

Viral Vector-Based Personalized Cancer Vaccine: Current Mechanisms, Clinical Evidence and Future Directions

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Abstract. Cancer immunotherapy has become a more popular method to treat cancer. It uses patients' own immune system to recognize and eliminate cancer cells. Within the different forms of immunotherapy, personalized cancer vaccines (PCVs) stand out as a revolutionary option as they target individual-specific neoantigens. This allows for precise interventions that can trigger long-term immune responses. PCVs are usually developed using three major platforms: mRNA, DNA, and viral vector vaccines. This review focuses on the viral vector strategies, with representative examples of NOUS-PEV, GRANITE, and TG4050. Viral vector vaccines are very good at delivering antigens effectively, trigger strong immune response, and activate both innate and adaptive immunity, leading to strong CD8+ and CD4+ T cell responses. Early clinical trials have shown encouraging safety and immunogenicity, as well as signals of efficacy across different tumor types. However, there are still obstacles remaining. This includes limited accuracy of neoantigen prediction, complex manufacturing process, and tumor-mediated immunosuppression. Future progress is likely going to rely on multi-omics integration, AI-driven epitope prioritization, innovative delivery platforms, and combination strategies with other immunotherapies. Collectively, PCVs have the potential to become the cornerstone of precision oncology to provide personalized and durable therapeutic benefits to cancer patients.

Keywords: Personalized Cancer Vaccine, Viral vector, Neoantigen, Immunotherapy.

1. Introduction

In recent decades, cancer immunotherapy has opened new research approach for treating cancer. Unlike traditional chemotherapy and radiotherapy, immunotherapy recognizes and eliminates cancer cells by using the host's own immune system, providing durable effects through immune memory. Personalized cancer vaccines, PCVs, has become one of the most popular research hotspots. Due to different patients' genetic mutations and tumor heterogeneity, off-the-shelves vaccines usually cannot offer effective immune response. However, personalized vaccines can target on patient's specific neoantigens, giving them a more precise treatment and sustain their anti-tumor immune response.

The main platform of PCVs being researched includes mRNA vaccines, DNA vaccines, and viral vector-based vaccines. Among them, mRNA vaccines are noticed because they can be synthesised quickly and has flexible design. But the progress is slow due to limited molecular stability and delivery efficiency. In comparison, viral vector-based vaccines are effective at delivering genes and promoting the production of antigen, which in turn boost the immune response against tumours due to their ability to stimulate the immune system.

While personalized cancer vaccines hold major promise, they are still facing obstacles. Challenges includes the limited accuracy of neoantigen prediction, long manufacturing timeline, safety concerns related to delivery system, and immune tolerance [1]. Viral vector vaccines provides some ways to address these limitations, but their design strategies, immune mechanisms and clinical outcomes varies widely across platforms [2]. Therefore, a thorough comparison and systematic review of viral vector-based PCVs is essential. This study will first provide a comparative overview of major PCV platforms, followed by an in-depth discussion on the mechanisms, clinical application and challenge of three representative viral vector PCVs: NOUS-PEV, GRANITE and TG4050.

2. Comparative Overview of Major PCV Platforms

The distinctive feature of different PCV platforms have been systematically summarized in preclinical studies [1]. To present the advantages and limitations of these three types of personalized cancer vaccine more intuitively, this study has summarized their key features in Table 1.

Table 1. Comparison of major platforms for personalized cancer vaccine, including mRNA, DNA, and viral vector vaccines [1]

Platform	Advantages	Limitations
mRNA vaccines	Rapid synthesis Flexible design Non-integrating Good safety profile	Limited stability Cold chain delivery dependent
DNA vaccines	Sustained antigen expression Easy storage and manufacture	Limited transfection efficiency Weak immunogenicity Slow clinical translation
Viral vector vaccines	High gene delivery efficiency Strong immunogenicity May activate innate and adaptive immunity	High complexity in manufacture Safety concerns of pre-existing immunity

Compared with mRNA and DNA vaccines, the advantage of viral vector vaccines in personalized cancer vaccine is more pronounced. On the one hand, viral vector vaccines have stronger gene delivery capacity, which can achieve high efficiency antigen expression in dendritic cells and therefore trigger strong responses in cytotoxic T lymphocytes (CD8⁺ T cells) and helper T cells (CD4⁺ T cells) [2]. On the other hand, the natural immunostimulatory signals carried by viral vectors like adenovirus and modified vaccinia Ankara (MVA) can enhance innate immune responses, providing better environment for developing adaptive immunity [3]. These features make viral vector vaccines popular in personalized cancer vaccine clinical trials, showing superiority in aspects of triggering polyclonal T cell responses and building immune memory. Therefore, viral vector vaccines have become one of the most important research approaches for personalized cancer vaccine.

3. Mechanisms of Personalized Cancer Vaccines

The basic principle of viral vector personalized cancer vaccine is to deliver patient-specific cancer neoantigen-encoding sequence to the host cells, enabling their intracellular processing and MHC I/II mediated antigen display [2,3]. This process will activate both CD8⁺ cytotoxic T lymphocytes (CTLs) and CD4⁺ helper cells, and this will start a targeted immune response that effectively recognizes and destroys tumor cells [1].

The development process of a viral vector PCV needs several steps. Firstly, tumors and corresponding healthy tissues will be collected from the patient. Secondly, DNA and RNA sequencing are conducted, and the resulting data are combined with HLA typing to predict potential neoantigens. Thirdly, bioinformatic algorithms will be employed to rank the predicted epitopes, with the highest-scoring ones selected for further development [4]. Then, a viral vector is built to encode selected epitopes to guarantee that the antigen are properly expressed in host cells [3]. Depending on patient's specific immune and clinical characteristics, individualized vaccination strategy will be created [2]. The vaccine production and quality control will be carried under Good Manufacturing Practice (GMP) to make sure it is safe to use and to keep consistency [3]. Eventually, the vaccine will be administered clinically, with the aim to induce a long-lasting and tumor-targeted immune reaction [4]. The step-by-step process of viral vector based PCV development is summarized in Figure 1.

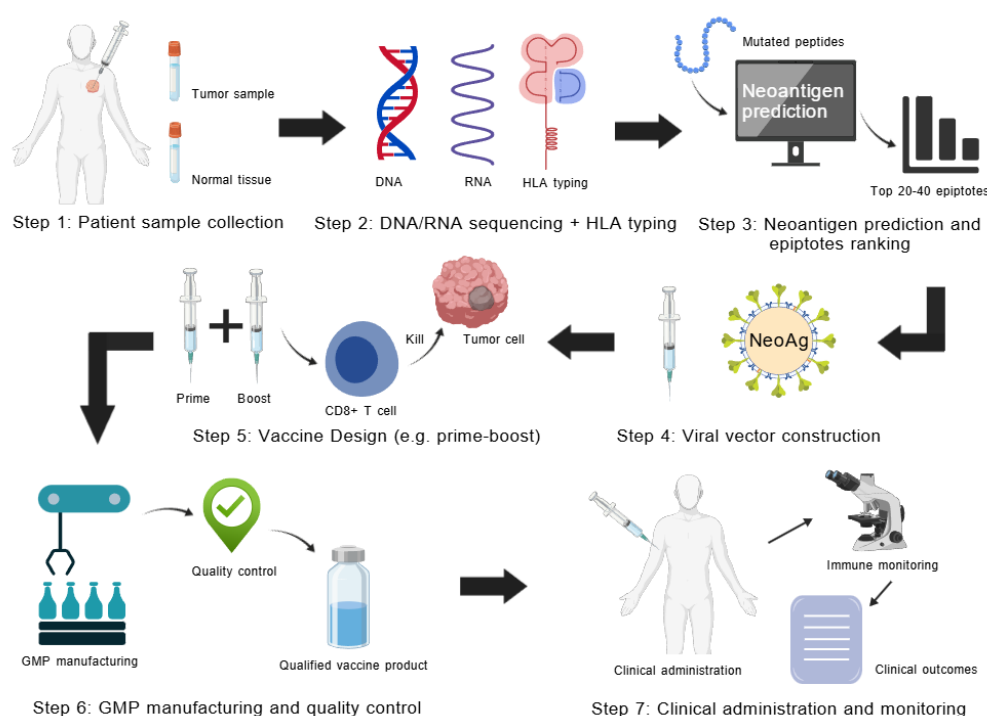


Fig 1. Procedure of viral-based personalized cancer vaccine development.

Aside from the overall workflow, various viral vectors provide unique immunological advantages. Some of the most commonly used viral vectors include adenovirus, adeno-associated virus (AAVs) and modified vaccinia Ankara (MVA). Adenoviruses are known for carrying a relatively large amount of genetic material and their ability to efficiently deliver genes into cells [5]. AAVs offer long-term gene expression and tend to trigger a relatively mild immune response [6]. MVAs have powerful capacity to activate the immune system and can demonstrate a strong safety profile during clinical trials [7]. Each viral vector delivers antigen in different ways, such as by enhancing MHC-I pathway to activate CD8+ T cells or altering cytokine secretion to adjust the tumor microenvironment [1]. These features show how adaptable viral vector platforms are in generating strong immune responses for PCVs.

4. Clinical applications

4.1. NOUS-PEV

NOUS-PEV is a personalized cancer vaccine platform that uses a heterologous prime-boost approach. It uses GAd20 adenovirus as the priming vector and MVA as the boosting vector. A key feature of NOUS-PEV is it can combine about 60 patient-specific neoantigens into a single vaccine [8]. These neoantigens are selected through next generation sequencing and bioinformatics prediction based on tumor mutations and HLA binding affinity. Viral vectors are engineered to effectively deliver and assist the expression of neoantigen sequences within antigen-presenting cells, particularly dendritic cells. The expressed antigens are processed and presented through both MHC class I and II pathways, causing the activation of cytotoxic CD8+ and helper CD4+ subsets of T cells, respectively. NOUS-PEV offers higher transduction efficiency and more robust T cell priming compared with other types of vaccine platforms like DNA or mRNA vaccines. These elements make NOUS-PEV adaptable for personalized immunotherapy and create great potential for clinical translations. The vaccine mechanism is outlined in Figure 2.

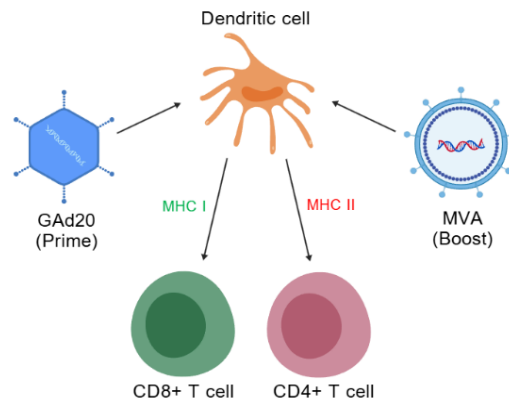


Fig 2. Mechanism of action of the NOUS-PEV personalized cancer vaccine.

In the early stage of clinical trials, NOUS-PEV has presented excellent safety and immunogenicity among several kinds of tumors, especially among melanoma and non-small cell lung cancer (NSCLC) patients [8,9]. The results suggested that NOUS-PEV can induce dual immune response, activating both CD8+ cytotoxic T lymphocytes (CTLs) and CD4+ helper T cell to enhance the ability of tumor cell identification and elimination [10]. At the same time, emerging evidence suggest that NOUS-PEV itself can maintain anti-tumor activity. However, its immune activation seems to be stronger when combined with PD-1 inhibitors. This means NOUS-PEV has the potential to be used as a standalone treatment, but it may offer even more benefits when combined with immune checkpoint inhibitors like PD-1.

Overall, NOUS-PEV is an exciting viral vector platform for PCV. It can deliver multiple neoantigen, trigger tumor-specific immune response and has excellent safety. It shows promise both as a single treatment and in combination with immune checkpoint inhibitors. To truly assess its effectiveness and translational potential, larger clinical trials and long-term studies are required.

4.2. GRANITE

GRANITE is a personalized cancer vaccine platform launched by Gritstone Bio using heterologous prime-boost strategy. It uses chimpanzee adenovirus vector (ChAd68) as the priming vector to initiate strong immune response. Once the neoantigen sequences are expressed within dendritic cells, they are routed through both MHC-I and MHC-II presentation route, which lead to prime cytotoxic and helper T-cell responses. The priming phase is followed by a self-amplifying (samRNA) as the boosting vector to expand and maintain immunity which further expands CD8+ and CD4+ T cell responses and promotes the generation of long-term CD8+ memory T cells. Also, GRANITE can integrate 20 patient-specific neoantigen into one vaccine which is selected through bioinformatic pipelines to balance immunogenic quality. This design enables specific and diversified immune responses and therefore positioning GRANITE as a potential strategy for the field of PCVs [10]. The overall vaccination strategy is schematically represented in Figure 3.

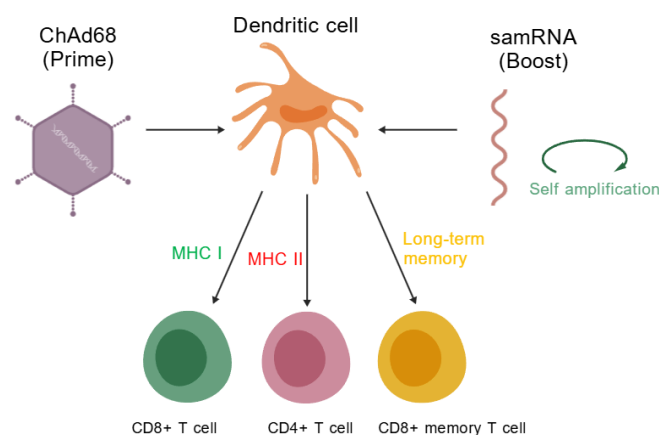


Fig 3. Mechanism of action of the GRANITE personalized cancer vaccine.

During preclinical studies, GRANITE displayed strong and durable immune response ability. Recent data have shown that the vaccination substantially expand neoantigen specific CD8+ T cells, which are crucial for killing tumor cells directly, accompanied by supportive activation of CD4+ helper T cells [11,12]. More importantly, these induced T cells demonstrated a broad recognition spectrum across multiple patients-specific epitopes, suggesting that it can overcome tumor heterogeneity by targeting diverse clones within the tumor [10,13]. Furthermore, repeated boosting will generate long term immunological memory which is the key for sustained tumor control. In mouse tumor models, the data indicate that vaccines targeting on neoantigens can slow down tumor growth and extend survival times [3]. These results suggest that this approach has promising potential for application beyond the laboratory. It means that GRANITE can effectively expand and strengthen anti-tumor immune repertoire, which will provide GRANITE with a solid foundation for clinical studies.

Preclinical trials have proven the feasibility and safety of GRANITE. In the on-going phase I/II study (NCT03639714), the platform was well tolerated and elicited strong neoantigen-specific immune responses across several tumor types. For example, one cohort focused on microsatellite-stable colorectal cancer, and others explored on gastroesophageal junction carcinoma and pulmonary malignancies [14]. These findings support GRANITE as a promising backbone for personalized cancer immunotherapy.

4.3. TG4050

TG4050 is a PCV made by Transgene in collaboration with NEC based on MVA viral vector using Transgene's myvac® platform [7]. This platform can integrate about 30 patient-specific neoantigen per vaccination, selected through NEC's artificial intelligence and machine learning algorithms. NEC's algorithms integrate mutational, expression and HLA-binding data to improve the accuracy of immunogenicity prediction. Once delivered, the MVA vector transduces dendritic cells to enable antigen processing and display through both class I and II MHC pathways. This dual presentation leads to the activation of CD8+ cytotoxic T cells and CD4+ helper T cells respectively. The activated CD8+ T cells mediate cytotoxic killing of tumor cells while CD4+ T cells provide support to sustain immune response. These effects lead to tumor apoptosis and an AI-optimized immune response tailored to each patient's tumor profile. Figure 4 provides an overview of the TG4050 mechanism of action.

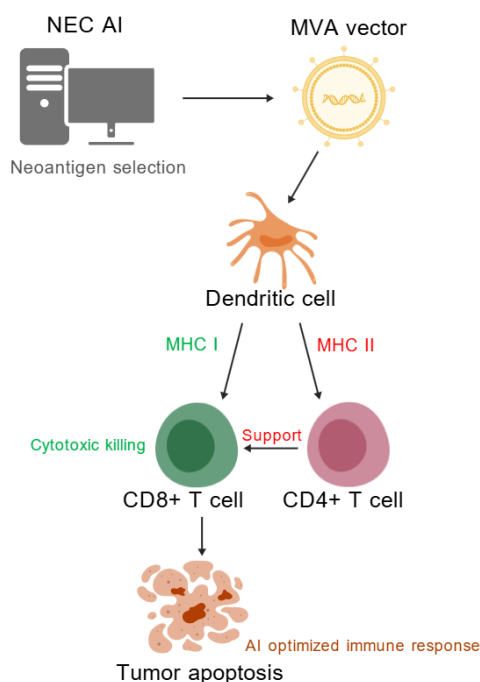


Fig 4. Mechanism of the TG4050 personalized cancer vaccine.

Preclinical studies stated that MVA viral vectors can induce strong CD8⁺ cytotoxic and CD4⁺ helper T cell reaction [15]. Also, TG4050 demonstrated the ability to trigger multi-epitope immune responses against AI-predicted neoantigen, proving the accuracy of the new selection process [16]. It is noteworthy that the MVA vector are inherently trigger innate sensors and also drive adaptive immune activation without requiring additional adjuvants [15]. These designs help to overcome the limitation of earlier neoantigen vaccine strategies.

TG4050 entered clinical evaluation through two Phase I studies. The first trial on ovarian cancer patients (NCT03839524) was completed in November 2024, showing safety, feasibility and immunogenicity of the platform [16]. The second trial, targeting HPV-negative head and neck squamous malignant tumor(NCT04183166) is still open but no longer recruiting [16]. Its interim data shows that patients developed diverse T cell responses targeting multiple neoantigens and increased immune cell infiltration within the tumor milieu [16]. According to company press communications (Transgene/NEC, 2020-2025) , TG4050 was well tolerated without evidence of dose-limiting toxicities during both trials. These results indicate TG4050 as a promising AI-driven, MVA-based personalized vaccine platform.

5. Limitation and Future Perspective

Although the outcomes from early-phase clinical trial were promising, there are still several limitations of PCVs. Firstly, the complexity of neoantigen identification and ranking remains a technical barrier. Despite the improvements in sequencing technologies and AI-based epitopes prediction, the accuracy of prediction on which neoantigens will elicit robust and durable responses is still limited [13,17]. False positive prediction may reduce the effectiveness of the vaccine. Secondly, due to highly individualized manufacturing process, both cost and manufacturing time may increase dramatically [13,18]. This may delay patients' treatment time and reduce scalability. Thirdly, tumor heterogeneity and immune suppression within the tumor microenvironment remain a challenge to the efficiency of the vaccine [17]. Even in the same type of tumor, the distribution and immunogenicity of neoantigens may vary substantially [13]. Vaccine induced T-cell activity may be dampened by immune tolerance, checkpoint upregulation, and metabolic suppression within the TME [17]. Fourthly, delivery efficiency is another bottleneck as how to effectively deliver antigens into dendritic cell and sustain antigen presentations is the key for long-lasting immune responses [1,13]. Lastly, most of current clinical data come from small-scale trials with limited evidence on survival benefit and optimal combination strategies [19]. It is critical to overcome these challenges by translating PCVs into routine clinical practice.

Looking ahead, several avenues may help to overcome these limitations. By integrating multi-omics profiling and AI algorithms, the precision of neoantigen may be prioritized, allowing more effective and consistent vaccine designs [17]. New novel delivery platforms like lipid nanoparticles, self-amplifying RNA vectors, and engineered viral backbones may increase immunogenicity as well as improve manufacturing efficiency [20]. Moreover, by using PCVs with other methods like checkpoint inhibitors, cytokine therapies, or oncolytic virus may increase antitumor immunity [9]. It is also important to standardize and decentralize PCVs' manufacturing procedures to reduce cost and time for making personalized vaccines [13].

6. Conclusion

Personalized cancer vaccines represent an innovative approach in immunotherapy. It focuses on the unique tumor mutations of each patient to enhance treatment effectiveness. This paper has reviewed principles of neoantigen identification and vaccine design with a particular focus on viral vector platforms such as NOUS-PEV, GRANITE, and TG4050. Clinical studies show that these vaccines can lead to strong cytotoxic and helper T cells activation to demonstrate the signals of efficacy across different cancer types.

However, there are still lots of problems to solve, such as limited accuracy of neoantigen prediction, high cost and long personalized manufacturing timeline, and the barrier caused by tumor heterogeneity and immunosuppressive microenvironment. Continued advancement is likely to depend on advances in integrating omics data, computational epitope ranking, innovative delivery platforms, and combination strategies with checkpoint inhibitors or other immunotherapies.

To conclude, PCVs represent the combination of genomics, bioinformatics, and immunology. By solving current limitations, PCVs have the potential to become the cornerstone of precision oncology. It will provide durable and personalized therapeutic benefits to cancer patients around the world.

Acknowledgment

The author gratefully acknowledges all researchers whose studies have advanced the understanding of personalized cancer vaccines. Figures 1-4 were prepared using BioGDP (www.biogdp.com) and the author sincerely appreciates its contribution to scientific illustration.

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