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Advancing Personalized Cancer Immunotherapy through the Novel PeptiCRAd Platform

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Abstract

The rapid evolution of cancer immunotherapy has transformed treatment paradigms across multiple malignancies, yet durable clinical responses remain limited to only a subset of patients. One of the major challenges remains the presence of immunologically “cold” tumors, which are characterized by poor immune-cell infiltration and limited responsiveness to immune checkpoint blockade. In this context, oncolytic virotherapy has emerged as an attractive therapeutic strategy capable of both directly lysing malignant cells and reshaping the tumor microenvironment to stimulate anti-tumor immunity. The study by Ylösmäki and colleagues introduces an innovative approach designed to enhance these immunological effects through the development of VALO-D102, a dual OX40L/CD40L-expressing oncolytic adenovirus integrated into the PeptiCRAd cancer vaccine platform.

Keywords

Oncolytic adenovirus; PeptiCRAd; cancer immunotherapy; personalized cancer vaccine; PD-1 blockade; tumor microenvironment; neoantigens.

Introduction

The rapid evolution of cancer immunotherapy has transformed treatment paradigms across multiple malignancies, yet durable clinical responses remain limited to only a subset of patients [1]. One of the major challenges remains the presence of immunologically “cold” tumors, which are characterized by

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poor immune-cell infiltration and limited responsiveness to immune checkpoint blockade [2]. In this context, oncolytic virotherapy has emerged as an attractive therapeutic strategy capable of both directly lysing malignant cells and reshaping the tumor microenvironment to stimulate anti-tumor immunity [3–7]. The study by Ylösmäki and colleagues introduces an innovative approach designed to enhance these immunological effects through the development of VALO-D102, a dual OX40L/CD40L-expressing oncolytic adenovirus integrated into the PeptiCRAd cancer vaccine platform [8].

The significance of this work lies in the development of a multifaceted immunotherapeutic strategy that combines oncolytic virotherapy with precision cancer vaccination. The authors utilized a novel oncolytic adenovirus, VALO-D102, engineered to encode two potent immune co-stimulatory ligands, OX40L and CD40L, and incorporated it into the PeptiCRAd platform by coating viral particles with tumor-associated antigens [8]. Unlike conventional oncolytic viruses that primarily rely on direct tumor lysis, this strategy is designed to simultaneously enhance antigen presentation, T-cell priming, and long-term anti-tumor immunity. CD40L is known to activate antigen-presenting cells and promote efficient cytotoxic T-cell activation, whereas OX40L supports T-cell expansion, survival, and memory formation [9,10]. By integrating these immune-stimulatory pathways with tumor antigen delivery, the PeptiCRAd platform aims to amplify both innate and adaptive immune responses while promoting a more inflamed and immunologically active tumor microenvironment.

The incorporation of VALO-D102 into the PeptiCRAd platform further distinguishes this strategy from conventional oncolytic virus therapies. PeptiCRAd enables rapid coating of adenoviral particles with tumor-specific peptides through electrostatic interactions between the viral capsid and polylysine-modified antigens. In the present study, peptides derived from NY-ESO-1 and MAGE-A3 were selected to generate the clinical candidate PeptiCRAd-1. This modular design offers substantial flexibility and aligns with the growing interest in personalized cancer vaccines tailored to individual tumor antigen profiles. The ability to rapidly adapt the platform to patient-specific neoantigens may represent a significant advantage in overcoming tumor heterogeneity and acquired immune resistance.

The preclinical findings presented in murine melanoma models further support the therapeutic potential of this approach. The murine surrogate virus VALO-mD901 induced stronger anti-tumor responses than unarmed adenoviral vaccines, resulting in improved tumor growth control and increased infiltration of tumor-specific CD8+ T cells into both tumors and tumor-draining lymph nodes. Particularly noteworthy was the observation that treatment generated systemic antigen-specific T-cell responses, suggesting the induction of durable immunological memory rather than solely localized tumor control. This aspect is especially relevant because insufficient induction of tumor-specific T-cell responses remains a major limitation of many current oncolytic virotherapy platforms.

Another notable aspect of the study is the investigation of combination therapy with PD-1 blockade. The integration of PeptiCRAd with anti-PD-1 therapy produced superior tumor control and survival compared with either treatment alone. These findings reinforce the growing consensus that oncolytic viruses may function as immune sensitizers capable of converting poorly infiltrated tumors into checkpoint-responsive lesions. The increased proportion of complete responders observed in the combination therapy group

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highlights the therapeutic promise of integrating virotherapy with immune checkpoint inhibition in future clinical applications.

Despite these encouraging findings, several limitations should be acknowledged. Human adenovirus 5 does not efficiently replicate in murine cells, restricting the ability of the animal models to fully reproduce viral replication-dependent tumor destruction observed in human tissues. Consequently, the therapeutic efficacy observed in the study may underestimate the potential clinical activity of the platform in patients. Additionally, the murine surrogate virus utilized a CMV promoter to facilitate transgene expression in mouse cells, resulting in expression patterns that differ from the tumor-selective regulation expected for VALO-D102 in human tumors. These factors should be considered when interpreting the translational relevance of the preclinical data.

From a clinical perspective, the study arrives at a particularly relevant moment in the development of next-generation cancer immunotherapies. The ongoing Phase I clinical trial, *START: Safety and Anti-Tumor Activity of PeptiCRAd-1 in Treatment of Cancer* (ClinicalTrials.gov ID: NCT05492682), is currently evaluating PeptiCRAd-1 in patients with triple-negative breast cancer, melanoma, non-small cell lung cancer, colorectal cancer, and sarcoma. The study reflects the increasing demand for therapies capable of overcoming resistance to immune checkpoint inhibitors in advanced solid tumors. While definitive proof-of-concept efficacy data are expected following study completion, interim clinical observations have already demonstrated an acceptable safety profile together with preliminary evidence of anti-tumor activity [11]. Furthermore, the selection of NY-ESO-1 and MAGE-A3 as target antigens is supported by extensive prior evidence demonstrating their immunogenicity and broad expression across multiple tumor types.

Overall, the work by Ylösmäki et al. represents an important contribution to the field of oncolytic immunotherapy. By integrating tumor-selective viral therapy, antigen delivery, immune co-stimulation, and checkpoint sensitization into a single therapeutic platform, the authors provide a promising framework for the future development of personalized cancer vaccines. The PeptiCRAd strategy illustrates how rationally engineered viral platforms may help overcome current limitations in immunotherapy and improve outcomes for patients with immunologically resistant cancers.

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Competing interests

Author LK is an employee and/or shareholder of Valo Therapeutics.

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