Journal of Experimental and Basic Medical Sciences 2022;3(2):158-172

Review

How Can a Virus Infection Treat Cancer? Relevance to Non-Human Viruses and the Use of Oncolytic Viruses

Pemra Nesil[1], Züleyha Pestil[2], Oytun Erbaş[1]

ABSTRACT

Oncolytic viruses (OVs) are effective in curing cancer as they selectively infect and kill malignant tissues while causing no harm to healthy tissues. Every virus has a unique cellular tropism that dictates which tissues are preferentially infected and what disease is caused. Numerous naturally occurring viruses have a preferred, but not exclusive, affinity for tumors and tumor cells. This likely has more to do with tumor biology than virus biology since most tumors have evolved to resist apoptosis and translational suppression, which are essential responses used by normal cells to limit a virus infection. This means that tumor biology rather than virus biology is more likely to be at play here. Infected cancer cells can be eliminated by OVs in a variety of ways, from direct virus-mediated cytotoxicity to diverse cytotoxic immune effector pathways. Viruses typically infect a small number of host species, and productive infection beyond the native host range only rarely occurs. A novel host species' infection may present as a unique disease. In this context, using non-human viruses in clinical treatment can raise some red flags. It may give the viruses a chance to adapt to the new host and spread to the recipient's family members, healthcare providers, or even the typical host species. Clearly, such environmental damage is not desired, particularly in light of the coronavirus disease 2019 pandemic. This review primarily attempts to evaluate the impact of the most prevalent OVs and their action mechanism and explore potential future consequences of non-human viruses on human cancer therapy.

Keywords: Cancer immunotherapy, engineered viruses, oncolytic virus, tumor receptors, virotherapy

Cancer immunotherapy is an approach that has been more popular in preclinical research and clinical application during the past decade.[1] In addition to surgery, radiation, chemotherapy, and targeted therapy, cancer immunotherapy is now considered to be the fifth cornerstone of cancer treatment.[2-4]

Traditional oncolytic therapy appears to immediately eliminate or destroy cancer cells, but it has a high probability of recurrent or seriously negative side effects.[5] To focus treatment with targeted therapy, it is necessary to identify known oncogenic sites. Immunotherapy, on the other hand, fights cancer by using certain parts of the body's immune system.[6,7] It aims to improve the host immune system's capacity to eliminate cancer cells and aid in tumor regression, the development of anti-tumor immunological memory, and eventually persistent responses.[8]

Immunotherapy has great potential to cure cancer with very low side effects and high tumor elimination expectations. It includes adaptive cell therapy, immune checkpoint blockade, cytokine therapy, cancer vaccines, and oncolytic virotherapy as one the most encouraging therapies.[9,10] Now it's supplied in the treatment of multiple cancers. The aim of the paper is to provide a conceptual theoretical framework based on the most popular oncolytic viruses (OVs) and non-human viruses' considerable position in this content.

VIRAL ONCOLYSIS: HISTORICAL PERSPECTIVE

There has long been interesting in developing an approach by which tumor cells can be selectively

[1]ERBAS Institute of Experimental Medicine, Illinois, USA & Gebze, Turkey
[2]Pendik Veterinary Control Institute, İstanbul, Turkey

Correspondence: Pemra Nesil. Institute of Experimental Medicine, 41470 Gebze-Kocaeli, Türkiye

E-mail: pemranesil@gmail.com

Cite this article as: Nesil P, Pestil Z, Erbaş O. How Can a Virus Infection Treat Cancer? Relevance to Non-Human Viruses and the Use of Oncolytic Viruses. JEB Med Sci 2022;3(2):158-172.

doi: 10.5606/jebms.2022.1023

Received : July 8, 2022
Accepted : July 14, 2022
Published online : September 12, 2022

and specifically targeted and destroyed. Surprisingly OVs viral strains can infect and kill malignant cells without harming normal cells while simultaneously stimülate the immune system and creating a system anti-tumor immunıty. Although viruses have been utilized as therapeutic agents in the form of vaccines since the late 1700s.[11] Their potential application as a cancer therapy was not explored until a series of earliest clinical reference reports dating back to the early 1900s. The first case was in 1904 in which a 42 years old woman with chronic myelogenous leukemia experienced a marked reduction in white blood cells during a flu-like illness.[12] Later, a range of other tumor types and viruses were involved in tentative oncolytic therapies, but because of the dreadful side effects, interest in OVs declined from the 1970s through the 1980s until the 1990s. In clinical studies, 22 patients with Hodgkin's disease were treated with a total of 35 sera or tissue extracts containing "the hepatitis virus.". These individuals had either infectious hepatitis, a self-limited picornavirus infection, or serum hepatitis, most likely caused by hepatitis B.[13] Flavivirus infections such as West Nile, Uganda, dengue, and yellow fever were highly common in the United States and elsewhere in 1952 and hence were among the first to be employed for OVs. Most patients had viremia and intra-tumoral viral multiplication, although tumor responses were uncommon. Immunocompromised individuals with leukemia or lymphoma were more likely to respond to medication, but they were also at a greater risk of fatal neurotoxicity. So, out of eight leukemia or lymphoma patients, five had severe encephalitis.[14,15]

Adenoidal-pharyngeal-conjunctival (APC, now known as an adenovirus) virus was discovered to be an antitumor agent in preclinical models in the 1950s. It quickly advanced to the point of care and was found to have fairly symptoms: most who received APC infrequently experienced pharyngeal or eye inflammation, were able of encephalitis, and, better yet, were quite alive after inoculation.[16] The development of genetic engineering in the 1990s made it possible to author viral genomes, and viral therapy has achieved a leap from laboratory to clinical.[17]

Four OVs have been authorized internationally till now. Professor Aina Muceniece led a team of Institute of Microbiology and Virology researchers to discover that human intestinal viruses may eliminate tumors in the 1960s in Latvia. To conduct the research Muceniece founded the Cancer Virotherapy Laboratory in 1965. Upon the analysis of 60 intestinal viruses, five were deemed the most effective in fighting cancer cells. One of them is the Riga virus (Rigvir). Extensive studies were carried out and permission was granted to use the virus in clinical practice but the process was delayed due to the shifting political climate. Rigvir is the first OV to be filed and approved. It was formally registered in Latvia in 2004. Rigvir is an OV of the *Picornaviridae* family, Enterovirus genus, enteric cytopathic human orphan (ECHO) virus group, type-7, which is not genetically changed but has been chosen and optimized for melanoma however it was never broadly adopted.[18] Encouragingly the adenovirus mutant H101 became the world's first OV drug approved for cancer treatment in 2005 in China to treat head and neck cancer.[19] An engineered herpes simplex virus (HSV)-1, named Talimogene laherparepvec (T-VEC) became the first OV approved by the Food and Drug Administration (FDA) in October 2015 for the intralesional treatment of melanoma.[20] At last, a modified herpes simplex virus was approved in Japan in 2021 for brain malignancies including glioblastoma.[21] Now the technologies of other forms of immunotherapy gaining ground and cancer despite all advances remains a major cause of mortality.

CHARACTERISTICS OF ONCOLYTIC VIRUSES AND CLINICAL TRIALS

Herpes Simplex Virus

Herpes simplex virus type 1 belongs to the alpha herpesvirus family, which also involves the varicella species. It is a DNA virus that includes a wide genome (152 kilobase/kb), 30 kb of which transmit genomes that are not obligated for the disease process. Upregulation of many receptors in cancer cells, like nectin-1 and the tumor necrosis factor (TNF) superfamily member herpesvirus entry mediator (HVEM), is necessary for oncolytic HSV infection of cancer cells.[22] HSV-1 replication materialized in the nucleus, but it is not mutagenic to its host.[23] The neurotoxicity of HSV can be significantly reduced by gene editing techniques that delete out or modify the HSV gene RL1, decreasing the production of the neurotoxic protein ICP34.5 (infected cell protein 34.5).[24] These characteristics make HSV-1 a promising option for the formation of OVs. HSV has quite a wide and adaptable genome. To enhance the anti-tumor impact, several foreign genes may be inserted, and the glycoprotein on the surface of HSV is either modified.[25] The essential to utilizing HSV for oncolytic therapy is genetically modified techniques, which involve removing the primary genes that enter

normal cells, multiply and flourish in healthy cells, and infect tumors selectively.

Table 1 lists a number of the mutant HSV strains that are currently in use as OVs.

Virus	Family	Nucleic acid	Modifications
Herpes Simplex Virus-1 (HSV-1)	*Herpesviridae*	Double Stranded DNA (dsDNA)	
Dlsptk			Deleted HSV thymidine kinase (HSVTK) gene at UL23
R3616			Deleted ICP34.5
HSV-1716			Deleted ICP34.5
G-207			Deleted ICP34.5 Inserted LacZ
G47Δ			Deleted ICP34.5, ICP47 and ICP6
HF10			UL43, UL49.5, UL55, UL56, LAT Loss of expression UL53, UL54 Overexpression
M032			Deleted ICP34.5 Inserted IL 12
T-VEC			Deleted ICP34.5 and ICP 47 Inserted hGM-CSF

Table 1. Some types of oncolytic herpes simplex virus.

1) The first type 1 HSV mutant, dlsptk, has a mutation in its UL23 gene that inhibits it from making the protein thymidine kinase, which can stop mouse gliomas from spreading.[26] Direct injection of dlsptk into developing human gliomas in the brains of athymic mice resulted in dose-dependent tumor cell killing, improved animal survival, and in some cases, total cure for cancer.[27] Increasing the dosage will have major side effects, including encephalitis.[28]

2) The R3616 strain of HSV-1(F) greatly increases its anti-tumor efficacy by knocking out two genes that express ICP34.5.[29] Technical studies have demonstrated that R3616 can enter tumor antigen-specific lymphocytes, destroy the original tumor, and limit distant metastasis and recurrence.[30] Clinical trials showed that R3616 reduced tumor size in immunodeficient mice implanted with glioma cells.[31]

3) HSV1716, a strain generated from the HSV-1 (17+) strain, double-deletes the neurotoxicity-determining gene RL1. Protein kinase R (PKR) phosphorylates eukaryotic initiation factor 2a (eIF2a), which prevents translation and triggers apoptosis in tumor cells as well as virus mortality.[32] HSV1716 can be employed in cancer cells with unregulated protein production because the ICP34.5-mediated dephosphorylation of eIF2a can enhance protein translation and prevent cell death.[33] An OV clinical study using HSV1716 for malignant pleural mesothelioma revealed that it was well-tolerated and has anticancer activity. In seven of 12 patients' tumor lesions, HSV proliferation and existence were consistently found. Within week eight, the patient's stable disease (SD) was reported by half of them.[34]

4) G207 was the first HSV to be tested in medical trials on cancer. The virus can now integrate only in cancerous cells thanks to the lacZ gene that was placed into the removed ICP34.5 locus. Via PKR, the knockdown mutant ICP34.5 causes the suppression of late viral genes, such as US11. G207 stimulates cytotoxic T cells and causes the patient to develop systemic anti-tumor immunity.[35] Human glioma cells were killed by G207 treatment in monolayer cultures, while nude mice with subcutaneous or intracerebral U-87MG gliomas were treated intratumorally to slow tumor development and/or extend life. Additionally, intracerebral injection of mice and HSV-sensitive non-human primates with G207 revealed that it was avirulent.[36] Intracranial gliomas implanted in mice were subjected to cellular effects of oncolytic G207 treatment, which demonstrated broad regions of viral infection and replication (plaques), lower growth indices, and increased apoptotic frequencies in infected parts of the lesions. This study discovered a considerable reduction in the size of blood vessels in the lesions in addition to the direct death of tumor cells, indicating that G207 had both tumoricidal and antiangiogenic effects.[37] Based on phase I/II study data recently published at Tokyo University Hospital and Tokyo University Institute of Medical Sciences (data cutoff date, November 27, 2014; survival confirmed to March 1, 2022); After a 2-year monitoring period following the last G47 treatment, 10 out of 13 patients had died. One patient who demonstrated partial remission (PR) endured G47 treatment for more than 11 years (as of March 1, 2022). This patient lives without experiencing any more recurrences and does not have any long-term unfavorable effects from G47, such as an autoimmune disease in the central nervous system, which was one of the apparently predicted side effects.[38]

5) The G47Δ strain of HSV, which was confined from the G207 strain, has genetic changes in the RL1 and ICP47 genes as well as an addition of the lacZ gene fragment into its ICP6 gene. This decrease in the large subunit of the ribonucleic acid reductase gene that it encodes causes the oncolytic HSV to be more actively replicated in cancer cells.[39] G47 was given intratumorally and repeatedly for up to six dosages. The main objective was 1-year survival rate following G47 start, which was 84.2% (95% confidence interval/CI), 60.4-96.6; 16 of 19). The experiment was discontinued early since the predetermined endpoint was fulfilled. In terms of secondary endpoints, the median overall survival after G47 commencement was 20.2 (16.8-23.6) months and 28.8 (20.1-37.5) months after the original operation. Fever (17 of 19)

was the most prevalent G47-related adverse event, followed by vomiting, nausea, lymphocytopenia, and leukopenia.[40]

6) The virus HF10 underwent spontaneous mutation without the addition of any foreign genes. The linear double-stranded DNA (dsDNA) HF10 genome contains 6,127 kb of naturally occurring deletion, 6,027 base pair (bp) of insertions, and frame-shift mutations at various nucleotide locations. The UL43, UL49.5, UL55, UL56, and latency-associated transcript (LAT) gene activity was lost as a result of these deletions and insertions, while UL53 and UL54 were overexpressed.[41] In the phase I clinical investigation, HF10 was inoculated intratumorally into cutaneous or subcutaneous spreading nodules of recurrent breast tumors to assess its safety and effectiveness at the Nagoya University Graduate School of Medicine, in Japan. No significant side effects were experienced by any of the patients despite good treatment compliance. Histologically, tumor mortality of 30 to 100% was seen along with tumor cell distortion. Unexpectedly, after the elimination of tumor cells, a wide spectrum of melting-like fibrosis was seen.[42.43] In Japan, after intratumoral injection of HF10 [1x105 plaque forming units/milliliter (pfu/mL) or 0.5 mL for 3 days], adverse effects, viral replication, and immune response were assessed. With considerable infiltration of the cluster of differentiation 4 (CD4+) or CD8+ cells in both patients, HF10 replicated efficiently and caused apoptosis of tumor cells. After receiving the injection, individuals had a cold temperature, but no other overt side effects.[44] From 2005 through 2009, eight male patients with aggressive pancreatic ductal carcinoma underwent a phase I clinical study at Nagoya University's School of Medicine in Japan. Without after-treatment side effects being noticed, all patients tolerated the therapy properly. The tumor marker carbohydrate antigen 19-9 (CA19-9) decreased in three cases. Three patients had complete remission as their therapy response, one patient had a limited response, and four individuals had advancing illnesses. With an average of 180 days, the survival period varied from 98 to 318 days.[45,46] Twenty-six patients with melanoma and other resistant and superficial cancers were involved in a phase I study to evaluate the safety of intratumoral (IT) delivered HF10. Eighteen of the 24 patients who got therapy experienced adverse events, six that were attributable to HF10. Chills (two patients), redness, edema, and discomfort at the injection site (one patient), lethargy (one patient), pruritus (one patient), and hypotension (one patient). After a single injection, one patient experienced ulceration of tumor sites at both injected and non-injected lesions, but healthy tissue did not show any ulcers.[47]

7) M032 is a c134.5 deleted HSV-1 virus that expresses human interleukin (IL)-12. The experimental effectiveness and safety of M002 were shown, however, if this virus was used in human clinical trials, there was a risk of an unfavorable immunological reaction to the murine IL-12 protein.[41] Scientists constructed the c134.5-deleted oncolytic HSV M032, which has the same structure as M002 but expresses the human IL-12, p35, and p40 subunits. A clinical study of M032 in patients with malignant gliomas is still being tested. Nonhuman primate (NHP) models were assessed following intracerebral injections of saline, 1106 pfu, or 1108 pfu of M032.[48]

8) Talimogene laherparepvec remove ICP34.5 area factor genes were merged with HSV genes encoding ICP34.5 and ICP47, as well as a number of cytokines, including granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-12, interferon alpha (IFN-α), TNF-alpha, and others. As a result, oncolytic HSV's anti-tumor immune function is improved, antigen-specific T lymphocytes' immunostimulatory capacity is increased, CD4+ T cell's negative immune regulation is decreased, and CD8+ T cells exhibit a particular anti-tumor impact.[49,50] The first OV authorized by the FDA for the treatment of melanoma was T-VEC, an HSV-1 virus that encodes GM-CSF.[51] T-VEC was utilized as an adjuvant medication following melanoma surgery in phase II clinical research. With or without T-VEC postoperatively, 150 postoperative patients with stage IIIB-IVM1a melanoma were split equally into two groups for the purpose of assessing the surgical risk of melanoma recurrence. After three years of monitoring, 17.1% of patients who received T-VEC treatment post-surgery experienced pathological complete remission (pCR) and elevated CD8+ in tumor lesions. Postoperative adjuvant therapy decreased total melanoma recurrence by 25% in the T-VEC arm when opposed to the surgery solo group.[52]

Adenoviruses

Adenovirus is an icosahedral capsid with a virion width ranging from 70 to 90 nanometers (nm). It is a naked (non-enveloped), double-stranded DNA virus with a linear genome of around 35 kb. Its enormous genome allows for the incorporation of lengthy DNA sequences, enabling several engineered changes. Both animals and humans are frequently infected with adenoviruses, which can spread by aerosols and making contact. Therefore, the vast

majority of people are seropositive for adenovirus exposure. Adenoviral infections can cause diseases in infants and vulnerable people even when they are asymptomatic in immunocompetent hosts.[53] The coxsackie-adenovirus receptor (CAR) allows adenovirus to get into the cell. When an adenovirus enters a cell, it travels to the nucleus and expresses adenovirus early genes (encoding E1A and E1B), which are required for viral replication. To enhance cell cycle entrance, E1A and E1B intentionally target the tumor suppressors p53 (a tumor suppressor gene that produces a protein that controls cell growth and proliferation) and retinoblastoma-associated protein (pRb). In normal cells, however, adenoviral E1A and E1B protein binding of host cell cycle regulators p53 and pRb culminate in death and virus elimination.[54,55] Adenovirus is an appealing vector for clinical testing due to its capacity to effectively decrease viral pathogenicity and encode big foreign transgenes. Human serotype 5 adenoviruses, a frequently used oncolytic adenovirus vector, is ineffective in infecting tumor cells because most tumor cells have poor or no CAR expression on their membrane.[56] As a result, some experiments insert RGD (a short peptide made up of the amino acids arginine) glycine, and aspartic acid, into the viral capsid fibers.[57] Antitumor adenovirus vectors with RGD are more able to actively target tumor cells because they can bind the highly expressed integrin αvβ3 receptors in cancerous tissue.[58] Adenovirus can be altered with usable targeting groups in addition to RGD. Examples include targeting CD46, which is elevated in colorectal and breast cancer[59], or desmoglein, which is highly expressed in a range of malignant epithelial tumors.[60] After showing that adenovirus can successfully reproduce in huge numbers in tumor cells, the researchers included a variety of foreign genes, such as TNF-related apoptosis-inducing ligand (TRAIL)[61] or adenoviral death protein (ADP)[62], into the genome of the oncolytic adenovirus vector. Another type of gene that has been used is the prodrug activator, whose expression encourages the transformation of nontoxic prodrugs into toxic compounds in the limited region of the tumor and also delivers these toxic substances to nearby non-infected tumor cells through gap junctions between tumor cells, improving the tumor suppressor effect.[63] For instance, viruses that can encode the herpes simplex virus type 1 thymidine kinase (HSV-tk)[64] or bacterial cytosine deaminase (CD).[65] These encoded proteins can help cancer areas convert prodrugs like acyclovir or 5-fluorocytosine into hazardous compounds, greatly increasing the anticancer effect of adenovirus.[66] Adenoviruses are able to immediately destroy tumor cells, but they can also create a lasting, particular anti-tumor immunological memory in the body, which is crucial for the body's long-term prognosis. However, adenovirus replication must continue in order to maintain this immunological response.[67] When adenoviruses in tumor cells are eliminated, the total viral population decreases, reducing the long-term therapeutic effect. Over the last ten years, research on oncolytic adenoviruses has shifted from optimizing the rapid destruction of cancer cells to increasing the immune response induced by viral oncolysis. This concept leads to the addition of additional immunomodulatory adenoviral vectors to oncolytic adenoviral vectors, such as GM-CSF, CD40 ligands, or IFN-1.[68]

Adenoviruses have two stages to their cell replication. Accordingly, early (E1-E4) and late (L1-L5) transcription units are organized into the adenoviral genome. The two primary isoforms, 12S and 13S, which are encoded by the early region 1A (E1A) and are necessary for early replication, are five distinct proteins.[69,70] While E1A 12S missing CR3, the E1A 13S protein has 289 amino acids and four conserved domains (CR1-CR4), allowing it to transactivate the other early transcription units E1B, E2, E3, and E4.[71] Adenoviruses with the E1 gene removed are thought to be replication-deficient and are employed in gene therapy or immunization as transport vectors. In oncolytic adenovirus treatment, replication-competent adenoviruses that are only capable of reproducing in cancer cells are known as conditionally replicating adenoviruses (CRAds).[72]

Table 2 lists several mutant adenovirus strains that have been identified and exploited as OVs.

Virus	Family	Nucleic acid	Modifications
Adenovirus	*Adenoviridae*	Stranded DNA (dsDNA)	
CRAd-Survivin-pk7			Inserted survivin and fiber protein(pk7)
Ad2xTyr			Synthetic fusion core E1A, E4 promoter
Telomelysin (OBP-301)			Inserted hTERT-E1A-IRES-E1B
DNX-2401			Inserted Δ24-RGD
VCN-01			Inserted PH20 hyaluronidase
Onyx-015			Deleted Type 2/5 chimaera,E1B
Colo-Ad1			Chimeric Ad11/3 group B complex

Table 2. Some mutants of oncolytic adenovirus

1) Tumor-specific promoters are distinguished by their capacity to increase the expression of particular genes that are essential for a malignant phenotype. Replication is limited to the proper cells when E1A-mediated viral proliferation is controlled by a tumor- or tissue-specific promoter.[73] Therefore, the E1A regulatory region of exogenous promoters is often inserted without any or with minor deletions, leaving the E1A enhancer/encapsidation intact as in CRAd-Survivin-pk7.[74] CRAd-Survivin-pk7 has a high affinity for heparan sulfate proteoglycans seen in tumors because a polylysine modification with a binding domain for heparan sulfate was integrated into the fiber protein (pk7).[74] It was also successful to limit adenoviral replication to particular tissues and tumor types. It was decided to employ the alpha-fetoprotein (AFP) promoter for hepatocellular carcinoma (HCC)[75] and the probasin promoter for prostate tissue in order to drive E1A and E1B, respectively.[76]

2) Ad2xTyr, an oncolytic adenovirus with replacements for the E1A gene promoter and the E4 promoter, was created using a synthetic fusion construct of the core promoter and enhancers of the human tyrosinase. Instead of normal fibroblasts and keratinocytes, Ad2xTyr demonstrated tumor selectivity towards melanoma cells.[77]

3) Telomelysin (OBP-301) is an oncolytic adenovirus in which the human telomerase reverse transcriptase (hTERT) promoter controls both E1A and E1B, which are connected by the internal ribosome entry site (IRES).[78] A single intratumoral injection resulted in a partial response in 56.7% of patients in an early phase I dosage progression study of 16 patients with solid tumors. Only adverse effects of grade 1/2 were found.[79] A phase I clinical research of locoregional administration of OBP-301 as monotherapy in patients with advanced malignancies, such as head and neck cancer or metastatic melanoma, was conducted in the United States to assess the safety of OBP301 in the treatment of cancer.[79] OBP-301 and radiotherapy are believed to work synergistically in both directions, according to a therapeutic strategy used at Okayama University Hospital.[80]

4) pRB interacts with members of the E2F transcription factor family in non-replicating cells to operate as a negative regulator and govern cell cycle progression.[81] An alteration to the adenovirus E1A CR2 in Delta-24 results in a loss of 24 base pairs, which precludes E1A from binding to pRB.[82] Due to its inability to proliferate, this virus cannot release E2F in healthy cells. E2F is no longer negatively controlled by pRB in tumor cells with mutant or dysregulated pRB, and this enables viral gene transcription and hence replication.[83] DNX-2401 (Delta-24-RGD) is the first AdDelta-24 derivative that has undergone clinical testing. has already finished four phases I studies, mostly for the treatment of gliomas. Progression-free survival of three years was achieved in three of the 25 patients, five of whom lived longer than three years following therapy and three of whom had tumors that shrank dramatically.[84] Forty-nine patients with recurrent glioblastoma participated in a phase II study of DNX-2401 combined with the anti-PD-1 antibody pembrolizumab. The outcomes with the oncolytic adenovirus were positive, with median overall survival of 12.5 months and survival at 18 months of 20.2% compared to the median overall survival of 7.2 months with monotherapies of temozolomide.[85] In a phase I study, ICOVIR-5 (Ad5-E2F-Delta-24-RGD) was given systemically intravenously to patients with melanoma, and it was well tolerated. Twelve individuals did not have tumor shrinkage, but four of them had metastatic skin or liver lesions, demonstrating that ICOVIR-5, when given intravenously, can target and identify metastatic cancer cells.[86]

5) VCN-01 (Ad5-E2F-Delta-24-RGD-PH20) produces hyaluronidase (PH20), which promotes viral intratumoral dissemination.[87] It is now being evaluated in many clinical studies for advanced pancreatic cancer and head and neck squamous cell carcinoma in conjunction with chemotherapy or immune checkpoint inhibitors. Administration of VCN-01 was well tolerated in a retinoblastoma study and showed an anti-tumor effect in retinoblastoma vitreous seeds.[88]

6) The first oncolytic adenovirus used in clinical studies to treat head and neck cancer was ONYX-015 (dl1520).[89] A stop codon and an E1B55K (the viral E1B55K product, which binds and introduces ubiquitination substrates.[90]) deletion characterize ONYX-015, a chimeric adenovirus (Ad5/2) that prevents the translation of the protein. Tumor destruction at the injection site was seen in 5 out of 22 patients, despite the fact that there was no objective response seen. The Oncorine (also named H101, a genetically modified adenovirus) phase I clinical studies were started in China in 2000. Three out of fifteen patients experienced impressive tumor reduction in addition to an acceptable safety profile. In patients with squamous cell carcinoma of the head and neck (SCCHN), Oncorine had a higher positive response rate (79%) when combined with chemotherapy

than when chemotherapy was used alone (40%). The State Food and Drug Administration (SFDA) of China authorized it as the first commercially available oncolytic in 2005 on the basis of this research.[91]

7) The first OV produced by this unique approach was enadenotucirev (Colo-Ad1), a complex Ad3/Ad11p hybrid virus.[92] Colo-Ad1, a new adenoviral vector that was specifically chosen to replicate solely in colon cancer cells, was developed by controlled evolution from a pool of several serotypes of species B to F.[93] There was three phases I trials. One of them compared the effectiveness of intratumoral vs intravenous administration on 17 patients with solid tumors. Eleven out of 12 patients who received intravenous infusions and two out of five patients who had intratumoral injections had viral DNA found in tumor samples. No significant adverse effects associated with the therapy were recorded, and both approaches were well tolerated. Patients with rectal cancer who will receive enadenotucirev in combination with radiotherapy and chemotherapy are being sought for two other phases I trial with enadenotucirev that are currently recruiting individuals with colon cancer, head, and neck cancer, or other epithelial tumors for combination therapy with enadenotucirev and nivolumab (PD-1 inhibitor) or individuals with these conditions (capecitabine).[94] NG-350A, which expresses the CD40 antibody, and NG-641, which expresses the bispecific T-cell engager (BiTE), fibroblast activation protein (FAP)/CD3 chemokine ligands nine and 10 (CXCL9 and CXCL10), as well as IFN-α, are two variants of enadenotucirev that are currently being studied in phase I clinical.[73]

Reovirus

The *Reoviridae* family of viruses, including the nonenveloped, double-stranded RNA virus known as reovirus (RV), has identified hosts in a variety of organisms, including fungi, plants, fish, reptiles, birds, and mammalians.[94,95] The double-stranded RNA is classified into three sizes: large (L1-3), medium (M1-3), and small (S1-3).[96] The filamentous attachment protein, known as σ1, is used by reoviruses to bind to target tissues. All reovirus serotypes sigma 1 protein (σ1) -the reovirus cell attachment protein- interacts with junctional adhesion molecule (JAM)-A, a crucial element of intercellular tight junctions. The kind of carbohydrate that the σ1 protein attaches to on the surface of cells varies by serotype.[97] Reovirus internalization is mediated by beta 1 integrin after binding to JAM-A and carbohydrates, most likely via clathrin-dependent endocytosis. The discharge of viral progeny and RV replication both depend on the Ras (term derived from the "rat sarcoma virus," which acts as an on/off switch for chemicals that indicate cell proliferation.) signaling system, according to data.[98] Reovirus also activates the Ras/RalGEF (Ras-like (Ral) small GTPases)/p38 pathway, which causes cell death.[99] As a result, Ras-overexpressing tumor cells are the focus of RV exclusively. Reovirus serotypes type one Lang, type two Jones, and type three Abney and Dearing have all been discovered.[100] The most effective oncolytic RNA virus for treating cancer is Reolysin (also known as Pelareorep), serotype 3 RV, which has successfully completed a number of clinical trials as a mono or in combination with other treatments.[101]

Vaccinia virus

The vaccinia virus (VV) is an enclosed virus with double-stranded DNA that belongs to the family *Poxviridae*'s Orthopoxvirus genus.[102] The 190 kb-long VV genome, which has a diameter of 70 to 100 nm, enables the insertion and strong expression of big foreign genes.[103,104] One of the most popular strategies to improve the selective replication and lytic capabilities of VV is the deletion of viral thymidine kinase (TK), vaccinia type I IFN-α binding protein (B18R), or vaccinia growth factor (VGF).[105] Vaccinia virus demonstrated natural tumor selectivity as an oncolytic drug and the potential for systemic delivery.[106] A Wyeth strain VV-derived OV called JX-594 is equipped with GM-CSF and beta-galactosidase but lacks the TK gene.[107] The selectivity of vaccinia to tumors was markedly improved by the deletion of the viral TK gene.[108]

The prototype poxvirus vaccinia virus, which may cause transitory macropinocytosis, endocytic internalization, and infection, all vitally depend on the presence of exposed phosphatidylserine in the viral membrane, suggesting that vaccinia virus mimics apoptosis to penetrate the host cells.[109]

Studies have shown that JX-594 delivered through intravenous injection constantly promotes infection inside tumors but does not affect healthy tissue.[110,111]. The JX-594 was demonstrated to be well tolerated following intravenous infusion in phase I/II clinical studies and to cause no dose-limiting toxicities; the maximum tolerated dosage was not attained.[110-113] However, a phase III trial involving patients with advanced HCC who had not had prior systemic treatment and JX-594 failed to demonstrate a survival advantage.[114] There are still numerous problems that need to be resolved before JX-594 may be used, such as in conjunction with other immunotherapies.

Newcastle Disease Virus

The Newcastle disease virus (NDV) belongs to the family *Paramyxoviridae* and is an enclosed virus containing negative-sense single-stranded RNA.[115] Its genome is about 15 kb long and expresses at least eight proteins: nucleocapsid (N), phosphoprotein (P), matrix protein (M), fusion protein (F), hemagglutinin-neuraminidase protein (HN), large polymerase protein (L), and two other proteins, V and W. Its diameter range from 100 to 500.[116]. The HN protein, which engages with sialic acid receptors located on the host cells to attach tumor cells, then fuses with the engaged F protein to join the virus to the host cell membrane. Consequently, the virus' genome penetrates the cytoplasm of the host.[117,118] The insertion location of foreign genes between P/M is advised since the genomes have a considerable capacity (>5 kb) for gene transfer. Numerous clinical trials have shown that NDV, an OV, has a very excellent safety record for cancer patients and demonstrates considerable antitumor activity.[119]

Measles Virus

The measles virus (MeV) belongs to the genus Morbillivirus in the *Paramyxoviridae* family and is an enveloped virus containing negative-sense single-stranded RNA. Its genome is approximately 16 kb in length and has six genes that code for eight proteins, including two auxiliary proteins and six anti-genome configurations. Its results of various from 100 to 200 nm (V and C).[120] Three receptors, CD46, the signaling lymphocyte activation molecule (SLAM)/CD150, and poliovirus-receptor-like-4 (PVRL4), are used by MeV to connect with host cells.[121] Measles virus is inherently selective for infecting tumor cells since SLAM/CD150 is often overexpressed on many hematological malignancies whereas CD46 is constitutively overexpressed on many tumor cells.[122] However, CD46 is not a tumor-selective receptor because it is also expressed basally in normal cells.[121] MeV is a viable OV option due to its good potency, which includes the lack of dose-limiting toxicities and spontaneous oncotropism.[123]

EFFECTS OF ONCOLYTIC VIRUSES ON ANTITUMOR MECHANISMS

The oncolytic viruses that are now being used in therapy, as mentioned above and shown in Figure 1, naturally prefer cell surface proteins that are expressed abnormally in cancer cells. After connecting and infiltrating tumor cells (some viruses in order to promote virus entrance or infection, exposed phosphatidylserine on the viral surface interacts either wholly or partly with phosphatidylserine receptors,[124] OVs can use a variety of lytic mechanisms, some of which may or may not be connected to the actual level of viral replication inside the target cells, to destroy the infected cancer cells.

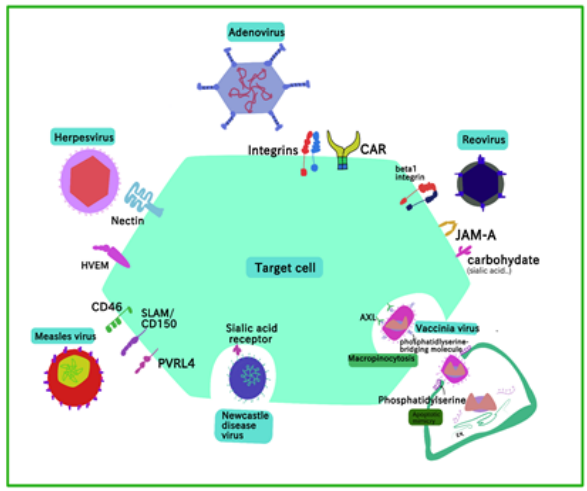

Figure 1. Cell surface receptors, which are typically overexpressed on cancer cells, are just one of the entry points that oncolytic viruses employ to infiltrate host cells. Some viruses enter cells by endocytosis, which is facilitated by cell fusion and syncytia forming. Through phosphatidylserine acquisition and incorporation into the viral membrane, a virus mimics apoptosis. (CAR; coxsackievirus-adenovirus receptor, HVEM; herpesvirus entry mediator, JAM-A; junctional adhesion molecule-A, PVRL4; poliovirus-receptor-like-4, SLAM; signaling lymphocytic activation molecule, AXL; phosphatidylserine receptor.)

The precise processes of viral oncolysis are still poorly known, vary greatly amongst viruses, and can even vary significantly among various target cancer cell types.[125] Multiple pathways are considered to be involved in how OVs mediate anticancer activity:

(a) specific viral replication inside cancer cells that results in primary cytolytic effects (a process also referred to as oncolysis)[126-128];

(b) indirect cell death (e.g., apoptosis-like vs. necrosis-like) impacts on both healthy and infected cancer cells, as well as related endothelial cells in the tumor-associated vasculature, which result in decreased angiogenesis[129];

(c) the infiltration of immune cells that have been triggered into the tumor microenvironment (TME).[130,131]

However, the way in which the OV, TME, and host immune system act overall, the form and kind of cancer cells and these processes vary greatly from virus to virus. The majority of viruses interfere with the mechanisms that the host activates to cause cell death after viral infection. Virus-encoded peptides are sometimes known to target various cell death processes as stimulants or inhibitors.[132,133]

Immunogenic cell death (ICD) is commonly used to characterize cancer cell death that can reveal cancer cell antigens to resident immune cells in the TME and is generally evaluated in cultured cells by extracellular release of normally intracellular signals or cell release of intracellular agents. Oncolytic viruses have the benefit of being able to activate multi-mechanistic cell death cascades inside the tumor site. Immunogenic cell death is thought to be important in promoting innate anti-tumor immunity.[134,135]

The discharge of tumor-associated antigens (TAAs), damage-associated molecular patterns (DAMPs) such as ATP, high mobility group box 1 protein (HMGB1), heat shock protein (HSP), ecto-calreticulin and proinflammatory cytokines, OV-derived pathogen-associated molecular patterns (PAMPs), and increased expression of numerous inflammatory cytokines occur when the copying of OVs in cancer cells provokes ICD. These events then activate both innate and adaptive immune reactions. These PAMPs and DAMPs are detected by pattern recognition receptors (PRRs) on immune cells, including stimulator of IFN genes (STING), toll-like receptor (TLR) adaptor molecule 1, and TLR3,[136,137] generating a proinflammatory milieu by promoting the expression of proinflammatory cytokines, such as type I IFNs, IL-1, IL-6, IL-12, TNF-α, GM-CSF, and chemokines, such as CCL2, CCL3, CCL5, and CXCL10, which causes immunologically "cool" tumors to turn into "hot" tumors.[138]

First, chemokines that are locally released, such as CCL3 also known as macrophage inflammatory protein 1-alpha (MIP-1α) and CXCL10, attract the first cell mediators, including neutrophils and macrophages, to the site of infection.[139] These cytokines are also implicated in the generation of efficient antitumor reactions.[140]

The effects of OVs on tumor cells are illustrated in Figure 2 below.

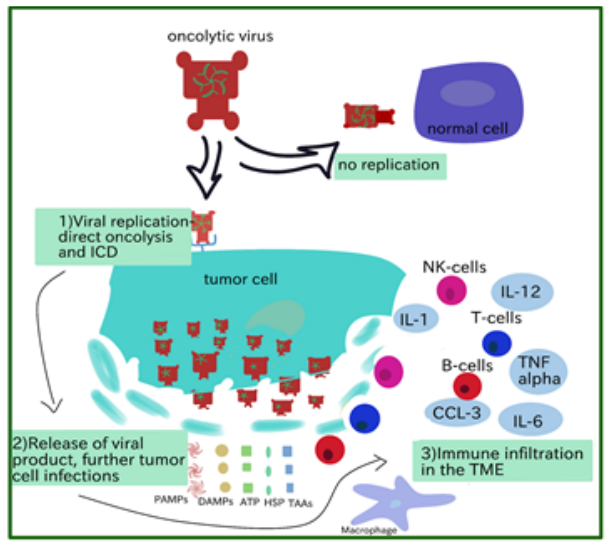

Figure 2. The mechanism that oncolytic viruses function in cancer cells. When OVs infect normal, non-cancerous cells, they are unable to proliferate, leaving the cells undamaged. The viruses may successfully reproduce once they enter cancer cells, producing additional viral products and eventually inducing immunogenic cell death (ICD). After cell lysis, the tumor microenvironment is exposed to the viral products, pathogen-associated molecular patterns (PAMP), damage-associated molecular patterns (DAMP), heat shock protein (HSP), (adenosine triphosphate) ATP, and tumor-associated antigens (TAA), tumor microenvironment (TME). The virus transmission is continued by the discharged virus product, which further infects the functional tumor cells. Immune cells are drawn to the TME by immunogenic molecules delivered there.

OVERCOMING PATHOGENICITY: ANIMAL VIRUSES IN HUMAN THERAPY

It was once thought that a non-human animal virus would preserve oncolytic activity even in a host not typically sensitive to that specific virus in an effort to manage virulence and avoid the issue of fast virus elimination caused by or before antiviral immunity. Moore's[141] early research using the human disease Russian Far East encephalitis virus, which showed efficacy against a mouse tumor, supported this notion. A panel of human cancer cell lines was used in early work to carry out a high-throughput search for non-human animal viruses with oncolytic activity. In this instance, adaptation through *in vitro* transmission was still seen to be favorable since the original strain was either non-pathogenic or

non-infectious to people. Therefore, it was assumed that the viruses would not acquire any extra cell tropism in the lack of normal cells beyond that for which they were already equipped.[142]

Twenty-seven non-human virus species were identified that are in (pre) clinical development, mainly as oncolytic agents.[143] In a thorough examination of the six viruses, Yohn et al.[144] assessed the oncolytic potential by determining if the viruses could prevent the growth of heterotransplanted human cancers or cause the tumors that had already grown to necrose and return. Two of these herpes viruses-equine rhinopneumonitis and infectious bovine rhinotracheitis- which are not pathogenic to humans have been found to be oncolytic for one or perhaps more human cancers.

After the relatively underwhelming clinical results of a virus known as the "MP" virus (after the authors Molomut and Padnos), which is now known to be a strain of lymphocytic choriomeningitis virus, arenaviruses have not been widely used as oncolytic. The MP virus, as is typical for virotherapy, caused substantial tumor regressions in rat models and, in some cases, increased survival by more than 60% compared to controls[144]; however, it had a little therapeutic effect in human trials and failed to extend survival.[145]

A non-human virus may develop changes that might boost its pathogenicity in a host that is not typically vulnerable, but these adaptations have not received nearly as much notice as viral changes that are useful for targeting. Nowadays, with the effect of the coronavirus disease 2019 pandemic, it would be regarded as highly perilous to introduce wild-type viruses into a typically gullible host whose populations have not developed any viral resistance. In fact, the feline panleukopenia virus, which was employed in virotherapy, developed on its own to be transmissible to dogs, leading to the pandemic canine parvovirus that is thought to have infected more than 80% of wild and domestic dogs between 1978 and 1979 worldwide.[146]

In conclusion, cancer immunotherapy is a sort of cancer treatment that activates our own immune system to fight cancer. Oncolytic viral treatment is one of the most popular forms of cancer immunotherapy. The majority of cancer cells lack the typical antiviral defense systems, making them prone to viral infections. Cancer cells are modified healthy cells. A modified virus is administered to patients during oncolytic viral treatment, allowing the virus to infect cancer cells. These modified viruses move to the tumor side and create substances that draw nearby immune cells, and they are specifically instructed not to infect healthy cells since their capacity to infect cells has been reduced. The viruses can cause infected cancer cells to explode, releasing more of the previously hidden cancer antigens to the surrounding area and drawing additional immune cells to destroy the surviving cancer cells. The fact that humans lack the same protection as the viral reservoir host makes new infections so hazardous. And since there are so many, it's presently impossible to forecast when or which particular viruses will spread, but we do know the circumstances under which it may happen. More information on how to stop the non-human virus from spreading conditions would help us to establish a greater degree of accuracy on this matter. Further work needs to be done to identify realistic methods that simplify application while obtaining tolerable risk levels, a list might be employed. To safeguard mankind against potential virus-induced pandemics, it will be required to establish such methods and identify solutions that support research that might provide oncolytic viral treatment.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Taefehshokr S, Parhizkar A, Hayati S, Mousapour M, Mahmoudpour A, Eleid L, et al. Cancer immunotherapy: Challenges and limitations. Pathol Res Pract. 2022 Jan;229:153723.
2. Yürekli A, Erbaş O. Cancer and Immunosuppression. JEB Med Sci 2021;2:116-21.
3. Çağlar O, Özyılmaz E. Effect of Quercetin in Hepatocellular Carcinoma. Research & Reviews in Health Sciences, 2020;311-28.
4. Tekin E, Çağlar Ö, Özyılmaz E, Erbaş O. Multiple Myeloma Treatment. JEB Med Sci 2021;2:206-10.
5. Zhang S, Rabkin SD. The discovery and development of oncolytic viruses: are they the future of cancer immunotherapy? Expert Opin Drug Discov. 2021 Apr;16:391-410.
6. Atasoy O, Cini N, Erdogan MA, Yaprak G, Erbas O. Radiotherapy and high bilirubin may be metformin like effect on lung cancer via possible AMPK pathway modulation. Bratisl Lek Listy. 2022;123:100-9.
7. Erbaş O, Solmaz V, Aksoy D, Yavaşoğlu A, Sağcan M,

Taşkıran D. Cholecalciferol (vitamin D3) improves cognitive dysfunction and reduces inflammation in a rat fatty liver model of metabolic syndrome. Life Sci. 2014 May 17;103:68-72.

8. Kelly E, Russell SJ. History of oncolytic viruses: genesis to genetic engineering. Mol Ther. 2007 Apr;15:651-9.
9. Topal E, Aydemir K, Çağlar Ö, Arda B, Kayabaşı O, Yıldız M, Özyılmaz E, Erbaş O. Fatty Liver Disease: Diagnosis and Treatment. JEB Med Sci 2021;2:343-57.
10. Erbaş O, Akseki HS, Aktuğ H, Taşkıran D. Low-grade chronic inflammation induces behavioral stereotypy in rats. Metab Brain Dis. 2015 Jun;30:739-46.
11. Pavli A, Maltezou HC. Travel vaccines throughout history. Travel Med Infect Dis. 2022 Mar-Apr;46:102278.
12. Dock, G (1904). The influence of complicating diseases upon leukemia. Am J Med Sci 127:563–92.
13. Hoster HA, Zanes RP Jr, Von Haam E. Studies in Hodgkin's syndrome; the association of viral hepatitis and Hodgkin's disease; a preliminary report. Cancer Res. 1949 Aug;9:473-80.
14. Southam CM, Moore AE. Clinical studies of viruses as antineoplastic agents with particular reference to Egypt 101 virus. Cancer. 1952 Sep;5:1025-34.
15. Moore AE. Effects of viruses on tumors. Annu Rev Microbiol. 1954;8:393-410.
16. Huebner RJ, Bell JA, Rowe WP, Ward TG, Suskınd RG, Hartley JW, et al. Studies of adenoidal-pharyngeal-conjunctival vaccines in volunteers. J Am Med Assoc. 1955 Nov 5;159:986-9.
17. Choi AH, O'Leary MP, Fong Y, Chen NG. From Benchtop to Bedside: A Review of Oncolytic Virotherapy. Biomedicines. 2016 Aug 2;4:18.
18. Doniņa S, Strēle I, Proboka G, Auziņš J, Alberts P, Jonsson B, et al. Adapted ECHO-7 virus Rigvir immunotherapy (oncolytic virotherapy) prolongs survival in melanoma patients after surgical excision of the tumour in a retrospective study. Melanoma Res. 2015 Oct;25:421-6.
19. Liang M. Clinical development of oncolytic viruses in China. Curr Pharm Biotechnol. 2012 Jul;13:1852-7.
20. Garnock-Jones KP. Talimogene Laherparepvec: A Review in Unresectable Metastatic Melanoma. BioDrugs. 2016 Oct;30:461-8.
21. Sugawara K, Iwai M, Ito H, Tanaka M, Seto Y, Todo T. Oncolytic herpes virus G47Δ works synergistically with CTLA-4 inhibition via dynamic intratumoral immune modulation. Mol Ther Oncolytics. 2021 May 19;22:129-42.
22. Yu Z, Adusumilli PS, Eisenberg DP, Darr E, Ghossein RA, Li S, et al. Nectin-1 expression by squamous cell carcinoma is a predictor of herpes oncolytic sensitivity. Mol Ther. 2007 Jan;15:103-13.
23. Li Z, Bi Y, Xiao H, Sun L, Ren Y, Li Y, et al. CRISPR-Cas9 system-driven site-specific selection pressure on Herpes simplex virus genomes. Virus Res. 2018 Jan 15;244:286-95.
24. McKie EA, MacLean AR, Lewis AD, Cruickshank G, Rampling R, Barnett SC, et al. Selective in vitro replication of herpes simplex virus type 1 (HSV-1) ICP34.5 null mutants in primary human CNS tumours--evaluation of a potentially effective clinical therapy. Br J Cancer. 1996 Sep;74:745-52.
25. Thomas S, Kuncheria L, Roulstone V, Kyula JN, Mansfield D, Bommareddy PK, et al. Development of a new fusion-enhanced oncolytic immunotherapy platform based on herpes simplex virus type 1. J Immunother Cancer. 2019 Aug 10;7:214.
26. Martuza RL, Malick A, Markert JM, Ruffner KL, Coen DM. Experimental therapy of human glioma by means of a genetically engineered virus mutant. Science. 1991 May 10;252:854-6.
27. Kwon, Hee-Chung. "Strategies and Clinical Trials of Oncolytic Herpesvirus and Adenovirus in Treatment of Cancer." Proceedings of the Microbiological Society of Korea Conference. The Microbiological Society of Korea, 2005.
28. Markert JM, Malick A, Coen DM, Martuza RL. Reduction and elimination of encephalitis in an experimental glioma therapy model with attenuated herpes simplex mutants that retain susceptibility to acyclovir. Neurosurgery. 1993 Apr;32:597-603.
29. Pyles RB, Warnick RE, Chalk CL, Szanti BE, Parysek LM. A novel multiply-mutated HSV-1 strain for the treatment of human brain tumors. Hum Gene Ther. 1997 Mar 20;8:533-44.
30. Dambach MJ, Trecki J, Martin N, Markovitz NS. Oncolytic viruses derived from the gamma34.5-deleted herpes simplex virus recombinant R3616 encode a truncated UL3 protein. Mol Ther. 2006 May;13:891-8.
31. Markert, James M., et al. "Reduction and elimination of encephalitis in an experimental glioma therapy model with attenuated herpes simplex mutants that retain susceptibility to acyclovir." Neurosurgery 32.4:597-603.
32. MacKie RM, Stewart B, Brown SM. Intralesional injection of herpes simplex virus 1716 in metastatic melanoma. Lancet. 2001 Feb 17;357:525-6.
33. Kwan A, Winder N, Atkinson E, Al-Janabi H, Allen RJ, Hughes R, etal. Macrophages Mediate the Antitumor Effects of the Oncolytic Virus HSV1716 in Mammary Tumors. Mol Cancer Ther. 2021 Mar;20:589-601.
34. Danson SJ, Conner J, Edwards JG, Blyth KG, Fisher PM, Muthana M, et al. Oncolytic herpesvirus therapy for mesothelioma - A phase I/IIa trial of intrapleural administration of HSV1716. Lung Cancer. 2020 Dec;150:145-51.
35. Friedman GK, Johnston JM, Bag AK, Bernstock JD, Li R, Aban I, Kachurak K, et al. Oncolytic HSV-1 G207 Immunovirotherapy for Pediatric High-Grade Gliomas. N Engl J Med. 2021 Apr 29;384:1613-22.
36. Mineta T, Rabkin SD, Yazaki T, Hunter WD, Martuza RL. Attenuated multi-mutated herpes simplex virus-1 for the treatment of malignant gliomas. Nat Med. 1995 Sep;1:938-43.
37. Huszthy PC, Immervoll H, Wang J, Goplen D, Miletic H, Eide GE, et al. Cellular effects of oncolytic viral therapy on the glioblastoma microenvironment. Gene Ther. 2010 Feb;17:202-16.
38. Todo T, Ino Y, Ohtsu H, Shibahara J, Tanaka M. A phase I/II study of triple-mutated oncolytic herpes virus G47Δ

in patients with progressive glioblastoma. Nat Commun. 2022 Jul 21;13:4119.

39. Saha D, Martuza RL, Rabkin SD. Macrophage Polarization Contributes to Glioblastoma Eradication by Combination Immunovirotherapy and Immune Checkpoint Blockade. Cancer Cell. 2017 Aug 14;32:253-67.
40. Todo, Tomoki, et al. "Intratumoral oncolytic herpes virus G47Δ for residual or recurrent glioblastoma: a phase 2 trial." Nature medicine: 1-10.
41. Eissa IR, Naoe Y, Bustos-Villalobos I, Ichinose T, Tanaka M, Zhiwen W, et al. Genomic Signature of the Natural Oncolytic Herpes Simplex Virus HF10 and Its Therapeutic Role in Preclinical and Clinical Trials. Front Oncol. 2017 Jul 14;7:149.
42. Nakao A, Kimata H, Imai T, Kikumori T, Teshigahara O, Nagasaka T, et al. Intratumoral injection of herpes simplex virus HF10 in recurrent breast cancer. Ann Oncol. 2004 Jun;15:988-9.
43. Kimata H, Imai T, Kikumori T, Teshigahara O, Nagasaka T, Goshima F, et al. Pilot study of oncolytic viral therapy using mutant herpes simplex virus (HF10) against recurrent metastatic breast cancer. Ann Surg Oncol. 2006 Aug;13:1078-84.
44. Fujimoto Y, Mizuno T, Sugiura S, Goshima F, Kohno S, Nakashima T, et al. Intratumoral injection of herpes simplex virus HF10 in recurrent head and neck squamous cell carcinoma. Acta Otolaryngol. 2006 Oct;126:1115-7.
45. Kasuya H, Kodera Y, Nakao A, Yamamura K, Gewen T, Zhiwen W, et al. Phase I Dose-escalation Clinical Trial of HF10 Oncolytic Herpes Virus in 17 Japanese Patients with Advanced Cancer. Hepatogastroenterology. 2014 May;61:599-605.
46. Nakao A, Kasuya H, Sahin TT, Nomura N, Kanzaki A, Misawa M,et al. A phase I dose-escalation clinical trial of intraoperative direct intratumoral injection of HF10 oncolytic virus in non-resectable patients with advanced pancreatic cancer. Cancer Gene Ther. 2011 Mar;18:167-75.
47. Hirooka Y, Kasuya H, Ishikawa T, Kawashima H, Ohno E, Villalobos IB, et al. A Phase I clinical trial of EUS-guided intratumoral injection of the oncolytic virus, HF10 for unresectable locally advanced pancreatic cancer. BMC Cancer. 2018 May 25;18:596.
48. Roth JC, Cassady KA, Cody JJ, Parker JN, Price KH, Coleman JM, et al. Evaluation of the safety and biodistribution of M032, an attenuated herpes simplex virus type 1 expressing hIL-12, after intracerebral administration to aotus nonhuman primates. Hum Gene Ther Clin Dev. 2014 Mar;25:16-27.
49. Moesta AK, Cooke K, Piasecki J, Mitchell P, Rottman JB, Fitzgerald K, et al. Local Delivery of OncoVEXmGM-CSF Generates Systemic Antitumor Immune Responses Enhanced by Cytotoxic T-Lymphocyte-Associated Protein Blockade. Clin Cancer Res. 2017 Oct 15;23:6190-202.
50. Liu BL, Robinson M, Han ZQ, Branston RH, English C, Reay P, et al. ICP34.5 deleted herpes simplex virus with enhanced oncolytic, immune stimulating, and anti-tumour properties. Gene Ther. 2003 Feb;10:292-303.
51. Greig SL. Talimogene Laherparepvec: First Global Approval. Drugs. 2016 Jan;76:147-54.
52. Dummer R, Gyorki DE, Hyngstrom J, Berger AC, Conry R, Demidov L, et al. Neoadjuvant talimogene laherparepvec plus surgery versus surgery alone for resectable stage IIIB-IVM1a melanoma: a randomized, open-label, phase 2 trial. Nat Med. 2021 Oct;27:1789-96.
53. Huang, H., Liu, Y., Liao, W. et al. Oncolytic adenovirus programmed by synthetic gene circuit for cancer immunotherapy. Nat Commun 10, 4801 (2019).
54. Rao L, Debbas M, Sabbatini P, Hockenbery D, Korsmeyer S, White E. The adenovirus E1A proteins induce apoptosis, which is inhibited by the E1B 19-kDa and Bcl-2 proteins. Proc Natl Acad Sci U S A. 1992 Aug 15;89:7742-6.
55. Bischoff JR, Kirn DH, Williams A, Heise C, Horn S, Muna M, et al. An adenovirus mutant that replicates selectively in p53-deficient human tumor cells. Science. 1996 Oct 18;274:373-6.
56. Lee CH, Kasala D, Na Y, Lee MS, Kim SW, Jeong JH, et al. Enhanced therapeutic efficacy of an adenovirus-PEI-bile-acid complex in tumors with low coxsackie and adenovirus receptor expression. Biomaterials. 2014 Jul;35:5505-16.
57. Lang FF, Conrad C, Gomez-Manzano C, Yung WKA, Sawaya R, Weinberg JS, et al Phase I Study of DNX-2401 (Delta-24-RGD) Oncolytic Adenovirus: Replication and Immunotherapeutic Effects in Recurrent Malignant Glioma. J Clin Oncol. 2018 May 10;36:1419-27.
58. Pathak V, Nolte T, Rama E, Rix A, Dadfar SM, Paefgen V, et al. Molecular magnetic resonance imaging of Alpha-v-Beta-3 integrin expression in tumors with ultrasound microbubbles. Biomaterials. 2021 Aug;275:120896.
59. Liu M, Yang YJ, Zheng H, Zhong XR, Wang Y, Wang Z, et al. Membrane-bound complement regulatory proteins are prognostic factors of operable breast cancer treated with adjuvant trastuzumab: a retrospective study. Oncol Rep. 2014 Dec;32:2619-27.
60. Belani CP, Chakraborty BC, Modi RI, Khamar BM. A randomized trial of TLR-2 agonist CADI-05 targeting desmocollin-3 for advanced non-small-cell lung cancer. Ann Oncol. 2017 Feb 1;28:298-304.
61. Atasheva S, Emerson CC, Yao J, Young C, Stewart PL, Shayakhmetov DM. Systemic cancer therapy with engineered adenovirus that evades innate immunity. Sci Transl Med. 2020 Nov 25;12:eabc6659.
62. Wang Z, Liu W, Wang L, Gao P, Li Z, Wu J, et al. Enhancing the antitumor activity of an engineered TRAIL-coated oncolytic adenovirus for treating acute myeloid leukemia. Signal Transduct Target Ther. 2020 Apr 24;5:40.
63. Wu H, Mei YF. An oncolytic adenovirus 11p vector expressing adenovirus death protein in the E1 region showed significant apoptosis and tumour-killing ability in metastatic prostate cells. Oncotarget. 2019 Mar 8;10:1957-74.
64. Hossain JA, Latif MA, Ystaas LAR, Ninzima S, Riecken K, Muller A, et al. Long-term treatment with valganciclovir improves lentiviral suicide gene therapy of glioblastoma. Neuro Oncol. 2019 Jul 11;21:890-900.

65. Akbulut H, Coleri A, Sahin G, Tang Y, Icli F. A Bicistronic Adenoviral Vector Carrying Cytosine Deaminase and Granulocyte-Macrophage Colony-Stimulating Factor Increases the Therapeutic Efficacy of Cancer Gene Therapy. Hum Gene Ther. 2019 Aug;30:999-1007.
66. Wang P, Li X, Wang J, Gao D, Li Y, Li H, et al. Re-designing Interleukin-12 to enhance its safety and potential as an anti-tumor immunotherapeutic agent. Nat Commun. 2017 Nov 9;8:1395.
67. Charman M, Herrmann C, Weitzman MD. Viral and cellular interactions during adenovirus DNA replication. FEBS Lett. 2019 Dec;593:3531-50.
68. Xue Q, Li X, Yang C, Ji B, Li Y, Yan Y,et al. Efficacy of recombinant adenovirus expressing a fusion gene from GM-CSF and Epstein-Barr virus LMP2A in a mouse tumor model. Hum Vaccin Immunother. 2017 Oct 3;13:2260-68.
69. Stephens C, Harlow E. Differential splicing yields novel adenovirus 5 E1A mRNAs that encode 30 kd and 35 kd proteins. EMBO J. 1987 Jul;6:2027-35.
70. Perricaudet M, Akusjärvi G, Virtanen A, Pettersson U. Structure of two spliced mRNAs from the transforming region of human subgroup C adenoviruses. Nature. 1979 Oct 25;281:694-6.
71. King CR, Zhang A, Tessier TM, Gameiro SF, Mymryk JS. Hacking the Cell: Network Intrusion and Exploitation by Adenovirus E1A. mBio. 2018 May 1;9:e00390-18.
72. Suzuki K, Fueyo J, Krasnykh V, Reynolds PN, Curiel DT, Alemany R. A conditionally replicative adenovirus with enhanced infectivity shows improved oncolytic potency. Clin Cancer Res. 2001 Jan;7:120-6.
73. Mantwill K, Klein FG, Wang D, Hindupur SV, Ehrenfeld M, Holm PS, et al. Concepts in Oncolytic Adenovirus Therapy. Int J Mol Sci. 2021 Sep 29;22:10522.
74. Blackhall FH, Merry CL, Davies EJ, Jayson GC. Heparan sulfate proteoglycans and cancer. Br J Cancer. 2001 Oct 19;85:1094-8.
75. Hallenbeck PL, Chang YN, Hay C, Golightly D, Stewart D, Lin J, et al. A novel tumor-specific replication-restricted adenoviral vector for gene therapy of hepatocellular carcinoma. Hum Gene Ther. 1999 Jul 1;10:1721-33.
76. Yu DC, Chen Y, Seng M, Dilley J, Henderson DR. The addition of adenovirus type 5 region E3 enables calydon virus 787 to eliminate distant prostate tumor xenografts. Cancer Res. 1999 Sep 1;59:4200-3.
77. Banerjee NS, Rivera AA, Wang M, Chow LT, Broker TR, Curiel DT, et al. Analyses of melanoma-targeted oncolytic adenoviruses with tyrosinase enhancer/promoter-driven E1A, E4, or both in submerged cells and organotypic cultures. Mol Cancer Ther. 2004 Apr;3:437-49.
78. Kawashima T, Kagawa S, Kobayashi N, Shirakiya Y, Umeoka T, Teraishi F, Tet al. Telomerase-specific replication-selective virotherapy for human cancer. Clin Cancer Res. 2004 Jan 1;10:285-92.
79. Nemunaitis J, Tong AW, Nemunaitis M, Senzer N, Phadke AP, Bedell C, et al. A phase I study of telomerase-specific replication competent oncolytic adenovirus (telomelysin) for various solid tumors. Mol Ther. 2010 Feb;18:429-34.
80. Shirakawa Y, Tazawa H, Tanabe S, Kanaya N, Noma K, Koujima T, et al. Phase I dose-escalation study of endoscopic intratumoral injection of OBP-301 (Telomelysin) with radiotherapy in oesophageal cancer patients unfit for standard treatments. Eur J Cancer. 2021 Aug;153:98-108.
81. Weintraub SJ, Prater CA, Dean DC. Retinoblastoma protein switches the E2F site from positive to negative element. Nature. 1992 Jul 16;358:259-61.
82. Whyte P, Ruley HE, Harlow E. Two regions of the adenovirus early region 1A proteins are required for transformation. J Virol. 1988 Jan;62:257-65.
83. Fueyo J, Gomez-Manzano C, Alemany R, Lee PS, McDonnell TJ, Mitlianga P, et al. A mutant oncolytic adenovirus targeting the Rb pathway produces anti-glioma effect in vivo. Oncogene. 2000 Jan 6;19:2-12.
84. Zhu ZB, Makhija SK, Lu B, Wang M, Rivera AA, Kim-Park S, et al. Incorporating the survivin promoter in an infectivity enhanced CRAd-analysis of oncolysis and anti-tumor effects in vitro and in vivo. Int J Oncol. 2005 Jul;27:237-46.
85. Liikanen I, Ahtiainen L, Hirvinen ML, Bramante S, Cerullo V, Nokisalmi P, et al. Oncolytic adenovirus with temozolomide induces autophagy and antitumor immune responses in cancer patients. Mol Ther. 2013 Jun;21:1212-23.
86. García M, Moreno R, Gil-Martin M, Cascallò M, de Olza MO, Cuadra C, et al. A Phase 1 Trial of Oncolytic Adenovirus ICOVIR-5 Administered Intravenously to Cutaneous and Uveal Melanoma Patients. Hum Gene Ther. 2019 Mar;30:352-64.
87. Rodríguez-García A, Giménez-Alejandre M, Rojas JJ, Moreno R, Bazan-Peregrino M, Cascalló M, et al. an oncolytic adenovirus combining fiber HSG-binding domain replacement with RGD and hyaluronidase expression. Clin Cancer Res. 2015 Mar 15;21:1406-18.
88. Pascual-Pasto G, Bazan-Peregrino M, Olaciregui NG, Restrepo-Perdomo CA, Mato-Berciano A, Ottaviani D,et al. Therapeutic targeting of the RB1 pathway in retinoblastoma with the oncolytic adenovirus VCN-01. Sci Transl Med. 2019 Jan 23;11:eaat9321.
89. Ganly I, Kirn D, Eckhardt G, Rodriguez GI, Soutar DS, Otto R, et al. A phase I study of Onyx-015, an E1B attenuated adenovirus, administered intratumorally to patients with recurrent head and neck cancer. Clin Cancer Res. 2000 Mar;6:798-806.
90. Cheng CY, Gilson T, Wimmer P, Schreiner S, Ketner G, Dobner T, et al. Role of E1B55K in E4orf6/E1B55K E3 ligase complexes formed by different human adenovirus serotypes. J Virol. 2013 Jun;87:6232-45.
91. Liang M. Oncorine, the World First Oncolytic Virus Medicine and its Update in China. Curr Cancer Drug Targets. 2018;18:171-176.
92. Kuhn I, Harden P, Bauzon M, Chartier C, Nye J, Thorne S, et al. Directed evolution generates a novel oncolytic virus for the treatment of colon cancer. PLoS One. 2008 Jun 18;3:e2409.
93. Kuhn I, Harden P, Bauzon M, Chartier C, Nye J, Thorne S, et al. Directed evolution generates a novel oncolytic

virus for the treatment of colon cancer. PLoS One. 2008 Jun 18;3:e2409.
94. Millward S, Graham AF. Structural studies on reovirus: discontinuities in the genome. Proc Natl Acad Sci U S A. 1970 Feb;65:422-9.
95. Steyer A, Gutiérrez-Aguire I, Kolenc M, Koren S, Kutnjak D, Pokorn M, et al. High similarity of novel orthoreovirus detected in a child hospitalized with acute gastroenteritis to mammalian orthoreoviruses found in bats in Europe. J Clin Microbiol. 2013 Nov;51:3818-25.
96. Shatkin AJ, Sipe JD, Loh P. Separation of ten reovirus genome segments by polyacrylamide gel electrophoresis. J Virol. 1968 Oct;2:986-91.
97. Danthi P, Holm GH, Stehle T, Dermody TS. Reovirus receptors, cell entry, and proapoptotic signaling. Adv Exp Med Biol. 2013;790:42-71.
98. Marcato P, Shmulevitz M, Pan D, Stoltz D, Lee PW. Ras transformation mediates reovirus oncolysis by enhancing virus uncoating, particle infectivity, and apoptosis-dependent release. Mol Ther. 2007 Aug;15:1522-30.
99. Errington F, White CL, Twigger KR, Rose A, Scott K, Steele L, et al. Inflammatory tumour cell killing by oncolytic reovirus for the treatment of melanoma. Gene Ther. 2008 Sep;15:1257-70.
100. RosenL, Hovıs JF, Mastrota FM, Bell JA, Huebner RJ. Observations on a newly recognized virus (Abney) of the reovirus family. Am J Hyg. 1960 Mar;71:258-65.
101. Chaurasiya S, Fong Y, Warner SG. Oncolytic Virotherapy for Cancer: Clinical Experience. Biomedicines. 2021 Apr 13;9:419.
102. Haller SL, Peng C, McFadden G, Rothenburg S. Poxviruses and the evolution of host range and virulence. Infect Genet Evol. 2014 Jan;21:15-40.
103. Smith GL. Rapid spreading and immune evasion by vaccinia virus. Adv Exp Med Biol. 2014;808:65-76.
104. Parato KA, Breitbach CJ, Le Boeuf F, Wang J, Storbeck C, Ilkow C, et al. The oncolytic poxvirus JX-594 selectively replicates in and destroys cancer cells driven by genetic pathways commonly activated in cancers. Mol Ther. 2012 Apr;20:749-58.
105. Scholl SM, Balloul JM, Le Goc G, Bizouarne N, Schatz C, Kieny MP, et al. Recombinant vaccinia virus encoding human MUC1 and IL2 as immunotherapy in patients with breast cancer. J Immunother. 2000 Sep-Oct;23:570-80.
106. Haddad D. Genetically Engineered Vaccinia Viruses As Agents for Cancer Treatment, Imaging, and Transgene Delivery. Front Oncol. 2017 May 23;7:96.
107. Lee JH, Roh MS, Lee YK, Kim MK, Han JY, Park BH, et al. Oncolytic and immunostimulatory efficacy of a targeted oncolytic poxvirus expressing human GM-CSF following intravenous administration in a rabbit tumor model. Cancer Gene Ther. 2010 Feb;17:73-9.
108. Stanford MM, McFadden G. Myxoma virus and oncolytic virotherapy: a new biologic weapon in the war against cancer. Expert Opin Biol Ther. 2007 Sep;7:1415-25.
109. Mercer J, Helenius A. Vaccinia virus uses macropinocytosis and apoptotic mimicry to enter host cells. Science. 2008 Apr 25;320:531-5.
110. Breitbach CJ, Burke J, Jonker D, Stephenson J, Haas AR, Chow LQ, et al. Intravenous delivery of a multi-mechanistic cancer-targeted oncolytic poxvirus in humans. Nature. 2011 Aug 31;477:99-102.
111. Cripe TP, Ngo MC, Geller JI, Louis CU, Currier MA, Racadio JM, et al. Phase 1 study of intratumoral Pexa-Vec (JX-594), an oncolytic and immunotherapeutic vaccinia virus, in pediatric cancer patients. Mol Ther. 2015 Mar;23:602-8.
112. Park SH, Breitbach CJ, Lee J, Park JO, Lim HY, Kang WK, et al. Phase 1b Trial of Biweekly Intravenous Pexa-Vec (JX-594), an Oncolytic and Immunotherapeutic Vaccinia Virus in Colorectal Cancer. Mol Ther. 2015 Sep;23:1532-40.
113. Breitbach CJ, Moon A, Burke J, Hwang TH, Kirn DH. A Phase 2, Open-Label, Randomized Study of Pexa-Vec (JX-594) Administered by Intratumoral Injection in Patients with Unresectable Primary Hepatocellular Carcinoma. Methods Mol Biol. 2015;1317:343-57.
114. Cripe TP, Ngo MC, Geller JI, Louis CU, Currier MA, Racadio JM, et al. Phase 1 study of intratumoral Pexa-Vec (JX-594), an oncolytic and immunotherapeutic vaccinia virus, in pediatric cancer patients. Mol Ther. 2015 Mar;23:602-8.
115. Schirrmacher V, van Gool S, Stuecker W. Breaking Therapy Resistance: An Update on Oncolytic Newcastle Disease Virus for Improvements of Cancer Therapy. Biomedicines. 2019 Aug 30;7:66.
116. Ganar K, Das M, Sinha S, Kumar S. Newcastle disease virus: current status and our understanding. Virus Res. 2014 May 12;184:71-81.
117. Meng Q, He J, Zhong L, Zhao Y. Advances in the Study of Antitumour Immunotherapy for Newcastle Disease Virus. Int J Med Sci. 2021 Mar 30;18:2294-302.
118. Schirrmacher V. Immunobiology of Newcastle Disease Virus and Its Use for Prophylactic Vaccination in Poultry and as Adjuvant for Therapeutic Vaccination in Cancer Patients. Int J Mol Sci. 2017 May 20;18:1103.
119. Schirrmacher V. Fifty Years of Clinical Application of Newcastle Disease Virus: Time to Celebrate! Biomedicines. 2016 Jul 20;4:16.
120. Horikami SM, Moyer SA. Structure, transcription, and replication of measles virus. Curr Top Microbiol Immunol. 1995;191:35-50.
121. Bhattacharjee S, Yadava PK. Measles virus: Background and oncolytic virotherapy. Biochem Biophys Rep. 2018 Jan 2;13:58-62.
122. Leber MF, Neault S, Jirovec E, Barkley R, Said A, Bell JC, et al. Engineering and combining oncolytic measles virus for cancer therapy. Cytokine Growth Factor Rev. 2020 Dec;56:39-48.
123. Mühlebach MD. Measles virus in cancer therapy. Curr Opin Virol. 2020 Apr;41:85-97.
124. AA. Roulston A, Marcellus RC, Branton PE. Viruses and apoptosis. Annu Rev Microbiol. 1999;53:577-628.
125. Rahman MM, McFadden G. Oncolytic Viruses: Newest Frontier for Cancer Immunotherapy. Cancers (Basel). 2021 Oct 29;13:5452.
126. Seegers SL, Frasier C, Greene S, Nesmelova IV, Grdzelishvili VZ. Experimental Evolution Generates Novel Oncolytic

Vesicular Stomatitis Viruses with Improved Replication in Virus-Resistant Pancreatic Cancer Cells. J Virol. 2020 Jan 17;94:e01643-19.

127. Altomonte J, Marozin S, Schmid RM, Ebert O. Engineered newcastle disease virus as an improved oncolytic agent against hepatocellular carcinoma. Mol Ther. 2010 Feb;18:275-84.
128. Wollmann G, Rogulin V, Simon I, Rose JK, van den Pol AN. Some attenuated variants of vesicular stomatitis virus show enhanced oncolytic activity against human glioblastoma cells relative to normal brain cells. J Virol. 2010 Feb;84:1563-73.
129. Breitbach CJ, Arulanandam R, De Silva N, Thorne SH, Patt R, Daneshmand M, et al. Oncolytic vaccinia virus disrupts tumor-associated vasculature in humans. Cancer Res. 2013 Feb 15;73:1265-75.
130. Xu B, Tian L, Chen J, Wang J, Ma R, Dong W, et al. An oncolytic virus expressing a full-length antibody enhances antitumor innate immune response to glioblastoma. Nat Commun. 2021 Oct 8;12:5908.
131. Uche IK, Kousoulas KG, Rider PJF. The Effect of Herpes Simplex Virus-Type-1 (HSV-1) Oncolytic Immunotherapy on the Tumor Microenvironment. Viruses. 2021 Jun 22;13:1200.
132. Nichols DB, De Martini W, Cottrell J. Poxviruses Utilize Multiple Strategies to Inhibit Apoptosis. Viruses. 2017 Aug 8;9:215.
133. Imre G. Cell death signalling in virus infection. Cell Signal. 2020 Dec;76:109772.
134. Ahmed A, Tait SWG. Targeting immunogenic cell death in cancer. Mol Oncol. 2020 Dec;14:2994-3006.
135. De Munck J, Binks A, McNeish IA, Aerts JL. Oncolytic virus-induced cell death and immunity: a match made in heaven? J Leukoc Biol. 2017 Sep;102:631-43.
136. Melchjorsen J. Learning from the messengers: innate sensing of viruses and cytokine regulation of immunity -clues for treatments and vaccines. Viruses. 2013 Jan 31;5:470-527.
137. Guo ZS, Liu Z, Bartlett DL. Oncolytic Immunotherapy: Dying the Right Way is a Key to Eliciting Potent Antitumor Immunity. Front Oncol. 2014 Apr 10;4:74.
138. Gujar S, Pol JG, Kim Y, Lee PW, Kroemer G. Antitumor Benefits of Antiviral Immunity: An Underappreciated Aspect of Oncolytic Virotherapies. Trends Immunol. 2018 Mar;39:209-21.
139. Kleijn A, Kloezeman J, Treffers-Westerlaken E, Fulci G, Leenstra S, Dirven C, Debets R, Lamfers M. The in vivo therapeutic efficacy of the oncolytic adenovirus Delta24-RGD is mediated by tumor-specific immunity. PLoS One. 2014 May 27;9:e97495.
140. Jiang H, Clise-Dwyer K, Ruisaard KE, Fan X, Tian W, Gumin J, et al. Delta-24-RGD oncolytic adenovirus elicits anti-glioma immunity in an immunocompetent mouse model. PLoS One. 2014 May 14;9:e97407.
141. MOORE AE. Inhibition of growth of five transplantable mouse tumors by the virus of Russian Far East encephalitis. Cancer. 1951 Mar;4:375-82.
142. HAMMON WM, YOHN DS, CASTO BC, ATCHISON RW. ONCOLYTIC POTENTIALS OF NONHUMAN VIRUSES FOR HUMAN CANCER. I. EFFECTS OF TWENTY-FOUR VIRUSES ON HUMAN CANCER CELL LINES. J Natl Cancer Inst. 1963 Aug;31:329-45.
143. Koppers-Lalic D, Hoeben RC. Non-human viruses developed as therapeutic agent for use in humans. Rev Med Virol. 2011 Jul;21:227-39.
144. Yohn DS, Hammon WM, Atchison RW, Casto BC. Oncolytic potentials of nonhuman viruses for human cancer. II. Effects of five viruses on heterotransplantable human tumors. J Natl Cancer Inst. 1968 Aug;41:523-9.
145. Molomut N, Padnos M. Inhibition of transplantable and spontaneous murine tumours by the M-P virus. Nature. 1965 Dec 4;208:948-50.
146. Parrish CR, Kawaoka Y. The origins of new pandemic viruses: the acquisition of new host ranges by canine parvovirus and influenza A viruses. Annu Rev Microbiol. 2005;59:553-86.