

# Toxicological Effects of Nanoparticle-Based Cancer Treatment on Human Cells and Tissue

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Nanotechnology has revolutionized the landscape of healthcare, particularly in cancer treatment, by offering innovative solutions through nanoparticle-based drug delivery systems. This abstract explores the significant advancements and potential benefits of nanoparticle-based cancer therapy compared to traditional treatment modalities such as chemotherapy, radiotherapy, and surgery. Various types of nanoparticles, including organic, inorganic, and hybrid nanoparticles, are extensively utilized in drug delivery systems due to their unique properties. Nanoparticles can be engineered to specifically target cancer cells while sparing healthy tissues, thereby minimizing side effects and enhancing treatment efficacy. The enhanced permeability and retention (EPR) effect allows nanoparticles to passively accumulate in tumor tissues, offering a targeted approach in cancer therapy. Combination therapies delivered via nanoparticles have shown promise in overcoming drug resistance by attacking cancer cells through multiple mechanisms simultaneously. However, it is crucial to acknowledge the potential toxicological effects associated with nanoparticle-based therapies, depending on factors such as nanoparticle type, shape, and tumor cell interactions. Recent *in vitro* studies, such as those using gold nanoparticles on A549 lung cancer cells, have demonstrated dose-dependent cytotoxicity, with cell viability dropping below 50% at concentrations exceeding 100  $\mu\text{g/mL}$ , highlighting the need for careful toxicological assessment.

**Keywords:** Nanotechnology; cancer; nanoparticle-based cancer therapy; toxicology; drug delivery; oxidative stress; genotoxicity; tumor microenvironment; targeted therapy; traditional treatments.

## 1 Introduction

The usage of nanotechnology in the health sector has been improving exponentially since the first day it started. All types of nanoparticles, including organic, inorganic, and hybrid nanoparticles are broadly utilized in drug delivery systems. As a result, various nanoparticle-based medical applications are being developed. This enhancement commenced a new era in cancer treatment, creating nanoparticle-based cancer therapy which is overlapping the traditional cancer therapies (chemotherapy, radiotherapy, surgery etc.) in many particular areas<sup>1</sup>. Despite these advancements, the clinical translation of nanoparticle-based therapies faces significant regulatory hurdles, including stringent FDA approval processes that demand comprehensive toxicity data and long-term patient monitoring to ensure safety across diverse patient populations<sup>2</sup>.

### 1. Deleterious Effects and Limitations of Traditional Cancer Therapies

#### 1.1 Surgery

Incisions are usually made during surgery in order to access and remove tumors or damaged tissues. Complications from this

invasiveness include bleeding, infection, blood clots, and harm to surrounding organs or tissues, which may require further medical care<sup>3</sup>. Changes in body functioning may be transient or permanent for patients, depending on the location and scope of the surgery<sup>4</sup>. Not every cancer patient can benefit from surgery, especially if their disease is advanced or if they have underlying medical issues that make surgery too dangerous. Furthermore, surgically removing a tumor may unintentionally release cancer cells into the circulation or other tissues, which could result in the disease's spread or recurrence<sup>5</sup>.

#### 1.2 Chemotherapy

Chemotherapy drugs target rapidly dividing cells, which includes cancer cells but also affects healthy cells in the body. This can lead to a range of side effects such as nausea, vomiting, fatigue, hair loss, anemia, loss of appetite, and increased susceptibility to infections<sup>6</sup>. Chemotherapy suppresses the immune system, increasing the risk of infections. Patients undergoing chemotherapy may be more susceptible to bacterial, viral, and fungal infections, which can be serious or life-threatening<sup>7</sup>. Furthermore, cancer cells can develop resistance to chemotherapy drugs over time, rendering them less effective. This can neces-

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sitate changes in treatment regimens or the use of combination therapies to overcome resistance<sup>8</sup>.

### 1.3 Radiotherapy

Radiotherapy can cause side effects both during and after treatment. These can include fatigue, skin changes (such as redness, itching, and blistering in the treated area), hair loss (in the treated area), nausea, vomiting, diarrhea, and urinary or bowel problems depending on the location of the treatment<sup>9</sup>. Some side effects of radiotherapy may not appear until months or even years after treatment. These can include fibrosis (thickening and scarring of tissues), lymphedema (swelling due to lymph fluid buildup), and secondary cancers in the radiation field<sup>10</sup>. Moreover, radiation therapy to the pelvic area or reproductive organs can affect fertility in both people with either male or female reproductive organs. It may cause temporary or permanent infertility, depending on the radiation dose and duration of treatment<sup>11</sup>.

## 2. Pros of Nanoparticle-Based Cancer Therapy

Unlike typical cancer-therapeutic agents, nanoparticles can be engineered to specifically target cancer cells while sparing healthy tissues. This targeted delivery minimizes side effects and enhances the efficacy of the treatment. Nanoparticles can passively accumulate in tumor tissues through the EPR effect, wherein leaky tumor blood vessels allow nanoparticles to accumulate more in tumors compared to normal tissues<sup>12</sup>. Additionally, combination therapies delivered via nanoparticles can help overcome drug resistance by attacking cancer cells through multiple mechanisms simultaneously, making it more difficult for cancer cells to develop resistance. However, limitations such as the instability of lipid-based nanoparticles *in vivo*, where they may degrade prematurely and release payloads nonspecifically, can lead to systemic toxicity and reduced efficacy, necessitating further optimization<sup>13</sup>. Though nanoparticle-based cancer treatment has a lot of benefits over traditional cancer therapies, it has a lot of toxicological effects, depending on nanoparticles' type, shape and the tumor cell that it medicates. This paper mainly focuses on the toxicological effects of nanoparticles on human cells and organs in clinical cancer applications, aiming to improve nanoparticle-based cancer therapy<sup>14</sup>. Compared to traditional therapies, nanoparticle-based treatments often exhibit improved safety profiles, such as reduced myelosuppression compared to chemotherapy, though their long-term toxicity remains less characterized due to limited clinical data<sup>15</sup>.

## What Are Nanoparticle-Based Cancer Treatments?

Nanoparticle-based cancer treatments encompass a diverse array of approaches leveraging the unique properties of nanoparticles. One notable strategy involves using nanoparticles as drug delivery systems. These nanoparticles can encapsulate chemotherapeutic agents, genes, or other therapeutic payloads, shielding them from degradation in the bloodstream and allowing for precise targeting of cancer cells. By functionalizing nanoparticles with specific ligands or antibodies, researchers can enhance their affinity for cancer cells while reducing off-target effect<sup>16</sup>. Additionally, the tunable properties of nanoparticles enable controlled drug release kinetics, optimizing therapeutic efficacy while minimizing systemic toxicity<sup>17</sup>. Current clinical trials, such as the Phase II study of PEGylated liposomal doxorubicin (NCT02596373), have reported improved tumor response rates (up to 40%) compared to free doxorubicin, though challenges like variable patient pharmacokinetics persist<sup>18</sup>.

### 1. Inorganic Nanoparticles:

Inorganic nanoparticles, such as gold nanoparticles and iron oxide nanoparticles, offer unique properties that make them attractive candidates for drug delivery in cancer therapy. Gold nanoparticles, for example, possess excellent biocompatibility, chemical stability, and surface plasmon resonance properties, which can be exploited for targeted drug delivery and imaging applications<sup>19</sup>. Iron oxide nanoparticles, on the other hand, exhibit superparamagnetic properties that enable magnetic targeting and manipulation under external magnetic fields, facilitating site-specific drug delivery and hyperthermia-based cancer therapy. Additionally, inorganic nanoparticles can be engineered to carry therapeutic payloads and surface-functionalized with targeting ligands or antibodies for enhanced tumor specificity<sup>20</sup>. However, their unique toxicological profile includes a higher propensity to generate reactive oxygen species (ROS), with studies showing gold nanoparticles inducing up to 3-fold higher ROS levels in HepG2 cells compared to polymer-based nanoparticles at similar doses<sup>21</sup>.

### 2. Polymer-Based Nanoparticles:

Polymer-based nanoparticles, such as polymeric micelles and dendrimers, offer versatility and flexibility in drug delivery applications. These nanoparticles are typically composed of biocompatible and biodegradable polymers, allowing for controlled drug release and prolonged circulation time *in vivo*<sup>22</sup>. Polymer-based nanoparticles can encapsulate hydrophobic and hydrophilic drugs within their core-shell structures, protecting them from degradation and facilitating targeted delivery to tumor sites. Moreover, the surface properties of polymer-based

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nanoparticles can be tailored to enhance cellular uptake and tumor penetration, improving therapeutic outcomes. For instance, surface modification with polyethylene glycol (PEG) can impart stealth properties to nanoparticles, reducing clearance by the reticuloendothelial system and prolonging circulation time in the bloodstream. Yet, their degradation products, such as lactic acid from PLGA, can lower local pH and trigger inflammation, with *in vitro* studies showing a 20% reduction in cell viability at concentrations above 50  $\mu\text{g/mL}$ <sup>23</sup>.

### 3. Lipid-Based Nanoparticles:

Lipid-based nanoparticles, including liposomes and lipid-based carriers, are widely utilized for drug delivery due to their biocompatibility, versatility, and ability to encapsulate various types of therapeutic agents. Liposomes, composed of phospholipid bilayers, can encapsulate hydrophobic and hydrophilic drugs within their aqueous core or lipid bilayers, enabling efficient drug loading and controlled release<sup>24</sup>. Moreover, the surface of liposomes can be modified with targeting ligands or antibodies to facilitate active targeting of cancer cells and tissues<sup>25</sup>. Lipid-based nanoparticles offer advantages such as high drug-loading capacity, stability, and tunable release kinetics, making them valuable platforms for the delivery of chemotherapy drugs, nucleic acids, and imaging agents in cancer therapy. However, their susceptibility to lipid peroxidation *in vivo* can lead to unintended ROS production, with studies reporting a 30% increase in oxidative stress markers in MCF-7 cells exposed to liposomes at 200  $\mu\text{g/mL}$ <sup>26,27</sup>.

### 4. Hybrid Nanoparticles:

Hybrid nanoparticles, combining the properties of different nanoparticle types, represent a promising approach in cancer therapy. By incorporating multiple components, such as inorganic cores and polymer or lipid coatings, hybrid nanoparticles can synergistically enhance drug delivery efficiency, targeting specificity, and therapeutic efficacy. For example, hybrid nanoparticles composed of gold cores and lipid shells have been developed for combined photothermal therapy and chemotherapy, enabling dual-mode cancer treatment with enhanced therapeutic outcomes. Additionally, hybrid nanoparticles can be engineered to carry multiple therapeutic payloads or imaging agents, allowing for multifunctional applications in cancer diagnosis and treatment<sup>28</sup>. Their complex composition, however, increases the risk of unpredictable toxicity, with *in vivo* studies showing hybrid nanoparticles accumulating in the spleen at levels 2-fold higher than single-component nanoparticles, raising concerns about splenotoxicity<sup>29</sup>.

In summary, inorganic, polymer-based, and lipid-based nanoparticles offer distinct properties and advantages for drug delivery in cancer therapy. Their ability to encapsulate thera-

peutic payloads, target specific cell types, and modulate drug release kinetics makes them promising candidates for enhancing the efficacy and safety of cancer treatments. Ongoing research efforts are focused on further optimizing nanoparticle design and formulation to overcome existing challenges and maximize their therapeutic potential in clinical applications.

## Biochemical Mechanisms and Properties of Nanoparticles Used In Cancer Therapy

Nanoparticles play a pivotal role in revolutionizing cancer therapy, offering unique properties that enable targeted drug delivery, imaging, and therapeutic monitoring. Understanding the diverse properties of nanoparticles is crucial for optimizing their performance in cancer treatment. Below, we explore key properties of various nanoparticle types utilized in cancer therapy:

### 1. Lipid-Based Nanoparticles:

Lipid-based nanoparticles, such as liposomes and lipid nanoparticles, are versatile carriers for delivering a wide range of therapeutic agents. These nanoparticles possess several advantageous properties:

- Lipids are inherently biocompatible and can be metabolized or excreted from the body, minimizing the risk of toxicity. Liposomes, composed of phospholipid bilayers, mimic natural cell membranes, facilitating cellular uptake and intracellular drug delivery.
- Lipid-based nanoparticles offer high drug loading capacities due to their encapsulation within lipid bilayers or cores. Drug release from liposomes can be modulated by adjusting lipid composition or incorporating stimuli-responsive components, enabling controlled release profiles tailored to specific therapeutic needs.
- Lipid nanoparticles exhibit stability in physiological conditions, with liposomal formulations demonstrating prolonged circulation times in the bloodstream. Surface modifications, such as PEGylation, enhance stability by reducing recognition by the reticuloendothelial system (RES) and prolonging systemic circulation.

### 2. Polymer-Based Nanoparticles:

Polymer-based nanoparticles, including polymeric micelles, dendrimers, and nanogels, offer customizable properties for targeted drug delivery and controlled release. Key properties of polymer-based nanoparticles include:

- Polymers can be synthesized with precise control over size, shape, and surface properties, allowing for tailored

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nanoparticle design. This versatility enables optimization of cellular uptake, biodistribution, and pharmacokinetics for enhanced therapeutic efficacy.

- Biodegradable polymers, such as poly(lactic-co-glycolic acid) (PLGA) and polyethylene glycol (PEG), are widely used in nanoparticle formulations due to their biocompatibility and ability to degrade into non-toxic byproducts. Biodegradable polymers minimize long-term accumulation and toxicity, making them suitable for in vivo applications.
- Polymer-based nanoparticles can achieve sustained drug release profiles through diffusion-controlled or degradation-controlled mechanisms. The choice of polymer and formulation parameters dictate release kinetics, allowing for sustained drug exposure at the tumor site and reduced dosing frequency.

### 3. Inorganic Nanoparticles:

Inorganic nanoparticles, such as gold nanoparticles, iron oxide nanoparticles, and quantum dots, offer unique properties for cancer diagnosis, imaging, and therapy. Key properties of inorganic nanoparticles include:

- Inorganic nanoparticles can be functionalized with targeting ligands, imaging agents, or therapeutic payloads to enhance tumor specificity and efficacy. Surface modifications enable precise control over nanoparticle interactions with biological systems, facilitating targeted drug delivery and imaging.
- Inorganic nanoparticles often exhibit multifunctional capabilities, serving as contrast agents for imaging modalities such as magnetic resonance imaging (MRI), computed tomography (CT), or optical imaging. Additionally, some inorganic nanoparticles possess inherent therapeutic properties, such as photothermal or photodynamic therapy, which can be harnessed for cancer treatment.
- Inorganic nanoparticles are engineered to exhibit stability in biological environments, with surface coatings or ligands preventing aggregation and ensuring biocompatibility. Biocompatible coatings, such as silica or polymers, enhance nanoparticle stability and minimize adverse effects in vivo.

### 4. Hybrid Nanoparticles:

Hybrid nanoparticles combine the advantageous properties of multiple nanoparticle types, offering synergistic benefits for cancer therapy. These nanoparticles incorporate components from different materials, such as lipids, polymers, and inorganic nanoparticles, to achieve enhanced functionality and performance.

- Hybrid nanoparticles can overcome limitations associated with individual nanoparticle types, such as low drug loading capacity or poor stability, by combining complementary properties. For example, lipid-polymer hybrid nanoparticles combine the high drug loading capacity of polymers with the biocompatibility of lipids, enabling efficient drug delivery and controlled release.
- The modular nature of hybrid nanoparticles allows for precise tuning of size, shape, and surface properties to optimize therapeutic outcomes. By judiciously selecting component materials and formulation parameters, hybrid nanoparticles can be tailored for specific cancer types, drug payloads, and treatment modalities.

In conclusion, nanoparticles exhibit diverse properties that make them versatile platforms for cancer therapy. Lipid-based, polymer-based, inorganic, and hybrid nanoparticles offer unique advantages for targeted drug delivery, imaging, and combination therapies. Understanding the properties of different nanoparticle types is essential for designing effective and safe cancer treatments tailored to individual patient needs. Ongoing research aims to further refine nanoparticle formulations and exploit their unique properties for improved cancer management<sup>30</sup>.

## Toxicological Effects of Nanoparticle-Based Cancer Therapies

Nanoparticle-based cancer therapies represent a burgeoning field in oncology, offering targeted and efficient treatment modalities. However, along with their immense therapeutic potential, understanding the toxicological effects of nanoparticles is crucial for ensuring patient safety and optimizing therapeutic outcomes. This section delves into the multifaceted toxicological impacts of various nanoparticle types utilized in cancer therapy.

### 1. Induction of Oxidative Stress and Inflammation

#### 1.1 Lipid-Based Nanoparticles

One of the primary concerns associated with lipid-based nanoparticles is their potential to induce oxidative stress. Lipid oxidation processes within nanoparticles can lead to the generation of reactive oxygen species (ROS), triggering oxidative stress and subsequent cellular damage. Furthermore, the release of liposomal contents upon nanoparticle degradation may exacerbate oxidative stress within cells. Additionally, lipid-based nanoparticles can activate immune cells and stimulate pro-inflammatory cytokine release, contributing to inflammation at the cellular level. In vitro studies with PEGylated liposomes on RAW 264.7 macrophages have shown a dose-dependent increase in TNF- $\alpha$  production, peaking at 150 pg/mL at a 100  $\mu$ g/mL dose, underscoring their inflammatory potential<sup>31</sup>.

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## 1.2 Polymer-Based Nanoparticles

Polymer-based nanoparticles can induce oxidative stress through the generation of ROS, leading to cellular damage and oxidative injury. The physicochemical properties of polymers, including surface charge and composition, can influence their potential to generate ROS and elicit inflammatory responses in biological systems. Quantitative data from studies on PLGA nanoparticles reveal a 25% decrease in cell viability and a 2-fold increase in ROS levels in HeLa cells at doses above 75  $\mu\text{g/mL}$ , highlighting dose-dependent toxicity<sup>32</sup>.

## 1.3 Inorganic Nanoparticles

Inorganic nanoparticles have been shown to induce oxidative stress through various mechanisms, including the generation of ROS and disruption of cellular redox balance. The unique surface properties of inorganic nanoparticles, such as surface charge and surface chemistry, can influence their potential to generate ROS and elicit inflammatory responses in biological systems<sup>33</sup>. For instance, gold nanoparticles (20 nm) have been shown to increase ROS production by 3-fold in A549 cells at 50  $\mu\text{g/mL}$ , with a corresponding 40% reduction in cell viability, indicating a clear dose-response relationship<sup>34</sup>.

## 2. Impact on Cellular Signaling Pathways and Gene Expression

### 2.1 Lipid-Based Nanoparticles

Lipid-based nanoparticles have been shown to modulate cellular signaling pathways and gene expression patterns, influencing critical processes such as apoptosis, cell proliferation, and differentiation. The interaction of nanoparticles with cellular membranes and intracellular components can disrupt signaling cascades, leading to dysregulated gene expression profiles and altered cellular functions. Studies have demonstrated that liposomes can upregulate p53 expression by 2-fold in MCF-7 cells at 100  $\mu\text{g/mL}$ , potentially triggering apoptosis, though higher doses may lead to off-target effects<sup>35</sup>.

### 2.2 Polymer-Based Nanoparticles

Polymer-based nanoparticles have been shown to interfere with cellular signaling pathways and gene expression profiles, disrupting cellular homeostasis and functional integrity. Alterations in gene expression patterns may result from direct interactions between nanoparticles and cellular DNA or RNA, leading to dysregulated cellular processes and potential adverse effects on cellular function. For example, PEG-PLGA nanoparticles at 50  $\mu\text{g/mL}$  have been shown to downregulate Bcl-2 expression by 30% in HepG2 cells, affecting anti-apoptotic pathways and increasing cytotoxicity<sup>36</sup>.

## 2.3 Inorganic Nanoparticles

Inorganic nanoparticles can interfere with cellular signaling pathways and gene expression profiles, leading to dysregulated cellular processes and potential adverse effects on cellular function. Interaction of nanoparticles with cellular components, such as DNA or RNA, can result in alterations in gene expression patterns and disrupt cellular homeostasis<sup>37</sup>. Iron oxide nanoparticles at 25  $\mu\text{g/mL}$  have been reported to increase NF- $\kappa\text{B}$  activation by 50% in THP-1 cells, promoting inflammation and potentially exacerbating toxicity<sup>38</sup>.

## 3. Organ Specific Toxicity

### 3.1 Lipid-Based Nanoparticles

In vivo studies have demonstrated organ-specific toxicity associated with lipid-based nanoparticles. Accumulation of these nanoparticles in the liver and spleen has been reported, leading to hepatotoxicity and splenotoxicity. Hepatic clearance mechanisms may become overwhelmed, resulting in nanoparticle accumulation and potential hepatocellular injury. Additionally, prolonged exposure to lipid-based nanoparticles may lead to immune responses and inflammation within the liver and spleen, further exacerbating toxicity in these organs. A mouse study revealed that liposomes at 10 mg/kg accumulated in the liver at 15  $\mu\text{g/g}$  tissue after 24 hours, causing a 20% increase in ALT levels, indicating hepatotoxicity [39].

### 3.2 Polymer-Based Nanoparticles

Polymer-based nanoparticles can accumulate in various organs, including the kidneys, liver, and spleen, raising concerns about potential organ-specific toxicity. Renal clearance pathways may become overloaded, leading to nanoparticle accumulation in the kidneys and potential nephrotoxicity. Additionally, hepatic accumulation of polymer-based nanoparticles may result in hepatotoxicity and impair hepatic function. In vivo data from rats treated with PLGA nanoparticles (5 mg/kg) showed a 30% increase in serum creatinine after 48 hours, suggesting dose-dependent nephrotoxicity [40].

### 3.3 Inorganic Nanoparticles

Inorganic nanoparticles may exhibit organ-specific toxicity, with accumulation observed in organs such as the liver, spleen, lungs, and kidneys. Hepatic and splenic accumulation of inorganic nanoparticles may result in hepatotoxicity and splenotoxicity, impairing hepatic and splenic function. Additionally, pulmonary accumulation of nanoparticles may lead to pulmonary toxicity and impair respiratory function<sup>21</sup>. Long-term studies in mice with gold nanoparticles (2 mg/kg) showed a 25% reduction

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in lung function after 90 days, with nanoparticle levels reaching  $10 \mu\text{g/g}$  in lung tissue, emphasizing the need for extended monitoring<sup>39</sup>.

#### **4. Potential Long-Term Effects and Carcinogenicity**

Long-term exposure to nanoparticles and their potential carcinogenicity is an area of ongoing research and concern in the field of nanomedicine. While nanoparticles hold immense promise for targeted cancer therapy, their interactions with biological systems over extended periods raise questions about their safety and potential adverse effects, including oncogenic potential. Here are some additional insights into the potential long-term effects and carcinogenicity of nanoparticles:

##### **4.1 Chronic Inflammation:**

Chronic inflammation is a well-established risk factor for cancer development. Nanoparticles can induce and sustain inflammatory responses in biological systems, leading to chronic inflammation. Prolonged exposure to inflammatory stimuli, such as cytokines and chemokines released in response to nanoparticle exposure, may promote tumorigenesis by creating a microenvironment conducive to cancer cell survival, proliferation, and metastasis<sup>40</sup>. A 6-month study in rats exposed to silica nanoparticles ( $5 \text{ mg/kg}$ ) revealed persistent lung inflammation and a 15% increase in tumor incidence, suggesting a link between chronic inflammation and carcinogenesis<sup>41</sup>.

##### **4.2 Genotoxicity:**

Nanoparticles have the potential to induce genotoxic effects by directly interacting with DNA or indirectly disrupting DNA repair mechanisms. Surface-modified nanoparticles may penetrate cellular nuclei and interact with chromosomal DNA, leading to DNA damage, chromosomal aberrations, and mutations. Persistent genotoxic insults from nanoparticles may increase the risk of cancer initiation and progression over time. For example, titanium dioxide nanoparticles ( $50 \text{ nm}$ ) at  $100 \mu\text{g/mL}$  caused a 2-fold increase in DNA double-strand breaks in CHO cells, with comet assays confirming dose-dependent genotoxicity<sup>42</sup>.

##### **4.3 Immune Dysregulation:**

Nanoparticles can modulate immune responses, including immune cell activation, cytokine production, and antigen presentation. Dysregulated immune responses may impair immune surveillance mechanisms, allowing transformed or cancerous cells to evade detection and elimination by the immune system. Furthermore, chronic immune activation or suppression induced by nanoparticles may contribute to immune evasion and tumor progression.

##### **4.4 Nanoparticle Accumulation and Distribution:**

The biodistribution and accumulation of nanoparticles in various tissues and organs over time are crucial determinants of their long-term effects. Nanoparticles may undergo slow clearance or sequestration in tissues, leading to prolonged exposure and potential toxicity. Accumulation of nanoparticles in target tissues or organs may disrupt cellular homeostasis and physiological functions, predisposing cells to malignant transformation and cancer development.

##### **4.5 Tumor Microenvironment Modulation:**

Nanoparticles can interact with the tumor microenvironment, including cancer cells, stromal cells, and extracellular matrix components. Nanoparticles may alter the tumor microenvironment to favor tumor growth, angiogenesis, and metastasis. Persistent exposure to nanoparticle-induced alterations in the tumor microenvironment may promote the development of aggressive and invasive cancer phenotypes. Studies with gold nanoparticles in 4T1 breast cancer models have shown a 30% increase in VEGF expression at  $50 \mu\text{g/mL}$ , enhancing angiogenesis and potentially worsening toxicity and tumor progression<sup>43</sup>.

##### **4.6 Carcinogenicity Testing and Risk Assessment:**

Despite the growing evidence implicating nanoparticles in carcinogenesis, comprehensive carcinogenicity testing and risk assessment strategies for nanoparticles are still lacking. Standardized protocols for evaluating the long-term effects of nanoparticles on carcinogenic potential, including *in vivo* studies assessing tumor incidence, latency, and histopathological changes, are needed to accurately assess their safety profiles and regulatory implications.

In summary, understanding the toxicological effects of nanoparticles is essential for ensuring their safety and optimizing their therapeutic potential in cancer treatment. Lipid-based, polymer-based, and inorganic nanoparticles exhibit unique toxicological profiles, influenced by their physicochemical properties and interactions with biological systems. Safety thresholds remain poorly defined, but preliminary data suggest that doses below  $25 \mu\text{g/mL}$  for gold nanoparticles and  $50 \mu\text{g/mL}$  for liposomes maintain cell viability above 80% *in vitro*, though these thresholds vary with nanoparticle size and surface charge<sup>44</sup>.

#### **Strategies to mitigate toxicological effects of nanoparticle-based cancer therapies**

Nanoparticle-based cancer therapies represent a promising approach in the fight against cancer, offering targeted drug delivery and enhanced therapeutic efficacy. However, the unique physicochemical properties of nanoparticles can also lead to unintended

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toxicological effects, which may hinder their clinical translation and application. Mitigating these toxicities is essential to ensure the safety and effectiveness of nanoparticle-based cancer treatments. This article discusses various strategies aimed at reducing toxicological effects associated with these innovative therapies.

### 1. Rational Design of Nanoparticles

**Surface Modification:** Modifying the surface properties of nanoparticles can enhance their biocompatibility and reduce toxicity. Coating nanoparticles with biocompatible polymers or modifying them with targeting ligands can prevent nonspecific interactions, minimizing off-target effects and reducing toxicity to healthy tissues. The size and shape of nanoparticles play a crucial role in their biological behavior and toxicity<sup>45</sup>. Engineering nanoparticles with optimal size and shape can improve their circulation time, cellular uptake, and biodistribution, thereby minimizing toxicity while maximizing therapeutic efficacy.

### 2. Stimuli-Responsive Nanoparticles

Designing nanoparticles that respond to specific stimuli, such as pH, temperature, or enzymatic activity, can enable controlled drug release at the tumor site while minimizing systemic toxicity. Stimuli-responsive nanoparticles offer the potential for targeted drug delivery and reduced off-target effects. Incorporating external triggers, such as light, magnetic fields, or ultrasound, can enable on-demand drug release at the tumor site. Triggered drug release strategies allow for precise control over drug delivery, minimizing toxicity to healthy tissues.

### 3. Biocompatible Materials:

Utilizing biocompatible polymers derived from natural sources, such as chitosan, alginate, or hyaluronic acid, can reduce nanoparticle-associated toxicity. Natural polymers offer excellent biocompatibility and biodegradability, minimizing adverse effects on the body. Selecting FDA-approved materials for nanoparticle formulation ensures their safety and compatibility with clinical use<sup>46</sup>. Using approved materials streamlines the regulatory approval process and facilitates the clinical translation of nanoparticle-based cancer therapies.

### 4. Targeted Delivery Systems:

Functionalizing nanoparticles with targeting ligands, such as antibodies or peptides, enables specific recognition and binding to cancer cells. Targeted delivery systems minimize systemic toxicity by delivering therapeutic agents directly to the tumor site while sparing healthy tissues.

Exploiting tumor-specific characteristics, such as overexpressed receptors or unique microenvironments, allows for active targeting of nanoparticles to cancer cells<sup>47</sup>. Active targeting strategies enhance the accumulation of nanoparticles in tumors, reducing off-target effects and toxicity.

### 5. Pharmacokinetic and Pharmacodynamic Profiling:

Comprehensive preclinical studies are essential for evaluating the pharmacokinetics and pharmacodynamics of nanoparticle-based cancer therapies. Preclinical evaluation helps identify potential toxicological effects and optimize treatment strategies to minimize toxicity while maximizing efficacy. Computational modeling techniques can predict the pharmacokinetic behavior of nanoparticles in biological systems, aiding in the design and optimization of nanoparticle-based therapies. Predictive modeling allows researchers to assess potential toxicological effects and refine nanoparticle formulations to enhance safety<sup>46</sup>.

### 6. Multimodal Imaging and Monitoring:

Incorporating multimodal imaging techniques, such as magnetic resonance imaging (MRI) or fluorescence imaging, enables real-time monitoring of nanoparticle biodistribution and accumulation in tumors. Real-time monitoring facilitates early detection of toxicological effects and enables timely intervention<sup>47</sup>. Non-invasive monitoring techniques, such as biomarker analysis or molecular imaging, offer valuable insights into the biological effects of nanoparticle-based therapies. Non-invasive monitoring allows for early detection of toxicity and facilitates personalized treatment approaches.

### 7. Combination Therapies

Combining nanoparticle-based therapies with conventional chemotherapy, radiotherapy, or immunotherapy can enhance therapeutic efficacy while minimizing toxicity. Synergistic combinations of therapies offer the potential for improved treatment outcomes with reduced adverse effects.

Furthermore, designing multifunctional nanoparticles capable of delivering multiple therapeutic agents or modalities simultaneously offers synergistic effects against cancer. Combinatorial nanomedicine approaches maximize therapeutic efficacy while minimizing toxicity through targeted drug delivery and controlled release<sup>48</sup>.

Nanoparticle-based cancer therapies hold great promise for improving cancer treatment outcomes, but their clinical translation requires addressing potential toxicological effects. Strategies such as rational nanoparticle design, controlled drug release, the use of biocompatible materials, targeted delivery systems, pharmacokinetic profiling, multimodal imaging, and combination therapies can help mitigate toxicities associated with nanoparticle-based cancer treatments. By implementing these

strategies, researchers can enhance the safety and efficacy of nanoparticle-based therapies, bringing us closer to realizing their full potential in cancer treatment.

## Conclusion

The utilization of nanotechnology in the field of healthcare, particularly in cancer treatment, has shown remarkable progress and potential. Nanoparticles offer a promising avenue for targeted drug delivery systems, allowing for enhanced efficacy and reduced side effects compared to traditional cancer therapies. The ability to engineer nanoparticles to specifically target cancer cells while sparing healthy tissues is a significant advancement in cancer treatment. However, it is crucial to acknowledge that nanoparticle-based therapies also come with potential toxicological effects that need to be carefully addressed and studied. Factors such as nanoparticle type, shape, and interaction with tumor cells play a role in determining their toxicity. Long-term in vivo studies, such as those tracking gold nanoparticle biodistribution in mice over 12 months, indicate persistent accumulation in the liver (up to 20  $\mu\text{g/g}$ ) and a 10% incidence of hepatic lesions, underscoring the need for extended monitoring timelines<sup>49</sup>. Therefore, further research and development are necessary to fully understand and mitigate these toxicological effects, ensuring the safety and effectiveness of nanoparticle-based cancer therapies in clinical applications. Overall, nanoparticle-based cancer therapy represents a promising approach that has the potential to revolutionize cancer treatment by overcoming challenges such as drug resistance and enhancing treatment outcomes. Continued research and advancements in this field will contribute to improving patient outcomes and quality of life in cancer care.

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