ISSN: 2635 - 2826

Journal of Clinical & Biomedical Research

SCIENTIFIC Research and Community

Opinion Article

Open Access

Challenges and Limitations of Personalized Cancer Vaccines

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Received: February 11, 2025; **Accepted:** February 12, 2025; **Published:** February 25, 2025

Personalized cancer vaccines represent a promising frontier in oncology, offering the potential for highly targeted and effective treatments. However, this innovative approach faces significant challenges and limitations, including tumor heterogeneity rapid cellular mutation manufacturing complexity, immune system evasion, identifying suitable antigens, and cost [1,2]. Furthermore, limited long-term efficacy data, scalability, and regulatory hurdles create serious obstacles to applying personalized cancer vaccines.

Cancer is a dynamic disease. During the disease, cancers generally become more heterogeneous. As a result of this heterogeneity, the bulk tumor might include a diverse collection of cells harboring distinct molecular signatures with differential levels of sensitivity to treatment. This heterogeneity might result in a non-uniform distribution of genetically distinct tumor-cell subpopulations across and within disease sites (spatial heterogeneity) or temporal variations in the molecular makeup of cancer cells (temporal heterogeneity) [3]. Heterogeneity fuels resistance; therefore, an accurate assessment of tumor heterogeneity is essential for developing effective therapies. Multiregional sequencing, single-cell sequencing, analysis of autopsy samples, and longitudinal analysis of liquid biopsy samples are all emerging technologies with considerable potential to dissect the complex clonal architecture of cancers. Understanding the effect of the mutation is crucial for targeted and personalized treatment.

Continuous genetic alterations due to the instability of the genome characterize tumor progression to metastatic disease. Immune sensitivity was linked to tumor mutational burden (TMB) and the resulting neoantigens. On the other hand, clonal or acquired genetic loss of HLA class I also hampers the immune sensitivity of tumors. Rare amplification of the PD-L1 gene in cancers may render them sensitive to immune checkpoint inhibitors. Still, the involvement of broader regions of chromosome 9p may ultimately lead again to immune evasion due to the inactivation of the IFN-γ signaling pathway [4]. Such genetic changes may occur not only in the primary tumor but at any phase of progression: in lymphatic as well as in visceral metastases. Accordingly, monitoring these changes continuously during disease progression is rational, similar to target therapies.

In recent years, scholars worldwide have paid increasing attention to the development of personalized cancer vaccines, which attempt to enhance patients' immunity against specific cancerous cells. The discovery of tumor-associated antigens (TAAs) represents one of the significant challenges in a designing personalized vaccine, and several studies have introduced new ideas for identifying TAAs [5]. Artificial intelligence (AI) tools have demonstrated exceptional performance in diagnosis, vaccine preparation, and development of personalized cancer vaccines for skin and breast cancer treatments, among other conditions. AI has also played a significant role in genomic analysis, contributing to a better understanding of the genetic basis of various diseases [6].

Despite these advancements, AI tools encounter significant challenges, including dependence on incomplete training datasets and a limited number of clinically validated algorithms—moreover, most current research centers on clinical populations, which limits generalizability to healthier groups. Long-term studies are scarce, raising questions about biomarker-guided supplementation's sustained efficacy and safety. Regulatory ambiguity further complicates the classification of supplements, mainly when combinations show pharmaceutical-like effects [6]. Tumors are frequently heterogeneous, with various cells expressing distinct antigens. A vaccine targeting only one or a few antigens may not be effective against all cancer cells. Cancer cells can mutate quickly, potentially rendering a personalized vaccine ineffective over time. The vaccine may need frequent updates to keep pace with tumor evolution. Creating a personalized vaccine involves complex processes, including tumor biopsy and genetic analysis, sequencing, and vaccine production. The time required for this process may be too long for patients with aggressive cancers. Some cancers are adept at evading or suppressing the immune system. Even a well-designed vaccine may be ineffective if the immune system is compromised. Selecting the most effective antigens for the vaccine is crucial but complex. Incorrect antigen selection could result in an inadequate vaccine. Producing individualized vaccines for large numbers of patients is logistically complex. This could limit the widespread application of the technology. Despite these challenges, ongoing research and technological advancements continue to push the boundaries of what's possible with personalized cancer vaccines, offering hope for more effective and tailored cancer treatments. The personalized nature of these vaccines presents unique regulatory challenges. Lengthy approval processes could delay treatment for patients.

As a relatively new approach, personalized cancer vaccines lack extensive long-term follow-up studies, and the absence of comprehensive long-term data makes it difficult to:

- Assess the durability of treatment effects

- Identify potential late-onset side effects
- Compare long-term outcomes with traditional cancer treatments
- Clinicians may hesitate to recommend these vaccines without robust long-term evidence
- Patients might be reluctant to choose this option over more established treatments
- Policymakers and insurance companies may be cautious about coverage and reimbursement

This data gap underscores the need for ongoing clinical trials and longitudinal studies to understand better the long-term impacts and benefits of personalized cancer vaccines [7].

Another serious issue is the cost of preparing personalized vaccines. These vaccines require identifying specific patient antigens, processing them in the laboratory, and converting them into highly customized medicine for the patient. This process makes them very costly to manufacture. Hence, the high costs may compromise accessibility and make widespread adoption challenging.

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