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# Oncolytic Virotherapy in Cancer Treatment

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**ABSTRACT:** Oncolytic virus therapy (OVT), a form of immunotherapy, is based on the use of genetically engineered viruses that selectively infect cancerous cells; produce progeny which are capable of lysing the infected malignant cells as well as elicit a systemic anti-tumor immune response. Advances in molecular virology, synthetic biology, and immuno-oncology have allowed for significant improvements in the tumor specificity, safety, and efficacy of all forms of oncolytic viral systems. This review will discuss the various mechanisms by which OVT achieves tumor cell selectivity, methods of genetic modification for enhancing the therapeutic potential of these systems, how they modulate the tumor microenvironment (TME), their current clinical applications, their application in combination with other therapeutic modalities, their limitations, the development of biomarkers for monitoring the therapeutic response and emerging technologies being developed for translation into the clinic through 2026.

**KEYWORDS:** Oncolytic viruses; Cancer immunotherapy; Tumor microenvironment; Genetic engineering; HSV-1; Adenovirus; CRISPR; Immune checkpoint inhibitors

## INTRODUCTION

The most common cause of mortality worldwide remains cancer; however, advances in chemotherapy, radiotherapy, targeted therapy, and immune checkpoint inhibitors have improved outcomes for patients with cancer. However, drug-resistant cancers and toxicities remain significant challenges. Oncolytic viruses (OVs) offer a dual mechanism of action: direct killing of tumor cells via oncolytic effects and activation of systemic anti-tumor immunity (1).Early evidence for the use of viruses in treating cancer was based on observations of spontaneous tumor regressions after viral infections.

These early studies were used as the basis for developing the first oncolytic virus engineered genetically (ONYX-015); it is a selective - replication adenovirus that is specifically created to infect tumor cells inadequately in p53 (2). Since those initial studies, the field has continued to evolve and develop new technologies; the most recent examples include the FDA approval of Talimogene Laherparepvec (T-VEC) and the development of additional next-generation viruses, including G47Δ, which utilizes advanced genetic engineer techniques to enhance specificity and stimulation of immune response (3).

Oncolytic viruses (OVs) are either genetically engineer or innate viruses that selectively replicate and kill cells tumor while normal tissues was sparing. The mechanism of selectivity involves the exploitation of the inherent defective signaling pathways present in tumor cells, such as the p53 pathway, using the virus's genetic alteration to generate a therapeutic transgene using a tumor cell-specific promoter. When tumor cells are directly lysed, tumor material is released that associated antigens (TAAs) and damage associated molecular patterns (DAMPs) resulting in a immunological activation cascade, also referred to as Immunogenic Cell Death (ICD). This transformation of an "immunologically cold" tumor to an "immunologically hot" tumor is marked by a rise in immune cell activation and infiltration (4).Molecular Mechanisms of Tumor specificity occurs due to defects in antiviral signaling pathways present in tumor cells, especially in the interferon response pathways. Many tumors have dysregulation in Ras, p53, or Rb signaling pathways allowing for selective viral replication (5).

Immune Activation and Direct Oncolysis Infection of a tumor cell by an oncolytic virus leads to immunogenic cell death (ICD) resulting in the production of cytokines, danger-associated molecular patterns (DAMPs), and tumor associated antigens (TAAs), which cause dendritic cells to mature and cytotoxic T-cells to become activated. Viral replication causes cytopathic consequences, which cause the tumor cell to burst and release offspring virions when the virus has specifically infected a tumor cell (6).

OVs' therapeutic activity is mainly mediated by two interconnected processes, as shown in Figure 1: the direct killing of tumor cells through oncolytic effects and the induction of an anti-tumor immune response.

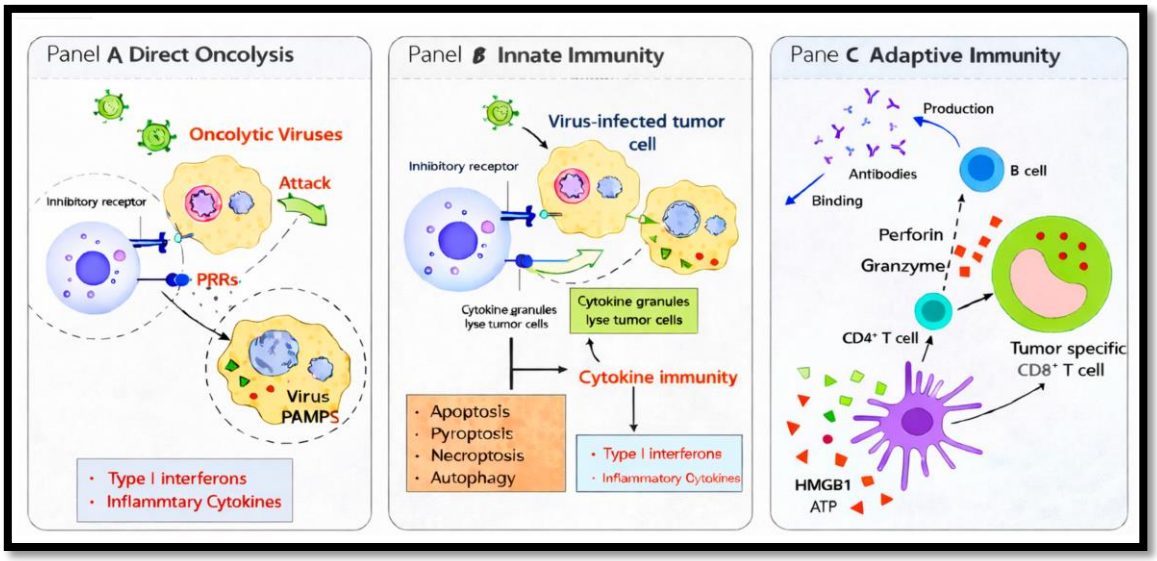


**Figure 1. Coordination of innate and adaptive antitumor immunity and immunogenic cell death (ICD) brought on by OV (7).**

**Panel** (**A**): Direct Oncolysis: OVs cause direct tumor cell lysis by preferentially infecting tumor cells and multiplying intracellularly. PRRs detect the PAMPs produced by viral replication, which causes type I IFNs and inflammatory cytokines to be produced. Tumor antigen release is further enhanced by OV-mediated lysis, which also aids in local immune activation. **Panel** (**B**): These signals encourage cytokine-driven immunity and trigger innate immune pathways. By combining activating and inhibiting receptor signals, NK cells are able to identify virus-infected tumor cells. They also aid in the early cytotoxic clearance process by releasing cytokines and lysing tumor cells via granules.. **Panel** (**C**): T cells that cause cytotoxicity. While CD4+ T cells play crucial supporting roles to maintain and enhance the antitumor response, activated CD8+ T cells destroy tumor cells via granzyme and perforin. Antiviral and anticancer immunity are strengthened concurrently by B cells' recognition of viral antigens and production of antibodies. When these adaptive immune responses work together, they produce a long-lasting, systemic anticancer response that targets both virus-infected and uninfected tumor cells.

**TUMOR MICROENVIRONMENT REMODELING**

Oncolytic Viruses (OVs) turn "immunologically cold" tumors into "hot" tumors through increased infiltration of CD8 + T-cells; decreased numbers of regulatory T-cells; and, altered suppressive cytokines (8).Engineering of Genes There are several major engineering approaches for oncolytic viruses:

• Elimination of virulence genes to limit the viral replication to tumor cells.
• Immune-stimulation gene transfection (e.g., GM-CFS, IL-12, IFN-β).
• Alteration of viral tropism by modifying the viral glycoproteins.
• Genome optimization using CRISPR/Cas.
• The use of a tumor cell promoter (9).

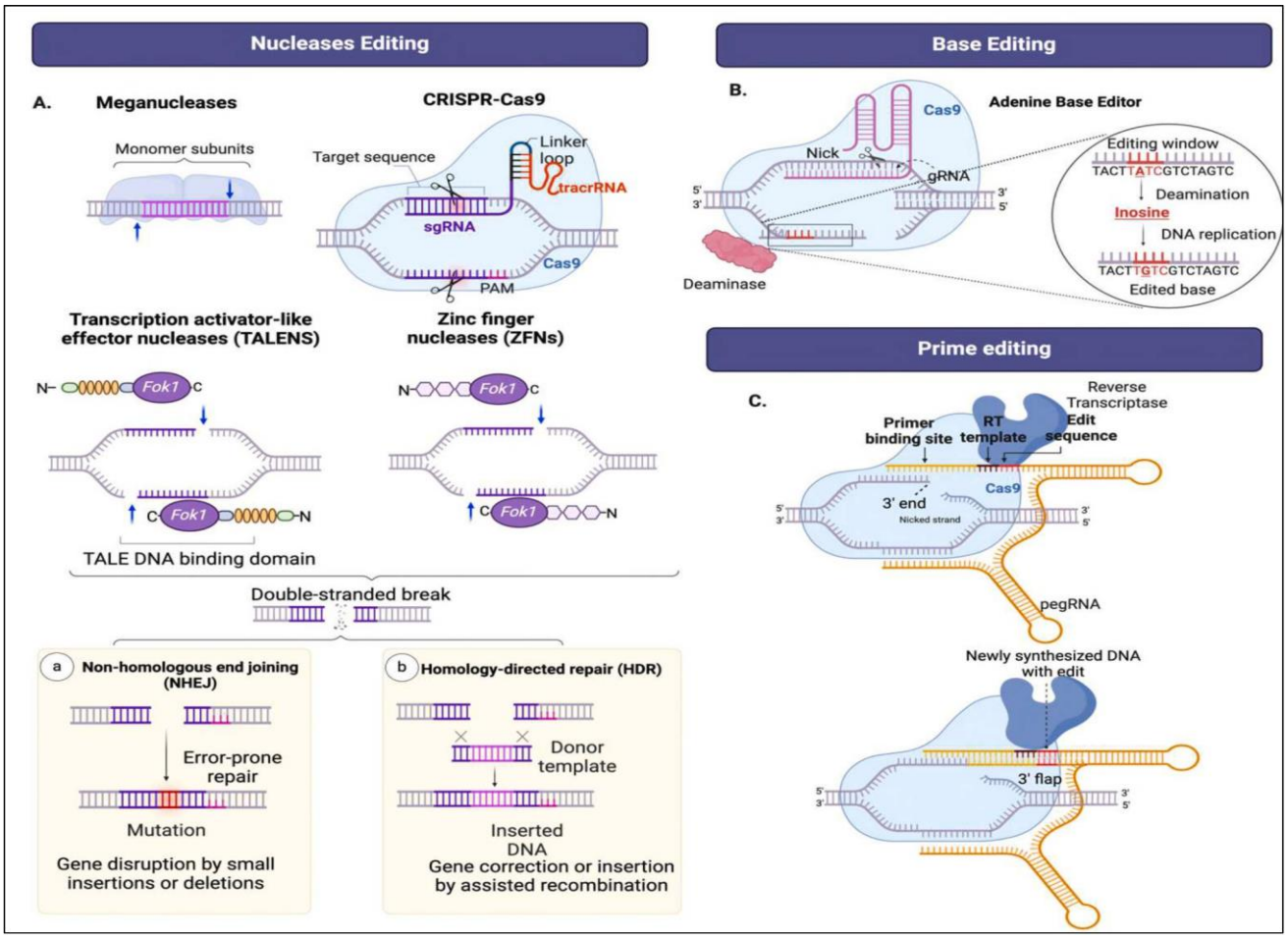


**Figure 2. How genome editing tools work (10).**

Meganucleases lack distinct DNA binding and cleavage domains, yet they are able to identify certain sequences between 14 and 40 base pairs. An RNA-guided endonuclease called CRISPR-Cas9 is steered by a guide RNA (gRNA) to the target location next to the protospacer adjacent motif (PAM), where it produces a double-strand break (DSB)(11). Non-homologous end joining (NHEJ), which frequently results in insertions or deletions (indels) and loss-of-function mutations, and homology-directed repair (HDR), which employs a template DNA for precise repair and may correct preexisting mutations, are the two primary mechanisms by which cells repair these DSBs (12).

**Major Oncolytic Viral Platforms**

| Virus | Engineering Features | Clinical Status |
|---|---|---|
| **HSV-1** | Large genome; GM-CSF insertion; neurovirulence gene deletion | T-VEC approved (melanoma) |
| **Adenovirus** | E1B deletion; tumor-specific promoters | Phase I–III trials |
| **Reovirus** | Natural Ras-pathway selectivity | Advanced trials |
| **Vaccinia virus** | Large gene capacity; rapid replication | Clinical development |
| **Measles virus** | CD46 targeting; vaccine strain modifications | Early trials |
| **VSV / NDV** | Strong immunogenicity; experimental platforms | Preclinical/early trials |

## Oncolytic Virotherapy in Cancer Treatment

There are many different characteristics that can be used as criteria for selecting an OV platform to achieve a balance among therapeutic efficacy, safety and manufacturability (13). Characteristics such as the size and type of genetic material each virus can carry, how well they target tumors, their ability to activate the immune system and the ease with which they can be produced all contribute to selecting a suitable OV platform based on the needs of both the patient and the development process for a given therapy (14).Approved Therapies and Clinical Translation The first FDA approved oncolytic virus for advanced melanoma was talimogene laherparepvec (T-VEC), demonstrating prolonged responses in clinical studies as well as immune activation. There are numerous clinical trials currently underway testing combination strategies involving T-VEC and other agents including anti-DP-1 and anti-CLTA-4 therapies (15).Combination Immunotherapy and Biomarkers and Precision Oncology Oncolytic virus combinations with immune checkpoint inhibitors, CAR-T cells, radiation therapy and chemotherapy have synergistic effects by enhancing T-cell priming and overcoming tumor-based immune suppression (16).Emerging biomarkers that could identify patients who would best benefit from oncolytic virotherapy include the level of interferon signaling within a tumor, the tumor's mutation burden, the profile of immune cells present in the tumor and the presence or absence of viral receptors at the surface of the tumor (17).

Challenges and Limitations with Future Directions

- Pre-existing immunity to the virus.
- Neutralizing antibodies preventing the virus from circulating throughout the body.
- Tumor-specific micro-environmental barriers (e.g., hypoxia, fibrosis).
- Regulatory and manufacturing issues (18).

Next generation oncolytic viruses are being engineered utilizing synthetic biology platforms, multi-armed immunomodulatory constructs, nanoparticle-shielding systems, and customized viral designs that specifically target a patient's individual tumor (19).Oncolytic virotherapy is rapidly changing the field of cancer immunotherapy. The use of next-generation precision engineered OVs in combination with multiple other treatments has made it clear that OVs will become a significant component of future cancer treatment paradigms (20).

## CONCLUSION

Oncolytic virotherapy has emerged as a potential cancer immunotherapy technique may be to its dual mode of action, which includes both direct tumor cell destruction and systemic antitumor immune activation. Advances in genetic engineering and tumor-targeting strategies have significantly improved the, specificity, safety and therapeutic promise of oncolytic viral platforms. The clinical approval of talimogene laherparepvec that the translational success of the technique and promotes also clinical development. Despite enduring challenges such delivery limitations, antiviral immunity, and tumor heterogeneity, ongoing developments in combination therapy and precision-based viral design are expected to increase treatment success. All things considered, oncolytic viruses are anticipated to be a major part of future multimodal cancer therapy strategies.

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