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SHORT COMMUNICATION

Nanoparticles in Cancer Therapy: Current Progress, Challenges, and Future Perspectives in Clinical Translation

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Abstract

Cancer treatment is evolving with the advent of nanotechnology, shifting from conventional therapies to precision medicine. Nanoparticles (1 nm –100 nm) which encapsulate drugs and direct them to tumor sites offer unique advantages in cancer therapy, including enhanced drug delivery, reduced toxicity, and improved specificity. This editorial examines various types of nanoparticles, with focus on those that have progressed to clinical trials, while addresses the challenges in translating these innovations from the laboratory to clinical practice. Despite the growing body of research, the number of approved nanodrugs remains limited. Hence a deeper understanding of nano formulations and their targeting mechanisms will be crucial to advancing cancer treatment in the future.

Key Words: *Nanoparticles; Cancer therapy; Drug delivery; Nano chemotherapy; Multidrug resistance*

Introduction

Cancer is a major global public health concern, with its incidence and mortality rates steadily increasing, contributing to approximately 10 million deaths each year [1-3]. Chemotherapy continues to be one of the most used and effective treatments for cancer [4,5]. However, its effectiveness is limited by a lack of selectivity for tumor cells, difficulties in delivering drugs efficiently to the tumor site, and the emergence of multi-drug resistance [6-11]. In this perspective, there is relentless on-going work across the globe achieving an alternative to chemotherapy and to find a better cure for cancer [12-14]. The emergence of nanotechnology has opened new possibilities for nanomedicines to overcome many of the limitations of traditional chemotherapy, and ongoing research is actively exploring these advancements. Nanoparticle-based drug delivery systems offer significant benefits in cancer treatment, including improved pharmacokinetics, precise targeting, reduced side effects, and the ability to overcome drug resistance [15-17]. With the growing momentum in nanotechnology, numerous therapeutic drugs have been commercialized, and many others are currently undergoing clinical trials. This editorial primarily focuses on the fundamental principles behind the application of nanotherapeutics,

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explores current challenges and prospects, and outlines the future direction of research in this field.

Nanotechnology in cancer therapy

Nanotechnology uses materials with nano size generally ranging 1–100 nm and are currently being extensively used in biomedical applications. Due to their unique size and physical properties (such as mass, charge, and density), nanomaterials have the advantage of effectively binding with biomolecules like DNA [18], RNA [19], peptides [20], aptamers [21], and antibodies [22]. With these properties, nanomaterials offer significant benefits, such as enhanced targeted drug delivery, controlled release, and permeability for crossing biological barriers in cancer therapeutics [23,24]. The nanomaterials that are well-developed and currently in clinical use can be categorized into several types, as shown in (Figure 1). A detailed description of each nanoparticle type is beyond the scope of this editorial due to the space constraints. In brief, to be considered as an ideal nanomaterial, it must meet several essential criteria, including stimulus-responsive materials or structures, stable nanometer-scale size, adjustable surface charge, high encapsulation capacity, biocompatibility, degradability, and low toxicity. Currently, there are thirteen most widely studied types of nanomaterials that are categorized into four types and those include [25]:

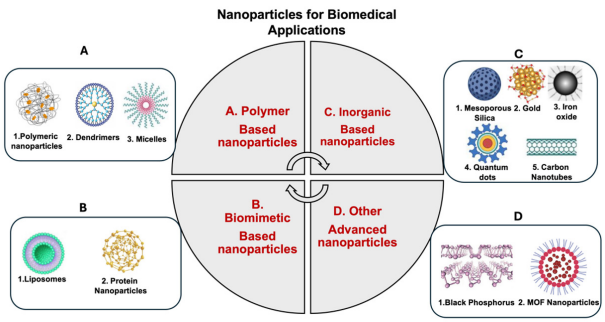

Figure 1) *Various types of nanomaterials used in cancer therapy. A. Polymer-based nanomaterials. B. Biomimetic-based nanomaterials. C. Inorganic-based nanomaterial. D. Other advanced nanomaterial.*

- Polymer-based nanomaterial, such as polymeric nanoparticles, dendrimers, and micelles.
- Biomimetic-based nanomaterial, including liposomes and protein nanoparticles.
- Inorganic-based nanomaterial, such as mesoporous silica, gold nanoparticles, iron oxide, quantum dots, and carbon nanotubes.
- Other advanced nanomaterial, including black phosphorus and metal-organic frameworks (MOFs).

Mechanism of action of nanoparticles

For effective cancer therapy, drug or gene delivery systems must selectively target tumor cells. In this scenario, successful nanoparticle-based drug delivery requires the following characteristics [25]. 1) Stability in the bloodstream to reach the tumor microenvironment (TME).2) Escape from the reticuloendothelial and mononuclear phagocyte systems (RES/MPS). 3) Accumulation in the TME via tumor vasculature. 4) Ability to penetrate the tumor's high-pressure fluid environment. 5) Specific interaction with tumor cells, avoiding healthy cells. So far, two distinct methods have been used for targeting: 1) Passive targeting and 2) Active targeting. In passive targeting, the process relies on the physical properties of both the tumor and nanoparticles, but it does not involve specific targeting to tumor cells [26-29]. In certain tumors, preferential accumulation of macromolecules allows nanoparticles to enter, accumulate, and target cancer cells [30-32]. Drugs like paclitaxel (Abraxane-in albumin bound as nanoparticle) and Genexol (PEG deblock co-polymers as nanoparticle) exploit this phenomenon to effectively treat cancers such as breast, lung, and ovarian cancer. While this property enhances nanoparticle delivery, tumor heterogeneity can limit drug accumulation, posing a major challenge to this strategy [33-35]. In the active

targeting, efficiency of nanoparticle binding to tumor cells is improved by using ligands such antibodies, peptides or small molecules without affecting the nanoparticle's physical property [36-41]. EGFR, a tyrosine kinase receptor implicated in various cancers, is targeted using gold nanoparticles specific to EGFR. HER2, overexpressed in breast cancer, can be targeted with HER2-specific PEGylated liposomal doxorubicin. Additionally, folate-targeted nanoparticles offer an effective strategy for selective cancer treatment by targeting overexpressed folate receptors on tumor cells [42-47]. Furthermore, nanoparticles have been effectively used to target ABC transporters, which are linked to multidrug resistance in breast and ovarian cancers. By bypassing these transporters, silica nanoparticles encapsulating miRNA-495 and doxorubicin have shown promise in overcoming drug resistance in lung cancer [11,48-52]. Nanoparticles generally induce cell death in cancer cells through apoptosis by various mechanisms, with reactive oxygen species (ROS)-mediated apoptosis being the most extensively studied. Other mechanisms include the regulation of proteins, immunological interventions, transcriptional inhibition, and site-specific cytotoxicity. A brief description of each mechanism is outline below:

Generation of ROS: ROS-induced apoptosis is a key mechanism in nanoparticle-induced cancer cell cytotoxicity, with both pro-apoptotic and anti-apoptotic effects. Pro-apoptotic ROS cause cell cycle arrest, apoptosis, and necrosis, while anti-apoptotic ROS promote cell proliferation and metastasis. Nanoparticles, such as silver nanoparticles and silica-carbon nanoparticles, generate excessive ROS due to their increased surface area, leading to oxidative stress, DNA damage, and inflammation. For instance, silver nanoparticles enclosed in polysaccharides induce apoptosis through ROS-mediated autophagy, while mitochondria-targeted nanoparticles inhibit ATP synthesis, effectively suppressing multidrug-resistant tumor growth [53-56].

Regulation of proteins: Nanoparticles have shown potential in regulating proteins involved in cancer cell signaling, influencing oncogenic behavior. For example, copper oxide nanoparticles (CuO-NPs) down-regulate apoptotic proteins (Bcl2 and BclxL), promoting cell death in HT-29 cells [57]. Selenium nanoparticles (SeNP) alter apoptotic protein expression and affect unfolded protein response (UPR) signaling pathways, enhancing the expression of selenoproteins and antioxidant enzymes like glutathione peroxidases [58]. SeNP also selectively regulate pro-apoptotic proteins via Cx43 hemichannel activation [59]. Similarly, silver nanoparticles (AgNPs) increase γ-H2AX expression in MCF-7 cells, triggering cell death after Ag ion release [60]. Gold nanoparticles (AuNPs) regulate cyclin-dependent kinase 4 (CDK4), inducing G1 arrest and apoptosis in ER-positive breast cancer cells (MCF-7), while also inhibiting key MAPK signaling pathways, thereby reducing migration and colony formation [61].

Site-specific cytotoxicity: Nanoparticles can facilitate the intracellular delivery of DNA, mRNA, siRNA, and proteins, offering targeted cytotoxicity with fewer side effects compared to traditional systemic drug formulations [62]. For instance, hyaluronic acid-based nanoparticles, with their negative charge, exhibit site-specific cytotoxicity toward CD44-positive tumor cells [63]. Titanium phosphate nanoparticles, used for targeted delivery of chemotherapeutic drugs, demonstrate real-time monitoring capabilities and enhanced cell uptake via folate receptors [64]. Zinc oxide (ZnO) nanoparticles, with inherent cytotoxicity, induce apoptosis by generating ROS, selectively entering cancer cells due to high anionic phospholipid expression. When conjugated with other metal oxide nanoparticles, like Fe_3O_4, ZnO's cytotoxic potential is enhanced [65]. Cationic solid lipid nanoparticles (SLNs) conjugated with streptavidin and anti-HER2 antibodies exhibit selective cytotoxicity in HER2-overexpressing

breast cancer cell lines, such as BT-474 and MCF-7[66].

Nanoparticles in clinical translation

While nanoparticles for cancer treatment are still largely in the developmental phase, currently there are 16 nanocarrier-based drugs have already been approved by FDA, with 75 more nano-formulations therapeutics undergoing clinical trials. Two of the most well-known FDA-approved nanomedicines—Doxil [67] and Abraxane [68] have been successfully used in clinical practice for several years [69,70]. Among the FDA-approved nanoparticles for cancer treatment, 56% are lipid-based, while the remaining 44% consist of protein-based (38%) and metallic-based (6%) formulations [71,72]. Several lipid-based nanomedicines have been approved for cancer treatment, including Doxil, Caelyx, and Myocet, which encapsulate doxorubicin to reduce cardiotoxicity and enhance tumor targeting [73,74]. By utilizing liposomes, the drugs improve circulation time, protect against degradation, and accumulate in tumors through the enhanced permeability and retention effect (EPR) effect, allowing for safer and more effective chemotherapy with fewer side effects. DaunoXome encapsulates daunorubicin for advanced HIV-associated Kaposi's sarcoma [75,76], while Mepact delivers Mifamurtide for osteosarcoma [76]. Other formulations like Ameluz [77], Marqibo [78], Onivyde, and Vyxeos [79] target various cancers, improving drug stability, circulation time, and reducing side effects. Below is a brief list of cancer-related nanoparticles that have received approval from the FDA and other regulatory agencies worldwide (Table 1).

TABLE 1
List of approved cancer drug therapies based on nanoparticles. (EMA: European medicine agency; FDA: US Food and Drug Administration. Adapted from [71, 80].

Drug Name	Nanoparticle material used	Type of cancer	Approval authority
Hensify (NBTXR3)	Hafnium oxide nanoparticle	Locally advanced soft tissue sarcoma (STS)	EMA (2019)
		Metastatic breast cancer, metastatic adenocarcinoma of the pancreas, non-small cell lung	
Pazenir	Nanoparticle-bound albumin	cancer	EMA (2019)
Vyxeos	Liposome	Acute myeloid leukemia	FDA (2017) EMA (2018)
Onivyde	Liposome	Pancreatic cancer, colorectal cancer	FDA (2015)
NanoTherm	Iron oxide nanoparticles	Glioblastoma, prostate, and pancreatic cancer	EMA (2010, 2013)
Margibo	Liposome	Acute lymphoblastic leukemia	FDA (2012)
Mepact	Liposome	Osteosarcoma	EMA (2009)
Genexol-PM	PEG-PLA polymeric micelle	Breast, lung, ovarian cancer	South Korea (2007)
Oncaspar	Polymer protein conjugate	Acute lymphoblastic leukemia	FDA (1994, 2006)
Abraxane	Nanoparticle-bound albumin	Breast and pancreatic cancer, non-small-cell lung cancer	FDA (2005)
DepoCyt	Liposome	Neoplastic meningitis	FDA (1999)
DaunoXome	Liposome	Kaposi's sarcoma	FDA (1996)
Doxil, Caelyx, Myocet, and	Metastatic breast cancer, ovarian cancer, Kaposi's	FDA (1995, 1999, 2007), EMA (1996, 2000),	
Lipo-Dox	Liposome	sarcoma, multiple myeloma	Taiwan (1998)

Nanoparticles in clinics- challenges & future perspective

Nanoparticles show great promise for cancer treatment, but their long-term side effects and potential impact on public health remain largely unknown. Concerns are increasing regarding the unique "nano" toxicity associated with nanoparticles, attributed to their small size and enhanced ability to penetrate biological systems [81,82]. Additionally, challenges such as biological toxicity, restricted administration routes, immune system clearance, scaling up production, optimizing formulations, and predicting nanoparticle performance continue to persist.

The physicochemical properties of nanoparticles including size, shape, surface functionalization, surface chemistry, chemical composition, and concentration, are crucial in their function [83]. These properties influence how nanoparticles interact with cell membranes and organelles, and thereby important in understanding "nano" toxicity [84]. Therefore, thorough characterization of both the core and surface properties of nanoparticles is essential before assessing their biological responses, toxicity and cellular interactions [85]. Below summary outlines the effects of various nanoparticles on different organ systems based on animal and cell experiments.

- Respiratory System: SiO_2 nanoparticles increase cytotoxicity by adsorbing apolipoprotein and promote atherosclerosis [86]. CuO nanoparticles induce oxidative stress, inflammation, and tumor lesions [87].

- Nervous System: Polystyerene nanoparticles cause intestinal inflammation and developmental issues in zebrafish, linked to disruption in the brain-gut-microbiota axis [88]. SiO_2 nanoparticles enter the brain via intranasal instillation, causing oxidative damage and inflammatory responses in the striatum [89]. Fe_2O_3 nanoparticles lead to oxidative damage and neurotoxicity in the mouse brain [90].

- Endocrine System: SiO2 nanoparticles disrupt thyroid hormone function in juvenile zebrafish, increasing PCBPA bioaccumulation [91]. TiO_2 nanoparticles disrupt both thyroid and neuronal systems in larval zebrafish through bioconcentration of lead [92].

- Immune System: Cadmium nanoparticles impair immune functions in both Crassostrea gigas and mice, leading to phagocytosis reduction and immunodeficiency [93]. Carbon black nanoparticles increase pro-inflammatory cytokines and decrease macrophage phagocytic capacity [94]. These Nanoparticles can also accumulate in testes, causing oxidative stress, inflammation, and germ cell damage. Au nanoparticles induce oxidative stress, DNA damage, and disruption in testosterone production in TM3 Leydig cells [95].

There are also currently no standardized regulatory methods to assess the risks associated with specific engineered nanoparticles [96-99]. To address the challenges associated with nanotechnology, the FDA, in collaboration with the National Nanotechnology Initiative (NNI) and the Nanotechnology Characterization Laboratory (NCL), has established programs to coordinate efforts in nanoscale science, engineering, and technology. These initiatives include to draft guidance on the use of nanotechnology and nanomaterials in FDA-regulated products [100]. The FDA is also committed to implementing a science-based approach to regulating nanomaterial-containing products, advancing regulatory science, fostering collaborations, and ensuring clear communication—all while prioritizing public health. Similarly, the European Medicines Agency (EMA), in partnership with the European

Technology Platform on Nanomedicine (ETPN) and the European Nano-characterization Laboratory (EU-NCL), is developing regulatory guidelines for nanomedicine products [101]. Both the FDA and EMA are active members of the Innovation Task Force (ITF), an international, multidisciplinary group that addresses the scientific, regulatory, and legal aspects of nanotechnology products [102].

The challenges encountered by nanoparticles in cancer therapy can potentially be overcome through recent and cutting-edge research developments. CRISPR for precise gene editing [103,104], thermos responsive nanoparticles for temperature variation [105]. Additionally, PROTACs (Proteolysis Targeting Chimeras) enables selective protein degradation [106,107], while protein therapy presents a promising substitute for traditional chemotherapy [108,109]. Innovations like functionalized DNA for personalized cancer treatment are further pushing the boundaries of nanoparticle-based therapies [110,111]. Moreover, strategies to modulate the protein content around nanoparticles and targeted radionuclide therapy are being explored to enhance therapeutic efficacy [112,113]. Further developments and the advancements of these strategies are extensively discussed elsewhere [17,25,98,114-120].

Conclusion

In conclusion, the successful development and application of patient-centric nanodrugs in cancer therapy requires a collaborative effort between academia, regulatory agencies, and industry. Academia plays a pivotal role in advancing the fundamental understanding of nanomaterials and their interactions with biological systems, while regulatory agencies are essential for ensuring the safety, efficacy, and ethical approval of these novel therapies. The industry, on the other hand, is crucial for scaling up production, optimizing formulations, and translating research into clinically viable treatments. By working in close collaboration, one can accelerate the transition of promising nanomedicines from the laboratory to the clinic, ultimately revolutionizing cancer treatment. This integrated approach holds the potential to overcome many of the current challenges in cancer therapy, such as drug resistance and toxicity, paving the way for more effective, personalized, and less harmful treatments for patients worldwide.

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