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# Revisit the biosafety of anticancer nanoparticles

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## Highlights:

- Systematically reviews the biosafety concerns of anticancer nanoparticles from payload, nanomaterial, and bio-corona perspectives.
- Reveals how drugs and nanoparticles lead to long-term toxicity.
- Emphasizes the need for comprehensive toxicological evaluation of nanoparticle distribution and accumulation *in vivo*.
- Proposes targeted strategies including biodegradable materials, antifouling surfaces, and organ-specific delivery systems.

**Abstract:** Cancer remains one of the most important threats to human health, with its high incidence and mortality rates consistently being a focus of global medical research. In recent years, nanomedicines have attracted explosive growth in cancer therapy research due to their enhanced permeability and targeting capabilities. However, the biosafety of anticancer nanoparticles cannot be overlooked, as their potential toxicity may not only compromise therapeutic efficacy but also cause additional harm to the organisms. Thus, we explored the underlying toxicity mechanisms of anticancer nanoparticles from three aspects: payload, nanomaterials, and bio-corona in this article. To address these challenges, we proposed targeted strategies including enhancing nanoparticles targeting design, using the biodegradable natural polymers, and implementing advanced antifouling strategy. We hope that our work can provide a reference for more researchers to pay attention to the biosafety of anticancer nanoparticles and develop safer and more effective methods to fight cancer.

**Keywords:** biosafety; anticancer; nanoparticle

## 1. Introduction

According to the latest CA: A Cancer Journal for Clinicians report [1], cancer remains a major threat to human health. Lung, breast, and colorectal cancers are among the most common types, with lung cancer having the highest mortality rate. Current cancer treatments primarily involve non-drug therapies (e.g., surgery and radiotherapy), and drug therapies (e.g., chemotherapy, targeted therapy and immunotherapy) [2–6].

In recent years, nanomedicines have gained growing attention due to their potential to improve drug delivery efficiency. Advantages such as small size, enhanced permeability, and retention (EPR) effect [7–9] have driven rapid advances in this field, making clinical translation increasing feasible.

However, current studies focus largely on improving therapeutic efficacy, while systematic attention to the biosafety of anticancer nanoparticles remains insufficient. There is still a lack of comprehensive summaries regarding their potential toxicity risks. In this article, we have addressed this gap by summarizing three major concerns: first, the payload may leak and cause damage to normal tissues; second, the nanomaterials themselves are often poorly degradable, and long-term accumulation in the body may cause inflammation or organ damage; and third, their surfaces readily adsorb biomolecules to form a "bio-corona", which can alter targeting specificity and trigger immune responses, increasing the risk of toxicity.

By providing a focused overview of these biosafety issues, this article aims to offer a theoretical reference and raise awareness for the balanced development of anticancer nanoparticles (Figure 1).

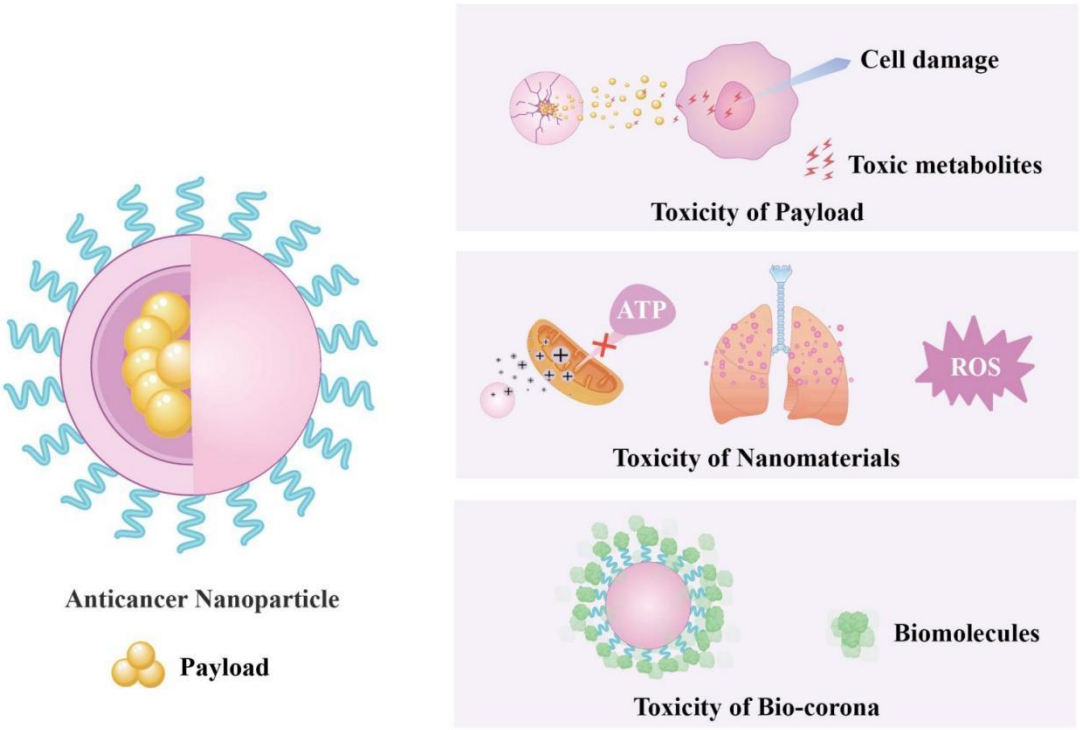


**Figure1.** The three major aspects of the biosafety concerns of anticancer nanoparticles.

## 2. Toxicity of payload

Anticancer drugs encompass a variety of types, which can be broadly categorized into anthracyclines, platinum-based drugs, topoisomerase inhibitors, taxanes, natural polyphenols/phytochemicals, antimetabolites, alkylating agents and molecular targeted therapies based on their mechanisms of action and chemical structures. Their molecular weights and mechanisms of action are listed in Table 1.

Although nanocarrier systems significantly improve drug delivery efficiency, the inherent toxicity of the payload remains a critical issue. Taking doxorubicin as an example, its cardiotoxicity may be alleviated after nanoencapsulation. However, the prolonged circulation time of nanoparticles *in vivo*, along with their complex distribution and metabolic pathways, may still lead to drug accumulation in

off-target tissues, potentially causing long-term toxicity [10,11]. It is worth noting that the distribution of doxorubicin within tumors is significantly affected by tumor acidity and efflux pumps, and its accumulation in hypoxic tumor spheroids is limited, which further impacts its efficacy [12].

The controlled drug release from temperature-responsive systems can be compromised by physiological temperature variations, potentially triggering premature burst release and associated toxic effects [13]. Similarly, while pH-responsive nanocarriers (including those designed for 8-hydroxyquinoline glycoside conjugates and doxorubicin delivery) promote targeted drug release in tumor microenvironments, they may also undergo unintended activation in naturally acidic tissue regions, resulting in unintended toxicity in healthy tissues [14].

Polyphenolic drugs like curcumin and resveratrol present particularly pronounced challenges in nanocarrier design: their unique properties often lead to low drug encapsulation efficiency, inadequate stability, and compromised controlled release behavior [15]. These limitations not only reduce therapeutic efficacy but may also exacerbate toxicity risks. Studies have shown that curcumin is primarily metabolized in the gastrointestinal tract after oral administration, and its metabolites may mediate its biological activity [16,17]. Furthermore, studies have shown that under certain conditions, resveratrol may be oxidized into quinone and semiquinone metabolites, causing cellular damage [18]. Resveratrol metabolites such as sulfated conjugates and glucuronides also demonstrate certain biological activities, which may contribute to its overall health benefits. At higher doses, resveratrol may cause gastrointestinal discomfort and other side effects, and may potentially trigger drug interactions by inhibiting cytochrome P450 enzymes [19].

In addition to the intrinsic toxicity of the drugs themselves, their *in vivo* distribution, metabolic processes, and the resulting metabolites are also key factors in eliciting toxic responses.

The direct toxicity of metabolites is the root cause of adverse effects for many drugs. For instance, the cardiotoxicity of anthracyclines such as doxorubicin is not only attributed to metabolites associated with oxidative stress but also closely related to other metabolites, such as doxorubicinol and aglycones. Moreover, the level of doxorubicinol is positively correlated with the cumulative administered dose [20], which is a major factor for chronic cardiotoxicity [21]. Many of the therapeutic and toxic effects of cyclophosphamide result from the actions of its active metabolites formed by the hepatic microsomal cytochrome P450 mixed-function oxidase system. Some of these metabolites, such as acrolein, have been demonstrated to cause cardiotoxicity both *in vitro* and *in vivo* [22–24]. The metabolic fate of 5-fluorouracil reveals that 85%–90% of administered doses undergo rapid hepatic catabolism, yielding highly cardiotoxic fluoroacetate [25] with confirmed presence in biological systems [26], though its complete chemical characterization requires further investigation.

Therefore, we must comprehensively consider the intrinsic toxicity of the payload and the transport process of the nanoparticles in human body to design safer nanoparticles.

**Table 1.** Representative payloads commonly used in anticancer nanoparticle formulations.

| Category | Name | Molecular Weight (g/mol) | Mechanism of Action | Reference |
|---|---|---|---|---|
| Anthracyclines | Doxorubicin | 543.52 | Intercalates into DNA, inhibits topoisomerase II, disrupting replication and transcription | [27] |
| Platinum-based | Cisplatin | 300.05 | Forms DNA intra- and inter-strand crosslinks, inhibiting replication and transcription | [28–30] |
| | Oxaliplatin | 397.29 | Third-generation platinum agent; forms DNA adducts with a distinct toxicity profile | |
| Topoisomerase Inhibitor | Camptothecin | 348.35 | Inhibits topoisomerase I, causing DNA single-strand breaks | [31] |
| Taxanes | Paclitaxel | 853.91 | Stabilizes microtubules, inhibits mitosis, induces apoptosis | [32] |
| Natural Polyphenols/Phytochemicals | Resveratrol | 228.25 | Control protein activity via interaction with transmembrane and intracellular enzymes | [33] |
| | Curcumin | 368.38 | Interfer with the cell cycle; induce apoptosis in colon carcinoma cells | [34] |
| | Quercetin | 302.24 | Reduce oxidative stress; interfere with the RAS; improve endothelial and vascular function | [35–37] |
| Antimetabolites | Methotrexate | 454.44 | Inhibition of DHFR disrupts folate metabolism, leading to suppressed purine and pyrimidine synthesis and resulting in the blockade of DNA replication and cell division | [38,39] |
| | Gemcitabine | 263.20 | Incorporated into DNA causing chain termination; inhibits ribonucleotide reductase | [40,41] |
| | 5-Fluorouracil | 130.08 | Misincorporation of fluoronucleotides into RNA and DNA; the inhibition of the nucleotide synthetic enzyme thymidylate synthase | [42] |
| Alkylating Agents | Cyclophosphamide | 261.09 | Apoptosis | [43,44] |
| Molecular Targeted Therapy | Imatinib | 589.70 | Specifically inhibits the BCR-ABL tyrosine kinase, blocking its downstream pro-proliferative signaling pathways | [45] |

## 3. Toxicity of nanomaterials

Commonly used nanoparticles for anticancer include lipid-based, polymer-based, metallic, metal oxide, carbon-based, dendrimers, and protein/pepitide-based nanoparticles. Their representative examples, common preparation methods and typical size ranges are summarized in Table 2.

In the development of nanomedicines, the biosafety of various nanomaterials is a critical consideration.

Studies have found that lipid nanoparticles for DNA delivery can result in severe toxicity in mice [46]. Another significant challenge with liposomal drug delivery systems is their instability in biological system, where blood lipoproteins can compromise liposome integrity by triggering surface lipid rearrangement [47]. To address limitations such as insufficient stability, limited drug loading, rapid drug release, and short circulation time, lipid nanoparticles are often functionalized via polyethylene glycol (PEG) modification or ligands such as peptides, antibodies and carbohydrates [48]. However, some negatively charged PEG-lipid nanoparticles often cause complement activation, hyper sensitivity reactions (HSRs), and cardiopulmonary distress. Hoven *et al.* studied the impact of negatively charged PEGylated liposomes. They investigated liposomes with variations in PEG in terms of liposomal size, chain length, surface concentration, and anchor molecule. While other changes resulted in effects ranging from none to mild, PEG anchored with cholesterol showed the greatest complement activation [49]. Another similar study conducted by Szebeni *et al.* evaluated the effects of doxil and hynic PEG liposomes on complement activation and hyper sensitivity [50]. Their findings confirmed that negatively charged PEGylated liposomes could indeed trigger complement activation and associated hypersensitivity reactions, underscoring the significant role of surface properties in nanocarrier-induced immune responses. These studies emphasize the critical role of surface chemistry in nanoparticle biosafety, and suggest that similar trade-offs between surface modification and toxicity may exist in other nanomaterials.

Among metallic nanoparticles, gold nanoparticles (AuNPs) are non-biodegradable and can easily accumulate in the body after long-term application, leading to uncertain side effects. *In vitro* study has shown that AuNPs can disrupt the interactions between endothelial cells and the tumor microenvironment, effectively inhibiting the process of angiogenesis [51]. Moreover, their photothermal efficacy is constrained by the limited tissue penetration of near-infrared lasers, consequently reducing targeted drug release accuracy and immunomodulatory functions [52]. Notably, the toxicity of AuNPs is related to size: smaller colloidal AuNPs (10–50 nm) exhibit greater toxicity compared to larger particles (100–200 nm) [53]. Another report demonstrated that AuNPs within the size range of 2.8–38 nm are more toxic and can induce immune reactions [54]. Similar dimensional and concentration-dependent cytotoxicity patterns are observed in silver nanoparticles, which promote ROS generation, induce DNA damage, suppress cellular proliferation, trigger immune-inflammatory cascades, and pose genotoxic risks [55]. *In vitro* studies on hepatocytes revealed size-dependent adverse effects of AgNPs, including decreased mitochondrial function, lactate dehydrogenase (LDH) leakage, and abnormal cell morphology [56]. Zinc nanoparticles tend to accumulate in the liver, spleen, and bone marrow, increasing toxicity in these organs. Numerous studies have identified the liver as the primary organ responsible for the reticuloendothelial capture of nanoparticles, largely due to phagocytosis by Kupffer cells. Hepatotoxicity has been observed in mice treated orally with nano-zinc particles [57]. Excessive exposure to cobalt nanoparticles can affect auditory, visual, nervous, cardiovascular, and endocrine functions [58,59]. Metallic nanoparticles can also demonstrate reproductive toxicity. Studies have found that AuNPs can diffuse into embryos and cause teratogenic deformities [60]. Furthermore, Braydich-Stolle *et al.* reported that metallic nanoparticles also impact the female reproductive system, with silver nanoparticles having the biggest toxicity [61]. This toxicity is closely linked to free radical generation and induction of inflammatory mediators [62]. These factors collectively constitute complex safety challenges for metallic nanoparticles, while similar size-dependent toxicity and oxidative stress mechanisms also play key roles in the toxicity of metal oxide nanoparticles.

Among metal oxide nanoparticles, zinc oxide nanoparticles (ZnO-NPs) carry potential risks such as accumulation in excretory organs and lack of biodegradability [63]. Studies indicate that ZnO-NPs exhibit concentration-dependent cytotoxicity in human hepatocellular carcinoma cells (HepG2). By increasing the production of reactive oxygen species (ROS), they induce lipid peroxidation and glutathione depletion, leading to apoptosis [64]. This oxidative stress-mediated toxic mechanism highlights the potential risks of nanomaterials in biological systems. Titanium dioxide nanoparticles ($TiO_2$-NPs) demonstrate cytotoxic and genotoxic effects on the respiratory system [65].

Among carbon-based nanomaterials, single-walled carbon nanotubes are lightweight, can become airborne and reach the lungs, causing peribronchial inflammation and necrosis [66]. Due to the hydrophobicity of graphene surfaces, it can significantly interact with cell membrane lipids, leading to toxicity [67]. Exposure of platelets to reduced graphene oxide (rGO) can trigger a strong cumulative response and extensive pulmonary thromboembolism [68]. Furthermore, rGO can act through ROS on alveolar macrophages and alveolar epithelial cells, causing inflammatory responses and apoptosis via mitochondrial dysfunction [69]. The unique hazards of carbon-based nanomaterials to the respiratory system are well established, while the toxicological mechanisms of dendrimers exhibit different characteristics.

Dendrimers such as PAMAM may cause toxicity of human liver cells by inducing cell growth inhibition, mitochondria damage, and apoptosis [70]. It's worth noting that charge can affect the oral toxicity of PAMAM. Specifically, positively charged dendrimers cause more toxicity, with severe signs including hemobilia and splenomegaly [71]. Studies have demonstrated that cationic PAMAM may cause liver damage when administered intravenously in mice [72]. The toxicity characteristics of dendrimers remind us that the surface charge and chemical structure of nanomaterials jointly determine their biocompatibility, and this understanding is crucial for comprehensively evaluating the *in vivo* behavior of various anticancer nanoparticles.

Many nanoparticles like metallic nanoparticles exhibit cytotoxicity *in vitro*, which in cancer therapy may not only kill cancer cells but also damage healthy cells [73]. Although some nanomaterials show low toxicity *in vitro*, their biodistribution and long-term toxicity *in vivo* require further investigation. For example, cisplatin-loaded chitosan-sodium alginate nanoporous carriers have been shown to mitigate pulmonary toxicity while concurrently enhancing hepatotoxicity in rat models. This observation underscores how *in vivo* distribution and metabolic pathways critically determine the overall toxicity profile of nanomaterials [74].

Beyond the inherent properties of nanoparticles, their degradation products *in vivo*, such as metal ions, can exert significant toxic effects even at low concentrations. For instance, metal ions released from nanoparticles like zinc oxide, silver, cadmium selenide, and iron oxide can interfere with cellular pathways, induce the generation of reactive oxygen species (ROS), and disrupt intracellular metal homeostasis [75]. These ions may reform nanoparticles within cells, gradually dissolve, be expelled via exocytosis, or migrate to different cellular organelles, ultimately contributing to long-term cytotoxicity and genotoxicity [76]. Studies have shown that the dissolution products of zinc oxide and copper oxide nanoparticles can provoke inflammatory responses and cell death both *in vitro* and *in vivo*, with their toxicity depending on dissolution rates and ion-specific properties [77]. While silver nanoparticles show toxicity similar to silver salts, zinc ions exhibit more acute toxicity compared to zinc nanoparticles [78,79]. The primary toxic mechanism of cadmium-based quantum dots originates from the release of $Cd^{2+}$ ions during particle degradation. Due to the fact that toxic effects may be significantly influenced by

environmental conditions, exposure concentration, and duration, current studies report varying findings regarding the relative toxicity of nanoparticles and their degradation products [80]. Further research is needed to evaluate the immune responses triggered by nanoparticles and their metabolites both *in vivo* and *in vitro*.

Therefore, the development of anticancer nanoparticles must comprehensively consider the *in vivo* behavior, distribution characteristics, and long-term toxicity through comprehensive toxicological assessments.

**Table 2.** Composition, synthesis methods, and size characteristics of common nanomaterials.

| Category | Examples of Nanomaterials | Common Preparation Methods | Typical Size Range | Reference |
|---|---|---|---|---|
| Lipid-based | Phospholipids, Cholesterol, Cationic lipids (e.g., DOTAP) | Thin-film Dispersed Hydration, Solvent Emulsification Diffusion | 50–200 nm | [81,82] |
| Polymer-based | PLGA, PEG-PLA, Chitosan | Nanoprecipitation Dropping Technique, Double Emulsion Solvent Evaporation Method | 50–300 nm | [83,84] |
| Metallic Nanoparticles | Gold Nanoparticles (AuNPs), Silver Nanoparticles (AgNPs), Zinc Nanoparticles (ZnNPs), Cobalt Nanoparticles (CoNPs) | Chemical reaction (Photoreduction), Laser ablation, Sonochemical Approach | 10–200 nm | [85–87] |
| Metal Oxide Nanoparticles | Zinc Oxide (ZnO), Titanium Dioxide ($TiO_2$), Iron Oxide ($Fe_3O_4$), Cobalt Oxide ($Co_3O_4$) | Sol-Gel, Co-precipitation, Thermal Decomposition | 10–100 nm | [88–90] |
| Carbon-based | Single-Walled Carbon Nanotubes (SWCNTs), Carbon Nanotubes (CNTs), Graphene Oxide (GO) | Chemical Vapor Deposition, Hummers' Method | Diameter: 0.5–5 nm (SWCNT), 1–100 nm (Others); Length: up to μm | [91,92] |
| Dendrimers | Polyamidoamine (PAMAM) | Convergent and divergent synthesis method of chemical polymerization | 3–15 nm | [93,94] |
| Protein/Peptide-based | Albumin, Gelatin | Desolvation, Self-assembly | 50–300 nm | [95] |

## 4. Toxicity of bio-corona

Bio-corona refers to the dynamic complex layer formed by the spontaneous and rapid adsorption of biomolecules (mainly including proteins, lipids, and nucleic acids) onto the surface of nanoparticles when they enter a biological environment (such as bodily fluids, serum, or tissues). This corona's compositional and structural characteristics fundamentally govern the subsequent biological behavior and fate of nanoparticles within living systems [96].

Studies indicate that the formation of bio-corona may improve the biocompatibility of nanoparticles. For instance, serum protein-coated single-walled carbon nanotubes (SWCNTs) exhibit lower cytotoxicity compared to uncoated ones and can alter cellular interaction pathways [97]. Dutta *et al.* revealed that albumin adsorption on SWCNT surfaces mediates cellular uptake in RAW264.7 macrophages through specific receptor interactions [98]. Similarly, when silica nanoparticles are pre-adsorbed with γ-globulin,

protein binding further modifies the nanoparticle surface, effectively inhibiting the action of opsonins and preventing their recognition by target receptors [99]. Yallapu *et al.* indicated that after protein corona formation, magnetic nanoparticles undergo a targeted uptake process characterized by enhanced dynamics or increased interaction with membrane structures, promoting overall endocytosis in cancer cell lines [98]. Furthermore, the bio-corona can increase the payload capacity of certain nanocarrier systems [100].

However, the formation of the bio-corona may induce multiple toxic effects, primarily due to its fundamental alteration of the nanoparticles' original physicochemical properties and their interactions with biological systems. Specifically, certain biomolecules adsorbed in the corona layer, such as immunoglobulins or fibrinogen, can serve as "eat-me signals". This process can induce inflammatory cascade and resultant tissue damage [101]. Studies have shown that human plasma protein corona formed on the surfaces of silica and polystyrene nanoparticles significantly modify their cellular uptake behavior [102], while inducing protein conformational alterations and functional modifications [103], collectively influencing their toxicity characteristics.

In addition, the bio-corona can completely obscure targeting molecules on the surface of nanoparticles, thereby weakening their targeting function [104]. For example, albumin adsorbed on single-walled carbon nanotubes may interfere with innate immune responses by engaging scavenger receptors [98]. Furthermore, the composition of the protein corona is influenced by multiple factors including the characteristics of the nanoparticles, biological fluid, and exposure duration [105].

The protein corona can also exacerbate immune-inflammatory responses. Black phosphorus quantum dots (BPQDs) complexed with plasma proteins significantly enhance the release of inflammatory cytokines [106], while fibrinogen adsorption can trigger inflammatory activation through Mac-1 receptor engagement. Notably, species-specific bio-coronas present significant toxicity risks. When $SiO_2$ nanoparticles pre-coated with fetal bovine serum (FBS) were administered to zebrafish embryos, the "non-self" protein corona characteristics induced vascular integrity disruption and inflammatory activation, revealing potential toxicity mechanisms arising from interspecies mismatch between protein corona and biological systems [107].

Finally, the corona layer can alter the aggregation state and drug release kinetics of nanoparticles, potentially leading to capillary embolism or off-target drug release. Additionally, the composition of the bio-corona exhibits individual variability influenced by health status, disease type, and other factors [108], resulting in unpredictable toxic responses to the same nanoparticles in different individuals and posing serious challenges for clinical applications.

## 5. Recommendations

Based on the above issues, we propose the following recommendations to reduce the toxicity risks of anticancer nanoparticles and enhance their therapeutic safety:

(1) Regarding the payload, it is recommended to select drugs with higher selectivity for tumor cells and modify the surface of nanocarriers with specific targeting molecules to improve targeting capability and reduce non-specific damage to normal tissues.

(2) Regarding nanomaterials, it is advisable to prioritize naturally derived, biodegradable materials (e.g. lecithin, albumin, *etc.*) to minimize long-term toxicity risks caused by the accumulation of the materials *per se* and their metabolites in the body. For non-biodegradable materials (e.g. gold

nanoparticles), establishing safe size thresholds and implementing surface charge modulation strategies are essential to alleviate acute toxicity and charge-related toxic effects.

(3) Regarding bio-corona, we can implement antifouling strategy to effectively reduce the adsorption of biomolecules onto nanomaterials, maintain the functional integrity of nanoparticle surfaces, and mitigate toxicity risks such as immune activation and off-target accumulation.

In addition, we should consider developing specific drug delivery strategies for certain types of tumors to reduce drug exposure in other organs and improve overall safety. For instance, topical formulations such as creams, gels or patches can be used for skin tumors to achieve localized drug release at the disease site, while inhalable nanoformulations can be used for lung cancer to achieve direct respiratory delivery to the relevant regions of the lung, reducing the toxicity of the drugs to other tissues. Moreover, for nanoparticles that tend to accumulate in the liver (such as metal nanoparticles), we should explore liver-avoiding surface modifications to reduce hepatotoxicity.

These above strategies address both the carrier material characteristics and their biological interactions from multiple perspectives, providing systematic guidance for the development of safer anticancer nanoparticles.

## 6. Conclusions

We must think twice before assuring that nanoparticles are readily prepared for clinical application. This article discussed the potential toxicity of anticancer nanoparticles from three aspects: payload, nanomaterials, and bio-corona, emphasizing that their biosafety cannot be overlooked. The payload itself often has inherent toxicity, which can damage normal cells while killing tumor cells. Nanomaterials may trigger inflammatory responses after long-term circulation or accumulation in human body. The formation of bio-corona may change the behavior of nanoparticles and cause toxic effects. In response to these issues, we had proposed corresponding strategies to improve anticancer efficiency and reduce side effects. We look forward to developing more efficient anticancer nanoparticles, but we also urge researchers to prioritize safety concerns in order to promote the development of anticancer nanoparticles for safer applications.

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## Authors' contribution

Conceptualization, Zhengwei Huang; investigation, resources, data curation, and writing—original draft preparation, Naixuan Deng; writing—review and editing, Yeqi Huang, Yue Gao, Chuanbin Wu and Zhengwei Huang; visualization, supervision, project administration, and funding acquisition, Zhengwei Huang. All authors have read and agreed to the published version of the manuscript.

## Conflicts of interests

The authors declare no conflict of interest.

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