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Nanotechnology in Cancer Treatment: Innovative Approaches to Overcoming Drug Resistance in Tumors

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Abstract

Nanotechnology has emerged as a groundbreaking approach in oncology, offering innovative solutions to one of the most significant challenges in cancer treatment: drug resistance. This literature review explores the role of nanotechnology in overcoming multidrug resistance (MDR) in tumors, focusing on the use of nanoparticles for targeted drug delivery, gene therapy, and immunotherapy. By penetrating biological barriers and modulating the tumor microenvironment, nanocarriers enhance the efficacy of anticancer agents while minimizing side effects. Additionally, this review provides a comprehensive analysis of recent clinical trials, offering insights into the real-world effectiveness of nanotechnology-based treatments. Ethical, regulatory challenges, and nanotoxicity are discussed to ensure the safe translation of nanomedicine to clinical practice. The review concludes with future directions in personalized nanomedicine, highlighting nanotechnology's transformative potential in revolutionizing cancer treatment and improving patient outcomes by addressing the pervasive issue of drug resistance.

Keywords: *Nanotechnology, Drug resistance, Nanoparticles, Targeted drug delivery, Cancer therapy, Clinical trials, Nanotoxicity.*

INTRODUCTION

Nanotechnology, defined as the manipulation of materials on an atomic or molecular scale, has significantly influenced various fields of medicine, particularly oncology. Its ability to create nanoscale materials and devices, typically ranging from 1 to 100 nanometers, has opened up new avenues in cancer treatment and diagnosis. These nanoscale entities can be engineered to interact with biological molecules at the cellular level, thereby enhancing the specificity and efficacy of therapeutic interventions (Mosleh-Shirazi, *et al*., 2022).

The integration of nanotechnology into oncology initially focused on improving drug delivery systems by utilizing nanoparticles to enhance the solubility, stability, and bioavailability of chemotherapeutic agents. However, the scope of nanotechnology has since expanded. The development of multifunctional nanoparticles now enables precise targeting of tumors, efficient drug delivery, and the simultaneous provision of diagnostic information. This shift from conventional therapies, which often suffer from poor targeting

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and systemic toxicity, highlights the superiority of nanomaterials in improving therapeutic outcomes (Bhatia, *et al*., 2022).

Nanomedicine's current landscape is characterized by its diverse applications across therapeutic and diagnostic domains. These include not only targeted drug delivery but also gene therapy, immunotherapy, and theranostics a combination of therapy and diagnostics within a single platform. Nanoparticles can bypass biological barriers, target cancer cells with high specificity, and release therapeutic agents in response to stimuli within the tumor microenvironment, thereby reducing collateral damage to healthy tissues and enhancing the therapeutic index of anticancer drugs. Furthermore, nanoparticle-mediated photothermal and photodynamic therapies are gaining prominence as innovative approaches to overcoming the limitations of traditional treatments, particularly in drug-resistant cancers (Sun, *et al*., 2023).

METHODOLOGY

This review follows a systematic approach, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, which is now recognized as a standard methodology for evidence synthesis in biomedical research. The process involved several key steps: defining eligibility criteria, conducting a comprehensive search, selecting studies, and synthesizing the data.

Search Strategy

A comprehensive systematic search was performed across several major academic databases, including PubMed, Scopus, Web of Science, and Google Scholar. The search strategy utilized a combination of keywords and Medical Subject Headings (MeSH) terms such as "Nanotechnology", "Drug Resistance", "Nanoparticles", "Targeted Drug Delivery", "Cancer Therapy", and "Tumor". Boolean operators (AND, OR) were applied to refine the search results and ensure the retrieval of relevant studies. The search was restricted to studies published in English between January 1976 and June 2024, with a primary focus on literature from 2015 to 2024 to capture the most recent advancements and insights in the field. This time frame was selected to ensure the inclusion of the latest and most relevant research on nanotechnology's role in overcoming drug resistance in cancer.

Eligibility Criteria

To ensure the inclusion of high quality studies, predefined eligibility criteria were applied: Inclusion criteria:

- Peer-reviewed articles published in English.
- Studies focusing specifically on the application of nanotechnology in overcoming drug resistance in cancer treatment.
- Experimental studies, clinical trials, systematic reviews, and meta-analyses that provided quantitative or qualitative data on the effectiveness of nanotechnology-based interventions in cancer therapy.

Exclusion criteria:

- Articles not related to cancer treatment or drug resistance.
- Non-peer-reviewed literature, such as opinion pieces, commentaries, and editorials.
- Studies with insufficient methodological details or lacking clear outcomes related to nanotechnology and drug resistance.

Study Selection

A total of 2,134 records were identified through the initial database search. After removing duplicates, 1,850 unique studies remained. These studies underwent a two-stage screening process. In the first stage, titles and abstracts were reviewed to exclude irrelevant studies, resulting in 180 articles. In the second stage, the full texts of these articles were assessed for eligibility, and 40 studies met the inclusion criteria for detailed review.

Data Extraction and Synthesis

Data were extracted from the included studies using a standardized form, which captured essential information such as study design, sample size, type of nanotechnology employed, cancer type, outcomes related to drug resistance, and key findings. The extracted data were then synthesized qualitatively, with a focus on identifying patterns and trends in the use of nanotechnology to overcome drug resistance in cancer therapy.

To further clarify the study selection process, a PRISMA flow diagram (Figure 1) is provided below, detailing the number of records identified, screened, and included, alongside reasons for exclusion at each stage. This approach ensures a comprehensive and systematic evaluation of the available literature, addressing both broad trends in multimodal cancer treatment and more specific neoadjuvant/adjuvant surgical interventions.

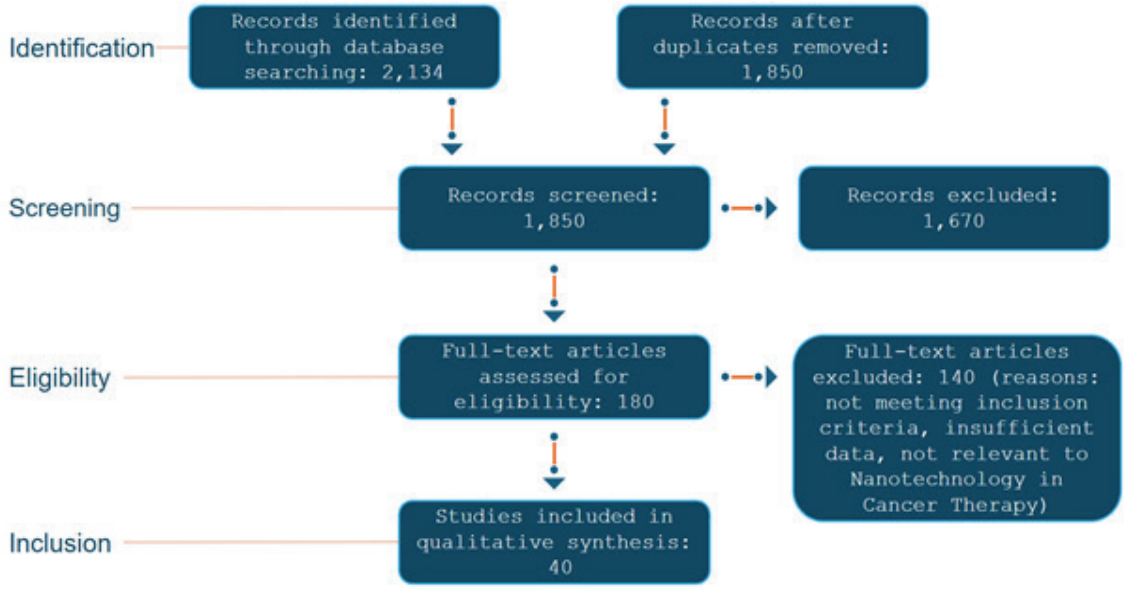

Figure 1. Illustrates the PRISMA flow diagram.

MECHANISMS OF DRUG RESISTANCE IN CANCER

Drug resistance in cancer remains a significant challenge that undermines the efficacy of many oncological treatments. Understanding the biological mechanisms behind this resistance is crucial for improving therapeutic strategies (Figure 2). One of the primary contributors to drug resistance is the genetic instability of cancer cells, which leads to the development of mutations that can alter drug targets or activate alternative survival pathways, thereby enabling the tumor to evade treatment. Moreover, the overexpression of efflux pumps, such as P-glycoprotein (P-gp), actively transports drugs out of cancer cells, reducing the intracellular concentration of chemotherapeutic agents and further promoting resistance (Fojo, 2007; Phi, *et al*., 2018).

The tumor microenvironment also plays a critical role in drug resistance. This protective niche for cancer cells induces resistance through mechanisms such as hypoxia, which diminishes the effectiveness of radiation therapy and some chemotherapeutic drugs. Additionally, interactions between cancer cells and stromal cells in the

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microenvironment can activate survival pathways that further enhance resistance (Greaves & Maley, 2012; Synold, *et al*., 2001). The review also highlights recent studies detailing how nanotechnology can target these microenvironmental factors to improve drug efficacy, an area that remains underexplored in standard treatments.

Cancer stem cells (CSCs) contribute significantly to drug resistance due to their unique ability to self-renew and differentiate. These cells can enter a quiescent state, rendering them less sensitive to therapies targeting rapidly dividing cells. Upon treatment cessation, they can repopulate the tumor, leading to relapse (Torgovnick & Schumacher, 2015; Lowe, *et al*., 1993). CSCs also express higher levels of efflux pumps and exhibit enhanced DNA repair mechanisms, both of which contribute to their resistance (Nowell, 1976). Expanding on these mechanisms can highlight why targeting CSCs is crucial for overcoming drug resistance, especially in resistant cancers.

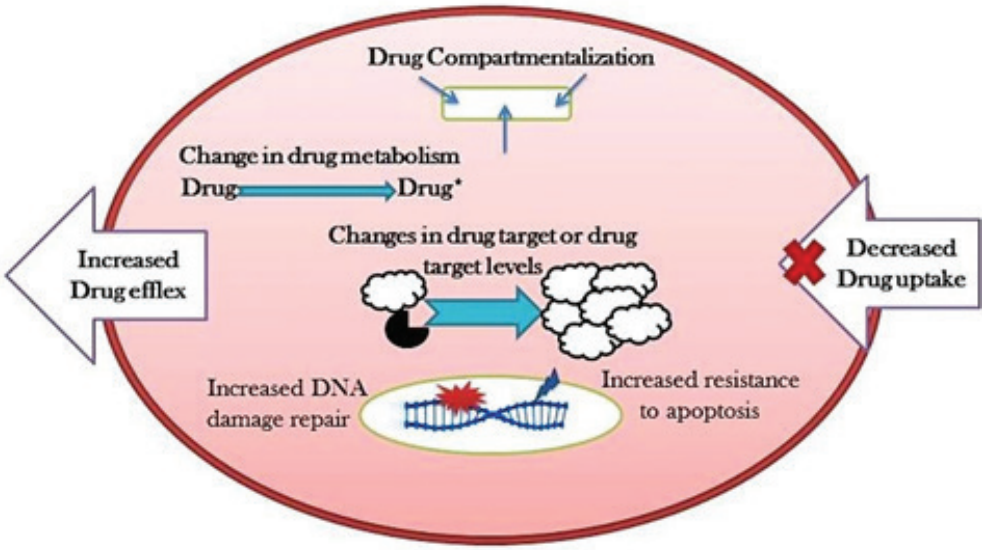

Figure 2. Illustrates the mechanisms of drug resistance in cancer cells. (Adapted from: doi.org/10.15171/apb.2017.041)

NANOPARTICLES AS DRUG DELIVERY SYSTEMS

Nanoparticles have emerged as powerful tools in cancer therapy, particularly as drug delivery systems. Various types of nanoparticles, including polymeric nanoparticles, liposomes, dendrimers, quantum dots, and gold nanoparticles, have been successfully employed in oncology. Each has distinct properties that make them suitable for different therapeutic applications.

Polymeric nanoparticles (PNPs), synthesized from natural or synthetic polymers, offer flexibility in drug delivery by carrying both hydrophilic and hydrophobic drugs (Figure 3). These nanoparticles can be engineered to have a core-shell structure, where drugs are either encapsulated within the core or attached to the surface. Their versatility makes PNPs excellent candidates for targeted cancer therapy, as they can be modified to improve biocompatibility and reduce toxicity (Hauser, *et al*., 2019). Dendrimers, a subclass of PNPs, are highly branched, tree-like structures that provide precise control over size and surface functionality, making them suitable for delivering therapeutic agents such as nucleic acids and small molecules (Yoo, *et al*., 2019).

Liposomes, composed of a lipid bilayer, are another widely used class of nanoparticles. They encapsulate drugs and protect them from degradation before reaching the tumor site. Liposomal formulations like Doxil have already demonstrated clinical success by enhancing drug bioavailability and reducing side effects (Aloss & Hamar, 2023). Recent clinical trials on liposomal therapies have shown promising results, reinforcing their relevance in overcoming drug resistance, though challenges remain in improving their targeting specificity.

Quantum dots (QDs) and gold nanoparticles (GNPs) are also gaining prominence. QDs, with their unique optical properties, are used for precise tumor imaging and diagnostics. GNPs are valued for their stability and ease of functionalization and are often employed in photothermal therapy, where they absorb light and convert it into heat to kill cancer cells (Wahab, *et al*., 2019). The integration of these therapies with existing modalities like immunotherapy can enhance treatment efficacy and offer new avenues for combination therapies.

Nanoparticles offer the advantage of tumor-specific targeting, minimizing damage to healthy tissues. This targeted delivery is often achieved through surface modifications that enable nanoparticles to bind to specific cancer cell receptors (Yu, *et al*., 2010). Additionally, nanoparticles can penetrate biological barriers, such as the blood-brain barrier, enhancing the treatment of cancers like glioblastoma (Fan, *et al*., 2023). However, recent advances suggest that nanoparticle-mediated drug delivery must further address concerns about nanotoxicity, as highlighted in several clinical studies.

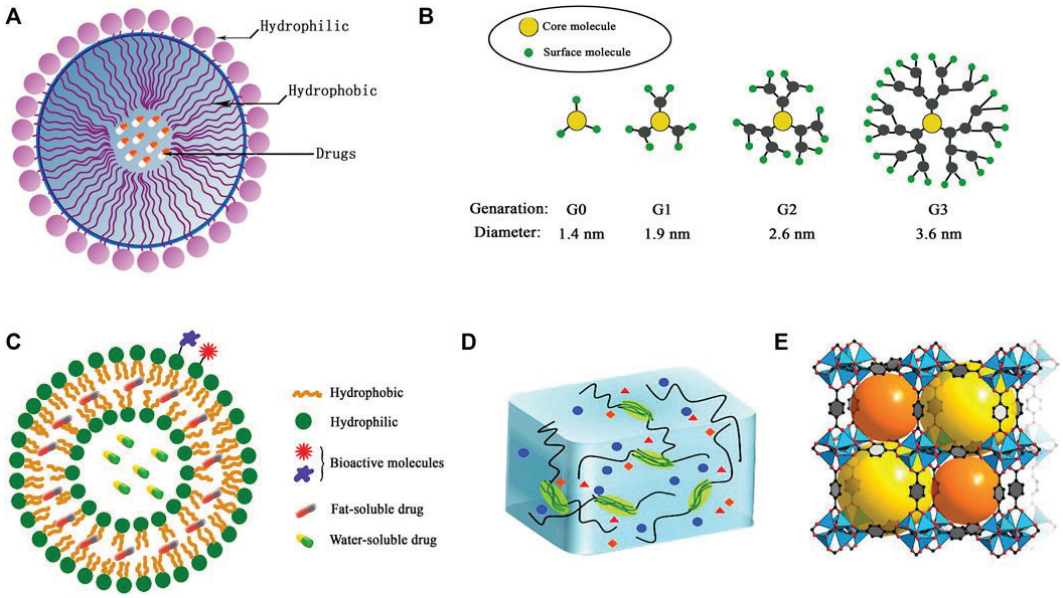

Figure 3. Illustrates the structures of typical polymeric nanoparticles: (A) micelles, (B) dendrimers, (C) polymersomes, (D) hydrogel, (E) metal-organic framework (MOF). (Adapted from: doi.org/10.3389/fbioe.2022.1024143)

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NANOTECHNOLOGY AND MULTIDRUG RESISTANCE (MDR)

Multidrug resistance (MDR) remains a major hurdle in effective chemotherapy, as it allows tumor cells to evade the cytotoxic effects of various drugs. Nanotechnology presents a promising solution to overcoming MDR by enabling the design of nanoparticles that can bypass or overcome resistance mechanisms.

MDR in cancer typically arises from several mechanisms, including the overexpression of efflux pumps like P-glycoprotein (P-gp), alterations in drug target sites, enhanced DNA repair capabilities, and the evasion of apoptosis (Figure 4). Nanoparticles help counteract these mechanisms by facilitating intracellular drug delivery, reducing the likelihood of drug expulsion via efflux pumps. For example, nanoparticles can encapsulate chemotherapeutic agents, shielding them from recognition and expulsion by P-gp (Hu & Zhang, 2012). Recent clinical findings indicate that nanoparticle encapsulation enhances drug retention in resistant cancer cells, showing promise in early-stage clinical trials.

In addition to bypassing efflux mechanisms, nanoparticles are instrumental in combination therapies, co-delivering chemotherapeutic agents with chemosensitizers or other drugs that inhibit resistance pathways. Certain nanoparticles co-deliver an anticancer drug along with an inhibitor that suppresses P-gp or other resistance proteins, thus restoring drug efficacy (Nieto Montesinos, *et al*., 2012). This strategy not only helps overcome MDR but also minimizes systemic toxicity by ensuring that drugs are released specifically at the tumor site.

Nanotechnology also enables the development of multifunctional nanoparticles that target multiple resistance mechanisms. For instance, nanoparticles loaded with both siRNA to silence resistance-related genes and chemotherapy drugs to induce cytotoxicity offer a dual approach to tackling drug resistance at both the genetic and biochemical levels (Majidinia, *et al*., 2020). Expanding this approach could pave the way for personalized treatment strategies, leveraging gene silencing and combination therapies to combat MDR on a patient-specific basis.

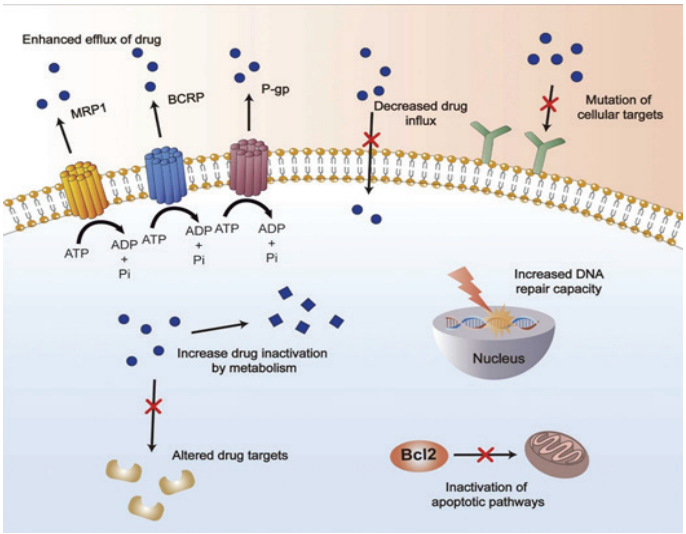

Figure 4. Illustrates the main mechanism of MDR, including: 1) Drug efflux mediated by ATP-dependent efflux pumps such as P-gp (ABCB1), BCRP (ABCG2), and MRP1 (ABCC1); 2) Increased expression of drug-metabolizing enzymes to inactivate drugs; 3) Changes in drug targets to diminish drug-target interactions; 4) Enhanced DNA repair mechanisms to reduce drug-induced DNA damage. (Adapted from: doi.org/10.1016/j.biopha.2024.117327)

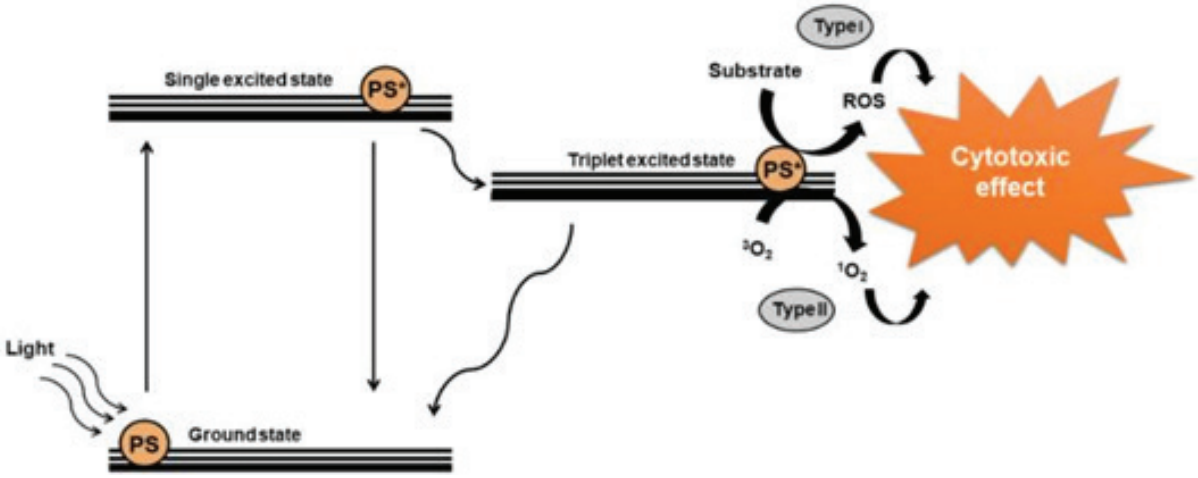

Figure 5. Jablonski diagram representation and the photodynamic therapy mechanism of action. (Adapted from: doi.org/10.3390/nano11113132)

NANOCARRIERS FOR GENE THERAPY AND RNA INTERFERENCE

Nanotechnology has become a pivotal tool in overcoming multidrug resistance (MDR) in cancer, especially through gene therapy and RNA interference (RNAi) approaches. Nanocarriers, such as liposomes and polymeric nanoparticles, are now employed to deliver gene-editing tools like CRISPR-Cas9, which can precisely target and correct genetic mutations driving drug resistance in tumors. These nanocarriers enhance the stability, specificity, and cellular uptake of CRISPR components, leading to more effective gene therapy interventions (Huang, *et al*., 2022; Severi & Akbari, 2024). Recent studies suggest that the co-delivery of CRISPR-Cas9 with other therapeutic agents holds potential for tackling MDR at both genetic and biochemical levels. Clinical trials exploring CRISPR-based nanocarriers could provide critical insights into the feasibility of this approach in cancer treatment.

In addition to gene therapy, nanocarriers are instrumental in delivering small interfering RNA (siRNA) and microRNA (miRNA) for RNA interference (RNAi) therapies. These nanoparticles protect RNA molecules from degradation and enhance their delivery to tumor cells, where they silence genes responsible for drug resistance. This method shows great promise in overcoming resistance mechanisms that hinder the effectiveness of conventional chemotherapy (Li, *et al*., 2018; Shui, *et al*., 2023). Despite these advances, nanotoxicity and off-target effects in RNAi therapies require further exploration to ensure their safety in clinical settings.

PHOTOTHERMAL AND PHOTODYNAMIC THERAPY

Nanoparticle-mediated photothermal and photodynamic therapies represent innovative approaches in cancer treatment, particularly for addressing drug-resistant tumors. In photothermal therapy (PTT), nanoparticles such as gold nanostructures convert light to heat upon exposure to near-infrared (NIR) light, inducing localized hyperthermia that selectively kills cancer cells. Gold nanoparticles are advantageous because of their ease of functionalization, enhancing their accumulation in tumors through the enhanced permeability and retention (EPR) effect (Kim & Lee, 2018; Han & Choi, 2021).

Photodynamic therapy (PDT) uses photosensitizers that, when activated by specific wavelengths of light, generate reactive oxygen

species (ROS) that cause cell death. The combination of PTT and PDT can have a synergistic effect, making these therapies more effective when used together (Báez, 2023; Nasir, *et al*., 2021). Recent studies highlight the potential of combining PTT and PDT with nanoparticles designed for dual therapy, which enhances therapeutic efficiency and minimizes resistance from the tumor microenvironment (Alvarez & Sevilla, 2024).

Furthermore, integrating phototherapy with chemotherapy or immunotherapy can further enhance treatment efficacy (Figure 5). For instance, heat generated in PTT can increase tumor cell membrane permeability, improving the uptake of chemotherapeutic drugs. Similarly, PDT-induced cell death can release tumor antigens, potentially amplifying the immune response and enhancing immunotherapy (Fang, *et al*., 2018; Pinho, *et al*., 2024). While preclinical trials have demonstrated promising outcomes for these combination therapies, more clinical data are needed to evaluate their long-term effectiveness and safety.

NANOPARTICLES IN IMMUNOTHERAPY

Nanoparticles have emerged as a transformative tool in immunotherapy, offering innovative strategies to modulate the immune response and the tumor microenvironment (TME), both of which are critical for overcoming drug resistance in cancer treatment. Nanoparticles can be engineered to deliver immunotherapeutic agents more effectively, targeting specific immune cells or components of the TME, thereby boosting the efficacy of treatments like checkpoint inhibitors and CAR-T cells (Lu, *et al*., 2024). Recent trials involving nanoparticle-based delivery of checkpoint inhibitors have shown promising results, indicating enhanced immune activation and tumor targeting.

One key application of nanoparticles in immunotherapy is enhancing the activation and proliferation of immune cells. Nanoparticles can be designed to deliver adjuvants, which enhance the body's immune response to tumor antigens. These adjuvant-loaded nanoparticles can present antigens to dendritic cells, resulting in robust cytotoxic T lymphocyte (CTL) activation, which is crucial for the destruction of cancer cells (Buabeid, *et al*., 2020).

Additionally, nanoparticles can alter the TME, which is often immunosuppressive, to facilitate more effective immune responses. By delivering agents that modulate the TME, such as cytokines or immune checkpoint inhibitors, nanoparticles can make the environment more conducive to immune attack. For example, nanoparticles delivering PD-1/PD-L1 inhibitors directly to the tumor site can reduce systemic side effects and enhance local immune activation (Zhang, *et al*., 2018). This localized delivery approach not only reduces off target effects but also increases the therapeutic index of immunotherapies.

Nanoparticles also help overcome physical barriers within the TME, such as dense stroma or abnormal vasculature, which impede therapeutic delivery. By improving the penetration and retention of these agents, nanoparticles enhance immunotherapy's overall effectiveness, leading to better treatment outcomes and potentially overcoming resistance mechanisms that limit conventional therapies (Selvaraja & Gudipudi, 2020).

CLINICAL TRIALS AND CURRENT CHALLENGES

Nanotechnology has significantly advanced cancer treatment, particularly in addressing drug-resistant tumors. Recent clinical trials have explored nanotechnology-based approaches to improve drug delivery, enhance treatment efficacy, and minimize side effects. Trials involving liposomal nanoparticles, such as Doxil (liposomal doxorubicin), have shown promising results in treating various drug-resistant cancers, including ovarian and breast cancers. In these trials,

nanoparticle-based formulations have demonstrated enhanced targeting, reduced systemic toxicity, and improved patient outcomes, although challenges such as optimal dosing and biodistribution remain under investigation. Other trials are investigating the combination of nanoparticles with immunotherapy to boost immune responses against resistant tumor cells, particularly in the context of personalized and precision medicine strategies (Garg, *et al*., 2024; Bukhari, 2022).

However, despite these advances, significant challenges remain in translating nanotechnology from bench to bedside. One primary concern is toxicity. While nanoparticles improve drug delivery specificity, their long-term effects and potential toxicity are not yet fully understood, posing a hurdle to widespread clinical adoption. Recent preclinical studies indicate a need for more rigorous toxicity testing, particularly regarding nanoparticle accumulation in non-target tissues. Another challenge is scalability; producing nanoparticles at a large scale while maintaining consistent quality is technically demanding and costly. Regulatory hurdles are also substantial, as the complexity of nanoparticle formulations requires rigorous testing and validation to meet safety and ethical standards (Garg, *et al*., 2024; Joudeh & Linke, 2022).

Table 1. The development of clear regulatory frameworks is crucial to facilitate the clinical translation of nanotechnology-based therapies, ensuring patient safety and treatment efficacy.

Ethical/Regulatory Challenge	Description	Considerations for Clinical Translation
Toxicity Concerns	Nanoparticles may exhibit unforeseen toxicity due to their small size, high reactivity, and prolonged circulation in the body.	Requires rigorous toxicological assessments including *in vitro* and *in vivo* studies to understand short-term and long-term effects on human health and the environment.
Long-Term Effects and Biocompatibility	The long-term biological interactions of nanoparticles are not fully understood, raising concerns about potential accumulation in tissues and organs over time.	Development of standardized biocompatibility tests to assess nanoparticle accumulation, degradation, and elimination from the body, ensuring no chronic effects or latent toxicity.
Patient Safety and Informed Consent	There are concerns about patient safety, particularly regarding how much patients understand about novel nanomedicine interventions, their risks, and potential harms.	Ensuring transparency and patient education on nanomedicine risks during informed consent processes. Ethical guidelines need to include clear, patient-friendly communication of possible outcomes.
Regulatory Approval Pathways	Nanomedicine products often don't fit neatly within existing regulatory frameworks, complicating the approval process for clinical use.	Development of specific guidelines for evaluating nanotechnology-based products, focusing on their unique characteristics (size, surface chemistry) and behavior in biological systems.
Environmental Impact	The production and disposal of nanoparticles raise environmental concerns, as they may contaminate water sources or ecosystems.	Environmental impact assessments and eco-toxicology studies need to be integrated into regulatory approval, ensuring safe production and disposal of nanomaterials.
Scalability and Manufacturing Standards	Manufacturing consistent, high-quality nanoparticles at scale poses challenges, especially in maintaining uniform size, shape, and surface properties.	Regulatory agencies must establish standards for nanoparticle production, requiring manufacturers to demonstrate consistency and scalability without compromising the efficacy or safety of the product.
Data Privacy and AI Integration	With the rise of AI in nanomedicine, especially for personalized treatments, issues around data privacy and algorithm transparency are becoming more prominent.	Need for robust data protection regulations to safeguard patient information, particularly when using AI to guide nanomedicine treatment. Clear protocols on how AI decisions are made are essential.

FUTURE DIRECTIONS AND INOVATIONS

Emerging nanotechnologies hold significant promise for addressing the persistent challenge of drug resistance in cancer treatment. Innovations in nanoparticle-based drug delivery systems are being developed to enhance the precision and efficacy of cancer therapies. For instance, nanoparticles can be engineered to deliver chemotherapy drugs directly to tumor cells, increasing drug concentration at the target site while minimizing systemic side effects. Recent preclinical trials have demonstrated the potential of this approach to bypass resistance mechanisms, such as efflux pumps, that commonly reduce the efficacy of conventional chemotherapy (Mitchell, *et al*., 2021; "Nanoethics: It's Time", 2019).

Personalized nanomedicine is another rapidly growing area. By tailoring nanotechnology based treatments to the genetic and molecular profile of an individual patient's tumor, researchers are designing more effective therapies that are less likely to encounter resistance. This approach not only increases the likelihood of successful treatment but also opens the door to previously unimaginable strategies. For example, the integration of artificial intelligence (AI) with nanotechnology is being explored to predict and optimize treatment responses, enhancing the potential of personalized cancer therapy (Mitchell, *et al*., 2021). AI driven models can assist in real-time decision-making, helping clinicians choose the most effective nanoparticle formulations for each patient's unique tumor biology.

However, as nanotechnology advances in oncology, it also raises critical ethical and regulatory concerns. Issues such as patient consent, data privacy, and the potential for long-term side effects must be carefully addressed as these technologies are developed. Additionally, the regulatory landscape for nanomedicine is still evolving. The complexity of nanoparticle formulations creates challenges in standardizing safety and efficacy testing. Comprehensive regulatory frameworks that account for the unique properties of nanomedicines are crucial to ensure that these therapies are both safe and accessible to patients ("Nanoethics: It's Time", 2019, Junyaprasert & Thummarati, 2023).

Addressing these challenges will be key to the successful integration of nanotechnology into routine clinical practice. Continued research is essential to not only optimize therapeutic outcomes but also ensure patient safety and address long-term health implications.

CONLUSION

In conclusion, nanotechnology represents a transformative approach in the fight against drug-resistant cancers, offering innovative solutions across multiple treatment modalities. From targeted drug delivery systems to advances in immunotherapy and gene therapy, nanotechnology is playing a pivotal role in overcoming drug resistance. The development of nanoparticles such as liposomes, dendrimers, and gold nanoparticles has significantly improved the precision and efficacy of cancer treatments.

Moreover, the integration of nanotechnology with personalized medicine promises more individualized and effective therapies, enabling treatments that are specifically tailored to the genetic and molecular profile of each patient's tumor. This personalized approach has the potential to revolutionize oncology by offering more targeted, less toxic, and more effective cancer treatments.

However, significant challenges remain. Ethical, regulatory, and technical hurdles must be carefully navigated to bring these groundbreaking innovations safely into clinical practice. Issues such as toxicity, scalability, and the need for clear regulatory frameworks are pressing concerns that require continued attention.

As research continues to evolve, the potential for nanotechnology to overcome

drug resistance and improve cancer treatment outcomes remains immense. The integration of new technologies, such as AI, into nanomedicine, further enhances this potential, heralding a new era in oncological care. With ongoing research and innovation, nanotechnology is poised to revolutionize cancer treatment, offering hope for more effective therapies in the fight against resistant cancers.

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