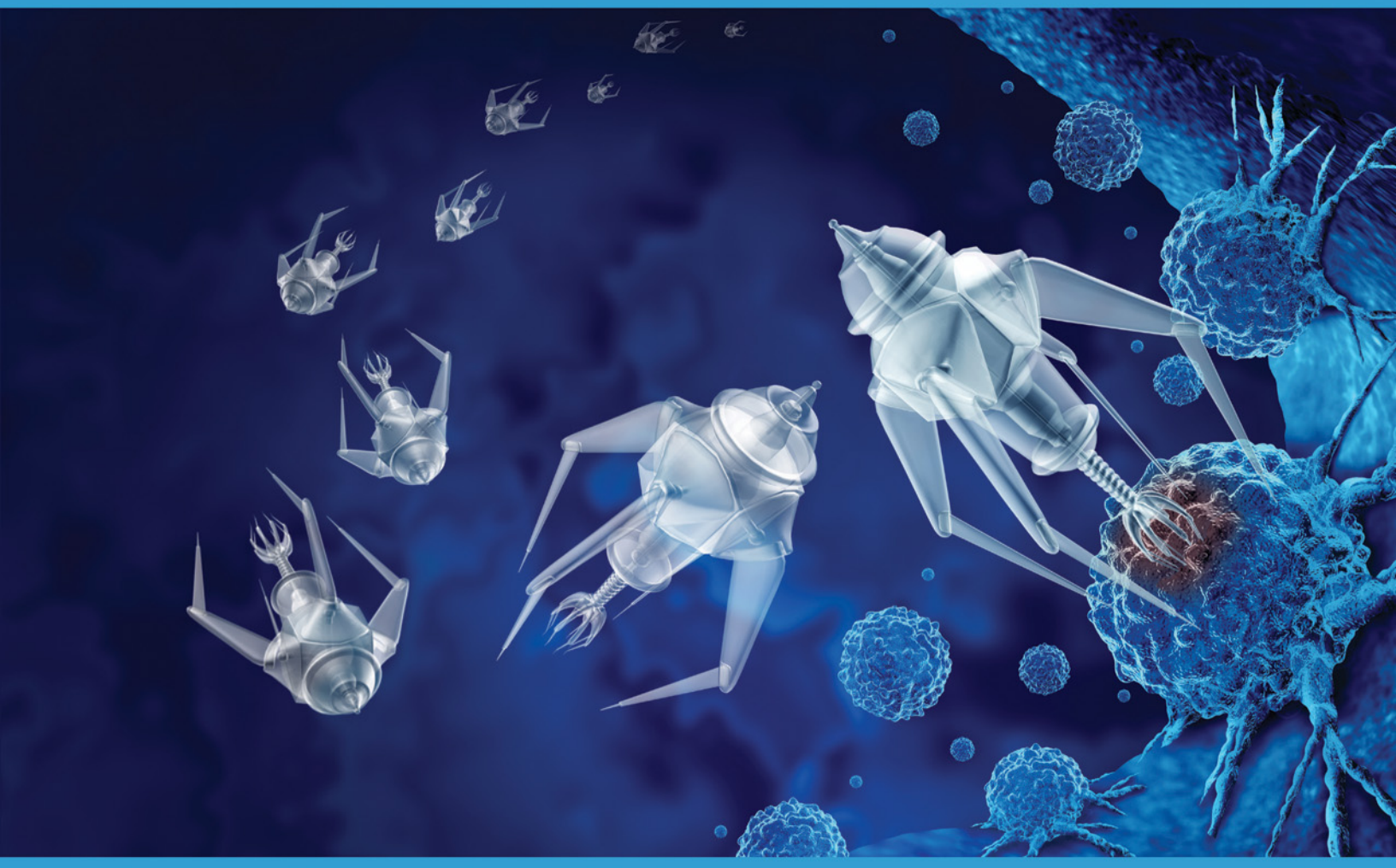
# Two Sides of Nanovaccines and Nanomedicines in Cancer Treatments



Edited by
Tuan Anh Nguyen
Bhupendra G. Prajapati
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Edited by

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# Dedication

**Dedicated to the memory of those who lost their lives to the side effects of nanovaccines and nanomedicines**

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Part 1

# Fundamentals

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Chapter 10

# Side effects and toxicity of nanovaccine in cancer treatment

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## Abbreviations

| | |
|---|---|
| **AIE** | Aggregation-Induced Emission |
| **ALNP** | Aluminum Nanoparticles |
| **AI** | Artificial Intelligence |
| **APCs** | Antigen-Presenting Cells |
| **CARPA** | Complement Activation-Related Pseudoallergy |
| **$CD4^+$** | Cluster of Differentiation 4 Positive |
| **$CD8^+$** | Cluster of Differentiation 8 Positive |
| **CNS** | Central Nervous System |
| **CpG** | Cytosine–Phosphate–Guanine |
| **CRS** | Cytokine Release Syndrome |
| **CTLs** | Cytotoxic T Lymphocytes |
| **DCs** | Dendritic Cells |
| **EVs** | Extracellular Vesicles |
| **GMP** | Good Manufacturing Practice |
| **ICIs** | Immune Checkpoint Inhibitors |
| **IFN-γ** | Interferon Gamma |
| **IL-6** | Interleukin-6 |
| **IL-10** | Interleukin-10 |
| **IV** | Intravenous |
| **LNPs** | Lipid Nanoparticles |
| **mRNA** | Messenger Ribonucleic Acid |
| **MHC** | Major Histocompatibility Complex |
| **MPLA** | Monophosphoryl Lipid A |
| **NCT** | National Clinical Trial |
| **PD-1** | Programmed Death-1 |
| **PD-L1** | Programmed Death-Ligand 1 |
| **PEG** | Polyethylene Glycol |
| **PLGA** | Poly(lactic-co-glycolic acid) |
| **PRRs** | Pattern Recognition Receptors |
| **RNA** | Ribonucleic Acid |
| **ROS** | Reactive Oxygen Species |
| **siRNA** | Small Interfering Ribonucleic Acid |
| **TLR** | Toll-like Receptor |
| **TME** | Tumor Microenvironment |
| **TNF-α** | Tumor Necrosis Factor-alpha |
| **tEVs** | Tumor-Derived Extracellular Vesicles |
| **Tregs** | Regulatory T Cells |
| **TSAs** | Tumor-Specific Antigens |
| **WHO** | World Health Organization |

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## 10.1 Introduction

Nanovaccines represent a cutting-edge approach in cancer immunotherapy, utilizing nanoscale materials to deliver antigens and immunomodulatory agents directly to the immune system. By leveraging nanotechnology, these vaccines enhance the specificity, stability, and delivery of therapeutic agents, thereby improving their efficacy against malignancies. Unlike conventional vaccines, nanovaccines can be engineered to overcome the immunosuppressive tumor microenvironment (TME), stimulate robust immune responses, and achieve targeted delivery with minimal systemic exposure. Globally, cancer remains a leading cause of death, accounting for approximately 10 million deaths in 2020, nearly one in six deaths worldwide [1]. The most common cancers include lung, breast, colorectal, prostate, and stomach cancers. Despite advances in treatment, many patients still face poor prognoses due to late diagnosis and treatment resistance. For example, lipid nanoparticles (LNPs) have been successfully employed to deliver mRNA encoding tumor antigens in KRAS-mutant nonsmall cell lung cancer (NSCLC). In a Phase I trial (NCT03639714), an mRNA nanovaccine targeting melanoma-associated antigens demonstrated enhanced intratumoral $CD8^+$ T-cell infiltration and a favorable safety profile, with mild local inflammation reported [2].

Cancer cells employ sophisticated strategies to evade immune detection, including immunoediting, a process in which the immune system selectively eliminates highly immunogenic tumor cells while permitting the survival of less detectable variants. This results in a more evasive and heterogeneous TME, where immune resistance mechanisms predominate. Solid tumors such as melanoma and NSCLC frequently overexpress PD-L1, a protein that binds to T-cell receptors and inhibits their cytotoxic function. High mutational burdens further contribute to resistance against immune checkpoint blockade therapies. Tumors also secrete immunosuppressive cytokines like TGF-β and IL-10 and recruit regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), which dampen immune responses. Additionally, downregulation of tumor-specific antigens (TSAs) and major histocompatibility complex (MHC) molecules impairs T-cell recognition, facilitating immune evasion. This immune complexity underscores the delicate balance nanovaccines must maintain. While their multifaceted compositions are designed to enhance antigen presentation and immune memory, the inclusion of potent adjuvants and nanocarriers increases the risk of hypersensitivity, cross-reactivity, or unintended immune activation, especially in immunocompromised patients.

In response, scientists are developing novel nanovaccines targeting personalized tumor antigens derived from tumor-specific extracellular vesicles (EVs), aiming to enhance antigen-specific immune responses while minimizing inflammation-related adverse effects [3]. According to the American Cancer Society (2024), the 5-year survival rate for advanced cancers has improved significantly with the advent of immunotherapy, particularly immune checkpoint inhibitors (ICIs). Clinical data show that patients receiving ICIs achieve a median overall survival of 34.8 months, compared to 15.7 months with traditional chemotherapy [4]. However, these advancements also introduce safety concerns, as combining immune checkpoint blockade with nanovaccines may overstimulate nonspecific T cells and lead to serious systemic reactions, including cytokine storms. Nanovaccines co-delivering tumor antigens and TLR agonists such as CpG have been shown to induce significant systemic cytokine responses, including elevated levels of IL-6 and TNF-α within 24 hours of administration [5].

Nanovaccines protect encapsulated antigens from degradation and facilitate their uptake by antigen-presenting cells (APCs), resulting in sustained immune activation. Their ability to co-deliver multiple antigens and adjuvants enhances polyfunctional T-cell responses and offers personalized therapy using patient-specific neoantigens. However, this complexity introduces variability in biological interactions, potentially causing unpredictable toxicity profiles. For instance immune modulators incorporated to overcome TMEs may provoke off-target immune stimulation and systemic inflammation. The development of personalized nanovaccines requires accurate antigen identification through integration of biotechnologies and computational tools [6]. Approaches such as coating nanoparticles with cancer cell membranes offer high specificity but present manufacturing challenges. Nanovaccine production currently faces instability, batch-to-batch variability, and high costs. Moreover, the use of biodegradable and biocompatible nanomaterials must be balanced against the need for structural stability and targeted delivery.

As of 2025, numerous clinical trials are investigating nanovaccine candidates for various cancers, though most remain in Phase I or II due to ongoing challenges related to safety, scalability, and regulatory approval [7]. Adverse effects such as cytokine storms, hepatotoxicity, and off-target immune activation have been observed, particularly in formulations containing potent adjuvants or poorly degradable materials. Advanced analytical platforms, including single-cell RNA sequencing and high-resolution mass cytometry, are increasingly used to dissect immune responses and identify early toxicity signals. The long-term safety of nanovaccines remains uncertain, emphasizing the need for robust toxicological profiling and standardized regulatory frameworks. To ensure clinical translation, future strategies must focus on safety-by-design principles, predictive in silico modeling, and ethical testing approaches that account for patient heterogeneity.

## 10.2 Mechanisms of action of nanovaccines

Nanovaccines constitute an emerging class of immunotherapeutics that utilize nanotechnology to elicit potent, targeted immune responses against cancer. Unlike traditional cancer vaccines, which often suffer from rapid antigen degradation, poor lymphatic uptake, and limited immunogenicity, nanovaccines offer enhanced delivery efficiency, antigen stability, and immune system activation [8]. By integrating TSAs or patient-specific neoantigens with nanoscale delivery platforms [9,10], nanovaccines facilitate targeted immune engagement and robust cytotoxic responses capable of overcoming the complex immunosuppressive TME [11]. Nanovaccines can be precisely delivered to target tissues and cells using specialized nanocarriers and nanoplatforms, enhancing therapeutic efficacy, prolonging antitumor immune responses, and reducing off-target side effects [12].

Nanovaccines possess several unique advantages over traditional vaccine modalities. Their nanoscale size (10–100 nm) optimizes lymph node targeting and cellular uptake [13]. Moreover, nanocarriers can provide sustained antigen release and co-deliver multiple components, antigens, adjuvants, checkpoint inhibitors, or RNA interference agents in a single formulation [14]. This multimodal capability enables simultaneous immune activation and modulation of the TME, making it possible to induce strong immune responses even in immunologically "cold" tumors [15]. By facilitating precise control over antigen presentation, co-stimulatory signaling, and immune modulation, nanovaccines generate a polyfunctional and durable T-cell repertoire. This is critical for targeting heterogeneous tumor cell populations and establishing long-term immunological memory to prevent recurrence [16].

The immune activation process initiated by nanovaccines is multifaceted. Typically, antigens are encapsulated within or attached to nanoparticles composed of lipid-based, polymeric, or inorganic materials [17]. These carriers protect antigens from enzymatic degradation and promote their targeted delivery to APCs, particularly dendritic cells (DCs). Upon administration, nanoparticles drain into the lymphatic system and accumulate in lymph nodes, key sites for immune priming [18]. Once internalized by DCs through endocytosis, nanovaccine components undergo processing, and antigens are presented on MHC class I and II molecules to naive T cells [19]. Co-delivered immunostimulatory adjuvants, such as Toll-like receptor (TLR) agonists (e.g., cytosine-phosphate-guanine (CpG), polyinosinic: polycytidylic acid (poly I:C), or monophosphoryl lipid A (MPLA)), enhance DC maturation and support effector T cell generation [20]. Some nanovaccine formulations are engineered to disrupt endosomal membranes, allowing antigen escape into the cytosol and favoring cross-presentation via MHC class I ,crucial for eliciting cytotoxic CD8+ T cell responses [21]. The mechanism by which nanovaccines stimulate antitumor immunity involves targeted delivery to APCs, enhanced antigen processing, and activation of T cell responses within lymphoid tissues (Fig. 10.1). This multistep process enables efficient priming of cytotoxic T lymphocytes (CTLs) and modulation of the TME to support durable immune-mediated tumor clearance.

## 10.3 Types of toxicity of cancer nanovaccine

Acute versus chronic toxicity: Acute toxicity refers to adverse effects that emerge shortly after nanovaccine administration. Common manifestations include fever, diarrhea, nausea, lethargy [12], and allergic reactions [9]. These symptoms typically result from immediate immune activation or hypersensitivity [22]. In contrast, chronic toxicity evolves over prolonged periods and may include liver and spleen toxicity [16]. Such effects are particularly relevant when nanoparticles persist in the body or induce long-term immune modulation. Nanoparticles introduce the possibility of unpredictable adverse effects in cancer patients [23]. Beyond the well-known hazards linked to poor degradation, DNA damage, or metal-induced central nervous system toxicity, nanoformulations may also cause persistent, chronic, and often irreversible immune-related side effects, adding another layer of complexity to their utilization [23]. Therefore efficiently reducing nanotoxicity while preserving consistent antitumor benefits in patients treated with cytokine nanoformulations remains an ongoing significant challenge.

Local versus systemic toxicity: Local toxicity is confined to the site of injection and may present as pain, swelling, or subcutaneous induration [24]. It is often influenced by the formulation's pH, excipients, or adjuvants. Systemic toxicity refers to the adverse effects caused by nanovaccine administration when using nanoparticles as carriers or adjuvants, that include fever, diarrhea, nausea, and tiredness [9]. The major toxicological pathways activated by nanoparticles in cells include oxidative stress, inflammation, and genotoxicity [25].

Nanovaccine safety profiles vary widely depending on both the nanomaterial and delivery strategy, often resulting in a combination of acute/chronic and local/systemic toxicities (Fig. 10.2). Following are the examplesexamples from specific nanoplatforms.

- Lipid-based nanoparticles (LNPs) (e.g., mRNA cancer vaccines): These systems, such as those used in COVID-19 vaccines, have shown effective delivery of nucleic acids. However, adverse effects include fatigue, pain at the injection

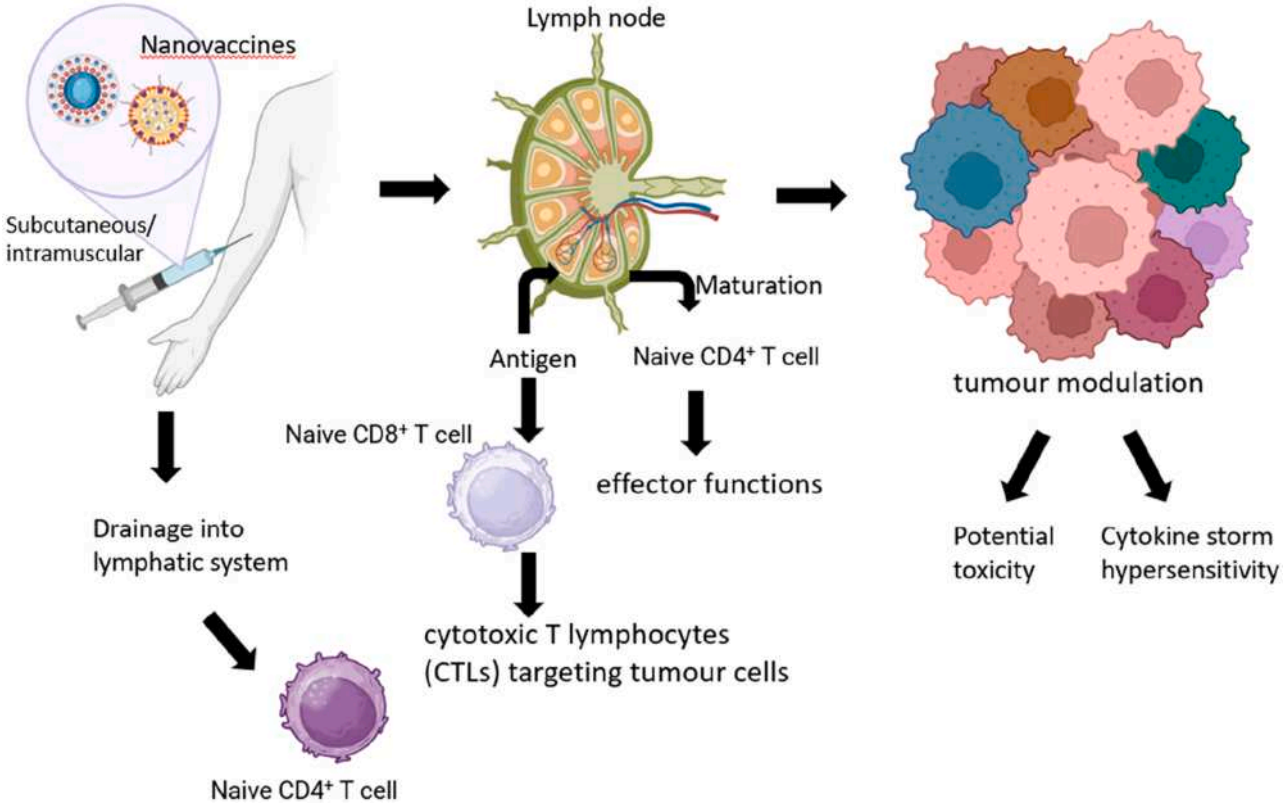


FIGURE 10.1 Mechanism of action of nanovaccines in cancer immunotherapy. This diagram illustrates the key steps in the immune activation process induced by nanovaccines for cancer treatment. Nanovaccines containing tumor-specific antigens and immunostimulatory adjuvants are administered via subcutaneous or intramuscular injection. These nanoparticles drain into the lymphatic system and accumulate in lymph nodes, where they are internalized by dendritic cells (DCs). Inside DCs, antigens are processed and presented on MHC molecules to activate naïve $CD8^+$ and $CD4^+$ T cells. $CD8^+$ T cells differentiate into cytotoxic T lymphocytes (CTLs) targeting tumor cells, while $CD4^+$ T cells mature and support effector functions. The immune response leads to tumor modulation and eradication. However, overactivation may result in potential toxicity such as cytokine storm or hypersensitivity reactions.

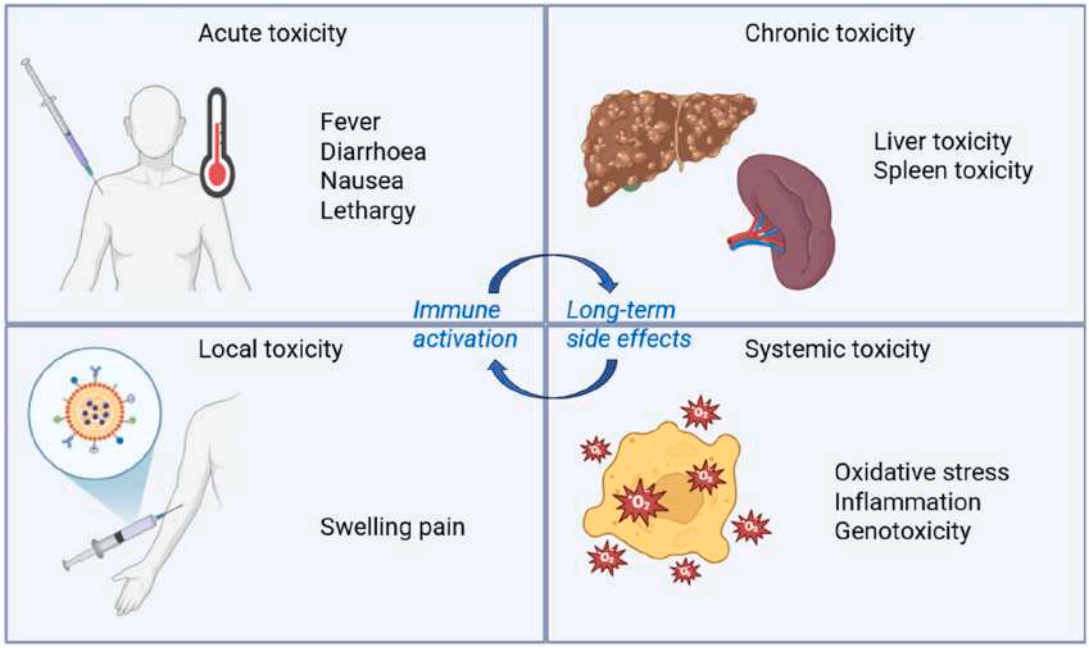


FIGURE 10.2 Types and mechanisms of nanovaccine-associated toxicity in cancer therapy. This figure illustrates the major classifications and mechanisms of nanovaccine-induced toxicity in cancer therapy. The top panel categorizes toxicity into acute, chronic, local, and systemic, detailing their interconnectedness, clinical manifestations, and target organs. Mechanistic pathways such as oxidative stress, inflammation, immune stimulation, and hypersensitivity are highlighted as key contributors to nanotoxicity. The lower panel describes examples from three major nanoplatforms, including lipid based, polymeric, and inorganic nanoparticles, and highlights their unique toxic effects, biological responses, and the risks associated with long term exposure or with biodegradation byproducts.

site, myalgia, narcolepsy, neurological side effects, anaphylaxis, immune activation, cytotoxicity, and nausea, while in PEGylated-lipids, PEG may cause allergic reactions [26].

- Polymeric nanoparticles**:** Composed of biodegradable materials like PLGA or chitosan, these carriers can degrade into acidic or reactive byproducts [27]. High doses may overwhelm cellular detoxification mechanisms, resulting in oxidative stress, inflammation, or cell death via apoptosis [28].
- Inorganic nanoparticles (Gold, Silica, etc.): These offer high stability and surface functionalization but are not easily metabolized. Studies have shown that gold nanoparticles can induce primary DNA damage, oxidative DNA damage, chromosomal damage, alterations in gene expression, and effects on epigenetic regulation [29], while silica particles can cause pulmonary inflammation and fibrosis upon inhalation [30].

To contextualize these toxicities within the broader design of nanovaccines, Table 10.1 summarizes key aspects of formulation strategies, their immunological advantages, and associated toxicological concerns. By mapping specific design features such as antigen delivery, personalization, and immune modulation to their benefits and risks, this table provides a critical framework for understanding the complex balance between efficacy and safety in nanovaccine development.

## 10.4 Immunogenicity and autoimmune reactions

Nanovaccines are designed to robustly stimulate the immune system to recognize and eliminate cancer cells. However, this potent immunogenicity can sometimes lead to unintended immune consequences, including immunotoxicity and adverse inflammatory responses [36]. This section outlines the key mechanisms by which nanovaccines may trigger such immune-related complications and highlights the importance of long-term safety evaluation. Despite their therapeutic promise, nanovaccines may induce immunological and organ-specific toxicities if not properly engineered or dosed. Fig. 10.3 summarizes these adverse effects, including immune-related complications such as cytokine storm [37], molecular mimicry [38], and immunotoxicity [36], as well as organ-specific toxicities in the liver, kidneys, lungs, and brain due to nanoparticle accumulation and systemic exposure.

**Heightened immunogenicity and aberrant immune activation:** While immune activation is critical for vaccine efficacy, excessive or poorly regulated immune stimulation can be detrimental. Nanovaccines often incorporate adjuvants and surface ligands that amplify antigen presentation and immune cell recruitment [17]. In some cases, these stimuli may provoke uncontrolled immune responses, leading to systemic inflammation and adverse immune-mediated effects [16]. The activation of DCs, macrophages, and T cells must be carefully modulated to avoid hyperresponsiveness.

**Molecular mimicry and cross-reactivity with host tissues:** One of the major risks associated with nanovaccine-induced autoimmunity is molecular mimicry [38]. If the antigens presented by the nanovaccine share structural similarities with endogenous proteins, the immune system may inadvertently attack healthy tissues. This cross-reactivity can result in the development of autoimmune diseases such as type 1 diabetes, thyroiditis, or lupus-like syndromes. The risk is heightened when targeting tumor-associated antigens that are also expressed, albeit at lower levels, in normal tissues.

**Autoantibody production and immune dysregulation:** In some cases, exposure to nanovaccines has been linked to the production of autoantibodies, which are antibodies that mistakenly attack the body's own proteins. These autoantibodies may play a role in various disorders, including vasculitis and autoimmune encephalitis. Moreover, dysregulation of T regulatory cells (Tregs) and loss of peripheral tolerance mechanisms may exacerbate these autoimmune processes. The balance between effector and regulatory immune cells is therefore crucial in maintaining immune homeostasis [39].

## 10.5 Organ-specific toxicities

Liver and kidney toxicity**:** Some LNPs induce mitochondrial dysfunction and oxidative stress in hepatocytes [40]. High-dose aluminum nanoparticles (ALNP) exhibit renal tubular necrosis, glomerular swelling, intertubular hemorrhage, and hepatocyte degeneration [41].

Pulmonary effects (e.g., Inflammation, Fibrosis)**:** Nanoparticles that reach the lungs via systemic circulation or inhalation may disrupt alveolar integrity [42] and induce inflammation. In rodents, inhalation of silver nanoparticles has resulted in increased silver in the lungs, lymph nodes, liver, kidney, spleen, ovaries, and testes [43]. Acute effects in humans of the inhalation of silver include lung failure that involves increased heart rate and decreased arterial blood oxygen pressure [43]. Argyria, a blue-gray discoloration of skin due to deposited silver, was observed after pulmonary

**TABLE 10.1** Comparative overview of nanovaccine design strategies and associated toxicities.

| Aspect | Mechanism/design feature | Benefits | Potential toxicities/concerns | Examples | References |
|---|---|---|---|---|---|
| Antigen delivery | Encapsulation or surface attachment | Protects antigens; promotes uptake by APCs | May trigger unintended immune activation | Lipid/polymer nanoparticles | Wang et al. [31] |
| Personalization | Incorporation of neoantigens | High specificity; low autoimmunity risk | Requires sequencing infrastructure | mRNA-loaded lipid nanoparticles | Cao and Xia [32] |
| Immune modulation | Co-delivery of adjuvants, checkpoint inhibitors | Enhances immune activation | Systemic inflammation, cytokine storms | TLR agonists like CpG, MPLA | Nie et al. [33] |
| TME reprogramming | Delivery of siRNAs, modulators of immune cells | Converts “cold” to “hot” tumors | Off-target gene silencing | siRNA for PD-L1 silencing | Yi et al. [34] |
| Carrier material | Lipids, metals, polymers | Enables tunable delivery and release | ROS generation, organ accumulation | Iron oxide, gold nanoparticles | Ramos-Pan et al. [29] |
| Endosomal escape | Ionizable lipids | Promotes cytosolic antigen access | Lipid peroxidation, innate immune activation | Ionizable LNPs | Zelkoski et al. [35] |
| Stability enhancer | PEGylation | Prolonged circulation | Anti-PEG antibodies, hypersensitivity | PEGylated LNPs | Cao et al. [26] |
| Inflammatory risk | Systemic cytokine activation | Strong immune priming | Cytokine storm, multiorgan dysfunction | mRNA nanovaccines in preclinical models | Cao et al. [26] |

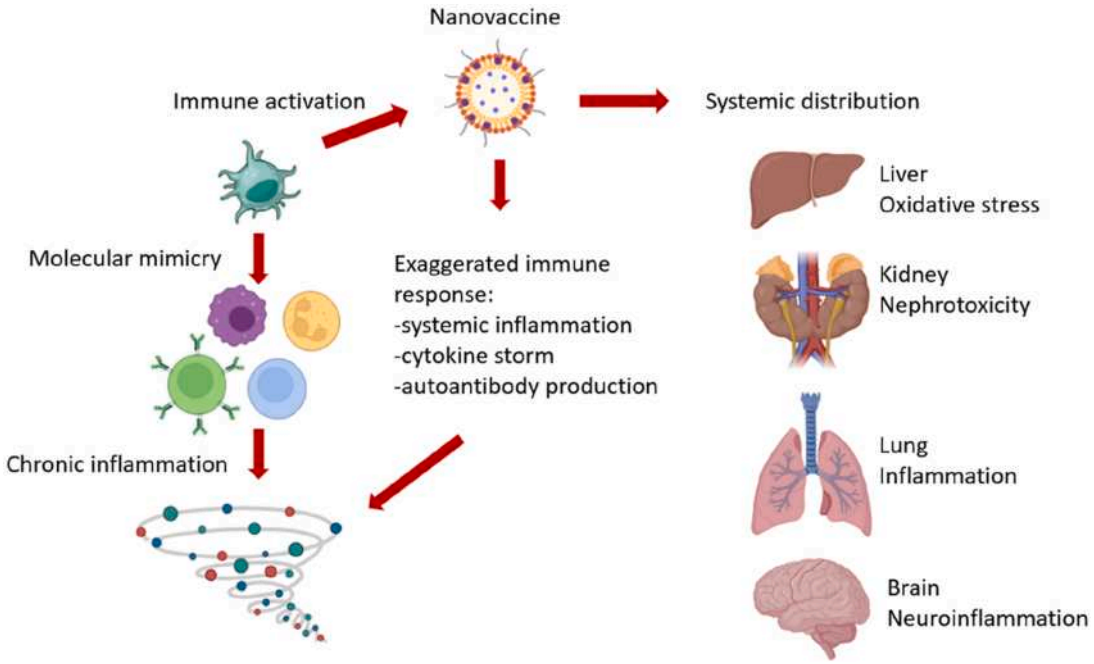


FIGURE 10.3 Immunological and organ-specific toxicities induced by nanovaccines. This diagram presents the immunological and organ-specific toxicities associated with nanovaccines. On the left, immune system activation is shown to occasionally result in exaggerated responses such as cytokine storms, molecular mimicry, and autoantibody production, which can target healthy tissues like the pancreas, thyroid, and joints, potentially leading to chronic inflammation and autoimmune disorders. On the right, systemic distribution of nanoparticles to major organs such as the liver, kidneys, lungs, and brain is depicted. Accumulation in these organs may cause oxidative stress, nephrotoxicity, pulmonary inflammation, and neuroinflammation, highlighting the importance of safety profiling in nanovaccine development.

exposure in three individuals [43]. In rats, $CeO_2$ nanoparticles penetrate the alveolar space and show lung tissue inflammation with increasing severity post-exposure [44].

Neurotoxicity**:** Nanoparticles can also raise concerns about neurotoxicity [21]. Nanomaterials may induce neurotoxicity through multiple mechanisms, including oxidative stress, DNA damage, lysosomal dysfunction, inflammatory cascade, apoptosis, genotoxicity, and ultimately necrosis of neuronal cells [45].

## 10.6 Factors influencing nanovaccine toxicity

Particle size, surface charge, shape**:** Nanoparticle size influences tissue penetration, cellular uptake, and clearance rates. Smaller particles (<100 nm) can penetrate tissues more efficiently but may accumulate in sensitive organs [46]. Surface charge affects protein corona formation and cell membrane interactions; positively charged particles tend to have higher cellular uptake but also greater cytotoxicity [47]. Particle shape influences circulation dynamics—spherical particles tend to circulate longer, while rod-shaped or irregular particles may be more rapidly cleared [48].

Route of administration (IV, subcutaneous, intramuscular)**:** Different administration routes result in distinct biodistribution profiles [49]. Intravenous delivery ensures systemic distribution but increases the risk of systemic toxicity [50]. Subcutaneous and intramuscular routes allow depot formation and slower release but may cause localized inflammation or granuloma formation [51,52]. The chosen route must align with therapeutic goals and toxicity risk profiles.

Dose and frequency**:** Nanovaccine toxicity is dose-dependent [52]. Higher doses can overwhelm detoxification pathways, while repeated doses may result in bioaccumulation and immune sensitization [53]. Dosing intervals must be optimized to minimize toxicity while maintaining therapeutic efficacy. Cumulative exposure should be carefully monitored in clinical settings.

Tumour microenvironment interactions**:** The TME presents unique challenges, including hypoxia, acidic pH, and immunosuppressive signaling [54]. Nanoparticles may behave differently within the TME compared to healthy tissue [55]. For example, acidic pH may trigger premature payload release [56], while tumor-associated macrophages may sequester nanoparticles and alter their biodistribution [57]. These interactions can modulate both efficacy and toxicity.

## 10.7 Types of nanoparticles and their associated toxicities in cancer nanovaccines

The rapid development of nanovaccine technologies has introduced various nanoparticle types, each with specific therapeutic advantages and toxicity risks.

### 10.7.1 Nucleic acid-based platforms (DNA/RNA)

Nucleic acid-based nanovaccines particularly DNA and RNA formulations represent a transformative approach to cancer immunotherapy by enabling endogenous antigen production. These vaccines activate both cytotoxic ($CD8^+$) and helper ($CD4^+$) T cells through engagement of MHC class I and II pathways, thereby mimicking natural infection-induced immunity [11]. However, their delivery systems introduce important toxicological challenges. DNA-based nanovaccines, which require nuclear localization for transcription, suffer from low efficiency in non-dividing tumor cells. Moreover, the long persistence of plasmid DNA raises concerns over insertional mutagenesis and potential oncogenic risk. Although nonviral DNA nanoparticles are generally considered safer than viral vectors, their effects on epigenetic regulation and genomic stability remain incompletely understood. RNA-based nanovaccines notably mRNA vaccines, avoid nuclear entry but are inherently unstable. Their encapsulation in LNPs is critical for protection from degradation, but LNPs are known to induce systemic immune activation. Toxicity includes elevation of pro-inflammatory cytokines (e.g., IL-6), complement activation, and rare cases of myocarditis or laryngeal edema [11]. Additionally, RNA vaccines depend on strict cold-chain logistics, complicating deployment and increasing the risk of degradation and inconsistent dosing.

### 10.7.2 Antigen-based nanovaccines

Antigen-based nanovaccines deliver predefined tumor antigens directly, offering greater stability and ease of storage compared to nucleic acid-based platforms [11]. However, their immunogenic profiles are often less robust and may require adjuvants or repeated dosing. Fixed antigen content can also limit adaptability to tumor evolution, reducing efficacy in heterogeneous cancers. From a toxicity standpoint, antigen-based nanovaccines may cause local inflammatory reactions at the injection site, especially when combined with potent adjuvants. Their ability to trigger lasting memory responses is variable, and overuse could lead to immunological exhaustion or unwanted tissue reactivity.

### 10.7.3 Tumor-derived extracellular vesicles

Recent innovations have led to the engineering of tumor-derived EVs (tEVs) into multifunctional nanovaccines. These vesicles naturally incorporate tumor antigens and can be modified to act as self-adjuvanting carriers. Notably, some platforms utilize mitochondria-targeted sonosensitizer molecules with aggregation-induced emission (AIE) characteristics, which have shown potent antitumor prophylactic effects in preclinical models [3]. While promising, tEV-based nanovaccines may raise safety concerns related to autoimmunity or the unintended promotion of tumor signaling pathways. The inclusion of endogenous tumor-derived proteins could also pose risks of tolerogenic responses or immune deviation. Furthermore, their biodistribution and clearance remain poorly understood, necessitating comprehensive pharmacokinetic studies [58].

### 10.7.4 Lipid-based nanoparticles and liposomes

LNPs, including liposomes, are among the most widely used delivery vehicles in cancer nanovaccine platforms [59]. They offer high biocompatibility and efficient encapsulation of nucleic acids or antigens. However, they are not devoid of toxicity. Liposomes, due to their bilayer structure, can become destabilized *in vivo*, leading to premature drug or antigen release [60]. Moreover, they can activate the complement cascade, triggering complement activation-related pseudoallergy (CARPA), which manifests as hypersensitivity reactions ranging from mild rashes to severe anaphylaxis [61]. LNPs used in mRNA vaccines have been implicated in cytokine release and innate immune activation. The use of ionizable lipids, crucial for endosomal escape, can cause mitochondrial damage, lipid peroxidation, and inflammation, especially when they interact with pattern recognition receptors (PRRs) [31,36]. Additionally, the presence of polyethylene glycol (PEG) on the surface of LNPs may provoke anti-PEG antibodies [62], potentially resulting in reduced efficacy and hypersensitivity reactions over repeated doses.

### 10.7.5 Polymeric nanoparticles

Polymeric nanoparticles, particularly those formulated from poly(lactic-co-glycolic acid) (PLGA), are favored for their controlled degradation and tunable release properties [63]. These systems are generally considered biocompatible and

have received regulatory approval for various drug delivery applications. However, the degradation rate and byproducts of vaccines can influence immunogenicity and toxicity [64]. Accumulation of acidic monomers may disrupt local tissue pH, provoke inflammatory responses, or impair antigen stability. Non-biodegradable polymers carry greater toxicity risks, including tissue accumulation, long-term oxidative stress, inflammation, and fibrotic responses [36,65]. Careful material selection and dosing regimens are required to mitigate these effects.

### 10.7.6 Inorganic nanoparticles

Inorganic nanoparticles, including gold, silica, and iron oxid,e offer unique advantages such as intrinsic imaging capability, magnetic responsiveness, and high surface area for functionalization. Nonetheless, their clinical translation in cancer nanovaccines remains limited due to significant toxicity concerns [21]. These particles tend to accumulate in reticuloendothelial organs like the liver and spleen and may persist for prolonged periods [66]. Their presence can disrupt cellular homeostasis, induce oxidative stress, and impair mitochondrial function. Studies have shown that metal ions released from these nanoparticles may also interfere with normal enzymatic activity, contributing to systemic toxicity [11]. Strategies such as coating, surface passivation, and controlled degradation are being explored to mitigate these risks.

### 10.7.7 Viral and DNA nanoparticles

Viral vector-based nanovaccines remain potent tools for delivering genetic material due to their high transduction efficiency. However, they come with substantial safety concerns [67]. Integration of viral DNA into the host genome poses the risk of insertional mutagenesis, which can trigger oncogenesis. Moreover, pre-existing immunity to viral vectors may limit effectiveness and exacerbate inflammatory responses. Non-viral DNA nanoparticles, although comparatively safer, are not free of risks. The potential for unintended genetic effects, epigenetic alterations, or immune sensitization requires thorough preclinical evaluation [68,69]. These risks are particularly relevant in the context of cancer, where immune tolerance and genomic instability are already prevalent.

As illustrated in Fig. 10.4, different nanoparticle platforms exhibit distinct physicochemical properties and toxicological profiles relevant to their use in cancer nanovaccines. Nucleic acid-based platforms (e.g., mRNA-LNPs) offer high immunogenicity but may trigger systemic inflammation or hypersensitivity reactions. Lipid-based systems are widely used due to biocompatibility, but can induce CARPA and mitochondrial stress. Polymeric nanoparticles allow controlled release but may generate inflammatory acidic byproducts. Inorganic materials, though advantageous for imaging and surface modification, face limitations due to oxidative stress and metal toxicity. tEVs and viral/DNA vectors raise additional safety questions related to immune modulation, autoimmunity, or genomic integration.

## 10.8 Combination therapies and clinical validation

Combining nanovaccines with immunotherapies or conventional modalities offers synergistic benefits. ICIs (e.g., anti-PD-1/PD-L1) can reverse T cell exhaustion, amplifying vaccine-induced immune responses. Concurrently, chemotherapy or radiotherapy can induce immunogenic cell death, increase tumor antigen availability ,and enhance vaccine efficacy. Such combinations may also reduce individual drug dosages, thereby limiting cumulative toxicity and expanding the therapeutic window. Early-phase clinical trials of nanovaccines, including liposomal and mRNA-based LNP formulations, have shown encouraging safety profiles. Reported adverse events are typically mild and transient, such as localized pain, flu-like symptoms, and low-grade fever. For instance liposomal nanovaccines maintain efficient antigen delivery while minimizing off-target immunogenicity. PLGA-based platforms strike a favorable balance between sustained antigen release and biocompatibility. Real-world data reinforce these findings, with most adverse effects being manageable and immune-related (e.g., fatigue, chills, myalgia). However, transient elevations in liver enzymes observed with iron oxide nanoparticles highlight the need for continued hepatic monitoring. These outcomes underscore the importance of preclinical toxicology screening and post-treatment surveillance in clinical settings.

## 10.9 Progress, challenges, and future directions

Animal studies demonstrate nanovaccine-induced tumor regression, enhanced DC activation, and CTL priming in models of melanoma, breast cancer, and glioblastoma. Multifunctional nanoparticles co-delivering antigens and immunostimulatory molecules can remodel the TME, shifting it from immunosuppressive to immunogenic. Clinically, personalized mRNA nanovaccines such as BioNTech and Roche's BNT122 and Moderna's mRNA-4157 have shown potent neoantigen-specific T cell responses. In metastatic melanoma, these vaccines have demonstrated improved recurrence-

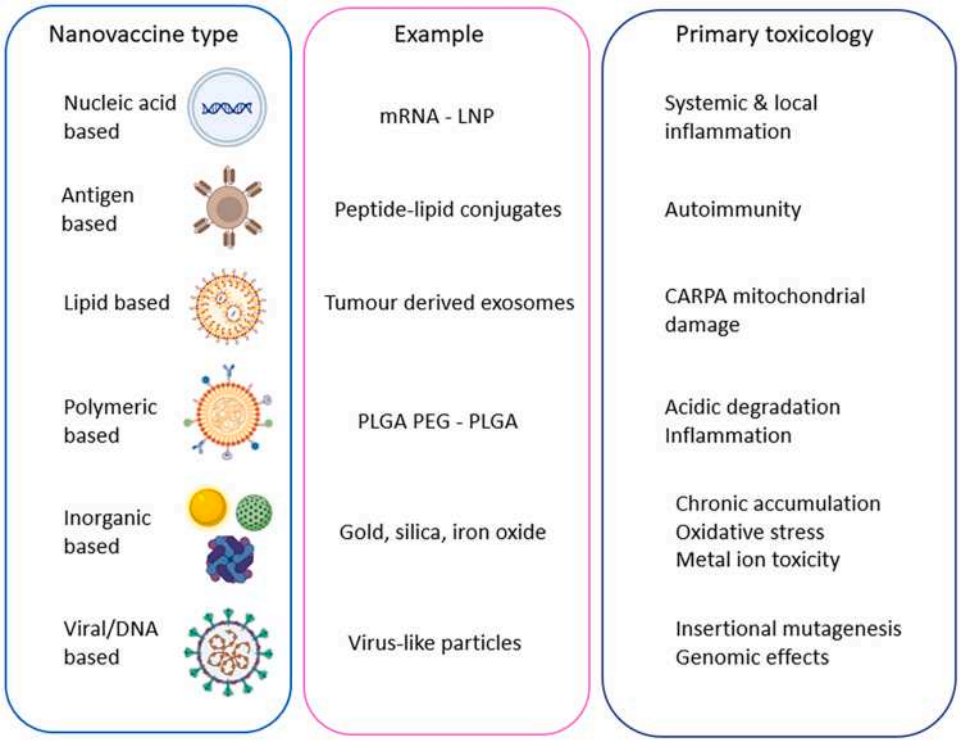


FIGURE 10.4 Comparative overview of nanoparticle types used in cancer nanovaccines and their associated toxicities. This infographic presents a comparative chart of key nanoparticle platforms employed in cancer nanovaccines, detailing their composition, major therapeutic advantages, and associated toxicological risks. Nanoparticle classes include nucleic acid-based, antigen-based, tumor-derived extracellular vesicles (tEVs), lipid-based, polymeric, inorganic, and viral/DNA-based systems. The figure highlights both clinical readiness and major safety concerns, such as systemic inflammation, CARPA, oxidative stress, mitochondrial damage, insertional mutagenesis, and poor biodistribution. *CARPA*, Complement activation-related pseudoallergy.

free survival, especially when combined with checkpoint inhibitors like pembrolizumab. These results highlight the potential of combining precision immunotherapy with nanotechnology for enhanced clinical outcomes.

Despite significant progress, several challenges hinder the widespread clinical translation of nanovaccines, including clinical trial design and biosafety of nanomaterials [23]. Manufacturing complexity and batch variability affect particle size, surface charge, and antigen loading consistency, all of which influence safety and efficacy. Regulatory frameworks for nanomedicine are still evolving, requiring harmonization and clear GMP compliance for large-scale production. Immune overactivation remains a serious concern, particularly in formulations with potent adjuvants or self-antigen cross-reactivity. Risks of cytokine release syndrome (CRS) and autoimmune reactions necessitate rigorous preclinical immune toxicity testing and careful clinical dosing strategies. Gradual immune priming and personalized dosing schedules may help mitigate these risks.

Looking forward, personalized nanovaccines designed using patient-specific neoantigen profiles offer an exciting avenue for precision oncology. The integration of genomic sequencing and artificial intelligence can improve epitope selection, reduce off-target toxicity, and enhance treatment response. Meanwhile, innovations in self-degrading nanoparticle systems and biocompatible materials continue to push the boundaries of safety and functionality. Together, these strategies form a comprehensive roadmap toward the safe, effective, and scalable application of nanovaccines in cancer immunotherapy.

## 10.10 Conclusion

The rapid evolution of nanovaccines has opened new frontiers in cancer immunotherapy by enabling precise antigen delivery, potent immune activation, and tumor-specific targeting. However, these advancements are paralleled by complex safety challenges. This chapter has outlined the multifaceted toxicities associated with nanovaccines ranging from acute and local injection site reactions to chronic and systemic effects such as hepatic stress, inflammatory syndromes, and

immune overactivation. These adverse events are shaped by the physicochemical properties of nanoparticles, their route of administration, and the immunological context of the host.

Preclinical and clinical data underscore the dual-edged nature of nanovaccines: while offering enhanced efficacy through antigen presentation and immune stimulation, they can also provoke unintended toxicities through oxidative stress, cytokine storms, or off-target effects. Notably, the diversity of nanoplatforms including lipid-based, polymeric, and inorganic systems results in distinct risk–benefit profiles, underscoring the need for tailored design strategies and rigorous safety assessments.

Mitigating toxicity requires a systems-level approach involving rational material selection, surface modifications (e.g., PEGylation), controlled-release mechanisms, and tumor-targeting technologies. Personalized vaccine design, informed by genomic profiling and machine learning, represents a promising strategy to enhance specificity while minimizing immunotoxicity. Moreover, combination therapies with checkpoint inhibitors or traditional cancer treatments can boost efficacy without proportionally increasing systemic burden if dose-optimized and clinically validated.

Despite encouraging early-phase trials, key translational barriers persist, including manufacturing consistency, regulatory standardization, and immune unpredictability. Addressing these issues will demand rigorous preclinical models, robust clinical monitoring, and interdisciplinary collaboration. In conclusion, while the side effects and toxicity of nanovaccines remain a critical concern, they are not insurmountable. By integrating advances in nanotechnology, immunology, and systems biology, the field is well-positioned to deliver safer, more effective cancer vaccines. Continued innovation and vigilance will be essential to realize the full therapeutic potential of nanovaccines while safeguarding patient health in both early trials and eventual clinical practice.

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# Two Sides of Nanovaccines and Nanomedicines in Cancer Treatments

## Edited by Tuan Anh Nguyen, Bhupendra G. Prajapati, and Devesh U. Kapoor

*Two Sides of Nanovaccines and Nanomedicines in Cancer Treatments* provides a balanced exploration of the dual roles of nanotechnologies in oncology. Structured in four parts, this book begins with the foundational knowledge of nanovaccines and nanomedicines, detailing their applications in cancer care and highlighting their precision in targeting cancer cells while reducing systemic toxicity.

Importantly, this book addresses potential drawbacks, discussing side effects and safety concerns associated with these innovations. The final section emphasizes ethical, regulatory, and safety challenges, underscoring the need for careful oversight as nanotechnologies advance.

For the academic audience, this book serves as a vital resource, offering insights that equip researchers and healthcare professionals to make informed decisions regarding clinical applications. Its focus on both the benefits and risks, alongside forward-looking perspectives, ensures that readers are well prepared for future developments in the field of nanomedicine and cancer therapy.

### Key Features

- Provides an in-depth foundation on nanovaccines and nanomedicines, detailing their mechanisms, roles, and applications in cancer treatment
- Addresses both the advantages and potential side effects of nanovaccines and nanomedicines
- Emphasizes the ethical, safety, and regulatory aspects of nanotechnology in cancer therapy, offering valuable guidance for responsible usage and oversight in clinical settings

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