Narrative Review Article

Therapeutic Cancer Vaccines: Mechanisms, Clinical Evidence and Translational Challenges

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ABSTRACT

Cancer has persisted as one of the major causative agents of death around the world, fueled by factors associated with the uncontrolled growth of mutated cells that are normally difficult to recognize by the body's immune system or to combat using conventional therapeutic approaches that include chemotherapy, irradiation, and surgery. This paper reviews various cancer vaccines, which have emerged as among the most promising immunotherapies. Cancer vaccines induce anticancer responses by activating the body's adaptive immune system to recognize and destroy cancer cells. Fundamentally, cancer vaccines fall into several categories, including preventive, cell-based, nucleic acid-based, peptide/protein-based, and oncolytic viral vaccines. Currently, several clinical studies indicate that several forms of cancer vaccines offer effective promise in their ability to induce effective T cell responses in cancer patients, although these vaccines remain far from having achieved widespread clinical implementation due to several underlying challenges associated with cancer vaccines, including immunosuppressive tumor microenvironments, antigens' immunogenicity, and the high production and engineering complexity of personalized vaccines. Nonetheless, cancer vaccines show unequivocal promise as one of the most effective approaches in cancer therapy in the near future.

Keywords: Cancer vaccines; Cancer immunotherapy; Neoantigens; Personalized cancer vaccines; Dendritic cell vaccines

INTRODUCTION

Each year in the world, approximately 9.7 million people die of cancer (1). Within the body of each cancer patient, the mutated cells divide uncontrollably and form a cancer tumor. If left untreated, the growing mass of cells proliferates uncontrollably, diverting nutrients, oxygen, and blood away from healthy cells (2). The adaptive immune system, specifically killer T cells and natural killer cells, patrols the body, identifying and killing cancerous cells (3). Through random alterations in a cell's genetic code, the cancer cells become increasingly challenging for the immune system to eliminate.

Tumors can either be classified as benign or malignant. A benign tumor is a slow-growing mass of cells that doesn't spread to other parts of the body. A malignant tumor is a cancerous growth of cells that can spread to other parts of the body (4). Currently, there are 3 standard treatments for cancer: chemotherapy, radiation, and surgery. Chemotherapy uses drugs to kill cells. Radiation uses high amounts of X-rays or gamma rays to damage the DNA in cells, triggering cell death. However, both cause cell death in healthy, functioning cells, leading to

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side effects. Surgery requires the surgical resection of the cancer tumor, but it is an expensive procedure and can increase the risk of post-surgery complications such as infections, bleeding, or blood clots. All these methods have their benefits and save lives, but ultimately, they have limitations as well.

Scientists considered how the lethality of many viruses and bacteria was significantly reduced: vaccines. Traditional vaccines work by containing inactivated or dead proteins from a pathogen, triggering an immune response and boosting immunity to that specific pathogen (5). A cancer vaccine works by introducing your immune system to cancer-specific proteins called tumor antigens. The immune system would recognize these antigens, triggering an immune response and thus increasing sensitivity to those antigens. If cancer vaccines work, treatments for cancer can be manufactured cost-effectively and quickly, as well as being mass-produced. Currently, however, this is far from reality, and numerous technological and medical advancements would need to be made for cancer vaccines to become a widespread form of treatment.

This review focuses primarily on therapeutic cancer vaccines, with an emphasis on platforms that have produced the most clinically advanced evidence from human trials, including dendritic cell vaccines, personalized neoantigen vaccines, and nucleic acid-based vaccines. Studies were prioritized based on FDA (Food and Drug Administration) approval status or relevance to late-stage clinical trials, availability of long-term follow-up outcomes, and representation of key mechanistic categories. While many additional vaccine approaches exist, this review highlights representative examples to illustrate the major strengths and limitations shaping clinical translation.

HISTORY OF CANCER VACCINES

In 1891, William B. Coley, a bone surgeon, observed that the tumors in cancer patients had shrunk after contracting a bacterial infection. Coley developed "Coley toxins", a mixture of dead and inactivated bacteria, but this treatment had mixed and unpredictable results (6). However, this was the first time in history that the idea of boosting the immune system to treat cancer was observed, a process now called cancer immunotherapy. In the 1990s, rapid innovation in oncolytic vaccines emerged. These vaccines use genetically modified viruses to infect cancer cells, inducing an inflammatory response and stimulating your immune system (7). In 2020, the COVID-19 pandemic generated a pressing need for a vaccine. The urgency to create the vaccine helped increase understanding of mRNA vaccines, which contain a piece of genetic code that encodes a viral protein, triggering an immune response. Their adaptability and ability to be manufactured quickly make them a promising solution, especially for cancer (8).

CANCER VACCINES: FROM THEORY TO PRACTICE

Among all human innovations in medicine, vaccines have been one of the most successful preventive treatments against pathogenic infections. Due to the progressive enhancement of vaccines, smallpox has been eradicated globally, and once common diseases such as measles and pertussis (whooping cough) have been pushed to the brink of extinction. The vaccine has been so successful, especially in recent years, in harnessing the immune system's existing power to make it more sensitive to foreign pathogens.

This section first introduces the major classification of cancer vaccines, then outlines the five primary vaccine platforms, and finally summarizes clinical trial evidence and the remaining challenges for cancer vaccines.

Antigen Specific vs. Antigen Agnostic

In vaccines, a major component is the antigen, which is a substance or protein on the surface of pathogens that triggers an immune response. Vaccines can be classified as antigen-specific or antigen-agnostic.

These antigens, collectively referred to as tumor antigens, can be divided into tumor-specific antigens (TSAs), which are unique to cancer cells and include neoantigens arising from mutations in the genetic code, and tumor-associated antigens (TAAs), which are overexpressed or aberrantly expressed self-proteins. Vaccines presenting these tumor antigens stimulate cytotoxic T lymphocytes to recognize and eliminate cancer cells (9).

Antigen-agnostic vaccines contain both antigens and an adjuvant, which enhances the immune response. These vaccines do not require unique antigen selection for individual patients, and they confer protective immunity against future infection. They a type of generalized vaccines, ensuring unique vaccines won't have to be manufactured for each patient. They work by priming the immune system to kill a range of cancer cells. These vaccines use mechanisms to enhance the immune response in an area, rather than specifically

targeting cancer cells. Oncolytic vaccines are an example of antigen-agnostic vaccines - they use viruses to trigger an immune response, targeting cancer cells. The non-specific nature of these vaccines means that the immune response can shrink or eliminate the tumor size of many cancer tumors in a patient, not just one. Additionally, it also doesn't require the costly and time-consuming aspect of identifying patient-specific tumor antigens.

Cancer Vaccine Mechanisms

Beyond antigen classification, cancer vaccines can also be categorized based on their immunological mechanisms of action. Figure 1 shows that these mechanisms include preventive, cell-based, nucleic acid-based, peptide/protein-based, and oncolytic viral vaccines.

Preventive vaccines function by containing antigens from a virus with cancer-inducing properties. These viruses include the HPV (human papillomavirus), which can lead to cervical cancer, and Hepatitis B, which can lead to liver cancer. HPV harms a cell by integrating its DNA into the genome of its host cell, which disrupts the cell's tumor-suppressor genes, greatly increasing the risk of cancer (10). Hepatitis B viral infections can induce mutations in the hepatocyte genome, ultimately leading to cancer (11). Vaccines that elevate the immune response to these viruses can reduce the risk of many types of cancer, which is why around 78% of adolescents have received at least one dose of the HPV vaccine and why 85% of infants worldwide are vaccinated against Hepatitis B (12).

Cell-based vaccines use whole cells extracted from a patient's cancer tumor. Since they have a wide range of antigens, these vaccines also have the potential to trigger a larger and more intense immune response. These vaccines also include allogeneic cell vaccines, which are vaccines made from another individual's cells and can stimulate an immune response in the patient. These vaccines contain multiple antigens from the cell, increasing the chance of an immune response (13). However, further clinical research is needed before a cell-based cancer vaccine is approved. Research done by Tiwari *et al*. in 2024 revealed that only one cell-based vaccine, the Sipuleucel-T vaccine, a vaccine used to treat

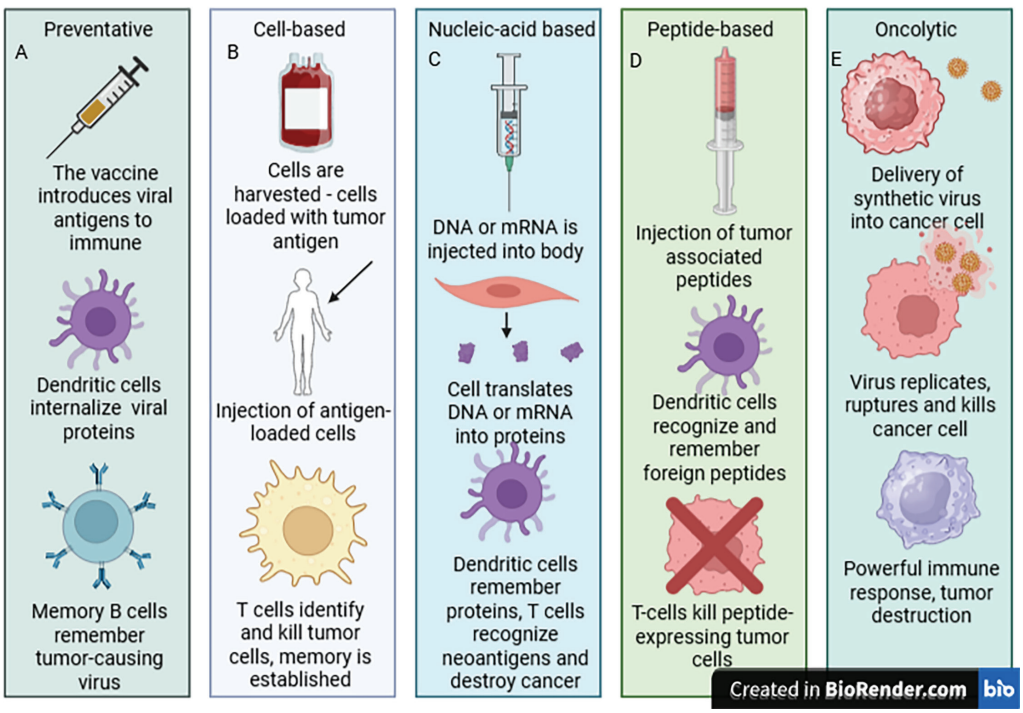

Figure 1. ***Major mechanistic categories of cancer vaccines.*** *(A) Preventive vaccines target oncogenic viruses and generate immune memory. (B) Cell-based vaccines activate T cells using antigen-loaded cells. (C) Nucleic acid-based vaccines encode tumor antigens for intracellular expression. (D) Peptide/protein vaccines deliver defined tumor antigens. (E) Oncolytic viral vaccines lyse tumor cells and stimulate immune activation. Figure was created in https://BioRender.com.*

castrate-resistant prostate cancer, is FDA-approved, and most clinical trials have produced a minimal effect, with some even having a negative impact on the patient (14). More research is needed to understand the biological mechanisms of these vaccines, as well as their potential safety and efficacy.

Nucleic acid-based vaccines work by inducing host cells to express TSAs, triggering an immune response. The development of nucleic acid-based vaccines is much more efficient than that of other vaccine types. Research by Liao *et al.* in 2025 illustrates that these cancer vaccines have been successful in clinical trials when combined with other immunotherapies, resulting in an objective response rate of 30.6%. This rate is notably higher than the approximately 17% response rate observed with pembrolizumab monotherapy. This shows the enhanced efficacy of combining immune checkpoint inhibitors with nucleic acid-based vaccines in a clinical setting. However, these vaccines must overcome numerous challenges at the cellular level. The genetic material needs to pass through the lipid bilayer of cells, which means that it must be stored within a carrier. These carriers must also prevent the genetic material from disintegrating in the bloodstream. Another critical issue is that the genetic material can be taken up by non-target cells, which can lead to potentially dangerous side effects for the patient (15).

Protein/peptide-based vaccines are the most similar to traditional pathogenic vaccines. The vaccine contains selected tumor antigens that trigger an immune response in the patient. Using the specific amino acid sequencing of the patient's cancer cells, the T cells of your immune system differentiate and destroy the cancer cells. A 2021 study by Stephens *et al.* reports a 10% cure rate with their Pam3CSK4-TLR-SLP fusion, a peptide-based cancer vaccine, as monotherapy. In contrast, when used in combination with the cervical cancer chemotherapy drug Cisplatin, survival increased to 71%, and with photodynamic therapy, survival increased to 89% (16).

Oncolytic vaccines contain genetically modified viruses that infect and kill cancer cells, also enhancing immune sensitivity. The process of creating these vaccines involves growing viruses in cell cultures, genetically modifying them to target cancer cells, and then purifying the remaining viruses. According to a 2013 study by Bartlett *et al*., the survival duration of patients at a critical stage of cancer showed a strong correlation with the viral dose, with average survival times of 14.1 months at the high dose and 6.7 months at the low dose. However, the nature of these vaccines makes it challenging to work in many scenarios. The immune system can eliminate the foreign viruses before they reach cancer growth, or tumors can have physical barriers that prevent the viruses from entering. Also, injecting a virus into a patient's body can have unintended side effects, such as inflammation or autoimmune reactions (17).

CLINICAL TRIAL EVIDENCE AND OUTCOMES

This section summarizes representative clinical studies across major cancer vaccine platforms. While many trials report strong immune activation, clinical outcomes are often inconsistent, and results must be interpreted in the context of trial design, small sample sizes, and differences in patient populations and disease stage. Many studies are early-phase trials designed primarily to assess safety and immunogenicity rather than tumor regression. Therefore, comparisons across platforms should be interpreted cautiously, but broad patterns in efficacy, durability, and translational feasibility can still be identified.

Current research on cancer vaccines is a rapidly developing field, encompassing many different types of cancer vaccines. Research done by Greg L Plosker in 2010 evaluates the benefits of using Sipuleucel-T, a cell-based vaccine, to treat advanced prostate cancer in men. In this study, a double-blind, placebo-controlled IMPACT study in patients with metastatic castration-resistant prostate cancer, which is cancer that is resistant to hormone therapy, sipuleucel-T was associated with a 22% relative reduction in the risk of death. The study followed 512 men, divided into a vaccine group and a placebo group. On average, the patients who took the vaccine lived longer than those who didn't. They found that the cancer vaccine did not shrink the tumor size, but it did increase the life expectancy of patients, which suggests an immune–system–based benefit unrelated to tumor size or mass. The majority of the patients saw mild symptoms, such as mild-to-moderate chills (54 %), fever (29 %), headache (16 %), myalgia (9 %), and influenza-like symptoms (9 %). Very few, around 1.5%, experienced any severe symptoms such as autoimmune responses or neurological events compared to the placebo group. Ultimately, this study shows that cell-based vaccines have helped significantly increase the life expectancy of patients with advanced stages of cancer. While the study demonstrates a survival benefit, interpretation is limited by cohort size and disease

specificity, and broader applicability across cancer types remains to be established (18). Strengths of this study include a strong correlation between the vaccine and increased lifespan.

In another 2021 study, Hu *et al.* assessed how personalized neoantigen vaccines can increase the immune response for cancer cells in patients with melanoma. In the clinical trial, each patient was given a personalized peptide vaccine containing 20 neoantigens specific to each patient. The study followed a group of 8 patients over a 4.5-year timespan. The patients all had surgically-resected high risk melanoma, and after surgery, they were given a personalized vaccine, called "NeoVax". Ultimately, the trials yielded positive results. Around 16 weeks into the study, immune responses to many of the peptides in the vaccine were detected. T cell responses to the peptides were detected from 2.3 to 4.7 years after vaccination. All patients had detectable immune responses to tumor-related antigens, and none experienced severe side effects beyond mild symptoms (19). However, these findings remain preliminary due to the limited cohort size and follow-up duration, which constrain assessment of long-term efficacy and relapse outcomes.

A 2020 study conducted by Ott *et al.* evaluated the use of personalized neoantigen cancer vaccines to treat advanced melanoma, lung cancer, and bladder cancer. The study included 82 patients. Each patient received NEO-PV-01, a type of personalized cancer vaccine, as well as a PD-1 checkpoint inhibitor, a type of cancer immunotherapy. Immune system checks were conducted to evaluate cell responses post-vaccination, and to assess T cell phenotype and their ability to destroy cancer cells before and after vaccination. The study monitored any serious treatment-related side effects or toxins, and none were reported. All patients developed neoantigen-specific T cell responses after vaccination. The new T cells had a cytotoxic phenotype, meaning that they developed the ability to identify and target the unique cancer cells. The study showed that personalized peptide vaccines can work in real-world situations - the treatment was ultimately successful in boosting immune response to the cancer cells, despite all patients having advanced stages of cancer. It also shows how combination therapy can be extremely beneficial for treating cancer, compared with monotherapy. However, the absence of extended follow-up limits the evaluation of durability and long-term clinical benefit (20). This study provides clear clinical evidence that cancer vaccines boost immune responses. Additionally, the study supports the idea that cancer vaccines and standard therapy used together can be a potent tool to help patients with cancer.

In a 2018 study, Dillman *et al.* assessed the effects of 2 different vaccines on patients who had metastatic melanoma, an advanced form of skin cancer. A group of 42 patients was divided into two groups: one with 22 patients who were all given a vaccine made from their immune cells, specifically dendritic cells, and the other was given a control. In the lab, these cells were exposed to tumor-derived antigens from a patient's own tumor, thereby increasing the dendritic cells' ability to recognize and destroy the cells that make up the tumor. The other group had 20 patients, and they were given vaccines that contained their own tumor cells. The cells were irradiated in a lab to prevent unintended growth, then inserted back into the body to stimulate an immune response. The researchers found that the median survival rate for the dendritic cell vaccine was 43.4 months, while the median survival rate for the tumor cell vaccine was 20.5 months. They also found that the five-year survival rate for the dendritic cell vaccine was 46%, while the five-year survival rate for the tumor cell vaccine was 13%, nearly 70% lower. Both vaccines showed no serious side effects, with only mild reactions such as redness at the injection site, fatigue, or flu-like symptoms. All in all, the conclusion of this study is that using "trained" dendritic cells is significantly effective against cancer than using whole tumor cells. A long-term benefit was observed in nearly 50% of patients who survived for 5 years after receiving the dendritic cell vaccine, but further research is needed to support these conclusions on a larger scale (21). Although long-term survival outcomes appear favorable, the lack of a robust control group limits definitive conclusions regarding comparative efficacy.

In another study by Maeng *et al.* in 2021, the effects of an autologous dendritic cell vaccine containing genetically engineered HER2, a growth factor found on cell surfaces, were examined. The study enrolled 33 participants with a wide range of HER2-positive cancers, such as breast, gastric, and others. All participants in the study had cancer tumors that continued to grow and metastize despite going through the standard cancer treatments. The participants got 5 doses of the vaccine through injection. The results indicate that most patients experienced mild, short-term side effects. Among 21 evaluable patients, one showed a complete response, one a partial response, and five a stable disease. 23% of patients had antibody responses, 91% had cellular

responses (T-cell activation), and 73% produced multiple cytokines, indicating a strong immune response. The study showed that around 33% of patients achieved tumor control with the vaccine. In conclusion, this study demonstrates the beneficial effects of a dendritic–cell vaccine in patients for whom other forms of therapy failed, highlighting its potency (22). One point to note is that many dendritic cell vaccines in various clinical trials have elicited positive immune responses. While these results suggest measurable immune activation and partial tumor control, the heterogeneity of cancer types within the cohort makes it difficult to interpret efficacy across specific indications.

Not all research on cancer vaccines could be included in this manuscript, but current research shows the potential of cancer vaccines, as shown in these clinical trials. Ultimately, many studies have shown positive effects of cancer vaccines in patients, characterized by increased lifespan and decreased tumor growth.

CONCLUSION

In conclusion, cancer vaccines remain one of the most conceptually compelling strategies in immunotherapy because they aim to induce tumor-specific adaptive immunity and long-term immune memory. In various immunotherapy approaches including dendritic cell vaccines, peptide/protein vaccines, nucleic acid-based vaccines, and oncolytic vector-based vaccines—clinical studies consistently demonstrate that therapeutic vaccination can induce immunogenicity, particularly tumor-specifiic T-cell responses. At the same time, the broader clinical record highlights a key limitation: immunogenicity does not consistently translate into durable tumor regression or survival benefit, most notably when vaccines are used as monotherapy in advanced stages of cancer. This gap reflects both biological complexity and practical barriers that continue to limit widespread clinical effectiveness.

A central scientific challenge is tumor heterogeneity, which facilitates the immune escape mechanism through the expansion of antigen-negative subclones or shifts in antigen expression over time. Even when vaccines successfully targets specific tumor antigens, cancers can evolve under immune pressure, limiting the durability of responses. In parallel, immune evasion within the tumor microenvironment is one of the main challenges. Many tumors actively suppress immune infiltration and function through the use of various immunosuppressive mechanisms (23). As a result, vaccine-primed T cells may be generated systemically but fail to effectively penetrate tumors or maintain cytotoxic activity within the suppressive tumor environment. In addition, many TAAs exhibit limited immunogenicity due to their similarity to normal self-proteins, thereby limiting the strength of vaccine-induced responses and making it difficult to balance efficacy and safety.

Beyond biology, cancer vaccines face substantial translational constraints. Personalized neoantigen vaccines have the advantage of specificity and a lower theoretical risk of autoimmunity, but their clinical deployment is limited by complex, multi-step process that involve tumor sequencing, neoantigen prediction, individualized manufacturing, and quality control. These processes remain time-intensive and expensive, creating barriers for patients with rapidly progressing disease and limiting scalability. In different studies, differences in trial design, disease stage, and clinical endpoints have made it difficult to compare platforms and determine which immune readouts most reliably predict meaningful clinical benefit.

Future progress will depend on coordinated advances in both scientific strategy and implementation. Important aspects that must be addressed include improved patient stratification using genomic and immune biomarkers to identify settings where vaccination is more likely to work, as well as more accurate antigen selection pipelines that account for clonal structure and antigen presentation. Rational combination strategies will also be essential, particularly approaches that pair vaccines with checkpoint blockade, radiation, chemotherapy, or other immune-modulating therapies to overcome tumor-mediated immune suppression and improve intratumoral T-cell function. In addition to this, better standardized manufacturing workflows—especially for personalized platforms—will be critical for reducing cost, shortening manufacturing times, and enabling broader access. Moreover, the development of standardized clinical endpoints and validated immune responses will be necessary to help late-stage trials and support reproducible cross-study comparisons.

In summary, cancer vaccines have shown to be capable of tumor-directed immune responses, but success in a clinical trial will require overcoming tumor heterogeneity, immunosuppression, and translational barriers. With continued progress in patient selection, combination regimens, scalable manufacturing, and standardized evaluation, therapeutic vaccination may become a more reliable and widely applicable component of comprehensive cancer treatment.

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CONFLICT OF INTEREST

The author declares that there are no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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