

# Personalized Cancer Vaccines and Their Efficacy

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## ABSTRACT

Cancer continues to be a worldwide health issue, causing approximately 9.7 million deaths around the world in 2022. Tumor heterogeneity presents a significant challenge to all cancer therapies. Tumors of the same cancer type can have different genetic mutations, making it difficult for traditional cancer therapies to work for every patient. Personalized cancer vaccines are attempting to overcome this challenge by using the body's immune system to recognize tumor-specific antigens, which are different for every patient. This review integrates evidence for three platforms: peptide-based vaccines, neoantigen vaccines, and granulocyte-macrophage colony-stimulating factor secreting K562 (GM-K562) cell-based vaccines, with an emphasis on mechanisms, clinical outcomes, manufacturing considerations, safety signals, and development status. While each vaccine type demonstrates safety and immunogenicity, the impact of these vaccines has been limited by small trial sizes and variable tumor-level responses. Next development steps include improved antigen selection through advanced sequencing and bioinformatics, combining vaccines with checkpoint inhibitors or adoptive cell therapies, and overcoming tumor heterogeneity. With continued optimization and larger controlled trials, personalized cancer vaccines have the potential to evolve from experimental promise to a central component in precision oncology.

**Keywords:** Personalized Cancer Vaccines; Peptide; Neoantigen; GM-K562; Cancer immunotherapy; Precision oncology

## INTRODUCTION

Vaccination protects populations by priming the adaptive immune system to recognize pathogens; however, the application of vaccination principles to cancer presents unique challenges. Unlike infectious agents, tumors arise from self-tissue and exhibit extensive genetic heterogeneity. This distinction motivates growing interest in personalized cancer vaccines, which adapt

classical immunologic principles to individualized tumor biology. Vaccines expose the immune system to harmless components of a pathogen, such as inactivated microbes, proteins, or fragments that trigger the activation of T cells, B cells, and antibody production. This process also generates memory cells that enable the body to mount a faster and more effective response upon future exposure, providing long-lasting protection.

Cancer is characterized by uncontrolled growth and spread of abnormal cells that can invade surrounding tissues and metastasize to distant organs. Under normal conditions, cells divide in a regulated manner, and those that accumulate mutations or sustain damage undergo programmed cell death, also known as apoptosis. However, cancer cells can bypass cell cycle checkpoints, allowing them to replicate indefinitely (1).

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**Accepted** February 12, 2026

<https://doi.org/10.70251/HYJR2348.41695708>

Genetic predisposition and unhealthy lifestyle habits such as smoking, alcohol consumption, and obesity were associated with a higher occurrence of most cancers (2). The immune system protects the body against cancer by identifying and destroying abnormal cells through a process called immune surveillance. T cells, natural killer cells, and macrophages recognize tumor-associated antigens or stress signals and eliminate the threat before the cells become numerous. However, cancer tends to evade these cells by decreasing antigen presentation, creating immunosuppressive cytokines, recruiting regulatory T cells, and expressing checkpoint proteins, such as PD-L1, that downregulate immune responses, thereby enabling the tumor to grow and metastasize (3).

According to the National Center for Health Statistics, an estimated 2 million cancer cases and 600,000 deaths are expected in the U.S. in 2025 (4). Patient outcomes vary significantly depending on cancer type, stage, and individual factors (5). Because of this complexity, multiple treatment modalities have been developed to address the diverse APC biological and clinical characteristics of cancer. Cancer treatment modalities range from surgery and radiation to systemic approaches such as chemotherapy, targeted therapy, and immunotherapy. Although these treatments have improved outcomes, their effectiveness is limited by tumor heterogeneity and resistance.

Surgery, a local treatment, involves the physical removal of cancerous tissue and is most effective for early-stage, localized tumors. However, it may not be feasible for cancers located near vital structures, and complete removal of all malignant T cells is often challenging (6). Radiation therapy, another local treatment, uses high-energy waves to damage the DNA of cancer cells, preventing further division and growth. Its use is limited to tumors visible on imaging, such as CT scans, and it can also damage surrounding healthy tissues. In addition, some cancers may be resistant to radiation (6). Chemotherapy, a systemic treatment, uses cytotoxic drugs to inhibit the proliferation of cancer

cells. Because it targets rapidly dividing cells, it can also harm normal tissues such as hair follicles and bone marrow, and tumors may develop drug resistance over time (7). Targeted therapy, another systemic approach, acts on specific molecular pathways or receptors, such as trastuzumab for human epidermal growth factor receptor 2 (HER2)-positive cancers. However, not all cancers express suitable molecular targets, and even effective agents may lose efficacy as resistance develops (8). Immunotherapy, another systemic treatment, enhances the immune system's ability to overcome cancer. Examples include primary disease immunization and immune checkpoint inhibitors such as ipilimumab, pembrolizumab, and nivolumab. However, drawbacks include the difficulty in predicting which patients will benefit meaningfully from immunotherapy, the lack of robust biomarkers to guide treatment selection, the potential for resistance from both tumors and the immune system, and the substantial financial burden associated with these therapies (9).

Personalized cancer vaccines aim to stimulate a patient's immune system to recognize tumor-specific antigens that are unique to the individual's cancer. Unlike conventional methods, which use a combination of treatments, personalized vaccines are tailored to the molecular profile of the patient's tumor. This targeted approach allows for more effective management of tumor heterogeneity and resistance compared to traditional methods. These vaccines also aim to counteract cancer's immune evasion mechanisms, particularly when used in combination with adjuvants or immune checkpoint inhibitors (10). Personalized cancer vaccines can be broadly categorized into three types: peptide-based vaccines, neoantigen vaccines, and GM K562 cell-based vaccines, as tabulated in Table 1. This narrative review synthesizes representative clinical studies across these platforms, with emphasis on immunologic mechanisms, clinical outcomes, and key limitations relevant to future development.

**Table 1. Overview of personalized vaccines used for various cancer types.**

Cancer type	Vaccine type (platform)	Vaccine formulation & delivery (summary)	References
Hepatocellular carcinoma (HCC)	Peptide - Personalized Peptide Vaccination (PPV)	Selected HLA-matched peptides (patient-specific selection from a panel), emulsified in Montanide ISA-51; subcutaneous injections weekly ×6 then biweekly boosters; immune-monitoring by ELISpot/IgG.	(11)

*Continued Table 1. Overview of personalized vaccines used for various cancer types.*

Cancer type	Vaccine type (platform)	Vaccine formulation & delivery (summary)	References
Colorectal cancer (CRC)	Peptide - OCV-C02 (RNF43 & TOMM34 peptides)	Two synthetic peptides (RNF43-721, TOMM34-299) with Montanide ISA-51 adjuvant; subcutaneous administration; ELISpot and ICS assays used for monitoring.	(12)
Pancreatic ductal adenocarcinoma (PDAC)	Neoantigen - mRNA vaccine autogene cevumeran	WES/RNA → predicted neoantigens (median ~15 per patient) → uridine-modified mRNA formulated in lipoplex nanoparticles; intravenous administration following surgery and chemotherapy; immune monitoring by ELISpot and TCR sequencing.	(13)
Pancreatic ductal adenocarcinoma (PDAC)	Neoantigen - mRNA vaccine autogene cevumeran	U-modified mRNA encoding up to 20 neoantigens; lipoplex nanoparticle formulation; IV administration; combined with PD-L1 inhibitor + chemotherapy; TCR tracking (CloneTrack).	(14)
Non-small cell lung cancer (advanced)	Neoantigen - Neo-DCVac (dendritic cell vaccine)	Autologous DCs pulsed ex vivo with 12–30 patient-specific neoantigen peptides (matured with GM-CSF/IL-4/TNF $\alpha$ ); delivered intradermally or into lymph nodes; IFN- $\gamma$ ELISpot assay	(15)
Hepatocellular carcinoma	Neoantigen - (long-peptide personalized vaccine)	Tumor WES/RNA → selected neoantigen peptides (6–20 aa) synthesized as personalized long-peptides; multi-dose priming series (four doses) $\pm$ boosters; ctDNA used for monitoring.	(16)
Follicular lymphoma (FL)	Neoantigen - synthetic long-peptide vaccines	WES/RNA → predicted neoantigens (median ~15 per patient) → synthetic long-peptides given with PD-1 blockade; immune monitoring by ELISpot	(17)
Microsatellite-stable colorectal cancer (MSS CRC)	Neoantigen - synthetic peptides	Personalized peptide cocktails (13–30 aa peptides), administered subcutaneously in bilateral axilla/groin on days 1,4,8,15,22 with boosters at weeks 12 & 20; adjuvant polycytidylic acid used; monitored by IFN- $\gamma$ ELISpot and ctDNA.	(18)
Glioma (malignant glioma)	GM-K562 - (autologous tumor cells with GM-K562 cells)	Irradiated autologous tumor cells mixed with irradiated GM-CSF-secreting K562 cells ( $5-10 \times 10^6$ K562 cells); subcutaneous injections; DTH, antibody assays, and flow cytometry used for immune readouts.	(19)
Follicular lymphoma	GM-K562 - tumor cells mixed with GM-CSF-secreting K562 cells	Lethally irradiated autologous tumor cells admixed with GM-CSF-secreting K562 cells; subcutaneous vaccines; variable immune activation reported — some trials showed minimal DTH responses, others observed antibody/lymphocyte activation when combined with other modalities.	(20)

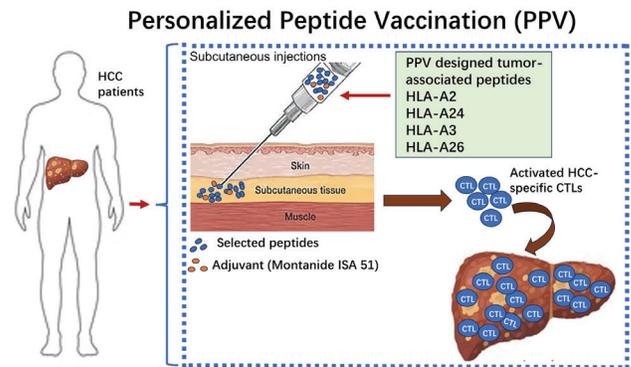
## PEPTIDE VACCINES

Peptide vaccines consist of short segments of tumor-associated proteins that stimulate the immune system's CD4+ and CD8+ T cells to recognize and kill cancer cells. The peptides are frequently derived from characterized tumor antigens and selected for their ability to bind to major histocompatibility complex (MHC) molecules on

the surface of antigen-presenting cells (APCs). Once introduced, the peptides are presented by APCs to T cells, thereby activating antigen-specific cytotoxic and helper T cell responses against tumor cells. Their goal is to enhance immune recognition of cancer cells with minimal toxicity. Clinical trials have demonstrated that peptide vaccines are generally safe and well-tolerated (11, 12).

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, typically arising in individuals with chronic liver disease or cirrhosis caused by hepatitis B or C infection, alcohol use, or fatty liver disease. HCC has a median survival time of 10.9 months with limited treatment options. Sorafenib is a multikinase inhibitor that targets rapidly accelerated fibrosarcoma (RAF), vascular endothelial growth factor receptor (VEGFR), and platelet-derived growth factor receptor (PDGFR) signaling pathways to slow tumor growth and angiogenesis. However, it provides limited benefits because it also suppresses adaptive immune responses by inhibiting dendritic cell and T cell activation. Personalized Peptide Vaccination (PPV), developed by Yutani, was designed to overcome sorafenib-associated immune suppression by tailoring peptides to each patient's human leukocyte antigen (HLA) subtype and immune profile which is shown in Figure 1. This approach aims to stimulate a robust adaptive immune response, particularly by activating tumor-specific cytotoxic T lymphocytes (CTLs). In a clinical trial involving 56 patients with HCC (11) who were refractory to locoregional and/or systemic therapies, the PPV protocol consisted of subcutaneous injections of selected peptides emulsified with an adjuvant (Montanide ISA 51), administered weekly for six weeks, followed by biweekly booster doses based on immune monitoring results. The peptides were chosen and optimized based on each patient's HLA type and pre-existing peptide-specific immune responses. For example, prior evidence of T cell or antibody reactivity to those tumor-associated peptides before vaccination. A total of 31 peptide candidates were available for selection—12 for HLA-A2, 14 for HLA-A24, 9 for HLA-A3 supertypes, and 4 for HLA-A26—allowing individualized vaccine composition tailored to each patient's immunologic profile (11).

Immunity was measured by titers of peptide-specific IgG and by CTL function using enzyme-linked immunospot (ELISpot) assays in peripheral blood cells, showing that over 90% of patients developed peptide-specific CTL responses, and some exhibited stable disease or tumor shrinkage. PPV generated significant CTL and antibody responses in most patients, with a median survival of 18.7 months in the locoregional refractory group, an improvement of 7.8 months compared with historical controls, and 8.5 months in the systemic refractory group. These findings suggest that PPV is capable of stimulating tumor-specific immunity, supporting its potential as a safe and individualized immunotherapy for patients with HCC (11).



**Figure 1. Personalized peptide vaccination (PPV) strategy for hepatocellular carcinoma (HCC).** Patient-specific tumor-associated peptides are selected based on individual human leukocyte antigen (HLA) class I subtypes, including HLA-A2, HLA-A24, HLA-A3, and HLA-A26. Selected peptides are administered via subcutaneous injection in combination with an immune adjuvant (Montanide ISA 51). Antigen presentation promotes activation of HCC-specific cytotoxic T lymphocytes (CTLs), which infiltrate tumor tissue and mediate targeted antitumor immune responses. This schematic was created by the author based on concepts described in the cited literature.

Colorectal cancer (CRC) is a malignancy that begins in the tissues of the colon or rectum. In unresectable or metastatic cases, it carries a poor prognosis, with a 5-year survival rate of approximately 12.5%. Advances in genomic and transcriptomic profiling technologies, such as next-generation sequencing (NGS) and microarray analysis, have enabled the identification of numerous tumor-associated antigens (TAAs). These include ring finger protein 43 (RNF43) and translocase of outer mitochondrial membrane 34 (TOMM34), which are highly expressed in colorectal cancer (CRC) tissues and can stimulate immune responses when presented by HLA molecules. RNF43 and TOMM34 were identified as promising tumor-associated antigens in preclinical models, and researchers developed OCV-C02, a peptide vaccine composed of RNF43-721 and TOMM34-299 peptides, administered to HLA-A\*24:02-positive CRC patients refractory to chemotherapy (12). Taniguchi *et al* conducted a phase I, open-label, dose-escalation trial enrolled 24 adults with advanced or relapsed CRC who tested positive for HLA-A\*24:02 and were refractory or intolerant to standard chemotherapy. The trial assessed three primary endpoints: safety, disease stability, and immunological response. The vaccine, composed of

RNF43- and TOMM34-derived peptides emulsified with the adjuvant Montanide ISA 51, was well tolerated with no dose-limiting toxicities observed. The goal was to identify any dose-limiting toxicity (DLT). Secondary endpoints included treatment-emergent adverse events (TEAEs), efficacy, and immunological responses (RNF43- and TOMM34-derived peptide-specific CTL responses).

Stable disease occurred in 25% of Taniguchi patients, most often at higher doses (3 mg and 6 mg). Immunologically, peptide-specific cytotoxic T-lymphocyte (CTL) responses to RNF43 and TOMM34 were detected in patients by ELISpot and intracellular cytokine staining, confirming successful activation of the adaptive immune system. By enhancing tumor-specific T cell activity while maintaining a safe profile, this peptide vaccine demonstrates potential as a viable option, particularly when combined with other therapies to further strengthen antitumor responses (12).

Although both trials aimed to evaluate immune activation through peptide vaccination, their designs and goals differed substantially. The HCC trial aimed to enhance adaptive immune responses and prolong patient survival by using a personalized vaccine tailored to each individual's HLA type and immune profile. In contrast, the CRC trial primarily focused on evaluating safety and identifying dose-limiting toxicity (DLT) using a fixed two-peptide formulation for HLA-A\*24:02-positive patients. Both studies demonstrated immune activation, but they interpreted their outcomes differently. The HCC trial provided more substantial evidence that the vaccine reliably stimulated tumor-specific immune responses, while the CRC trial emphasized its favorable safety profile and potential for combination therapy (11, 12).

### **Advantages of peptide vaccines**

Peptide vaccines are generally well tolerated, with minimal and mostly mild side effects. They can enhance immune responses, particularly by activating cytotoxic T lymphocytes (CTLs). Manufacturing is also straightforward and scalable. Findings suggest that peptide vaccines may offer a greater benefit when incorporated into combination strategies, such as those with checkpoint inhibitors or other immune-modulating therapies, rather than as standalone treatments.

### **Challenges for peptide vaccines**

Both hepatocellular carcinoma (HCC) and colorectal cancer (CRC) trials demonstrated a delayed onset of immune activation, typically requiring 4 - 6 weeks before

measurable T cell responses to the vaccine peptides were observed. This latency highlights the time needed for the immune system to mount an effective response. As monotherapy, peptide vaccines have shown limited clinical efficacy, with most studies reporting stable disease rather than objective tumor regression. A further limitation is tumor heterogeneity and immune escape. Because most peptide vaccines target common tumor-associated antigens rather than unique, patient-specific mutations, cancer cells may evade recognition over time. This restricts their potential for durable responses compared to truly personalized approaches.

Clinical trials evaluating peptide-based cancer vaccines were predominantly early-phase and exploratory in nature. Most studies enrolled small, heterogeneous patient cohorts and lacked randomized control arms, limiting the ability to draw causal conclusions regarding clinical efficacy. Immunologic endpoints, including enzyme-linked immunospot (ELISpot)-based cytotoxic T-lymphocyte responses, were primarily descriptive and not statistically powered as prespecified efficacy outcomes. Differences in antigen expression across tumors and variability in host immune competence likely contributed to inconsistent immune activation and modest clinical effects, such as transient disease stabilization. These limitations suggest that peptide vaccines may be more effective as components of combination regimens rather than as standalone therapies.

While peptide-based vaccines demonstrate favorable safety profiles and reproducible manufacturing, their reliance on shared tumor-associated antigens limits their ability to address interpatient tumor heterogeneity and immune escape. These limitations motivated the development of neoantigen vaccines, which personalize antigen selection based on patient-specific tumor mutations to enhance immune specificity and durability.

## **NEOANTIGEN VACCINES**

Neoantigen vaccines build on the idea of personalized immunotherapy by targeting mutations that are unique to each person's cancer. They are made by sequencing a patient's tumor DNA to find mutated protein fragments—called neoantigens—that do not exist in normal tissue. This makes the vaccine highly specific to the tumor while reducing the chance of triggering harmful autoimmune reactions. Clinical trials in patients with melanoma and pancreatic cancer have demonstrated that personalized neoantigen vaccines can elicit CD4+ and CD8+ T cell anti-tumor responses,

leading to tumor regression or extended recurrence-free survival (14). Because neoantigens arise from tumor-specific mutations not present in normal tissue, the risk of autoimmunity is lower than with shared tumor-associated antigens. Personalized mRNA cancer vaccines, such as autogene cevumeran, are considered a subtype of neoantigen vaccines because they encode individualized tumor-specific epitopes.

Pancreatic ductal adenocarcinoma (PDAC) has a 5-year survival rate of approximately 13% and a median recurrence time of less than 12 months, even after surgical resection and adjuvant chemotherapy, reflecting its immunologically cold tumor microenvironment. To address these limitations, autogene cevumeran, a personalized mRNA–lipoplex neoantigen vaccine, was developed to induce durable, tumor-specific CD8<sup>+</sup> T cell responses in the adjuvant setting. In an initial clinical study, Sethna *et al.* sequenced tumor DNA, tumor RNA, and matched normal DNA from resected PDAC patients to identify patient-specific neoantigens, selecting up to twenty mRNA-encoded epitopes per individual (13). The mRNA was formulated into lipoplex nanoparticles and administered over multiple doses following surgery, in combination with standard mFOLFIRINOX chemotherapy. Immune monitoring using single-cell RNA/TCR sequencing demonstrated that approximately 50% of patients developed vaccine-specific CD8<sup>+</sup> T cell responses, with responding T cell clones predicted to persist long term; these responders exhibited prolonged recurrence-free survival, with the median not reached at the time of analysis.

In a complementary clinical analysis of the same mRNA neoantigen platform, Rojas *et al.* further evaluated immune activation and recurrence outcomes in resected PDAC patients receiving autogene cevumeran in combination with immune checkpoint blockade (14). In this study, patients received a single dose of the PD-L1 inhibitor atezolizumab prior to vaccination to reduce immune suppression, followed by personalized mRNA–lipoplex vaccination generated in real time from genomic and transcriptomic sequencing. Immune responses were assessed using IFN- $\gamma$  ELISpot assays and CloneTrack analysis, which similarly demonstrated vaccine-induced CD8<sup>+</sup> T cell responses in treated patients. Vaccine-associated immune responses were correlated with longer recurrence-free survival, whereas nonresponders experienced a median recurrence-free survival of approximately 13.4 months. Collectively, these complementary studies suggest that autogene cevumeran is safe and capable of inducing durable,

tumor-specific immune responses in a subset of PDAC patients, although the findings remain exploratory and require validation in larger, controlled trials.

While PDAC studies focused on adjuvant vaccination in minimal residual disease, neoantigen strategies have also been explored in advanced-stage solid tumors. In a separate pilot trial, led by Zhenyu Ding (2021), investigated a personalized neoantigen dendritic cell vaccine (Neo-DCVac) in patients with advanced, heavily pre-treated lung cancer (15). Neoantigens are tumor-specific mutations that can be recognized by the immune system and are therefore ideal targets for personalized immunotherapy. Although neoantigen vaccines had been shown to activate the immune system in previous cancers, such as the trial conducted by Cai and his team on patients with HCC, they had not yet been used in lung cancer. Researchers hypothesized that pulsing a patient's dendritic cells with personalized neoantigen peptides would safely stimulate anti-tumor immune responses. To create the vaccine, tumor tissue samples were genomically sequenced to identify unique mutations that were then used to develop the vaccine. Computations of 12-30 neoantigen peptides per patient were made, which were then used to vaccinate the patient's own dendritic cells. Researchers matured dendritic cells with cytokines (GM-CSF, IL-4, TNF- $\alpha$ ). They assayed their activation markers, 4-1BB (CD137) and OX40 (CD134), which are of significant importance, as well as the secretion of cytokines, to ensure that they could activate T cells efficiently. Upon validation, the personalized vaccine was given intradermally or into lymph nodes. The treatment was well tolerated, with only mild adverse events reported. The vaccine achieved a 25% objective tumor response rate, a 75% disease control rate, and a median progression-free survival of 5.5 months compared to patients who did not receive the vaccine. The findings suggest that Neo-DCVac is safe and effective; however, the vaccine still needs further development to be viable as an immunotherapy for metastatic lung cancer (15).

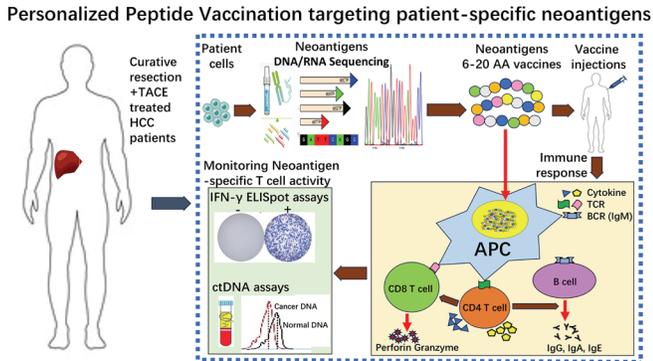
In contrast to PDAC and lung cancer, hepatocellular carcinoma presents a distinct immunologic challenge due to low tumor mutational burden and an immunosuppressive hepatic microenvironment. A research group led by Zhixiong Cai (2021) evaluated the safety and efficacy of a customized neoantigen peptide vaccine in patients with HCC following surgical resection (16). Patients who have vascular invasion have a high risk of recurrence. In contrast, other cancers have not been rendered responsive to immunotherapy. HCC is still restricted due to low tumor mutation burden

and immune-evasive nature. To address this, the investigators developed personalized long-peptide vaccines targeting patient-specific neoantigens derived from both somatic mutations and RNA editing events, thereby enhancing immune activation and reducing the risk of recurrence. They hypothesize that the vaccine can generate an immune response and lower the chances of recurrence. The trial included 10 HCC patients who had received curative resection and prophylactic Transcatheter Arterial Chemoembolization (TACE). Tumor and healthy DNA (and RNA in a few cases) from each patient were sequenced to detect individual neoantigen candidates. Subsequently, these neoantigens were synthesized into peptides ranging from 6 to 20 amino acids in length and formulated into vaccines. Patients received a four-dose priming series, and if no severe adverse events occurred, proceeded to enhanced doses. Neoantigen-specific T cell activity was monitored via IFN- $\gamma$  ELISpot assays, and personalized circulating tumor DNA (ctDNA) assays were developed to track tumor dynamics noninvasively over time, as shown in Figure 2. The vaccine was well-tolerated with minimal side effects, like injection-site reactions and fatigue. Five

of seven patients had robust T cell responses through the entire vaccination course. Using IFN- $\gamma$  ELISpot, responders with documented immune responses, as evidenced by the activation of CD4<sup>+</sup> and CD8<sup>+</sup> T cells, had significantly longer recurrence-free survival, with a median of 19.3 months, compared with 10.9 months in non-responders (16). Furthermore, personalized ctDNA was a valuable biomarker for tracking tumor burden and detecting recurrence because it is a non-invasive method for identifying specific tumor mutations. In a single patient, the vaccine-induced immune pressure was observed to cause the loss of vaccine-specific mutations in the relapse tumor, suggesting immune editing and resistance development. Overall, the findings support that personalized neoantigen vaccines incorporating RNA editing-derived targets are safe and potentially effective for postoperative immunoprevention in high-risk HCC, with ctDNA serving as a valuable biomarker for immune efficacy and recurrence detection (16).

Furthermore, the study led by Ramirez *et al* (2024) demonstrated the potential of patient-tailored neoantigen vaccines as a therapeutic strategy for follicular lymphoma (FL), a slow-growing yet difficult-to-cure blood cancer (17). Through sequencing, scientists can now identify patient-specific tumor mutations and immunoglobulin clonotypes that could be vaccine targets. The study hypothesized that a personalized, multi-target vaccine could be safely designed and activate strong immune responses in most FL patients. Researchers sequenced tumor tissue from 57 patients with FL using whole-exome and RNA sequencing to detect mutations and B cell receptor sequences. They used bioinformatics to predict neoantigens based on their expression and MHC binding affinity. Most of the patients had numerous high-quality neoantigens (median of 15). In a pilot trial, four relapsed FL patients were treated with synthetic long-peptide vaccines containing patient-specific neoantigens, combined with PD-1 checkpoint inhibitors, to amplify immune function. The vaccine worked by exposing peptide fragments of tumor mutations to the immune system. The blockade of PD-1 activated the T cell response by inhibiting immune suppression. The treatment was well tolerated, with all four patients developing neoantigen-specific T cell responses, as demonstrated by ELISpot, and some showing immune responses. This evidence suggests that genomics-guided vaccines targeting B cell clonotypes, as well as somatic mutations, are safe but will require further clinical development (17).

Microsatellite stable colorectal cancer (MSS CRC) is



**Figure 2. Personalized neoantigen peptide vaccine strategy following curative resection in hepatocellular carcinoma (HCC).** Tumor and matched normal tissue undergo DNA and RNA sequencing to identify patient-specific neoantigens. Selected neoantigen peptides, typically 6–20 amino acids in length, are formulated into a personalized vaccine and administered by injection. After vaccination, antigen-presenting cells (APCs) process and present neoantigens to T cells, promoting activation of CD8<sup>+</sup> cytotoxic T cells, CD4<sup>+</sup> helper T cells, and B cells. Immune responses may be monitored using interferon-gamma (IFN- $\gamma$ ) ELISpot assays and circulating tumor DNA (ctDNA) analysis. This schematic was created by the author based on concepts described in the cited literature.

poorly prognostic in the recurrent or metastatic setting, with little benefit from immune checkpoint inhibitors despite prior standard chemotherapy regimens of fluoropyrimidines, oxaliplatin, and irinotecan. Advances in tumor genomic and transcriptomic analysis have enabled the identification of numerous patient-specific tumor neoantigens, which can elicit robust T cell immune responses when presented via HLA molecules. Although immunotherapy has shown encouraging results in microsatellite instability-high (MSI-H) CRC, MSS tumors have remained largely unresponsive, prompting the development of a personalized neoantigen peptide vaccine strategy for MSS CRC patients failing standard therapies. The study conducted by Yao-Jun Yu *et al* hypothesized that a customized neoantigen vaccine, comprising synthetic peptides curated from each patient's tumor mutations and administered with the immune adjuvant polyinosinic polycytidylic acid (poly I: C), would be safe, induce neoantigen-specific immune activation, and show preliminary clinical benefits. A Phase Ib, open-label clinical trial was conducted in patients with recurrent or metastatic MSS CRC, involving whole-exome and RNA sequencing of tumor and matched normal tissue to predict candidate neoantigens. Personalized peptide cocktails (13 to 30 amino acids each) were administered subcutaneously in the bilateral axilla and groin on days 1, 4, 8, 15, and 22, with boosters at weeks 12 and 20. Immune monitoring was performed using *ex vivo* IFN- $\gamma$  ELISpot assays with PBMCs stimulated with neoantigen pools. Clinical endpoints included progression-free survival (PFS), imaging, circulating tumor DNA (ctDNA), tumor markers, and quality of life as measured by the FACT-C. All treatments were well tolerated, and no dose-limiting toxicities were observed. 66.7 percent generated vaccine-induced neoantigen-specific T cell responses, and responders also had longer PFS (median 19 months) than non-responders (11 months), with better quality of life scores. ELISpot validated neoantigen-specific immunity, and ctDNA levels decreased in some patients. These results provide the rationale for the ongoing clinical development of personalized neoantigen vaccines for MSS CRC, particularly in combination with other immunomodulatory agents, due to the absence of severe toxicities and the promising immune activation observed (18).

The six studies employ different strategies with varying goals, each tailored to the biology of the specific cancer type under investigation. For example, the HCC trial used synthetic peptides with adjuvants, relying on

the patient's own antigen-presenting cells, administered over repeated doses to induce T cell responses associated with improved recurrence-free survival. In contrast, the lung cancer study directly pulsed mature dendritic cells *ex vivo* with dozens of peptides, enabling more immediate and broader activation of CD4 and CD8 T cells. The pancreatic RNA vaccine studies share a platform that uses mRNA to produce neoantigens within host T cells, thereby promoting robust and durable CD8<sup>+</sup> memory T cell responses, which are essential for overcoming typically cold tumors, such as pancreatic cancer. In contrast, the follicular lymphoma study focused on the fundamental question of whether enough high-quality neoantigens exist to justify personalized vaccines. At the same time, the MSS colorectal cancer trial demonstrated that even tumors with modest mutational burdens can elicit measurable immune responses through peptide vaccination.

Across these trials, most groups employed whole-exome sequencing (WES) in conjunction with RNA sequencing to identify tumor-specific mutations. WES captures nearly all coding mutations, which are the primary source of neoantigens, while RNA-seq verifies that the mutated genes are actually expressed and helps refine HLA-binding predictions. Then the research groups, guided by each patient's HLA type, predicted which peptides would be most likely to bind MHC molecules and be recognized by T cells. This is why every study converged on using WES and RNA sequencing. Without these methods, they would risk targeting mutations that either do not exist in that patient's tumor or are not presented to the immune system. The multi-peptide design was also a common similarity, since tumors are heterogeneous and can escape single-target therapies. IFN- $\gamma$  ELISpot and TCR sequencing are most often used to measure immunogenicity, as they are reliable, standardized assays for detecting functional T cell responses in blood. The reliance on peripheral blood instead of tumor biopsies was essentially pragmatic since serial tumor sampling is invasive, though this creates a limitation in fully capturing the intratumoral immune response.

Where the trials varied, the reasoning behind the design decisions explains the outcomes. The pancreatic cancer trial used intravenous uridine-mRNA lipoplex nanoparticles instead of subcutaneous peptides because mRNA enables rapid, scalable manufacturing and can encode multiple antigens in a single molecule. In contrast, intravenous delivery enhances antigen presentation in lymphoid tissues. They paired this with

PD-L1 blockade in the adjuvant setting, reasoning that newly rendered post-surgical minimal residual disease, combined with checkpoint inhibition, would enhance the likelihood that T cells could eliminate micrometastases. That logic likely contributed to their dramatic benefit in recurrence-free survival among vaccine responders.

On the other hand, the lung cancer trial used *ex vivo*-loaded dendritic cells because DCs are professional antigen-presenting cells; however, this approach was attempted in advanced disease, when the immune system is already compromised. The approach was safe but had minimal activity, emphasizing that both the delivery platform and the stage of disease matter. The HCC trial included RNA-editing–derived antigens, a departure from most pipelines, as patients had very low tumor mutational burden; by using a broader pool of antigens, they were still able to generate T cell responses. Meanwhile, experiments that paired vaccination with checkpoint blockade (e.g., in pancreatic cancer and follicular lymphoma) generally generated more potent immunity than vaccination alone, recapitulating the reasoning that vaccines initiate new T cells, while checkpoint inhibitors prevent exhaustion. Finally, several groups incorporated personalized ctDNA monitoring not just to follow tumor burden, but also to track mutations that the vaccine had targeted, a more direct way to correlate immune responses with molecular clearance than was possible with imaging.

Neoantigen vaccines induce immune responses in several cancers, including HCC and PDAC. They are also able to stabilize or postpone cancer recurrence. However, there is variable immunogenicity, and some epitopes fail to generate an immune response. Many studies to date have been small pilot trials, emphasizing the need for larger, controlled studies to validate efficacy and optimize antigen selection.

### **Advantages of Neoantigen Vaccines**

Neoantigen vaccines offer the highest degree of personalization because they target tumor-specific mutated epitopes identified through sequencing. They consistently generate strong CD4<sup>+</sup> and CD8<sup>+</sup> T-cell activation and demonstrate efficacy even in cancers traditionally resistant to immunotherapy. They also allow integration of circulating tumor DNA (ctDNA) monitoring to track tumor dynamics.

### **Challenges for Neoantigen Vaccines**

Development requires extensive sequencing and bioinformatics analysis. Manufacturing is time-intensive

and costly. Immunogenicity varies across cancer types, and predicting optimal neoantigen candidates remains complex.

Neoantigen vaccine trials demonstrated more consistent induction of tumor-specific T cell responses than peptide vaccines, particularly in cancers with higher tumor mutation burden or in the adjuvant setting following surgical resection. However, these studies were similarly constrained by small sample sizes, individualized vaccine manufacturing, and nonrandomized designs. Although immune responses were frequently detected, immunologic endpoints were exploratory and not statistically powered to establish efficacy. Variability in cancer type, disease stage, and tumor immune microenvironment, including differences between immune-inflamed and immune-cold tumors, likely influenced observed clinical outcomes. Consequently, while neoantigen vaccines show mechanistic promise, their apparent success remains context dependent and requires validation in larger controlled trials.

Despite their increased specificity, neoantigen vaccines face practical challenges related to individualized sequencing, computational prediction, and patient-specific manufacturing, which constrain scalability and clinical accessibility. Across platforms, manufacturing considerations differ substantially: peptide vaccines are relatively scalable and reproducible, neoantigen vaccines require individualized sequencing and patient-specific manufacturing workflows, and GM-K562 vaccines involve complex cell-based production and storage requirements. These limitations have prompted exploration of alternative strategies, including cell-based vaccine platforms designed to deliver broad antigenic stimulation using standardized immune-adjuvant scaffolds such as GM-K562 cells.

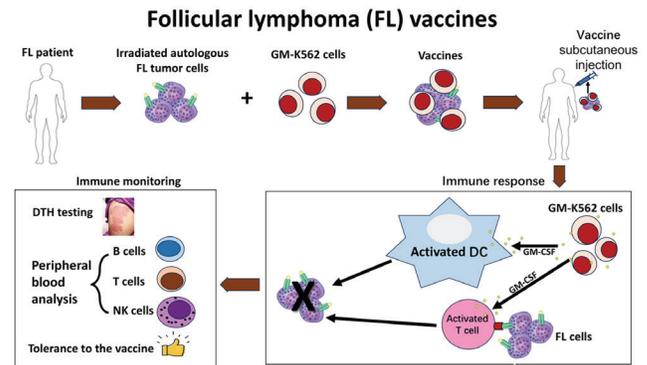
### **GM-K562 (GVAX-STYLE) CELL-BASED VACCINES**

The GM-K562 cell-based vaccine, also known as GVAX, uses irradiated tumor cells genetically engineered to secrete granulocyte-macrophage colony-stimulating factor (GM-CSF). GM-CSF is a signaling protein (cytokine) that recruits and activates dendritic cells—specialized immune cells responsible for detecting, processing, and presenting foreign antigens to T lymphocytes (T cells). By doing so, dendritic cells serve as key messengers between the innate and adaptive immune systems, initiating a targeted anti-tumor

response. The K562 cell line, derived from a patient with chronic myeloid leukemia, is often used as an “off-the-shelf” antigen-presenting platform to stimulate immune activation. K562 cells are specifically selected because they lack expression of HLA class I and II molecules, which minimizes immune-mediated rejection following administration. This property permits sustained cytokine secretion, facilitating effective recruitment and activation of dendritic cells and enhancing downstream tumor antigen presentation and T-cell priming. When paired with tumor lysates or patient-derived tumor cells, these modified K562 cells expose a broad range of tumor-associated antigens, promoting recognition by dendritic cells and subsequent activation of cytotoxic T cells. In leukemia, GM-K562 vaccines have demonstrated the capacity for inducing durable remission and potent anti-tumor immune responses when combined with donor lymphocyte infusions or checkpoint inhibitors (19). A recent publication also demonstrated that combining GM-K562 vaccines with immune checkpoint blockade improved relapse-free survival in high-risk AML patients by augmenting T cell activity (20). However, cell-based vaccines are complex to manufacture and store, and their broad antigen expression raises the potential for off-target effects.

A phase I trial tested a vaccine comprising lethally irradiated autologous follicular lymphoma (FL) tumor cells mixed with GM-CSF-secreting K562 cells to activate anti-tumor immunity. Follicular lymphoma is a slow-growing B-cell malignancy for which earlier vaccine strategies have produced inconsistent clinical benefit. This study aimed to enhance immune activation by integrating patient-derived tumor cells, which provide a comprehensive array of patient-specific tumor antigens, with GM-CSF-secreting K562 cells, which function as immune adjuvants. The secreted GM-CSF recruits and activates dendritic cells at the vaccination site, promoting the presentation of tumor antigens and subsequent activation of T cells. Participants received up to six subcutaneous vaccinations containing  $1 \times 10^5$  to  $5 \times 10^7$  GM-K562 cells admixed with irradiated autologous tumor cells, depending on the number of tumor cells available. Immune monitoring was conducted through delayed-type hypersensitivity (DTH) testing and peripheral blood analysis of B cells, T cells, and natural killer (NK) cells to evaluate whether the vaccine successfully elicited tumor-specific immune responses, as shown in Figure 3. The vaccine was well tolerated at all dose levels, demonstrating both feasibility and safety for further study. The study, however, did not detect

any evidence of immune activation; there were no DTH responses and no significant changes in lymphocyte populations. The findings indicate that although this method of vaccine administration is safe and practical, it is insufficient to induce an immune response, and more potent immunostimulatory approaches or combinations must be developed for future FL vaccines (20).



**Figure 3.** GM-K562 (GVAX-style) cell-based vaccine strategy for follicular lymphoma (FL). Autologous FL tumor cells are harvested, lethally irradiated, and combined with genetically engineered K562 cells that secrete granulocyte-macrophage colony-stimulating factor (GM-CSF). After subcutaneous administration, GM-CSF promotes recruitment and activation of dendritic cells (DCs), which process tumor antigens and stimulate tumor-specific CD4<sup>+</sup> and CD8<sup>+</sup> T-cell responses. Immune monitoring may include delayed-type hypersensitivity (DTH) testing and peripheral blood analysis of B cells, T cells, and natural killer (NK) cells. Immune tolerance and variable effector activation may limit clinical response. This schematic was created by the author based on concepts described in the cited literature.

A clinical trial led by William T. Curry Jr. evaluated a customized cancer vaccine in patients with recurrent malignant glioma, an aggressive brain tumor with limited treatment options and poor prognosis (19). The study aimed to enhance immune activation using GM-K562 cells to stimulate a more effective anti-tumor response. The researchers hypothesized that this combination vaccine would be safe, feasible to produce from patient tumors, and capable of generating a measurable immune response. The vaccine paired each patient’s irradiated autologous tumor cells with GM-K562 cells, an engineered cell line designed as a potent immune adjuvant that provides strong costimulatory signals to amplify antitumor immune responses. In the study, 11

patients underwent surgery to remove their tumors. The tumor cells were then irradiated and combined with either 5 million or 10 million irradiated GM K562 cells. The combination was administered subcutaneously as a vaccine. The trial assessed two primary endpoints: whether the vaccine could be successfully produced and administered to patients, and whether it had any serious adverse effects. Immune responses were assessed by delayed-type hypersensitivity (DTH) testing and T-cell function measurements. Most participants demonstrated strong immune reactivity, including local skin reactions and antibody formation against tumor-associated proteins such as angiopoietin-1 (Ang1) and angiopoietin-2 (Ang2), which play roles in tumor angiogenesis and progression. Flow cytometry analysis revealed activation of lymphocyte subsets, indicating a vaccine-induced immune response. However, this activation was accompanied by an increase in regulatory T cells (Tregs), which can suppress immune activity; this effect was measured by FoxP3 expression, a key marker of Treg function. Overall, the vaccine was well tolerated, demonstrated a manageable safety profile, and showed potential to stimulate immune activity against glioma. These findings support continued investigation of GM-K562-based vaccines as a therapeutic approach for malignant glioma (20).

Notably, immune responses observed in the glioma cohort must be interpreted within the context of the central nervous system's immune-privileged environment. The brain is protected by the blood-brain barrier, which limits immune cell trafficking, antigen presentation, and lymphatic drainage compared with peripheral tissues. In addition, gliomas actively shape an immunosuppressive microenvironment through the secretion of inhibitory cytokines, recruitment of regulatory T cells, and expression of immune checkpoint molecules, all of which can constrain effective antitumor immunity. As a result, even when systemic immune activation is detected following vaccination, intratumoral immune penetration and durable tumor control may remain limited in CNS malignancies.

Both GM-K562 vaccine studies utilized lethally irradiated autologous tumor cells combined with K562 cells engineered to secrete granulocyte-macrophage colony-stimulating factor (GM-CSF). Despite their shared design, the biological context of each cancer profoundly influenced immune activation. Glioma is a rapidly growing, highly immunosuppressive brain tumor that arises within the central nervous system (CNS)—an immune-privileged site with restricted lymphocyte

access—whereas follicular lymphoma is a slow-growing, systemic B-cell malignancy that circulates within the lymphatic system. Consequently, the glioma trial emphasized systemic immunomonitoring, using circulating biomarkers to evaluate global immune activation. Serial analyses of T-cell activation and regulatory markers (CTLA-4, PD-1, OX40, CD137, and FoxP3) were conducted via flow cytometry, while plasma ELISAs measured antibodies against tumor-associated proteins, providing time-resolved insight into both cellular and humoral immunity. These data were also correlated with MRI findings, such as pseudoprogession, to interpret local inflammatory changes within the tumor microenvironment.

In contrast, the follicular lymphoma study focused on localized, antigen-specific responses. Investigators performed delayed-type hypersensitivity (DTH) punch biopsies and peripheral blood analyses to assess lymphoid subsets and memory phenotypes (CD45RO, CD62L, CD27, and IgD), enabling evaluation of long-term recall responses. However, results showed minimal immune activation despite the use of GM-K562 cells, underscoring how tumor location and microenvironment dictate vaccine responsiveness. Gliomas, confined to the CNS, required systemic immune mobilization measurable through circulating biomarkers, whereas lymphoid cancers like follicular lymphoma demanded localized immune activation detectable in tissue and memory cell subsets. Collectively, these findings highlight the need to tailor immunomonitoring strategies to tumor biology and emphasize the broader challenge of eliciting durable, site-appropriate immune responses across distinct cancer types.

Both trials identified GM-CSF-secreting K562 cells as a reliable instrument for cancer vaccines. One advantage was that K562 cells facilitated vaccine manufacturing and recruited dendritic cells by secreting GM-CSF, enhancing antigen presentation. This circumvented the intricacy of employing patient-derived APC. However, a key negative aspect was that K562 cells alone did not elicit strong immune responses. The lymphoma trial observed no delayed-type hypersensitivity or lymphocyte activation, and the glioma trial observed only moderate immune activation, implying that it may be necessary to pair the K562 cells with other immune boosters.

### **Advantages and Challenges of GM-K562 Vaccines**

GM-K562 vaccines provide broad antigen exposure when mixed with autologous tumor lysate. GM-CSF secretion enhances dendritic cell recruitment, improving

antigen presentation. This cell-based approach eliminates the need for patient-specific peptide prediction.

Immune activation can vary significantly depending on the tumor type. Expansion of regulatory T cells (Tregs) may suppress beneficial immune responses. Manufacturing these vaccines is complex, and early-phase trials show limited clinical efficacy. GM-K562 (GVAX-style) vaccine studies primarily established feasibility and safety but demonstrated variable immunogenicity across cancer types. Most trials were limited by small cohorts and lacked control arms, with immune endpoints assessed descriptively rather than as statistically powered outcomes. In central nervous system malignancies, immune activation was further constrained by the immune-privileged nature of the brain and restricted lymphocyte trafficking, whereas systemic hematologic malignancies showed limited immune activation despite broad antigen exposure. These findings indicate that tumor location and immune context strongly modulate vaccine responsiveness, and that nonspecific immune stimulation alone may be insufficient to generate durable antitumor immunity.

## CONCLUSION

Peptide, neoantigen, and GM-K562 vaccines are distinct approaches to cancer immunotherapy, intended to activate tumor-specific T cells, but they vary in design, specificity, and complexity. Peptide vaccines use short, preselected tumor-associated antigens that are shared across patients. They have demonstrated favorable safety profiles and modest activation of CD8<sup>+</sup> cytotoxic T cells in clinical studies of hepatocellular and colorectal cancers. Neoantigen vaccines refine personalization with greater sophistication using patient-specific tumor mutations to trigger precise immune responses. GM-K562 vaccines, however, employ genetically modified cell lines secreting GM-CSF to activate antigen presentation and are supplemented by autologous tumor cells, as experimented with in glioma and follicular lymphoma. Taken together, these strategies cover the continuum from uniform antigen-based vaccines to highly personalized, cell-based methods to target cancer.

Across these platforms, tradeoffs exist between immunity, personalization, and practicality. These tradeoffs extend to manufacturing, with peptide vaccines offering greater scalability, neoantigen vaccines requiring individualized production, and GM-K562 vaccines involving complex cell-based fabrication and storage. Peptide vaccines are safe, reproducible,

and scalable; however, they are limited in their ability to adapt to tumor heterogeneity, which restricts their efficacy and makes them vulnerable to immune escape. Neoantigen vaccines tailor their targets to patient-specific mutations, increasing specificity and durability, but at the cost of high sequencing, bioinformatics, and tailored manufacturing requirements that restrict reproducibility and scalability. GM-K562 vaccines fall between these approaches, offering broad antigen coverage through a universal immune-stimulating scaffold. In contrast, this strategy avoids precise antigen selection and may lead to nonspecific immune stimulation and expansion of inhibitory cell populations. Overall comparisons suggest that peptide vaccines induce stable but limited immune responses, neoantigen vaccines demonstrate robust immune activation in early-phase studies but remain of uncertain standalone clinical effectiveness, and GM-K562 vaccines provide broad antigen exposure with variable immunogenicity. Despite these differences, all three may demonstrate acceptable safety, measurable T cell function, and preliminary clinical benefits, including prolonged survival and delayed recurrence. However, clinical advancement is limited by small sample sizes, heterogeneous cohorts, short follow-up periods, and a reliance on blood-based rather than tumor-based immune assessments, leaving uncertainty about whether systemic immune responses translate into accurate tumor control. Clinically, peptide vaccines remain the most developed, with several phase I/II trials confirming safety but limited standalone efficacy, suggesting their optimal use may be in combination therapies. Neoantigen vaccines are emerging rapidly, demonstrating durable responses and synergy with checkpoint inhibitors, as well as the potential for monitoring circulating tumor DNA (ctDNA). However, their role as effective standalone therapies remains a hypothesis requiring validation in larger, controlled comparative trials. GM-K562 vaccines are still in early development; while biologically appealing, they exhibit inconsistent immune activation and will likely require further refinement or combination strategies to achieve meaningful clinical outcomes.

Overall, the field has established the feasibility and safety of multiple cancer vaccine platforms but has yet to define a single prevailing strategy. Peptide vaccines have reached a plateau as monotherapies due to limited efficacy, while GM-K562 approaches, though conceptually appealing, exhibit inconsistent immunogenicity. Future progress will depend on rationally designed combination strategies that pair vaccine backbones with immune checkpoint inhibitors,

adoptive cell therapies, or other immunomodulatory agents to translate early proof-of-concept responses into sustained and clinically meaningful benefit. Persistent challenges such as tumor heterogeneity, immune evasion, manufacturing complexity, and small study size, continue to hinder broad clinical implementation. As larger and more standardized trials emerge, these barriers are expected to diminish, facilitating the translation of early experimental promise into durable, patient-centered outcomes.

New directions include testing vaccines in earlier stages of disease, where tumor burden is lower and immune activation is more effective, as well as developing multi-antigen or hybrid vaccine designs that balance personalization with practicality. If these innovations succeed, personalized cancer vaccines may evolve from experimental therapy to a cornerstone of precision oncology, offering adaptive, durable, and individualized protection against cancer recurrence and progression.

## ACKNOWLEDGEMENTS

The first author, Jeron S. Leonard, sincerely thanks Ashley N. Pearson for her guidance in literature evaluation, scientific interpretation, and critical feedback throughout the development of this manuscript.

## FUNDING SOURCES

The authors received no external funding for this work.

## CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest related to this work.

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