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Nanovaccines in Cancer Immunoprevention and Immunotherapy: Current Insights and Future Directions

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ABSTRACT

Cancer immunotherapy has emerged as a powerful approach to harness the immune system to combat tumors, while cancer immunoprevention aims to elicit protective immunity before cancer onset. Nanovaccines engineered nanoparticles that deliver tumor-associated antigens (TAAs), adjuvants, and immunomodulators have revolutionized the field by enhancing the stability, targeting, and efficacy of cancer vaccines. This review provides a comprehensive overview of nanovaccine platforms, including liposomes, polymeric nanoparticles, virus-like particles, and inorganic nanocarriers, and their role in reshaping cancer immunoprevention and immunotherapy. We examine how nanovaccines promote dendritic cell maturation, T-cell priming, and tumor infiltration, as well as their capacity to reverse immunosuppression in the tumor microenvironment. Special attention is given to the integration of nanovaccines with immune checkpoint blockade, CAR-T therapy, and neoantigen-based personalized vaccines. Furthermore, we discuss preclinical and clinical studies, regulatory challenges, and potential toxicity concerns. Finally, we outline future directions such as the development of smart and stimuli-responsive nanovaccines, AI-guided vaccine design, and scalable manufacturing processes. Nanovaccines represent a transformative modality that bridges prevention and therapy, offering hope for more precise, durable, and personalized cancer treatments.

INTRODUCTION

Cancer remains one of the most formidable global health challenges, ranking as a leading cause of death worldwide[1–4]. Despite significant advancements in conventional treatment modalities including surgery, chemotherapy, and radiotherapy these approaches often face limitations such as non-specific targeting, systemic toxicity, development of drug resistance, and limited long-term efficacy[5]. Moreover, these traditional treatments focus on eradicating established tumors but offer little in terms of preventing tumor initiation or recurrence. This has prompted a paradigm shift in cancer management strategies, with increasing emphasis on harnessing the power of the immune system for both prevention and treatment[6].

Two major immunological strategies have emerged in this context: immunoprevention and immunotherapy. Immunoprevention focuses on preventing the onset of cancer by inducing long-term protective immunity against oncogenic pathogens or tumor-specific antigens, thereby reducing cancer incidence in high-risk populations[7]. This approach is exemplified by the success of prophylactic vaccines against human papillomavirus (HPV) and hepatitis B virus (HBV), which have significantly lowered the incidence of cervical and liver cancers, respectively. In contrast, cancer immunotherapy aims to treat existing malignancies by enhancing the body's immune responses to recognize and eliminate tumor cells. This includes immune checkpoint inhibitors, adoptive T-cell therapies, and cancer vaccines, which have all demonstrated varying degrees of clinical success[8–10].

Among these, cancer vaccines designed to train the immune system to recognize and destroy tumor cells by targeting tumor-associated antigens (TAAs) or tumor-specific antigens (TSAs) are gaining significant attention[11]. However, several critical challenges have limited their efficacy. One major hurdle is the poor immunogenicity of many tumor antigens, which fail to elicit strong and durable immune responses. Additionally, rapid degradation of antigens in the body before they reach their target and inefficient delivery to professional antigen-presenting cells (APCs), particularly dendritic cells (DCs), further compromise vaccine effectiveness. Moreover, the immunosuppressive tumor microenvironment (TME)—characterized by regulatory T cells,

myeloid-derived suppressor cells, and immunosuppressive cytokines—can blunt immune activation and promote immune escape[12–14].

To address these limitations, researchers have turned to nanotechnology-based platforms, specifically nanovaccines, as a promising next-generation solution for both cancer immunoprevention and immunotherapy. Nanovaccines are engineered nanoscale delivery systems, typically ranging from 10 to 200 nanometers, designed to enhance the stability, targeting, and immunogenicity of cancer vaccines[15, 16]. These platforms are capable of **co**-delivering tumor antigens, adjuvants, and immune modulators in a single formulation, thereby orchestrating a more robust and coordinated immune response. The nanoscale size of these vaccines allows them to efficiently traffic through biological barriers and be preferentially taken up by APCs, particularly dendritic cells, which are crucial for initiating and regulating adaptive immune responses[17].

One of the most important features of nanovaccines is their ability to control the spatial and temporal release of their cargo[15, 18]. This controlled release can ensure prolonged antigen exposure, enhanced cross-presentation, and sustained immune activation. Furthermore, nanovaccines can be functionalized with targeting ligands, such as mannose, peptides, or antibodies, that selectively bind to receptors on dendritic cells or tumor cells, ensuring precise delivery to the desired site of action[19]. The biodegradable and biocompatible nature of many nanomaterials such as liposomes, polymeric nanoparticles, dendrimers, gold nanoparticles, and virus-like particles—further enhances their safety and translational potential. Another significant advantage of nanovaccines is their ability to modulate the tumor microenvironment[20]. For example, certain nanomaterials can be engineered to reverse immune suppression by delivering immune checkpoint inhibitors or cytokines directly into the TME, thus reprogramming it into an immune-permissive state. This is particularly important for overcoming the immunosuppressive barriers that often limit the success of traditional cancer vaccines. Additionally, nanovaccines are adaptable for personalized medicine, as they can be tailored to carry neoantigens unique to an individual's tumor[21, 22]. This offers the exciting potential for patient-specific cancer vaccines that induce highly specific immune responses, minimizing off-target effects and enhancing therapeutic outcomes.

In sum, nanovaccines represent a powerful technological advancement in the field of oncology, addressing many of the shortcomings associated with traditional cancer vaccines. Their unique properties such as efficient antigen delivery, enhanced immunogenicity, targeted action, and modulation of the tumor microenvironment make them highly promising candidates for both immunoprevention and immunotherapy. As research in this area continues to evolve, nanovaccine platforms are poised to transform cancer care by not only treating established tumors but also preventing their occurrence, paving the way for more effective and durable cancer control strategies.

2. Nanovaccine Platforms and Mechanisms

2.1 Liposomes

Liposomes are nanoscale spherical vesicles comprising one or more phospholipid bilayers surrounding aqueous cores[23–25]. This amphiphilic structure allows them to encapsulate both hydrophilic substances (within the core) and hydrophobic substances (within the lipid bilayer), making them highly versatile carriers for vaccine components such as tumor-associated antigens (TAAs), adjuvants, and immunomodulatory agents. Their inherent biocompatibility, low toxicity, and biodegradability render them ideal candidates for clinical use. Furthermore, liposomes can be engineered for controlled release, enhancing the pharmacokinetics of loaded biomolecules[24, 26].

A key feature that enhances the efficacy of liposomal vaccines is PEGylation, the attachment of polyethylene glycol (PEG) chains to the liposome surface. PEGylation stabilizes liposomes in circulation by reducing opsonization and subsequent clearance by the mononuclear phagocyte system, thereby prolonging systemic half-life[27, 28]. Additionally, surface functionalization with targeting ligands (such as mannose or antibodies) facilitates active targeting of antigen-presenting cells (APCs), particularly dendritic cells (DCs), enhancing antigen uptake and presentation.

Moreover, liposomes can be engineered to exhibit pH-sensitive or enzyme-responsive release profiles, ensuring that antigen release occurs preferentially in intracellular compartments such as endosomes or lysosomes[26, 29]. This can enhance cross-presentation on major histocompatibility complex (MHC) class I molecules, crucial for the activation of cytotoxic T lymphocytes (CTLs). Liposomes also allow co-encapsulation of TAAs with adjuvants, ensuring spatiotemporal co-delivery that mimics natural infection cues. Collectively, these attributes make liposomes a leading platform in nanovaccine development for cancer immunotherapy and immunoprevention.

2.2 Polymeric Nanoparticles

Polymeric nanoparticles, particularly those made from biodegradable polymers like poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLA), and natural polymers such as chitosan or alginate, are extensively studied nanocarriers for cancer vaccines[30–32]. These nanoparticles protect encapsulated antigens from premature degradation, ensure sustained release, and enhance the immune response by mimicking pathogen-like particle sizes and structures. Their ability to encapsulate and co-deliver antigens with immune-stimulating adjuvants makes them powerful tools for activating robust and long-lasting immune responses [33].

One of the major advantages of polymeric nanoparticles lies in their tunability. By modifying polymer composition, molecular weight, and surface chemistry, it is possible to control particle size, degradation rate, and release kinetics[31, 34, 35]. These properties are essential for tailoring vaccines to achieve optimal immune stimulation, especially for chronic or poorly immunogenic tumor antigens. Furthermore, surface modification with targeting ligands (e.g., mannose, folate, or antibodies) allows enhanced uptake by APCs such as dendritic cells and macrophages.

Importantly, polymeric nanoparticles can facilitate endosomal escape, a critical step for antigen cross-presentation on MHC class I molecules[36]. This pathway is essential for eliciting cytotoxic T lymphocyte (CTL) responses, which are pivotal for eliminating tumor cells. Chitosan-based particles, in particular, exhibit intrinsic mucoadhesive and immunostimulatory properties, adding to their appeal for mucosal vaccine delivery[36, 37].

Additionally, these nanoparticles can serve as platforms for co-delivering multiple components, such as antigens, cytokines, and TLR agonists, thereby mimicking the multifactorial nature of pathogen recognition. Overall, polymeric nanoparticles offer a highly flexible and potent strategy for engineering effective cancer nanovaccines[38].

2.3 Virus-Like Particles (VLPs)

Virus-like particles (VLPs) are self-assembled nanostructures derived from viral capsid proteins that resemble the morphology and size of actual viruses but lack infectious genetic material[39]. This structural mimicry enables them to efficiently engage the immune system, especially the humoral arm, without the risks associated with live or attenuated viral vectors. VLPs are highly immunogenic due to their multivalent surface presentation of repetitive epitopes, which cross-link B-cell receptors and induce strong antibody responses[39].

These particles can be produced using recombinant DNA technologies in a variety of expression systems, including yeast, insect, plant, and mammalian cells. VLPs have an established safety profile and are already approved in prophylactic vaccines, such as those against human papillomavirus (HPV) and hepatitis B virus (HBV)[40]. These vaccines have demonstrated remarkable success in preventing virus-associated cancers, such as cervical and hepatocellular carcinomas, establishing VLPs as a clinically validated nanovaccine platform.

VLPs can also be genetically or chemically modified to display tumor-associated antigens (TAAs) **or** neoantigens**,** making them suitable for therapeutic cancer vaccination[40]. Their particulate nature facilitates efficient uptake by APCs and trafficking to lymphoid organs. Furthermore, their intrinsic ability to activate innate immune pathways, such as toll-like receptors (TLRs), further boosts their immunostimulatory potential. Innovative approaches involve hybrid VLPs or chimeric designs incorporating multiple antigens or immunostimulatory molecules to enhance breadth and potency. Overall, VLPs offer a unique combination of safety, immunogenicity, and modularity**,** positioning them as a promising scaffold for both prophylactic and therapeutic cancer nanovaccines[41].

2.4 Inorganic Nanoparticles

Inorganic nanoparticles, such as gold nanoparticles (AuNPs), silica nanoparticles (SiNPs), iron oxide nanoparticles, and carbon-based nanomaterials like carbon nanotubes and graphene oxide, represent a diverse and multifunctional class of platforms in nanovaccine development[42, 43]. These materials offer unique physicochemical properties, including high surface area, tunable size and shape, magnetic responsiveness, and distinct optical signatures, making them valuable for both therapeutic and diagnostic (theranostic) applications.

One of the chief advantages of inorganic nanoparticles is their surface versatility**,** allowing for the conjugation or adsorption of multiple biomolecules. Tumor-associated antigens, immunostimulatory adjuvants (e.g., CpG oligonucleotides or TLR agonists), and targeting ligands can be simultaneously presented to immune cells.[44, 45] This co-delivery capacity enables precise spatial and temporal control over immunological signaling. Gold nanoparticles, in particular, are renowned for their biocompatibility and surface plasmon resonance properties, which can be harnessed for photo-thermal therapy and imaging[43, 46, 47]. Similarly, iron oxide nanoparticles provide magnetic properties useful in magnetic resonance imaging (MRI) and magnetic field-guided targeting to lymphoid tissues or tumors. Mesoporous silica nanoparticles offer a highly porous structure that can encapsulate a large payload and release it in a stimuli-responsive manner, such as pH or redox-triggered mechanisms.

Despite their promise, inorganic nanoparticles pose some challenges, especially in terms of long-term biocompatibility and clearance. Accumulation in off-target tissues and potential for chronic toxicity necessitate thorough safety evaluations[48]. Nonetheless, the capacity for multimodal use combining immune activation, imaging, and therapy positions inorganic nanoparticles as powerful tools in the advancement of nanovaccine platforms for cancer prevention and treatment[48].

3. Nanovaccines in Immunoprevention

Nanovaccines are emerging as a powerful tool in the immunopreventive landscape of cancer, offering the potential to stop malignancies before they fully develop. Unlike traditional vaccines that focus primarily on infectious diseases, cancer nanovaccines aim to prime the immune system against tumor-associated antigens (TAAs) or viral oncoproteins, thereby preventing cancer initiation or progression[49]. These vaccines are

particularly beneficial for individuals with high genetic predisposition (e.g., BRCA mutations, Lynch syndrome) or persistent viral infections like HPV and HBV, which are major risk factors for cervical and liver cancers, respectively[49].

Nanoparticles enable the precise delivery and sustained release of antigens and adjuvants to immune cells, enhancing immunogenicity and creating long-lasting memory responses. For instance, HPV vaccines formulated with nanoparticles have demonstrated stronger and more durable immune responses compared to conventional formulations[50]. These long-term immune responses are critical in maintaining immune surveillance to eliminate nascent transformed cells before they establish tumors. Furthermore, nanovaccine platforms can be customized to deliver neoantigens tumor-specific mutations unique to individual patients—allowing for personalized immunoprevention. In individuals with precancerous lesions, such as adenomas in colorectal cancer or ductal carcinoma in situ (DCIS) in breast cancer, nanovaccines may help prevent malignant progression by stimulating effective T-cell–mediated clearance[50].

Emerging strategies also focus on combining nanovaccines with checkpoint blockade or anti-inflammatory agents to reverse early immune suppression in the tumor microenvironment. Ultimately, nanovaccines may shift cancer management from treatment to prevention, especially in high-risk populations, representing a transformative advancement in public health and personalized medicine.

4. Nanovaccines in Cancer Immunotherapy

4.1 Enhancing Antigen Presentation

One of the primary advantages of nanovaccines in cancer immunotherapy lies in their ability to improve antigen presentation, a critical step in initiating effective T-cell responses. Nanoparticles are readily taken up by antigen-presenting cells (APCs), such as dendritic cells, due to their optimal size (20–200 nm) and surface characteristics[51]. Once internalized, these nanocarriers can promote cross-presentation of antigens on MHC class I molecules, which is crucial for activating cytotoxic CD8+ T cells capable of killing tumor cells.[51]

Co-delivery of adjuvants**,** such as toll-like receptor (TLR) agonists or STING activators, within the same nanoparticle enhances innate immune stimulation. This localized activation of innate immune pathways within APCs results in increased expression of co-stimulatory molecules (e.g., CD80, CD86) and pro-inflammatory cytokines (e.g., IL-12, IFN-γ), fostering a more robust adaptive immune response[52].

Moreover, nanoparticles can be engineered to respond to intracellular cues (like pH or redox conditions), enabling timed release of antigens and adjuvants precisely within endosomes or the cytosol[53]. This ensures that antigens are processed through the desired pathways to facilitate both MHC I and MHC II presentation, engaging both cytotoxic and helper T-cell responses. By enhancing antigen processing and immune priming, nanovaccines significantly improve the efficacy of cancer immunotherapy, particularly in tumors with low immunogenicity or poor antigen visibility[54].

4.2 Tumor Microenvironment Modulation

The tumor microenvironment (TME) presents a major barrier to effective immunotherapy, as it is often characterized by immunosuppressive elements such as regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), and inhibitory cytokines like TGF-β and IL-10[26, 55, 56]. These factors inhibit T-cell infiltration, antigen presentation, and cytotoxic activity, allowing tumors to evade immune surveillance. Nanovaccines can be designed to modulate the TME**,** converting it from immunosuppressive to immunostimulatory. This can be achieved by co-delivering antigens with agents that neutralize suppressive signals such as siRNAs targeting PD-L1 or IDO or immunostimulatory molecules like IL-12, GM-CSF, or TLR agonists. These payloads can reprogram TAMs from an M2 (pro-tumor) to M1 (anti-tumor) phenotype, deplete MDSCs, or inhibit Treg recruitment[57].

Additionally, nanoparticles can be functionalized to home selectively to the TME via ligands recognizing tumor vasculature or extracellular matrix components. Upon reaching the TME, stimuli-responsive nanoparticles release their contents in response to acidic pH, enzymatic activity, or oxidative stress, ensuring localized and potent immunomodulation[58]. This strategy not only enhances T-cell activation but also improves their infiltration and persistence within the tumor bed. Combining TME modulation with antigen presentation in a single nanoplatform ensures a coordinated attack on the tumor, overcoming immune resistance and improving overall therapeutic outcomes in cancer immunotherapy[58].

4.3 Combination Therapies

Nanovaccines have shown great promise when used in combination with other immunotherapeutic approaches, offering synergistic benefits that can overcome monotherapy limitations. One of the most successful strategies involves pairing nanovaccines with immune checkpoint inhibitors (ICIs)**,** such as antibodies against PD-1, PD-L1, or CTLA-4. While ICIs relieve T-cell exhaustion, nanovaccines ensure a continuous supply of activated, tumor-specific T cells. This combination has demonstrated enhanced efficacy in both preclinical models and early-phase clinical trials[59].

Another promising avenue is combining nanovaccines with adoptive cell therapies, including CAR-T and TCR-engineered T cells. Nanovaccines can be administered prior to or alongside cell transfer to prime the host immune system and broaden the antigen-specific T-cell repertoire, thereby improving engraftment, persistence,

and tumor-killing efficacy of infused cells[60]. Nanovaccines can also be integrated with radiotherapy or chemotherapy, which may increase tumor antigen release and immunogenic cell death, further enhancing vaccine-induced responses. In addition, some nanoparticles are engineered for co-delivery of multiple therapeutic agents, such as a tumor antigen, a checkpoint inhibitor, and a cytokine, within a single formulation. This ensures synchronized delivery and reduced systemic toxicity[61].

The versatility of nanovaccines allows for precise control over dose, timing, and localization, which is critical for optimizing combination regimens. As multi-modal cancer immunotherapies evolve, nanovaccines will play a central role in orchestrating coordinated immune responses, leading to improved survival and durable remissions across a range of malignancies[62].

5. Clinical Translation and Challenges

The clinical translation of nanovaccines for cancer therapy has progressed steadily, with several candidates entering Phase I and II trials. Notably, lipid nanoparticle-based mRNA vaccines such as BNT111 (BioNTech) and mRNA-4157 (Moderna) have shown promising results when used in combination with checkpoint inhibitors like anti-PD-1 antibodies[63]. These vaccines are designed to encode multiple tumor antigens and are delivered directly to dendritic cells, inducing robust T-cell responses against tumors such as melanoma and non-small cell lung cancer[63]. Despite these advances, significant challenges persist in bringing nanovaccines from bench to bedside. Manufacturing complexity is a major hurdle, as large-scale, reproducible synthesis of nanocarriers with consistent size, charge, and antigen loading is technically demanding and cost-intensive. Furthermore, regulatory uncertainties exist because nanovaccines straddle the boundaries of biologics and devices, leading to ambiguities in classification, evaluation criteria, and approval processes by agencies like the FDA and EMA.

Another critical issue is safety and biodistribution. Nanoparticles may accumulate in off-target organs such as the liver, spleen, or kidneys, leading to potential immunotoxicity or chronic inflammation. Long-term studies are needed to evaluate the persistence and metabolism of different nanomaterials. Moreover, immunogenicity must be balanced carefully to avoid triggering autoimmune responses or exacerbating systemic inflammation.

To overcome these obstacles, collaborative efforts among researchers, clinicians, regulatory bodies, and industry stakeholders are essential. The development of standardized characterization assays**,** predictive animal models, and clear regulatory guidelines will be pivotal in unlocking the full clinical potential of nanovaccine technologies.

6. Future Directions

The future of nanovaccines in cancer therapy and prevention is rapidly evolving, with several innovative approaches poised to transform the field. One major direction involves the development of smart and stimuli-responsive delivery systems, which release their therapeutic payload in response to specific triggers such as pH, redox potential, or enzymatic activity. These systems enable site-specific and time-controlled drug release, minimizing off-target effects and improving therapeutic efficacy.

Another exciting frontier is personalized nanovaccination. Advances in next-generation sequencing (NGS) and artificial intelligence (AI) are enabling the rapid identification of patient-specific neoantigens mutated peptides uniquely expressed in an individual's tumor. These neoantigens can be formulated into customized nanovaccines tailored to each patient's tumor mutanome, offering the promise of precision immunotherapy with maximal specificity and minimal toxicity. Emerging delivery platforms such as microneedle patches and oral nanovaccines are also under active exploration. These approaches facilitate non-invasive, self-administered vaccination, enhancing accessibility and patient compliance particularly valuable for large-scale immunoprevention programs in resource-limited settings. Finally, the integration of theranostics nanoparticles that combine diagnostic and therapeutic capabilities is a growing trend. These multimodal systems can monitor antigen delivery, track immune responses via imaging, and deliver therapy simultaneously, enabling real-time treatment optimization.

Looking ahead, the convergence of nanotechnology, immunology, bioinformatics, and systems biology will usher in a new era of personalized, efficient, and safe cancer immunotherapies. Nanovaccines are poised to become central to both prophylactic and therapeutic strategies in oncology.

CONCLUSION

Nanovaccines represent a promising frontier in cancer prevention and treatment by unifying advances in nanotechnology, immunology, and oncology. Their ability to enhance antigen presentation, modulate the immune landscape, and synergize with other therapies makes them pivotal in the next era of precision oncology. Continued research, multidisciplinary collaboration, and regulatory innovation are essential to fully realize their clinical potential.

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