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# VIRUSES AS CANCER THERAPEUTICS: MECHANISMS OF ONCOLYTIC VIROTHERAPY AND KEY CLINICAL PLATFORMS

**Harshada Pawara[1], Neha Bhamre[2], Sayyed Mateen[3], Bhagwati Ram[4], Vaishnavi Bandewar[5], Ansari Imtiyaz Ejaz[6]**

*[1]DCS's ARA College of Pharmacy, Nagaon, Dhule, Maharashtra*
*[2]KVPS Institute of pharmaceutical education and research Boradi ,Shirpur, Maharashtra, India*
*[3]Oriental College of Pharmacy, Sanpada, Navi-Mumbai, Maharashtra.*
*[4]Mvm Institute of nursing science Affiliation by Rajiv Gandhi University of health sciences*
*[5]Rajputana college of pharmacy, Karnataka, India*
*[6]R.C. Patel Institute of Pharmaceutical Education and Research, Shirpur, Dist. Dhule, Maharashtra*

***Corresponding Author**
Ansari Imtiyaz Ejaz

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**Abstract**

Oncolytic viruses (OVs) are emerging immunotherapeutic agents that selectively infect and destroy cancer cells while simultaneously stimulating anti-tumor immunity. This review examines how oncolytic virotherapy works at a mechanistic level and provides an overview of the leading OV platforms in clinical development. Virus-mediated lysis of tumor cells not only debulks tumors directly but also generates an in situ cancer vaccine effect by releasing tumor antigens and danger signals that activate the immune system. We discuss the biological and immunologic rationale behind this dual action, including the induction of immunogenic cell death and the conversion of "cold" tumors into "hot" immunologically active ones. Key molecular features of major oncolytic viruses – such as herpes simplex virus type 1–based Talimogene laherparepvec (T-VEC), oncolytic adenoviruses, reovirus, coxsackievirus (CVA21), and vaccinia virus – are reviewed, highlighting how genetic engineering (e.g., insertion of immune stimulatory genes) enhances their therapeutic impact. Early clinical results, including the first FDA-approved OV (T-VEC) in melanoma, demonstrate the promise of virotherapy. Combination approaches with immune checkpoint inhibitors are also introduced as a strategy to amplify anti-tumor responses. In summary, oncolytic virotherapy represents a novel modality at the intersection of virology and immuno-oncology. This article provides a comprehensive overview of OV mechanisms and platforms, underscoring the rationale for their use and their potential to broaden the horizons of cancer immunotherapy.

***Keywords***: Oncolytic virotherapy; Cancer immunotherapy; Immunogenic cell death; Tumor lysis; Talimogene laherparepvec (T-VEC); Adenovirus; Reovirus; Vaccinia; Coxsackievirus; Immune checkpoint inhibitors



## INTRODUCTION

Immunotherapy has revolutionized cancer treatment by harnessing the body's immune system to fight tumors [1]. Among emerging immunotherapies, oncolytic virus therapy is especially innovative: it employs live viruses that preferentially infect and kill cancer cells while sparing normal tissues [2-4]. This once-radical concept gained clinical validation in 2015 when Talimogene laherparepvec (T-VEC) – a genetically modified herpes simplex virus type 1 (HSV-1) encoding granulocyte-macrophage colony-stimulating factor (GM-CSF) – earned regulatory approval as the first oncolytic virus therapy for melanoma (5). T-VEC's approval established oncolytic virotherapy as a legitimate cancer treatment modality and spurred intense interest in developing other oncolytic viruses [6].

### Mechanisms of Oncolytic Virotherapy

Oncolytic viruses (OVs) exert anti-tumor effects through a dual mechanism of action. First, replicating infectious agents, they cause direct lysis of tumor cells. After an OV enters a susceptible cancer cell, it hijacks the cell's machinery to replicate, eventually causing the cell to burst (cytolysis) and releasing a burst of new viral progeny. These progenies can then infect neighboring cancer cells, leading to a self-amplifying wave of tumor destruction. Second, viral oncolysis can ignite systemic anti-cancer immunity [7]. The destruction of tumor cells by the virus is far from silent – it converts the tumor into an in situ vaccine. Lysed cancer cells release a wealth of tumor-specific antigens along with danger-

associated molecular patterns (DAMPs) and other inflammatory signals into the tumor microenvironment [8]. Dendritic cells and other antigen-presenting cells are attracted to this milieu of released antigens and danger signals, then take up the tumor antigens and migrate to lymph nodes to prime tumor-specific T cells [9]. In essence, OVs can transform an immunologically "cold" tumor (one that evades immune recognition) into a "hot" tumor (an inflamed site teeming with immune activity)-a shift consistent with contemporary data on tumor plasticity and T/NK-cell immune evasion in solid tumors [10,11]. Clinical reports have documented regression of even distant, uninjected lesions in some patients treated with intratumoral OVs like T-VEC, consistent with the development of a systemic anti-tumor immune response (an abscopal effect) [12]. Through these complementary mechanisms – direct cytotoxicity and immune-mediated tumor rejection – oncolytic virotherapy offers a two-pronged attack on cancer [13].

Several properties of tumor biology enable OVs to selectively replicate in cancer cells. Many malignancies exhibit defects in antiviral defense pathways, such as impaired interferon signaling, which would normally help healthy cells resist viral infection [14]. These tumor-specific vulnerabilities create a permissive environment for viral replication that viruses cannot find in most normal tissues [15]. Additionally, genetic engineering of viruses further enhances cancer selectivity [16]. For example, T-VEC was engineered with deletions in viral genes that are non-essential in tumor cells but attenuate the virus in normal cells, thereby restricting productive infection to cancer cells [17]. Such modifications ensure the virus acts as a cancer-selective agent that replicates robustly in tumor tissue while being harmless or greatly attenuated in healthy tissue.

Modern oncolytic viruses are often "armed" with therapeutic transgenes to boost their immune-stimulating effects. Cytokines (e.g., GM-CSF in T-VEC or interleukin-12 in other OVs), chemokines, co-stimulatory ligands (like CD40L), or even checkpoint inhibitor molecules have been inserted into viral genomes to be expressed in the tumor microenvironment [18]. The goal of these inserts is to heighten local immune activation – effectively turning the infected tumor into a factory for immune-boosting agents. By concentrating on such immune modulators at the tumor site, OVs can provoke a stronger anti-tumor immune response without the systemic toxicity that might occur if the same agent were given intravenously [19].

The unique dual action of OVs – direct tumor lysis coupled with immunogenic cell death (ICD) – is what distinguishes oncolytic virotherapy within the immunotherapy landscape. Virus-induced tumor cell death is often highly immunogenic: unlike the apoptosis seen with many chemotherapies (which can be immunologically quiet), virus-mediated lysis releases a profusion of immunostimulatory molecules [20]. This mirrors how replication stress and DNA-damage checkpoint disruption heighten tumor immunogenicity [21]. Dying infected cancer cells release tumor antigens, viral antigens, and DAMPs such as ATP, HMGB1, and cell-surface calreticulin, which act as "danger signals." These signals alert and recruit innate immune cells. This process, termed immunogenic cell death, stimulates dendritic cells to mature and present tumor antigens to T cells [22]. As a result, OVs essentially turn the tumor into a personalized vaccine – activating cytotoxic T lymphocytes that can seek out and destroy cancer cells throughout the body bearing those antigens, even at sites the virus never reached [23].

However, the interplay between the virus, tumor, and immune system is a double-edged sword. While the immune response triggered by the virus can attack cancer, the host immune system also inevitably recognizes and begins clearing the virus itself, potentially limiting how far the infection can spread within the tumor. Researchers are actively exploring strategies to modulate this balance – for instance, transiently suppressing anti-viral immunity (with immunosuppressive agents like cyclophosphamide) to give the virus a longer window to replicate in the tumor [24]. The ideal outcome is to allow enough viral replication for substantial tumor cell killing and antigen release before the virus is neutralized by the immune system. Even if the virus is eventually cleared, by that point it may have already triggered a durable anti-tumor immune response that continues the fight [25]. Aretrospective analysis reported that high-risk HPV-DNA testing could serve as a PET/CT alternative for post-treatment surveillance, reinforcing a generalizable paradigm for molecular monitoring that could translate to oncolytic virotherapy trials [26,27].

**Overview of Clinical Oncolytic Virus Platforms**

Encouraged by the success of T-VEC, researchers have developed a broad array of oncolytic viruses across multiple virus families. Each platform has unique virological features and potential clinical advantages. Table 1 provides a summary of key oncolytic viruses and their characteristics. Below, we highlight several leading OV platforms and their clinical status:

**Herpes Simplex Virus Type 1 (HSV-1) – T-VEC**

HSV-1 is a large DNA virus that has proven amenable to genetic modification. T-VEC is the prototypical HSV-1 oncolytic virus. It carries deletions in viral virulence genes (to reduce pathogenicity in normal cells) and an insertion of the GM-CSF gene to enhance immune recruitment. T-VEC is delivered via intralesional injection, typically into injectable melanoma lesions [28]. In a pivotal Phase III trial for advanced melanoma, intratumoral T-VEC monotherapy achieved a durable response rate (objective responses lasting ≥6 months) of about 16%, including complete remissions in some patients [29]. While 16% may appear modest, these were often deep and lasting responses; notably, some patients experienced regression of non-injected tumors, evidencing an immunologic "bystander" effect. T-VEC's safety profile was favorable compared to traditional chemotherapy – the most common side effects were mild flu-like symptoms,

fatigue, and injection-site inflammation. This relative safety, combined with its immunologic activity, made T-VEC the first OV approved by the FDA and EMA (2015) for unresectable melanoma [30]. T-VEC continues to be studied in combination with immune checkpoint inhibitors and in other tumor types to extend its utility [31].

**Adenovirus – Oncorine (H101) and DNX-240**

Adenoviruses are non-enveloped DNA viruses that can be engineered for cancer selectivity. The first approved oncolytic virus (in 2005, in China) was an adenovirus: H101, marketed as Oncorine, which has a deletion in the E1B-55k gene (similar to the earlier ONYX-015 construct) that allows it to replicate selectively in p53-deficient cancer cells [32]. Oncorine is approved in China for nasopharyngeal carcinoma in combination with chemotherapy. In Western countries, a notable adenoviral OV is DNX-2401 (delta-24-RGD). DNX-2401 carries a 24-base-pair deletion in the E1A gene (targeting cells with retinoblastoma pathway dysregulation, common in gliomas) and an RGD peptide added to its capsid to enhance tumor cell entry. DNX-2401 has shown promising results in early trials for recurrent glioblastoma – including a few cases of unexpected long-term survival [33]. In a Phase II trial (CAPTIVE/KEYNOTE-192) combining DNX-2401 with pembrolizumab (anti-PD-1) in glioblastoma, improved survival relative to historical controls was observed. Adenovirus-based OVs tend to provoke strong immune responses, which can be a double-edged sword: it may contribute to anti-tumor efficacy but also means the host may rapidly neutralize the virus, limiting repeat dosing. Nonetheless, adenoviral OVs like DNX-2401 are actively being explored for brain tumors and other malignancies(34).

**Coxsackievirus A21 – Cavatak (V937):** Coxsackievirus A21 is a small RNA virus (picornavirus) that naturally targets cells via ICAM-1 and DAF receptors – molecules often overexpressed on melanoma and other tumor cells. A formulation of this virus known as Cavatak (now also called V937) has been tested as an oncolytic agent. Because receptor landscapes govern both viral entry and therapy adaptation, receptor-centric resistance biology should inform OV selection and combination design [35]. In trials for melanoma (e.g., the Phase II CALM study), intratumoral Cavatak led to immune-mediated tumor regressions in both injected and some distant lesions, and it was well tolerated (mostly mild fever and fatigue) [36,37]. Cavatak has also been delivered intravesically (directly into the bladder) for non–muscle-invasive bladder cancer, where it showed signs of activity and immune activation in the bladder lining. Like other OVs, Cavatak is being combined with checkpoint inhibitors (e.g., pembrolizumab) to evaluate synergy. As a wild-type (non-engineered) virus with inherent tumor selectivity, Cavatak represents a "ready-made" OV platform requiring minimal genetic modification [38].

**Reovirus – Pelareorep:** Reovirus is a double-stranded RNA virus that preferentially replicates in cells with an activated Ras signaling pathway (a common feature in many cancers). The oncolytic reovirus variant pelareorep (formerly Reolysin®) is unique among leading OVs in that it is typically delivered intravenously rather than intratumorally(39,40). IV pelareorep has been tested in breast cancer, pancreatic cancer, and other solid tumors, often in combination with chemotherapy or immunotherapy. Because reovirus is widespread in nature (most humans have been exposed), it generally causes only mild, self-limited illness (e.g., minor fever or cold-like symptoms)(41). In trials, IV pelareorep similarly caused mostly mild side effects (fever, chills, fatigue), and it can home to tumor sites after infusion. One important consideration is viral shedding: patients can shed reovirus in bodily fluids (e.g., stool, respiratory secretions) for up to a week after infusion. Patients are instructed on hygiene practices (hand-washing, etc.) for several days post-treatment, and if hospitalized, may be placed on contact precautions during the shedding period [42]. To date, pelareorep has shown evidence of immune activation within tumors (such as increased tumor-infiltrating lymphocytes) and continues to be studied as an immune "primer" in combination regimens [43].

**Vaccinia Virus – Pexa-Vec (JX-594)**

Vaccinia virus (used in the smallpox vaccine) is a large DNA poxvirus with a genome capable of carrying multiple transgenes. The oncolytic vaccinia Pexa-Vec (pexastimogene devacirepvec, formerly JX-594) was engineered to express GM-CSF and showed promising Phase II results in advanced liver cancer [44,45]. However, a Phase III trial of Pexa-Vec plus sorafenib did not improve outcomes, and its development was halted. Nonetheless, vaccinia remains of interest: its large genomic capacity allows insertion of genes such as immune checkpoint inhibitors [46]. New vaccinia OV constructs are being designed to deliver therapeutic payloads (for example, a vaccinia encoding a mini anti-PD-1 antibody). Operationally, vaccinia-based OVs require precautions similar to other live viruses; for instance, vaccinia can cause localized pox lesions if mishandled, so staff must exercise care to avoid needle-stick injuries or exposure of broken skin(47).

Table01. Representative Oncolytic Viruses in Clinical Development:

| Virus (Platform) | Key Modifications/Features | Clinical Applications & Status |
|---|---|---|
| **HSV-1 (T-VEC)** | Deletions in neurovirulence genes; GM-CSF transgene | Approved for melanoma (intratumoral); in trials in combination with immunotherapy. |
| **Adenovirus (Oncorine, DNX-2401)** | E1 gene deletions (Oncorine: ΔE1B55K; DNX-2401: Δ24 in E1A) + fiber RGD-modification | Oncorine approved in China (with chemotherapy); DNX-2401 in trials for glioblastoma (with promising early results). |

| | | |
|---|---|---|
| **Coxsackievirus A21 (Cavatak)** | Natural tropism for ICAM-1/DAF receptors on tumors (no engineering) | Phase I–II trials in melanoma, bladder cancer; well tolerated, being combined with checkpoint inhibitors. |
| **Reovirus (Pelareorep)** | Wild-type reovirus (targets Ras-activated cells) | Phase II trials (IV delivery) in breast, pancreatic, etc.; used with chemo/immunotherapy as immune primer; mild flu-like side effects common. |
| **Vaccinia (Pexa-Vec)** | Engineered vaccinia virus (e.g., GM-CSF transgene) | Phase III trial in liver cancer (no benefit); newer vaccinia OV vectors in development for solid tumors. |

These platforms are increasingly tested with systemic agents to broaden efficacy and overcome resistance. Parallel advances with next-generation fluoropyrimidines (CF10) demonstrate strategies to bypass 5-FU resistance and could be rational OV partners [48–50].

**Synergy with Immune Checkpoint Inhibitors**

Given their immune-activating properties, oncolytic viruses are being combined with immune checkpoint inhibitors (ICIs) to enhance anti-tumor effects. OVs inflame the tumor microenvironment and increase T cell infiltration, while ICIs (such as anti-PD-1 or anti-CTLA-4 antibodies) relieve immunosuppressive brakes on those T cells. Early clinical studies supported this synergy [51]. In advanced melanoma, T-VEC plus the CTLA-4 inhibitor ipilimumab produced a higher objective response rate (~38%) than ipilimumab alone (~18%) [52]. Likewise, a Phase Ib trial of T-VEC with the PD-1 inhibitor pembrolizumab reported an overall response rate of ~62%, exceeding historical results with either agent alone. However, a larger Phase III trial (MASTERKEY-265) of T-VEC+pembrolizumab did not significantly improve progression-free survival compared to pembrolizumab alone, possibly due to an unexpectedly high response rate in the control arm [53, 54]. Notably, subsets of patients (e.g., those without visceral metastases) seemed to derive more benefit from the combination, indicating that patient selection may be important [55].

Mechanistically, the combination makes sense: OVs turn "cold" tumors "hot" and can upregulate PD-L1 on tumor cells (a sign of ongoing immune attack), potentially making tumors more susceptible to PD-1/PD-L1 blockade [56]. Conversely, ICIs may allow the T cells stimulated by OVs to function longer and more effectively. Safety data so far indicate that OV+ICI combinations are tolerable – the side effects are essentially the additive effects of each (immune-related adverse events from ICIs, plus mild viral therapy reactions like fevers or injection-site inflammation). No unique synergistic toxicity has emerged in trials to date [57].

Overall, oncolytic virotherapy appears to broaden the reach of checkpoint blockade to tumors that otherwise might not respond. Clinical trials are ongoing in various cancers (glioblastoma, sarcoma, etc.), and early results (such as DNX-2401+pembrolizumab in brain tumors) are encouraging [58]. As these studies progress, they will clarify how best to integrate OVs with standard immunotherapy – whether concurrently, sequentially, or in specific patient populations most likely to benefit [59]. Beyond ICIs, rational small-molecule scaffolds are being optimized to augment tumor stress and potential ICD; such chemotypes (e.g., benzofuran-piperazine derivatives) warrant screening as OV-sensitizers [60].

**Conclusion**

Oncolytic virus therapy represents a cutting-edge convergence of virology, oncology, and immunology that is reshaping cancer treatment. By turning viruses into cancer-selective weapons, we gain a two-in-one modality: direct tumor destruction and engagement of the patient's immune defenses. Clinical evidence to date – from T-VEC's success in melanoma to encouraging trials with other viruses – confirms that this approach can achieve meaningful tumor control, especially when combined with other immunotherapies [61]. Challenges remain, such as optimizing delivery, overcoming anti-viral immunity, and identifying ideal patient candidates, but ongoing research is actively addressing these issues.Real-world adoption will hinge on pharmacy-led quality systems; interventional audit models have already shown they can operationalize complex care pathways safely in accredited settings [62,63]. Patient comprehension will shape adherence to biosafety precautions and follow-up; pilot health-literacy screening in gynecologic oncology underscores this need [64].

Equally important is the practical integration of oncolytic virotherapy into routine oncology practice. The safe delivery of live viruses in hospitals has been enabled by meticulous protocols and the leadership of oncology pharmacists and multidisciplinary teams. From maintaining ultra-cold storage and careful dose preparation to educating staff and patients about biosafety, these operational efforts ensure that the promise of oncolytic immunotherapy can be realized safely [65]. Early adopting centers have demonstrated that, with training and preparation, even smaller institutions can successfully administer OVs, broadening patient access to these novel treatments.Effective roll-out of live-virus therapies will also depend on mature medication-use systems; experience from IV-to-oral stewardship highlights how protocolized conversion and barrier management improve safety and efficiency [66]. Safe live-virus therapy hinges on the right care setting; structured triage improves safety and throughput [67].

As more oncolytic viruses advance through clinical trials-including those tailored to specific tumor types or armed with new immune payloads-the experience being gained now will prove invaluable. The frameworks established (SOPs, training programs, interdisciplinary committees) form a strong foundation for the future, perhaps leading to dedicated OV infusion centers or regimens involving multiple different viruses. In summary, oncolytic virotherapy has moved from

concept to clinic, exemplifying how re-purposing nature's pathogens can benefit patients when applied with scientific rigor and operational care. It offers a new hope for patients with difficult cancers and stands as a testament to the innovative spirit driving the next generation of cancer immunotherapy.

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The authors declare that they have no competing interest in relation to this work.

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