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REVIEW

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Cancer vaccines: current status and future directions

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Abstract

Cancer continues to be a major global health burden, with high morbidity and mortality. Building on the success of immune checkpoint inhibitors and adoptive cellular therapy, cancer vaccines have garnered significant interest, but their clinical success remains modest. Benefiting from advancements in technology, many meticulously designed cancer vaccines have shown promise, warranting further investigations to reach their full potential. Cancer vaccines hold unique benefits, particularly for patients resistant to other therapies, and they offer the ability to initiate broad and durable T cell responses. In this review, we highlight the antigen selection for cancer vaccines, introduce the immune responses induced by vaccines, and propose strategies to enhance vaccine immunogenicity. Furthermore, we summarize key features and notable clinical advances of various vaccine platforms. Lastly, we delve into the mechanisms of tumor resistance and explore the potential benefits of combining cancer vaccines with standard treatments and other immunomodulatory approaches to improve vaccine efficacy.

Keywords Cancer vaccine, Tumor antigen, Clinical outcome, Tumor resistance, Combination therapy

Background

Cancer presents a significant global health challenge, with 20 million new cases and 9.7 million deaths reported in 2022 [1]. Despite advancements in traditional cancer treatments such as surgery, chemotherapy, and radiotherapy, many cancers remain difficult to cure, particularly in advanced stages where treatment options are limited. Recently, immunotherapies such as immune checkpoint inhibitors (ICIs), adoptive cell therapy (ACT), and cancer vaccines have emerged as promising approaches to leverage the host immune system against malignancies [2]. While ICIs and ACT have shown efficacy in specific patient populations, their success remains limited, with only a subset of patients achieving sustained responses [3]. Cancer vaccines, however, offer a unique advantage by priming new T cells, potentially targeting a broader array of tumor antigens and inducing more durable immune responses [4, 5].

Cancer vaccines deliver target antigens, often in combination with adjuvants, to evoke or amplify the host immune system, especially T-cell immunity, to recognize and eliminate malignant cells. [6–8].They are broadly categorized into two types: therapeutic and prophylactic cancer vaccines. Therapeutic cancer vaccines are post-exposure treatments that induce potent cellular immune responses to eliminate existing cancer cells and establish long-lasting immune memory to prevent recurrence, such as the first Food and Drug Administration (FDA)-approved DC vaccine Sipuleucel-T [6]. In contrast, prophylactic cancer vaccines are designed to stimulate the immune system in tumor-free individuals, generating antibodies and immune memory cells that reduce the risk of cancer development [9]. Oncoviruses, such as human papillomavirus (HPV), hepatitis B virus (HBV), and Epstein-Barr virus, are responsible for approximately

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12% of newly diagnosed cancer cases. Prophylactic vaccines targeting some of these viruses, including HPV and HBV, have significantly contributed to the prevention of virus-related cancers [10]. For instance, a nationwide study showed that the quadrivalent HPV vaccine reduced the incidence of invasive cervical cancer by half [11]. The FDA has approved prophylactic vaccines targeting HPV and HBV, which are highly recommended by the Advisory Committee on Immunization Practices [12, 13].

In this review, we first discuss antigen repertoires for vaccines, highlighting the identification of neoantigens. Next, we introduce how cancer vaccines activate the immune system, and point out the influence of adjuvants and administration routes on shaping the vaccine efficacy. Following this, we introduce various vaccine platforms currently in use, describing their strengths, limitations, and important clinical applications. Finally, we summarize the resistance mechanisms posed by tumors and evaluate the benefits of combination therapies, which may help to overcome these barriers and improve the efficacy of cancer vaccines in the management of solid tumors.

The mechanism of cancer vaccines

The selection of targeted antigens

Heterogeneity, an important characteristic of cancer, encompasses intertumoral differences across cancer types and individuals, as well as intratumoral genomic variations within tumor subclones [14]. For example, molecular subtypes of breast cancer determine treatment strategies, with tamoxifen for estrogen receptor-positive patients and trastuzumab for human epidermal growth factor receptor 2 (HER2)-positive patients [15]. Cancer genetic instability presents both challenges and opportunities. While higher mutation burden leads to stronger specific T cell responses and better clinical outcomes with ICIs, it also enables cancer to develop immune escape and drug resistance [16–18]. Therefore, the optimal selection and design of targeted antigens are critical. Ideal antigens are considered to be safe, highly immunogenic, tumor-specific, and applicable to a broad patient population [19].

Generally, tumor antigens are classified into two types: tumor-associated antigens (TAAs) and tumor-specific antigens (TSAs) (Table 1) [20]. TAAs are "self-antigens" abnormally expressed in tumors, including overexpressed proteins, cancer germline proteins, and tissue-differentiation proteins [5]. TAAs can be found across different cancers and are shared among patients, which facilitates large-scale production of vaccines. However, the efficacy of cancer vaccines targeting TAAs is limited due to central thymus tolerance, which restricts high-affinity T cell receptors for self-peptides, necessitating additional immunostimulatory interventions [21]. Since TAAs are not exclusive to tumors, vaccines targeting them carry the risk of on-target/off-tumor toxicity, which can potentially harm normal tissues [22]. In contrast, TSAs, including viral oncoproteins and neoantigens, provide high specificity and immunogenicity [23]. But neoantigens are highly individual-specific, posing challenges for vaccine development in terms of complexity, feasibility and cost.

Table 1 The category of tumor antigens for cancer vaccines

Type	Subsets	Examples
Tumor-associated antigens (TAAs)	Over-expressed proteins	WT-1, MUC1, HER2, EGFR, survivin
	Cancer germline proteins	MAGE, NY-ESO-1
	Tissue-differentiation proteins	PSA, PAP, gp100, MART-1
Tumor-specific antigens (TSAs)	Viral oncoproteins	HPV (E6/E7), LMP, HBsAg
	Shared neoantigens	Mutated RAS, p53
	Individual neoantigens	Patient-specific

WT-1, Wilms tumor protein 1; MUC1, mucin 1; HER2, human epidermal growth factor receptor 2; EGFR, epidermal growth factor receptor; MAGE, melanoma-associated antigen; NY-ESO-1, New York esophageal squamous cell carcinoma 1; PSA, prostate-specific antigen; PAP, prostatic acid phosphatase; gp100, glycoprotein 100; MART-1, melanoma antigen recognized by T cells 1; HPV, human papillomavirus; LMP, latent membrane protein; HBsAg, hepatitis B virus serum antigen

Neoantigens derive from various genomic alterations including single-nucleotide variants, insertions and deletions, frameshifts, gene fusions, and human endogenous retroelements. They can also result from aberrant transcriptions (such as splicing events, polyadenylation, RNA editing), alternative translation involving non-canonical open reading frame (ORF), long non-coding RNA, and changed start codons, as well as abnormal proteasome process and post-translational modifications (like phosphorylation, glycosylation, and methylation) [20, 24, 25]. Typically, a comprehensive neoantigen identification pipeline comprises three components: prediction of neoantigens based on human leukocyte antigen (HLA) typing, filtration and prioritization of candidate neoantigens, and validation of their immunogenicity. [26].

Advancements in high-throughput sequencing and bioinformatic technologies have made next-generation sequencing more cost-effective and accessible. Possible tumor-specific mutations can be thoroughly screened through computational algorithm by comparing the whole-exome sequencing, RNA sequencing, and mass spectrometry data from tumor and matched normal tissues [24, 25, 27, 28]. RNA-sequencing provide extensive biological information at the gene transcription level, such as alternative splicing events and gene copy number alterations, and is also used to validate

the expression of mutant genes [29]. Mass spectrometry directly identify abnormal peptides loaded on HLA molecules, enabling the discovery of noncanonical antigens [30].

Neoantigen prediction is fundamentally dependent on the patient's HLA genotypes, which determines the repertoire of antigens that can be presented for T cell recognition. Numerous bio-informatic tools have been developed to identify HLA genotypes, such as OptiType and Polysolver for HLA class I alleles, and HLA*PRG, ATHLATES, and HLA-HD for both class I and II alleles [31–35]. Based on HLA typing, the binding of the peptides derived from identified mutations to specific HLA molecules is predicted by computational algorithms like NetMHC, NetMHCpan, and MHCflurry [36]. Notably, the prediction of HLA class II epitopes has limited accuracy due to their varied length and high polymorphism. Studies have shown the essential role of antigen-specific $CD4^+$ T cells, and many algorithms such as MixMHC2pred and NetMHCIIpan have been developed for HLA class II epitopes prediction. [37–40].

After the initial prediction, filtration is conducted to refine the list of candidate neoantigens. Factors such as expression level, dissimilarity to self-protein, mutation clonality, presentation efficacy, HLA binding affinity, and the stability of the peptide-HLA complex are considered, resulting in a ranked list of candidates [41, 42]. Given the complexity of the immune system and the limitations of technologies, it is understandable that even highly ranked neoantigens candidates fail to elicit robust T cell immune responses [43]. Consequently, predicted antigen sets must undergo validation for their ability to activate specific T cells, achieved through experimental methods such as T cell-based assays, enzyme linked immunospot assay, flow cytometry, multicolor-labeled major histocompatibility complex (MHC) tetramers, and T-cell repertoire profiling (Fig. 1).

As most neoantigens are individually unique, shared neoantigens, arising from common mutations in oncogenes or tumor suppressor genes across patients, are promising candidates for developing public vaccines [44]. While personalized vaccines require a long manufacturing period (7–16 weeks), developing ready-to-use shared-neoantigen vaccines is cost-effective and time-efficient, especially for patients with limited treatment windows [45, 46]. For example, Malekzadeh et al. identified broad "hotspot" immunogenic *TP53* mutations across patients with epithelial cancers and provided an effective screening approach for common mutated tumor neoantigens, including but not limited to *KRAS* and *PI3KCA* [47].

Immune responses activation

After vaccination, innate immune cells like natural killer (NK) cells, neutrophils, and macrophages use pattern recognition receptors (PRRs) to recognize foreign substances rapidly and initiate specific immune responses. Antigen-presenting cells (APCs) in peripheral tissues capture, process, and present peptides on diverse MHC molecules (known as HLA in humans). Endogenous proteins are lysed by proteasome and loaded onto MHC-I molecules to activate $CD8^+$ T cells, while exogenous proteins are digested in lysosomes and then form antigen-MHC-II complexes for $CD4^+$ T cells [48]. Although the mechanism is still not fully understood, DCs are capable of translocating endocytosed proteins into the cytosol for proteasomal degradation and MHC-I presentation, a process known as "cross-presentation" [49].

DCs are the most potent APCs, playing a crucial role in regulating innate and adaptive immune responses. Human DCs are primarily classified into $CD123^+$ plasmacytoid DCs (pDCs) and conventional DCs (cDCs), with cDCs further divided into $CD141^+$ cDC1s and $CD1c^+$ cDC2s, which resemble mouse $B220^+$ pDCs, $CD8\alpha^+$ and/or $CD103^+$ cDC1s, and $CD11b^+$ cDC2s, respectively [50]. DC subsets display different surface phenotypes and immune functions. cDC1s are superior at antigen cross-presentation to activate $CD8^+$ T cell and prime type 1 T helper cell (Th1 cell), aided by the secretion of interleukin 12 (IL-12) and interferon γ (IFN-γ) [51, 52]. cDC2s are vital in initiating $CD4^+$ T cell, and priming Th2 and Th17 cell [53–55]. pDCs, expressing the toll-like receptor (TLR) 7 and TLR9, excel at recognizing nucleic acids and producing type I IFN, which can be enhanced by granulocyte–macrophage colony-stimulating factor (GM-CSF) [56, 57].

Upon activated, immature DCs change the expression of surface molecules, mature with enhanced antigen presentation and migration ability, and move to second lymphoid organs (SLOs), where they cooperate with lymphoid DCs to prime naïve T cells [58, 59]. T cell activation begins once they recognize antigen-MHC complexes via T cell receptors, delivering the first signal. For full activation, T cells require sufficient expression of costimulatory molecules and cytokines. APCs express key co-stimulatory molecules, including CD80/CD86, OX40L, CD70, and CD137L, which interact with CD28, OX40, CD27, and CD137 on T cells respectively, to enhance T cell activation, proliferation, and effector functions [60, 61]. On the contrary, the interaction between CD80/CD86 and CTLA-4, as well as between PD-L1/2 and PD-1, inhibits T cell activities, which is crucial for preventing autoimmunity but also contributes to tumor resistance [61].

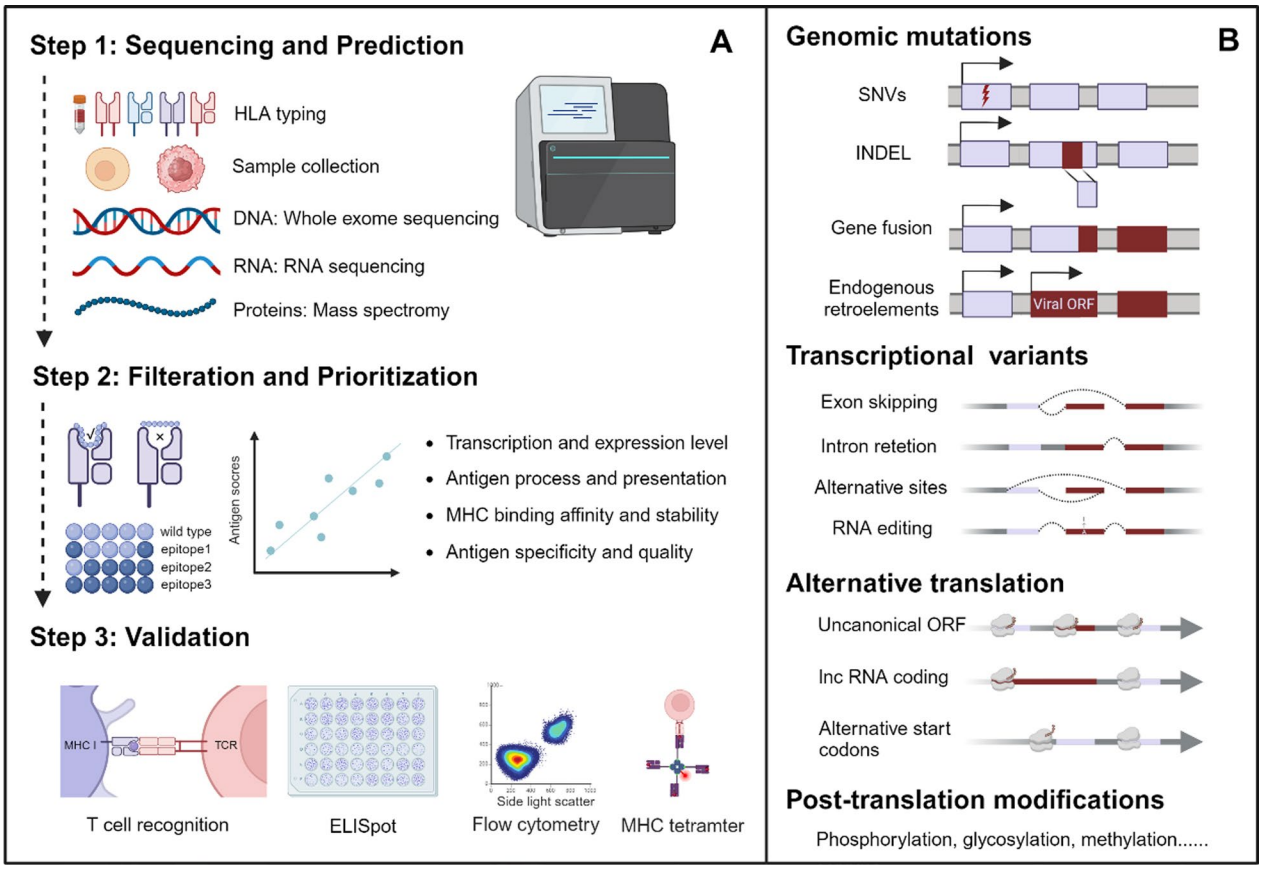

Fig. 1 Neoantigens identification and their deriving sources. **A** The neoantigen prediction process follows a systematic three-step pipeline: Prediction involves identifying tumor-specific mutations based on patient HLA typing through tumor DNA, RNA, and protein sequencing using computational tools; Filtration ranks the predicted neoantigens by assessing features such as expression levels, the likelihood of being processed and presented on major histocompatibility complex (MHC), MHC binding affinity, and antigen specificity; Validation is carried out through experimental methods to confirm the ability of neoantigens to elicit specific T cell responses. **B** Neoantigens originate from several mechanisms, including genomic alterations (such as point mutations, gene fusions, and deletions), aberrant transcriptional events, alternative splicing or translation, and post-translational modifications. These mechanisms generate tumor-specific antigens that are absent in normal tissues, making them ideal targets for personalized cancer immunotherapies aimed at inducing precise immune responses. ELISpot, enzyme linked immunospot; SNVs, single-nucleotide variants; INDEL, insertions and deletions; ORF, open reading frame; lncRNA, long non-coding RNA

$CD4^+$ Th cells and $CD8^+$ cytotoxic T lymphocytes (CTLs) exit lymphoid organs, infiltrate tumors, and exert anti-tumor effects. CTLs induce tumor cell apoptosis through granule exocytosis (perforin and granzymes), and death receptor engagement (Fas ligand and tumor necrosis factor-related apoptosis-inducing ligand) [62]. B cells can present tumor antigens to $CD4^+$ T cells. The interaction between CD40 on B cells and its ligand on activated T cells is critical for B cell proliferation, germinal center formation, and differentiation into long-lived plasma cells [63]. Antibodies produced by B cells activate the complement system and bind to tumor cells, leading to their destruction through direct lysis, the release of cytotoxic granules, and phagocytosis [63]. B cell responses within the tumor microenvironment (TME) promote anti-tumor immunity and enhance sensitivity to ICIs [64]. Also, tumor-specific B cells are necessary for the generation of IL-21-producing $CD4^+$ T follicular helper cells, which support effector $CD8^+$ T cell activity [65]. Thus, the complex interactions between immune components determine the efficacy of cancer vaccines (Fig. 2).

The role of adjuvants

Adjuvants are critical in enhancing the effectiveness of cancer vaccines, broadly categorized into three main groups: immunomodulatory molecules, delivery systems with adjuvant properties, and combinations of both [66]. They amplify immune responses through several mechanisms including mimicking pathogen-associated

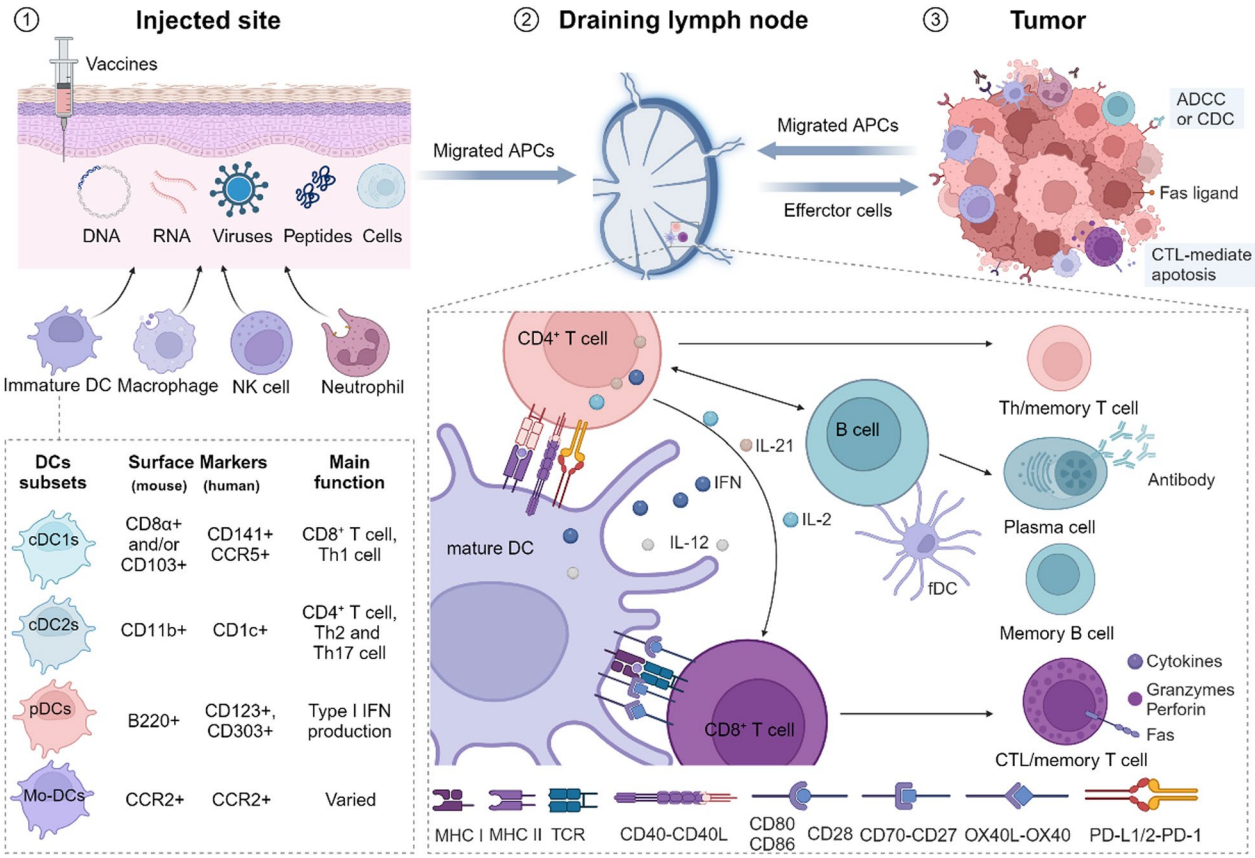

Fig. 2 Immune responses induced by cancer vaccines. (1) Upon vaccination, antigen-presenting cells (APCs), particularly dendritic cells (DCs), capture, process, and present antigens on their surface. Different DC subsets possess distinct abilities to activate specific T cell subsets. As DCs mature, they migrate to secondary lymphoid organs like draining lymph nodes. (2) For effective T cell activation, three critical signals are required. Signal 1 is the combination between antigen-MHC complexes on the APC and T cell receptors. Signal 2 involves co-stimulatory molecules, which amplify the activation signal. Signal 3 consists of immunomodulatory cytokines and chemokines that influence T cell differentiation and functions. Once activated, T cells differentiate into effector cells, including $CD4^+$ helper T (Th) cells, cytotoxic $CD8^+$ T lymphocytes (CTLs), and memory T cells. $CD4^+$ T cells, along with follicular dendritic cells (fDCs), assist in the B cells maturation, leading to the differentiation into antibody-producing plasma cells and memory B cells. (3) Activated immune cells infiltrate the tumor and exert anti-tumor functions. CTLs induce tumor cell apoptosis through perforin, granzymes, and Fas ligand engagement, while B cells employ antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). Tumor-infiltrating APCs can also present antigens to boost cellular immune responses against tumor. cDCs, conventional DCs; pDCs, plasmacytoid DCs; Mo-DCs, monocyte-derived DCs; CCR, C–C motif chemokine receptor; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor; CD40L, CD40 ligand; PD-1, programmed death-1; PD-L1, programmed death ligand-1

molecular patterns, triggering the release of damage-associated molecular patterns (DAMPs), enhancing APCs activation, extending antigen bioavailability, and promoting efficient antigen delivery [67].

Common immunomodulators include aluminum salts, TLR agonists such as CpG oligonucleotides (TLR9 agonist) and polyinosinic-polycytidylic acid (poly-ICLC, a TLR3 agonist), and cytokines like GM-CSF and IL-2. Delivery systems are designed to protect antigens from degradation, enhance their bioavailability, and improve targeting, encompassing both physical and chemical approaches. Physical delivery systems, such as electroporation, gene gun, and microneedles, primarily function as mechanical tools to efficiently transport antigens [68–70]. Chemical delivery systems, including water-in-oil emulsions, lipid nanoparticles (LNPs), polymeric particles, and nanomaterials, are widely used and some possess intrinsic immunostimulatory properties that qualify them as adjuvants [71]. What's more, many advanced adjuvants combine both immunomodulatory and delivery properties. For example, TLR-7/8 agonists-conjugated peptide vaccines, chemically designed for nanoparticle self-assembly, significantly enhanced $CD8^+$ T cell responses against cancer antigens by boosting innate immune responses and increasing antigen uptake by DCs [72]. Despite

Table 2 Features of different cancer vaccine platforms

Vaccine platform	Advantages	Limitations	Examples
Peptide	Easy of production; Minimal toxicity; High specificity and safety	Limited immunogenicity; Short half-life; HLA restriction	OSE2101, IO101
DNA	Cost-effectiveness; Stable; Durable immunity	Risk of gene integration; Limited immunogenicity; Low transfection efficacy	GX-188E, VGX-3100
mRNA	Flexibly modified; Rapid production; Potent immune activation	Instability; Inefficient delivery; Prone to be degraded	BNT111, mRNA-4157(V940)
Replication-defective viruses	High immunogenicity; High delivery efficiency	Pre-existing immunity; Unintended viral spread	TG4010, TroVax
Virus-like particles	High immunogenicity; No risk of infection; Stable and Scalable production	Limited T-cell activation; Formulation issues;	Gardasil 9, ES2B-C001, CMP-001
Oncolytic viruses	Direct tumor lysis; Potent immune activation; Strong targeting	Safety risks; Immune clearance; Complex production	T-VEC, RP-1, JX-594
Tumor cells	Broad antigen coverage; Reduced off-target effects	Risk of tumorigenicity; Complex production	GVAX, M-Vax, Canvaxin
Dendritic cells	Effective antigen presentation; Strong T cell activation	High cost; Complex production	Sipuleucel-T, Ilixadencel

these advancements, challenge lies in selecting the appropriate adjuvant for different cancer vaccines to optimize immunogenicity, which can also be influenced by the administration route, disease stage, and patient characteristics.

The route of administration

Cancer vaccines can be administered through intramuscular, subcutaneous, intradermal, intravenous, intratumoral, oral, and mucosal route, each with distinct effects on vaccine efficacy, immune response, and safety. The subcutaneous route was demonstrated to enhance nanoparticle delivery to drain lymph nodes and elicit more neoantigen-specific T cells compared to intramuscular route [73]. In tumor-bearing mice, both subcutaneous and intravenous administration of vaccine generated specific tumor-infiltrating T cells (TILs), but only intravenous route mediated tumor regression and downregulated immunosuppressive monocytes [74]. Mucosal administration, like atomization, intranasal, and sublingual routes, shows promise for inducing mucosal immunity. Tissue-resident memory T cells (TRMs), preferentially induced by mucosal immunization, are attractive biomarkers due to their strategic tissue localization and direct cytotoxic capacities, associated with better survival rates [75–77]. When choosing the administration route, factors like the vaccine type and volume, desired immune response, tumor location, and patient condition should be considered to optimize outcomes.

The features and clinical landscape of different vaccine platforms

This section provides an overview of the advantages and limitations of various vaccine platforms (Table 2), each characterized by unique action mechanisms and immunogenicity profiles. We highlight innovative preclinical studies and key clinical outcomes associated with these platforms. Furthermore, given the rapid advancements and significant potential of neoantigen-based vaccines, a dedicated subsection is included to explore this promising area in detail.

Peptide-based cancer vaccines

Peptide-based cancer vaccines are minimally toxic, cost-effective to manufacture, and highly stable. However, they face several limitations including low immunogenicity, short half-life, susceptibility to degradation, and the most critical one, HLA restriction [78]. Short peptides (SPs), typically 8–11 amino acids in length, are exact MHC binding epitopes, but they can directly bind to MHC-I molecules on non-professional APCs, which cannot provide enough co-stimulatory signals for full T cell activation, potentially leading to immune anergy or tolerance [79, 80]. SP vaccine only transiently activated $CD8^+$ effector T cells with insufficient migration to secondary lymphoid organs, which can be addressed by adding MHC-II peptide or using longer peptide [81].

Table 3 Selected phase II-III clinical trials of peptide/protein-based cancer vaccines

Platform	Vaccine: targets	Year, Phase, reference	Target cancer Sample number	Route	Results
Lipo-peptide	Tecemotide (L-BLP25): MUC1	2014, phase III, NCT00409188 [301]	Unresectable stage III NSCLC after chemoradiotherapy/1239	Subcutaneous	No improvement compared to placebo
Peptide	IMA901: ten tumor-associated peptides	2016, phase III, NCT01265901 [95]	HLA-A*02-positive, metastatic and/or locally advanced cell renal cell carcinoma/1171	Intradermal	No improvement compared to sunitinib
Peptide	Nelipepimut-S: E75 with GM-CSF	2019, phase III, NCT01479244 [101]	T1–T3, HER2 IHC 1 + /2 +, node-positive BC/758	Intradermal	No improvement compared to placebo
		2020, phase IIb, NCT01570036 [102]	HER2 IHC 1 + /2 +, FISH nonamplified BC, node positive and/or hormone receptor-negative BC/275		No improvement compared to GM-CSF alone
Peptide	GP2 with GM-CSF	2021, phase IIb, NCT00524277 [99]	HER2 1–3 +, node-positive and high-risk node-negative BC/168	Intradermal	100% 5-year DFS in HER2 IHC 3 + BC
Peptide	OSE2101: peptides targeting five TAAs plus PADRE	2023, phase III, NCT02654587 [97]	HLA-A2-positive advanced NSCLC with resistance to immunotherapy/219	Subcutaneous	Improved median OS (11.1 vs 7.5 months) compared to chemotherapy
Peptide	IO102-IO103: IDO and PD-L1	2023, Phase II, NCT03047928 [105]	Anti-PD-1 naïve patients with metastatic melanoma/30	Subcutaneous	ORR: 80%, median PFS: 25.5 months
Peptide	GV1001: 16 amino acids from human telomerase reverse transcriptase	2024, phase III, NCT02854072 [302]	Untreated advanced PDAC with high serum eotaxin levels/148	Intradermal	Improved median OS (11.3 months) compared to chemotherapy alone (7.5 months)
Protein	MAGE-A3 protein combined with AS15	2016, phase III, NCT00480025 [303]	Resected stage IB, II, and IIIA MAGE-A3-positive NSCLC/2312	Intramuscular	No improvement compared to placebo
		2018, phase III, NCT00796445 [304]	Resected, stage IIIB or IIIC, MAGE-A3-positive cutaneous melanoma/1345		No improvement compared to placebo

NSCLC, non-small cell lung cancer; BC, breast cancer; IHC, immunohistochemistry; GM-CSF, granulocyte–macrophage colony-stimulating factor; DFS, disease-free survival; OS, overall survival; ORR, overall response rate; PFS, proliferation-free survival; PDAC, pancreatic ductal adenocarcinoma

SurVaxM, a bulging SP vaccine targeting survivin, when combined with GM-SCF and temozolomide, prolonged median overall survival (OS) to 25.9 months in patients with newly diagnosed glioblastoma, compared with 14.6–16.0 months of standard care [82].

In contrast, synergic long peptides (SLPs), 22–45 amino acids, contain both MHC-I and II epitopes and must be processed by professional APCs [83]. Therefore, SLP vaccines induce effective anti-tumor $CD4^+$ and $CD8^+$ T cells responses, as $CD4^+$ T cells greatly enhance $CD8^+$ T cell recruitment, proliferation, and antitumor function by secreting IL-2 and IFN-γ [83, 84]. SLPs elicit a higher quality of CTL than SPs due to a prolonged antigen presentation duration by DCs [80]. Also, SLPs are more rapidly and efficiently processed by DCs than whole proteins [85]. SLP vaccine targeting HPV16 E6/E7 induced specific T cell immunity in all patients [86, 87]. Notably, self-renewing specific $CD8^+$ memory T cell was identified beyond 10 years in patients with longer survival after peptide vaccination, underscoring its pivotal role in sustaining durable antitumor immunity [88].

In hindsight, many peptide-based cancer vaccines simultaneously targeted several epitopes and combined adjuvants or other therapies in clinic setting, which have elicited potent immunologic responses across various malignancies, but clinical outcomes are controversial (Table 3) [89–93]. A mucin 1 (MUC1) peptide vaccine, mixed with poly-ICLC, elicited robust immune responses but failed to prevent recurrence in patients with resected colorectal adenoma [94]. Similarly, adding a ten-peptide vaccine with GM-CSF to first-line sunitinib significantly increased the number of $CD8^+$ T cells, but did not yield clinical improvements in patients with metastatic or advanced renal cell carcinoma [95]. OSE2101, composed of nine peptides targeting five TAAs and a pan-DR T helper cell epitope, achieved a median survival of 17.3 months in patients with advanced non-small cell lung cancer (NSCLC) in an early phase II study [96].

Later, in a larger phase III clinical trial, OSE2101 monotherapy demonstrated better efficacy and safety than standard chemotherapy, significantly prolonging median OS (11.1 vs 7.5 months) and post-progression survival (7.7 vs 4.6 months) in patients with secondary resistance to immunotherapy [97].

Peptide-based vaccines for breast cancer have been extensively explored and some demonstrate therapeutic potential, such as E75, GP2, and AE37 vaccines targeting HER2 [98, 99]. E75 vaccine reduced the recurrence rate in patients with breast cancer in phase II clinical trial, but failed to meet the primary survival endpoint in subsequent phase III trial [100, 101]. Furthermore, the combination of E75 vaccine with trastuzumab did not improve disease-free survival (DFS) in high-risk HER2 low-expressing breast cancer [102]. Nevertheless, subgroup analyses indicated potential benefits in patients with triple-negative breast cancer (TNBC) or those who are HLA-24 positive [98, 103].

What's more, innovations aiming at immune modulation rather than direct tumor antigen targeting offer new and generalized strategies. IO101, an indoleamine 2,3-dioxygenase (IDO)-derived HLA-A2-restricted peptide vaccine, targets IDO-expressing tumor cells and immunosuppressive cells, elicited long-lasting disease stabilization in patients with advanced NSCLC [104]. IO102-IO103, a bispecific vaccine targeting IDO and PD-L1, reached 80% objective response rate (ORR) and 25.5-month median progression-free survival (PFS) in anti-PD-1 therapy naïve patients with metastatic melanoma [105]. Moreover, the phase III trial examining the combination of IO102-IO103 with pembrolizumab is ongoing in patients with advanced melanoma (NCT05155254).

Nucleic acid-based cancer vaccines

Nucleic acid-based vaccines, including DNA and RNA formulations, elicit robust humoral immune responses due to their intrinsic adjuvant immunogenicity. RNA can directly translate in the cytoplasm using the host's cellular machinery. In contrast, DNA must enter the nucleus, allowing for prolonged target protein production but posing a risk of integration into the host genome [106]. After protein translation, specific T cells are elicited either through direct antigen presentation by the transfected cells or cross-presentation by DCs. Owing to the capability of covering multiple epitopes simultaneously, nucleic acids are powerful platform for eliciting broader CTL responses. Additionally, the sequences of DNA and RNA can be flexibly adjusted, enabling the design of vaccines that express cytokines, chemokines, and tumor suppressors.

DNA-based vaccines

DNA cancer vaccines are typically double-stranded bacterial plasmid DNA containing eukaryotic gene regulatory elements, which are well tolerated, stable, and easy of manufacturing, but exhibit low immunogenicity and transfection efficacy [106]. Double-strand DNA activates the stimulator of interferon genes via cyclic GMP-AMP synthase (cGAS), triggering the expression of inflammatory molecules like IFNs, while CpG motifs are recognized by TLR9 and Z-DNA by Z-DNA binding protein 1 [107–109]. Conventional administration of naked DNA is inefficient, which can be improved by physical delivery technologies such as electroporation, gene gun, and microneedle, but these methods face challenges in clinical implementation [110]. Enhancing vaccine immunogenicity involve using chimeric DNA, optimizing sequence or delivery system, and incorporating adjuvants. For example, a xenogeneic tyrosinase DNA vaccine broke immune tolerance and induced detectable immune responses [111]. Wu et al. developed a red blood cell hitchhiking strategy for the spleen-targeted delivery of polymeric nanoparticle-encapsulated DNA vaccine, resulting in complete tumor regression in mice model [112].

In a phase 1 nonrandomized clinical trial, a plasmid DNA vaccine encoding the HER2 intracellular domain demonstrated safety and immunogenicity in patients with advanced-stage HER2-positive breast cancer, with some evidence of clinical benefit [113]. GX-188E, a therapeutic HPV E6/E7 DNA vaccine, incorporated with Fms-related tyrosine kinase 3 (Flt3) and the tissue plasminogen activator signal sequence, enhanced the antigen process and presentation by DCs [114]. After vaccination, patients diagnosed with grade 3 cervical intraepithelial neoplasia (CIN3) displayed robust Th1-polarized cellular immune responses, with a majority exhibiting specific multifunctional $CD8^+$ T cells [114]. The combination of GX-188E and pembrolizumab is currently being tested in a phase II trial for patients with inoperable cervical cancer, and the interim results have been positive [115]. Also, intramuscular administration of VGX-3100, targeting HPV E6/E7, followed by electroporation, yielded significant histopathological regression and virus clearance rate in patients with confirmed CIN2/3 [70]. The therapeutic effects were associated with the magnitude of perforin expression, antibody production, and the presence of specific $CD8^+$ T cells [70]. The phase III clinical trial of VGX-3100 (NCT03721978) has been reported to achieve positive results. Another therapeutic DNA vaccine, GNOS-PV02, encoding up to 40 personalized neoantigens co-administered with plasmid-encoded IL-12 plus pembrolizumab, yielded a 30.6% ORR with 8.3% complete response (CR) in patients with advanced

hepatocellular carcinoma [116]. Notably, the level of antigen-specific T cell responses, induced by GNOS-PV02, was found to be positively correlated with the number of neoantigens [116]. These findings underscore the potential of therapeutic DNA vaccines and highlight the employment of immunomodulators and neoantigens.

mRNA-based vaccines

mRNA vaccines hold promise due to their safety, efficacy, and cost-effective production, which has been indicated to be a superior vaccine platform than DNA and recombinant protein [117]. The most common method for synthesizing mRNA is in vitro transcription, utilizing bacteriophage RNA polymerase and linear DNA template, which is simple, quick, and enables large-scale production [118]. Importantly, the purification of mRNA is crucial to avoid excessive immune responses triggered by impurities like double-stranded RNAs (dsRNAs), which can undermine vaccine efficacy [119]. Guanosine and uridine-rich single-stranded RNAs can activate endosomal TLR7/8 in immune cells, resulting in the secretion of inflammatory cytokines like IFN-α and tumor necrosis factor-α (TNF-α) [120, 121]. dsRNAs, generated from in vivo or in vitro transcription process, can activate intracellular receptors such as TLR3 and retinoic acid-inducible gene-I, which in turn activate nuclear factor-kappa B and IFN regulatory factor 3, inducing antiviral molecules like type-I IFN [122–124]. However, excessive IFNs can lead to RNA degradation, prevent RNA replication and translation, and impair CTL responses [125]. Challenges related to stability, in vivo delivery, and high immunogenicity remain, promoting efforts in sequence optimization, chemical modification, and improved delivery technology [126].

mRNA vectors have evolved into several types, with the two classic types being conventional non-replicating mRNA and self-amplifying mRNA (saRNA). Both types consist of 5′ cap, 5′-untranslated region (UTR), ORF, 3′-UTR and poly (A) tail [126]. Unlike conventional mRNA, which contains a single ORF for the targeted antigens, saRNA includes an additional ORF derived from alphavirus for viral replication machinery, facilitating persistent RNA amplification and antigen expression within host cells [127]. A novel advancement, trans-amplifying mRNA (taRNA), places the replicase and target gene on two separate molecules, which prevents viral protein expression and thus enhances safety [128]. TaRNA has higher translational efficiency, allowing for shorter RNA with less interference with host cellular protein translation [128]. Additionally, simplified taRNA exhibits enhanced replicative proficiency, resulting in higher antibody titers in immunized mice with minimal antigen-coding transreplicon [129]. Circular RNA (circ-RNA) is highly stable but difficult to synthesize, and its closed ring structure protects it from exonuclease-mediated degradation [130]. Circ-RNA has been demonstrated to mediate stronger and long-lasting expression of neutralizing antibodies [118]. Short dsRNA has been designed as an adjuvant to tether onto linear mRNA, with immune response intensity adjustable by modifying its length, sequence, and quantity [131]. A comb-structured mRNA vaccine formulated in anionic lipoplex (LPX) achieved significant therapeutic effects in a mouse lymphoma model [131].

RNA packaging and delivery technologies have advanced to protect naked RNA from ubiquitous RNase and ensure effective delivery to target organs. Various carriers such as protamine, polymers, cationic emulsions, virus-like particles (VLPs), LPXs, and especially LNPs, have been explored [132]. For instance, complemented with optimally adjusted LPX, an intravenously injected mRNA vaccine effectively reached APCs in body-wide SLOs, triggering pDCs in the spleen to release IFN-α, eliciting profound T cell responses and tumor regression [133]. Additionally, selective organ targeting nanoparticle was developed for extrahepatic targeting to minimize hepatotoxicity [134]. LNP 113-O12B mediated lymph node-targeting mRNA delivery, while Iso-A11B5C1, ionizable LNPs, showed muscle-specific delivery with minimized off-target effects in the lung and liver [135, 136]. The employment of adjuvants in mRNA vaccines remains controversial, as most mRNA vaccines used in the clinic are adjuvant-free [137]. In conclusion, selecting the optimal mRNA vectors and delivery systems is crucial for the effectiveness of mRNA-based cancer vaccines.

Building on the successful application of mRNA vaccines during the COVID-19 pandemic, mRNA-based cancer vaccines hold great promise and are being tested in clinical trials, with only one entering phase III so far, prompting more researches (Table 4). RNActive® vaccines, protamine-formulated, including CV9103 targeting various prostate cancer antigens, CV9104 containing prostate cancer antigens and MUC1, and CV9201 comprising five antigens: New York esophageal squamous cell carcinoma 1 (NY-ESO-1), melanoma-associated antigen (MAGE) C1/C2, trophoblast glycoprotein, and survivin, were well tolerated and immunogenic, but barely showed clinical benefit [138–140]. Notably, combining CV9202 (including antigens from CV9201 along with MUC1) with local radiation achieved 46.2% stable disease in stage IV NSCLC patients [141]. Furthermore, an investigation combining CV9202 with ICIs has been completed, with results pending publication (NCT03164772).

The use of LPX and LNP for mRNA vaccines, particularly in neoantigen vaccines, has become a prominent area of focus. The first-in-human study of a

Table 4 Selected clinical trials of nucleic acid-based cancer vaccines

Platform	Vaccine: targets	Year, Phase, Reference	Target cancer Sample number	Route	Results
DNA	VGX-3100: HPV-16/18 E6 and E7	2015, Phase IIb, NCT01304524 [70]	Adult women with histologically confirmed HPV-16 or HPV-18-positive stage 2/3 cervical intraepithelial neoplasia/167	Intramuscular	Higher histopathological regression rate (49.5%) versus placebo (30.6%)
		Phase III, NCT03721978			Completed
DNA	GX-188E	2020, phase II, single-arm, NCT03444376 [115]	Histologically confirmed recurrent or advanced HPV-positive inoperable cervical cancer/36	Intramuscular	42% OR, 58% disease control, and 4.9-month median PFS
DNA	GNOS-PV02: up to 40 neoantigens	2024, phase I-II, single-arm, NCT04251117 [116]	Advanced HCC previously treated with a multityrosine kinase inhibitor/36	Intradermal	30.6% ORR and 8.3% CR
mRNA	mRNA-4157 (V940): up to 34 neoantigens	2024, phase IIb, NCT03897881 [146]	Completely resected stage IIIB–IV melanoma/157	Intramuscular	Longer recurrence-free survival versus pembrolizumab
		Phase III, NCT05933577	High-risk stage II-IV cutaneous melanoma		Active, not recruiting
		Phase III, NCT06077760	Completely resected Stage II, IIIA or IIIB NSCLC		Recruiting
mRNA	CV9202: six TAAs	Phase I-II, NCT03164772	Metastatic NSCLC	Intradermal	Completed
mRNA	BNT112: five prostate cancer TAAs	Phase I-IIa, NCT04382898	Metastatic castration-resistant prostate cancer and newly diagnosed high risk localized prostate cancer	Intravenous	Terminated
mRNA	BNT113: HPV E6 and E7	Phase I-II, NCT04534205	Unresectable recurrent or metastatic $HPV16^{+}$ HNSCC expressing PD-L1	Intravenous	Recruiting
mRNA	BNT116	Phase I, NCT05142189	Advanced, metastasized, and unresectable NSCLC	Intravenous	Recruiting
mRNA	CLDN6 (claudin 6)	Phase I, NCT04503278	CLDN6-positive relapsed or refractory advanced solid tumors	Intravenous	Recruiting

OR, overall response; HCC, hepatocellular carcinoma; CR, complete response; HNSCC, Head and neck squamous cell carcinoma

personalized therapeutic mRNA vaccine targeting poly-neoantigens showed activated neoantigen-specific T cell responses in patients with stage III-IV melanoma, markedly reducing the recurrent metastatic events and potentially improving sensitivity to PD-1 therapy [45]. BNT111, an mRNA-LPX vaccine incorporating four TAAs (NY-ESO-1, tyrosinase, MAGE-A3, transmembrane phosphatase with tensin homology) and combined with anti-PD-1, showed durable partial responses in anti-PD-1 resistant melanoma patients in a phase I trial, supporting the feasibility of utilizing TAAs with potent adjuvant in low-mutation-burden cancers [142]. However, disappointing outcomes exist. mRNA-4650, targeting neoantigens identified from TILs, successfully induced specific T cell responses but without discernible clinical benefit in metastatic gastrointestinal cancer [143]. The clinical trial of mRNA-5691, a personalized mRNA-LNP vaccine targeting KRAS driver mutations, was terminated during phase 1 (NCT03948763). Therefore, the application of mRNA neoantigen vaccines in patients with advanced cancer requires further research.

BNT122, an mRNA vaccine encoding maximum 20 neoantigens individually and formulated with uridine LPX, demonstrated significant clinical efficacy when combined with atezolizumab and chemotherapy, greatly decreasing the risk of recurrence and death in patients with resected pancreatic ductal adenocarcinoma (PDAC) [144]. Patients with robust antigen-specific T cell responses experienced a longer median recurrence-free survival (not reached) compared to non-responders (13.4 months) [144]. Notably, one patient developed liver metastasis but eventually disappeared on imaging, indicating the potential of this vaccine to generate T cells capable of eradicating micrometastases [144]. Similarly, mRNA-4157(V940), an LNP-formulated personalized vaccine consisting of up to 34 neoantigens, demonstrated its ability to elicit specific T cell responses [145]. A phase 2b clinical trial showed that V940-adjuvanted therapy reduced the recurrence or death event rate

compared with pembrolizumab monotherapy (22% vs 40%) in patients with resected IIIB–IV melanoma [146]. This combination therapy shows great promise and has become the first mRNA vaccine to progress into phase 3 clinical trials (NCT05933577, NCT06077760). These trials underscore the potential of personalized neoantigen mRNA vaccines as effective postsurgical adjuvant treatments. Other mRNA-LPX vaccines under clinical investigation include BNT112 (five antigens for metastatic prostate cancer, NCT04382898), BNT113 (HPV16 E6/E7, NCT04534205), BNT116 (TAAs for NSCLC, NCT05142189) and CARVac (Claudin 6 for advanced solid tumors, NCT04503278).

Virus-based cancer vaccines

Virus-based vaccines can be categorized into three main types: oncogenic virus vaccines, replication-defective viral vector vaccines, and oncolytic viruses (OVs) vaccines. Oncogenic virus-based vaccines have several forms, including inactivated virus, live attenuated virus, viral subunits, and VLPs, which are primarily used in prophylactic settings [9]. Live attenuated viruses are highly immunogenic but present risks of virulence reversal and disease induction in immunocompromised individuals, whereas inactivated viruses are safer but less effective in eliciting cellular immune responses [9]. VLPs, composed of self-assembling viral capsid, core, or envelope proteins, are recognized for their high immunogenicity and safety. Currently approved prophylactic VLP-based cancer vaccines on the market include Gardasil, Gardasil 9, Cervarix, and Cecolin, targeting HPV L1 epitope, and Engerix-B, Recombivax HB, Heplisav-B and PreHevbrio, targeting HBV [147, 148]. Recent studies have shown the potential of VLP vaccines in treating HER2-positive breast cancer and melanoma. ES2B-C001, a human HER2 vaccine candidate, displayed powerful anti-tumor efficacy, achieving a 70% tumor-free rate and complete inhibition of lung metastases in mice $HER2^+$ mammary carcinoma model [149]. The prototypic VLPs with high-density HER2 exposure induced robust anti-HER2 antibodies, and effectively inhibited the growth of $HER2^+$ tumor in mice [150]. Similarly, in melanoma, VLP-based vaccines targeting germline epitopes and neoepitopes have demonstrated therapeutic effects in mice [151]. The vaccine CMP-001, which does not specifically target an antigen but packages a TLR9 agonist, effectively activates pDCs, triggering cytokine secretion and systemic anti-tumor T cell responses [152]. In situ immunization with CMP-001 has shown promising tumor control in preclinical experiment [153]. A phase II clinical trial reported that CMP-001 in combination with pembrolizumab was well tolerated and achieved 24% ORR in patients with advanced melanoma [154].

Viral vectors such as adenovirus (Ad), adeno-associated virus, vaccinia virus (VV), measles virus (MV), herpes simplex virus (HSV), and poxvirus have the adjuvant-like function to induce innate immune responses. Ads are widely used in gene therapy and are the most extensively tested in clinical trials. Early-generation Ad vectors, engineered with deletion of the E1 and/or E3 region in the genome, can accommodate DNA insertion of 4.5–8 kb [155]. Ads have extensive tissue tropism, effective gene transfect ability, and high safety, as they do not integrate into the host genome. However, a major drawback is the high prevalence of pre-existing immunity against Ads in the population. Both VV and HSV can accommodate DNA insertion of up to 40 kb [156]. Difference is that VV replicates in the cytoplasm, while HSV replicates in the nucleus, posing a higher risk of genomic integration [156]. One challenge of viral vectors is that they may express highly immunogenic epitopes, potentially hinder specific CTL responses against targeted tumor antigens [157]. Moreover, viral vectors can elicit neutralizing antibodies that impede the repeat use of the same vector, which can be addressed by employing different vectors or heterologous regimens [158]. Viral vector-based vaccines can be divided into replication-defective and replication-complete viral vector vaccines, the latter also referred to as OV vaccines.

Replication-defective viral vector-based vaccines

Replication-defective viral vectors are engineered to deliver target proteins into the host. TG4010, a modified vaccinia Ankara (MVA) strain vaccine encoding MUC1 and IL-2, significantly improved PFS (5.9 vs 5.1 months) and OS (12.6 vs 10.6 months) in advanced NSCLC patients when combined with standard chemotherapy [159, 160]. Additionally, low baseline level of CD16, CD56, CD69 triple-positive lymphocytes was validated as a predictive biomarker for clinical outcomes [159]. Nadofaragene firadenovec, an Ad vaccine delivering *IFNA2B* to bladder epithelium cells, achieved 53.4% CR within 3 months of the first injection, with 45.5% maintaining response at 12 months in a phase III trial [161]. This led to its FDA approval for treating Bacille Calmette-Guérin (BCG) -unresponsive non-muscle-invasive bladder cancer in 2022 [162]. Trovax, another MVA-based vaccine delivering oncofetal antigen 5T4, has shown great potential in eliciting specific immune responses in several cancers [163]. In a randomized trial, Trovax prolonged PFS (5.6 vs 2.4 months) and OS (20.0 vs 10.3 months) in patients with inoperable metastatic colorectal cancer [164].

Novel strategies, including heterologous regimens and combined immunizations, have been explored. Studies have demonstrated that concurrent administration of

multiple viral vaccines was safe and immunogenic [165, 166]. PROSTVAC-VF, a heterologous prime-boost regimen utilizing recombinant vaccinia and fowlpox viruses expressing prostate-specific antigen (PSA) alongside three T cell costimulatory molecules (B7.1, leukocyte function-associated antigen-3, and intercellular adhesion molecule-1) plus GM-CSF, increased three-year OS rate (30% vs 17%) and extended median survival by 8.5 months in a phase II trial in patients with metastatic castration-resistant prostate cancer, though without prolonged PFS or detectable antibody to PSA [167]. The subsequent phase III trial was halted early due to the absence of improvement in OS or event-free survival [168]. Similarly, sequential immunization with chimpanzee adenovirus and MVA, both delivering 5T4, induced strong immune responses in patients with low- and intermediate-risk prostate cancer, but its clinical efficacy remains uncertain [169]. These findings show that replication-defective viral vector-based cancer vaccines hold potential but need continued exploration to optimize their effectiveness.

Oncolytic virus-based vaccines

While replication-defective vaccines offer safety by avoiding viral replication, OV vaccines harness the inherent ability to selectively replicate in and destroy tumor cells, presenting a more aggressive but potentially more effective approach [170]. OVs induce the release of viral components and a broad spectrum of tumor antigens, triggering robust immune responses and fostering an inflammatory TME. To reduce viral pathogenicity and enhance tumor targeting, natural viruses are often genetically engineered by deleting non-essential viral genes and inserting target genes, such as tumor antigens and cytokines. Immunomodulatory factors like GM-CSF, IL-2, IL-18, IFN-γ, and TNF-α, either alone or in combination, have been incorporated into OVs to bolster antitumor immunity [171, 172]. Commonly used vectors in clinics include Ad, HSV-1, and VV [172]. To date, four OV vaccines have been approved for advanced cancer: Rigvir in 2004, H101 in 2005, talimogene laherparepvec (T-VEC) in 2015, and DELYTACT in 2021.

Rigvir, an unmodified ECHO-7 enterovirus, was approved for melanoma in several European countries, with two post-marketing studies showing prolonged survival in patients with early-stage melanoma, but it is not widely used [173]. H101, an E1B-deleted adenovirus, achieved a 78.8% ORR when combined with chemotherapy, compared to 39.6% with chemotherapy alone, leading to its approval in China for nasopharyngeal carcinoma [174]. T-VEC, an attenuated HSV-1 expressing GM-CSF, improved median OS (23.3 vs 18.9 months) in patients with unresectable melanoma compared to GM-CSF, thus became the first FDA-approved OV vaccine in 2015 [175, 176]. The combination of T-VEC with chemotherapy achieved a 45.9% pathological CR and an estimated 89% 2-year DFS in TNBC patients [177]. Worth mentioning, the FDA-approved standard treatment of pembrolizumab plus chemotherapy achieved 64% pathological CR and 84.5% 3-year event-free survival rate [178, 179]. Furthermore, the combination of T-VEC with ICIs has shown mixed results, necessitating the need for further studies on optimal ICI selection and refined immune strategies. In a phase II trial of advanced melanoma, the combination of T-VEC and ipilimumab elicited a higher ORR versus ipilimumab alone (35.7% vs 16.0%) [180]. However, combining T-VEC with pembrolizumab failed to make clinical improvement in a global phase III trial [181]. RP-1, an HSV-1-based OV expressing GM-CSF and a fusogenic protein GALV–GP–R–, increased the extent and immunogenicity of tumor cell death, as well as the level of $CD8^+$ T cells and PD-L1 expression in TME [182]. The latest results from IGNYTE-3 clinical trial showed that about one-third of melanoma patients responded to RP-1 and nivolumab combination, with rapid and durable responses, achieving a median duration of 21.6 months [183, 184]. The evolution from T-VEC to RP-1 underscores the potential of refining OV vaccines, especially when combined with ICIs, for better efficacy.

Other OVs, such as G207 and DELYTACT, have demonstrated efficacy in treating gliomas. G207, a modified HSV-1 with deletions in γ34.5 and ICP6, prolonged the median OS (12.2 vs 5.6 months) in 12 pediatric patients with recurrent or progressive high-grade glioma [185]. DELYTACT, a third-generation HSV-1 vaccine developed by deleting the α47 gene from parental G207, is approved in Japan for malignant glioma and shows potential against various solid tumors [186, 187]. Furthermore, OVs armed with cytokines, chemokines, and or used in combination with other treatments have shown therapeutic promise. JX-594, a thymidine kinase gene-inactivated oncolytic VV expressing GM-CSF, selectively targets cancer cells with EGFR/Ras pathway mutations [188]. Despite being safe and immunogenic in clinical trials for primary liver cancer and metastatic colorectal cancer, combinations of JX-594 with cyclophosphamide (Cy), sorafenib, or avelumab have yet to yielded improved clinical outcomes [189–194]. VG161, a novel HSV-1 oncolytic virus encoding IL-12, IL-15, IL-15 receptor alpha subunit isoform 1, and a PD-1/PD-L1 blocking peptide, induced robust antitumor effects [195]. VG161 received FDA orphan drug designation in 2023, and completed a phase I clinical trial in patients with advanced primary liver cancer refractory to standard treatment, now undergoing multiple clinical Phase II trials [196]. In summary, while OV-based cancer

Table 5 Selected phase II-III clinical trials of virus-based cancer vaccines

Platform	Vaccine	Year, Phase, reference	Target cancer Sample number	Route	Results
Viral vector (modified vaccinia Ankara)	TG4010: encoding MUC1 and IL-2	2016, phase IIb and III, NCT01383148 [159]	Stage IV NCSLC without activating EGFR mutation and with high expression of MUC1/222	Subcutaneous	Improved PFS (5.9 vs 5.1 months) and OS (12.6 vs 10.6 months) compared to chemotherapy alone
Viral vector (Vaccinia, fowlpox)	PROSTVAC-VF: encoding PSA and three immune costimulatory molecules	2010, phase II, NCT00078585 [167]	Minimally symptomatic mCRPC/125	Subcutaneous	Increased three-year OS rate (30% vs 17%) and extended median survival by 8.5 months
		2019, phase III, NCT01322490 [168]	Asymptomatic or minimally symptomatic mCRPC/1297		No improvement compared to placebo
Viral vector (adenovirus)	Nadofaragene firadenovec: IFNA2B	2021, phase III, NCT02773849 [161]	BCG-unresponsive non-muscle-invasive bladder cancer/151	Intravesical	53.4% CR at 3-month; 45.5% of 12 month-maintained response
OVs (adenovirus)	H101	2004, phase III, not found [174]	Advanced squamous cell carcinomas of the head and neck or esophagus/123	Intratumoral	Higher ORR (78.8% vs 39.6%) compared to Chemotherapy alone
OVS (HSV)	Talimogene laherparepvec (T-VEC): encoding GM-CSF	2019, phase III, NCT00769704 [176]	Unresected stage IIIB to IVM1c melanoma/436	Intralesional	Higher DRR (19% vs 1.4%) and longer median OS (23.3 vs 18.9 months) compared to GM-CSF alone
		2023, phase III, NCT02263508 [181]	Unresectable IIIB-IVM1c melanoma/692		No improvement compared to pembrolizumab
		2023, phase II, NCT01740297 [180]	Unresectable stage IIIB–IV melanoma/198		Higher ORR (35.7% vs 16.0%) and DRR (33.7% vs 13.0%)
OVs (HSV)	RP-1: encoding GM-CSF and a fusogenic protein	Phase I/II, NCT03767348	Anti–PD-1–failed advanced melanoma	Intratumoral	Recruiting

mCRPC, metastatic castration-resistant prostate cancer; IL-2, interleukin 2; BCG, Bacille Calmette-Guérin; HSV, herpes simplex virus; DRR, durable response rate

Table 6 Selected phase II-III clinical trials of cell-based cancer vaccines

Platform	Vaccine	Year, Phase, reference	Target cancer, Sample number	Route	Results
Tumor cells	Oncovax: autologous tumor cells	2001, phase III [201]	Resected stage II/III colon cancer /728	Intradermal	Recurrence-free interval: annual odds reduction 25 ± 13% compared to placebo
Tumor cells	Belagenpumatucel-L: four allogeneic NSCLC cell lines	2015, phase III, NCT00676507 [204]	Stage III/IV NSCLC/532	Intradermal	No improvement compared to placebo
Tumor cells	Canvaxin: three allogeneic melanoma cell lines plus BCG	2017, phase III, NCT00052156 [205]	Complete resection of stage IV melanoma/496	Intradermal	No improvement compared to placebo
Tumor cells	GVAX, Cy, and CRS-207	2019, phase IIb, NCT02004262 [213]	Previously treated metastatic PAAD/213	Intradermal	No improvement compared to chemotherapy
	GVAX and ipilimumab	2020, phase II, NCT01896869 [211]	Metastatic PDAC/82	Intradermal	No improvement compared to chemotherapy
	GVAX, Cy, nivolumab and urelumab	2023, NCT02451982 [214]	Resectable PAAD/40	Intradermal	No improvement compared to GVAX and Cy
DCs	Sipuleucel-T (Provenge)	2010, phase III, NCT00065442 [224]	Metastatic castration-resistant prostate cancer/512	Intravenous	Reduced 22% death risk and enhanced 4.1-month median survival compared to placebo
DCs	DCVAC/Pca: autologous DCs exposed to a human prostate adenocarcinoma cell line	2022, phase III, NCT02111577 [234]	Metastatic castration-resistant prostate cancer/1182	Subcutaneous	No improvement compared to placebo, docetaxel, and prednisone
DCs	DCVax-L: autologous DCs loaded with autologous tumor lysate	2023, phase III, NCT00045968 [233]	Newly diagnosed and recurrent glioblastoma/331	Intradermal	Extended OS in new (19.3 vs 16.5months) and recurrent glioblastoma (13.2 vs 7.8 months) compared to placebo and temozolomide

PAAD, pancreatic adenocarcinoma; Cy, cyclophosphamide

vaccines exhibit significant therapeutic potential, most clinical trials remain in early stage (Table 5), underscoring the need to optimize treatment regimens to enhance efficacy [172].

Cell-based cancer vaccines

Tumor cells serve as excellent antigens sources for vaccines, utilizing formats such as whole tumor cell (WTC), lysates, or components. DC-based vaccines are particularly effective as they directly activate T cells. Both tumor cell- and DC-based vaccines have been widely tested in clinical trials (Table 6). Additionally, other immune cells, such as NK cells, B cells, and T cells, are also being explored for their potential in cancer vaccines.

Tumor cell-based vaccines

Living tumor cells exhibit low immunogenicity due to immune evasion mechanisms such as downregulation of MHC molecules and secretion of immunosuppressive factors, necessitating their inactivation for vaccine production. Different manufacturing methods such as irradiation, freeze–thaw cycles, hyperthermia, hypothermia, and hypochlorous acid, affect vaccine immunogenicity differently [197]. Here, we primarily focus on WTC vaccines, containing a complete antigen spectrum, which are promising to overcome the challenge of HLA restriction and reduce the risk of tumor escape.

Approaches to enhance the immunogenicity of WTC vaccines include gene modifications, incorporating adjuvants, and utilizing innovative delivery platforms. BCG and immune-stimulating molecules such as IFN, IL, and GM-CSF have been utilized as adjuvants. Modifying tumor cells to produce immune stimulators has been widely employed, with GVAX being a classic example. For instance, Chen et al. engineered living tumor cells to secrete IFN-β and GM-CSF, which possessed the ability to directly kill tumor cells and improve the TME, along with an implemented double kill-switch to prevent secondary tumor initiation [198]. The efficacy of this therapeutic vaccine was confirmed in immunocompetent and humanized mice models with primary, recurrent, and metastatic cancers [198]. Additionally, Meng et al. developed a photothermal nanoparticles platform activated by near-infrared laser irradiation, enabling on-demand release of the WTC vaccine, which exhibited potent antitumor efficacy in six mice models [199].

Various WTC vaccines derived from autologous and allogeneic sources have been evaluated in clinic. OncoVAX, combined with BCG, enhanced recurrence-free period and OS in patients who had colon cancer surgery, but these benefits were mainly observed in stage II patients, with further testing ongoing (NCT02448173) [200, 201]. M-Vax, an autologous melanoma cell vaccine mixed with BCG, induced delayed-type hypersensitivity, which was positively correlated with longer OS [202]. The combination of M-vax with IL-12 has entered phase III clinical trial (NCT00477906). Gemogenovatucel-T, modified to encode GM-CSF and suppress furin and TGF-β1/2, decreased the recurrence risk in patients with stage III/IV $BRCA^{WT}$ ovarian cancer as a maintenance treatment compared to placebo [203]. However, Belagenpumatucel-L, comprising four TGF-β2-antisense gene-modified allogeneic NSCLC cell lines, failed to achieve improvement as a maintenance therapy [204]. Similarly, Canvaxin, made from three allogeneic melanoma cell lines, did not improve clinical outcomes as a postsurgical adjuvant therapy [205]. Additionally, cancer stem and stem-like cell-based vaccines are emerging as alternative strategies. [206]. For example, AGI-101H, consisting of two modified allogeneic cell lines encoding IL-6 linked with the soluble IL-6 receptor and transforming into a stem-like phenotype, led to longer survival in melanoma patients in a phase II clinical trial [207].

GVAX has the ability to induce potent immune responses, but its clinical benefits have been limited, especially when compared to standard therapies. GVAX was shown to elevate the intratumoral ratio of effector T cell to Treg and stimulate the formation of intratumoral tertiary lymphoid aggregates in patients with resected PDAC, which may be associated to longer OS [208, 209]. In a phase II trial of advanced PDAC, combining GVAX with ipilimumab enhanced median OS (5.7 vs 3.6 months) and 12-month OS rate (27% vs 7%) versus ipilimumab monotherapy [210]. However, when compared to front-line maintenance chemotherapy, this combination did not show improvement in metastatic PDAC [211]. A prime/boost regimen of Cy, GVAX, and CRS207, a live-attenuated Listeria monocytogenes-expressing mesothelin, extended OS in patients with metastatic pancreatic adenocarcinoma [212]. But this regimen failed to surpass the efficacy of chemotherapy [213]. As a neoadjuvant therapy, the combination of Cy, GVAX, nivolumab, and urelumab, a CD137 agonist antibody, showed promise, extending OS to 35.55 months in a small sample, which requires further investigation [214].

Furthermore, recent advancements have been made in cancer vaccines leveraging immune cells. NK cells, known for their direct tumor-lysing capability, displayed effective antitumor activity, and when combined with TLR agonist, promoted a pro-inflammatory shift of the TME [215]. Additionally, autologous B cell and monocyte-based vaccines, transfected with tumor antigens and loaded with the NKT cell ligand alpha-galactosyl ceramide, have demonstrated immunogenicity and safety in clinical trials involving small sample patients with gastric cancer or cervical cancer [216–218]. However, more robust data from larger trials are needed to confirm these findings.

DC-based vaccines

Current DCs used in clinical settings are derived from $CD14^+$ peripheral blood monocytes or $CD34^+$ hematopoietic precursors, cultured with cytokines to differentiate into mature DCs, which are then loaded with antigen sources for vaccine production [219, 220]. The selection of antigen sources is critical. DC vaccine pulsed with hypochlorous acid-oxidized tumor cell lysates downregulated suppressive cytokines, improved antigen presentation, and prolonged mouse survival, compared to those using irradiated or freeze-thawed tumor cell lysates. [221]. In patients with advanced recurrent ovarian cancer, this vaccine decreased peripheral Treg cells, activated $CD8^+$ responses against multiple antigens, and yielded radiographic lesion regression. [221]. Additionally, DC vaccines loaded with tumor-stressed lysates induced higher levels of TAA-specific T cells, Th1-type chemokines, and CTLs than irradiation tumor lysates [222]. Notably, monocyte-derived DCs are highly adaptable cells responding to inflammatory conditions, which share some characteristics with bona fide DC subsets but also exhibit distinct differences [223]. DC-based vaccines have demonstrated effectiveness in both preclinical and clinical studies, although the manufacturing process is complicated, costly, and time-consuming [219].

Sipuleucel-T (Provenge), derived from autologous monocytes, loaded with a recombinant fusion protein (PA2024) that comprises prostate antigen, prostatic acid phosphatase, and GM-CSF, greatly prolonged the OS of men with metastatic castration-resistant prostate cancer (mCRPC) in a phase III clinical trial [224]. Ilixadencel, intratumorally injected allogeneic DCs, has shown promising clinical results [225, 226]. A multi-center phase II study evaluated the combination of ilixadencel with sunitinib in patients with newly diagnosed metastatic renal cell carcinoma, with the latest results demonstrating a higher 42.2% ORR in the ilixadencel group versus 24.0% in the control group [225]. To date, ilixadencel has received FDA orphan drug status for soft tissue sarcoma and hepatocellular carcinoma, along with regenerative medicine advanced therapy status for kidney cancer. In a phase I/II clinical trial, a DC vaccine pulsed with two HER2-derived peptides demonstrated immunogenicity

when combined with monoclonal antibody and chemotherapy, offering a promising approach for HER2-positive breast cancer [227].

DC vaccines loaded with tumor cells have been extensively studied. In a phase II clinical trial, autologous DC vaccine loaded with tumor cells led to longer median survival (43.4 vs 20.5 months) and 70%-reduced death risk compared to autologous tumor cell vaccine in metastatic melanoma [228]. TLPLDC and TLPO, autologous tumor lysates, yeast cell wall particle-loaded ex vivo or in vivo respectively, DC vaccines, improved DFS and OS in preventing the recurrence in resected stage III/IV melanoma [229]. Due to TLPO's advantages in reducing production costs and time, a phase III study is planned to evaluate its effectiveness in combination with standard therapy [229]. Combing tumor cell-loaded DC vaccine with chemotherapy has shown clinical improvements over chemotherapy alone, such as the use of DCVAC/LuCa with carboplatin/pemetrexed for NSCLC and DCVAC/OvCa with first- or second-line chemotherapy for ovarian cancer [230–232]. The application of DCVax-L with temozolomide greatly improved medium OS in newly diagnosed (19.3 vs 16.5 months) and recurrent glioblastoma patients (13.2 vs 7.8 months), and notably enhanced the 5-year survival rate in newly diagnosed patients (13.0% vs 5.7%). [233] However, DCVAC/PCa combined with docetaxel and prednisone did not extend OS in patients with mCRPC [234].

DC cancer vaccines loaded with mRNA, exosome, and immunomodulator have shown significant promise. TriMixDC-MEL, autologous DCs electroporated with synthetic mRNA encoding MAGE-A3, MAGE-C2, tyrosinase, and gp100, was safe and immunogenic [235]. The combination of TriMixDC-MEL and ipilimumab was evaluated in a phase II trial and showed a 38% ORR in patients with pretreated advanced melanoma, outperforming ipilimumab monotherapy [236]. Tumor exosomes were proved to be superior than tumor cell lysates, with prolonged persistence and preferential processing in the MHC-II-loading compartment [237]. Exosome-loaded DC vaccines improved TME and achieved significant tumor growth inhibition in mice [237, 238]. DEC205 is an endocytosis-mediating receptor on DCs. Fusing target-DEC205 single-chain fragments variable to MAGE-A3 was found to enhance the MHC-II-restricted antigen presentation capability of DCs, along with higher T cell responses than RNA-electroporated or peptide-pulsed DCs [239]. Flt3 ligand, critical for DCs differentiation and maturation, was combined with poly-ICLC and a fusion protein linking NY-ESO-1 with 3G9 IgG1 (anti-DEC205), evoking strong and lasting immune responses in patients with high-risk melanoma [240]. Moreover, personalized neoantigen-pulsed autologous DC vaccine has shown its immunogenicity and clinical therapeutic benefits in patients with advanced lung cancer, presenting a promising alternative treatment [241]. Although DC vaccines show considerable potential, their high production costs and complex manufacturing pose major barriers to widespread application. Nevertheless, with the advancements in technology, particularly in the antigen sources and immune regulatory targets, DC vaccines remain to be an important component of cancer immunotherapy.

Neoantigen cancer vaccines

Neoantigen vaccines have emerged as a promising frontier in cancer immunotherapy, leveraging various platforms to target specific tumor mutations. For example, Neovax, a long-peptide vaccine targeting up to 20 neoantigens per melanoma patient, achieved a median PFS of 25 months in six patients and induced specific memory T cells persisting for 2–4.5 years, along with a broad T cell epitope spectrum [40, 242]. When applied to glioblastoma patients, this neoantigen vaccine regimen enhanced intratumoral T cell activation, further highlighting its potential [243].

The combination of neoantigen vaccines with ICIs has been validated in many trials. For instance, two patients who received Neovax following disease progression and subsequently anti-PD-1 therapy experienced complete tumor regression [40]. A personalized neoantigen peptide vaccine NEO-PV-01, combined with nivolumab, prolonged PFS in patients with cancers [244]. Moreover, a personalized neoantigen-loaded DC vaccine, followed by nivolumab, achieved 25 months of complete regression in a metastatic gastric cancer patient [245]. Another heterologous vaccine, using chimpanzee adenovirus and saRNA to deliver 20 neoantigens in combination with nivolumab and ipilimumab, mounted potent and long-lasting neoantigen-specific $CD8^+$ T cell responses in patients with advanced metastatic solid tumors. [246].

Peptides and proteins from unconventional regions, such as long non-coding RNA, 5′ UTR, and circ-RNA, have demonstrated immunogenicity and show promise as anti-tumor targets [247]. To illustrate, a circ-RNA-derived protein HER2-103 was associated with poor prognosis in TNBC patients but indicated strong response to pertuzumab [248]. Similarly, cryptic peptides from noncanonical circ-RNA exhibited high MHC affinity, effectively primed naïve T cells, and elicit specific $CD8^+$ T cells, driving tumor control in mice [249].

In addition to personalized vaccines, shared neoantigen vaccines are also under investigation. The vaccine ELI-002 2P, incorporating amphiphilic modified KRAS G12D and G12R mutant long peptides with CpG oligonucleotides, delayed tumor recurrence via improved

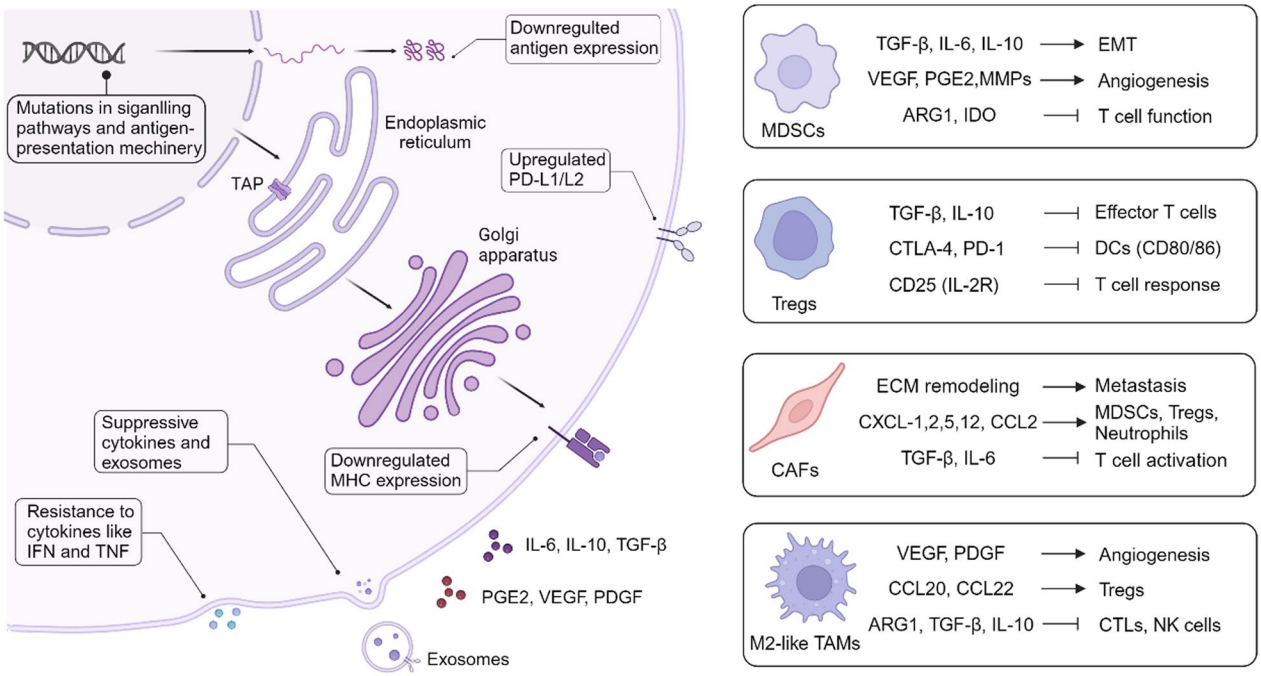

Fig. 3 Mechanisms of tumor resistance to vaccine therapy. Tumors utilize intrinsic resistance mechanisms such as mutations in key signaling pathways and defects in antigen presentation machinery, to evade immune control, as well as the downregulation or loss of antigen expression. Moreover, the upregulation of immune checkpoints like PD-L1/L2, acquired resistance to IFN and TNF, and secretion of suppressive cytokines, all impair T cell functionality and reduce immune-mediated tumor clearance. Tumor cells also exploit extrinsic resistance mechanisms by recruiting surrounding cells to establish an immunosuppressive environment. Immunosuppressive cells such as myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), cancer-associated fibroblasts (CAFs), and M2-like tumor-associated macrophages (TAMs) work together to solid tumor extracellular matrix, promote tumor angiogenesis, secrete suppressive cytokines, and inhibit effector T cell activation, thereby fostering tumor growth, metastasis, and immune evasion. TAP, transporter associated with antigen presentation; EMT, epithelial-to-mesenchymal transition; VEGF, vascular endothelial growth factor; PGE2, prostaglandin E2; MMPs, matrix metalloproteinases; ARG1, arginase 1; IDO, indoleamine 2,3-dioxygenase; ECM, extracellular matrix; PDGF, platelet-derived growth factor; FGF, fibroblast growth factor; CXCL, C-X-C motif chemokine ligand; CCL2, CC chemokine ligand 2; NK, natural killer

targeting of lymph nodes and enhanced immunogenicity [250]. SLATE v1, designed to encode 20 shared neoantigens, was well-tolerated and immunogenic in patients harboring KRAS mutations [251]. This study also pointed the phenomenon of immune dominance when antigens are expressed from a common vector, and an advanced vaccine iteration, SLATE-KRAS targeting four highly prevalent KRAS neoantigens, was developed for further evaluation (NCT03953235) [251]. These findings underscore the powerful potential of neoantigen-based cancer vaccines, offering highly specific approaches to target and eliminate tumor cells, marking a significant advancement for precision medicine.

Mechanisms of resistance to cancer vaccines

The immune system performs the 'immune surveillance' function to identify and eliminate malignant cells [252]. But the interaction between cancer and the immune system is complex and dynamic. Schreiber et al. proposed the concept of 'immunoediting', containing three envisaged stages: elimination, equilibrium, and escape, which describes how cancer cells evolve to survive, with those possessing survival advantages gradually proliferating [253]. Cancer resistance arises from a combination of intrinsic and extrinsic mechanisms within the tumor and its surrounding microenvironment, involving diverse cellular and non-cellular components, is crucial for tumor progression, metastasis, and resistance to therapies (Fig. 3).

Tumor intrinsic factors

Tumors inherently modify the expression of cytokines and chemokines, shaping their microenvironment and impairing immune responses. For example, PDA produces CXCL1 to recruit immunosuppressive cells, reducing T cell infiltration [254]. Tumor-derived colony-stimulating factor downregulates IFN regulatory factor 8 in cDC progenitors, inhibiting the development of

cDC1s [255]. Metastatic melanoma releases exosomes with PD-L1 on the surface to suppress $CD8^+$ T cell function [256]. Moreover, tumors can evade immune recognition through mutations in antigen presentation machinery, such as mutations in MHC molecules and β2-microglobulin [257–261]. Signaling pathway dysregulation fosters T cell exclusion and immune escape. Examples include IFN signaling mutation, WNT/β-catenin activation, and the loss of phosphatase and tensin homolog [262–265]. Furthermore, under immune selection pressure, tumors may acquire mutations that downregulate highly immunogenic proteins or even lose mutant alleles to escape T cell recognition [266].

Tumor extrinsic factors

Over the long-lasting hard fight against cancer, immune cells may become exhausted and lose their ability to eliminate cancer cells, while some plastic immune cells adopt pro-tumor characteristics. The accumulation of regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), cancer-associated fibroblasts (CAFs), pro-tumor N2 neutrophils, and M2-like tumor-associated macrophages (TAMs) is associated with poor prognosis. These cells collaborate to foster suppressive TME by upregulating immune checkpoint (PD-1, CTLA-4), secreting immunosuppressive cytokines (IL-6, IL-10, TGF-β), inhibiting the function of immune cells, promoting angiogenesis, and solidifying the extracellular matrix, which in turn strengthen their capabilities to resist immune attack [267–272]. For example, M2-like TAMs restrict $CD8^+$ T cell function through collagen deposition and metabolic reprogramming within TME [273]. CAFs remodel the extracellular matrix, hinder immune cell infiltration, and contribute to tumor invasion [274]. TGF-β increase pDC-derived IDO and myeloid DCs-derived CCL22, which recruits Tregs into the TME [275]. Immunosuppressive cells also counteract vaccine-induced responses, as seen in melanoma patient where MDSCs and Tregs inhibited anti-tumor T cell function after vaccination [276, 277]. Thus, understanding these intrinsic and extrinsic resistance mechanisms is vital for developing strategies to enhance the effectiveness of cancer vaccines.

Combination therapies to overcome limitations

Although cancer vaccines have the potential to improve the TME, they often fail to abolish tumors when used alone. To address this, researchers have extensively explored combining cancer vaccines with other treatments including surgery, chemotherapy, radiotherapy, ICIs, ACT, monoclonal antibodies, and small-molecule inhibitors. Importantly, cancer vaccines have been identified with the ability to induce epitope spreading, broadening the T cell responses and potentially optimizing efficacy of combination therapies [160, 244, 278]. By utilizing strengths of different therapies, combination approaches overcome the limitations of single therapy and collaborate to offer a multifaceted attack on tumors (Fig. 4).

Chemotherapy and radiotherapy can debulk tumors, induce immunogenic tumor cell death, increase MHC molecules expression, and induce nonsynonymous mutations [279]. Under the stress from cytotoxic agents and radiation, apoptotic tumor cells release numerous DAMPs such as surface-exposed hot shock proteins, calreticulin, secreted adenosine triphosphate, and released high mobility group protein B1, which stimulate intensive inflammation and promote efficient DC maturation and antigen presentation to T cells [280–283]. For instance, gemcitabine and Cy can reduce the level of MDSCs, Tregs, and TGF-β, and increase the effector T cells to Tregs ratio [164, 284]. Carboplatin and paclitaxel have been shown to suppress immunosuppressive cells, allowing for an extended immunological window for following vaccination, resulting in robust T cell responses and improved clinical survival [285, 286]. Radiation therapy preferentially targets highly proliferative cells, killing cancer cells directly and mediating out-of-field abscopal effects through triggered systematic immune responses. The released cytosolic DNA activates the cGAS-STING signaling pathway, inducing type I IFN production that aids anti-tumor activity [287]. However, contradictory findings regarding the induction of immunosuppressive TME by radiotherapy exist, which may stem from the varying sensitivity of tumor compartments to different radiation schedules [288]. Hence, future studies should explore optimal radiation dose, schedule, and fraction.

The combinations of ICIs and cancer vaccines have shown encouraging results [40, 46, 142, 244, 245]. Adding nivolumab to GVAX increased T cell infiltration, Th1 to Th2 ratio, and Th17 density, which also led to improved $CD137^+$ CTL function and $CD11b^+$ neutrophil degranulation [289]. The co-therapy of nivolumab and ISA101, an HPV-16 SLP vaccine, provoked specific T-cell responses and doubled the response rate in patients with incurable HPV 16-positive solid tumors compared to nivolumab monotherapy [290]. One patient with HPV-associated head and neck cancer, who was vaccinated with a DNA vaccine expressing HPV E6/E7 protein and IL-2, developed metastasis but showed rapid and complete tumor regression after subsequent anti-PD-1 treatment [291]. These findings suggest that cancer vaccines and ICIs complement each other to enhance immune responses, providing an alternative particularly for those resistant to ICIs. However, the optimizing administration schedule of ICIs and vaccines is crucial for maximizing

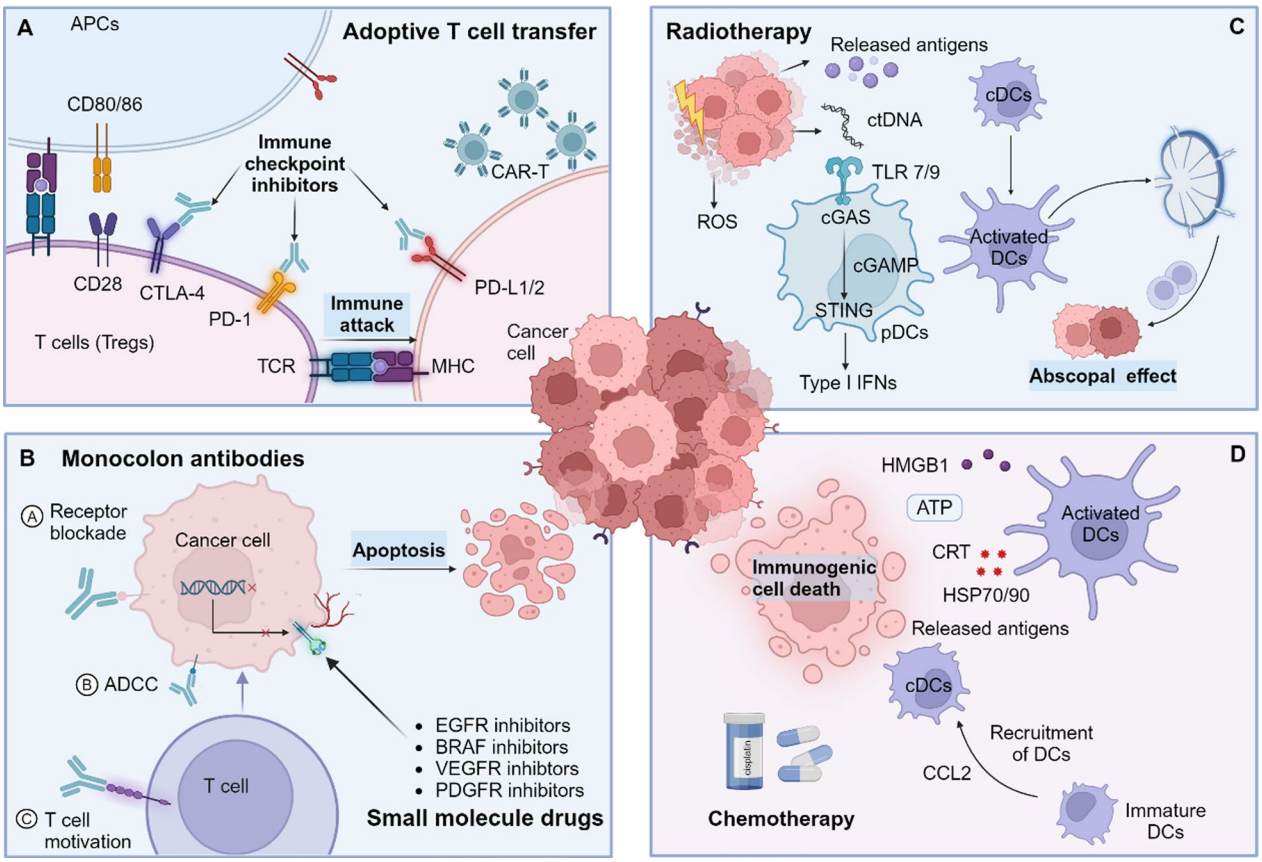

Fig. 4 Key mechanisms underlying the efficacy of combination therapies. **A** Inhibitors that target immune checkpoints reactivate exhausted T cells, restoring their capacity to initiate immune attacks on cancer cells. Adoptive cell therapies involving chimeric antigen receptor (CAR) T cells or engineered T cells directly target specific tumor antigens, enhancing tumor cell destruction. **B** Targeted therapy: monoclonal antibodies and small molecule drugs block or inhibit essential molecules for tumor survival. Monoclonal antibodies can obstruct surface receptors, disrupt cell proliferation, or mediate antibody dependent cell mediated cytotoxicity (ADCC). They can also stimulate T cell activation by engaging surface antigens. **C** Irradiated tumor cells undergo cell death, releasing reactive oxygen species (ROS), circulating tumor DNA (ctDNA), and tumor antigens. ctDNA activates toll-like receptor (TLR) 7 and TLR9 on pDCs, promoting type I IFN secretion, thereby enhancing immune responses. cDCs also process and present antigens to draining lymph nodes, leading to T cell activation and infiltration into tumor sites, known as the "abscopal effect." **D** Chemotherapy: cytotoxic drugs induce immunogenic cell death, releasing damage-associated molecular patterns to activate DCs and trigger specific T cell responses, aided by the secretion of CCL2, which recruits immature DCs to the tumor microenvironment. CTLA-4, cytotoxic T lymphocyte antigen-4; cGAS, cyclic GMP-AMP synthase; cGAMP, cyclic GMP-AMP; STING, stimulator of interferon genes; VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptor; HMGB1, high mobility group protein B1; ATP, adenosine triphosphate; CRT, calreticulin; HSP, hot shock protein

therapeutic efficacy and requires further investigations. In a tumor-bearing mice model, administrating PD-1 blockade before vaccination resulted in suboptimal primed dysfunctional PD-1^{+}CD8^{+} T cells, which was reversed by simultaneous PD-1 blockade and vaccination [292]. Additionally, combing vaccines with ACT has been explored to enhance the therapeutic potential of transferred T cells, leading to improved anti-tumor responses in preclinical studies [293, 294].

Targeted therapies, including monoclonal antibodies and small molecule drugs, inhibit tumor growth, normalize tumor vasculature, and regulate immune responses by targeting key proteins involved in oncogenesis, T cell activation, and signaling pathways. Cetuximab, an EGFR-blocking monoclonal antibody, fostered immunogenic death of tumor cells when combined with chemotherapy [295]. Agonist antibodies targeting CD27 and anti-CD40 boosted cancer vaccine efficacy by activating T cells [296, 297]. The addition of urelumab, an anti-CD27 agonist antibody, to GVAX, increased intra-tumoral T cell infiltration and improved DFS and OS [214]. Small molecule inhibitors have been widely tested, and some have been approved as adjuvant therapies or first-line options for recurrent or metastatic disease [298]. However,

combinations of cancer vaccines with tyrosine kinase inhibitors like sunitinib and sorafenib have yielded mixed clinical results [95, 192, 225].

In conclusion, given the variability among different tumors and individuals, selecting appropriate combination therapy tailored to specific tumor and patient characteristics is essential for achieving optimal clinical outcomes.

Conclusions and prospects

Numerous cancer vaccines have progressed to clinical evaluation, demonstrating the ability to elicit strong immune responses. However, despite some early successes, the majority have not achieved durable responses or significant clinical efficacy in large phase III trials, presenting both opportunities and challenges for future development. Decades of research have greatly deepened our understanding of cancer vaccines, and the design of an optimal vaccine remains a delicate process. This process requires careful consideration of antigen selection, adjuvant incorporation, administration methods, combination with other therapies, and identification of the appropriate patient population.

Evidence suggests that higher tumor burdens, simply defined as tumor amount, negatively impact the effectiveness of immunotherapy [299]. This can be attributed to the immunosuppressive TME in advanced stages, which inhibits the immune system's ability to mount a strong and sustained response. This may partially explain the limited success of cancer vaccines in patients with advanced or unresectable tumors, where the TME poses significant barriers to effective treatment.

Neoantigen-based vaccines and mRNA vaccine platforms have gradually moved toward clinical application and shown immense potential. Although few neoantigen-based vaccines have reached phase III trials so far, they are advancing rapidly. A key challenge remains the high cost of manufacturing personalized vaccines, which limits their widespread application. In terms of combination therapies, ICIs have shown great promise, but clinical trial outcomes have been mixed, and there is a lack of standardized criteria for drug selection.

Advanced technologies, such as single-cell sequencing and high-resolution imaging, have enabled a deeper understanding of TME, providing new insights into the interaction between vaccines and cancer cells [2]. These tools offer the potential to optimize vaccine design by enabling more precise targeting of cancer cells and enhancing immune responses. The evaluation of vaccine efficacy has primarily focused on adaptive immune responses, particularly the activation of antigen-specific $CD8^+$ T cells, and TRMs have also gained attention. However, clinical outcomes remain the definitive benchmark of success, emphasizing the need for robust and standardized criteria to assess the clinical impact of cancer vaccines [300].

As the field continues to advance, numerous innovative platforms, adjuvants, delivery systems, and combination strategies are under development. Addressing current challenges such as the high cost of personalized vaccines and optimizing patient-specific treatment protocols will be crucial in ensuring that cancer vaccines achieve their full potential in clinical settings. We are optimistic that these innovations will drive the next generation of cancer vaccines, offering transformative benefits to cancer patients in the near future.

Abbreviations

ICIs	Immune checkpoint inhibitors
ACT	Adoptive cell therapy
CTLA-4	Cytotoxic T lymphocyte antigen-4
PD-1	Programmed death-1
PD-L	Programmed death ligand
FDA	Food and Drug Administration
HPV	Human papillomavirus
HBV	Hepatitis B virus
BCG	Bacille Calmette-Guérin
T-VEC	Talimogene laherparepvec
WT-1	Wilms tumor protein 1
MUC1	Mucin 1
TAAs	Tumor-associated antigens
TSAs	Tumor-specific antigens
HER2	Human epidermal growth factor receptor 2
EGFR	Epidermal growth factor receptor
MAGE	Melanoma-associated antigen
NY-ESO-1	New York esophageal squamous cell carcinoma 1
PSA	Prostate-specific antigen
PAP	Prostatic acid phosphatase
gp100	Glycoprotein 100
MART-1	Melanoma antigen recognized by T cells 1
LMP	Latent membrane protein
HBsAg	Hepatitis B virus serum antigen
HLA	Human leukocyte antigen
ELISpot	Enzyme linked immunospot
MHC	Major histocompatibility complex
SNVs	Single-nucleotide variants
INDEL	Insertions and deletions
ORF	Open reading frame
NK	Natural killer
PRRs	Pattern recognition receptors
APCs	Antigen-presenting cells
TAP	Transporter associated with antigen presentation
ER	Endoplasmic reticulum
pDCs	Plasmacytoid DCs
cDCs	Conventional DCs
Mo-DCs	Monocyte-derived DCs
SLOs	Second lymphoid organs
IL	Interleukin
IFN	Interferon
Th	T helper
TLR	Toll-like receptor
GM-CSF	Granulocyte–macrophage colony-stimulating factor
CCL	CC chemokine ligand
Flt3	Fms-related tyrosine kinase 3
CCR	C–C motif chemokine receptor
CXCL	C-X-C motif chemokine ligand
CTLs	Cytotoxic T lymphocytes
CD40L	CD40 ligand
TME	Tumor microenvironment

fDCs	Follicular dendritic cells
DAMPs	Damage-associated molecular patterns
poly-ICLC	Polyinosinic-polycytidylic acid
LNPs	Lipid nanoparticles
TILs	Tumor-infiltrating T cells
TRMs	Tissue-resident T cells
SP	Short peptide
OS	Overall survival
SLP	Synergic long peptide
TGF-β	Tumor growth factor-beta
NSCLC	Non-small cell lung cancer
DFS	Disease-free survival
TNBC	Triple-negative breast cancer
IDO	Indoleamine 2,3-dioxygenase
cGAS	Cyclic GMP-AMP synthase
cGAMP	Cyclic GMP-AMP
STING	Stimulator of interferon genes
RFS	Relapse-free survival
CIN	Cervical intraepithelial neoplasia
ORR	Objective response rate
CR	Complete response
dsRNAs	Double-stranded RNAs
TNF	Tumor necrosis factor
saRNA	Self-amplifying mRNA
UTRs	Untranslated regions
taRNA	Trans-amplifying mRNA
circ-RNA	Circular RNA
LPX	Lipoplex
OVs	Oncolytic viruses
VLPs	Virus-like particles
Ad	Adenovirus
VV	Vaccinia virus
MV	Measles virus
HSV	Herpes simplex virus
PFS	Progression-free survival
MVA	Modified vaccinia Ankara
Cy	Cyclophosphamide
mCRPC	Metastatic castration-resistant prostate cancer
WTC	Whole tumor cells
PDAC	Pancreatic ductal adenocarcinoma
PAAD	Pancreatic adenocarcinoma
Tregs	Regulatory T cells
MDSCs	Myeloid-derived suppressor cells
CAFs	Cancer-associated fibroblasts
TAMs	Tumor-associated macrophages
CCL22	CC chemokine ligand 22
EMT	Epithelial-to-mesenchymal transition
VEGF	Vascular endothelial growth factor
PGE2	Prostaglandin E2
MMPs	Matrix metalloproteinases
ARG1	Arginase 1
PDGF	Platelet-derived growth factor
FGF	Fibroblast growth factor
CAR	Chimeric antigen receptor
ROS	Reactive oxygen species
ctDNA	Circulating tumor DNA
VEGFR	Vascular endothelial growth factor receptor
PDGFR	Platelet-derived growth factor receptor
HSP	Hot shock protein
CRT	Calreticulin
ATP	Adenosine triphosphate
HMGB1	High mobility group protein B1

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Availability of data and materials
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Declarations

Ethics approval and consent to participate
No ethics approval was required for this review that did not involve patients or patient data.

Consent for publication
All authors consent to publication.

Competing interests
The authors declare no competing interests.

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