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REVIEW

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Personalized nanovaccines for treating solid cancer metastases

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Abstract

Cancer vaccines have garnered attention as a potential treatment for cancer metastases. Nevertheless, the clinical response rate to vaccines remains < 30%. Nanoparticles stabilize vaccines and improve antigen recognition and presentation, resulting in high tumor penetration or accumulation, effective co-distribution of drugs to the secondary lymphatic system, and adaptable antigen or adjuvant administration. Such vaccine-like nanomedicines have the ability to eradicate the primary tumors as well as to prevent or eliminate metastases. This review examines state-of-the-art nanocarriers developed to deliver tumor vaccines to metastases, including synthetic, semi-biogenic, and biogenic nanosystems. Moreover, it highlights the physical and pharmacological properties that enhance their anti-metastasis efficiency. This review also addresses the combination of nanovaccines with cancer immunotherapy to target various steps in the metastatic cascade, drawing insights from preclinical and clinical studies. The review concludes with a critical analysis of the challenges and frameworks linked to the clinical translation of cancer nanovaccines.

Keywords Cancer vaccine, Clinical translation, Metastasis, Nanoparticle, Tumor

Introduction

Owing to the high risk of metastasis, cancer continues to be the most malignant illness globally, despite enormous advancements in therapy and diagnostics [1] Specifically, metastases are the leading causes of cancer and mortality in patients with cancer, accounting for approximately 90% of cancer-associated fatalities [2, 3]. An efficient and highly specific anti-metastatic therapeutic strategy should effectively remove primary tumors as well as induce systemic immunity to inhibit distant metastases [4]. Tumor metastasis reprograms distant organ microenvironments systemically, impacting immune cell function or phenotypes [5]. Environmental regulation throughout the metastatic cascade can enhance tumor cell dissemination [6]. Therefore, eliminating metastatic tumors requires systemic immune activation and long-term immune memory. However, metastatic tumors are characterized by their immunosuppressive tumor microenvironment (TME), thus limiting the efficacy of systemic anti-tumor immune responses for the majority of patients [7–9]. Nonetheless, metastatic cells outside of the immunosuppressive TME are more vulnerable to immune elimination, providing a therapeutic opportunity to utilize immune cells in the metastatic cascade [10]. Immunotherapy is considered optimal for treating metastasis because it functions by boosting the immune response of the body and selectively countering the inherently immunosuppressive effects of the TME. Rather than directly combating metastatic tumor cells such as in traditional therapies, immunotherapy

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stimulates immune cells to target rare metastatic tumor cells [11].

Cancer vaccines represent a potentially effective immunotherapeutic strategy that activate the immune system of a patient, facilitating the establishment of long-term immune memory for fighting tumors. This approach has the potential to prevent metastasis, highlighting its stance as a favorable treatment option [12]. However, to date, sipuleucel-T is the only Food and Drug Administration-authorized anti-tumor vaccine for metastatic cancer [13]. Despite active preclinical and clinical investigations, numerous therapeutic cancer vaccines have failed to demonstrate efficacy [14]. A majority of the candidate vaccines featuring "minimalist" compositions have not met expectations because of factors including poor immunogenicity of certain antigens, the immunosuppressive nature of the TME, challenges with in vivo instability, and the random dispersal of vaccine formulations [15, 16]. Owing to the low immunogenicity of tumor antigens and the immunosuppressive TME, another challenge in cancer vaccine therapy is triggering a controlled yet robust tumor-specific T-cell response by delivering antigens and adjuvants efficiently [17]. This is particularly challenging because it is necessary to disrupt the immunosuppressive TME throughout the metastatic cascade [18].

Considering metastatic cells spread extensively to distant organs and are highly heterogeneous and small in size, tracking and treating tumor metastases present unique challenges. Systemic factors influencing the nutritional, metabolic, and inflammatory activity of the body can affect all stages of metastasis via reprogramming the metastasis-specific immunosuppressive systemic microenvironment [19]. Furthermore, surface markers of metastatic cells exhibit marked variability among patients, as well as within the same patient or similar cell types [20]. This heterogeneity further enhances the metastatic potential of tumor cells. The TME of immune cells and their expression of immune-regulatory receptors increase immunosuppression in metastatic tumors, establishing a vicious cycle that further augments tumor cell growth and alteration in the metastasis-specific microenvironment (Fig. 1) [21]. Consequently, there is a growing demand for the application of precision medicine in the context of targeting metastasis [22]. Precision medicine aims to provide a personalized treatment with a foundation undergirded by the application of patient-specific data, i.e., genetic profiles, comorbidities, or environmental exposure [23]. This approach is intended to improve overall survival rates for a wide array of malignancies [24]. Precision medicine makes use of enhanced medication specificity, more precise patient stratification, and optimal doses or combinatorial approaches, including nanomedicine [23].

The cascade of cancer vaccines involves multiple stages: antigen identification, encapsulation, delivery, release,

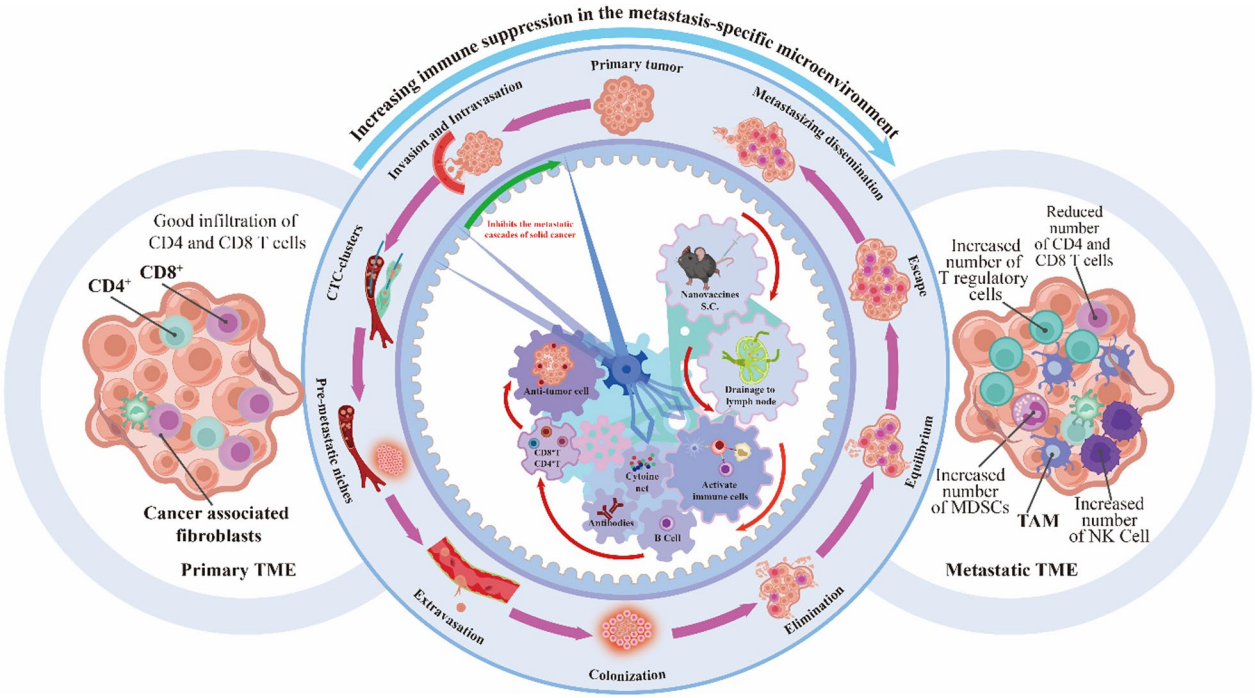

Fig. 1 Schematic illustration of cancer nanovaccine therapy and increasingly immunosuppressive TME of metastatic cascade

and presentation to T cells, especially in lymphatic vessels (inner ring). Increasing immunosuppression of immune cells in the TME and expression of immune-regulatory receptors establish a vicious cycle that further enhances tumor cell growth and alteration in the metastasis-specific microenvironment (left and right ring). The metastatic cascade includes three main steps: (1) primary tumor, (2) metastasizing dissemination involving circulating tumor cells (CTCs), and (3) metastatic colonization involving pre-metastatic niches and disseminated tumor cell settlement and colonization (outer ring). tumor microenvironment (TME); subcutaneous (S.C.); tumor-associated macrophages (TAM); natural killer (NK).

Recently, several potential therapeutic advantages for metastatic cancer have been established using nanoparticles (NPs). NPs have been shown to exhibit a high capacity to precisely transport therapeutic chemicals to both primary and secondary cancers [25]. Additionally, NPs can facilitate the development of personalized vaccines, tailored for individual patient populations [26], to target tumor metastasis [27]. This is because NPs greatly improve the drug delivery capabilities of cancer vaccines. These capabilities are rooted in the optimization of the nanometer size or physicochemical performance of the nanomaterial carriers through modifying the nanomaterials with targeting molecules or co-encapsulating them with immunostimulators. Moreover, beyond improving the precision of cancer vaccines, NPs can be applied to stimulate the immune system [28].

Nanovaccines, a novel generation of vaccines utilizing NPs ranging from 50 to 200 nm in diameter as carriers and/or adjuvants [29], can effectively prime tumor-specific immunity to prevent distant organ metastasis, including in the lymph nodes (LNs) [30], lung [31–33], liver [34] and bones [35]. Nanovaccines co-deliver anti-tumor antigens and immunologic adjuvants to antigen-presenting cells (APCs) [36, 37] Nanocarriers with adjuvant effects augment the strength, breadth, and durability of immune responses to vaccines by efficiently facilitating key steps of the vaccination process, including the recognition, encapsulation, release, transport, and presentation of antigens to T lymphocytes [38]. For example, NP-based vaccines have been demonstrated to increase CD8 + T-cell activation and cross-presentation drastically by at least 55-fold when compared with soluble antigens [26, 39].

As anti-metastasis strategies evolve and novel nanovaccines emerge, attention toward anti-metastasis nanovaccines and nanovaccine-based strategies that target the metastatic cascade will increase in anti-cancer investigations and practice in the future. Therefore, this review focuses on advances in basic immunology and delves into design strategies for anti-metastasis nanovaccines. Recent developments and advantages of nanovaccines for anti-metastasis therapy are comprehensively reviewed across both preclinical and clinical settings, with a particular focus on individualized anti-metastasis nanovaccines.

Mechanisms underlying enhanced tumor immune activation by nanovaccines in cancer metastatic cascades

Interplay between *cancer* vaccines and metastasis

Cancer metastatic cascades

Cancer metastasis is a multistep process that is characterized by the following cascade of events: local invasion, intravasation, extravasation, micrometastatic colony formation, and cell proliferation [10]. In essence, progression of cancer can be categorized into three primary stages: (1) primary tumor; (2) metastasizing dissemination involving CTCs, and (3) metastatic colonization involving pre-metastatic niches and disseminated tumor cell settlement and colonization. CTCs travel primarily through two main routes, i.e., circulation within the blood vessels and through the lymphatic vessels to the blood vessels [40]. Notably, cancer cells have the ability to migrate to nearby LNs through the lymphatic arteries, thereby avoiding immune monitoring and facilitating the establishment of secondary tumors [41]. We propose that tumors have far-reaching consequences, mostly fueled by local and systemic immunosuppression involving several immunological components [42] such as regulatory T cells (Tregs), macrophages, Myeloid-derived suppressor cells, and neutrophils [43, 44].

Tumor metastasis is a complex process, and the complexity can be mediated partly by the activation and regulation of different signaling pathways [45]. Nanovaccines can intervene in pathways that are involved in cancer metastatic cascades and have been shown to inhibit hypoxia-inducible factors (HIFs) [46], transforming growth factor β (TGF-β) [47], and the Wnt/β-catenin pathway [48], and to activate the cGAS-STING cascade [39, 49] and the SHP-1/JAK2/STAT3 signaling pathway [50]. The pathways can influence epithelial–mesenchymal transition (EMT), cell stemness, the tumor hypoxic microenvironment, and anti-tumor immunity in vitro and in vivo, eventually impacting metastasis (Fig. 2).

Overall, during a metastasis cascade, the interruption of immunosuppressive components and relevant signaling pathways in any one of the steps leads to hypoxia-inducible factors (HIFs) [46], transforming growth factor β (TGF-β) metastasis failure. This insight has prompted numerous trials aimed at activating immune responses to combat tumor metastasis (Fig. 1).

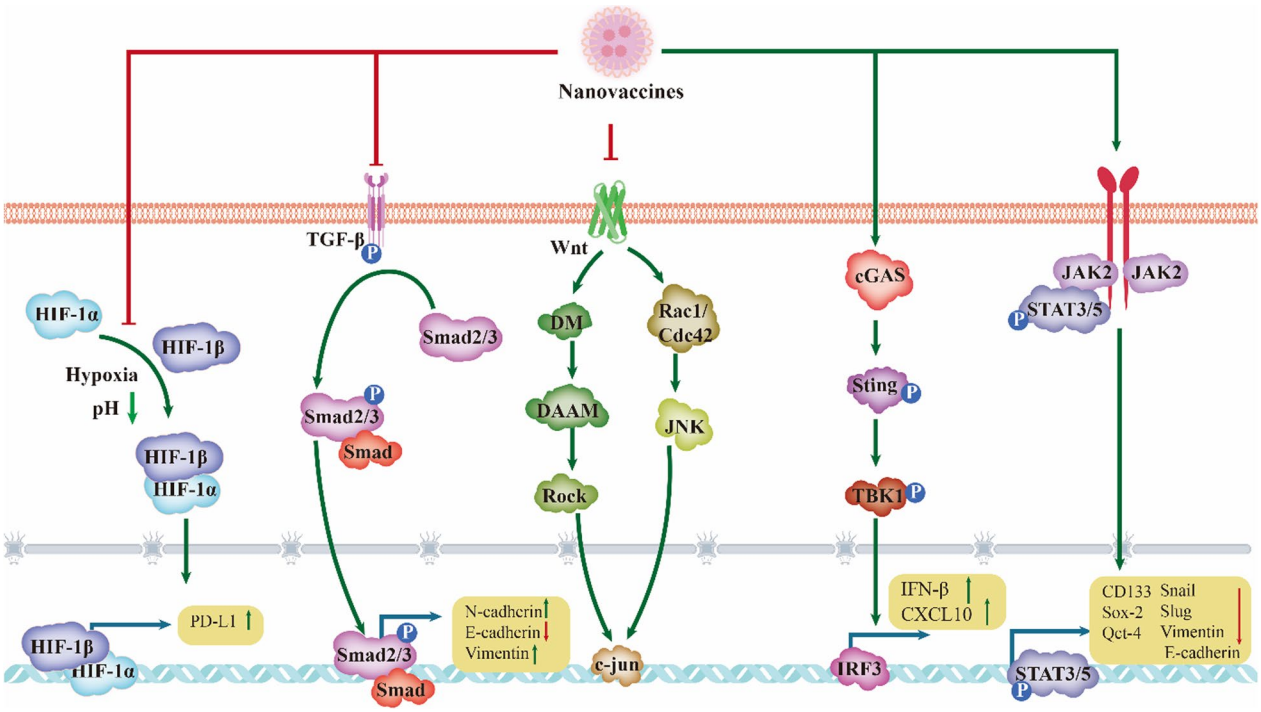

Fig. 2 Signaling pathways intervened by nanovaccines in tumor metastatic cascades

Cancer vaccination cascade

The cancer vaccine cascade can be encapsulated in five processes, which are as follows: antigen delivery aimed at LNs, antigen/adjuvant co-encapsulation, specific antigen identification, antigen internalization and release, and antigen cross-presentation for T-cell cross-priming [51]. Macrophages, dendritic cells (DCs), B cells, natural killer (NK) cells, CD4 + T cells, and CD8 + T cells are the immune cells primarily involved in these critical cascades (Fig. 1).

Immune responses are primed by tumor vaccines, which target APCs with adjuvants and antigens. APCs [52], including macrophages and DCs, are the primary adaptive and innate immune system mediators [53, 54] As DCs potentially regulate immunity and immunological tolerance, they are crucial to the design of nanovaccines and should be considered to lie at the core of the immune system [55]. Specifically, APCs, especially DCs, are the main immune cells that absorb the complete components of a vaccine when it is administered to a patient. Following stimulation by the adjuvant, such APCs use major histocompatibility complex class I/II (MHC I/II) to display antigens on their surface. When APCs are activated, they tend to translocate to secondary lymphoid organs, including the spleen or LNs, where they cause APC maturation [56]. This outcome culminates in the activation of the adaptive immune system, which primarily consists of T and B cells. Through the application of a peptide-bound MHC, CD8 + T cells eradicate tumor cells directly, whereas B cells require CD4 + T cells for sufficient activation and antibody production, which results in antibody-mediated secondary tumor cell death [14]. Cancer vaccines effectively facilitate T-cell differentiation from naïve CD8 + T cells into cytotoxic T lymphocytes (CTLs) and differentiate naïve CD4 + T cells into CD4 + T helper type 1 (Th1) or Th2 cells [57]. Th1 cells generate cytokines, including interleukin-2 (IL-2) and interferon-γ (IFN-γ), to promote CTL activation and the growth of cellular immunity [57]. Th2 interact with B cells and aid in their full activation through CD40–CD40L interaction [26].

Collectively, such results suggest that the immunosuppressive TME is responsible for metastasis. Numerous immune interactions between cancer vaccination and tumor metastasis indicate a potential therapeutic strategy against metastasis by leveraging cancer vaccines to reverse the immunosuppressive TME.

Targeting *cancer* metastasis using nanovaccines in precision medicine

Cancer vaccines intended to limit metastasis have not been able to effectively reach LNs due to the significant heterogeneity and low immunogenicity of tumors, coupled with instability in circulation and the poor

in vivo targeting ability of associated antigens. Recently, nanostrategies have emerged among the most promising approaches for addressing such specific barriers in vaccine delivery and considering the individual stages of solid tumor metastasis. Nanostrategies offer several advantages, including protection against enzymatic degradation, modified circulation time, solubility and bioavailability of various hydrophobic antigens, and increased tumor-targeting affinity. Such attributes collectively maximize immune stimulation (Fig. 3).

Antigens

In general, tumor antigens are divided into peptide [58], messenger RNA (mRNA)- [59, 60] DNA-, and protein-based antigens, depending on their composition [28]. Single-stranded mRNA functions as a template for protein translation [61]. mRNA vaccines rival the best available conventional vaccines due to their low side effects, as well as their rapid and cost-effective development potential [62]. The rationale behind the design of an mRNA cancer vaccination platform is to deliver the transcript(s) of interest, encoding one or more tumor-associated antigens (TAAs) or tumor-specific antigens (TSAs), into the host cell (typically APC) cytoplasm [63]. The recent discovery, identification, and usage of TSAs and TAAs facilitate mRNA-based personalized cancer vaccine treatment applications [64]. mRNA-encoded neoantigens with precise and potent anti-tumor immunity have become a key focus in the personalized vaccine campaign.

The identification of suitable tumor-specific immunogenic antigens is crucial for eliciting specific CD8 + CTL immunity against tumors. Cancer cell membranes contain the distinct TAA and TSA profiles of a particular patient, facilitating their application to the production of vaccines that do not necessitate antigen manufacturing or sequencing to meet tailored therapy goals [65].

Utilizing cancer cell materials such as lysates and membranes as antigen libraries holds promise in precision medicine applications. For example, personalized F-PEI/ovalbumin (OVA) NPs can be prepared by simply mixing a protein antigen fluoropolymer with a model antigen (OVA) or tumor cell membrane antigen from surgically resected tumors. Through the toll-like receptor 4 (TLR4)-mediated signaling cascade, the F-PEI/OVA NPs drive DC maturation and facilitate antigen delivery into the cytosol of DCs, which in turn activates OVA-specific T-cell responses, ultimately preventing metastases [66]. Autologous tumor cell lysates, presenting a comprehensive range of personal epitopes without the need for

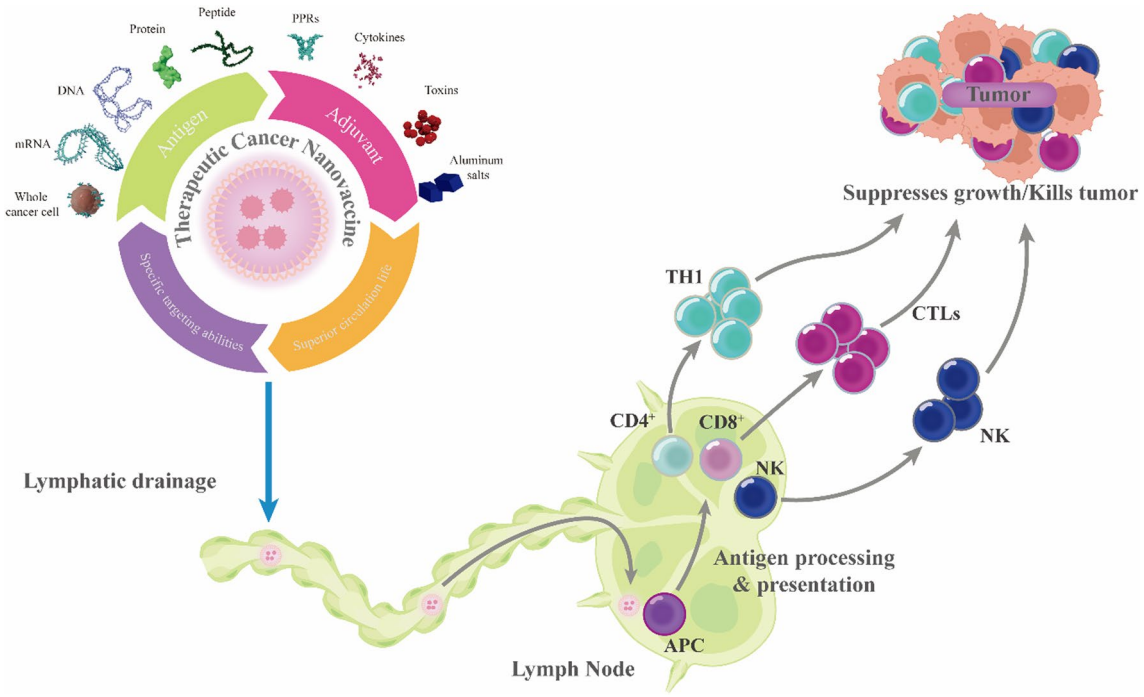

Fig. 3 Advantages of nanotechnology in vaccine delivery. NP delivery systems yield effective vaccine formulations. Additionally, these systems protect bioactive encapsulated payloads, co-delivering antigens and adjuvants in a unified formulation and targeting specific cell subsets via functional surface ligands. The inherent small size of these systems allows for them to efficiently reach the LNs, thus facilitating antigen presentation and enhancing the activation of immune cells, such as B cells, NK cells, CD4 + T cells, and CD8 + T cells

complex ex vivo processes such as sequencing, purification, and extraction, hold potential for developing personalized nanovaccines to prevent tumor metastasis [67]. Such personalized in situ nanovaccines activate a multistep cascade of anti-tumor immune responses involving antigen cross-presentation, DC maturation, NK cells, and tumor-related macrophage repolarization along with CTL infiltration [67]. To generate synergistic anti-tumor immune responses, nanoplatforms that are concurrently loaded with numerous different tumor antigens have been established, thereby abrogating metastasis [32–34].

Selecting the appropriate antigens for tumor vaccines is crucial due to the remarkable impact of antigens on the safety and efficacy of a vaccine [68]. Priority is given to antigens that are expressed specifically in tumor cells, with minimal or no expression in normal cells, in order to enhance the targeting of the vaccine and minimize potential side effects [69]. Examples include TSAs and TAAs [70]. Immunogenicity is another important consideration, and antigens are selected based on their ability to elicit an immune response in the host. This includes antigens that can activate T and B cells and produce specific antibodies [71]. Regarding expression frequency, antigens that are highly expressed in a majority of tumor cells in patients have the ability to improve the therapeutic efficacy of the vaccine [72]. Antigens should also be highly stable in tumor cells to ensure that they do not easily mutate or degrade during treatment [73]. The HLA-binding affinity of the antigen is also an important indicator to be considered [74]. The clinical relevance of the antigens should also be considered, and antigens that are associated with tumor progression, prognosis, or patient survival should be selected. Some antigens may undergo alterations during tumor progression or treatment, making antigen variability an important criterion to consider. Antigens should not be affected easily by the immune evasion mechanisms of tumor cells; particularly, those that are less likely to become ineffective due to mechanisms such as downregulation of MHC molecule expression should be selected [75]. Regarding more practical considerations, selecting antigens that are easy to obtain and identify from tumor tissue or blood for clinical application and research is critical.

Single-target vaccines may exhibit reduced efficacy due to tumor heterogeneity and antigen variability. Thus, strategies that utilize multi-target antigens are gradually gaining attention [76]. Multi-target antigen tumor vaccines can stimulate a broader immune response by targeting multiple tumor antigens, thereby enhancing the opportunities to recognize and attack tumor cells [76]. Tumor cells may evade immune surveillance by altering their surface antigens, and the multi-target strategy can overcome the tumor's escape mechanisms, reducing the risk of immune evasion [77]. Multi-target vaccines have the potential to perform better in different TMEs and adapt to the individualized needs of different patients. Additionally, targeting multiple antigens can enhance immune memory and promote long-term antitumor immunity [77].

Several mRNA vaccines exploit a multi-target design, thereby generating a stronger immune response. For instance, a personalized mRNA vaccine, autogene cevumeran (BNT122), has been developed for pancreatic cancer treatment in a phase I clinical trial [78]. The vaccine operates by using mRNA to express 20 neoantigens derived from patients with pancreatic ductal adenocarcinoma (PDAC), administered via intravenous injection using lipid NPs (LNPs). Following treatment with this mRNA vaccine, the T cells in some patients with pancreatic cancer were activated for up to 3 years, and the immune response induced by the vaccine was linked to a decreased risk of recurrence. Various treatment options for PDAC have shown limited efficacy and high recurrence rates, attributed to low mutation rates in PDAC, which lead to few neoantigens and weak antigenicity. However, recent evidence suggests that a majority of PDAC cases contain more neoantigens than predicted previously. Therefore, the strategy of delivering neoantigens to patients may stimulate neoantigen-specific T cells, thereby improving treatment outcome.

Adjuvant

The capacity of formulations based on NPs to co-deliver immunostimulatory adjuvants and antigenic components is another benefit [26]. This is crucial for appropriate immune activation given the spatial co-localization of the adjuvant and antigen to ensure uniform distribution to immune cells; overall, nanovaccine capacity facilitates a prompt and complete stimulation of antigen-specific immunity [79, 80]. By decreasing antigen dosages, shortening vaccination intervals, and boosting vaccine responses, adjuvants can influence the quantitative immune response [81]. Adjuvants achieve excellent immune-active effects by influencing antigen storage, presentation, and targeting, as well as the internalization of antigens into DCs and regulation of immune pathways [82, 83]. Historically, on the basis of oil emulsions or aluminum salts (alum), adjuvants that have been encapsulated in the NP core or NPs themselves can possess inherent stimulatory properties (self-adjuvanting) [29]. For instance, alum, a common adjuvant, relies on the injection site catalyzing inflammatory cell death and the generation of inflammatory cytokines in draining LNs for immune activation [84].

Adjuvants are typically classified as immunomodulatory agents and delivery systems. Immunostimulatory

adjuvants include ligands for natural or synthetic pattern recognition receptor (PRR) agonists, cytokines, and natural polysaccharides. A majority of immunostimulatory adjuvants target PRRs, namely, nucleotide oligomerization domain-like receptors, retinoic acid-inducible gene-like receptors, C-type lectin receptors, cytosolic DNA receptors, scavenger receptors [85], and ligands for TLRs [29]. TLR ligands include cytosine–phosphate–guanosine oligonucleotides (CpG), poly (I: C) (TLR3 ligand), and stimulators of interferon gene (STING) agonists [86].

Owing to their capacity to transfer antigens into the cytosol, nanovaccines based on fluoropolymer have notably exhibited more efficacy in inducing anti-tumor immune responses when compared with that of vaccines employing traditional immune adjuvants, such as alum and CpG, facilitating antigen cross-presentation [66]. Overall, immune activation, DC maturation, and tumor antigen release are all increased by the application of adjuvants that function as immune promoters.

An effective adjuvant should meet the following criteria: high chemical purity, clear configuration, no induction of autoimmune responses, ability to activate vaccines, and promote strong humoral and T-cell immune responses [87]. The adjuvant should be suitable for classification as a supplementary vaccine, enhancing immune memory or long-term immunity while remaining stable under varying conditions of time, storage, temperature, and pH [88]. Additionally, the adjuvant should be biocompatible, biodegradable, safe, sterile, cost-effective, and easy to handle and store [89].

The selection of vaccine adjuvants, in addition to meeting basic standards, must primarily consider their effectiveness, specifically their ability to work in conjunction with the vaccine to achieve the optimal anti-tumor efficacy and therapeutic outcomes [69]. To further improve the efficiency of tumor antigen cross-presentation and T lymphocyte activation and enhance the anti-tumor effects of nanovaccines, researchers are continuously developing new tumor vaccine adjuvants. For instance, the use of freely soluble STING agonists as immune adjuvants in tumor vaccine design presents challenges such as poor delivery efficiency to lymphoid organs and an inability to enhance the cytoplasmic release of antigens. These issues lead to suboptimal clinical efficacy for physically mixed formulations of tumor antigens and immune adjuvants. In response to these challenges, Chen et al. developed a novel ionizable iron nanoadjuvant library, which specifically amplifies the activation of STING signals in draining LNs, providing a new strategy for personalized tumor vaccine therapy [39].

Superior circulation life

One of the main advantages of NP-based vaccines is their ability to safeguard the bioactivity of payloads that are enclosed. This outcome is important because of the bodily presence of several different types of enzymes that can degrade bioactive cargo and biomolecules in the circulatory system. Neoantigens and antigen peptides can be conjugated to a nanocarrier to encapsulate them, protecting the bioactivity and materials of the encapsulated payloads from host interactions during delivery [90]. To increase the circulation of NPs, bioactive nanovaccines, for example, are coated with a polyethylene glycol (PEG) shell, which may be shed in response to a TME that is slightly acidic [91].

Specific targeting abilities

NP uptake may be induced specifically and efficiently through the active targeting of particular cell types and introduction of functional surface ligands, which is an effective strategy for improving vaccine efficacy [65]. Tumor cell-targeting moieties on the NP surface include antibodies, carbohydrates, peptides, integrin ligands, glucose, transferrin 3, folic acid, and other ligands [23]. Advancements in technology have led to the incorporation of multiple targeting modalities into a single NP, further enhancing their targeting abilities [65].

In the LNs and peripheral tissues, including skin and muscle, an abundance of immature DCs exists. MHC II accumulates in endosomes for antigen presentation, whereas MHC II and CD86 are both expressed at low levels by immature DCs in LNs. Such DCs are still able to present and absorb antigens, react to antigens in LNs, and mature in the field. DCs that dwell in the LNs are potential targets for vaccines. Additionally, these vaccines can provide anti-tumor immunological responses when adjuvants and antigens are administered to LNs. To induce DC maturity and migration to the draining LNs, where DCs can interact with and stimulate T cell response, biomimetic NPs, for example, target peripheral immature DCs through biomolecules [92]. The advantages of existing cancer vaccination therapies have been hampered severely by the inadequate activation of the innate immune system in APCs and poor cytosolic transport of tumor antigens. Additionally, effective cytosolic delivery may be improved by designing NPs, potentially and significantly enhancing vaccine efficacy [39]. Robust anti-tumor responses in this phase depend on DCs delivering antigens cytosolically and cross-presenting them through the MHC I antigen-presenting pathway [66]. Conversely, the delivery of specific antigenic material into the cytosol circumvents endogenous cross-presentation systems and facilitates CD8 + T-cell activation.

Nanovaccines can also target specific organs, tissues [93], or cell types [94]. The surface protein corona and polymer composition, along with their organ-specific affinity, are important determinants of the in vivo destiny of polymersomes. For example, in mouse models of melanoma, acute myeloid leukemia, and melanoma lung metastasis, the spleen-targeted polymersome PH9-Aln-8020 has been employed as a systemic nanocarrier to co-deliver adjuvants and antigens, greatly increasing splenic immune responses [95].

Overall, NPs increase the cross-presentation, immunogenicity, and protection of antigens, as well as improve cellular and metastatic targeting abilities while enabling the controlled release of payloads. Such a multifaceted approach provides a robust platform for cancer vaccines to bolster systemic immune responses and reduce side effects, aiding in the development of more specialized medicines, including multidrug treatments. Overall, the enhancement of the local activity and specificity of NP delivery systems can improve the efficacy of precision medicine treatments, expanding their benefits to a wider population and ultimately improving overall patient outcomes.

Nanovaccine designs aimed toward overcoming metastasis

The use of NPs in personalized medicine is intended to harness detailed genomic information about the patient, account for existing comorbidities, and consider environmental exposures. These insights are then channeled toward the development of customized treatment. This approach aims to enhance drug specificity and optimize dosing, ensuring the accurate delivery of therapeutic agents to specific sites within the body. Conventional tumor therapeutic strategies host several limitations, whereas personalized nanoplatforms ensure the precise treatment of the metastatic cascade.

To develop precise anti-metastasis nanovaccines, selecting suitable NP platforms tailored to specific needs is crucial. Here, we present a summary of the main characteristics, nanostructural aspects, and therapeutic and diagnostic benefits of several NP platforms that show promise for facilitating the development of anti-metastasis nanovaccines (Fig. 4, Table 1).

Synthetic NANOCARRIERS

Organic NP platforms

Dendrimers: Dendrimers are intricate, highly branched polymers known for their dense molecular architecture and a multitude of functional end groups. They are composed of a central core molecule that gives rise to several branches, forming a distinct and hierarchical architecture [96–98]. These branches comprise monomers or repetitive units joined chemically in a controlled manner. Combining hydrophilic and hydrophobic medications, contrast agents, antibodies, peptides, and genes can be administered with dendrimers via physical encapsulation or environmentally responsive chemical bonding (Table 1). This facilitates efficient delivery to tumor sites, leveraging high permeability, prolonged retention, or targeted delivery factors. Finally, drug release is achieved through carrier swelling or the cleavage of sensitive chemical bonds. The inherent flexibility of dendrimers allows for the development of molecular vaccines that exhibit extreme specificity and predictability. Additionally, the immune-stimulating (adjuvant) qualities of dendrimers highlight their use as potential substrates for various medicinal applications, including vaccine development.

Symmetrically branching dendrimers and asymmetrical MAP systems have been studied and developed in the context of their usage as vaccinations [99]. For example, polyamidoamine dendrimer modified with guanidinobenzoic acid was found by Xu et al. to be an efficient protein carrier, facilitating the delivery of protein antigens and the efficient presentation of antigens (i.e., by DCs) for cross-presentation [100]. By applying GD2 or GD3 glycomimetic analogs to a dendrimer core, Tong et al. created a synthetic vaccine that stimulates specific humoral and cellular responses. This vaccine was shown to be effective against several malignancies that express GD2 or GD3 [101]. Furthermore, a programmed cell death ligand 1 (PD-L1) antibody-conjugated PAMAM dendrimer nanosystem has been applied toward the enhancement of PD-1/PD-L1 pathway-based immunotherapy, effectively preventing breast cancer (BC) [102].

Micelles: Micelles are self-assembled aggregates of surfactants or amphiphilic polymer molecules that are driven by thermodynamic forces. Consequently, micelles have a relatively sizable hydrophobic core, which aids in the encapsulation and transport of hydrophobic drugs (Table 1) [103–105]. Micelle-based delivery systems are remarkably versatile in their ability to carry various payloads, including DNA, proteins, peptides, medicines, and small interfering RNA (siRNA) [106–108].

A recent study demonstrated the use of a polyethyleneimine-based self-assembled polymeric micelle delivery system for the injection of mRNA vaccines [109]. Additionally, through the targeted delivery of immune-stimulating chemicals and tumor antigens, micelles hold promise to boost the effectiveness of cancer vaccines and to provoke robust immune reactions against tumors. Moreover, Ren et al. described a method formulated from block copolymers that have been chemically tailored with a hydrophobic, self-degradable linkage for delivering short peptide antigens to DCs. Following alteration,

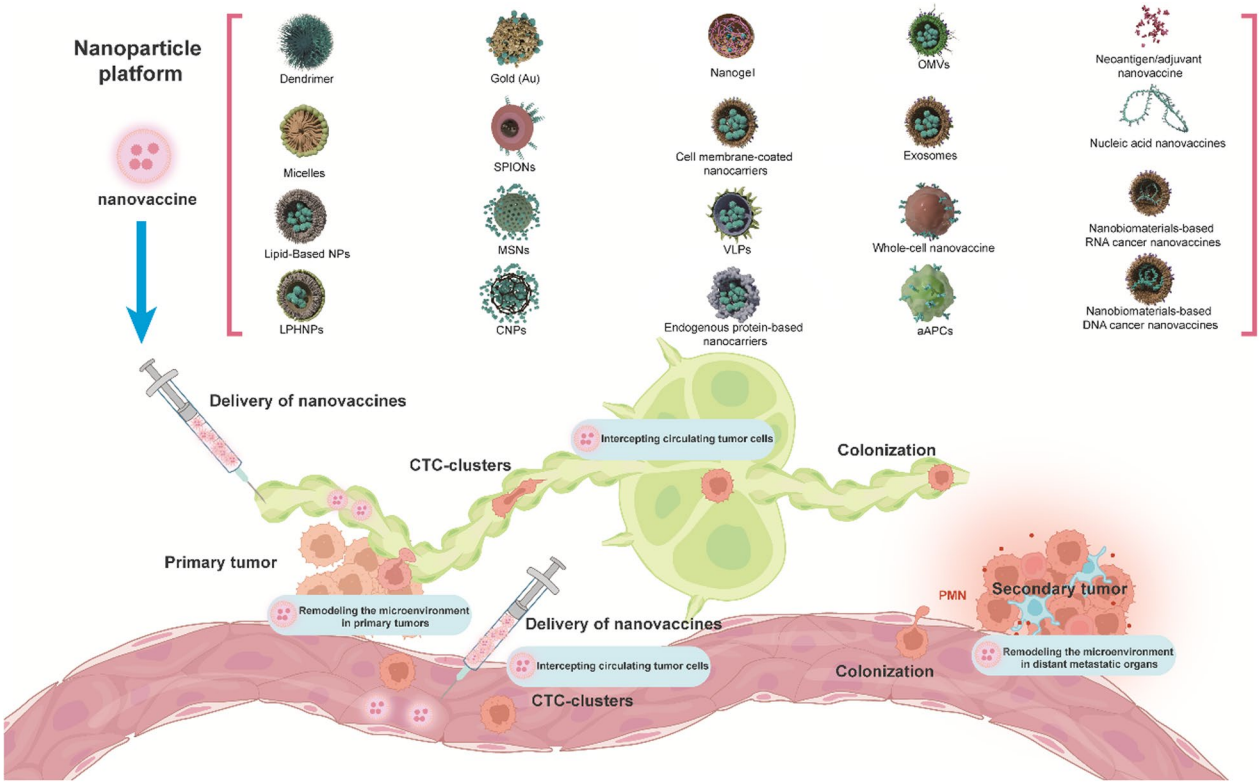

Fig. 4 Halting and counteracting cancer metastasis through nanovaccines. Summary of promising NP platforms for the development of anti-metastasis nanovaccines, including organic, inorganic, semi-biogenic, and biogenic nanocarriers. Targeting the entire metastatic cascade, multiple individual anti-metastasis approaches have been created using multiple phase-specific nanovaccines. These vaccines target and remodel the microenvironment in primary tumors, as well as intercepting circulating tumor cells and remodeling the microenvironment in distant metastatic organs

the micelles rapidly and efficiently bonded with the adjuvants and antigens in an aqueous solution through covalent bonds. Intracellular glutathione cleaved the polymer disulfide bond upon uptake by APCs, resulting in the release of pristine antigens and the increased expression of co-stimulatory molecules. In human papilloma virus, E6/E7 subcutaneous, and lung metastatic tumor models and murine B16OVA tumor models, the generated antigen-specific $CD8^+$ T lymphocytes demonstrated potent tumor cell-killing effectiveness. Overall, vaccine trafficking can be observed by delivering vaccines to LNs [110].

Lipid-based NPs: Liposomes are a type of spherical, self-enclosing vesicles that possess an aqueous core surrounded by a lipid bilayer membrane. The distinctive architecture of liposomes allows for the simultaneous encapsulation and delivery of agents of varying sizes, particularly hydrophilic and hydrophobic drugs, which are enclosed within the core and the shell, respectively (Table 1) [111]. Myocet (liposomal doxorubicin) is an excellent example of such an NP, which, when used in combination with cyclophosphamide, has received clearance for addressing the treatment of metastatic BC in Europe and Canada [112]. Another example is Vyxeos (liposomal daunorubicin and cytarabine), which was designed to treat acute myeloid leukemia and is available in Europe and the US [113]. Moreover, liposomes exhibit significant flexibility and deformability, allowing them to permeate the barrier of stacked corneocytes, which can be 10–20-mm thick [111].

Despite advancements in vaccine adjuvants, the development of suitable vaccinations for cancer treatment remains a challenge. Owing to their versatility, liposomes have been demonstrated to be highly effective as adjuvants and delivery systems. Additionally, they are expected to find expanded applications in this context. Notably, LNP technology facilitated mRNA vaccines in combating the SARS-CoV-2 epidemic [114]. However, in the context of cancer treatment, its application warrants further exploration. AS015, a liposomal adjuvant produced by GSK, has been used as an adjuvant for MAGE-A3-positive melanoma immunotherapy [115]. Arabi et al. reported a novel cancer vaccination approach using C3 liposomes to deliver the MUC1 antigen and immunostimulatory compounds to

Table 1 Nanoparticle platforms beneficial for nanovaccine construction

Classifications	Sub-classification	Nanoplatforms	Material properties	Advantages	Disadvantages	Refs.
Synthetic nanocarriers	Organic nanoparticle platform Inorganic nanocarriers	Dendrimer	High surface area; small nano-size, controllable biodegradation; functionally integratable	High payloads of drugs and imaging agents; controlled drug release	Difficult to purify or low yield	[96]
		Micelles	Biodegradable; functionally integratable	Multidrug co-loading and co-delivery; controlled drug release	Poor stability	[103]
		Lipid-based NPs	Biocompatibility; stability; small nano-size; surface charge	Enhanced cellular uptake of vaccine components; stimulating innate immune responses; versatility; ease of manufacturing	Biological barriers; potential toxicity; immunogenicity; limited payload capacity	[111]
		Lipid–polymer hybrid nanoparticles	Structural stability; tunable size and surface characteristics; payload flexibility; biocompatibility; sustained-release; protection of payload	Enhanced cellular uptake of vaccine components; Modulation of immune responses; improved stability and shelf Life; customizable formulations; potential for co-delivery; versatility in antigen presentation	Complex formulation and manufacturing; potential toxicity; immune recognition and clearance; storage and stability concerns; limited payload capacity; cost-effectiveness and widespread accessibility of vaccines	[120]
		Nanogel	Surface functionalization; charge and zeta potential; softness and flexibility; long-term stability in suspension; controlled degradation	Encapsulation capability; non-toxicity; low immunogenicity; efficient cellular uptake; pH or enzyme-sensitive release; protection of antigens; enhanced circulation time; enhanced immune activation; surface functionalization; safety profile; controlled release	Complex production processes; batch variability; unintended immune responses; clearance by the immune system; limited penetration in solid tumors	[125]
		RNA nanovaccines	RNA as a template; nanoparticle formulation; nucleotide sequence variability;	Innate immune stimulation; rapid development; customizable antigens; adaptability to variants; reduced production time; no risk of integration into host genome	Stability challenges; cold chain requirements; potential side effects; limited long-term stability	[139]
		DNA nanovaccines	DNA as a genetic template; nanoparticle formulation; customizable antigens; innate immune stimulation	Rapid development; adaptability to variants; customizable genetic information; no cold chain requirements; safety profile	Limited transfection efficiency; risk of genomic integration; immune tolerance;	[144]

Table 1 (continued)

Classifications	Sub-classification	Nanoplatforms	Material properties	Advantages	Disadvantages	Refs.
		Gold (Au)	Biochemically insert; structurally expandable; functionally integratable	NIR-photothermal therapy; drug delivery, controlled release; NIR-photothermal imaging; NIR-photoacoustic imaging;CT imaging; two-photon luminescence imaging; optical coherence tomography imaging	Biocompatibility and toxicity; biodegradability; immunogenicity; synthesis complexity; cost; limited payload capacity	[151]
		Superparamagnetic iron oxide nanoparticles (SPIONs)	Magnetic properties; biocompatibility; size tunability; surface functionalization; stability	Targeted delivery; enhanced cellular uptake; imaging capabilities; theranostic potential; prolonged antigen presentation; heat generation for hyperthermia; reduced dose requirements	Potential toxicity; immunogenicity; biodistribution and clearance; risk of aggregation; synthesis complexity; potential for oxidative stress; cost	[165]
		Mesoporous silica (or silicon) nanoparticles (MSNs)	Porosity and surface area; tunable pore size; biocompatibility; surface functionalization; stability	High loading capacity; controlled release; enhanced stability of payload; customizable surface; biodegradability; adjuvant delivery	Potential toxicity; immunogenicity; synthesis complexity; cost	[170]
		Carbon nanoparticles	Versatility; high surface area; electrical conductivity; biocompatibility; tailorable surface chemistry	High payload capacity; stimulatory effects; stability; customizable surface; ease of functionalization	Potential toxicity; immunogenicity; biodistribution concerns; synthesis complexity;	[178]
	Organic–inorganic hybrid NPs	Combine organic and inorganic NPs	Core–shell or composite structures; shape diversity; enhanced surface-to-volume ratio; tailorable chemical composition	Efficient encapsulation and protection of antigens; controlled release; targeted delivery to immune cells; simultaneous delivery of adjuvants; optimizable size for immune activation; surface functionalization; immunostimulatory properties	Complexity of design; batch-to-batch variability; inorganic component toxicity; clearance issues; unintended immune responses	[180]
Semi-biogenic nanocarriers	–	Cell membrane-coated nanocarriers	Cell membrane composition; nanocarrier core	Biocompatibility; mimicking native cell properties; enhanced targeting and homing; reduced immunogenicity; stability and stealth properties; potential for immune modulation	Complexity of production; limited cargo capacity; batch-to-batch variability; biodegradability	[185]

Table 1 (continued)

Classifications	Sub-classification	Nanoplatforms	Material properties	Advantages	Disadvantages	Refs.
		Virus-like particles	Protein composition; no genetic material	Safer than live vaccines; mimicry of viral structure; effective antigen presentation; broad applicability; induction of both humoral and cellular immunity; stability	Complex manufacturing process; potential batch-to-batch variability; limited induction of mucosal immunity; may require booster shots:	[188]
		Endogenous protein-based nanocarriers	Protein composition; structural stability:	Biocompatibility; reduced immunogenicity; native antigen presentation; diverse protein options; potential for multifunctionality; versatility	Potential for immune responses; Complexity of production; batch-to-batch variability; limited payload capacity;	[190]
Biogenic nanosystems	–	Exosome	Lipid bilayer composition; nanometer size; surface proteins; endogenous origin	Biocompatibility and rare immunogenicity; cellular targeting; antigen presentation; cargo diversity	Heterogeneity; limited payload capacity; biodistribution and clearance; immunosuppressive properties	[301]
		Outer membrane vesicles	Lipid bilayer structure; protein composition; nanometer size	Antigen presentation; bacterial membrane mimicry; stimulate both innate and adaptive immunity; bacterial source variety	Potential reactogenicity; heterogeneity; limited payload capacity; limited efficacy against intracellular pathogens	[302]
		Whole-cell nanovaccine	Cellular structure; diversity of antigens; nanometer size	Broad antigen presentation; cross-reactivity; adjuvant effects; memory immune responses; simplified formulation	Potential reactogenicity; risk of autoimmunity; limited control over antigen composition; risk of infection	[303]
		Artificial antigen-presenting cells	Polymeric or nanoparticle structure; surface modifications; incorporation of antigens and signaling molecules	Enhanced antigen presentation; customizable design; consistent antigen presentation; tunable immune response; inclusion of co-stimulatory signals; induction of memory responses	Biocompatibility and safety concerns; complex production processes; limited understanding of immune interactions; risk of immunogenicity	[304]
		Neoantigen/adjuvant nanovaccine	Nanoscale size; patient's cancer mutations; nature of adjuvants; biodegradability;	Personalized approach; induction of robust immunity; reduced toxicity; memory Immune responses; versatility	Complex production; heterogeneity; limited availability of neoantigens; tumor escape mutations; immune suppression in the tumor microenvironment	[131]

APCs. Their findings demonstrate enhanced immune responses to MUC1, particularly when combined with TLR agonists, suggesting the feasibility of antigen-specific cancer immunotherapy [116].

Lipid–Polymer Hybrid NPs: Polymeric (such as dendrimers and micelles) and LNPs for the delivery of anti-cancer agents, especially in the field of cancer vaccines, have specific advantages associated with their use, as previously discussed. Lipid–polymer hybrid NPs (LPHNPs) consist of three primary components: a hydrophilic polymeric shell on the outside, a central lipid layer, and an interior polymer core [117]. Treatments and antigens, such as nucleic acids or peptides, could be effectively enclosed within a polymer core. The central lipid layer serves as a protective barrier during preparation, preventing the leakage of chemicals. It functions as a molecular fence, restricting the inward flow of water and preventing the breakdown of the polymer, thereby enabling the continuous release of the encapsulated substance [118]. The external hydrophilic polymeric shell typically consists of PEG, which enhances steric stability, and extends the in vivo half-life of the LNPs, thus facilitating their ability to target specific ligands [119]. Furthermore, LPHNPs demonstrate higher in vivo cellular delivery effectiveness than NPs and liposomes. Designed to offer stability, high cargo loading, enhanced biocompatibility and medication half-life, rate-limiting controlled release, and therapeutic effectiveness while minimizing drawbacks, LPHNPs offer a promising approach for cancer therapy [120].

The use of CD44-targeting LPHNPs for the delivery of vaccines within tumors has been explored extensively. One example is the development of the CD44-targeting DOTAP-poly (lactic-co-glycolic acid) (PLGA) nanovaccine, which aims to elicit a robust immunological response primarily through cell-mediated mechanisms. However, the approach has been associated with significant cytotoxicity, raising concerns about its safety profile. Additionally, this particle formulation has been linked to a site-specific OVA antigen release of 80%. LPHNPs coated with hyaluronic acid have been shown to facilitate the controlled release of both drugs and antigens from NPs [121, 122]. Zhu et al. designed mannose-functionalized lipid-hybrid polymersomes (MAN-IMO-PS) for the co-delivery of the OVA antigen both inside and outside the lipid layer. These polymersomes encapsulate the TLR7/8 agonist imiquimod within the hydrophobic membrane, while the TLR4 agonist monophosphoryl lipid A is incorporated into the lipid layer. The objective of this adaptable nanovaccine was to enhance vaccination efficacy by concurrently triggering immunological responses. Upon effective internalization by DCs through TLR4 ligation and mannose targeting, MAN-IMO-PS markedly increased cytokine production and cross-presentation [123].

Nanogel: As reported by Soni et al. [124], nanogels (NGs) are three-dimensional nanoscale hydrogel materials that consist of cross-linked swellable polymer networks capable of retaining a significant amount of water without dissolving in the aqueous environment. The gel-like properties of NGs enable them to swell when exposed to physiological fluids. This characteristic provides flexibility, enabling them to closely approach the target site and improve the dispersion of pharmaceuticals and other healing substances. Furthermore, NGs can be designed to release drugs in response to specific physiological conditions [125]. NG-based cancer vaccines have shown great potential as customizable immune carriers. They improve the pharmacokinetics of antigens and adjuvants, as well as provide a larger surface area, enhancing antigen interaction with APCs and enabling the introduction of other immunomodulatory signals to enhance immune system reaction. NG-based vaccines have shown positive results in clinical and animal studies. Personalized cancer vaccines based on NGs are highly promising for inducing strong and lasting anti-tumor responses in cancer immunotherapy.

NG and nanocomplex formulations have been used as cancer vaccine platforms. Researchers have engineered a versatile nanogel-based vaccine designed to provoke a strong and enduring immune reaction. They have integrated CCL21a with ExoGM-CSF + Ce6 (which are tumor cell-derived exosomes loaded with GM-CSF mRNA and featuring the sonosensitizer chlorin e6 [Ce6]. on their exterior) and then combined this with nanoclay and gelatin methacryloyl to create a hydrogel known as CCL21a/ExoGM-CSF + Ce6 @nanoGel. With these dual programmed components, the innovative modular nanogel vaccine effectively suppresses tumor progression and spread by redirecting metastatic cancer cells from the tumor-draining lymph nodes (TdLN) to the nanogel, neutralizing the entrapped tumor cells and triggering a long-lasting and potent immunotherapeutic response in a synchronized fashion [126].

A self-immolative NG vaccine has been designed for traceless intracellular release and subsequent immune system activation. This NG is constructed from three cytosine-rich oligonucleotide building blocks that self-assemble into a precisely sized NG scaffold. Concurrently, the acid-labile linkers undergo hydrolytic cleavage, liberating the conjugated agonists and antigenic peptides in their native, unmodified forms [127].

An NP complex consisting of cholesteryl pullulan and the NY-ESO-1 antigen protein (CHP-NY-ESO-1) exhibits multiple epitope peptides to both MHC class I

and II pathways, which triggers responses in $CD8^+$ and $CD4^+$ T cells. Takeshi et al. carried out a phase 1 clinical trial involving the administration of CHP-NY-ESO-1 (a cancer vaccine) alongside poly-ICLC (an immune-stimulating adjuvant for the vaccine) to patients suffering from advanced or recurrent esophageal cancer. The trial resulted in all participants (100%) developing antibody responses after a median of 2.5 vaccine doses [128].

Neoantigen/Adjuvant Nanovaccines: Neoantigens are unique proteins or peptides resulting from non-synonymous gene mutations in tumor cells that offer distinct antigenic properties and high reactivity to the immune system [129]. Owing to their specificity, potential for personalization, and immune responsiveness, neoantigens have emerged as crucial targets in tumor immunotherapies, especially in therapeutic vaccines [130]. Tumor neoantigens are effective at activating a patient's immune system and eliciting anti-tumor immune responses [130, 131]. Such advantages encompass the enhancement of antigen stability, precise targeting of LNs, and facilitation of APC uptake, alongside facilitating lysosome elude and cross-presentation of antigens. The transportation of substances such as PLGA, aluminum NPs, or mesoporous silicon vectors can enhance the immunogenicity of neoantigen peptides significantly [132–135].

Nucleic Acid Nanovaccines:Over the last 10 years, vaccines based on nucleic acids have emerged as promising contenders to conventional subunit vaccines and those derived from live or attenuated viruses. Vaccines based on nucleic acids have several advantages, including being simple to manufacture, safe, and adaptable, and having the capacity to provoke both antibody-mediated and cell-mediated immune reactions [136, 137]. Despite such benefits, developing nucleic acid-based cancer immunotherapy vaccines has encountered several challenges. However, advancements in cancer nanovaccine technology utilizing nanobiomaterials provide viable approaches for enhancing the efficacy of nucleic acid treatments.

Nanobiomaterial-based RNA Cancer Nanovaccines: Nanobiomaterials play a dual role in RNA cancer nanovaccines by serving as gene carriers for tumor antigen expression and as immune adjuvants that activate APCs through interactions with PRRs [138, 139]. In recent years, advancements have been made in RNA cancer nanovaccines utilizing nanobiomaterials, which have shown promise as replacements for conventional immunizations. These improvements are credited to their capacity to protect RNA molecules against degradation by ribonucleases, diminish the immunogenicity of RNA, and enhance RNA transport into APCs for antigen production [140–142]. For instance, Zhang et al. have engineered a biomimetic nanovaccine edited with long noncoding RNA in combination with anti-TIM-3 to bolster immune checkpoint blockade (ICB) immunotherapy. This approach facilitated simultaneous enhancement of antigen cross-presentation and alleviation of T-cell suppression, thereby strengthening treatment efficacy [143].

Nanobiomaterial-based DNA Cancer Nanovaccines: DNA vaccines utilize plasmid DNA-encoding antigen sequences, which are injected into the body and are often combined with electroporation and transduction. Cells at the site of injection are incorporated into the nucleus, where the antigen is translated and then recognized by the body to mount an immune reaction. However, the method has drawbacks, including low efficiency and a risk of mutation due to DNA insertion. In contrast, mRNA vaccines do not need to enter cells; however, mRNA is not stable and is degraded easily, requiring more effective preparation and storage methods.

Third-generation DNA vaccines comprise closed circular DNA plasmids housing antigen-coding sequences and immunomodulatory molecules. These plasmids prompt transfected cells to produce the desired antigens, thus triggering immune responses [144]. DNA vaccines offer numerous advantages, such as being easy to produce, safe, stable at room temperature for transport, and cost-effective, in addition to exhibiting reduced risk of hypersensitivity reactions and replication interference. Furthermore, they provide an opportunity to immunize against multiple pathogens using a single vaccine [28].

Inorganic NPs

Gold: Gold NPs (AuNPs) possess two highly appealing characteristics for application in biomedicine. First, they offer multivalent surface coordination, allowing for simple surface conjugation using amines, carboxylates, and thiolates with medications and target compounds. This synchronization has been shown to facilitate accurate drug delivery and regulated drug release [145–148]. Second, photothermal treatment (PTT) effectively leverages the surface plasmon resonance phenomenon of AuNPs. By adjusting the surfaces, sizes, and shapes of these NPs, the plasmon absorption wavelengths could be adjusted to target the near-infrared (NIR) spectrum, increasing their suitability for NIR-PTT applications.

AuNPs, which are biocompatible and straightforward to produce, represent an alternative type of nanocarrier for vaccine delivery. Using seed-mediated growth techniques, AuNPs can be manufactured in various sizes (i.e., 1–150 nm) and shapes (i.e., spheres, rods, and cubes). Moreover, the surface of AuNPs can be chemically bound to stabilizers (i.e., surfactants) or absorbed, allowing for additional surface modifications with ligands or other compounds [149]. Notably, the size and structure of

AuNPs affect the generation of antibodies and the release of cytokines, among other immune responses [150–152].

For instance, Cai et al. developed an innovative composite material consisting of Fe_3O_4 supported by gold nanoparticles derived from biogenic lignin to evaluate its effectiveness against human lung cancer. This material was also studied in its role in the catalytic reduction of aromatic nitro compounds [153]. In contrast, Zhang et al. used human serum albumin (HSA@AuNPs) to establish a self-generated AuNP template. Specifically, peptides were administered via HSA@AuNPs, thereby enhancing the immune response and integrated PTT using immunotherapy. Furthermore, under NIR irradiation, studies performed both in vitro and in vivo have demonstrated that nanoparticles can facilitate the conversion of light into heat, resulting in tumor ablation and boosting antitumor immunity. In conclusion, such NPs can enhance the product yield, reduce flux, boost interactant transition efficiency, and insulate hazardous agents, all of which lay a foundation for a novel, easy-to-use method for the environmentally sustainable synthesis of nanovaccines [154].

Superparamagnetic Iron Oxide NPs: Iron oxide cores, which make up superparamagnetic iron oxide NPs (SPIONs), can be directed to a specific spot with the use of external magnets. Superparamagnetism, irreversibility in high fields, elevated saturation fields, extra anisotropy contributions, and loops that shift after field cooling are among their fascinating properties [155]. These properties render SPIONs advantageous as a platform for nanomedicine. These benefits include superparamagnetism for magnetic targeting, magnetothermal action for hyperthermia therapy, and good biodegradability (because of their acid-soluble nature) [156–162].

In the context of cancer vaccines, OVA-bound SPIONs (with a size and zeta potential of approximately 200 nm and − 22 mV, respectively) have been reported as effective vaccine delivery platforms and immune potentiators, as evidenced by their ability to induce cytokine production and activate immune cells [163]. Additionally, SPIONs can serve as platforms for the magnetic guidance of immune cells, including T cells, to a target area. Ortega et al. developed SPIONs coated with dextran (6 kDa), 3-aminopropyl-triethoxysilane, or dimercaptosuccinic acid. These SPIONs exhibited a zeta potential and size between − 34 and 38 mV and 82 and 120 nm, respectively. When subjected to an external magnetic field, they aided in the in vivo migration of T cells [164]. Furthermore, because of their adaptability and modular design, SPIONs exhibit extensive multifunctionality. Moreover, they have shown great safety, biocompatibility, and the capacity to transport drugs (i.e., in the context of chemotherapy and immune checkpoint inhibitors) while also possessing magnetic properties that facilitate their application in the context of magnetic hyperthermia and magnetic resonance imaging [165]. Copolymers that are acid-ionizable are combined with SPIONs and MSA-2 to form iron-based nanoadjuvants that stimulate STING activation in the lymph nodes. The top-performing iron nanoadjuvant (PEIM) efficiently delivers the model antigen OVA to $CD169^+$ antigen-presenting cells (APCs) and enhances cross-presentation of the antigen. This leads to a substantial 55-fold enhancement in the frequency of antigen-specific $CD8^+$ cytotoxic T lymphocyte responses compared to the use of soluble antigen alone. Immunization with the PEIM@OVA nanovaccine generates powerful and enduring anti-tumor immunity, preventing the metastasis of lung tumors and eradicating already-established tumors [39].

Mesoporous Silica (or Silicon) NPs: Mesoporous silica (or silicon) NPs (MSNs) are spherical NPs with several pores separated by a solid framework [166]. They offer a range of unique advantages. First, they feature extensive mesoporosity, with adjustable pore sizes (ranging from 2 to 20 nm), allowing for precise control over drug release. Second, a sizable drug payload is made possible by their huge pore capacity and high surface area. Third, the MSNs' particle size could be customized (from 10 to 1000 nm), and it is simple to functionalize their surfaces to enable precise medication distribution. Finally, MSNs possess flexible nanostructures and excellent biocompatibility and biodegradability, as shown in Table 1 [167–170].

H-XL-MSNs, created by coating poly(ethyleneimine) solution-coated core–shell MSNs, exhibit high loading efficiency for proteins and enhanced DC activation. H-XL-MSNs have shown promise as a potential cancer vaccine, resulting in enhanced tumor growth suppression and higher mouse survival rates [171]. Another study investigated employing MSNs with exceptionally large pores (XL-MSNs) to directly activate host DCs for cancer vaccines, thereby circumventing various limitations of current DC-based cancer vaccines. Antigen proteins and TLR 9 agonists can be loaded more efficiently using XL-MSNs, thereby enhancing DC activation and antigen presentation and stimulating antigen-specific CTLs. The high memory T-cell count of the resultant vaccination has demonstrated the ability to curb tumor growth and avert relapses in mouse model [172]. Incorporating photothermal and mildly immunostimulatory porous silicon@Au nanocomposites as the particulate core of a biomimetic nanovaccine boosts its biosafety and therapeutic efficacy in immunotherapy against solid tumors. This innovative nanovaccine, serving as a PTT agent, when combined with other immunotherapies, markedly inhibits the expansion and metastasis of established

solid tumors by provoking anti-tumor immune reactions and counteracting their suppressive microenvironments [173].

Many treatment combinations are being considered for boosting the effectiveness of cancer immunotherapy. Specifically, immune checkpoint inhibitors and TME reprogramming, such as M2-to-M1-like macrophage restoring the polarity of tumor-associated macrophages, show promise in enhancing the effectiveness of approved immunotherapies.

Carbon NPs: Carbon NPs (CNPs), which include carbon dots, mesoporous CNPs, nanographene oxide, and carbon nanotubes, all provide two unique benefits in nanomedicine: [1]. Outstanding surface area: these NPs provide an exceptionally high surface area, facilitating the efficient delivery of drugs and therapeutics [2]. Effective absorption of NIR light: CNPs exhibit efficient NIR optical absorption capabilities, making them suitable for imaging and NIR-PTT. This allows low-energy NIR lasers to generate substantial thermal energy because of their high photothermal conversion efficiencies [174–177]. The unique molecular structure of CNPs, characterized by alternating polycyclic aromatic hydrocarbons with only six-membered carbon rings, enables carbon nanotubes and nanographene oxide to absorb significant amounts of several photosensitizers, including doxorubicin, CPT, and porphyrins, as well as aromatic molecular medications. This is achieved through non-covalent π–π stacking interactions, resulting in an exceptional drug-loading capacity [178].

Wang et al. created novel oral vaccine adjuvants using hydrophobic CNPs (C1) with silica and sucrose. Characterized by their size (470 nm) and large mesopores and macropores [40–60 nm), these adjuvants are highly suitable for carrying antigens. For example, eliciting a potent mucosal immune response, observed in intestinal, salivary, and vaginal secretions, was demonstrated via an immunoglobulin G titer to reach levels comparable to those following oral immunization, after the injection of an antigen mixed with Freund's complete adjuvant with bovine serum albumin loaded in C1. Moreover, it induced both Th1- and Th2-mediated responses, indicating its potential utility in vaccine adjuvant design to enhance immune modulation [179].

Organic–inorganic Hybrid NPs

Organic–inorganic hybrid NPs take advantage of the structural stability and versatile functionalities of inorganic materials while incorporating the flexibility and tunability of organic components, creating systems with enhanced performance compared to their purely organic or inorganic counterparts [180]. Considering properties, these NPs are gaining popularity in the development of cancer vaccines, acting as platforms for delivery of antigens or adjuvants to provoke strong immune reactions.

A recent study [181] reported an organic–inorganic hybrid NP-based in situ cancer vaccine, which achieved outstanding cancer immunotherapy by simultaneously neutralizing reactive oxygen species and triggering the STING pathway in DCs. This vaccine triggers the STING signaling pathway via the combined action of Mn2 + and SN38, while also neutralizing existing H_2O_2 in the TME and Mn^{2+}-catalyzed hydroxyl radicals (•OH) through the antioxidant properties of diselenide and polyphenol. This strategy effectively activates dendritic cells (DCs), shields them from oxidative stress, and subsequently leads to significant activation of downstream T-cells and the establishment of systemic anti-tumor immunity.

Chen et al. [182] designed organic–inorganic hybrid hollow MSNs as a vaccine delivery platform, incorporating dopamine surface modification to enhance the ability to regulate biodegradation and drug delivery. The molecular backbone, featuring disulfide bonds, enabled stepwise degradation within the reductive TME. The organic–inorganic hybrid hollow MSNs exhibited an effective sustained-release profile, significantly suppressed tumor cell proliferation, and achieved notable anti-tumor effects in vivo via dual-reaction release mechanisms triggered by the TME. Zhuang et al. [183] engineered lipid-enveloped zinc phosphate hybrid nanoparticles to encapsulate peptides (TRP2180-188/HGP10025-33) along with toll-like receptor 4 agonists. The lipid-coated zinc phosphate hybrid NP vaccine, measuring 30 nm with an outer lipid layer, demonstrated anti-tumor immunity by boosting the secretion of cytokines and enhancing the $CD8^+$ T-cell response in vitro. The vaccine's anti-tumor efficacy was confirmed further through its performance in prophylactic, therapeutic, and metastatic melanoma tumor models, outperforming both free antigens and single peptide-loaded nanovaccines.

Semi-biogenic nanocarriers

Semi-synthetic nanocarriers partially blend biogenic and synthetic components. When designed effectively, these semi-synthetic nanocarriers can inherit certain attributes of biogenic nanocarriers, including biocompatibility and minimal toxicity. Simultaneously, they can incorporate the capabilities of synthetic NPs, such as their ability to be readily and consistently manufactured on a large scale. Within this context, we will explore three categories of semi-synthetic nanocarriers, concentrating particularly on nanocarriers derived from endogenous protein, VLPs, and nanocarriers coated with cell membranes.

Cell Membrane-coated nanocarriers

Cell membrane-coated nanocarriers consist of a synthetic core, typically composed of inorganic or organic materials enveloped within a natural cell membrane. This design combines elements of artificial synthesis and biological origin, hence earning the description "semi-biogenic." Recently, these nanocarriers, which mimic the properties of cell membranes, have emerged as promising platforms for medication delivery [184, 185]. The process involves extracting desired cell membranes, which are then used to coat NP surfaces or construct nanocarriers. Notably, the potential for cancer nanovaccines is rooted in the ability of NPs (i.e., coated with cancer cell membranes) to encapsulate a broad spectrum of antigens from cancer cell membranes. Furthermore, a strong anticancer immune response that resembles the reactions observed during bacterial infections could be triggered by blending an adjuvant with cell membrane antigens and specific ligands. Nanovaccines based on cell membrane camouflage exhibit significant therapeutic applicability; this outcome can be attributed to the fact that these vaccines are based on the use of the cancer cells of an individual patient as a source, simplifying the modification of adjuvants and cell membrane materials.

Fang et al. used the tumor cell line MDA-MB-435, which is known for its homotypic aggregation in vivo, to demonstrate thecancer-homing capabilities of NPs coated with cancer cell membranes. Applying a cell membrane to NPs augmented cellular adherence to the source cells significantly when compared with that of conventional NPs. Reduced particle binding was observed in red blood cell NPs, explained by the increased particle–cell adhesion to the homotypic cell membrane. MDA-MB-435 cancer cell membrane-coated NPs showed a somewhat higher affinity for human foreskin fibroblasts than bare PLGA cores, highlighting the cancer cell specificity of NPs [186]. Taken together, these studies underline the considerable potential of cell membrane-coated NPs in nanovaccines.

ZIF-8 NPs containing epirubicin, glucose oxidase, and hemin were coated with calreticulin produced through tumor cell membrane overexpression to create mEHGZ, a self-amplified biomimetic nanosystem. When this nanosystem was used in conjunction with an anti-PD-L1 antibody, lung metastasis and tumor growth were significantly inhibited [187].

VLPs

VLPs represent another category of semi-synthetic nanocarriers with considerable promise as cancer nanovaccines. VLPs possess a structural resemblance to viruses but do not contain viral genetic material, making them non-contagious. These nanocarriers self-assemble from structural viral proteins expressed in vitro. VLPs are particularly appealing as nanovaccines because of their adaptability to tailored engineering, enabling the precise manipulation of both VLPs and antigens present on their surfaces. Moreover, the design of repetitive antigenic structures in VLPs facilitates efficient immune activation. VLPs are internalized efficiently by APCs, and when engineered with specific antigens, they can initiate enduring adaptive immune responses [188].

S100A9, a notable inflammatory regulator, is essential for the development of polymorphonuclear neutrophil leukocyte (PMNs) in the lungs and plays a role in the advancement and spread of cancer. A vaccine against S100A9 (generated from VLPs) was designed by Chung et al. The vaccine decreased lung tumor nodules drastically following intravenous challenge or post-surgical excision of the main tumor in metastatic mouse models of BC and melanoma. Mechanistically, the vaccinations induced the lungs and sera to contain lower amounts of S100A9. This reduction then drove an increased in the expression of immunostimulatory cytokines, including IL-12 and IFN-γ. The cytokines exhibited anti-tumor properties while simultaneously decreasing levels of immunosuppressive cytokines; this outcome manifested as changes in the levels of TGF-β and IL-10 [189].

Endogenous protein-based nanocarriers

Endogenous protein-based nanocarriers utilize proteins sourced from within an organism, typically synthesized as intracellular or extracellular proteins. The preparation methods for these nanocarriers involve the extraction or synthesis of endogenous proteins from an organism, leveraging their natural biocompatibility and functional properties [190]. The constructed protein–drug nanocomplexes for vaccine delivery tend to be in a size range ideal for promoting effective lymphatic drainage and intracellular absorption. This property is particularly desirable for promoting vaccine delivery to APCs and lymphoid organs. This immunomodulatory effect translates into remarkable therapeutic outcomes in cancer and viral diseases.

Biogenic nanosystems

Nanomaterials derived from diverse biological sources, including cells, are collectively termed biogenic nanocarriers. These carriers are often regarded as inherently "self," exhibiting significant biodegradability, biocompatibility, and minimal toxicity. Biogenic nanocarriers encompass exosomes, outer membrane vesicles (OMVs), whole-cell nanovaccines, artificial APCs (aAPCs), and neoantigen nanovaccines.

Exosomes

Exosomes are naturally occurring NPs. These small membrane vesicles, typically measuring 30–150 nm in size, derive from late endosomes within various cell types and are discharged into the extracellular environment, retaining the properties of the original cells [191, 192]. They are characterized by a cup-shaped structure with a lipid bilayer [192, 193]. Their composition and natural origin render exosomes non-cytotoxic and endow them with a remarkable ability for precise homing to target sites, overcoming biological barriers encountered in vivo—a challenge faced by many exogenous NPs [194]. However, the use of exosomes in cancer vaccines remains challenging. For instance, the production and purification of tumor-derived exosomes in sufficient quantities for clinical use are technically demanding. Furthermore, tumor-derived exosomes can carry immunosuppressive molecules that induce immune tolerance rather than an anti-tumor response.

Researchers isolated DC-derived exosomes (DEX) and engineered them with a hepatocellular carcinoma (HCC)-targeting peptide (P47-P), an α-fetoprotein epitope (AFP212-A2), and a functional domain of high-mobility group nucleosome-binding protein 1 (N1ND-N), which serves as an immunoadjuvant for dendritic cell recruitment and activation. These components were incorporated using an exosomal anchor peptide to create a "trigger" DEX vaccine ($DEX_{P\&A2\&N}$). This engineered DEX vaccine specifically enhanced the recruitment, accumulation, and activation of DCs in mice with orthotopic HCC tumors, leading to improved cross-presentation of tumor neoantigens and a robust de novo T-cell response [195].

Outer membrane vesicles

OMVs are nanostructures that range in size from approximately 20 to 250 nm and originate from the budding or blebbing o shedding of the bacterial cell envelope [196]. These vesicles encapsulate a diverse range of components, yielding complex arrangements of antigenic materials (i.e., proteins that occur in the cytoplasm, inner membrane, and the outer membrane). OMV development is influenced by multiple factors, including the lipid composition of the outer membrane and the presence of envelope-crosslinking proteins. Moreover, factors in the environment like temperature and nutrient accessibility may alter the rate at which OMVs are produced. Although OMVs contain virulence factors, the precise mechanisms governing the selective incorporation of these factors into OMVs remain to be fully elucidated. OMVs function as decoys to evade antibiotics and phages, respond to stress, and scavenge nutrients in bacteria following their release from the bacterial cell membrane.

Whole-cell nanovaccines

The considerable heterogeneity within tumors presents a challenge in utilizing single-antigen immunotherapy for cancer treatment. Vast antigenic variety can lead to immune evasion because tumor cells can continue to grow and multiply even when they express little of the targeted antigen. Moreover, tumors may lose their ability to express immunogenic antigens, rendering CTLs produced by immunization with a single antigen useless [197]. The use of the entire population of cancer cells as a source of antigenic material has been proposed as a viable solution to this challenge [198].

Based on the abovementioned studies, several research teams have combined the benefits of NP delivery systems with the advantages of using tumor cell lysates as antigenic materials. Occasionally, lysate-loaded NPs, either with or without adjuvants, have been used to increase DC uptake and antigen presentation in vitro, especially in cell-based immunotherapies [199–201].

Artificial APCs

To guarantee the development of anti-tumor responses, vaccination techniques that directly deliver tumor antigen materials are employed. Nevertheless, many of these antigens are highly similar to those found in healthy cells and exhibit low immunogenicity. Therefore, it can be challenging to elicit immune responses with adequate strength to inhibit tumor growth. Recent developments in aAPC technology have attempted to avoid the requirement for endogenous antigen presentation instead of depending on the activation of APCs to elicit T-cell education with the appropriate specificities. These synthetic NPs, called aAPCs, are produced to mimic every signal needed to stimulate T cells [202].

aAPCs offer advantages over natural APCs, including the fact that their release can be controlled, they are highly targeted and customizable, and they exhibit consistent performance without relying on the body's natural antigen-processing mechanisms [203]. aAPCs can precisely activate T cells and reduce off-target effects, and they offer flexibility in genetic engineering to express specific co-stimulatory molecules or cytokines [204]. However, aAPCs find it challenging to mimic the intricate immune signals and the microenvironment that natural APCs provide, and they might be limited in overcoming the immune evasion tactics of tumors. Additionally, they could encounter issues with standardizing production, potential toxicity, and the absence of sustained cytokine release, which is vital for the long-term survival and function of T-cells.

Table 2 Summary of nanovaccines for tumor metastasis and their immune-enhancing mechanisms in preclinical studies

Metastatic stages	Formulations/ Metastatic site	Name	Antigen used	Immune adjuvant	Tumor model	Combined treatment	Injection route	Immune-enhancing mechanisms	Refs.
Primary tumor	Peptide	OVA	*Listeria-Ova* or OVA peptide	–	B16-OVA melanoma tumor	ICB	Subcutaneously	Promotes central memory T-cell formation rather than tissue-resident memory generation	[207]
	herpes simplex virus	AdC68-gDMelapoly	$CD8^+$T-cell epitopes, mTrp-1, hgp100, and mBrafV600E fused into herpes simplex virus glycoprotein	–	mouse model of melanoma	–	Intramuscularly	Reprogramming cells within tumors to increase fatty acid metabolism, providing T cells access to glucose in the TME	[208]
	$CaCO_3$ biomineralized Salmonella (Sal)	Sal@$CaCO_3$	*Salmonella*	–	mouse model of melanoma	–	Subcutaneously	Inducing cancer cells' immunogenic cell death and promoting the gap junction formation between tumor cells and (DCs) to promote antigen presentation	[210]
	mRNA	mPLA/mRNA	MAGE-A1 mRNA	mPLA	mouse model of lung		Nasal administration	Immune cell activation, IFN- γ/IL-12 cytokine secretion, and natural killer cell-mediated antibody-dependent cellular cytotoxicity	[217]
	DNA	Tem 1-TT	TEM1	tetanus toxoid (TT)	mouse model of lung and colon	–	Intramuscularly	Reduced tumor vascularity, increased infiltration of $CD3^+$T cells into the tumor; elicited $CD8^+$ cytotoxic T-cell responses against murine tumor-specific antigens	[305]

Table 2 (continued)

Metastatic stages	Formulations/ Metastatic site	Name	Antigen used	Immune adjuvant	Tumor model	Combined treatment	Injection route	Immune-enhancing mechanisms	Refs.
	Lipid-based NPs	FAP_{PEP}-SLNPs	αFAP	CpG	E.G7-OVA Lymphoma model, MC38 colorectal tumor	Doxorubicin	Subcutaneously	Depleting FAP^+ CAFs and thereby reducing ECM production in the TME while causing little appreciable adverse effects. Increased drug accumulation and resulted in a synergistic anti-tumor efficacy when combine with Doxorubicin	[240]
	Protein	TRXtr-Vimentin	Vimentin	CpG	Dog with transitional cell carcinoma of the bladder were recruited within their own veterinary practice. B16F10 melanoma mouse model	meloxicam	Recruited; Subcutaneously	extracellular vimentin contributes to immune suppression and functions as a vascular immune checkpoint molecule	[248]
	whole lysates based CCSC	MUC1/CCSC	MUC1	–	SW620 colorectal tumor	–	Subcutaneously	delay of tumor growth, increased cytotoxicity, antibody production, and generation of memory B cells	[254]
	Lipid calcium phosphate (LCP) nanoparticles	Frax NE/ BRAF	modified BRAFV600E peptide	CpG	BPD6 desmoplastic melanoma model	–	Subcutaneously	abrogating tumor-associated immune suppression and promoting infiltration of immune cells such as CTLs, NK cells and memory T cells	[257]

Table 2 (continued)

Metastatic stages	Formulations/ Metastatic site	Name	Antigen used	Immune adjuvant	Tumor model	Combined treatment	Injection route	Immune-enhancing mechanisms	Refs.
	OMV	SpC-OMVs + SpT-peptides	OMV	OMV	MB49 Transitional cell carcinoma model	ICB	Subcutaneously	reducing tumor growth by enhancing IFN-γ-$CD8^+$ T-cell responses and increasing the number of $CD8^+$ memory cells and antigen-specific T cells	[306]
	Cytokine	3xTx vaccine	3xTx	–	melanoma or head and neck carcinoma models	Radiotherapy; ICB	Intratumoral Injection	NK cells promote $CTLA4^+$ Treg apoptosis in non-targeted tumors. This is dependent on NK cell expression of CD8, which is upregulated downstream of KLRK1	[307]
Post-surgical tumor metastases	Polymer	F-PEI/OVA	OVA, cancer cell membrane	F_{13}-PEI	B16-OVA melanoma tumor, CT26 colon tumors 4T1 breast tumor (mice)	ICB	Subcutaneously	Induced DC maturation and antigen cross-presentation, OVA-specific T-cell responses (in vitro), immunological memory responses, decreased $CD4^+Foxp3^+$ T regulatory cells	[66]
Secondary metastases	Lung	PEIM@OVA, PEIM@Mem	OVA, tumor cell membranes	PEIM	B16-OVA melanoma, MC38 colorectal tumor	ICB	Subcutaneous	Activate STING/IFN-I cascade, stimulate APCs activation and antigen cross-presentation for priming $CD8^+$ CTL response	[39]

Table 2 (continued)

Metastatic stages	Formulations/ Metastatic site	Name	Antigen used	Immune adjuvant	Tumor model	Combined treatment	Injection route	Immune-enhancing mechanisms	Refs.
	porous silicon@Au	CCM@(PSiNPs@Au)	Tumor cell membranes	–	4T1 cancer cells	ICB	Subcutaneous injection near the inguinal lymph nodes of their left hind legs	Activate the antigen presentation of DCs for priming CTLs	[308]
	Lung	viruslike particles	Virus	CPMV and Qβ	B16F10 and 4T1Luc-lung metastatic Model	–	Subcutaneous	reduce the levels of S100A9 within the lungs, thereby increasing the expression of immunostimulatory cytokines with anti-tumor function (IL-12 and IFNγ) while reducing levels of immunosuppressive cytokines (IL-10 and TGFβ)	[189]
	Ovarian	Neoantigen vaccine	Neoantigen of personalized patients	–	metastatic ovarian cancer patients	–	Subcutaneous	riggers cytotoxic lymphocytes expressing polyclonal TCR against cancer	[309]
	Lymph node	Tu-NP_{FN} and Ln-NP_{R848}	situ antigen generation	R848	4T1 cancer cells	ICB	Subcutaneous	promoted the uptake and maturation of dendritic cells to initiate potent anti-cancer immune responses	[79]
	Lung	LN-IMQ	UT-Ags, PTX-Ags and PTX + Carb-Ags	LN	4T1-bearing mouse	ICB	intravenous injection	triggered the anti-tumor ability of macrophages, mobilized T-cell immunity, and promoted the secretion of anti-tumor cytokines	[132]

Table 2 (continued)

Metastatic stages	Formulations/ Metastatic site	Name	Antigen used	Immune adjuvant	Tumor model	Combined treatment	Injection route	Immune-enhancing mechanisms	Refs.
	Lymph node	TPOP	OVA	OMs	subcutaneous mouse colorectal cancer model and melanoma model	pretreatment with doxorubicin	intratumoral injection	manipulate TIDC lipid metabolism and inhibit de novo synthesis of fatty acids, thus improving the ability of TIDCs to cross-present by reducing their lipid accumulation	[209]
	Lung	LDHs-cGAMP	BSA-Cy5	LDH	hepa1-6 liver cancer	RFA	intratumorally inject	inducing a stronger IFN-I response, changed the tumor immune microenvironment and promoted the response efficiency ofαPD-L1 immunotherapy	[280]
Primary tumor/ lung metastasis	Lymphocytic choriomeningitis virus	LCMV-TRP2	melanoma-associated self-antigen TRP2	–	mouse model of melanoma	–	Applying DMBA in acetone onto the shaved back for primary melanoma; subcutaneously into the flank or intravenously for the lung metastasis	induce effective antigen-specific $CD8^+$ T-cell responses, renders previously "cold" tumors open to immune infiltration and reprograms tumor microenvironment to "hot."	[216]
Primary tumor/ lung metastasis	Peptide	CTAs Peptide	Cancer–testis antigens (CTAs) (Siglece and Lin28a)	Poly(I:C)	4T1 triplenegative breast cancer model	–	Subcutaneously	increased T-cell anti-tumor immunity and reduced primary tumor growth	[310]

ICB immune checkpoint blockade, *OMVs* outer membrane vesicles, *CAFs* cancer associated fibroblasts, *ECM* extracellular matrix, *TME* tumor microenvironment; *NPs* nanoparticles, *CCSC* colorectal cancer stem cells, *APC* antigen-presenting cells, *CTLs* cytotoxic T lymphocytes

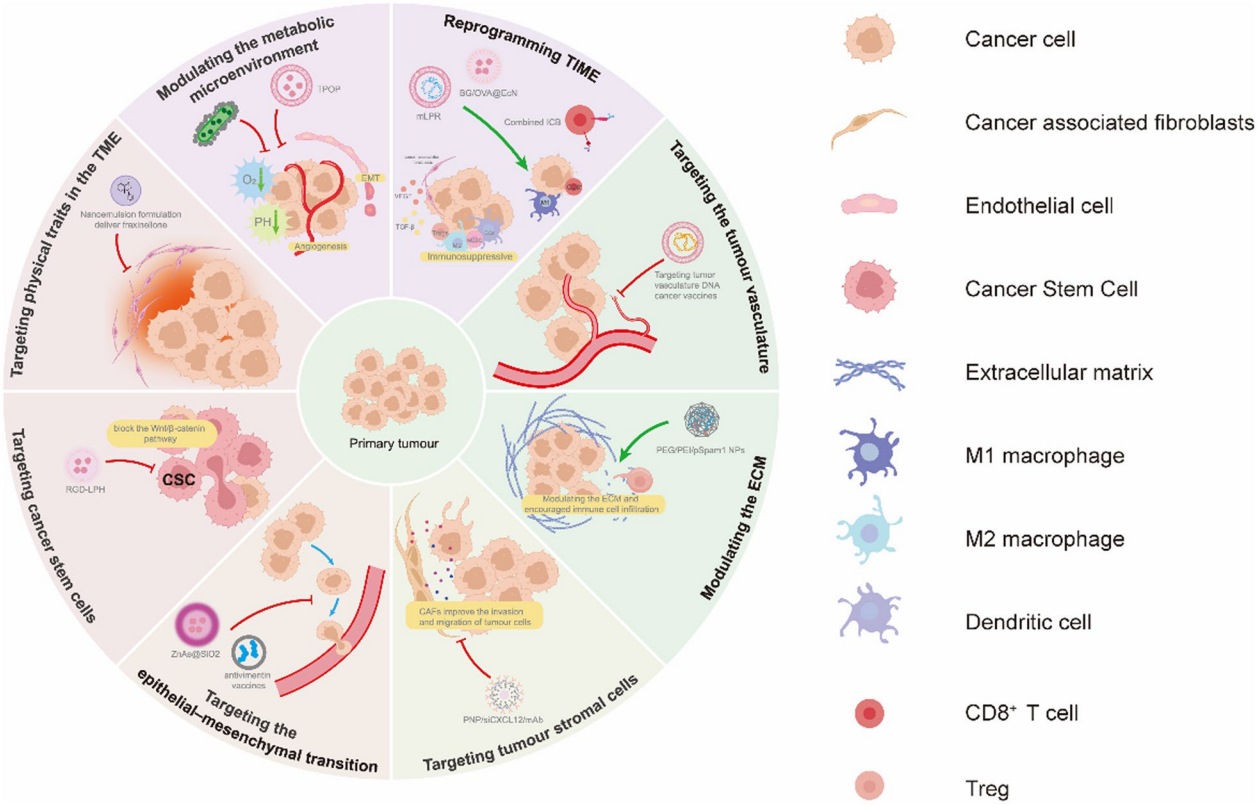

Fig. 5 Preventing and battling initial tumor metastasis with nanovaccines. Nanovaccines designed with the different NP platforms summarized in Sect. "Nanovaccine designs aimed toward overcoming metastasis" could target specific factors in the primary tumor TME, thus exerting a precise anti-tumor effect. These specific factors individually contribute to the initiation of metastasis; they are as follows: metabolic microenvironment, immune microenvironment, vasculature, extracellular matrix, stromal cells, epithelial–mesenchymal transition, cancer stem cells, and the physical structure of the TME

The generation of aAPCs involves the incorporation of two crucial components. MHC, which confers antigen specificity and binds to the matching T-cell receptor on effector T cells, presents a peptide epitope as part of its first component. For T cells to successfully activate and proliferate, a molecule that provides co-stimulatory signals, like CD80 or CD86, must be engaged simultaneously with the T cells. aAPCs are used to induce tumor-specific responses by mimicking the actions of natural APCs. This eliminates the need to administer antigens and adjuvants, which usually necessitate further processing by the body's innate immune system [52, 202].

Blocking and combating cancer metastasis using nanovaccines

With the aim of transcending the traditional, one-size-fits-all approach to medicine, personalized nanovaccines can be tailored for each stage of the metastatic cascade. These nanovaccines can be customized according to patient-specific metastatic processes, thereby improving therapeutic effectiveness and minimizing side effects (Fig. 3, Table 2). In this section, these strategies are discussed in further detail.

Utilizing nanomedicines to prevent and combat metastasis initiation from the primary tumor: remodeling the microenvironment in primary tumors

The complex ecosystem known as the TME, which includes a variety of cell types, stromal components, and other physical characteristics, envelops cancer cells (Fig. 5). It is essential for the growth and spread of cancer. Considering that specific approaches can inadvertently harm healthy tissues, personalized nanovaccines show potential in the context of facilitating controlled drug release while ensuring minimal side effects. Additionally, nanovaccines can be designed to safely carry a wide array of different active agents while being optimized to target specific factors in the primary tumor TME. In the following discussion, we outline the key components of the TME that contribute to cancer metastasis and discuss

how personalized nanovaccines can be used to counteract each of them.

Modulating the metabolic microenvironment

Hypoxia and acidosis are critical interdependent elements that contribute to the metabolic TME and establish favorable conditions for tumor growth. As tumors expand, the oxygen supply from nearby blood vessels becomes inadequate and is depleted gradually, giving rise to a hypoxic microenvironment. To maintain an oxygen balance, the HIFs HIF-1 and HIF-2 activate HIF signaling, which enhances oxygen delivery and synchronizes the cellular response to oxygen levels. Nearly all stages of the metastatic process, including invasion, EMT, and angiogenesis, involve active HIF signaling [205, 206].

Numerous studies have delved into the connection between immune cells fatty acid metabolism and immunological capacity, suggesting potential overlaps between cancer therapeutic vaccines and medications that target immune cell fatty acid metabolism in the TME. Although enhanced fatty acid oxidation in T cells improves spare respiratory capacity, increases peptide vaccine memory ability, and promotes anti-tumor immunity, the overexpression of PGC-1α increases CD8 central memory T-cell development [207]. Remarkably, in a mouse model of melanoma, the co-administration of a cancer vaccine and a PPARα agonist inhibited tumor growth. As tumor and stromal cells have an increased need for fatty acids, there is a greater chance that T cells may use glucose, which will improve anti-tumor immunity [208]. Qin and colleagues developed an in situ nanovaccine (TPOP) that leverages nanoparticles to modulate lipid metabolism and activate the innate immune system. Combined with immune checkpoint inhibitors, TPOP was able to substantially impede the growth of distant tumors by eliciting robust systemic anti-tumor immunity [209].

The modulation of the acidic microenvironment has the potential to reduce the metastatic propensity of tumor cells. Guo et al. introduced a novel bacteria-based autologous cancer vaccine. The vaccine produces an in situ cancer vaccine and modulates the systemic immune response by employing *Salmonella* biomineralized with $CaCO_3$ [210]. The $CaCO_3$ shell of this vaccine decomposes in acidic environments, reducing tumor acidity and facilitating the release of *Salmonella*. Therefore, this bio-vaccine exhibits exceptional effectiveness against cancers that are primary or metastatic.

Reprogramming the tumor immune microenvironment

The tumor immune microenvironment (TIME) is an intricate web made up of different parts within a tumor that inhibit the immune response to cancer and facilitate tumor immune evasion [211]. Patients with immunologically "hot" tumors have a higher likelihood of responding well to immunotherapies, resulting in improved survival rates. However, a majority of cancers are regarded as immunologically "cold," and the efficacy of immunotherapies in treating patients is comparatively low [212, 213]. Consequently, there is intense interest in innovative vaccination strategies aimed at reprogramming the TIME to render tumors "hot."

Within the TIME, immunosuppressive cells release a plethora of inhibitory signals such as TGF-β, vascular endothelial growth factor (VEGF), and PD-L1. These signals decrease the immune reaction against cancerous growths by acting either directly or indirectly on effector T cells [214]. Addressing the challenges posed by these immunosuppressive mechanisms within the TIME is imperative for developing effective cancer immunotherapy strategies.

Vaccination can reverse the suppressive TME and subsequently activate $CD8^+$ T cells, thereby transforming a cold TME into a hot TME. For example, the tumor vaccine vector TA-Met@MS triggers a metabolic switch from glycolysis to fatty acid oxidation. This photothermal metabolic manipulation boosts the longevity of T cells and encourages the maturation of memory $CD8^+$ T cells, thereby prolonging the effectiveness of vaccine [215]. Several nanovaccines have demonstrated the ability to successfully reprogram the TME. Purde et al. studied employment of viral vector-based cancer vaccines encoding a self-antigen associated with tumors (TRP2) in preclinical mouse models to cure existing melanomas. By effectively priming T cells, this method converts previously cold tumors into immune-infiltrated ones and sets the TME in a hot state [216]. With the aid of the TLR4 agonist mPLA, which promoted DC maturation, Ma et al. engineered an mPLA/mRNA tumor vaccine (mLPR) to redirect M2 macrophages towards the M1 phenotype, cross-activate innate and adaptive immune responses in vivo, and facilitate the delivery of mRNA into the cytoplasm to amplify the immune response [217]. Moreover, the inactivated probiotic strain *Escherichia coli* Nissle 1917 has been recently modified to incorporate tumor antigens along with β-glucan, a stimulator of trained immunity, in the creation of a personalized cancer vaccine. This vaccine, known as BG/OVA@EcN, induces trained immunity through subcutaneous injection of the model antigen OVA. This injection prompts macrophages at the injection sites to phagocytose the vaccine. Trained macrophages recruit DCs to aid in the phagocytosis of BG/OVA@EcN, leading to DC maturation and T-cell activation [218].

Immunotherapy, in conjunction with customized nanomedicine, shows great promise in yielding improved anticancer outcomes. For example, Kadam et al. have shown

that ICB enhances the action of therapeutic cancer vaccines. Therefore, patients with lung cancer may benefit from CCL21-DC tumor lysate vaccination treatment in addition to PD-1 inhibition [219].

Targeting the tumor vasculature

As tumor growth accelerates, the establishment of a vascular network becomes crucial for providing nutrition to tumor cells. To fulfill the escalating demand for proliferation, tumor cells secrete a variety of angiogenic agents that promote the quick development of immature vasculature, such as VEGF. This newly formed vasculature is known for its convoluted and leaky nature, which results in the significant intravasation of cancer cells, with higher blood vessel density correlating with increased tumor metastasis incidence [220].

Many nanosystems have shown impressive anti-angiogenic and -tumor activity [221, 222]. On the contrary, anti-angiogenesis-driven hypoxia could increase tumor aggressiveness, thereby catalyzing metastasis [223, 224]. Given this scenario, rather than inhibition, the normalization of vasculature should be viewed as a more suitable paradigm for addressing metastasis [225]. The doses of anti-angiogenic drugs should be closely monitored to accomplish this goal, and they should be used in conjunction with cytotoxic treatment modalities such photodynamic therapy and chemotherapy. One study showed that CD248 may be targeted immunologically to produce an anti-tumor vascular response using a DNA-based vaccine, providing a unique tool for cancer diagnostics and treatment [226].

Modulating the extracellular matrix

Matricellular proteins, glycoproteins, fibrous proteins, and enzymes make up the intricate three-dimensional network known as the extracellular matrix (ECM) [227]. The onset of angiogenesis and metastasis in primary cancers is significantly influenced by the ECM [228]. As cancer progresses, tumor cells continuously remodel their ECM. One well-recognized alteration in the ECM is the increased deposition of collagen, which controls the migration and polarity of cells and is intimately related to metastasis [229, 230]. Nanovaccines can effectively regulate the ECM. Hu et al. constructed PEG/PEI/pSpam1 NPs, in which Spam1 could express hyaluronidase. It was discovered that PEG/PEI/pSpam1 NPs could produce high hyaluronidase expression at the tumor location, which further broke down the tumor ECM and encouraged immune cell infiltration [231].

Among the various ECM components, matrix metalloproteinases (MMPs), which are overexpressed proteases that facilitate tumor migration by directly breaking down the ECM, are considered ideal targets for the treatment of metastasis. Therefore, over the past two decades, synthetic inhibitors of MMPs (MMPIs) have been studied for use against various types of cancer [232]. For example, a hyaluronic acid-paclitaxel prodrug was used to synthesize marimastat, a broad-spectrum MMPI with limited water solubility, into NPs for the treatment of metastatic cancer [233].

Targeting tumor stromal cells

Cancer-associated fibroblasts (CAFs) are a heterogeneous population of activated fibroblasts found within the primary TME plays vital roles in multiple pathways that facilitate the growth and dissemination of tumors. The increased release of cytokines and growth factors, including TGF-β, CXCL12, and IL-6, has been observed in CAFs, and these substances have been shown to improve the invasion and migration of tumor cells [234–236]. CAFs have emerged as a key target for intervention since they are among the most prevalent elements of the tumor stroma.

Zhao et al. showed that a localized reduction in CAFs can change the TME and increase the efficacy of chemotherapeutic drugs [237]. Notably, despite the effectiveness of this method, tumor cells may continue to invade or migrate if they are not completely eradicated [238]. To mitigate potential risks associated with tumor growth and metastasis, an siRNA was developed to silence CXCL12, a factor that sustains the active phenotype of CAFs. The nanosystem, named PNP/siCXCL12/mAb, specifically targeted CAFs [239]. Remarkably, PNP/siCXCL12/mAb significantly decreased CXCL12 expression by 64.4%, resulting in suppressed angiogenesis, migration, and tumor invasion. Importantly, in the major organs, relatively little tumor fluorescence was observed, indicating a strong suppression of metastasis. In a separate investigation, a cancer nanovaccine was designed to target CAFs expressing fibroblast activation protein (FAP) α. By reducing FAP-expressing CAFs, this study demonstrated a substantial suppression of tumor growth across various malignancies. It also identified immunodominant FAP-specific epitope peptides and established a vaccine based on NPs that displayed the selected epitope peptides. Furthermore, when paired with chemotherapeutic medications, the nanovaccines targeting FAP-expressing CAFs may have synergistic anti-tumor activity, indicating their potential utility as a "commercially available" pan-tumor vaccination as well as a platform for different combination therapies [240].

Targeting the EMT

Tumor cells undergo an EMT, which allows them to migrate toward arteries, thus subsequently penetrating into the bloodstream. Tumor cells at the beginning

of invasive cancers typically express more mesenchymal markers and fewer intercellular adhesions and epithelial markers [241]. Eventually, these cancerous cells change into mesenchymal phenotypes, which are characterized by increased contractility and motility as well as the increased production of markers associated with metastasis, such as VEGF and MMPs [242, 243]. Numerous substances, such as WNT, HIF-1a, TGF-β, and some cytotoxic medications, can cause EMT [244–247]. Therefore, targeting EMT holds promise in the context of preventing the initiation of metastasis.

For instance, ZnAs@SiO2 NPs, designed by Huang et al. [50], inhibited stemness while elevating levels of SHP-1. Simultaneously, they inhibited the JAK2/STAT3 pathway. This enabled the NPs to regulate the underlying gene networks. As mentioned previously, several chemotherapy drugs, such paclitaxel and doxorubicin, can induce EMT, which raises the possibility of metastasis. Zhou et al. used hydroxyethyl starch–polylactide NPs to co-deliver doxorubicin and a TGF-β receptor inhibitor in order to lessen these negative effects [47]. With this method, pulmonary metastasis was inhibited, and primary tumors were concurrently suppressed. By effectively blocking the active TGF-β pathway, the concomitantly delivered TGF-β receptor inhibitor decelerated the EMT process. In contrast, the uneven distribution of could worsen EMT and metastasis. Additionally, van Beijnum et al. created anti-vimentin vaccines by cloning sequences that code for vimentin from dogs and mice into the pET21a expression vector. These vaccines were then produced using *Escherichia coli* [248]. Targeting vimentin with the anti-vimentin vaccine (TRXtr-Vim) was found to elicit immunity and positively impact EMT-regulated processes, including angiogenesis and metastasis.

Targeting cancer stem cells

Owing to their multipotency, cancer stem cells (CSCs) generate new tumors and self-renew. The shift from an invasive mesenchymal phenotype to another that significantly enhances metastatic spread sometimes occurs along with the acquisition of stem-like features [249]. Only a small percentage of CTCs survive the metastatic dissemination phase and form micrometastases. Such micrometastases exhibit CSC traits and serve as seeds for colonization at secondary sites [249, 250]. Therefore, it is essential to target and eradicate CSCs to eradicate original tumors and prevent them from spreading.

Li et al. created NPs that specifically target integrin α5; they did this toblock the Wnt/β-catenin pathway, which is essential for the development and sustenance of stem cells [48]. These NPs demonstrated improved uptake and retention after systemic delivery. This strategy reduced β-catenin levels and curbed both primary and metastatic cancers. Notably, some chemotherapeutic drugs have been found to enhance stemness and metastasis through a "backdoor" mechanism facilitated by COX-2/PGE2 pathway [251]. To address this aspect, doxorubicin was co-delivered with a particular COX-2 inhibitor, which improved the overall anti-tumor efficacy and prevented doxorubicin from inducing the growth of cancer stem-like cells [252]. This combination of treatments effectively reduced pulmonary metastasis by 67% and slowed the growth of the main tumor by 91%. Moreover, it has been demonstrated that CSC-based tumor vaccines exhibit strong anti-tumor properties [253]. A recent study assessed the immunogenicity and protective effectiveness of CSC immunization against colorectal cancer in a mouse model using cells with high MUC1 expression. The CSC vaccine demonstrated a notable impact on tumor growth by selectively targeting CSCs, leading to reduced levels of $CD133^+$ and $ALDH^+$ cells within the tumors. In addition, increased NK cytotoxicity, perforin and granzyme B production, IFN-γ secretion, memory B-cell activation, and anti-MUC1 antibody production were observed following CSC vaccination [254].

In summary, developing nanocarriers to enhance CSC-targeting therapies holds promise for preventing metastatic dissemination and colonization.

Targeting physical traits in the TME

The mechanical TME is a crucial aspect of cancer biology that influences disease progression. It refers to the physical characteristics of a tumor, such as its structure, stiffness, pressure, and the impact of mechanical forces within the tumor [255]. Changes in these mechanical properties can significantly affect tumor growth and adaptation to the environment. They may also affect how well cancers respond to therapy. Certain studies have highlighted a correlation between increased liver tumor tissue hardness and resistance to immunotherapy in patients with colorectal cancer, crediting abnormal vascular distribution as a contributing factor. Leveraging anti-angiogenic therapies with immunotherapy opens up a promising treatment route for solid tumors and calls for the further exploration of the macroscopic influence of tumor matrix stiffness and mechanical forces in the TME on immunotherapies [256].

Nanovaccines offer potential solutions to address these challenges in the TME. For example, a study described the development of a nanoemulsion to deliver the antifibrotic agent fraxinellone to tumor-associated fibroblasts (TAFs) in desmoplastic melanoma. TAFs and tumor cells efficiently uptake the fraxinellone nanoemulsion, with a particle size of approximately 145 nm, at the tumor site,

r leading to a substantial decrease in TAFs and stromal deposition. By boosting the quantity of NK cells and cytotoxic T cells while decreasing the quantity of regulatory B cells and myeloid-derived suppressor cells, this strategy simultaneously alters the TIME [257].

Intercepting CTCs using nanovaccines

CTCs are cancer cells that have separated from the primary tumor and have entered into the bloodstream and lymphatic systems, where they circulate [258]. Upon detachment from primary tumors, metastatic tumor cells embark on a protracted voyage through the lymphatic system and/or bloodstream before arriving at a new location. Blood vessel circulation and lymphatic vessel-to-blood vessel circulation are the two main pathways through which CTCs migrate [258]. Within this category, there are two distinct pathways: scirculation from the sentinel lymph node to blood vessels and from distant lymph nodes to blood vessels.

Many methods have been investigated for CTC enrichment and detection. Filtration, density gradient separation, and immunomagnetic separation are examples of enrichment techniques, whereas direct microscopy, fluorescently activated cell sorting cytometric procedures, manual immunocytometry, and PCR-based approaches are examples of detection techniques [259]. Currently, the Cell Search system (Veridex, LLC, Warren, NJ, USA), which combines flow cytometry and immunomagnetic separation, is commercialized. This technology is suitable for the identification and evaluation of CTCs in patients with metastatic cancer [260, 261].

Compared with their spherical counterparts, NP with high aspect ratios and low surface curvatures—such as those that are rod-, discoid-, or worm-shaped—are better suited for evading phagocytosis, leading to longer circulating lifetimes and higher tumor accumulation [262, 263]. Furthermore, in a mouse model of lung metastasis derived from 4T1 cells, nanoparticles made of PEG–PLA encapsulating paclitaxel and modified with a peptide (K237) that targets tumor neovessels and an EpCAM aptamer (Ep23) were described to concurrently impair the primary tumor and capture and eliminate CTCs, particularly those that overexpressed EpCAM on their surface [264]. Mitchell et al. devised a technique wherein E-selectin was adhered onto the surface of liposomes filled with doxorubicin and rendered immobile inside a microtube apparatus. This method enables the selective targeting, collection, and elimination of CTCs [265].

Combating secondary metastatic tumors with nanomedicines: remodeling the microenvironment in distant metastatic organs

Modulating the PMN via nanovaccines: inhibiting metastatic colonization

As depicted in Fig. 5, although CTCs possess significant metastatic potential, their presence alone is insufficient to establish metastasis. To effectively enable the seeding of surviving CTCs at distant sites, the primary TME initiates a series of changes before tumor cell dissemination. During this process, tumor-derived factors and extracellular vesicles are secreted, collectively altering the PMN to form an environment conducive to hosting metastatic sites [266, 267].

These changes in the PMN include increased vascular permeability, the recruitment of myeloid cells, the upregulation of MMP-9 in the ECM, the overexpression of inflammatory molecules, and the induction of hypoxia [266, 268, 269]. These factors work in synergy to construct an environment characterized by immunosuppression and inflammation, which in turn facilitates the extravasation, invasion, and colonization of CTCs (Fig. 5).

A promising strategy to hinder the later stages of the metastatic cascade involves targeting the PMN, rendering it less suitable for CTCs. This approach has the potential to disrupt the formation of metastases and represents an ideal protocol for metastasis inhibition.

Recent reports on the modulation of the PMN have demonstrated promising therapeutic outcomes, underscoring the potential of the PMN as a target for treating tumor metastasis [270–272]. This highlights the growing recognition of the PMN as a valuable focal point in the battle against metastatic disease. Growing evidence indicates that S100A9, a critical inflammatory regulator, contributes to the formation of the PMN, particularly in the lungs. Researchers have devised a vaccine targeting S100A9 using VLPs and plant viruses, demonstrating the efficacy of S100A9 vaccine candidates in inhibiting the dissemination of metastatic disease and tumor seeding in the lungs [189]. Lu et al [273]. showed that exosomes derived from α-fetoprotein-expressing DCs (DEX_{AFP}) can be used to create a novel class of vaccines intended for customized immunotherapy. This outcome can be attributed to the possibility that DEX_{AFP} can alter the TME in HCC mice and elicit strong antigen-specific anti-cancer immune responses. The ES-exo/GM-CSF vaccine, which is produced from murine ESCs modified to create GM-CSF, has been shown in a recent mouse-model-based study to offer protection against metastasized lung cancers (Fig. 6) [274].

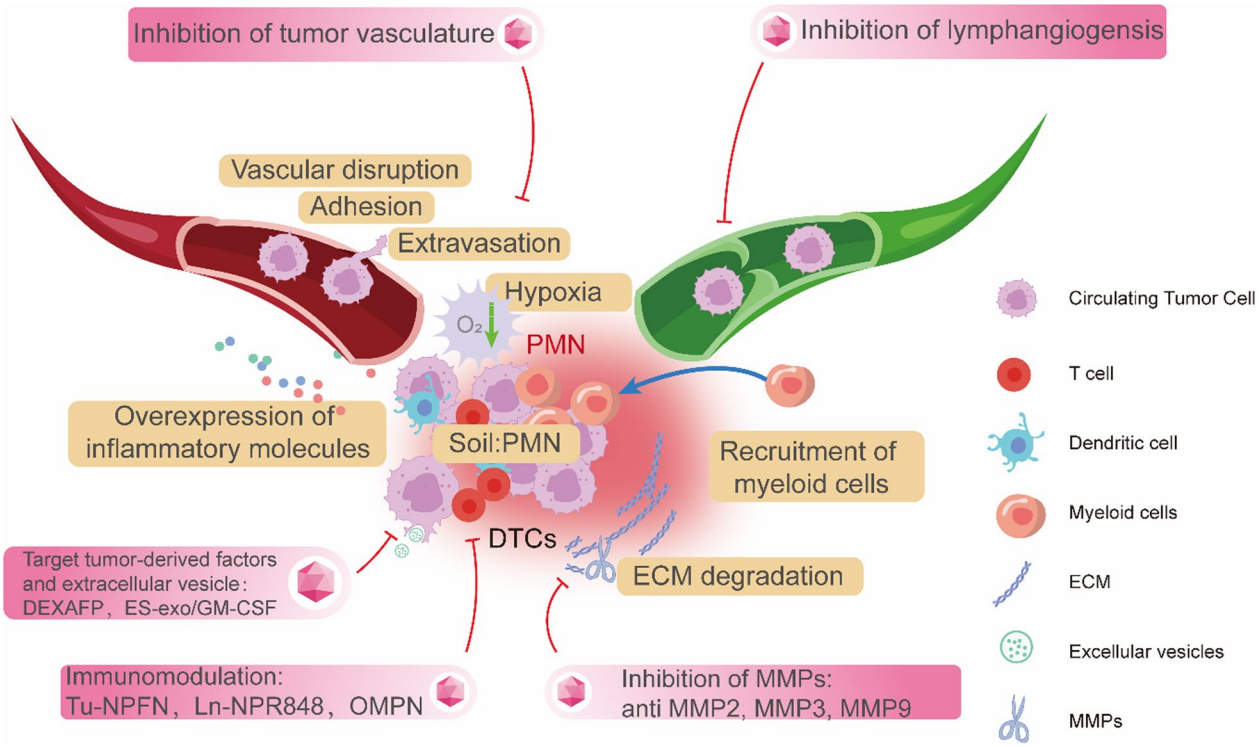

Fig. 6 Targeting circulating tumor cells (CTCs) and secondary tumors through nanovaccines. In the last stage of the metastatic cascade, CTCs attempt to transit through the blood or lymphatic vessels, colonizing distant sites as disseminated tumor cells. The basis of nanomedicine lies in halting this process. Specifically, personalized nanovaccines may modulate the polymorphonuclear neutrophil leukocyte (PMN), thus rendering it less suitable for CTCs. Alternatively, these vaccines may directly target established metastasis. Specifically, nanovaccines are designed to: (1) target extracellular vesicles, as with DEXAFP and ES-exo/GM-CSF; (2) target inflammatory molecules and hypoxia factors, as with virus-like particles (VLPs), plant viruses, and the hydrogel toolbox combined with PD-L1 blockade; and (3) target the immune environment, as with Tu-NPFN, Ln-NPR848, and OMPN. Nanovaccines with active targeting could be important for driving innovation in personalized medicine, as they allow for the treatment of patients using optimal and site-specific subtypes.

Combining personalized nanovaccines with ICB also shows promise in the treatment of the PMN. For example, Zhou et al [275]. developed a hydrogel-based toolkit to be used as a cancer vaccine to treat postoperative BC. This innovative approach integrates CXCR4 inhibition, immunogenicity activation, and PD-L1 blockade strategies. The hydrogel toolkit effectively inhibits local residual tumor cell "seeds," as well as produces an abscopal effect by disrupting the PMN "soil."

In the last stage of the metastatic cascade, CTCs attempt to transit through the blood or lymphatic vessels, colonizing distant sites as disseminated tumor cells. The basis of nanomedicine lies in halting this process. Specifically, personalized nanovaccines may modulate the polymorphonuclear neutrophil leukocyte (PMN), thus rendering it less suitable for CTCs. Alternatively, these vaccines may directly target established metastasis. Specifically, nanovaccines are designed to: [1]. target extracellular vesicles, as with DEX_{AFP} and ES-exo/GM-CSF; [2]. target inflammatory molecules and hypoxia factors, as with virus-like particles (VLPs), plant viruses, and the hydrogel toolbox combined with PD-L1 blockade; and [3]. target the immune environment, as with Tu-NPFN, Ln-NPR848, and OMPN. Nanovaccines with active targeting could be important for driving innovation in personalized medicine, as they allow for the treatment of patients using optimal and site-specific subtypes.

Targeting established metastasis with nanovaccines

Tumor cells look for places that are conducive to colonization as they travel throughout the body. The liver, brain, lungs, LNs, and bone are the most desirable organs for tumor colonization [276]. However, because of their inherent characteristics, certain organs and systems may present challenges for targeted drug delivery. An example is the metastasis to the central nervous system (CNS), where the blood–brain barrier hinders the passage of numerous therapeutic drugs from penetrating the affected area. Notably, tailored NPs have demonstrated an amazing capacity to move payloads across the blood–brain barrier [23]. A CXCL13-modified nanocapsule

was created by Wen et al. to encapsulate the anti-cancer antibody rituximab, which was later found in the CNS at low concentrations [277]. The permeability of rituximab across the blood–brain barrier was significantly enhanced by the cholinergic analogs of the polymer shell, resulting in its concentration being increased in the CNS, culminating in the effective treatment of brain lymphomas.

In addition to addressing brain metastasis, tackling lymphatic metastasis presents challenges; these challenges can largely be attributed to the unique anatomy of the lymphatic system. Smaller NPs can exploit this feature [278]. Liu et al. developed acidity-responsive, clustered NPs with adjustable diameters [279]. Initially sized at 100 nm and shrinking to 5 nm upon reaching the tumor site, these NPs facilitated the following processes: prolonged circulation and enhanced penetration into solid tumors, diffusion into interstitial fluid, and intravasation into tumor lymphatics. In contrast, Jin et al. proposed an innovative approach involving the synergistic application of two nanomedicines, Tu-NPFN and Ln-NPR848. Under the guidance of an alternating magnetic field, Tu-NPFN produced many antigens. Concurrently, Ln-NPR848 encapsulated the adjuvant R848, directing some of the produced antigens toward the synthesis of in situ nanovaccines and their targeted distribution to LNs. Remarkably, in conjunction with an anti-CTLA4 antibody, the therapy demonstrated notable efficacy in completely eradicating distant tumors in certain mice while simultaneously demonstrating evidence of an immunological memory effect that prevented tumor dissemination [79]. Another study introduced a multifunctional nanovaccine, OMPN, created using a simple one-pot method that included elements such as OVA, MnO_2, and polydopamine. This nanovaccine demonstrated significant anti-cancer efficacy against orthotopic melanoma and was efficient in preventing the spread in a mouse model of liver metastasis of tumor recurrence [34]. Importantly, magnetic resonance image tracking of the interaction between nanovaccines and DCs in the inguinal LNs indicated effective DC activation and an immunological response.

An ionized iron nanoadjuvant can be self-assembled with model antigen OVA to build a tumor nanovaccine. During the activation of STING signaling, the nanovaccine could effectively promote the cytoplasmic delivery of the antigen, thus achieving efficient antigen cross-presentation. This system demonstrated a nearly 170-fold enhancement in the antigen-specific $CD8^+$ T lymphocyte response, along with significant tumor growth and inhibition prevention in a B160VA melanoma mouse model. In addition to producing a long-lasting anti-tumor immunological memory effect, the combination of nanovaccine and ICB therapy dramatically reduced the postoperative recurrence and distal metastasis of B16OVA and MC38 tumors [39]. In addition, LN-IMQ monotherapy resulted in complete tumor regression in 6 out of 8 4T1-bearing mice, with the cured mice showing resistance to secondary tumor challenges. LN-IMQ also reduced the incidence of lung metastases and proved effective against advanced metastatic disease [132]. A general concept for tailored personalized nanovaccines based on fluoropolymers for post-surgical cancer immunotherapy has been reported. The fluoropolymer-based nanovaccine can trigger anti-tumor immune responses with excellent efficiency. The combination of nanovaccines and immune checkpoint inhibitors can effectively suppress distant tumor growth and metastasis after surgery [66]. In addition, an advanced in situ nanovaccine was developed using layered double hydroxides to carry cGAMP (a STING agonist) and adsorb TAAs, designed to enhance the anti-tumor immune response triggered by radiofrequency ablation. After treatment with the nanovaccine, there was a marked increase in CTLs and activated DCs in the tumors and LNs, resulting in a marked suppression of primary, distant, and metastatic lesions of liver cancer [280]. Furthermore, an in situ nanovaccine (TPOP) based on innate immunostimulatory NPs and lipid metabolism regulation can reportedly capture tumor antigens and cause specific recognition and uptake by TIDC through a systemic anti-tumor immune response. When paired with immune checkpoint inhibitors, TPOP can significantly inhibit the growth of distant tumors [209].

In many patients, the presence of tumor cells may remain unnoticed until they have already spread throughout the body or even established secondary colonies. Consequently, although the strategies discussed earlier can aid in preventing or delaying the progression of established metastases, they may not achieve complete eradication. To effectively address established metastases, therapeutic agents must possess the capacity to eliminate tumor cells rather than merely inhibit their growth.

Anti-metastatic nanovaccines and nanovaccine-based combination immunotherapies in clinical trials

To date, only a few nanovaccines have progressed into clinical trials for the treatment of cancer metastasis. This limited translation into clinical settings is primarily because of the challenges associated with large-scale manufacturing and quality control of complex nanobiomaterials. Nonetheless, several phase I/II clinical trials have demonstrated promising clinical translation potential for various types of nanovaccines in treating

Table 3 Tumor nanovaccines for metastasis and recurrence in clinical trials in the past 5 years

Classifications	Nanoplatforms	Name	Active component	Design and arms	Cancer type	Primary objective	Results	Phases	NCT Number (status)/ Refs.
Biomimetic nanovaccine	Whole-cell vaccine	Mixed vaccine	–	Control vs. mix vaccine	Metastatic colorectal cancer	Relief degree of tumors	–	I/II	NCT03357276 (Completed)
	Gene-modified tumor cell	Allogeneic GM-CSF-secreting breast cancer vaccine	–	Allogeneic GM-CSF-secreting breast cancer vaccine + Trastuzumab + Cyclophosphamide	HER-2/neu-overexpressing metastatic BC	Adverse events, clinical benefit	Overall median PFS and OS were 7 months and 42 months, respectively; the 5-year survival rate was 30% [6 of 20]	II	NCT00399529 (Completed) [311]
			–	Cyclophosphamide + Vaccine vs. -Cyclophosphamide + zVaccine + Trastuzumab	Metastatic HER2-negative breast cancer	Toxicity, clinical benefit	–	II	NCT00971737 (Completed)
				Trastuzumab + Cyclophosphamide + vaccine	High risk/metastatic HER-2/Neu-overexpressing BC	Safety	–	II	NCT00847171 (Completed)
	Genetically modified autologous DCs	Anti-HER2/HER3 DC		Anti-HER2/HER3 dendritic cell vaccine + Pembrolizumab	Brain metastatic malignancy, metastatic TNBC	CNS, ORR	–	II	NCT04348747 (Recruiting)
	Neoantigen DC vaccine	NA DC vaccine		Neoantigen DC vaccine + Nivolumab	Liver metastases from CRC	Relapse free survival, immune response	–	II	NCT04912765 (Recruiting)
	Antigen-loaded DC-based vaccines	Dendritic Cells for endometrial cancer		Dendritic Cells for endometrial cancer	Metastaticendometrial cancer	Immunologic efficacy	–	II	NCT04212377 (Completed)
	CAR-DC Vaccine	KRAS-EphA-2-CAR-DC	Autologous EphA2-targeting CAR-DC vaccine loaded with KRAS mutant peptide	KRAS-EphA-2-CAR-DC + Anti-PD-1/CTLA4 antibody	Metastatic solid tumors	Safety, efficacy, immune response	–	I	NCT05631899 (Recruiting)
	DC-based vaccines	Dendritic cell vaccination	Autologous DCs pulsed with lysate derived from an allogeneic stem-like cell line	Dendritic cell vaccination ± bevacizumab	Recurrent glioblastoma with minimal residual tumor	Safety, tolerability	mPFS 3.23 months, 6-month PFS 24%, mOS 11.97 months	I	NCT02010606 (Completed) [283]

Table 3 (continued)

Classifications	Nanoplatforms	Name	Active component	Design and arms	Cancer type	Primary objective	Results	Phases	NCT Number (status)/ Refs.
		DC IKKb	IKKb-matured, RNA-loaded DCs	DC IKKb	Metastasized uveal melanoma	Safety, Tolerability, DLTS, MTD	–	I	NCT04335890 (Active, not recruiting)
		MesoPher/Mitazalimab	DCs Loaded With Allogeneic Tumor Lysate (MesoPher) and a CD40 Agonist (Mitazalimab)	MesoPher/Mitazalimab	Metastatic pancreatic cancer	DLTs	–	I	NCT05650918 (Recruiting)
		PEP-DC vaccine	Autologous dendritic cell vaccine loaded with personalized peptides	PEP-DC vaccine + cyclophosphamide	Metastatic NSCLC	AEs	–	I	NCT05195619 (Recruiting)
		HER2-pulsed dendritic cell vaccine	DC1 vaccine	DC1 vaccine + Trastuzumab + Pepinemab + T-cell therapy	Metastatic HER2 + BC	MTD		I	NCT05378464 (Recruiting)
		DC/PANVAC	autologous DCs modified with PANVAC	Bcl-XL_42-CAF09b vaccine	Prostate cancer with lymph node metastases	Safety	–	I	NCT03412786(Completed)
		mRNA tumor antigen-pulsed DCs	mRNA-pulsed autologous DCs	mRNA-pulsed autologous DCs	Advanced cancer patients with brain metastases	Adverse events	Favorable overall survival, without obvious autoimmune adverse events	I	NCT02808416 (Completed) [282]
		αDC1-TBVA vaccine	DC vaccine incorporating tumor blood vessel antigen-derived peptides	Gemcitabine hydrochloride (GEM) + αDC1-TBVA vaccine	Metastatic breast cancer	Safety, clinical response	–	I	NCT02479230 (Completed)
		Prodencel	autologous dendritic cell vaccine	Prodencel; an autologous dendritic cell therapeutic tumor vaccine	mCRPC	Safety	–	I	NCT05533203 (Recruiting)
		MIDRIX4-LUNG	Tetravalent autologous dendritic cell vaccine	Intra-patient dose escalation of intravenous MIDRIX4-LUNG autologous DC vaccine	Metastatic NSCLC	Toxicity, maximal tolerated dose	–	I	NCT04082182 (Active, not recruiting)
		Multiepitope DC Vaccine	Autologous DCs	Therapeutic autologous dendritic cells + trastuzumab + vinorelbine	Locally recurrent or metastatic BC	Efficacy, toxicity	Safe and can induce immune responses	II	NCT00266110 (Completed) [312]

Table 3 (continued)

Classifications	Nanoplatforms	Name	Active component	Design and arms	Cancer type	Primary objective	Results	Phases	NCT Number (status)/ Refs.
		BPX101	PSMA- targeting autologous DC	BPX-201 + AP1903	Metastatic prostate cancer	Safety, tolerability	–	I	NCT01823978 (Completed)
	T cell-based vaccine	Allogeneic HPV-specific T Cells		Allogeneic bone marrow transplant, CD8-depleted donor lymphocyte infusion (DLI) per dose escalation scheme	Metastatic HPV16 + cancer	Safety, MTD	–	I/II	NCT04713046 (Not yet recruiting)
	Neoantigen vaccines	PNVAC		PNVAC + adjuvant ISA 51 (subcutaneously) following adjuvant chemotherapy (capecitabine/ S1 + oxaliplatin or S-1 + docetaxel)	Post-surgical resection/ recurrence of stage IIIB/IIIC/ IVA GC	Safety, immune response	Higher one- and two-year survival rates 96.6% (28/29), 82.4% (14/17)) than historical record)	I	ChiCTR1800017319/[295]
		EVAX-01-CAF09b		EVAX-01-CAF09b + Anti-PD-1 or Anti-PD-L1	Metastatic solid tumors	Adverse events	–	I/II	NCT03715985 (Active, not recruiting)
		OVM-200		OVM-200	Metastatic NSCLC, ovarian Cancer, prostate Cancer	Safety, tolerability	–	I	NCT05104515 (Recruiting)
		VB10.NEO		VB10.NEO + Atezolizumab	Metastatic solid tumors	AEs		I	NCT05018273(Recruiting)
		Neoantigen DNA vaccine		Neoantigen DNA vaccine + Ipilimumab/ Nivolumab	Metastatic hormone-sensitive prostate cancer	Safety, tolerability, immune response	–	I	NCT03532217 (Completed)
		AlloStim®		AlloStim vs. AlloStim + cryoablation	Metastati colorectal cancer	Safety	–	II	NCT02380443 (Completed)
		GVAX	Allogeneic colon cancer cell vaccine administered with a GM-CSF producing bystander cell line	GVAX + Cyclophosphamide	Metastatic colorectal cancer	Toxicity	The six of nine patients who underwent curative metastasectomy survived longer than 36 months, and four of these six patients were without disease recurrence	I	NCT00656123 (Completed) [313]

Table 3 (continued)

Classifications	Nanoplatforms	Name	Active component	Design and arms	Cancer type	Primary objective	Results	Phases	NCT Number (status)/ Refs.
		GVAX pancreas vaccine	Granulocyte–macrophage colony-stimulating factor-secreting allogeneic pancreatic tumor cells	Cyclophosphamide/GVAX + CRS-207 vs. CRS-207 vs. standard chemotherapy	Metastatic pancreatic cancer	OS	The combination of Cy/GVAX + CRS-207 did not improve survival; no treatment-related deaths occurred	II	NCT02004262 (completed) [314]
		GRT-C901/GRT-R902	Patient-specific neoantigen vaccine	Control vs. GRT-C901/GRT-R902 + Atezolizumab/Ipilimumab + fluoropyrimidine/bevacizumab vs. fluoropyrimidine/bevacizumab	Metastatic colorectal cancer	ctDNA, PFS	–	II/III	NCT05141721 (Active, not recruiting)
Peptide vaccines	–	Vigil™ vaccine	Autologous whole-cell vaccine, Vigil™	Placebo vs. Vigil™ Vaccine	Colorectal carcinoma with liver metastases	Immune analysis, percent of patients who progressed or survived after treatment	–	II	NCT01505166 (Terminated)
	–	IMU-131		IMU-131 + Chemotherapy or Pembrolizumab	Metastatic Gastric or Gastroesophageal Junction (GEJ) Adenocarcinomas	ORR, AEs		II	NCT05311176 (Recruiting)
	–	AE37		AE37 + Pembrolizumab	mTNBC	Adverse events, ORR	–	II	NCT04024800 (Active, not recruiting)
	Multi-peptide cancer vaccine	PVX-410		PVX-410 + Pembrolizumab + Chemotherapy	Metastatic TNBC	PFS	–	II	NCT04634747 (Not yet recruiting)
	Synthetic long peptides	ISA101b Vaccine		Cemiplimab + ISA101b Vaccine	Metastatic HPV 16 cervical cancer	ORR	–	II	NCT04646005 (Active, not recruiting)
	Multi-peptide vaccine	PolyPEPI1018		PolyPEPI1018 + Atezolizumab	mCRC	Adverse events	–	II	NCT05243862 (Active, not recruiting)
	Multi-peptide vaccine	PolyPEPI1018		PolyPEPI1018 + TAS-102	mCRC	Adverse events	–	I	NCT05130060 (Completed)

Table 3 (continued)

Classifications	Nanoplatforms	Name	Active component	Design and arms	Cancer type	Primary objective	Results	Phases	NCT Number (status)/ Refs.
	–	SurVaxM	Survivin long peptide vaccine	SVN53-67/M57-KLH peptide vaccine + sargramostim + octreotide acetate	Survivin positive metastatic pancreatic neuroendocrine tumor	safety, tolerability, toxicity	–	I	NCT03879694 (Recruiting)
	A recombinant protein	dHER2 + AS15 cancer vaccine		dHER2 + AS15 ASCI vs. dHER2 + AS15 ASCI + Lapatinib	Metastatic breast cancer	Safety	No cardiotoxicity; immunogenic with promising long-term survival in those with HER2-overexpressing breast cancers	I/II	NCT00952692 (Completed) [315]
	–	UCPVax	Universal cancer peptide-based vaccination	UCPVax	Metastatic NSCLC	DLT, dose-related immunogenicity	The 1-year PFS and the median OS were 17.2% and 11.6 months in immune responders (P = 0.015)	I/II	NCT02818426 (Active, not recruiting)[316]
DNA vaccines	Plasmid DNA vaccine	pTVG-HP, pTVG-AR		pTVG-HP + Pembrolizumab vs. pTVG-AR + pTVG-HP + Pembrolizumab	Metastaticprostate cancer	PFS	–	II	NCT04090528 (Recruiting)
Viral vaccine	Modified vaccinia Ankara (MVA) virus	MVA-BN-Brachyury		MVA-BN-Brachyury	Metastatic or unresectable locally advanced malignant solid tumors	DLT	Safe, tolerable	I	NCT04134312(Complete) [285]
	Autologous, cell-based, HPV therapeutic cancer vaccine	SQZ-eAPC-HPV	Autologous, cell-based, HPV therapeutic cancer vaccine	SQZ-eAPC-HPV vs. SQZ-eAPC-HPV + ICBs	HPV16 + metastatic solid tumors	AEs, DLTs	–	I/II	NCT05357898 (Recruiting)
	Autologous PBMCs modified to present HPV16 antigens	SQZ-PBMC-HPV		SQZ-PBMC-HPV + nivolumab/ipilimumab/atezolizumab	Metastatic solid tumors	AEs, ORR, PFS, OS		I	NCT04084951 (Completed)

Table 3 (continued)

Classifications	Nanoplatforms	Name	Active component	Design and arms	Cancer type	Primary objective	Results	Phases	NCT Number (status)/ Refs.
	autologous RBCs	SQZ-AAC-HPV	autologous RBCs engineered to deliver synthetic long peptides (SLP) of HPV16 E6, E7 and the adjuvant, poly I:C	SQZ-AAC-HPV vs. SQZ-AAC-HPV + nivolumab and/or ipilimumab	Metastatic HPV16 + solid tumors	AEs, DLT	–	I	NCT04892043 (Recruiting)
	Arenavirus Pichinde virus/ arenavirus lymphocytic choriomeningitis virus	HB-302/HB-301		HB-302/HB-301 Alternating 2-Vector Therapy	Metastatic prostate cancer	DLT, AEs, ORR		I/II	NCT05553639 (Recruiting)
	A modified measles virus	MV-s-NAP	Measles virus derivative expressing the helicobacter pylori neutrophil-activating protein	MV-s-NAP	Metastatic BC	Safety, toxicity	–	I	NCT04521764 (Recruiting)
	Poxviral-based vaccine	BN-CV301 vaccine	A recombinant poxviral vaccine targeting MUC1 and CEA with co-stimulatory molecules	SX-682 followed by BinTraFusp Alfa + CV301	Metastatic solid tumors	DLT, AEs	–	I/II	NCT04574583 (Active, not recruiting)
	Virus-based vaccine	ETBX-021	A modified adenovirus 5 that is inserted into the HER2 gene	ETBX-021	Metastatic HER2-low BC	MTD, DLTs, AEs,	-	I	NCT02751528 (Active, not recruiting)
	Adenovirus vaccine	AdMA3 vaccine	Adenovirus vaccine with transgenic MAGE-A3 insertion	MG1MA3 virus vs. AdMA3 vaccine vs. AdMA3 + MG1MA3	Metastatic MAGE-A3-expressing solid tumors	Toxicity, ORR	Feasible, induce anti-tumor immune response	I/II	NCT02285816 (Active, not recruiting) [317]
Lipid nanoparticle	mRNA Lipid NPs	mRNA-2752	mRNA encoding human OX40L, IL-23, and IL-36γ	mRNA-2752 alone vs. mRNA-2752 + Durvalumab	Relapsed/refractory solid tumor	Safety, tolerability, immune response	Elicit anti-tumor T cells	I	NCT03739931 (Recruiting)
	Pegylated liposome	Pegylated liposomal doxorubicin	Doxorubicin	Chemo only vs. Chemo + ipilimumab + nivolumab	Metastatic BC	Toxicity, PFS	Induce a Type I interferon immune response	II	NCT03409198 (Active, not recruiting)
Polymeric nanoparticles	–	NLG207 (CRLX101)	Camptothecin	CRLX101 + Enzalutamide	mCRPC	Anti-tumor activity	Study was closed for toxicity, two of the four patients experienced DLTs	II	NCT03531827 (Terminated) [293]

Table 3 (continued)

Classifications	Nanoplatforms	Name	Active component	Design and arms	Cancer type	Primary objective	Results	Phases	NCT Number (status)/ Refs.
Inorganic	allogenic large multivalent immunogen (LMI) vaccines in silica particles	LMI Vaccine With IL-2	–	LMI Vaccination + IL-2	Metastatic BC	Disease response	–	II	NCT00784524 (Terminated)
Exosomal vaccines	-	Chimeric exosomal tumor vaccines	–	Chimeric exosomal tumor vaccines	Metastatic BC	Clinical response rate, OS, safety	–	I	NCT05559177 (Recruiting)

BC breast cancer, *DCs* dendritic cells, *CNS* central nervous system symptoms, *RR* relative risk, *TNBC* triple-negative breast cancer, *CRC* colorectal cancer, *DLTS* dose-limiting toxicity, *MTD* maximum tolerated dose, *AEs* adverse events, *NSCLC* non-small cell lung cancer, *ORR* objective response rate, *PFS* progression-free survival, *OS* overall survival

metastatic solid cancers, including BC, glioblastoma, gastric cancer, colorectal cancer, prostate cancer, cervical cancer, endometrial cancer, uveal melanoma, pancreatic cancer, non-small cell lung cancer, and other solid cancers (Table 3).

Nanovaccine monotherapy

DCs exert critical effects in the initiation of the primary response and the induction of an anti-metastasis-specific immune response. DC vaccine therapies are developed to elicit tumor-specific cytotoxic T-cell responses. DC-derived exosome-based nanovaccines have shown favorable safety profiles in phase I clinical trials of patients with metastatic melanoma [281]. Moreover, mRNA tumor antigen-pulsed DCs induce TAA-specific $CD4^+$ and $CD8^+$ T-cell responses without severe autoimmune adverse events and are associated with favorable overall survival [282]. In a single-institution phase I trial involving 25 patients with recurrent glioblastoma multiforme, an autologous DC vaccine loaded with a lysate from an allogeneic stem-like cell line demonstrated safety and tolerability, with a six-month progression-free survival (PFS) rate of 24%, a median survival of 11.97 months, and a median PFS of 3.23 months, showing favorable outcomes compared to historical controls [283].

Besides TAAs and TSAs, CIGB-247, a multiple-TME-targeting vaccine that uses a variant of human VEGF mixed with the bacteria-derived adjuvant VSSP, was demonstrated to be safe and immunogenic for metastatic disease in a clinical trial [284]. For instance, a recent phase I study has been completed utilizing DCs pulsed with tumor blood vessel antigens (NCT02479230).

Bavarian Nordic (BN)-brachyury represents a novel prime–boost therapeutic tumor immunotherapy approach. It comprises a modified vaccinia Ankara (MVA)-vector vaccine followed by an FPV-vector booster vaccine, both targeting the transcription factor brachyury [285]. In a phase I open-label trial of the intravenous administration of the MVA-BN-brachyury-TRICOM vaccine among patients with advanced cancer, the maximal administered dose was 10^9 infectious units every three weeks for three doses [286]. This dose was recommended as phase II dose because of its safety and tolerability.

Nanovaccines have been shown to be safe and effective in the treatment of cancer, indicating good biocompatibility and few side effects. Overall, these outcomes warrant investment into their continued development in the context of general oncology.

Nanovaccine-based combination therapy

Suppressing tumors by inducing an anti-tumor immune response typically requires a considerable amount of time, making it challenging to completely eradicate progressive primary tumors solely through host anti-tumor immunity. Hence, the integration of nanovaccine-based immunotherapy with other complementary therapies (e.g., chemotherapy, PTT, and photodynamic therapy) can result in a synergistic response against metastasis [108].

Therapeutic mRNA vaccine technology has promoted the development of personalized neoantigen vaccines by facilitating the rapid development of personalized vaccines that express a wide array of new antigens and activate APCs. Additionally, these vaccines can be delivered using clinically validated LNPs. In a small phase I clinical trial (NCT04161755) of an mRNA pancreatic cancer vaccine, a personalized mRNA vaccine strategy was developed, namely, autogene cevumeran (BNT122). This strategy facilitates the expression of 20 new antigens of patients with PDAC, using LNPs for intravenous administration. The personalized mRNA vaccine, when combined with mFOLFIRINOX regimen and anti-PD-L1 antibody, resulted in 50% of pancreatic cancer patients who underwent tumor resection not showing signs of recurrence after 18 months; in addition, these patients showed no side effects [287].

After 30 years of failed attempts, this is the first successful trial of a pancreatic cancer mRNA vaccine. Although this innovation is still in its early stages, it is important to acknowledge it as a great milestone that shows great promise in yielding novel and highly effective anti-cancer treatments. The mRNA vaccine technology enables the rapid development, large-scale production, and delivery of vaccines without significantly delayed treatment of rapidly progressive pancreatic cancer.

Another innovative personalized cancer vaccine based on mRNA, mRNA-4157/V940, consists of a single mRNA encoding 34 tumor neoantigens. Theoretically, this vaccine should be capable of eliciting both MHC class I and MHC class II presentation pathways. The design of this vaccine is rooted in its high specificity for the genomic information of an individual patient. In the phase IIb KEYNOTE-942/mRNA-4157-P201 clinical trial (NCT03897881), the mRNA vaccine was combined with the anti-PD-1 therapy KEYTRUDA® for adjuvant treatment of completely resected stage III/IV melanoma patients; overall, 157 patients have thus far been recruited for this trial. Compared to KEYTRUDA alone, the use of mRNA-4157/V940 in combination with KEYTRUDA for adjuvant treatment has been shown to reduce the risk of recurrence or death by 44% [288].

A pivotal phase III clinical trial (NCT05933577) has been initiated to evaluate the efficacy and safety of the tumor neoantigen mRNA vaccine (mRNA-4157) combined with the PD-1 inhibitor KEYTRUDA as am

adjuvant therapy for high-risk cutaneous melanoma patients who have undergone surgical resection (stage IIB–IV). Additionally, in the past 2 years, trials combining mRNA-4157 with KEYTRUDA have been conducted for renal cell carcinoma (NCT06307431, phase II), non-small cell lung cancer (NCT06077760, phase III), cutaneous squamous cell carcinoma (NCT06295809, phase II/III), and bladder cancer (NCT06305767, phase II).

Nanovaccines have been combined with the aim of creating or re-establishing a TME that favors the generation of anti-tumor immune responses, offering promising clinical translation potential. For example, HER 3 overexpression in triple-negative and HER 2-positive brain metastatic breast cancer is a resistance factor to HER 2-targeted therapy as well as a driver of CNS metastasis. Therefore, a phase II clinical study is currently exploring the combination of the HER 2 / HER 3-targeting α DC1 vaccine with pembrolizumab in patients with asymptomatic brain metastases derived from triple-negative or HER 2-positive breast cancer. Similarly, a phase I clinical trial (NCT03739931) is evaluating mRNA-2752, which encodes human OX40L, IL-23, and IL-36γ and is loaded into LNPs; this approach is intended to manage recurring or treatment-resistant solid tumors. Notably, unlike other tumor types that elicit anti-tumor T cells, the efficacy of mRNA-2752 combined with ICB has not been explored in the treatment of colorectal cancer [289].

The ASPIRE nanovaccine is crafted from genetically modified nanovesicles that originate from the cell membranes of dendritic cells infected with adenovirus. This innovative vaccine combines antigen self-presentation with the reversal of immunosuppression. By utilizing a programmed approach to attach specific components, it markedly improves the delivery of antigens to lymphoid organs. The nanovaccine generates extensive T-cell responses that can eradicate existing tumors and offers a powerful vaccine formulation that can effectively activate both naive and exhausted T cells for cancer immunotherapy [290].

In vivo, the topical TLR-7 agonist imiquimod activates DCs, enhancing antigen processing and presentation through type 1 interferon secretion. This activation upregulates immune co-stimulatory molecules in tumors, leading to cancer growth inhibition [291]. The combination of imiquimod and systemic albumin-bound paclitaxel has shown to effectively reduce disease progression in treatment-resistant breast cancer of the chest wall while exhibiting manageable toxicity. Importantly, pre-existing levels of cells that indicate T-cell exhaustion or systemic immunosuppression may act as markers to identify patients likely to respond favorably to the treatment.

Enzalutamide, an androgen receptor antagonist, is the standard therapy option against metastatic prostate cancer [292]. A single-arm phase II study was conducted on patients with progressive, metastatic, castration-resistant prostate cancer who had already progressed on enzalutamide. In this study, a combination treatment of 1 mg/m of CRLX101, a NP topoisomerase I inhibitor containing camptothecin, was administered [293]. However, the study was terminated because of toxicity, with two of the four patients experienced dose-limiting toxicities.

Primary tumors have been shown to secrete high levels of granulocyte CSF, driving epigenetic changes in bone marrow granulocyte monocyte precursor cells. This trend culminates in the disruption of the immune system, with APCs being most impacted. Consequently, nanovaccines targeting metastases are rendered ineffective [294]. Debulking surgery can reverse tumor-growth-driven changes in the immune system; specifically, this approach corrects the dysfunction of APCs, thereby restoring the effectiveness of nanovaccines. These findings highlight the importance of the holistic consideration of the immune environment affected by tumor growth when designing and evaluating tumor nanovaccines. Combining primary tumor resection with NanoVac emerges as a promising and radical treatment for widely metastatic tumors [294]. In a phase I clinical trial (ChiCTR1800017319), researchers developed and assessed the safety and feasibility of a personalized neoantigen nanovaccine (PNVAC) platform targeting tumors. The focus of this trial was to use the PNVAC to slow the progression of gastric cancer in high-risk patients with gastric/gastroesophageal junction cancer after receiving adjuvant chemotherapy following surgery [295]. The trial demonstrated markedly improved 1- and 2-year disease-free survival rates compared to previously published outcomes. In another clinical study, patients received treatment with a PVNAC combined with PD-1 monoclonal antibody and/or anti-angiogenic drugs (ChiCTR1900022986). The PVNAC was shown to be safe and well-tolerated. Clinical responses were observed in combination with PD-1 monoclonal antibody and anti-angiogenic drugs, and neoantigen-specific T-cell responses were detected following vaccination. In terms of its mechanism, the PNVAC triggers CD4 + and CD8 + T-cell responses, along with the presence of antigen-experienced memory T cells that can still be detected 1 year after the administration of the vaccine.

The careful timing of administration is essential to avoid interference between the combined treatments. Overall, clinical trials evaluating nanovaccines for the treatment of metastatic cancer have failed to yield convincing results. Moreover, there is a scarcity of phase III trials involving patients with metastatic disease.

Challenges and future perspectives

Nanovaccines demonstrate significant anti-metastasis effects in animal tumor models, offering advantages such as safety and reduced side effects. However, several challenges still need to be addressed prior to their clinical translation.

First, the vast heterogeneity of biological barriers in patients with metastatic cancers presents a challenge in effectively evaluating NP platforms across diverse populations. This diversity may obscure the potential success of these platforms in treating specific subgroups. To tackle this issue, there is a need for increased stratified trials and customized nanovaccines [23]. However, the development of personalized vaccines requires the challenging task of efficiently and accurately identifying patient-specific antigens, underscoring the importance of enhancing the integration of biotechniques and computer simulation methods for antigen sequencing and identification. Cancer cell membranes derived from the tumor of an individual patient could be used to coat NPs, with the aim of ensuring the use of an optimal set of antigens for training the immune system.

The large-scale production of nanovaccines with acceptable batch-to-batch differences remains a significant challenge. This challenge can be attributed to the currently volatile nature of these vaccines and their inherently high manufacturing costs. For example, tumor immunotherapy using autologous APCs is expensive and time consuming [12]. For efficient large-scale production, nanobiomaterials require several key traits, including biodegradability, biocompatibility, and biostability. Additionally, their preparation methods should be well established and reliable. For example, the biocompatibility and biodegradability of nanocarriers, particularly inorganic nanocarriers, require further investigation [30]. Therefore, we should strive to find an efficient and economical method for up-scaling nanovaccine production. Furthermore, balancing functional complexity and structural simplicity in vaccine design is necessary for successful clinical applications. Simpler nanobiomaterials are more conducive to clinical translation. LNPs with straightforward compositions and established production methods appear promising for future human testing [38].

Challenges also persist in chemistry, manufacturing, and control processes. For instance, ensuring that cellular components are free of heat and pathogen contamination while eliminating denatured proteins is crucial to prevent potential immune responses against endogenous antigens. In addition, antigen/adjuvant leakage and the scaled-up production of biomimetic nanovaccines are significant hurdles in clinical translation [296]. Thus, establishing a quality control standard during chemistry, manufacturing, and control research is imperative [296].

The combined use of nanovaccines and immune checkpoint inhibitors has a complementary mechanism in tumor immunotherapy [297, 298]. Combining vaccines with immune checkpoint inhibitors could potentially lead to a synergistic effect, enhancing the immune response against tumors [299]. However, immune checkpoint inhibitors can activate both tumor-specific T cells and other non-specific T cells, which may lead to side effects such as cytokine storms. Ideally, the focus should be on eliminating inhibitory signals specifically targeting the activated tumor-specific T cells while preserving the inhibitory signals for other self-antigens. It would be most effective to selectively activate only those T cells that are able to recognize this specific group of antigens. However, this could increase the cost of drug development, thus highlighting the need for further investigation and consideration in future research.

In addition, the complete response rate for the strategy of combining a vaccine with immune checkpoint inhibitors remains unresolved. Liu et al. described a genetically engineered cell membrane nanocesicle antigen self-presentation and immunosuppression reversal (ASPIRE) strategy that may disrupt the general vaccine development routine, improve the efficiency of antigen presentation through antigen self-presentation, and drive CD8 T cell-led immunity against tumors with a strong CTL immune response [290].

The outcomes of nanovaccines with immunotherapy are also influenced by previous treatment history, specific tumor biology, and systemic effects of cancer on the immune system, which often cannot be predicted accurately by pre-clinical studies. Difficulty in assessing the limitations of preclinical models and the "over-interpretation" of preclinical data may lead to a lack of sufficient biological basis for combinatorial therapies. Pre-identified biomarkers could enhance the effectiveness of combinatorial therapies [300].

Overall, the investigation of NPs for vaccine delivery remains in its infancy, and numerous challenges remain for researchers to overcome. These challenges include understanding the mechanisms by which physiochemical properties determine the anti-tumor effect through their impact on NP biodistribution and targeting ability, maintaining consistent characteristics during manufacturing, and integrating nanovaccines with other therapeutic modalities to achieve more effective results. These challenges limit the clinical translation of nanovaccines and underscore the need for further extensive research.

Nanovaccines encapsulate antigens and adjuvants into nanocarriers, effectively enhancing the stability, durability, and immunogenicity of vaccines. Nanovaccines can be channeled toward addressing tumor metastasis by enhancing the immune memory effect of the immune

system. Additionally, these vaccines can facilitate precise treatment, since they can be designed on the basis of the immune characteristics of an individual patient and the specificity of the tumor, thereby achieving personalized treatment, improving treatment outcomes, and reducing side effects. Nanovaccines show great potential in their applicability toward the treatment of cancer metastasis, as they have thus far been shown to improve treatment outcomes and reduce treatment risks. Considering the continuous development and improvement of nanotechnology, nanovaccines are expected to yield a wide range of applications and breakthroughs in the context of cancer treatment.

Conclusions

Personalized anti-metastatic nanovaccines are unique in their ability to precisely target specific groups of cancerous cells, significantly setting them apart from traditional anti-cancer nanomedicines. Nanocarriers of various sizes, compositions, and physical parameters have been used to develop a range of nanovaccine strategies that target different stages of metastasis, thus preventing its progression. To develop precise anti-metastasis nanovaccines, the selection of appropriate NP platforms meeting specific requirements is crucial. This review has highlighted various promising NP platforms for developing anti-metastasis nanovaccines, including synthetic, semi-biogenic, and biogenic nanosystems, and emphasizes their physical and pharmacological properties in enhancing the efficacy of cancer vaccines against metastasis. Additionally, we have discussed the latest trends in combining nanovaccines with cancer immunotherapy to address various steps in the metastatic cascade, drawing insights from both preclinical and clinical research.

The design of personalized nanovaccines is based on the consideration of the crucial role of NPs in vaccine stability, antigen recognition, and delivery. These NPs can exhibit high tumor penetration, aid in the effective delivery of vaccine components to the lymphatic system and provide a suitable environment to enhance immune responses. The strategies discussed in this review can be used to combat the complex primary TME, modulate the metabolic microenvironment, reprogram the TIME, and target various cell types and stromal components within the TME. Furthermore, nanovaccines have the potential to intercept CTCs and combat secondary tumors by reshaping the microenvironment in distant metastatic organs, including modulating the PMN and targeting established metastases.

Although personalized nanovaccines hold promise in the treatment of solid cancer metastasis, challenges persist, including low clinical response rates. To overcome these challenges, researchers are continuously improving the design of nanocarriers, exploring more effective combinations of antigens and adjuvants, and integrating personalized nanovaccines with other cancer treatment methods to enhance therapeutic outcomes. The strategic development of nanovaccines will facilitate the precise administration of different antigens, adjuvants, and immune-regulatory substances, greatly transcending the capabilities of traditional vaccination methods. Thus, nanovaccines emerge as a promising strategy for both suppressing primary tumors and preventing tumor metastasis by enhancing long-term anti-cancer immune responses. The development of personalized nanovaccines holds even greater promise for patients with cancer in the future.

Abbreviations

aAPC	Artificial APC
APC	Antigen-presenting cell
AuNP	Gold nanoparticle
ASPIRE	Antigen self-presentation and immunosuppression reversal
BC	Breast cancer
BN	Bavarian Nordic
CAF	Cancer-associated fibroblast
CNP	Carbon nanoparticle
CNS	Central nervous system
CpG	Cytosine–phosphate–guanosine oligonucleotides
CSC	Cancer stem cell
CTC	Circulating tumor cell
CTL	Cytotoxic T lymphocyte
DC	Dendritic cell
DEX_{AFP}	Fetoprotein-expressing dendritic cell
ECM	Extracellular matrix
EMT	Epithelial–mesenchymal transition
FAP	Fibroblast activation protein
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HCC	Hepatocellular carcinoma
HIF	Hypoxia-inducible factor
HSA	Human serum albumin
ICB	Immune checkpoint blockade
IFN	Interferon
IL-2	Interleukin-2
LNP	Lipid nanoparticle
LN	Lymph node
LPHNP	Lipid–polymer hybrid nanoparticle
MAN-IMO-PS	Mannose-functionalized lipid-hybrid polymersomes
MHC	Histocompatibility complex class
mLPR	MPLA/mRNA tumor vaccine
MMPI	Matrix metalloproteinase inhibitor
MMP	Matrix metalloproteinase
MSN	Mesoporous silica (or silicon) nanoparticle
MVA	Modified vaccinia Ankara
NG	Nanogel
NIR	Near-infrared
NK	Natural killer
NP	Nanoparticle
OMV	Outer membrane vesicle
OVA	Ovalbumin
PD-L1	Programmed cell death ligand 1
PDAC	Pancreatic ductal adenocarcinoma
PEG	Polyethylene glycol
PFS	Progression-free survival
PLGA	Poly (lactic-co-glycolic acid)
PMN	Polymorphonuclear neutrophil leukocyte
PNVAC	Personalized neoantigen nanovaccine
PRR	Pattern recognition receptor
PTT	Photothermal treatment

siRNA	Small interfering RNA
SPION	Superparamagnetic iron oxide nanoparticle
STING	Stimulators of interferon gene
TAA	Tumor-associated antigen
TAF	Tumor-associated fibroblast
TGF	Transforming growth factor
Th1	T helper type 1
Th2	T helper type 2
TIME	Tumor immune microenvironment
TLR4	Toll-like receptor 4
TME	Tumor microenvironment
Treg	Regulatory T cell
TRP2	Tumor-associated self-antigen
TSA	Tumor-specific antigen
VEGF	Vascular endothelial growth factor
VLP	Virus-like particle

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

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