

Engineered Immune Cells and Oncolytic Viruses: Converging Pathways in Next-Generation Cancer Immunotherapy

Liren Zhang

*American International School of Cape Town, Cape Town, The Republic of South Africa
liren.uni@gmail.com*

Abstract. Cancer remains one of the most complex and persistent challenges in global health despite decades of therapeutic innovation. While surgery, chemotherapy, and radiotherapy have improved survival in selected early-stage malignancies, advanced cancers frequently develop resistance due to tumor heterogeneity, immune evasion, and systemic toxicity limitations. Immunotherapy has emerged as a transformative modality capable of harnessing endogenous immune mechanisms for tumor eradication. However, durable success remains largely confined to hematologic malignancies, with solid tumors demonstrating substantial resistance. This paper synthesizes current evidence from fourteen peer-reviewed studies to examine the immunological principles governing chimeric antigen receptor T-cell (CAR-T) therapy, T cell receptor–engineered T-cell (TCR-T) therapy, chimeric antigen receptor natural killer (CAR-NK) therapy, and oncolytic virotherapy. Particular emphasis is placed on the interplay between innate immunity, adaptive immunity, and tumor microenvironment remodeling. By analyzing both the mechanistic foundations and translational limitations of these platforms, this paper argues that the future of cancer immunotherapy depends on integrated, systems-level strategies rather than isolated therapeutic enhancement.

Keywords: Cancer, Immunotherapy, Integrated and systems-level strategies

1. Introduction

Cancer continues to impose a growing global health burden. Traditional treatments—including surgery, chemotherapy, and radiotherapy—remain effective primarily for early-stage disease and often fail in advanced tumors. These limitations arise from tumor heterogeneity, stromal barriers, metabolic constraints, and treatment toxicity. Even immune checkpoint inhibitors benefit mainly tumors with strong immunogenicity, leaving most solid tumors resistant and highlighting the need for more programmable and durable immunotherapies [1, 2].

Genetic engineering has enabled immune cells to be redesigned with synthetic receptors and enhanced functions. CAR-T therapy, particularly in CD19- and BCMA-targeted blood cancers, has shown unprecedented remission rates [1]. However, efficacy in solid tumors remains limited due to antigen escape, poor infiltration, stromal obstruction, and suppressive cytokine environments [3, 4]. TCR-engineered T cells and CAR-NK therapies expand antigen targeting and improve safety, yet still face similar challenges inherent to solid tumor biology [5-7]. Oncolytic viruses (OVs) have evolved from cytolytic tools into immunomodulatory platforms. T-VEC demonstrated that viruses

can induce tumor cell lysis while activating anti-tumor immunity [8]. Modern OV's promote immunogenic cell death, enhance antigen presentation, and recruit T cells into tumors [9, 10]. Engineering advances, including cytokine-armed viruses, further amplify immune activation while maintaining localized effects [11]. Emerging constructs such as NDV-GT introduce novel mechanisms, including hyperacute rejection-mediated tumor remodeling [12].

Although engineered immune cells and oncolytic viruses were developed as distinct modalities, increasing evidence suggests strong therapeutic synergy. OV's remodel the tumor microenvironment, enhancing antigen release and T-cell infiltration, enabling more effective function of engineered immune cells [2, 7]. Conversely, adoptive cell therapies can sustain immune pressure following viral debulking [4]. Despite rapid progress, these modalities are often studied in isolation, obscuring their combinatorial potential. This review addresses these gaps by comparing CAR-T, TCR-T, CAR-NK, and OV systems as coordinated immunotherapy strategies.

2. Current approaches in engineered immune cell therapies

2.1. CAR-T cells

Chimeric antigen receptor (CAR) T cell therapy has emerged as a transformative advance in cancer immunotherapy, demonstrating unprecedented remission rates in refractory B-cell malignancies. By encoding synthetic receptors into patient-derived T cells, CAR-T enables direct, MHC-independent recognition of tumor-associated antigens and bypasses limitations of endogenous activation. Durable responses in acute lymphoblastic leukemia (ALL), diffuse large B-cell lymphoma (DLBCL), and multiple myeloma establish CAR-T as a central platform [1]. Its success in hematologic cancers reflects favorable biological context, including homogeneous antigens and lack of stromal barriers, enabling efficient trafficking and expansion. In contrast, efficacy in solid tumors is limited by suppressive microenvironments, metabolic constraints, antigen heterogeneity, and T-cell exhaustion. CAR-T therapy also causes toxicities such as cytokine release syndrome (CRS) and ICANS due to systemic immune activation [3]. Next-generation strategies aim to enhance persistence, specificity, and resistance to immunosuppression through multi-antigen targeting, armored CAR-T cells, and combination approaches [4].

2.2. TCR-T cells

T cell receptor-engineered T (TCR-T) cell therapy complements CAR-T by enabling recognition of intracellular tumor antigens presented on human leukocyte antigen (HLA) molecules. Unlike CAR-T cells, TCR-T cells access a broader antigen landscape, including lineage-specific proteins and tumor-specific neoantigens, which is particularly relevant for solid tumors. Early clinical successes in synovial sarcoma and melanoma demonstrated durable tumor regression targeting antigens such as NY-ESO-1 [5], highlighting potential to address antigen heterogeneity and immune evasion. Despite these advantages, TCR-T therapy faces key constraints. HLA restriction limits patient eligibility, and high-affinity TCRs carry safety risks due to cross-reactivity with self-peptides. These challenges underscore the balance between sensitivity and specificity. Recent advances focus on affinity tuning and improved specificity, with structural approaches reducing off-target toxicity [13]. Neoantigen-specific TCRs further enable precise targeting. Collectively, TCR-T therapy expands adoptive cell therapy beyond surface antigens, though continued refinement and combination strategies remain essential.

2.3. CAR-NK cells

CAR-engineered natural killer (CAR-NK) cell therapy offers a complementary and potentially safer alternative to CAR-T cells by harnessing the innate cytotoxicity and allogeneic compatibility of NK cells. Unlike T cells, NK cells integrate activating and inhibitory signals through germline-encoded receptors such as NKG2D, NKp30/44/46, and KIRs, enabling recognition of "stressed" or HLA-I–downregulated tumor cells independent of a single antigen [6]. When equipped with CARs, NK cells gain targeted recognition while retaining endogenous killing pathways and antibody-dependent cellular cytotoxicity (ADCC), reducing immune escape. Clinically, CAR-NK cells show promising activity in B-cell malignancies with improved safety compared to CAR-T cells. Early trials using cord blood–derived CD19 CAR-NK cells reported high response rates with no graft-versus-host disease (GvHD), no ICANS, and only low-grade CRS [6]. A landscape analysis of 120 trials highlights rapid expansion across hematologic cancers, solid tumors, and autoimmune diseases using diverse platforms [14], supporting the feasibility of "off-the-shelf" CAR-NK products. Despite these advantages, CAR-NK therapies face similar barriers in solid tumors, including antigen heterogeneity, limited trafficking, and suppressive microenvironments [7]. Their short lifespan also limits persistence. To address this, next-generation designs incorporate IL-15 armoring, chemokine receptor engineering, and resistance to inhibitory signals [6, 14], supporting integration into multimodal immunotherapy strategies [7].

3. Oncolytic virotherapy

3.1. HSV-1–based T-VEC: foundation of clinical OV therapy

The clinical approval of talimogene laherparepvec (T-VEC), a genetically modified herpes simplex virus type 1 (HSV-1), marked a critical milestone in oncolytic virotherapy. Prior to T-VEC, oncolytic viruses were largely considered experimental with uncertain translational potential. A phase III trial in advanced melanoma demonstrated that oncolytic virotherapy could achieve durable responses with a manageable safety profile, establishing clinical feasibility [8]. Importantly, T-VEC represents a rationally designed, dual-action viral immunotherapy integrating tumor-selective replication with immune modulation. Following intratumoral administration, T-VEC replicates within tumor cells, causing oncolysis and release of tumor-associated antigens. It is engineered to express GM-CSF, promoting recruitment and activation of antigen-presenting cells. This converts viral lysis from a cytotoxic event into an immunologically productive process, facilitating antigen presentation and T-cell priming. Through this mechanism, T-VEC provided clinical evidence that oncolytic viruses can function as both tumor-debulking agents and initiators of anti-tumor immunity. Durable responses suggest benefits arise from sustained immune engagement. Thus, T-VEC established a foundational paradigm for oncolytic virotherapy based on localized delivery, tumor-selective replication, and immune activation.

3.2. Evidence across multiple OV platforms

While T-VEC established proof-of-concept for clinical oncolytic virotherapy, the broader viability of this approach depends on evidence that efficacy and safety extend beyond a single platform. Systematic evaluation across multiple OV platforms is therefore essential to assess whether oncolytic virotherapy represents a robust and generalizable modality. A meta-analysis synthesized randomized controlled trials of diverse oncolytic viruses, including adenoviruses and HSV-based

vectors [9]. OV-containing treatments showed improved objective response rates with acceptable safety across multiple cancer types. By focusing on randomized trials, this study provided high-level evidence supporting clinical activity beyond single-arm observations, while also highlighting variability depending on viral platform and delivery strategy. Complementing this, researchers analyzed advanced melanoma, confirming consistent clinical activity, particularly for HSV-based platforms [10]. OV therapy also showed enhanced efficacy when combined with immune checkpoint inhibitors, suggesting a role in sensitizing tumors to immune-mediated clearance. Safety profiles remained favorable. Together, these analyses demonstrate that OV efficacy is supported across platforms and contexts, reinforcing its clinical credibility while highlighting the importance of optimizing viral design and combination strategies.

3.3. Cytokine-armed HSVs

Although oncolytic viruses can initiate anti-tumor immune responses through virus-mediated tumor cell lysis, this intrinsic immunogenicity is often insufficient to overcome the immunosuppressive tumor microenvironment. Consequently, recent advances focus on engineering viral vectors to amplify immune responses through immunomodulatory payloads. Among these, cytokine-armed HSVs represent a well-developed strategy. Building on GM-CSF-expressing T-VEC, next-generation HSVs are engineered to express cytokines such as IL-12 and IL-15. These cytokines promote T-cell and NK cell activation, enhance persistence, and facilitate immune infiltration. Preclinical and early clinical studies show that cytokine-armed HSVs increase intratumoral immune recruitment, reduce tumor burden, and improve outcomes compared with unarmed vectors [11]. A key advantage of OV-based cytokine delivery is spatial and temporal restriction. By confining cytokine expression to infected tumor sites, this approach reduces systemic toxicity while enabling higher local concentrations and maintaining safety. Collectively, these advances illustrate a transition toward programmable immunotherapy platforms, where engineered OVs can be tailored to overcome specific tumor barriers. Cytokine-armed HSVs extend the T-VEC paradigm and provide a foundation for future combination strategies.

4. Other therapy

4.1. Hyperacute rejection–engineered NDV-GT

A major conceptual advance in oncolytic virotherapy is illustrated by the NDV-GT platform [12]. Rather than focusing on direct oncolysis, this engineered Newcastle disease virus exploits pre-existing innate immune memory by expressing the α -Gal epitope, engaging naturally occurring anti-Gal antibodies and activating the complement cascade to trigger hyperacute rejection–like responses. Mechanistically, NDV-GT induces complement deposition, endothelial damage, and thrombotic vascular shutdown, resulting in rapid tumor ischemia and collapse [12]. Tumor regression is driven primarily by immune-mediated vascular destruction and immune cell recruitment rather than viral replication. Validation in a CRISPR-engineered nonhuman primate model and early human data (n = 20) demonstrating high disease control with minimal toxicity underscore its translational potential.

4.2. OV-immune checkpoint inhibitor synergy

Beyond single-agent activity, oncolytic viruses have emerged as potent immune primers that enable downstream immunotherapies. By inducing type I interferon signaling, promoting tumor antigen release, and increasing immune cell infiltration, OV can convert immunologically "cold" tumors into ICI-responsive states. Researchers systematically review clinical and preclinical evidence demonstrating that OV pretreatment enhances the efficacy of immune checkpoint inhibitors, particularly in gastrointestinal malignancies characterized by low baseline immune infiltration [2]. Critically, this synergy reflects a sequential logic rather than additive efficacy: OVs establish a permissive immune microenvironment, while ICIs sustain and amplify pre-existing T cell responses [2]. These findings support the repositioning of OVs as upstream modulators that address immune exclusion and priming bottlenecks that limit ICI responsiveness.

4.3. Synergy with CAR-T and CAR-NK cell therapies

A similar enabling role for OVs has been demonstrated in combination with engineered cell therapies. Studies show that OV pretreatment enhances CAR-T and CAR-NK trafficking, disrupts stromal and vascular barriers, and improves effector cell persistence within solid tumors [4, 7]. In this context, OVs do not modify CAR design or antigen specificity; instead, they remodel the tumor microenvironment to permit effective cell therapy execution. Conversely, CAR-T and CAR-NK cells can eliminate residual disease following OV-mediated debulking, establishing a rational division of labor between microenvironmental conditioning and targeted cytotoxicity [4]. Together, these multimodal strategies highlight a unifying principle: the future of solid tumor immunotherapy lies in infrastructure-first approaches, where engineered viruses enable the successful deployment of downstream immune interventions.

5. Discussion

Despite substantial advances in engineered immune cell therapies and oncolytic virotherapy, durable efficacy in solid tumors remains limited. This reflects not insufficient potency of individual modalities, but a mismatch between therapeutic design and the biological architecture of solid tumors. Across CAR-T, TCR-T, CAR-NK, and oncolytic virus platforms, a recurring theme is the dominance of tumor microenvironmental constraints over cell-intrinsic cytotoxic capacity [3, 7]. Adoptive cell therapies exemplify this challenge. CAR-T cells show remarkable efficacy in hematologic malignancies but fail in solid tumors due to impaired trafficking, antigen heterogeneity, metabolic competition, and immunosuppressive signaling [3, 4]. TCR-engineered T cells expand antigen targeting but remain limited by HLA restriction, exhaustion, and safety risks [5, 13]. CAR-NK platforms improve safety and scalability yet still face barriers in persistence, infiltration, and suppression within hostile tumor niches [6, 7, 14]. These shared limitations indicate that optimizing immune cells alone is insufficient. Oncolytic viruses address complementary constraints by reshaping the tumor ecosystem. Viral infection and tumor lysis release neoantigens, activate type I interferon signaling, and recruit antigen-presenting cells [9, 10], while cytokine-armed viruses further amplify these effects [11]. Platforms such as NDV-GT induce vascular collapse and immune recruitment via α -Gal-mediated complement activation [12]. Collectively, these findings support a hierarchical model in which oncolytic viruses act as upstream conditioners and engineered immune cells as downstream executors, explaining why combination strategies outperform single-agent approaches [2, 7].

6. Conclusion

Engineered immune cells and oncolytic viruses represent powerful advances in cancer immunotherapy, yet each has limitations when used alone. CAR-T, TCR-T, and CAR-NK therapies offer high specificity but are constrained in solid tumors by antigen heterogeneity, immune suppression, and physical barriers. Oncolytic viruses, by contrast, reshape the tumor ecosystem but lack standalone durability. Evidence suggests these modalities are complementary: oncolytic viruses enable immune infiltration and activation, while engineered immune cells deliver targeted clearance. Platforms such as NDV-GT further highlight how viral engineering can unlock innate immune mechanisms. Future success will depend on integrated, systems-level strategies for durable cancer control.

References

- [1] June, C. H., & Sadelain, M. (2018). Chimeric antigen receptor therapy. *New England Journal of Medicine*, 379(1), 64–73. <https://doi.org/10.1056/NEJMr1706169>
- [2] Ren, Y., Tao, J., & Hua, J. (2022). Oncolytic viruses combined with immune checkpoint inhibitors: Multi-modal immunotherapy in gastrointestinal tumors. *Frontiers in Immunology*, 13, 961796. <https://doi.org/10.3389/fimmu.2022.961796>
- [3] Sterner, R. C., & Sterner, R. M. (2021). CAR-T cell therapy: Current limitations and potential strategies. *Blood Cancer Journal*, 11, 69. <https://doi.org/10.1038/s41408-021-00459-7>
- [4] Sanomachi, T., Katsuya, Y., Nakatsura, T., & Koyama, T. (2025). Next-generation CAR-T and TCR-T cell therapies for solid tumors: Innovations, challenges, and global development trends. *Cancers*, 17(12), 1945. <https://doi.org/10.3390/cancers17121945>
- [5] Shafer, P., & Leen, A. M. (2022). Cancer therapy with TCR-engineered T cells: Current strategies, challenges, and prospects. *Frontiers in Immunology*, 13, 835762. <https://doi.org/10.3389/fimmu.2022.835762>
- [6] Pang, Z., Wang, Z., Li, F., Feng, C., & Mu, X. (2022). Current progress of CAR-NK therapy in cancer treatment. *Cancers*, 14(17), 4318. <https://doi.org/10.3390/cancers14174318>
- [7] Peng, L., Zhang, Y., Qian, J., & Shi, J. (2024). CAR-T and CAR-NK as cellular cancer immunotherapy for hematologic malignancies and solid tumors. *Cellular & Molecular Immunology*, 21, 396–412. <https://doi.org/10.1038/s41423-024-01207-0>
- [8] Andtbacka, R. H. I., Collichio, F., Harrington, K. J., Kaufman, H. L., Dummer, R., DeRosa, F., Amatruda, T., & Chesney, J. (2015). Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. *Journal of Clinical Oncology*, 33(25), 2780–2788. <https://doi.org/10.1200/JCO.2014.58.3377>
- [9] Li, Z., Jiang, Z., Zhang, Y., Huang, X., & Liu, Q. (2020). Efficacy and safety of oncolytic viruses in randomized controlled trials: A systematic review and meta-analysis. *Cancers*, 12(6), 1416. <https://doi.org/10.3390/cancers12061416>
- [10] Wang, C., Lu, N., Yan, L., & Li, Y. (2023). The efficacy and safety assessment of oncolytic virotherapies in advanced melanoma: A systematic review and meta-analysis. *Virology Journal*, 20, 252. <https://doi.org/10.1186/s12985-023-02220-x>
- [11] Wang, H., Borlongan, M., Kaufman, H. L., & others. (2024). Cytokine-armed oncolytic herpes simplex viruses: A game-changer in cancer immunotherapy? *Journal for ImmunoTherapy of Cancer*, 12(5), e008025. <https://doi.org/10.1136/jitc-2023-008025>
- [12] Zhong, L., Gan, L., Wang, B., Wu, T., Yao, F., Gong, W., Peng, H., Deng, Z., Xiao, G., Liu, X., Na, J., Xia, D., Yu, X., Zhang, Z., Xiang, B., Huo, Y., Yan, D., Dong, Z., Fang, F., ... Zhao, Y. (2025). Hyperacute rejection-engineered oncolytic virus triggers broad antitumor immunity. *Cell*, 188(7), 1459–1477.e23. [https://www.cell.com/cell/fulltext/S0092-8674\(24\)01423-5](https://www.cell.com/cell/fulltext/S0092-8674(24)01423-5)
- [13] Baulu, E., Mailleux, L., & Michaux, A. (2023). TCR-engineered T cell therapy in solid tumors: State of the art and future prospects. *Science Advances*, 9(12), ead3700. <https://doi.org/10.1126/sciadv.adf3700>
- [14] Jørgensen, L. V., Christensen, E. B., Barnkob, M. B., & Barington, T. (2025). The clinical landscape of CAR NK cells. *Experimental Hematology & Oncology*, 14, 46. <https://doi.org/10.1186/s40164-025-00633-8>