Therapeutics, Pharmacology and Clinical Toxicology

Review

Ther Pharmacol Clin Toxicol
Volume: 23, Issue: 3, July–September 2025

Received: 8 August 2025
Accepted: 11 September 2025

Programmable immunotherapy in precision oncology: integrating oncolytic viruses and neoantigen vaccines

Camelia **Dascalu**[1,2]*, Miruna **Furtuna**[2], Constantin **Roman**[2], Georgiana **Gotcu**[2], Bogdan-Ionel **Tamba**[1,2]

[1] Department of Pharmacology, Clinical Pharmacology and Algesiology, Grigore T. Popa University of Medicine and Pharmacy, Iasi, Romania
[2] Prof. Ostin C. Mungiu Advanced Research and Development Center for Experimental Medicine – CEMEX, Grigore T. Popa University of Medicine and Pharmacy, Iasi, Romania

*** Correspondence to:** Camelia Dascalu, Prof. Ostin C. Mungiu Advanced Research and Development Center for Experimental Medicine – CEMEX, Grigore T. Popa University of Medicine and Pharmacy, 16 Universitatii Str., 700115, Iasi, Romania. E-mail: camelia-enascut@email.umfiasi.ro

Abstract

Oncolytic viruses and therapeutic cancer vaccines are two immunotherapy platforms whose trajectories increasingly intersect. Both aim not only to destroy malignant cells directly, but also to train the patient's immune system to mount long-lasting antitumor responses. Unlike conventional cytotoxic agents, whose effects follow relatively linear pharmacokinetic–pharmacodynamic principles, these biological platforms work by amplifying immune activity. Oncolytic virotherapy has moved far beyond the early observation that certain viruses preferentially replicate in tumor cells. It is now a deliberately engineered approach—programmable by design—that pairs direct viral lysis of cancer cells with an *in situ* vaccination effect generated by the release of tumor antigens. In parallel, therapeutic cancer vaccines, particularly those built on neoantigens, provide highly precise immune targeting by focusing on tumor-specific epitopes created by somatic mutations. By doing so, they circumvent the constraints of central immune tolerance and elicit more potent, tumor-restricted T-cell responses. Despite their strong mechanistic foundations and promising results in preclinical models, both oncolytic viruses and therapeutic cancer vaccines have shown only modest clinical efficacy when used as monotherapies. This gap between biological potential and clinical performance is shaped by several well-recognized barriers: the immunosuppressive nature of the tumor microenvironment, the heterogeneous expression of tumor antigens, patient-specific variability driven by immune status, and the substantial regulatory complexity associated with these evolving biologic platforms. Growing evidence now suggests that these limitations may be overcome by integrating oncolytic virotherapy with therapeutic or neoantigen-based vaccines and, increasingly, with immune checkpoint inhibitors. Such rational combinations appear to enhance immune priming, broaden antigenic targeting, and mitigate both primary and acquired forms of immune resistance. From a translational clinical pharmacology perspective, these platforms challenge the traditional assumptions that link dose, exposure, and therapeutic effect. Their activity is shaped largely by immune amplification rather than predictable pharmacokinetic behavior, making patient selection and response evaluation heavily dependent on immune-guided biomarkers. This review synthesizes the fundamental platform biology underlying oncolytic viruses and therapeutic cancer vaccines, highlights how their integration can advance precision oncology, and examines the key clinical pharmacology and regulatory hurdles that continue to limit their widespread clinical adoption.

Keywords: oncolytic virotherapy, therapeutic cancer vaccines, neoantigen vaccines, tumor microenvironment (TME), precision oncology, translational immunotherapy, immune checkpoint inhibition, clinical pharmacology.

© The Author(s) 2025. This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International Licence (https://creativecommons.org/licenses/by-nc/4.0/). The licence permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, provided you give appropriate credit to the original author(s) and the source, provide a link to the licence, and indicate if changes were made. For commercial reuse, permission must be obtained from the copyright holder.

Abbreviations: AI – Artificial intelligence, CAR-T – Chimeric antigen receptor T cell, CD – Cluster of differentiation, DC – Dendritic cell, DAMPs – Damage-associated molecular patterns, GM-CSF – Granulocyte–macrophage colony-stimulating factor, GMP – Good Manufacturing Practice, HSV-1 – Herpes simplex virus type 1, HLA – Human leukocyte antigen, ICIs – Immune checkpoint inhibitors, IFN – Interferon, MHC – Major histocompatibility complex, NK – Natural killer, OV – Oncolytic virus, OVT – Oncolytic virotherapy, PD-1 – Programmed cell death protein 1, PD-L1 – Programmed death-ligand 1, PAMPs – Pathogen-associated molecular patterns, RNA – Ribonucleic acid, TAAs – Tumor-associated antigens, TSAs – Tumor-specific antigens, TME – Tumor microenvironment, VSV – Vesicular stomatitis virus

Introduction

Cancer immunotherapy has transformed modern oncology by shifting the therapeutic focus from direct cytotoxic effects toward strategies that harness and sustain the body's own immune control of tumors. Advances such as immune checkpoint inhibitors, adoptive cell therapies, and cancer vaccines have shown that durable disease control is possible through targeted immune modulation [1–4]. On the other hand, only a subset of patients experiences long-lasting benefit. This gap underscores the pressing need for next-generation immunotherapeutic platforms capable of counteracting tumor immune evasion and overcoming both primary and acquired resistance.

Oncolytic virotherapy is among the most conceptually innovative approaches in immuno-oncology, leveraging the inherent ability of certain viruses to replicate preferentially within malignant cells. Contemporary oncolytic viruses have evolved far beyond their origins as naturally occurring replicating agents. They are now genetically engineered, programmable biological platforms designed to pair selective tumor cell lysis with robust systemic activation of antitumor immunity [5–9]. By inducing immunogenic cell death and promoting the release of tumor antigens, these viruses reshape the tumor microenvironment into an endogenous vaccination site, effectively connecting innate immune activation with the development of adaptive antitumor responses [5, 7, 9].

In parallel, therapeutic cancer vaccines have progressed far beyond early strategies targeting tumor-associated antigens, which often suffered from low immunogenicity. The field has shifted toward precision platforms built around tumor-specific neoantigens – unique peptides generated by somatic mutations. Advances in high-throughput sequencing, improved prediction of HLA binding, and artificial intelligence–driven epitope prioritization now make it possible to design personalized neoantigen vaccines capable of eliciting high-affinity, tumor-restricted T-cell responses [1, 3, 4, 10].

The convergence of oncolytic viruses and therapeutic cancer vaccines is giving rise to a new class of programmable immunotherapy platforms with the capacity to meaningfully transform precision oncology. Yet, their clinical translation remains limited by several persistent challenges, including the suppressive tumor microenvironment, substantial immune heterogeneity, non-linear pharmacokinetics shaped by immune dynamics, and regulatory frameworks that are still adapting to these evolving biologics [3, 6, 7, 8, 11]. From the standpoint of clinical pharmacology and translational medicine, fully harnessing these platforms will require their integration into biomarker-driven, combination-based therapeutic strategies designed to match patients with the most responsive immunologic contexts.

In this narrative review, we focused our attention on the biological foundations, translational integration, and clinical pharmacology considerations of oncolytic viruses and therapeutic cancer vaccines. Evidence was gathered through focused searches in PubMed, Embase, and Cochrane Library, with an emphasis on mechanistic studies, early-phase clinical trials, and combination-immunotherapy research. The purpose is to provide a coherent framework that informs future biomarker-guided and combination-based development strategies.

Mechanisms of action and immune activation

Oncolytic viruses (OVs) take advantage of several distinctive vulnerabilities found in cancer cells—such as weakened interferon signaling, disrupted antiviral defenses, and dysregulated oncogenic pathways—which allow them to replicate preferentially in malignant tissue while leaving healthy cells largely unharmed [4, 7, 9]. After entering tumor cells through specific surface receptors and replicating inside them, OVs trigger lytic cell death, releasing new viral particles that can spread to adjacent cancer cells.

At the same time, this virus-induced tumor destruction releases tumor-associated antigens along with pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). These signals activate dendritic cells, promoting cross-presentation of antigens to $CD8^+$ T cells and natural killer (NK) cells [4, 7, 9]. Through this dual mode of action—direct tumor lysis combined with potent immune activation—OVs

effectively act as *in situ* cancer vaccines, transforming immunologically "cold" tumors into inflamed, immune-responsive lesions [3, 9].

Viral backbones as modular platforms

From a translational perspective, OVs are best understood in terms of their underlying viral backbone rather than as isolated products. The most clinically advanced DNA-based backbones include adenovirus, herpes simplex virus type 1 (HSV-1), and vaccinia virus, while RNA-based platforms are built on reovirus, vesicular stomatitis virus (VSV), measles virus, and Newcastle disease virus [3, 6–9].

DNA viruses generally provide a larger genomic "cargo space", allowing insertion of therapeutic transgenes and offering greater genetic stability. In contrast, RNA viruses tend to stimulate a more robust innate immune response but can accommodate only small payloads. Each viral backbone therefore functions as a programmable chassis whose tissue tropism, safety characteristics, and immune-modulating properties can be tailored to match specific oncologic indications [7, 9].

Engineering strategies, nanotechnology and combination therapies

Modern oncolytic virus platforms incorporate a range of engineering strategies to enhance both safety and therapeutic potency. These include deleting virulence genes, directing viral replication through tumor-selective promoters or microRNA-responsive elements, inserting immunostimulatory transgenes such as granulocyte–macrophage colony-stimulating factor (GM-CSF), and retargeting viral entry by modifying capsid proteins [6, 7, 9].

Nanoparticle-based encapsulation offers an additional layer of refinement by improving systemic delivery, shielding viral particles from neutralizing antibodies, and increasing their accumulation within tumors [6, 9]. Clinically, OVs demonstrate strong synergy with other anticancer therapies—including immune checkpoint inhibitors, chemotherapy, radiotherapy, and adoptive cell therapies—by enhancing immune-cell infiltration and actively reshaping the tumor microenvironment [6, 8, 9, 11].

Therapeutic cancer vaccines and neoantigen platforms

Therapeutic cancer vaccines aim to train the immune system to recognize and eliminate malignant cells by directing responses against tumor-associated antigens (TAAs) or tumor-specific antigens (TSAs). Early vaccine efforts focused largely on TAAs—antigens derived from normal self-proteins that are overexpressed in cancer. However, because these antigens are not truly foreign, they often elicited weak immune responses due to immune tolerance and limited immunogenicity [2–4].

In contrast, neoantigens arise from non-synonymous somatic mutations, insertions or deletions (indels), gene fusions, or viral oncogenes. Because these altered peptides are not present in healthy tissues, they can provoke high-affinity, tumor-restricted T-cell responses [1, 7, 10]. Some neoantigens are shared across patients with similar mutations, while others are entirely personalized based on an individual tumor's mutational profile. Advances in high-throughput sequencing, improved algorithms for predicting human leukocyte antigen (HLA) binding, and artificial intelligence (AI)–assisted prioritization of neoepitopes now enable rapid identification of the most immunogenic targets [1, 7, 10].

Early-phase clinical trials of personalized neoantigen vaccines have demonstrated encouraging results, including strong $CD4^+$ and $CD8^+$ T-cell activation, good tolerability, and increased responsiveness to subsequent PD-1 checkpoint blockade [1, 3, 4, 10]. Still, several barriers—particularly tumor heterogeneity, immune escape through antigen editing, and the substantial time and cost of individualized manufacturing—continue to challenge large-scale clinical implementation [7, 10].

Translational integration of oncolytic viruses and neoantigen vaccines

Oncolytic viruses act as endogenous amplifiers of tumor antigens, promoting the *in situ* release of both tumor-associated antigens and neoantigens. In doing so, they serve as powerful biological adjuvants for therapeutic cancer vaccines [4, 6, 7, 9]. The immune priming induced by OVs enhances major histocompatibility complex (MHC) expression, activates dendritic cells, and increases infiltration of $CD8^+$ T cells into the tumor, collectively strengthening the impact of subsequent neoantigen vaccination [4, 7, 9].

Viewed together as complementary platforms, neoantigen-based vaccines contribute molecular precision, whereas OVs provide robust immune priming, targeted intratumoral delivery, and active remodeling of the tumor microenvironment. This synergy between the two technologies represents one of the most compelling translational strategies for overcoming resistance to immune checkpoint inhibitors in advanced solid tumors [4, 6, 9, 11].

Clinical pharmacology and regulatory challenges

Both oncolytic viruses and therapeutic cancer vaccines display non-linear pharmacokinetics driven largely by immune amplification rather than traditional dose–exposure relationships [5–8]. Factors such as viral replication kinetics, immune-mediated clearance, and variable biodistribution contribute to substantial differences in patient responses. The most common adverse effects resemble influenza-like symptoms and localized inflammation, whereas organ-specific toxicities, although uncommon, remain clinically important [5, 8, 9].

Personalized neoantigen vaccines introduce additional regulatory complexity, including batch-to-batch variability, the need for rigorous validation of bioinformatic pipelines, adaptive clinical trial designs, and individualized good manufacturing practice (GMP) production [1, 4, 10]. Together, these scientific and regulatory considerations place OV and vaccine platforms at the crossroads of precision oncology, advanced biologics regulation, and translational clinical pharmacology [5, 11].

Discussion

Despite strong mechanistic foundations and encouraging preclinical data, both OVs and therapeutic cancer vaccines have achieved only modest clinical benefit when used as monotherapies [1–11]. This gap between preclinical promise and clinical performance reflects a complex interplay of factors, including tumor heterogeneity, profound immune suppression within the tumor microenvironment, and patient-specific variability in immune-driven pharmacokinetics. The immune system itself plays a dual role—serving as the primary driver of therapeutic efficacy while simultaneously acting as a barrier through rapid viral clearance and the development of adaptive resistance [6–9].

From a clinical pharmacology perspective, these platforms challenge traditional dose–response assumptions and require the incorporation of immune-guided biomarkers for appropriate patient selection and response assessment [4, 5, 11]. Combining OV therapy with neoantigen-based vaccines and immune checkpoint inhibitors has emerged as a rational and increasingly compelling strategy to address both primary and acquired resistance [1, 4, 6, 9]. Nevertheless, realizing the full potential of these combination approaches will depend on improved biomarker validation, the development of standardized models that integrate immune and pharmacokinetic dynamics, and regulatory frameworks that accommodate platform-based therapies rather than fixed, single-agent products [5, 11].

Conclusion

Oncolytic viruses and therapeutic cancer vaccines represent a new generation of programmable immunotherapy platforms that unite direct tumor cell destruction with long-lasting immune education. Their ability to reshape the tumor microenvironment, enhance antigen presentation, and work synergistically with immune checkpoint inhibitors places them at the leading edge of precision oncology. Yet, their broader clinical application continues to be constrained by tumor heterogeneity, immune-driven pharmacokinetic variability, and the ongoing difficulty of identifying reliable predictive biomarkers.

Integrating oncolytic virotherapy with neoantigen-based vaccination offers a coherent and promising strategy to counteract immune escape and therapeutic resistance in advanced cancers. Looking ahead, meaningful progress will require biomarker-guided patient selection, standardized frameworks for modeling immune–pharmacokinetic interactions, adaptive clinical trial designs, and regulatory approaches that recognize these therapies as dynamic platform technologies rather than fixed biological products. A more deeply embedded translational clinical pharmacology perspective will be essential for turning these innovative modalities into cancer therapies that deliver consistent and durable benefit.

Acknowledgements

Conflict of interests

The authors declare no conflict of interest.

Funding

This research was funded by a project under The Health Program (PS) 2021–2027, Policy Objective 1, Priority 5, project title “Development of translational research for vaccines, serums and other biological drugs – Acronym CANTAVAC 2.0”, SMIS code 326920. The funders had no role in the design of the study; in the collection, analyses or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

References

1. Blass E, Ott PA. 2021. Advances in the development of personalized neoantigen-based therapeutic cancer vaccines. Nat Rev Clin Oncol 18:215–229. https://doi.org/10.1038/s41571-020-00460-2
2. Hollingsworth RE, Jansen K. 2019. Turning the corner on therapeutic cancer vaccines. NPJ Vaccines 4. https://doi.org/10.1038/s41541-019-0103-y
3. Jou J, Harrington K, Zocca MB, Ehrnrooth E, Cohen EE. 2020. The changing landscape of therapeutic cancer vaccines—novel platforms and neoantigen identification. Clin

Cancer Res 27:689–703. https://doi.org/10.1158/1078-0432.CCR-20-0245
4. Fan T, Zhang M, Yang J, Zhu Z, Cao W, Dong C. 2023. Therapeutic cancer vaccines: advancements, challenges and prospects. Signal Transduct Target Ther 8. https://doi.org/10.1038/s41392-023-01674-3
5. Macedo N, Miller D, Haq R, Kaufman HL. 2020. Clinical landscape of oncolytic virus research in 2020. J Immunother Cancer 8. https://doi.org/10.1136/jitc-2020-001486
6. Chen L, Zuo M, Zhou Q, Wang Y. 2023. Oncolytic virotherapy in cancer treatment: challenges and optimization prospects. Front Immunol 14. https://doi.org/10.3389/fimmu.2023.1308890
7. Martínez-Quintanilla J, Seah I, Chua M, Shah K. 2019. Oncolytic viruses: overcoming translational challenges. J Clin Invest 129:1407–1418. https://doi.org/10.1172/JCI122287
8. Chaurasiya S, Fong Y, Warner SG. 2021. Oncolytic virotherapy for cancer: clinical experience. Biomedicines 9. https://doi.org/10.3390/biomedicines9040419
9. Aljabali AAA, Bashatwah RM, Gammoh O. 2025. The dual promise of oncolytic viruses: selective targeting and therapeutic enhancement in cancer treatment. Exploration of Immunology. https://doi.org/10.37349/ei.2025.1003204
10. Li X, You J, Hong L, Liu W, Guo P, Hao X. 2023. Neoantigen cancer vaccines: a new star on the horizon. Cancer Biol Med 21:274–311. https://doi.org/10.20892/j.issn.2095-3941.2023.0395
11. Sierra-Davidson K, Cohen S, Emerick KS, Kaufman HL. 2025. Opportunities and challenges in the clinical application of anticancer virotherapy. Expert Rev Anticancer Ther. https://doi.org/10.1080/14737140.2025.2584499