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Cancer Vaccines: Navigating Immune Responses, Developmental Challenges and Emerging Solutions

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Abstract **Original Research Article**

Cancer vaccines are a novel approach in the fight against cancer, aiming to stimulate the immune system to recognize and destroy tumour cells. This review explores the primary mechanisms by which cancer vaccines induce immune responses, the role of antigen presentation, dendritic cell activation, and T-cell-mediated tumour destruction. While many vaccines have demonstrated success in clinical trials for cancers such as melanoma, prostate, and lung cancers, issues related to antigen selection, delivery systems, and vaccine-induced side effects remain. To address these challenges, we assessed the safety and efficacy of current cancer vaccines, using clinical trial data to highlight both successes and limitations. Emerging trends, such as neoantigen-based vaccines and mRNA platforms, offer novel solutions through personalized treatments that target patient-specific tumour mutations to enhance vaccine potency. Personalized vaccines and combination therapies represent pathways to overcoming current limitations, offering hope for more effective, durable, and patient-specific cancer treatments. Finding the right balance between future research directions and the challenges we face will be essential for overcoming immune resistance and fully advancing this promising field.

Keywords: Cancer Vaccines, Immune Evasion, Tumour Heterogeneity, Neoantigen-Based Vaccines, Personalized Treatment, Combination Therapy, Immune Response.

INTRODUCTION

In the 21st century, cancer is a significant social, public health, and economic problem that accounts for about one in six deaths (16.8%) and one in four deaths (22.8%) from noncommunicable diseases (NCDs) globally (Bray et al., 2024). As of 2024, global cancer cases continue to rise, primarily driven by an aging population, increased exposure to carcinogenic factors, and other modifiable risk factors such as tobacco use, poor diet, and physical inactivity. According to projections, cancer cases are expected to increase to 35 million by 2050 if these trends persist (American Cancer Society, 2024). In addition to being a significant barrier to improving life expectancy, cancer is associated with significant societal and macroeconomic costs that vary in degree among different types of cancer, geography, and gender (Chen et al., 2023).

The global COVID-19 pandemic provided a critical opportunity to assess the potential applications of immunotherapy, especially mRNA-based vaccines, which showed promise beyond infectious diseases (B. Wang et al., 2023). Leveraging similar technology, cancer vaccines are emerging as a novel immunotherapeutic strategy designed to elicit an anti-tumour immune response by encoding tumour-specific antigens (TSAs), tumour-associated antigens (TAAs), and immune modulatory factors (Drew, 2024). These components stimulate the adaptive immune system to recognize and destroy tumour cells, a mechanism that has already demonstrated effectiveness in various preclinical

studies and early-stage clinical trials during the pandemic era. As a result, researchers are now focusing on cancer vaccines' ability to generate long-lasting, targeted immune responses, which are pivotal in controlling tumour growth and preventing recurrence (Drew, 2024). Despite these advances, cancer cells often evade immune surveillance: this is the hallmark of tumour progression outstripping anti-tumour immunity (Topalian et al., 2020).

In this review, we evaluate the development of cancer vaccines, highlighting recent advancements from preclinical studies and clinical trials, while drawing attention to the ongoing challenges related to cancer vaccine development. Furthermore, we discussed strategies to enhance the efficacy and safety of cancer vaccines, particularly by addressing the issues of tumour heterogeneity and immune suppression, while exploring novel strategies that aim to boost the overall immune response.

History and Origin of Cancer Vaccines

In the late 1800s, research was motivated by observations that some cancer patients who developed infections experienced spontaneous tumour regression. This led to speculation that immune activation might have therapeutic effects on cancer. Cancer vaccines were first conceptualized in the early 20th century when scientists recognized that a strong immune response could fight cancers (Marabelle et al., 2017). Cancer vaccines are generally classified into two primary types: prophylactic and therapeutic cancer vaccines. Prophylactic vaccines, such as the human papillomavirus (HPV) vaccine, are designed to prevent cancer by inducing an immune response that targets viruses associated with the development of cancer (Elsheikh et al., 2023). On the other hand, therapeutic vaccines aim to treat patients who already have cancer by activating the immune system to recognize and destroy cancerous cells (Liu et al., 2022).

In the 1990s, the approval of the first prophylactic cancer vaccines like hepatitis B vaccine paved the way for other vaccines that seek to prevent virus-induced cancer including human papilloma viruses (HPV) vaccination used against cervical cancer (Garland et al., 2016). Sipuleucel-T, marketed as Provenge, is the first therapeutic cancer vaccine to be approved by The United States Food and Drug Administration (FDA) for metastatic castration-resistant prostate cancer (mCRPC). Also, Bacillus Calmette-Guerin (BCG) vaccine is a therapeutic cancer vaccine regarded as a standard treatment for bladder cancer to the present day (Redelman-Sidi et al., 2014). It is used to stimulate a localized immune response in the bladder, reducing tumour recurrence rates. These vaccines leverage tumour-specific antigens to enhance immune recognition and increase the body's capacity to fight cancer cells (Fan et al., 2023).

One of the first cancer vaccines proven effective in humans was developed in the 1980s for treating patients with melanoma, a type of skin cancer. This vaccine utilized patient-specific tumour cells, serving as a personalized treatment (Rosenberg et al., 2004). This innovation marked a new era in cancer therapy, shifting the focus from merely targeting tumours to harnessing the body's immune system. In addition, novel vaccine platforms are designed to elicit a more robust immune response by targeting tumour-specific antigens and have recently been developed through advances in molecular biology and immunology. They include peptide, DNA and mRNA vaccines (Melero et al., 2014). These vaccines have shown success in clinical trials for different types of cancers, including melanoma, prostate, lung and breast cancers (Ribas & Wolchok, 2018).

Table 1 summarizes the different classes of cancer vaccine technologies in development, their mechanisms, targeted cancers and key clinical trials associated with each type. Peptide vaccines work by activating T-cells in the body to identify and destroy tumour cells and have been tested in studies of melanoma as well as breast cancer. DNA vaccines insert tumour DNA into immune cells directly to induce a more personalized and potent activation of the immune system, with favourable results for prostate and lung cancers. Messenger RNA vaccines, which gained widespread attention due to their use in COVID-19 vaccines, encode antigens that instruct the immune system to target cancer cells, and are being explored for a variety of cancers, with promising results from recent trials.

Table 1: Summary of Cancer Vaccine Types and Their Mechanisms

Vaccine Type	Mechanism	Target Cancers	Notable Trials
Peptide Vaccines	Stimulate T-cell response	Melanoma, Breast	(Slingluff, 2011)
DNA Vaccines	Introduce tumour DNA to immune cells	Prostate, Lung	(Zahm et al., 2017)
mRNA Vaccines	Encode antigens for immune response	Multiple Cancers	(Fotin-Mleczek et al., 2011)
Dendritic Cell Vaccines	Use dendritic cells to present tumour antigens	Prostate, Glioblastoma	(Kantoff et al., 2017)
Viral Vector Vaccines	Use viral vectors to deliver tumour antigens	Colorectal, Pancreatic	(Jia et al., 2022; Seclì et al., 2023)
Whole Tumour Cell Vaccines	Use irradiated tumour cells to stimulate immunity	Melanoma, Renal Cell Carcinoma	(Parmiani et al., 2002)
CAR-T Cell Vaccines	Genetically modify T-cells to target cancer	Leukemia, Lymphoma	(Maude et al., 2018)
Oncolytic Virus Vaccines	Use modified viruses to infect and kill cancer cells	Melanoma, Glioblastoma	(Andtbacka et al., 2015)
Heat Shock Protein Vaccines	Use heat shock proteins to present antigens to the immune system	Renal Cell Carcinoma	(Belli et al., 2002)
Neoantigen Vaccines	Target patient-specific neoantigens	Melanoma, Lung	(Sahin et al., 2017)
Allogeneic Tumour Cell Vaccines	Use tumour cells from donors	Pancreatic, Melanoma	(Laheru & Jaffee, 2005)
Protein Subunit Vaccines	Use tumour-associated proteins as antigens	Breast, Prostate	(Scholl et al., 2000)
Bacterial Vector Vaccines	Use bacteria to deliver antigens	Pancreatic, Colorectal	(Gunn et al., 2001)
Toll-like Receptor (TLR) Agonist Vaccines	Stimulate TLRs to enhance immune response	Melanoma, Breast	(Chakraborty et al., 2023)

The Immune System and Cancer

The immune system is responsible for recognizing and eliminating abnormal cells, including cancer cells, through a process known as immune surveillance (Rao et al., 2019). This involves various immune cells, particularly T cells, which can identify and destroy tumour cells that present specific antigens. The presence of tumour-infiltrating lymphocytes (TILs) is often associated with better clinical outcomes in cancers such as melanoma and breast cancer (Gubin & Vesely, 2022). However, cancer cells have mechanisms to evade the immune system. They can alter their surface proteins to avoid detection, produce immunosuppressive factors, and recruit regulatory immune cells that inhibit anti-tumour responses. This phenomenon is known as "cancer immunoediting," where the immune system shapes the tumour's antigen, allowing less immunogenic variants to survive and proliferate (Gubin & Vesely, 2022).

The tumour microenvironment (TME) helps with immune responses to cancer. It consists of various cell types, including immune cells, fibroblasts, and endothelial cells, that interact dynamically (Gonzalez et al., 2018). Tumours recruit immunosuppressive cells, such as regulatory T cells

(Tregs) and tumour-associated macrophages (TAMs), which inhibit the activity of effector immune cells. This immunosuppressive environment leads to a state of "immune exclusion," where immune cells are present but ineffective against the tumour (Hiam-Galvez et al., 2021). Dendritic cells bridge innate and adaptive immunity by processing and presenting antigens to T cells. They influence the polarization of T cells towards either pro- or anti-tumour responses, depending on the signals they receive from the TME (Den Haan et al., 2014).

Mechanisms of Cancer Vaccine Immune Response Induction

Cancer vaccines primarily work by presenting specific antigens to the immune system. These antigens can be derived from various sources, including purified tumour proteins, DNA, mRNA, and synthetic peptides (Kaczmarek et al., 2023). The delivery of these antigens is often facilitated through dendritic cells (DCs), which are the most effective antigen-presenting cells (APCs) in the body (Del Prete et al., 2023). Once the antigens are presented by DCs, they activate naive T cells, leading to their proliferation and differentiation into effector T cells, particularly cytotoxic T lymphocytes (CTLs) that can recognize and destroy tumour cells (Fu et al., 2018).

The activation of T cells is important for the efficacy of cancer vaccines. Upon recognition of tumour antigens presented on major histocompatibility complex (MHC) molecules, cluster of differentiation 8+ (CD8+) T cells are stimulated to proliferate and differentiate into CTLs (Dhatchinamoorthy et al., 2021). These CTLs are responsible for directly killing tumour cells through the release of cytotoxic molecules such as perforin and granzymes (McKenzie et al., 2022). Additionally, CD4+ T helper cells play a supportive role by enhancing the activation and survival of CTLs, thereby contributing to a robust immune response (Swain et al., 2012).

Cancer vaccines also promote humoral immunity by stimulating B cells to produce antibodies against tumour antigens (Le et al., 2022). This process is essential for generating a long-lasting immune memory, which helps the body to recognize and respond more effectively to any future occurrences of the cancer. For instance, the vaccine Sipuleucel-T has been shown to elevate levels of IgG antibodies targeting specific tumour antigens, thereby improving clinical outcomes for patients (Madan et al., 2020).

However, a significant challenge in cancer immunotherapy is the ability of tumour cells to evade the immune response (Kim & Cho, 2022). Cancer vaccines aim to overcome this by enhancing the immunogenicity of tumour cells and promoting a more effective immune response (Kaczmarek et al., 2023). Strategies include targeting multiple neoantigens within a single vaccine to reduce the likelihood of tumour cells escaping immune detection due to antigen heterogeneity (Xie et al., 2023). Furthermore, the use of adjuvants in vaccines can enhance the immune response by promoting better antigen presentation and T cell activation (T. Zhao et al., 2023).

Figure 1: The mechanism of action of a cancer vaccine, showing the steps from administration to tumour destruction. Following the injection of the vaccine, dendritic cells engulf, process and present cancer antigens on major histocompatibility complex (MHC) molecules, leading to the activation of naive T-cells. The T-cells then differentiate and proliferate, targeting and destroying tumour cells. This sequence demonstrates how the immune system is stimulated to recognize and eliminate cancer cells following vaccination.

Current Clinical Trials in Cancer Vaccines

Clinical trials play a crucial role in validating vaccine efficacy, shaping future treatments, and advancing cancer immunotherapy (Fan et al., 2023). Clinical trials of cancer vaccines are mainly conducted in patients with advanced solid tumours, with safety, immunogenicity, and clinical benefits as the endpoints (Zhou et al., 2023). As of 22nd September 2024, 17 clinical trials have been registered in the United States National Library of Medicine's ClinicalTrials.gov website with the keyword "cancer vaccine", of which 847 have been completed, and 209 are actively recruiting (ClinicalTrials.gov, 2024). Table 2 presents the representative relevant clinical studies. Current findings indicate that the use of cancer vaccines alone does not yield effective

outcomes in prolonged patient survival, although antigen-specific T-cell immune responses have been detected in most clinical trials. Therefore, enhancing T-cell activation and anti-tumour efficacy is the most significant therapeutic challenge (Fan et al., 2023).

Table 2: Selected ongoing clinical trials of therapeutic cancer vaccines

Clinical trial	Target antigen	Platform	Indication	Combination therapy	Administration	Primary Endpoint	Start year
mRNA cancer vaccine							
NCT05933577 (Phase 3)	Neoantigen mRNA	LNP	High-risk melanoma	Pembrolizumab	Intramuscular injection	RFS	2023
NCT05886439 (phase 1b/2a)	Neoantigen mRNA	Autologous DC	Incurable lung cancer	Pembrolizumab or durvalumab	Not mentioned	DLT, AE	2023
NCT05198752 (Phase 1)	Neoantigen mRNA	Lipopolyplex	Multiple solid Tumors	———	Subcutaneous injection	DLT	2022
NCT04534205 (Phase 2)	HPV 16 E6 and E7 mRNA	LNP	HPV16 + Head and Neck Cancer	Pembrolizumab	Intravenous injection	AE, OS, ORR	2021
NCT04382898 (Phase ½)	KLK-2, KLK-3, PAP, HOXB13	LNP	Prostate cancer	Cemiplimab	Intravenous injection	DLT, ORR	2020
DNA cancer vaccine							
NCT03988283 (Phase 1)	Neoantigen DNA	TDS-IM v2.0	Recurrent brain Tumour	———	Intramuscular injection + electroporation	ST	2023
NCT05743595 (Phase 1)	Neoantigen DNA	TDS-IM	Glioblastoma	Retifanlimab		DLT	2023

NCT03199040 (Phase 1)	Neoantigen DNA	TDS-IM	TNBC	Durvalumab	Intramuscular injection + electroporation	AE, immune response	2017
NCT03655756 (early phase 1)	Emm55 streptococcal antigen plasmid	Not mentioned	Unresectable melanoma	———	Intramuscular injection + electroporation	SAE, DLT	2018
Peptide cancer vaccine				Vorasidenib	Intratumoral injection	SE	2023
NCT05609994 (Phase 1)	IDH1 peptide	Not mentioned	Recurrent IDH1 mutant lower grade glioma	———		RFS	2019
NCT04206254 (Phase 2/3)	Heat shock protein gp96-peptide	Not mentioned	Liver cancer		Intracutaneous injection	Immune response, ORR, AE	2011
NCT01461148 (Phase 1/2a)	AIM2, HT001, TAF1B neoantigen	Montanide ISA-51 VG	MMR-deficient colorectal cancer	———	Subcutaneous Injection Subcutaneous injection		

LNP: Lipid nanoparticle, **RFS:** Recurrence-free survival, **DC:** Dendritic cell, **DLT:** Dose-limiting toxicity, **AE:** Adverse events, **HPV:** Human papillomavirus, **OS:** Overall survival, **ORR:** Overall response rate, **KLK:** Kallikrein, **PAP:** Prostatic acid phosphatase, **TNBC:** Triple-negative breast cancer, **HOXB13:** Homeobox gene B13, **ST:** Safety and tolerability, **SAE:** Serious adverse event, **IDH1:** Isocitrate dehydrogenase 1, **MMR:** Mismatch repair, **AIM2:** Absent in melanoma 2, **TAF1B:** TATA box binding protein associated factor B, **TDS – IM:** Transdermal delivery system-intramuscular, **ISA-51 VG:** Incomplete Seppic Adjuvant -51 Vegetable grade, **NCT:** National clinical trial, **ICI:** Immune checkpoint inhibitor, **SLP:** Synthetic long peptide, **NEO:** Neoantigen, **PV:** Personalized vaccine, **NSCLC:** Non-small cell lung cancer, **PD:** Programmed death, **MHC:** Major histocompatibility

complex, **TME:** Tumour microenvironment, **KRAS:** Kirsten Rat Sarcoma

Challenges in Developing Cancer Vaccines

The successful translation of cancer vaccines into clinical practice faces several challenges, despite the numerous clinical trials in progress to assess the safety and efficacy of cancer vaccines (B. Wang et al., 2023). One of these challenges is tumour heterogeneity. This term describes the variation in the genetic, phenotypic, and functional properties of cancer cells both within a single tumour and between tumours in different patients. Tumour heterogeneity creates a significant barrier to the success of cancer vaccines, as it complicates the identification of universal tumour antigens, enhances immune evasion, and fosters therapeutic resistance (Dagogo-Jack & Shaw, 2018). The cornerstone of cancer vaccines is the identification of tumour-associated antigens (TAAs) that are expressed specifically or preferentially by cancer cells. However, the genetic variability seen within tumours leads to the differential expression of these antigens across cancer cell populations. The genetic and phenotypic diversity within a single tumour means that a vaccine targeting one antigen may not be effective against all tumour cells. This heterogeneity necessitates the development of personalized vaccines that can target multiple antigens simultaneously. However, creating such vaccines is complex and costly, adding another layer of challenge to vaccine development (Abu et al., 2021; Kim & Cho, 2022).

Intratumor heterogeneity in renal cell carcinoma results in distinct subclonal populations expressing varying antigenic profiles, limiting the efficacy of therapies targeting single antigens (Gerlinger et al., 2012). As a result, vaccines that target only a single or limited set of TAAs may fail to eliminate all cancer cells within a tumour, leaving behind resistant clones that contribute to disease recurrence. To overcome this, multi-epitope vaccines have been proposed, targeting several TAAs simultaneously to cover the broad spectrum of antigenic diversity present in tumours. However, designing such vaccines is complex and requires deep genomic and proteomic profiling of tumours, which is not always feasible in clinical settings (McGranahan & Swanton, 2017).

Immune Evasion Mechanisms

Tumour heterogeneity also plays a critical role in immune evasion. Some subclones within a tumour may acquire mutations that allow them to downregulate major histocompatibility complex (MHC) molecules or other immune markers, making them less recognizable to the immune system. This immune evasion is a significant barrier to the success of cancer vaccines, as vaccine-induced immune responses may only target the more immunogenic tumour cell populations, leaving immune-evasive clones to proliferate (Rooney et al., 2015). Consequently, the immune pressure exerted by vaccination can inadvertently select these immune-evasive populations (Anagnostou et al., 2017). However, the combination of cancer vaccines and immune checkpoint inhibitors (ICIs) enhances vaccine efficacy. ICIs work by reactivating T cells that have been rendered ineffective by tumour-induced immune suppression. When used in combination with vaccines, they may prevent immune escape and improve outcomes by ensuring a more robust and sustained anti-tumour immune response (Wei et al., 2018).

Figure 2: Immune escape mechanisms as core factors that hinder the effectiveness of cancer vaccines. Tumour cells have developed a variety of strategies to escape the immune system, which complicates the effectiveness of immunotherapies, including vaccines.

Therapeutic Resistance and Tumour Evolution

Tumour heterogeneity is a key driver of therapeutic resistance. The selective pressure imposed by cancer vaccines can lead to the clonal evolution of tumours, wherein resistant subclones proliferate while sensitive ones are eliminated. This phenomenon has been observed in various cancers, including non-small cell lung cancer (NSCLC), where clonal evolution following immunotherapy was shown to result in the expansion of resistant clones, undermining the long-term efficacy of treatment. To mitigate this, researchers are exploring personalized cancer vaccines, which are tailored to the unique mutational landscape of each patient's tumour. Personalized vaccines leverage neoantigens,

which are tumour-specific antigens that arise from unique mutations within a tumour's DNA. These neoantigens are particularly promising because they are not subject to the same immune tolerance mechanisms as non-mutated TAAs. Early clinical trials have shown that personalized vaccines can elicit robust immune responses against tumours, even in the face of heterogeneity (Ott et al., 2017).

Figure 2 shows that the creation of an immunosuppressive tumour microenvironment (TME) is a significant mechanism of immune evasion. Cancer cells primarily communicate with their environment through soluble molecules such as cytokines, chemokines, and growth factors to create a favourable tumour microenvironment (Braumüller et al., 2022). Hence, TME consists of a variety of cells, such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), which actively suppress the activity of cytotoxic T lymphocytes (CTLs). This suppression is critical because CTLs are responsible for killing tumour cells. By creating a TME that inhibits CTLs, tumours can effectively shield themselves from immune attack, thereby reducing the efficacy of cancer vaccines designed to stimulate a CTL response (Abu et al., 2021; Kim & Cho, 2022).

Another challenge is the modulation of antigen presentation by tumour cells. Tumours can downregulate the expression of major histocompatibility complex (MHC) molecules, which are essential for presenting tumour antigens to T cells. Without proper antigen presentation, T cells cannot recognize and attack tumour cells, leading to immune escape. Additionally, tumours can secrete immunosuppressive cytokines like interleukin 10 (IL-10) and transforming growth factor beta (TGF-β), which further inhibit the activation and function of CTLs, complicating vaccine efforts (You & Chi, 2023). They exploit immune checkpoint molecules such as programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) to avoid immune detection. By upregulating these checkpoint molecules, tumours can "turn off" the immune response, allowing for unchecked growth. While checkpoint inhibitors have been developed to counteract this mechanism, their efficacy can be limited by other forms of immune evasion, making it difficult to achieve complete tumour control with vaccines alone (Kim & Cho, 2022).

Side Effects of Cancer Vaccines: Interactions with Body Proteins

Cancer vaccines are designed to stimulate the immune system to recognize and destroy cancer cells, but they can also trigger unintended side effects due to interactions with body proteins. These interactions may lead to autoimmune responses, where the immune system mistakenly targets normal proteins and tissues (Postow et al., 2018). One of the primary concerns is molecular mimicry. In this mechanism, the vaccine-induced immune response against tumour antigens may cross-react with similar epitopes on normal proteins, leading to autoimmunity. For example, immune checkpoint inhibitors, a class of cancer vaccines, can lead to immune-related adverse events (irAEs) by disrupting the balance of immune regulation. These irAEs are thought to arise from the activation of autoreactive T-cells that target self-antigens, such as those present on normal tissues. Myocarditis has been reported as a serious irAE linked to immune checkpoint blockade, where T-cell infiltration and inflammation of heart tissues occur due to cross-reactivity with cardiac proteins (Johnson et al., 2016).

Additionally, neoantigen vaccines, which target unique tumour-specific mutations can sometimes result in the generation of antibodies that cross-react with similar peptides in normal tissues. This cross-reactivity can lead to tissue-specific autoimmune diseases, such as dermatitis or colitis, as the immune system begins to attack the body's cells. Some cancer vaccines may induce cytokine release syndrome (CRS), characterized by an overwhelming immune response that can lead to multi-organ failure. This syndrome is a result of the massive activation of T-cells and the subsequent release of pro-inflammatory cytokines that can damage healthy tissues (Jacobson et al., 2020). Moreover, the use of adjuvants, substances that enhance the immune response to vaccines can also exacerbate the reactions of protein interactions. Certain adjuvants may promote the presentation of self-antigens, increasing the risk of autoimmunity (Paston et al., 2021).

Emerging Trends and Innovations

Recent advancements in cancer vaccine therapeutics have seen progress in areas, including personalized cancer vaccines, combination therapies, and nanoparticle-based delivery systems (Alard et al., 2020). These innovations are reshaping the landscape of cancer immunotherapy by offering more targeted and effective treatment options.

Among the types of cancer immunotherapies, neoantigen-based vaccines are promising due to their potential for personalized treatment. One innovative approach to neoantigen-based cancer vaccines is the use of messenger RNA (mRNA) technology, which has gained significant attention following its successful application in COVID-19 vaccines (Barbier et al., 2022; Dolgin, 2021). mRNA cancer vaccines offer high specificity, better efficacy, and fewer side effects compared to traditional cancer treatments (Cao et al., 2024). These vaccines work by delivering mRNA encoding tumour-specific neoantigens directly into the body, where they are translated into neoantigen proteins and presented on the surface of cells, triggering an immune response (B. Wang et al., 2023). Several mRNA cancer vaccines are currently being evaluated in preclinical and clinical trials, showing promising early-phase results (Lorentzen et al., 2022).

Personalized cancer vaccines trigger T-cell responses against neoantigens—unique mutations specific to a patient's tumour (Adamik & Butterfield, 2022; Blass & Ott, 2021). This amplifies tumour-specific immune responses and has shown potential in early clinical trials, particularly for cancers with high mutational burdens such as melanoma and lung cancer (Oliveres et al., 2018; Redwood et al., 2022; X. Wang et al., 2024). Despite the promising results, several challenges remain in the development and implementation of neoantigen-based vaccines. One of the critical hurdles is the accurate prediction and selection of neoantigens that can effectively induce cytotoxic T-cell responses in individual patients. Unlike shared antigens, which are common across different patients, personalized neoantigens are unique to each patient's tumour and require advanced computational tools and algorithms for precise identification (Kiyotani et al., 2021). The use of advanced bioinformatics tools to predict the most immunogenic neoantigens enhances the precision of immunotherapy, although challenges remain in terms of tumour heterogeneity and cost of development (Blass & Ott, 2021; Hao et al., 2024).

Combining cancer vaccines with other immunotherapies, such as immune checkpoint inhibitors (e.g., PD-1/PD-L1 inhibitors) and CAR-T cell therapy, has emerged as a powerful strategy to boost the efficacy of cancer treatments (Almeida et al., 2014; Berti et al., 2022; Cai et al., 2021). Clinical trials have demonstrated that such combinations can significantly improve patient outcomes, especially in cases of resistant or recurrent cancers (Kwak et al., 2019; J. Zhao et al., 2019). These therapies work synergistically to create a more robust and sustained immune response, overcoming challenges posed by tumour heterogeneity and the immunosuppressive tumour microenvironment. Cancer vaccines have also been combined with chemotherapy with favourable outcomes for the patient (Leung & Van den Eynde, 2022).

Combining immune checkpoint inhibitors (ICIs) with cancer vaccines offers a promising approach to enhance the immune response in cancer therapy, warranting further investigation in upcoming clinical trials. A personalized cancer vaccine known as NEO-PV-01 has shown significant pathological responses in nine melanoma patients who had only limited or partial responses to nivolumab. Additionally, the combination of NEO-PV-01 with nivolumab resulted in epitope spreading, which released neoantigens that provided new targets for T cells (Ott et al., 2020). Future clinical studies may explore the combination of NEO-PV-01 with chemotherapy and anti-PD-1 therapies as a potential first-line treatment for non-squamous non-small cell lung cancer (NSCLC) (Awad et al., 2022).

Nanoparticle-based delivery systems are another innovative approach in cancer immunotherapy (Arbelaez et al., 2020; Berti et al., 2022; Chatzikleanthous et al., 2021; Chesson & Zloza, 2017). These systems leverage the unique properties of nanoparticles to enhance drug delivery and immune response activation (Shinde et al., 2022).

Also, nanoparticles can be engineered for controlled release, activating their payloads only within the tumour microenvironment, thereby improving treatment specificity and efficacy (Han et al., 2021).

CONCLUSION

While current cancer vaccines have shown promise in both preventive and therapeutic settings, significant challenges continue to impede their widespread adoption. This research has highlighted how these challenges, including immunosuppressive tumour microenvironments, antigen downregulation, and immune escape mechanisms, limit the efficacy of cancer vaccines across different cancer types. However, emerging trends such as neoantigen vaccines and the integration of immune checkpoint inhibitors could offer promising pathways for overcoming current limitations. We recommend further studies of the complex interplay between cancer cells and the immune system, as well as the development of novel strategies to enhance vaccine efficacy. The integration of cancer vaccines into personalized medicine holds immense potential, promising more tailored and effective treatment options for cancer patients. Continued efforts in these areas will not only enhance patient outcomes but also shape the future of oncology by establishing cancer vaccines as a vital component of cancer prevention and therapy.

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