtgg.2021.31.

Cripe, T.P., Ngo, M.C., Geller, J.I., Louis, C.U., Currier, M.A., Racadio, J.M., Towbin, A.J., Rooney, C.M., Pelusio, A., Moon, A., Hwang, T.H., Burke, J.M., Bell, J.C., Kirn, D.H., Breitbach, C.J., 2015. Phase 1 study of intratumoral pexa-vec (JX-594), an oncolytic and immunotherapeutic vaccinia virus, in pediatric cancer patients. Molecular Therapy 23, 602–608. 10.1038/mt.2014.243.

Danson, S.J., Conner, J., Edwards, J.G., Blyth, K.G., Fisher, P.M., Muthana, M., Salawu, A., Taylor, F., Hodgkinson, E., Joyce, P., Roman, J., Simpson, K., Graham, A., Learmonth, K., Woll, P.J., 2020. Oncolytic herpesvirus therapy for mesothelioma - A phase I/IIa trial of intrapleural administration of HSV1716. Lung Cancer 150, 145–151. 10.1016/j.lungcan.2020.10.007.

Davis, J.J., Fang, B., 2005. Oncolytic virotherapy for cancer treatment: Challenges and solutions. The Journal of Gene Medicine 7, 1380–1389. 10.1002/jgm.800.

Demissie, T., Abda, S., 2020. Review on application of oncolytic virotherapy of cancer cells in veterinary medicine. Advances in Life Science and Technology 10.7176/ALST/79-04.

Dispenzieri, A., Tong, C., LaPlant, B., Lacy, M.Q., Laumann, K., Dingli, D., Zhou, Y., Federspiel, M.J., Gertz, M.A., Hayman, S., Buadi, F., O'Connor, M., Lowe, V.J., Peng, K.W., Russell, S.J., 2017. Phase I trial of systemic administration of Edmonston strain of measles virus genetically engineered to express the sodium iodide symporter in patients with recurrent or refractory multiple myeloma. Leukemia 31, 2791–2798. 10.1038/leu.2017.120.

Doniņa, S., Strēle, I., Proboka, G., Auziņš, J., Alberts, P., Jonsson, B., Venskus, D., Muceniece, A., 2015. Adapted ECHO-7 virus Rigvir immunotherapy (oncolytic virotherapy) prolongs survival in melanoma patients after surgical excision of the tumour in a retrospective study. Melanoma Research 25, 421–426. 10.1097/CMR.0000000000000180.

Farassati, F., Yang, A.D., Lee, P.W., 2001. Oncogenes in ras signalling pathway dictate host-cell permissiveness to herpes simplex virus 1. Nature Cell Biology 3, 745–750. 10.1038/35087061.

Fares, J., Ahmed, A.U., Ulasov, I.V., Sonabend, A.M., Miska, J., Lee-Chang, C., Balyasnikova, I.V., Chandler, J.P., Portnow, J., Tate, M.C., Kumthekar, P., Lukas, R.V., Grimm, S.A., Adams, A.K., Hébert, C.D., Strong, T.V., Amidei, C., Arrieta, V.A., Zannikou, M., Horbinski, C., Zhang, H., Burdett, K.B., Curiel, D.T., Sachdev, S., Aboody, K.S., Stupp, R., Lesniak, M.S., 2021. Neural stem cell delivery of an oncolytic adenovirus in newly diagnosed malignant glioma: A first-in-human, phase 1, dose-escalation trial. The Lancet Oncology 22, 1103–1114. 10.1016/S1470-2045(21)00245-X.

Fukuhara, H., Ino, Y., Todo, T., 2016. Oncolytic virus therapy: A new era of cancer treatment at dawn. Cancer Science 107, 1373–1379. 10.1111/cas.13027.

Galanis, E., Hartmann, L.C., Cliby, W.A., Long, H.J., Peethambaram, P.P., Barrette, B.A., Kaur, J.S., Haluska, P.J., Aderca, I., Zollman, P.J., Sloan, J.A., Keeney, G., Atherton, P.J., Podratz, K.C., Dowdy, S.C., Stanhope, C.R., Wilson, T.O., Federspiel, M.J., Peng, K.W., Russell, S.J., 2010. Phase I trial of intraperitoneal administration of an oncolytic measles virus strain engineered to express carcinoembryonic antigen for recurrent ovarian cancer. Cancer Research 70, 875–882. 10.1158/0008-5472.CAN-09-2762.

García, M., Moreno, R., Gil-Martin, M., Cascallò, M., de Olza, M.O., Cuadra, C., Piulats, J.M., Navarro, V., Domenech, M., Alemany, R., Salazar, R., 2019. A phase 1 trial of oncolytic adenovirus ICOVIR-5 administered intravenously to cutaneous and uveal melanoma patients. Human Gene Therapy 30, 352–364. 10.1089/hum.2018.107.

Geletneky, K., Huesing, J., Rommelaere, J., Schlehofer, J.R., Leuchs, B., Dahm, M., Krebs, O., von Knebel Doeberitz, M., Huber, B., Hajda, J., 2012. Phase i/IIa study of intratumoral/intracerebral or intravenous/intracerebral administration of Parvovirus H-1 (ParvOryx) in patients with progressive primary or recurrent glioblastoma multiforme: ParvOryx01 protocol. BMC Cancer 12, 99. 10.1186/1471-2407-12-99.

Gentschev, I., Patil, S.S., Adelfinger, M., Weibel, S., Geissinger, U., Frentzen, A., Chen, N.G., Yu, Y.A., Zhang, Q., Ogilvie, G., Szalay, A.A., 2013. Characterization and evaluation of a new oncolytic vaccinia virus strain LIVP6.1.1 for canine cancer therapy. Bioengineered 4, 84–89. 10.4161/bioe.22462.

Gentschev, I., Stritzker, J., Hofmann, E., Weibel, S., Yu, Y.A., Chen, N., Zhang, Q., Bullerdiek, J., Nolte, I., Szalay, A.A., 2009. Use of an oncolytic vaccinia virus for the treatment of canine breast cancer in nude mice: Preclinical development of a therapeutic agent. Cancer Gene Therapy 16, 320–328. 10.1038/cgt.2008.87.

Goradel, N.H., Alizadeh, A., Hosseinzadeh, S., Taghipour, M., Ghesmati, Z., Arashkia, A., Negahdari, B., 2022. Oncolytic virotherapy as promising immunotherapy against cancer: Mechanisms of resistance to oncolytic viruses. Future Oncology 18, 245–259. 10.2217/fon-2021-0802.

Goshima, F., Esaki, S., Luo, C., Kamakura, M., Kimura, H., Nishiyama, Y., 2014. Oncolytic viral therapy with a combination of HF10, a herpes simplex virus type 1 variant and granulocyte-macrophage colony-stimulating factor for murine ovarian cancer. International Journal of Cancer 134, 2865–2877. 10.1002/ijc.28631.

Gujar, S., Pol, J.G., Kroemer, G., 2018. Heating it up: Oncolytic viruses make tumors 'hot' and suitable for checkpoint blockade immunotherapies. Oncoimmunology 7, e1442169. 10.1080/2162402X.2018.1442169.

Hammon, W.M., Yohn, D.S., Casto, B.C., Atchison, R.W., 1963. Oncolytic potentials of nonhuman viruses for human cancer. I. Effects of twenty-four viruses on human cancer cell lines. Journal of the National Cancer Institute 31, 329–345. URL: https://www.ncbi.nlm.nih.gov/pubmed/14046628.

Harrington, K., Freeman, D.J., Kelly, B., Harper, J., Soria, J.C., 2019. Optimizing oncolytic virotherapy in cancer treatment. Nature Reviews. Drug Discovery 18, 689–706. 10.1038/s41573-019-0029-0.

Hong, J., Yun, C.O., 2019. Overcoming the limitations of locally administered oncolytic virotherapy. BMC Biomedical Engineering 1, 17. 10.1186/s42490-019-0016-x.

Hu, J.C.C., Coffin, R.S., Davis, C.J., Graham, N.J., Groves, N., Guest, P.J., Harrington, K.J., James, N.D., Love, C.A., McNeish, I., Medley, L.C., Michael, A., Nutting, C.M., Pandha, H.S., Shorrock, C.A., Simpson, J., Steiner, J., Steven, N.M., Wright, D., Coombes, R.C., 2006. A phase i study of OncoVEXGM-CSF, a second-generation oncolytic herpes simplex virus expressing granulocyte macrophage colony-stimulating factor. Clinical Cancer Research 12, 6737–6747. 10.1158/1078-0432.CCR-06-0759.

Huang, P.Y., Guo, J.H., Hwang, L.H., 2012. Oncolytic Sindbis virus targets tumors defective in the interferon response and induces significant bystander antitumor immunity *in-vivo*. Molecular Therapy 20, 298–305. 10.1038/mt.2011.245.

Hwang, C.C., Umeki, S., Kubo, M., Hayashi, T., Shimoda, H., Mochizuki, M., Maeda, K., Baba, K., Hiraoka, H., Coffey, M., Okuda, M., Mizuno, T., 2013. Oncolytic reovirus in canine mast cell tumor. Plos One 8, e73555. 10.1371/journal.pone.0073555.

Jourdier, T.M., Moste, C., Bonnet, M.C., Delisle, F., Tafani, J.P., Devauchelle, P., Tartaglia, J., Moingeon, P., 2003. Local immunotherapy of spontaneous feline fibrosarcomas using recombinant poxviruses expressing interleukin 2 (IL2). Gene Therapy 10, 2126–2132. 10.1038/sj.gt.3302124.

Kanerva, A., Nokisalmi, P., Diaconu, I., Koski, A., Cerullo, V., Liikanen, I., Tähtinen, S., Oksanen, M., Heiskanen, R., Pesonen, S., Joensuu, T., Alanko, T., Partanen, K., Laasonen, L., Kairemo, K., Pesonen, S., Kangasniemi, L., Hemminki, A., 2013. Antiviral and antitumor T-cell immunity in patients treated with GM-CSF-coding oncolytic adenovirus. Clinical Cancer Research 19, 2734–2744. 10.1158/1078-0432.CCR-12-2546.

Kaufman, H.L., Ruby, C.E., Hughes, T., Slingluff, C.L., 2014. Current status of granulocyte-macrophage colony-stimulating factor in the immunotherapy of melanoma. Journal for Immunotherapy of Cancer 2, 11. 10.1186/2051-1426-2-11.

Kelly, E., Russell, S.J., 2007. History of oncolytic viruses: genesis to genetic engineering. Molecular Therapy 15, 651–659. 10.1038/sj.mt.6300108.

Koprowski, H., Love, R., Koprowska, I., 1957. Enhancement of susceptibility to viruses in neoplastic tissues. Texas Reports on Biology and Medicine 15, 559–576. URL: https://www.ncbi.nlm.nih.gov/pubmed/13495956.

Lang, F.F., Conrad, C., Gomez-Manzano, C., Yung, W.K.A., Sawaya, R., Weinberg, J.S., Prabhu, S.S., Rao, G., Fuller, G.N., Aldape, K.D., Gumin, J., Vence, L.M., Wistuba, I., Rodriguez-Canales, J., Villalobos, P.A., Dirven, C.M.F., Tejada, S., Valle, R.D., Alonso, M.M., Ewald, B., Peterkin, J.J., Tufaro, F., Fueyo, J., 2018. Phase I study of DNX-2401 (delta-24-RGD) oncolytic adenovirus: Replication and immunotherapeutic effects in recurrent malignant glioma. Journal of Clinical Oncology 36, 1419–1427. 10.1200/JCO.2017.75.8219.

Lauer, U.M., Schell, M., Beil, J., Berchtold, S., Koppenhöfer, U., Glatzle, J., Königsrainer, A., Möhle, R., Nann, D., Fend, F., Pfannenberg, C., Bitzer, M., Malek, N.P., 2018. Phase I study of oncolytic vaccinia virus GL-ONC1 in patients with peritoneal carcinomatosis. Clinical Cancer Research 24, 4388–4398. 10.1158/1078-0432.CCR-18-0244.

Lee, J.C., Shin, D.W., Park, H., Kim, J., Youn, Y., Kim, J.H., Kim, J., Hwang, J.H., 2020. Tolerability and safety of EUS-injected adenovirus-mediated double-suicide gene therapy with chemotherapy in locally advanced pancreatic cancer: A phase 1 trial. Gastrointestinal Endoscopy 92, 1044–1052.e1. 10.1016/j.gie.2020.02.012.

Levaditi, C., Nicolau, S., 1922. Sur le culture du virus vaccinal dans les neoplasmes epithelieux. CR Soc. Biol. 86, 928.

Liang, M., 2018. Oncorine, the world first oncolytic virus medicine and its update in China. Current Cancer Drug Targets 18, 171–176. 10.2174/1568009618666171129221503.

Liang, X.H., Jackson, S., Seaman, M., Brown, K., Kempkes, B., Hibshoosh, H., Levine, B., 1999. Induction of autophagy and inhibition of tumorigenesis by Beclin 1. Nature 402, 672–676. 10.1038/45257.

Lindenmann, J., 1963. Viral oncolysis with host survival. Experimental Biology and Medicine 113, 85–91. 10.3181/00379727-113-28284.

Lindenmann, J., 1970. Immunogenicity of oncolysates obtained from Ehrlich ascites tumors infected with vesicular stomatitis virus. Archiv fur die gesamte Virusforschung 31, 61–70. 10.1007/BF01241666.

Liu, B.L., Robinson, M., Han, Z.Q., Branston, R.H., English, C., Reay, P., McGrath, Y., Thomas, S.K., Thornton, M., Bullock, P., Love, C.A., Coffin, R.S., 2003. ICP34.5 deleted herpes simplex virus with enhanced oncolytic, immune stimulating, and anti-tumour properties. Gene Therapy 10, 292–303. 10.1038/sj.gt.3301885.

MacNeill, A.L., Weishaar, K.M., Séguin, B., Powers, B.E., 2018. Safety of an oncolytic Myxoma virus in dogs with soft tissue sarcoma. Viruses 10. 10.3390/v10080398.

Martuza, R.L., Malick, A., Markert, J.M., Ruffner, K.L., Coen, D.M., 1991. Experimental therapy of human glioma by means of a genetically engineered virus mutant. Science 252, 854–856. 10.1126/science.1851332.

Mohr, I., 2005. To replicate or not to replicate: Achieving selective oncolytic virus replication in cancer cells through translational control. Oncogene 24, 7697–7709. 10.1038/sj.onc.1209053.

Naik, S., Galyon, G.D., Jenks, N.J., Steele, M.B., Miller, A.C., Allstadt, S.D., Suksanpaisan, L., Peng, K.W., Federspiel, M.J., Russell, S.J., LeBlanc, A.K., 2018. Comparative oncology evaluation of intravenous recombinant oncolytic Vesicular Stomatitis virus therapy in spontaneous canine cancer. Molecular Cancer Therapeutics 17, 316–326. 10.1158/1535-7163.MCT-17-0432.

Omar, N.B., Bentley, R.T., Crossman, D.K., Foote, J.B., Koehler, J.W., Markert, J.M., Platt, S.R., Rissi, D.R., Shores, A., Sorjonen, D., Yanke, A.B., Gillespie, G.Y., Chambers, M.R., 2021. Safety and interim survival data after intracranial administration of M032, a genetically engineered oncolytic HSV-1 expressing IL-12, in pet dogs with sporadic gliomas. Neurosurgical Focus 50, E5. 10.3171/2020.11.FOCUS20844.

Packiam, V.T., Lamm, D.L., Barocas, D.A., Trainer, A., Fand, B., Davis, R.L., Clark, W., Kroeger, M., Dumbadze, I., Chamie, K., Kader, A.K., Curran, D., Gutheil, J., Kuan, A., Yeung, A.W., Steinberg, G.D., 2018. An open label, single-arm, phase II multicenter study of the safety and efficacy

of CG0070 oncolytic vector regimen in patients with BCG-unresponsive non-muscle-invasive bladder cancer: Interim results. Urologic Oncology 36, 440–447. 10.1016/j.urolonc.2017.07.005.

Parato, K.A., Breitbach, C.J., Le Boeuf, F., Wang, J., Storbeck, C., Ilkow, C., Diallo, J.S., Falls, T., Burns, J., Garcia, V., Kanji, F., Evgin, L., Hu, K., Paradis, F., Knowles, S., Hwang, T.H., Vanderhyden, B.C., Auer, R., Kirn, D.H., Bell, J.C., 2012. The oncolytic poxvirus JX-594 selectively replicates in and destroys cancer cells driven by genetic pathways commonly activated in cancers. Molecular Therapy 20, 749–758. 10.1038/mt.2011.276.

Parato, K.A., Senger, D., Forsyth, P.A.J., Bell, J.C., 2005. Recent progress in the battle between oncolytic viruses and tumours. Nature Reviews. Cancer 5, 965–976. 10.1038/nrc1750.

Patil, S.S., Gentschev, I., Adelfinger, M., Donat, U., Hess, M., Weibel, S., Nolte, I., Frentzen, A., Szalay, A.A., 2012. Virotherapy of canine tumors with oncolytic vaccinia virus GLV-1h109 expressing an anti-VEGF single-chain antibody. Plos One 7, e47472. 10.1371/journal.pone.0047472.

Peikert, T., Mandrekar, S., Mansfield, A., Van Keulen, V., Albelda, S., Aderca, S., Carlson, S., Dietz, A., Gustafson, M., Kratzke, R., Lowe, V., Maldonado, F., Molina, J., Patel, M., Roden, A., Sun, J., Tan, A., Tippmann-Peikert, M., Galanis, E., 2017. OA13.07 intrapleural modified vaccine strain Measles virus therapy for patients with malignant pleural mesothelioma. Journal of Thoracic Oncology 12, S296. 10.1016/j.jtho.2016.11.305.

Peng, K.W., Ahmann, G.J., Pham, L., Greipp, P.R., Cattaneo, R., Russell, S.J., 2001. Systemic therapy of myeloma xenografts by an attenuated Measles virus. Blood 98, 2002–2007. 10.1182/blood.v98.7.2002.

Pinho, S.S., Carvalho, S., Cabral, J., Reis, C.A., Gärtner, F., 2012. Canine tumors: A spontaneous animal model of human carcinogenesis. Translational Research 159, 165–172. 10.1016/j.trsl.2011.11.005.

Pol, J., Kroemer, G., Galluzzi, L., 2016. First oncolytic virus approved for melanoma immunotherapy. Oncoimmunology 5, e1115641. 10.1080/2162402X.2015.1115641.

Pond, A.R., Manuelidis, E.E., 1964. Oncolytic effect of Poliomyelitis virus on human epidermoid carcinoma (Hela tumor) heterologously transplanted to guinea pigs. The American Journal of Pathology 45, 233–249. URL: https://www.ncbi.nlm.nih.gov/pubmed/14202523.

Rahman, M.M., McFadden, G., 2020. Oncolytic virotherapy with Myxoma virus. Journal of Clinical Medicine 9. 10.3390/jcm9010171.

Raman, S.S., Hecht, J.R., Chan, E., 2019. Talimogene laherparepvec: Review of its mechanism of action and clinical efficacy and safety. Immunotherapy 11, 705–723. 10.2217/imt-2019-0033.

Ranki, T., Pesonen, S., Hemminki, A., Partanen, K., Kairemo, K., Alanko, T., Lundin, J., Linder, N., Turkki, R., Ristimäki, A., Jäger, E., Karbach, J., Wahle, C., Kankainen, M., Backman, C., von Euler, M., Haavisto, E., Hakonen, T., Heiskanen, R., Jaderberg, M., Juhila, J., Priha, P., Suoranta, L., Vassilev, L., Vuolanto, A., Joensuu, T., 2016. Phase I study with ONCOS-102 for the treatment of solid tumors - An evaluation of clinical response and exploratory analyses of immune markers. Journal for Immunotherapy of Cancer 4, 17. 10.1186/s40425-016-0121-5.

Rogers, S., Pfuderer, P., 1968. Use of viruses as carriers of added genetic information. Nature 219, 749–751. 10.1038/219749a0.

Russell, S.J., 2002. RNA viruses as virotherapy agents. Cancer Gene Therapy 9, 961–966. 10.1038/sj.cgt.7700535.

Saha, D., Wakimoto, H., Rabkin, S.D., 2016. Oncolytic herpes simplex virus interactions with the host immune system. Current Opinion in Virology 21, 26–34. 10.1016/j.coviro.2016.07.007.

Sanchez., D., Pelayo, R., Sarmiento, R.E., Medina, L.A., Cesarman-Maus, G.N., Nuñez, L., Carrillo, N., Paredes, J.d.J., Corona, H., Vadillo, E., 2014. *In-vitro* and *in-vivo* oncolytic activity of Lasota strain of Newcastle disease virus on a lymphoma B-cell line and a canine cutaneous T-cell lymphoma. Blood 124, 5504–5504. 10.1182/blood.V124.21.5504.5504.

Sauter, C., Lindenmann, J., Gerber, A., Martz, G., 1974. Acute myeloblastic leukemia: Replication of avian influenza virus in human myeloblasts and first attempt at clinical application, in: Mathé, G., Weiner, R., Allfrey, V.G., Allgöwer, M., Bauer, K.H., Berenblum, I., Bergel, F., Bernard, J., Bernhard, W., Blokhin, N.N., Bock, H.E., Bucalossi, P., Chaklin, A.V., Chorazy, M., et al. (Eds.), Investigation and stimulation of immunity in cancer patients. Springer Berlin Heidelberg, Berlin, Heidelberg. volume 47 of *Recent results in cancer research*, pp. 455–460. 10.1007/978-3-642-49284-6_66.

Sedmak, G.V., Taylor, M.W., Mealey, J., Chen, T.T., 1972. Oncolytic effect of bovine enterovirus on mouse and human tumours. Nature New Biology 238, 7–9. 10.1038/newbio238007a0.

Sharpless, G.R., Davies, M.C., Cox, H.R., 1950. Antagonistic action of certain neurotropic viruses toward a lymphoid tumor in chickens with resulting immunity. Experimental Biology and Medicine 73, 270–275. 10.3181/00379727-73-17651.

Shi, T., Song, X., Wang, Y., Liu, F., Wei, J., 2020. Combining oncolytic viruses with cancer immunotherapy: Establishing a new generation of cancer treatment. Frontiers in Immunology 11, 683. 10.3389/fimmu.2020.00683.

Smith, B.F., Curiel, D.T., Ternovoi, V.V., Borovjagin, A.V., Baker, H.J., Cox, N., Siegal, G.P., 2006. Administration of a conditionally replicative oncolytic canine adenovirus in normal dogs. Cancer Biotherapy & Radiopharmaceuticals 21, 601–606. 10.1089/cbr.2006.21.601.

Southam, C.M., 1960. Present status of oncolytic virus studies. Transactions of the New York Academy of Sciences 22, 657–673. 10.1111/j.2164-0947.1960.tb00739.x.

Southam, C.M., Moore, A.E., 1952. Clinical studies of viruses as antineoplastic agents, with particular reference to Egypt-101 virus. Cancer 5, 1025–1034. 10.1002/1097-0142(195209)5:5<1025::AID-CNCR2820050518>3.0.CO;2-Q.

Stojdl, D.F., Lichty, B., Knowles, S., Marius, R., Atkins, H., Sonenberg, N., Bell, J.C., 2000. Exploiting tumor-specific defects in the interferon pathway with a previously unknown oncolytic virus. Nature Medicine 6, 821–825. 10.1038/77558.

Streby, K.A., Geller, J.I., Currier, M.A., Warren, P.S., Racadio, J.M., Towbin, A.J., Vaughan, M.R., Triplet, M., Ott-Napier, K., Dishman, D.J., Backus, L.R., Stockman, B., Brunner, M., Simpson, K., Spavin, R., Conner, J., Cripe, T.P., 2017. Intratumoral injection of HSV1716, an oncolytic herpes virus, is

safe and shows evidence of immune response and viral replication in young cancer patients. Clinical Cancer Research 23, 3566–3574. 10.1158/1078-0432.CCR-16-2900.

Sugawara, K., Iwai, M., Ito, H., Tanaka, M., Seto, Y., Todo, T., 2021. Oncolytic herpes virus G47Δ works synergistically with CTLA-4 inhibition via dynamic intratumoral immune modulation. Molecular Therapy Oncolytics 22, 129–142. 10.1016/j.omto.2021.05.004.

Suter, S.E., Chein, M.B., von Messling, V., Yip, B., Cattaneo, R., Vernau, W., Madewell, B.R., London, C.A., 2005. *In-vitro* canine distemper virus infection of canine lymphoid cells: A prelude to oncolytic therapy for lymphoma. Clinical Cancer Research 11, 1579–1587. 10.1158/1078-0432.CCR-04-1944.

Ternovoi, V.V., Le, L.P., Belousova, N., Smith, B.F., Siegal, G.P., Curiel, D.T., 2005. Productive replication of human adenovirus type 5 in canine cells. Journal of Virology 79, 1308–1311. 10.1128/JVI.79.2.1308-1311.2005.

Touchefeu, Y., Vassaux, G., Harrington, K.J., 2011. Oncolytic viruses in radiation oncology. Radiotherapy and Oncology 99, 262–270. 10.1016/j.radonc.2011.05.078.

Varghese, S., Rabkin, S.D., 2002. Oncolytic herpes simplex virus vectors for cancer virotherapy. Cancer Gene Therapy 9, 967–978. 10.1038/sj.cgt.7700537.

Wei, D., Xu, J., Liu, X.Y., Chen, Z.N., Bian, H., 2018. Fighting cancer with viruses: Oncolytic virus therapy in China. Human Gene Therapy 29, 151–159. 10.1089/hum.2017.212.

Wennier, S.T., Liu, J., McFadden, G., 2012. Bugs and drugs: Oncolytic virotherapy in combination with chemotherapy. Current Pharmaceutical Biotechnology 13, 1817–1833. 10.2174/138920112800958850.

Westberg, S., Sadeghi, A., Svensson, E., Segall, T., Dimopoulou, M., Korsgren, O., Hemminki, A., Loskog, A.S.I., Tötterman, T.H., von Euler, H., 2013. Treatment efficacy and immune stimulation by AdCD40L gene therapy of spontaneous canine malignant melanoma. Journal of Immunotherapy 36, 350–358. 10.1097/CJI.0b013e31829d8a1b.

Wheelock, E.F., Dingle, J.H., 1964. Observations on the repeated administration of viruses to a patient with acute leukemia: A preliminary report. The New England Journal of Medicine 271, 645–651. 10.1056/NEJM196409242711302.

Zeng, J., Li, X., Sander, M., Zhang, H., Yan, G., Lin, Y., 2021. Oncolytic viro-immunotherapy: An emerging option in the treatment of gliomas. Frontiers in Immunology 12, 721830. 10.3389/fimmu.2021.721830.

Zheng, M., Huang, J., Tong, A., Yang, H., 2019. Oncolytic viruses for cancer therapy: Barriers and recent advances. Molecular Therapy Oncolytics 15, 234–247. 10.1016/j.omto.2019.10.007.