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Precision Warriors: Nanotechnology's Triumph in Cancer Therapy †

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Abstract: Nanotechnology has emerged as a pivotal platform in revolutionizing cancer treatment, offering a diverse array of strategies to enhance therapeutic efficacy while minimizing collateral damage to healthy cells. This review paper extensively explores the recent breakthroughs and applications of nanotechnology in the realm of cancer treatment. The unique physicochemical properties of nanoformulations, specifically nanoparticles, enable precise customization for targeted drug delivery, a hallmark feature of effective cancer therapy. Nanoformulations leverage their diminutive size to exploit enhanced permeability and retention within tumour tissues, thereby facilitating the accumulation of therapeutic agents at the tumour site. The utilization of nanocarrier-based formulations showcases their exceptional potential for precise drug delivery, ensuring optimal therapeutic impact. Beyond drug delivery, nanotechnology has fundamentally advanced cancer diagnosis and imaging techniques. The integration of functionalized nanoparticles with contrast agents has empowered the development of highly sensitive imaging modalities such as magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET). This heightened sensitivity allows for the detection of minute tumour masses, real-time monitoring of treatment responses, and the guidance of intricate surgical interventions. Throughout this comprehensive review, we delve into the multifaceted roles of nanomaterials, including nanoparticles, nanocarriers, and nanodevices, as they address pivotal challenges posed by conventional cancer therapies. Amidst our analysis of these advancements, we critically examine the obstacles faced by nanotechnology-based treatments, ranging from potential toxicities to safety considerations.

Keywords: cancer; nanotechnology; nanoparticle; drug delivery

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1. Introduction

Cancer, a complex and formidable disease, continues to be a pressing global health challenge, affecting millions of lives each year [1]. The significance of effective cancer treatment and early diagnosis cannot be overstated, as they are central to mitigating its devastating impact [2]. Conventional cancer therapies often come with limitations, including indiscriminate damage to healthy cells and insufficient precision in targeting malignant tumours [3]. In this context, nanotechnology has emerged as a pivotal platform that holds the promise of revolutionizing cancer care. Nanotechnology, the manipulation of materials and structures at the nanoscale, has ushered in a new era in medicine, offering unprecedented opportunities for innovation [4,5]. At this minuscule scale, the physicochemical

properties of materials can be harnessed and tailored to address specific challenges in cancer treatment and diagnosis. This review paper aims to provide an extensive exploration of the recent breakthroughs and applications of nanotechnology in the realm of cancer treatment [5]. The fundamental premise of nanotechnology in cancer care lies in its ability to enhance therapeutic efficacy while minimizing collateral damage to healthy cells [6]. This paper delves into the multifaceted ways in which nanotechnology achieves this goal. One hallmark feature is the precise customization for targeted drug delivery enabled by nanoformulations, particularly nanoparticles. These nanoparticles, owing to their unique properties, facilitate the selective delivery of therapeutic agents to tumour tissues [7]. They exploit the Enhanced Permeability and Retention (EPR) effect within tumours, leading to the accumulation of therapeutic agents at the precise site of action. Additionally, nanocarrier-based formulations play a pivotal role in encapsulating and transporting therapeutic agents, ensuring optimal therapeutic impact [6,7]. Beyond drug delivery, nanotechnology has also fundamentally advanced cancer diagnosis and imaging techniques. The integration of functionalized nanoparticles with contrast agents has empowered the development of highly sensitive imaging modalities, including magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET) [8]. These techniques have revolutionized the detection of minute tumour masses, enabled real-time monitoring of treatment responses, and enhanced the precision of intricate surgical interventions. Throughout this comprehensive review, we explore the multifaceted roles of various nanomaterials, including nanoparticles, nanocarriers, and nanodevices, as they address pivotal challenges posed by conventional cancer therapies. However, it is essential to critically examine the obstacles faced by nanotechnology-based treatments, ranging from potential toxicities to safety considerations. This review highlights the transformative potential of nanotechnology in the field of cancer treatment and diagnosis. It underscores the need for continued research, rigorous safety assessments, and clinical translation to fully harness the benefits of nanotechnology in improving patient outcomes and ushering in a new era of cancer care.

2. Nanotechnology in Cancer

Nanoformulations, particularly utilizing nanoparticles, have emerged as a groundbreaking approach in cancer treatment due to their ability to enhance the precision and efficacy of drug delivery [9]. This section explores the key elements of nanoformulations for targeted drug delivery, emphasizing the unique physicochemical properties of nanoparticles, the Enhanced Permeability and Retention (EPR) effect within tumour tissues, and the pivotal role of nanocarriers in ensuring precise drug delivery [9,10].

2.1. Unique Physicochemical Properties of Nanoparticles against Cancer

Nanoparticles, defined as particles with dimensions typically less than 100 nm, exhibit remarkable physicochemical properties that set them apart from larger-scale materials [11]. These properties are instrumental in their role as drug delivery vehicles for cancer treatment:

- Size: Nanoparticles' diminutive size allows them to navigate through biological barriers that larger drug molecules cannot penetrate [12]. This property is particularly advantageous when aiming to target tumour cells while avoiding healthy tissue [13].
- Large Surface Area: The high surface area-to-volume ratio of nanoparticles provides ample space for surface modifications. This allows for the attachment of targeting ligands or therapeutic molecules, enabling precise customization for specific cancer types and individual patient needs [14].
- Biocompatibility: Many nanoparticle materials are biocompatible and biodegradable, minimizing potential toxicity and ensuring safe delivery of therapeutic agents for cancer treatment [15].
- Stability: Nanoparticles can protect encapsulated drugs from degradation, extending their shelf life and enhancing drug stability until they reach the tumour site [16].

2.2. Enhanced Permeability and Retention (EPR) Effect in Tumour Tissues

The Enhanced Permeability and Retention (EPR) effect is a phenomenon that significantly benefits the targeted drug delivery capabilities of nanoformulations [17]. This effect is characterized by the abnormal and leaky blood vessels within tumour tissues, as well as reduced lymphatic drainage, which collectively lead to the accumulation of nanoparticles at the tumour site:

- Abnormal Vasculature: Tumours often develop a chaotic network of blood vessels with irregular shapes and sizes. These leaky vessels allow nanoparticles to passively extravasate into the tumour interstitium [18,19].
- Reduced Lymphatic Drainage: The impaired lymphatic drainage system in tumours hinders the removal of interstitial fluid, leading to the retention of nanoparticles and the drugs they carry within the tumour microenvironment [20,21].
- The EPR effect capitalizes on these unique tumour characteristics, enabling nanoparticles to selectively accumulate within malignant tissues while sparing healthy cells. This selective accumulation enhances the local concentration of therapeutic agents, thereby increasing their effectiveness in targeting and eradicating cancer cells [22].

2.3. Role of Nanocarriers

Nanocarriers play a crucial role in precise drug delivery for cancer treatment. They come in various forms, each with distinct properties and applications in targeting cancer cells while minimizing side effects. Here are different types of nanocarriers used for precise drug delivery in cancer (Table 1):

Liposomes: Liposomes are lipid-based vesicles that can encapsulate both hydrophilic and hydrophobic drugs. They are biocompatible, can be surface-modified for targeting, and are used for chemotherapy and immunotherapy drug delivery. Ruttala et al. formed transferrin ligand-conjugated liposomes from dextran sulphate-doxorubicin (DS-DOX) and alginate-cisplatin (AL-CIS) polymer–drug complexes. They found DS-DOX and AL-CIS-based combination liposomes customized with transferrin (TL-DDAC) useful for cancer treatment. Similarly, Ghosh et al. reviewed DOX-loaded liposomes. To improve efficiency and site-specific delivery, liposomes are modified with peptides, aptamers, antibodies, etc. to create pH, heat, UV-sensitive, and electro-magnetic nanocarriers for enabling regulated drug release [23–25].

A. Polymeric Nanoparticles: Polymeric nanoparticles, made from biodegradable polymers like Alginate and chitosan, offer versatility and tuneable drug release profiles for delivering various anticancer agents. Chitosan-based nanoparticles, such as chitosan ascorbate nanoparticles, demonstrated inhibition effects on cervical cancer. These nanoparticles, formed through ionotropic gelation, exhibited antioxidative properties, reduced cervical cancer cell viability (HeLa cells) while sparing normal cells (WI-38), highlighting their potential for cancer-targeted drug delivery [26].

B. Micelles, formed through self-assembly of amphiphilic molecules in aqueous solutions, enhance the solubility and delivery of poorly water-soluble chemotherapeutic agents. For instance, endosomal pH-activatable paclitaxel (PTX) prodrug micellar nanoparticles were created by linking PTX to water-soluble poly(ethylene glycol)-b-poly(acrylic acid) (PEG-PAA) block copolymers via an acid-labile acetal bond. These nanoparticles effectively inhibited the growth of human cancer cells in vitro, showcasing their potential as a versatile and potent platform for cancer therapy [27].

C. Dendrimers: Dendrimers are highly branched tree-like structures with a well-defined architecture. They can carry drugs on their surface or within their interior and are used for targeted drug delivery and imaging. One of the major applications of dendrimers is as a delivery vehicle for various anticancer drugs. The structure and tuneable surface functionality of dendrimers allows for the encapsulation/conjugation of multiple entities, either in the core or on the surface, rendering them ideal carriers for various anticancer drugs [28].

D. Inorganic Nanoparticles: Inorganic nanoparticles like gold or iron oxide nanoparticles have unique properties for drug delivery and imaging. They can be functionalized and used for targeted drug delivery and as contrast agents in imaging modalities. For example, Shi et al. discuss this approach in "Dendrimer-Entrapped Gold Nanoparticles (Au DENPs) as a Platform for Cancer-Cell Targeting and Imaging" [29].

E. Nanogels: Nanogels are hydrogel nanoparticles that can absorb and release drugs in response to environmental stimuli, such as pH or temperature changes. Nanogels (NGs) are among the nanosized superconstructs composed of amphiphilic or hydrophilic polymer networks. The materials used for the preparation of nanogels range from natural polymers like ovalbumin, pullulan, hyaluronic acid, methacrylated chondroitin sulphate, and chitosan, to synthetic polymers like poly (N-isopropylacrylamide), poly (Nisopropylacrylamide- co-acrylic acid), and poly (ethylene glycol)-b-poly (methacrylic acid) [30]. There are several studies that have reviewed stimuli-responsive poly(ethylene glycol) (PEG)-coated (PEGylated) nanogels for cancer diagnostics and treatment [31].

F. Carbon Nanotubes: During the past years, great progress has been made in the field of nanomaterials given their great potential in biomedical applications. Carbon nanotubes (CNTs), due to their unique physicochemical properties, have become a popular tool in cancer diagnosis and therapy. They are considered one of the most promising nanomaterials with the capability of both detecting cancerous cells and delivering drugs or small therapeutic molecules to these cells. Over the last several years, CNTs have been explored in almost every single cancer treatment modality, including drug delivery, lymphatic targeted chemotherapy, thermal therapy, photodynamic therapy, and gene therapy. Particularly, they are attractive as carriers and mediators for cancer therapy. Through appropriate functionalization, CNTs have been used as nanocarriers for anticancer drugs including doxorubicin, camptothecin, carboplatin, cisplatin, paclitaxel, Pt(II), and Pt(IV), and genes including plasmid DNA, small-interfering RNA, oligonucleotides, and RNA/DNA aptamers [32].

Table 1. Different nanomaterials use in cancer.

Nanomaterials	Type	Description	Target	Key Findings	Ref
Polymeric	Chitosan	Chitosan ascorbate nanoparticles for cervical cancer	Cervical cancer cells (HeLa cells)	Inhibited cervical cancer cell viability, showed antioxidative ability, spared normal cells (WI-38), potential for cancer-targeted drug delivery.	[26]
	Alginate	pH-sensitive and reduction-responsive alginate NPs	Colon cancer cells (HT-29 cells)	Selective uptake by HT-29 cells, enhanced cytotoxicity, spared normal cells (L929 cells), targeted delivery of docetaxel.	[33]
	Dextran	Carboxymethyl dextran nanoparticles for doxorubicin	SCC7 cells	Higher toxicity to SCC7 cells, efficient doxorubicin delivery to nuclei, enhanced permeation and retention (EPR) effect, improved therapeutic efficacy in a tumour-bearing mice model.	[34]
Micelles	Endosomal pH-activatable paclitaxel (PTX) prodrug micelles	Designed by conjugating PTX onto PEG-PAA block copolymers via an acid-labile acetal bond.	Potent growth inhibition of human cancer cells	Versatile and potent platform for cancer therapy.	[27]

Table 1. *Cont.*

Nanomaterials	Type	Description	Target	Key Findings	Ref
	Aminoflavone (AF)-loaded EGFR-targeted unimolecular micelles	Formulated for TNBC treatment	Triple negative breast cancer (TNBC)	Effective therapeutic option for EGFR-overexpressing TNBC.	[35]
Dendrimers	Dendritic Nanoformulation	2,2-bis (hydroxymethyl) propanoic acid-based dendritic scaffold for doxorubicin	In vitro and in vivo	Covalently bound doxorubicin to a high molecular weight 3-arm polyethylene oxide via a hydrazone linkage. Reduced cytotoxicity in vitro. In vivo experiments showed minimal accumulation of the DOX-dendrimer conjugate in vital organs plus increased doxorubicin half-life, highlighting the potential of nanocarrier systems to exploit the enhanced permeation retention (EPR) effect for enhanced drug efficacy.	[36]
Dendrimer-Based Inorganic Nanoparticles	Inorganic Nanoparticles	Dendrimer-Entrapped Gold Nanoparticles (Au DENPs) for Cancer-Cell Targeting and Imaging	Specific binding to KB cells (overexpressing folate receptors), internalization into lysosomes within 2 h	Potential as a versatile platform for cancer imaging and therapeutics.	[29]
	Inorganic Nanoparticles	Fe_3O_4 Nanoparticles Functionalized with Poly(amidoamine) Dendrimers for Specific Targeting and Imaging	Specific targeting of cancer cells overexpressing FA receptors, using layer-by-layer self-assembly method	New approach for functionalizing Fe_3O_4 NPs for biological sensing and therapeutic applications.	[37]
	Inorganic Nanoparticles	Acetylated Dendrimer-Entrapped Gold Nanoparticles (Acetylated Au DENPs) for CT Imaging	In vitro and in vivo CT imaging of cancer cells, predominantly uptaken in lysosomes	Potential for CT imaging of cancer cells with good biocompatibility.	[38]
Nanogel	siRNA Nanogels (NG) Delivery System	1. Utilizes intercalation between nucleic acid bis-intercalator and siRNA molecules. 2. Efficiently enters cells via various endocytosis pathways. 3. Successfully inhibits tumour growth in vivo.	Cancer cell	• Good physiological stability. • Effective in silencing target genes in vitro. • Significant tumour growth inhibition demonstrated.	[39]

Table 1. *Cont.*

Nanomaterials	Type	Description	Target	Key Findings	Ref
Carbon Nanomaterials	Carbon nanotube	ETO-loaded epidermal growth factor (EGF)–chitosan (CS)–single-walled CNTs (SWCNTs; EGF/CS/SWCNT–COOHs/ETO).	Cancer cell	- CS improves water dispersibility of CNTs and serves as a linker for EGF conjugation. - EGF/CS/SWCNT–COOHs exhibits minimal cytotoxicity. - Loading capacity of ETO is approximately 25–27% (*w*/*w*). - Induces 2.7-fold higher cell death in human alveolar carcinoma epithelial cells compared to ETO alone. - Potential to enhance the efficacy of ETO demonstrated.	[32]

3. Advanced Imaging Techniques with Functionalized Nanoparticles

Nanotechnology has brought about significant advancements in medical imaging, enabling more precise and sensitive detection, monitoring, and treatment of cancer [40]. In this section, we delve into the role of functionalized nanoparticles in imaging, explore the applications of nanotechnology in Magnetic Resonance Imaging (MRI), Computed Tomography (CT), and Positron Emission Tomography (PET), and highlight how these developments aid in surgical guidance and improved tumour resection [41,42].

Functionalized nanoparticles are engineered nanomaterials with specific properties and surface modifications that enhance their utility in medical imaging [40]. They play a vital role in improving the sensitivity and specificity of various imaging modalities in cancer diagnosis and treatment.

3.1. Targeting Ligands for Cancer Therapy and Diagnostics

Nanoparticles can be functionalized with targeting ligands, such as antibodies or peptides, that recognize cancer-specific markers on the cell surface. This enables precise targeting of nanoparticles to cancer cells, enhancing imaging specificity [43]. Some highlights are as follows:

- ➢ Monoclonal Antibodies: Monoclonal antibodies, such as trastuzumab (Herceptin), can be conjugated to nanoparticles to target breast cancer cells overexpressing the HER2 receptor. Choi et al. had prepared iron oxide nanoparticle and doxorubicin-loaded multifunctional nano-carrier (IONP/DOX-MFNC), capable of simultaneous cancer targeting via a herceptin monoclonal antibody, controlled anticancer drug delivery, as well as imaging modalities of magnetic resonance imaging (MRI) and near-infrared fluorescence (NIRF) imaging [44,45].
- ➢ Peptides: Peptides like RGD (Arg-Gly-Asp) can be attached to nanoparticles to target tumours with high expression of integrin receptors. These peptides have been used in various cancer types, including glioblastoma and melanoma [5]. Li et al. had synthesized and characterized PEGylated Au DENPs-RGD to investigate cyclo (Arg-Gly-Asp-D-Phe-Lys) peptide (RGD)-modified PEGylated dendrimer-entrapped gold nanoparticles (PEGylated Au DENPs-RGD) for targeted computed tomography (CT) imaging of breast carcinomas. They had concluded that the PEGylated Au DENPs-RGD can be used as targeted nanoprobes with good biocompatibility for targeted CT imaging and diagnosis of integrin-positive tumours [46,47].
- ➢ Folic Acid: Folic acid-conjugated nanoparticles are used to target cancer cells that overexpress folate receptors, which is common in ovarian, lung, and breast cancers [48].
- ➢ Transferrin: Transferrin receptor-targeting nanoparticles can be used for brain tumour imaging and therapy, as transferrin receptors are often overexpressed in brain tumour cells [49,50].

3.2. Applications of Nanomaterials in MRI, CT, and PET and Contrast Agents

Nanoparticles can serve as contrast agents that amplify the signal or contrast in imaging techniques. Nanotechnology has significantly advanced Magnetic Resonance Imaging (MRI), Computed Tomography (CT), and Positron Emission Tomography (PET) through the development of innovative contrast agents and imaging techniques. For instance, they can increase the signal intensity in MRI or CT scans, making it easier to visualize tumour tissues.

- Superparamagnetic Iron Oxide Nanoparticles (SPIONs) for MRI: SPIONs are commonly used as contrast agents in magnetic resonance imaging (MRI). These nanoparticles have a strong magnetic response, which enhances the contrast between different tissues in MRI scans. They are often employed to visualize tumours, including brain tumours, liver lesions, and lymph nodes [51].
- Gadolinium-Based Nanoparticles for MRI: Gadolinium-based nanoparticles, such as gadolinium chelates, are used as contrast agents in MRI. They can be functionalized with various coatings to improve stability and targeting. These nanoparticles enhance the signal intensity in MRI scans, aiding in the visualization of vascular abnormalities and tumours [52].
- Gold Nanoparticles for CT Imaging: Gold nanoparticles are used as contrast agents in computed tomography (CT) imaging. They have high X-ray absorption properties, which result in increased contrast in CT scans. Gold nanoparticles are employed to enhance the visualization of various tumours, including those in the liver, kidneys, and blood vessels [53].
- Nanoparticle-Based Ultrasound Contrast Agents: Microbubbles and nanodroplets composed of lipid or polymer nanoparticles are used as contrast agents in ultrasound imaging. These agents can be targeted to specific tissues or blood vessels and enhance the ultrasound signal, allowing for better visualization of tumours and vascular structures [54].
- Nanoparticle-Enhanced Fluorescence Imaging: Quantum dots and other fluorescent nanoparticles can be used to improve the contrast and sensitivity of fluorescence imaging techniques. They are often employed in cancer research for the detection and monitoring of tumours [55].
- Silica Nanoparticles for Optical Imaging: Silica nanoparticles can be loaded with fluorescent dyes or other imaging agents and used for optical imaging techniques, such as fluorescence imaging or photoacoustic imaging. These nanoparticles are versatile and can be tailored for specific imaging applications [56].

4. Obstacles and Safety Considerations

Nanotechnology-based cancer treatments offer immense promise, but they are not without challenges and safety concerns. This section discusses the potential obstacles and the importance of safety considerations in the field.

4.1. Discussion of Potential Challenges

Nanotechnology-based cancer therapies face several challenges that need to be addressed for successful clinical translation:

- Toxicity: Some nanoparticles may have inherent toxicity, depending on their composition, size, and surface properties. Ensuring the biocompatibility of nanomaterials is crucial to minimize adverse effects.
- Immunological Reactions: The immune system's response to nanoparticles can vary widely. Immune recognition and clearance of nanoparticles may impact their effectiveness and safety.
- Biodistribution: Understanding how nanoparticles are distributed throughout the body is essential. It can help mitigate off-target effects and ensure that therapeutic payloads reach the intended sites.

- ➢ Regulatory Hurdles: Regulatory agencies require rigorous safety assessments before approving nanotechnology-based treatments for clinical use. Meeting these regulatory standards is a significant challenge.

4.2. The Importance of Long-Term Safety Assessments

Long-term safety assessments are critical to ensure the continued safety of nanotechnology-based cancer treatments:

- ➢ Monitoring for Late Effects: Some adverse effects of nanomaterials may only become apparent after extended periods. Continuous monitoring is essential to detect and address late effects.
- ➢ Accumulation and Clearance: Understanding how nanomaterials accumulate in various tissues and their long-term clearance profiles is vital for predicting potential chronic toxicity.
- ➢ Patient Outcomes: Long-term studies on patient outcomes are necessary to assess the durability of treatment responses, the potential for secondary cancers, and any other late-onset effects.

5. Conclusions

In this comprehensive review, we have explored the recent breakthroughs and applications of nanotechnology in the realm of cancer treatment. The transformative potential of nanotechnology in cancer care is evident from the multifaceted roles of nanomaterials, including nanoparticles, nanocarriers, and nanodevices, in addressing the challenges posed by conventional cancer therapies. Key findings and insights from our exploration include the following: precise drug delivery [nanotechnology enables precise drug delivery to tumour sites, minimizing collateral damage to healthy tissues and improving therapeutic efficacy]; advanced imaging [functionalized nanoparticles have significantly enhanced the sensitivity and accuracy of imaging modalities like MRI, CT, and PET, allowing for early tumour detection and real-time treatment monitoring]; overcoming challenges [nanotechnology-based therapies offer solutions to challenges such as drug resistance, limited drug stability, and off-target effects]. The transformative potential of nanotechnology in cancer care cannot be overstated. It promises to revolutionize the field by enhancing precision, reducing side effects, and improving patient outcomes. However, it is essential to acknowledge and address potential obstacles and safety concerns. We emphasize the importance of continued research and development in nanotechnology to overcome these challenges and bring innovative treatments closer to clinical practice. Long-term safety assessments, rigorous regulatory evaluations, and ongoing monitoring of patient outcomes are paramount in ensuring the safe and effective use of nanotechnology-based cancer treatments. It is clear that nanotechnology will play a pivotal role in shaping the future of cancer care. By harnessing its potential, we can offer more personalized, effective, and patient-centric approaches to combatting this complex and devastating disease. The journey continues and we call for a collective commitment to advancing nanotechnology for the betterment of cancer patients worldwide.

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