A Review on Current Progress and Perspectives of Nanoparticles for Chemotherapy

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ABSTRACT: Cancer continues to be a major global health challenge, particularly in cases diagnosed at advanced stages with metastases, which are often considered untreatable. Such cases are usually managed to sustain a chronic state of health. The advent of nanotechnology has brought significant advancements to cancer diagnosis and treatment. Nanoparticles, which measure between 1 and 100 nm, present distinct advantages for cancer therapy, including biocompatibility, reduced toxicity, enhanced stability, improved permeability and retention effects, and precise targeting capabilities. They can be classified into various categories, with the nanoparticle drug delivery system designed to leverage the unique characteristics of tumors and their microenvironments. These nanoparticles not only overcome the limitations associated with conventional cancer treatments but also tackle issues related to multidrug resistance. As researchers continue to uncover new mechanisms contributing to this resistance, the interest in nanoparticle applications is steadily increasing. The therapeutic potential of nanoformulations introduces promising new strategies for cancer treatment. This overview will explore the role of nanotechnology in chemotherapy, examining the underlying mechanisms, types of nanoparticles employed, current perspectives, and the significant challenges encountered in the clinical application of these advanced therapies.

KEYWORDS: Cancer, Chemotherapy, Nanoparticles, Cellular targeting, drug delivery, Biomaterials.

INTRODUCTION

Cancer continues to be a leading cause of death worldwide, with around 4.5 million deaths (29.8%) attributed to the disease, as reported by the World Cancer Reports. This high mortality rate is largely due to late-stage diagnoses or the presence of metastases [1]. Common treatment options include surgery, radiotherapy, chemotherapy, hormone therapy, immunotherapy, or a combination of these methods. However, some treatments, particularly chemotherapy, encounter challenges such as non-specificity, issues with cytotoxicity, the growth of stem-like cells, and the development of multidrug resistance [2]. Treatment strategies for malignant diseases often involve the use of highly cytotoxic, non-selective agents in conjunction with targeted therapies aimed at specific molecular targets. Although targeted therapies can be effective, they frequently come with significant side effects and may not greatly enhance survival rates for patients with advanced metastatic disease. Furthermore, these therapies can also be quite costly [3-5].

Nanoparticles (NPs) possess unique physicochemical properties and the ability to selectively target tumor cells, making them highly promising for cancer therapy. They can be designed for the targeted delivery of drugs, genes, or imaging agents directly to tumor cells, which helps minimize toxicity to healthy tissues. By precisely manipulating the size, shape, and surface properties of NPs, their effectiveness can be increased while reducing undesirable side effects. Furthermore, NPs can overcome biological barriers that often hinder the efficacy of conventional cancer treatments. They address issues such as poor solubility, rapid clearance from the body, and limited penetration into solid tumors [6,7].

The application of nanoparticles in cancer therapy has demonstrated significant promise in preclinical studies, with several nanoparticle-based therapies already receiving clinical approval. Nevertheless, challenges remain, including the need to enhance the stability and biocompatibility of nanoparticles, optimize their pharmacokinetics and biodistribution, and develop more efficient methods for nanoparticle synthesis and characterization [8,9]. Additionally, nanoparticles can be designed for selective accumulation in tumor tissues through passive or active targeting strategies, which increases drug concentration at the tumor site. Furthermore, NPs can be engineered to release their therapeutic cargo in response to various triggers, such as changes in acidity, heat, or the presence of specific enzymes, thereby improving the efficacy of the treatments [10-12].

Recent years have seen a growing scholarly interest in the use of nanoparticles (NPs) for combination

therapy in cancer treatment. Combination therapy involves the simultaneous administration of two or more therapeutic agents with different mechanisms of action. NPs in combination therapy have demonstrated synergistic effects, where the combined use of multiple approaches results in a greater therapeutic impact than that of individual drugs alone [6,13,15]. This enhanced efficacy can be attributed to the complementary mechanisms of action of the therapeutic agents, as well as the ability of NPs to deliver multiple drugs simultaneously to the tumor site. However, the implementation of combination therapy is often limited by the adverse effects and toxicity associated with the drugs used. NPs offer a promising solution to these challenges by enabling the targeted delivery of multiple drugs to the tumor while minimizing their effects on healthy tissues [16,17].

This review highlights recent progress in the application of nanomaterials for cancer therapy, specifically examining liposomes, polymer nanoparticles, dendritic polymers, and micelles as drug carriers (Fig. 2). Each type of nanomaterial offers unique strengths and challenges. The main goal of this review is to explore the potential of various nanovectors for different therapeutic applications, as well as their associated molecular targets, benefits, and limitations.

Nanoparticles technology:

Lipid vesicles were the first nanoscale drug delivery systems introduced in the 1960s. Since then, there have been significant advancements in the development of nanoparticles (NPs) with multifunctional capabilities. Currently, a diverse array of NP technologies is available for cancer therapy, including micelles, liposomes, polymeric nanoparticles, dendrimers, protein nanoparticles, inorganic nanoparticles, exosomes, biomimetic nanoparticles, molecularly imprinted nanoparticles, and hybrid nanoparticles. This variety of delivery systems enables the creation of NPs with a wide range of shapes, sizes, and components, allowing for tailored applications in cancer treatment [6].

NANOTECHNOLOGY APPLIED IN CHEMOTHERAPY

Properties of nanomaterials:

Medical nanotechnology encompasses materials within the nanoscale range, generally between 1 and 100 nm, utilized in the design and development of therapeutic drugs and devices. At this scale, materials display unique optical, magnetic, and electrical properties that set them apart from conventional macromolecules [18]. Typical nanomaterials share several characteristics, including a high surface-to-volume ratio, enhanced electrical conductivity, superparamagnetic behavior, shifts in optical absorption spectra, and unique fluorescence properties. In medicine, these nanomaterials are employed for drug delivery and controlled release, taking advantage of their increased permeability, which enables them to traverse biological barriers, as well as their enhanced biocompatibility [19].

The unique properties of nanomaterials highlight their potential in cancer therapeutics. The high surface-to-volume ratio of certain nanomaterials enables more effective interactions with biomolecules, which enhances the specificity of drug complexes in targeted therapies. This increased specificity can improve treatment efficacy while reducing toxicity to normal cells [20]. Photodynamic therapy (PDT) and photothermal therapy (PTT) are two methods that utilize optical interference. In PDT, a photosensitizer accumulates at cancerous sites and generates singlet oxygen and other cytotoxic reactive oxygen species when exposed to specific wavelengths of light, leading to apoptosis or necrosis. Conversely, PTT employs materials with high photothermal conversion efficiency to elevate the temperature of targeted cancer areas, causing cancer cell death. Both PDT and PTT are promising treatment modalities, with ongoing research focused on optimizing the materials used in these therapies. Certain nanomaterials, with their unique fluorescence properties, can be effectively utilized in both PDT and PTT [21,22]. Moreover, the superparamagnetic behavior of nanomaterials provides various applications in cancer diagnosis and treatment. For instance, superparamagnetic iron oxide nanoparticles (SPIONs) hold promise in cancer hyperthermia treatment due to their small size, enhanced targeting specificity, controllable release rates, and ability to evade immune responses [23].

Progress of nanotechnology in targeted delivery:

Targeted delivery is a significant advantage of nanomaterial-based cancer therapies compared to traditional free drugs. Recent advancements in this area have concentrated on improving targeted delivery techniques. The main objective of targeted

delivery is to direct therapeutic agents specifically to cancer cells, which can be achieved through either passive or active targeting. Passive targeting utilizes the enhanced permeability and retention (EPR) effect, enabling nanoparticles to accumulate in tumor tissues due to the leaky characteristics of tumor vasculature. In contrast, active targeting involves attaching nanoparticles to antibodies, peptides, aptamers, or small molecules that selectively bind to cancer cell markers. When compared to free drugs, targeted delivery through nanomaterials can reduce toxicity to normal cells, safeguard drugs from degradation, and enhance their half-life, loading capacity, and solubility [18, 24].

MECHANISM OF TARGETING BY NANO DRUG VEHICLES

A key criterion for selecting a nanomedicine formulation for cancer therapy is its ability to specifically target cancer tissue while minimizing side effects on healthy tissues. Various nanoformulations developed to deliver anticancer drugs to tumor sites utilize different targeting mechanisms to achieve this goal. The drug delivery methods and advantages of nanocarriers can vary depending on the type of carrier employed. Nanocarriers facilitate the direct delivery of therapeutic agents into the bloodstream, enabling them to reach the targeted area. Once at the site, these carriers can induce DNA damage through the excessive production of reactive oxygen species (ROS), ultimately leading to apoptosis and cell death [25,26]. There are two primary targeting methods in nanoparticle-based drug delivery: passive targeting and active targeting.

Passive method:

In the passive targeting method (Fig. 1), the inherent characteristics of the tumor site are exploited to concentrate nanovehicles in that location. Key factors in this process include the Enhanced Permeability and Retention (EPR) effect and the properties of the Tumor Microenvironment (TME). Rapid tumor cell proliferation often leads to neovascularization, creating larger pores in the vascular walls that facilitate passive targeting. This abnormal angiogenesis enables nanoparticles to access and accumulate in the tumor area. Additionally, poor lymphatic drainage contributes to particle retention, enhancing the EPR effect [27-29]. However, high interstitial fluid pressure within the tumor microenvironment can impede the uptake and uniform distribution of nanoparticles. While the EPR effect allows for preferential accumulation of nanoparticles in tumor tissue compared to normal tissue, the dysfunctional nature of the tumor environment frequently results in heterogeneous distribution, with nanoparticles typically localized in the perivascular region and tumor periphery. To overcome these challenges, many nanocarriers leverage TME properties, such as acidic pH, elevated redox potential, and differential secretion of lytic enzymes, to achieve more uniform drug delivery throughout the tumor [30-32].

Active targeting:

Active targeting leverages (fig 1) the properties of tumor cells, specifically the cell surface receptors expressed by cancer cells. This method involves the use of various targeting molecules conjugated to the nanocarrier to specifically bind to these receptors. In this section, we will explore the different modes of targeting employed by various nanoformulations, along with their respective advantages and disadvantages.

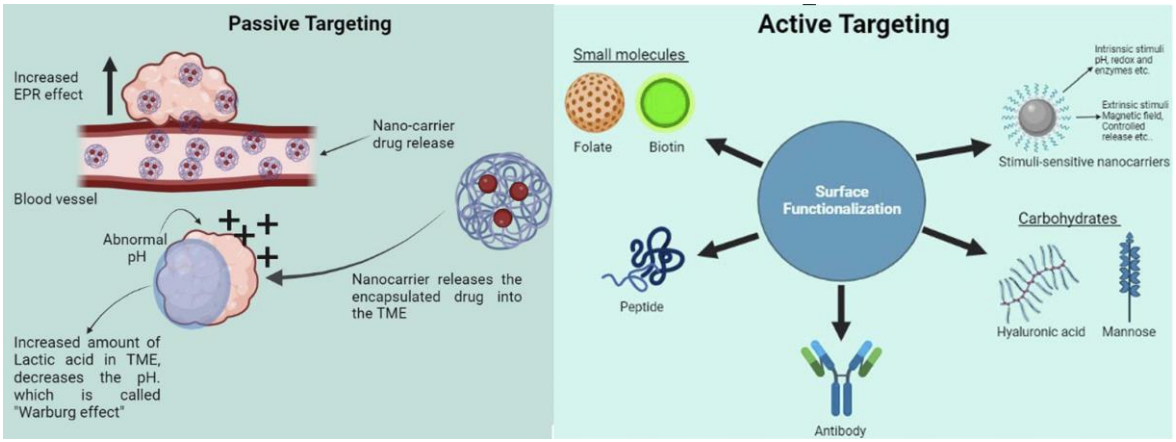

Figure 1: Passive and Active targeting

Passive targeting generally relies on diffusion mechanisms influenced by factors such as size, shape, and surface properties. Research indicates that nanoparticles sized between 40 to 400 nm can achieve high bioavailability and reduced renal clearance by prolonging circulation time. Specifically, maintaining particle sizes between 50 to 200 nm with a rigid, spherical shape enhances circulation duration and decreases kidney clearance [33]. Tumor cells exhibit features such as irregular neovascularization, increased expression of inflammatory factors, and inefficient lymphatic drainage. These characteristics create a leaky vascular structure, allowing nanoparticles to enter tumor tissues and remain in the tumor bed due to extended circulation times. While the EPR effect aids in drug accumulation within tumor cells, nanoparticles are cleared from normal tissues by the mononuclear phagocyte system (MPS) or through glomerular filtration in the kidneys [34,35]. Several barriers can impede the delivery of nanosized drugs, including abnormal tumor vasculature, growth-induced solid stress, and stress from the atypical stromal matrix. Additionally, acidic and hypoxic conditions within tumor cells, heterogeneous perfusion, and elevated interstitial fluid pressure can hinder nanoparticle penetration. These challenges can be addressed by optimizing drug delivery strategies that leverage the EPR effect and exploit the properties of the tumor microenvironment (TME) [36].

Maintaining the size of nanoparticles is crucial for enhancing the EPR effect. A neutral or negative surface charge can also improve circulation time and drug accumulation by increasing plasma half-lives. Additionally, using adjuvants such as nitric oxide donors can further enhance EPR effects [34]. Several factors influence the EPR effect, including extravasation, diffusion, and convection within the tumor vasculature and surrounding biological environment. It is important to recognize that the EPR effect is heterogeneous, varying according to tumor blood flow, hypoxic regions, vascular permeability, and penetration [35]. Once in the body, nanoparticles go through several stages, including circulation, endocytosis, and accumulation. However, they are susceptible to opsonization, resulting in a protein corona forming around them based on their characteristics. To address this, hydrophilic polymers like polyethylene glycol (PEG) can be used to reduce opsonin absorption. Another strategy involves silencing or depleting Kupffer cells, specialized macrophages that aid in the uptake of foreign materials [37]. Recent studies have explored innovative methods to improve nanoparticle efficacy. For instance, PEGylated Prussian blue nanoparticles have been shown to reduce tumor hypoxia and modulate polyethyleneimine cytotoxicity, offering dual-enhanced photodynamic therapy with self-supplied oxygen. This approach improved therapeutic efficacy in breast cancer cells and tumor-bearing mice following laser irradiation [38,39]. In another study, significant apoptosis and necrosis were noted in cancer cells treated with PEGylated nanographene oxide, emphasizing its potential in combination therapy. Furthermore, research on iron-dependent regulated cell death (ferroptosis) using liposomes embedded with PEG-coated 3 nm Fe_2O_3 nanoparticles demonstrated their ability to promote hydroxyl radical generation and lipid peroxidation. The inclusion of doxorubicin enhanced the chemotherapeutic effect, while the study also achieved traceable magnetic resonance imaging and pH/ROS dual-responsive drug delivery [40].

NANOPARTICLES IN CANCER THERAPY

Nanoparticles commonly employed in drug delivery systems can be categorized into three main types: organic nanoparticles, inorganic nanoparticles, and hybrid nanoparticles (Fig. 2).

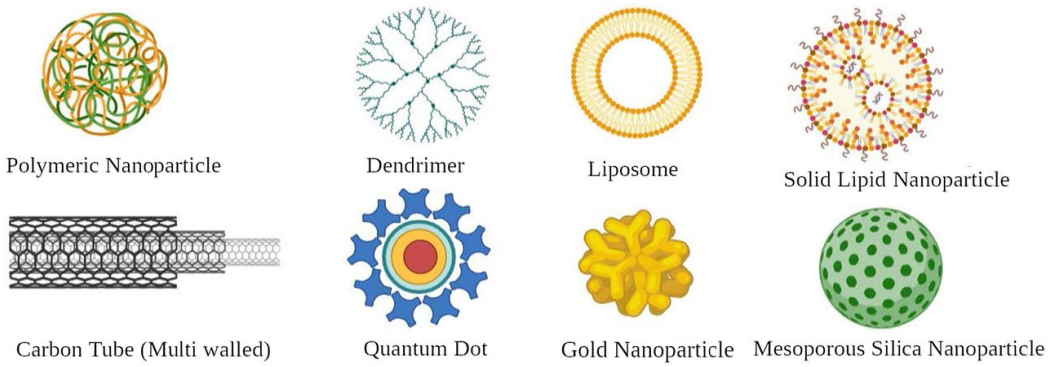

Figure 2: Deferent types of nanomaterial's used in cancer therapy

Table 1: Typical and fundamental characteristics of different NP technologies

Sr. No.	NPs technologies	Typical materials	Favorable size	Involved forces in drug loading
1	Polymeric NPs	Polymers	10-1000 nm	Hydrophobic force, hydrogen bond, electrovalent bond, and covalent bond
2	Dendrimer NPs	Globular polymers with branching architectures and surface functional group	<100 nm	Hydrophobic force, hydrogen bond, electrovalent bond, and covalent bond
3	Liposome	Amphiphilic lipid and excipients	-100 nm	Hydrophobic force and hydrogen bond
4	Micelles	Amphiphilic copolymer	10-100 nm	Hydrophobic force
5	Inorganic NPs	Metals, metaloxides, metalalloys, black phosphorus, and semiconductors	<1000 nm	Vander Waals forces, hydrogen bond, electro valent bond, and covalent bond
6	Exosomes	Exosomes	40-160 nm	Vander Waalsforces, hydrogen bond, and electrovalent bond
7	Biomimetic NPs	Cell membrane coating	<200 nm	Hydrophobic force, vander Waals forces, hydrogen bond, electrovalent bond, and covalent bond
8	Hybrid NPs	At least two different above-mentioned materials	<1000 nm	Vander Waals forces, hydrogen bond, electrovalent bond, and covalent bond

Polymeric Nanoparticles:

Polymeric nanoparticles (PNPs) are defined as colloidal macromolecules characterized by specific structural architectures composed of various monomers. These nanoparticles can encapsulate drugs within their matrix or attach them to their surface, resulting in either nanospheres or nanocapsules that facilitate controlled drug release at targeted sites. Initially, PNPs were constructed from non-biodegradable polymers such as polyacrylamide, polymethylmethacrylate (PMMA), and polystyrene [41]. However, concerns regarding toxicity due to the persistence of these materials in the body prompted a transition to biodegradable polymers like polylactic acid, poly(amino acids), chitosan, alginate, and albumin. These biodegradable options help reduce toxicity while enhancing drug release and biocompatibility [42,43]. Research has shown that coating PNPs with polysorbates can improve their interactions with the endothelial cell membrane of the blood-brain barrier (BBB). For instance, one study demonstrated that nanocapsules loaded with indomethacin significantly reduced tumor size and improved survival rates in a rat xenograft glioma model [44,45]. The field of polymeric nanoparticles is rapidly evolving, with over ten formulations containing anticancer drugs currently in clinical development. Notable examples include paclitaxel poliglumex (Xyotax), PEG-camptothecin (Prothecan), modified dextran-camptothecin (DE 310), HPMA copolymer-DACH-platinate (AP5346), HPMA copolymer-platinate (AP5280), HPMA copolymer-paclitaxel (PNU166945), and HPMA copolymer-doxorubicin galactosamine (PK2) [46].

Dendrimers:

Dendrimers are synthetic nanocarriers recognized for their radially symmetric, tree-like structure formed by monomer arrangements. Their high surface functionalization and targeting capabilities stem from their customizable design, enabling them to meet the specific requirements of different targets. This precise size control allows for passive targeting to tumor sites through the enhanced permeability and retention (EPR) effect [47]. Additionally, dendrimers can be hybridized with other nanocarrier types, such as being encapsulated in polymer shells, thereby increasing their efficacy as a drug delivery platform for cancer therapy. They have a considerable capacity for drug loading and can be engineered to support various drug release mechanisms. Common strategies include modifying the number of terminal

groups, incorporating degradable spacers, and employing pH-sensitive linkages. Furthermore, surface functionalization with vitamins, antibodies, and peptides can mitigate some challenges associated with dendrimer-mediated drug delivery, such as rapid clearance from the bloodstream [48-50].

mAb Nanoparticles:

Monoclonal antibodies (mAbs) are widely used in cancer treatment for their precise targeting abilities. When combined with nanoparticles, they form antibody–drug conjugates (ADCs), which have shown increased specificity and effectiveness compared to traditional cytotoxic drugs or mAbs alone. For instance, a nanoparticle incorporating a paclitaxel core and modified with trastuzumab demonstrated improved anti-tumor efficacy and reduced toxicity compared to administering either paclitaxel or trastuzumab separately in HER2-positive breast cancer cells [51,52].

Liposomes:

Liposomes, composed of cholesterol and various natural or synthetic phospholipids, are among the most successful platforms for nano-drug delivery. They can be administered through various routes, including oral and injectable options. Intravenous injection, which has FDA approval, is a primary method for delivering several liposome-based drugs, alongside subcutaneous, intradermal, intraperitoneal, and intramuscular routes [53-55]. The drug delivery mechanism of liposomes involves the accumulation, uptake, and release of drugs at targeted sites. They interact with drugs and tumor tissues using both passive and active targeting strategies. Passive targeting primarily takes advantage of the enhanced permeability and retention (EPR) effect, which is significant in tumor microenvironments, leading to improved retention of liposomes at tumor sites. [56-58].

Active targeting through surface functionalization has significantly improved the drug-targeting capability of liposomes. This strategy involves modifying the lipid surface of liposomes using various methods to enhance their specificity for tumor sites. Different agents, such as antibodies, small molecules, peptides, and carbohydrates, have been utilized for this purpose. Antibodies, in particular, exploit their specific targeting properties to bind to cancer-specific surface antigens, including the Melanoma Cell Adhesion Molecule (MCAM), HER2 receptor, CD44, and growth factor receptors like VEGFR and EGFR. This targeted delivery ensures that therapeutic agents are more effectively directed to cancerous cells [59].

Surface functionalization of liposomes with small molecules like folate, estrone, and anisamide has proven effective for targeting tumor surface receptors. Additionally, carbohydrates and proteins, such as mannose and beta-FGF, have been explored as potential targeting agents due to their ability to bind to specific cell surface receptors. Alongside molecule-based targeting, another strategy to enhance liposome targeting involves the use of stimuli-sensitive coatings. Polymers like PEG are often used to coat liposomes, which can increase their circulation time but may reduce their targeting effectiveness. To address this, various stimuli-responsive approaches have been developed to cleave these coatings. These methods take advantage of tumor microenvironment characteristics, such as altered pH, redox potential, and secreted enzymes, to trigger the cleavage of the surface coating, facilitating preferential drug release at the tumor site [59].

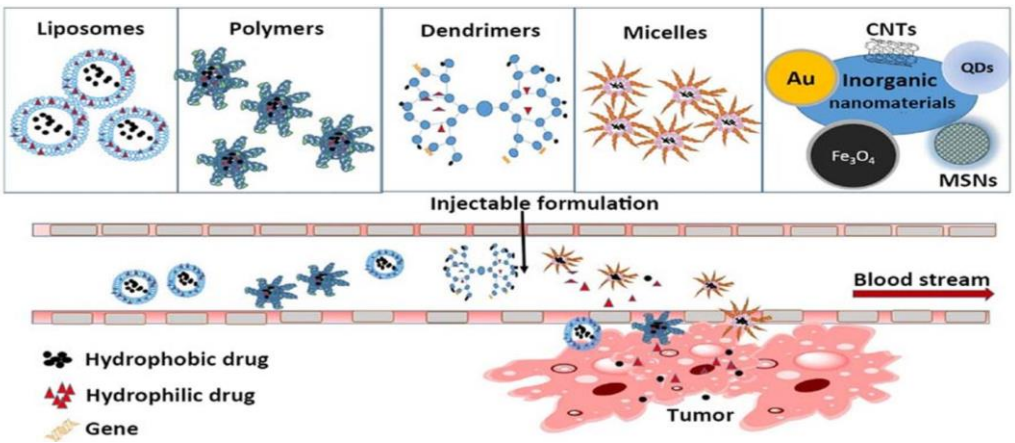

Figure 3: Nanomaterials used as drug carriers for cancer therapy [60].

Solid lipid nanoparticles (SLN):

Solid lipid nanoparticles (SLNs) are a colloidal drug delivery system where liquid lipids are replaced by solid lipids. As their name suggests, SLNs consist of solid lipids, emulsifiers, and water. Common lipid components include fatty acids, steroids, waxes, triglycerides, and partial glycerides. SLNs can be administered via various routes, including parenteral, oral, rectal, ophthalmic, and topical applications [61]. Two primary models of SLNs are the solid solution model and the core-shell model. SLNs are known for their higher drug release rates, attributed to their high surface area and homogeneous drug distribution, which promotes slow release. The mobility of the drug and the crystallization behavior of lipid carriers also facilitate faster release [62]. Delivery to the targeted area can occur through passive, active, or co-delivery mechanisms. Passive targeting primarily relies on the Enhanced Permeability and Retention (EPR) effect, while active targeting involves the recognition of receptors or transporters that are overexpressed on tumor cell surfaces. The co-delivery method enables the simultaneous delivery of two compounds within the drug delivery system [63]. Studies have shown that vorinostat-loaded SLNs enhance pharmacokinetics and efficacy against multidrug-resistant cancer cells, demonstrating effectiveness in cell lines such as MCF-7, A549, and MDA-MB-231 [64].

Nanoemulsions:

Nanoemulsions are colloidal nanoparticles that consist of heterogeneous mixtures of oil droplets dispersed in an aqueous medium, typically ranging from 10 to 1000 nm in size. They can be categorized into three main types: 1) oil-in-water systems, 2) water-in-oil systems, and 3) bi-continuous nanoemulsions. Research has thoroughly explored membrane-modified nanoemulsions. For instance, nanoemulsions loaded with spirulina and paclitaxel have demonstrated enhanced anti-tumor effects by modulating immune responses through the TLR4/NF-kB signaling pathways. Another example includes a nanoemulsion formulation combining rapamycin, bevacizumab, and temozolomide for the treatment of advanced melanoma [66,67]. Compared to liposomes, nanoemulsions offer advantages such as improved optical clarity, stability, and biodegradability. However, their clinical application faces challenges, including the need for high temperatures, pressures, and specialized equipment like homogenizers and micro-fluidizers, which can be costly [68].

Cyclodextrin Nanosponges:

Cyclodextrins are often employed as stabilizers to improve the drug-loading capacity of nanoparticles (NPs). Nanosponges, which are small, mesh-like structures, use β-cyclodextrin to enhance drug delivery. For example, β-cyclodextrin nanosponges loaded with paclitaxel have exhibited significant cytotoxic effects in MCF-7 cell line cultures. Additionally, camptothecin formulated with cyclodextrin-based nanosponges has shown improved solubility and stability [69,70].

Carbon quantum dots:

Carbon quantum dots (CQDs) are fluorescent carbon nanoparticles that are gaining popularity in cancer imaging and drug delivery applications. Their high targeting capabilities result from the ease of surface functionalization, which allows for the attachment of various targeting molecules [71]. The fluorescence properties of CQDs enhance their utility in bioimaging, contributing to their theranostic potential. With low toxicity, high biocompatibility, and effective targeting, CQDs are emerging as one of the most promising platforms for nano-drug carriers [72].

Metallic Nanoparticles:

Metallic nanoparticles, typically ranging from 1–100 nm in diameter, often consist of metal oxides or a metallic core coated with organic materials. They possess unique physical and chemical properties that are advantageous in cancer therapy. Some key benefits include ease of synthesis, functional surfaces that enhance affinity and selectivity for target molecules, and a large surface-area-to-volume ratio. Certain iron-based nanoparticles also exhibit magnetic properties [73,74]. The surfaces of metallic nanoparticles can be modified to facilitate interactions with targeting agents through hydrogen bonds, covalent bonds, and electrostatic interactions. Additionally, these nanoparticles demonstrate increased stability and extended circulation half-life, improving biodistribution and specific targeting to desired sites, which is crucial for clinical applications [75]. This enhanced targeting capability is often achieved through surface modifications using thiol groups, disulfide ligands, amines, nitriles, carboxylic acids, phosphines, or polyethylene glycol (PEG). Overall, metallic nanoparticles can effectively direct

therapeutic agents to specific sites, reducing effects on healthy tissues and allowing for controlled drug release [76,77].

Gold/silver nanoparticles:

Gold and silver nanoparticles are effective in delivering both small and large drug molecules to tumor sites. Their targeting capabilities primarily depend on the Enhanced Permeability and Retention (EPR) effect and the properties of the tumor microenvironment, such as altered redox potential and pH. Additionally, due to their metallic nature, these nanoparticles can be used for hyperthermic treatment when combined with an external heat source, such as microwave irradiation, following their targeting of the tumor [78]. However, challenges such as aggregation and increased cytotoxicity to healthy cells limit their application. To mitigate these issues, hybridization with polymers such as polyethylene glycol (PEG) is often employed, enhancing biocompatibility and stability [79].

Silica Nanoparticles:

Silica nanoparticles have gained attention in biological applications, particularly for gene delivery, by functionalizing their surfaces with amino-silanes. For example, N-(6-aminohexyl)-3-aminopropyl-trimethoxysilane-functionalized silica nanoparticles have shown high efficiency in transfecting Cos-1 cells with minimal toxicity and are currently available for commercial use [80]. Mesoporous silica nanoparticles are especially regarded as excellent drug carriers due to their favorable pharmacokinetic properties and have been widely utilized in immunotherapy. Studies have shown successful uptake of camptothecin-loaded mesoporous silica nanoparticles by colorectal cancer cells, highlighting their potential in targeted therapy [81].

Cancer Diagnosis Using Nanotechnology:

Cancer diagnosis primarily involves analyzing tissue morphology at the microscopic level, typically through biopsy or surgical tumor samples. Histopathological analysis utilizes staining techniques, such as hematoxylin and eosin, and is often enhanced by electron microscopy. Furthermore, bioconjugated nanoparticles are being developed for the early detection of cancer in body fluids like serum and blood [82,83]. These sensors commonly feature cancer-specific antibodies or ligands that produce electromechanical or optical signals when they bind to cancer cells or target proteins. The use of nanoparticles for detecting and assessing circulating cancer cells or their biomarkers in blood and serum is a promising area of research, particularly since these biomarkers are often found in low concentrations. [84-86]. Improving the capture and analysis of these rare circulating cancer cells can potentially be achieved by combining magnetic nanoparticles with semiconductor quantum dots [87]. Overall, nanotechnology holds significant potential for enhancing cancer treatment and monitoring by leveraging the unique architecture, vascularity, antigenicity, biomarkers, and microenvironment of tumors.

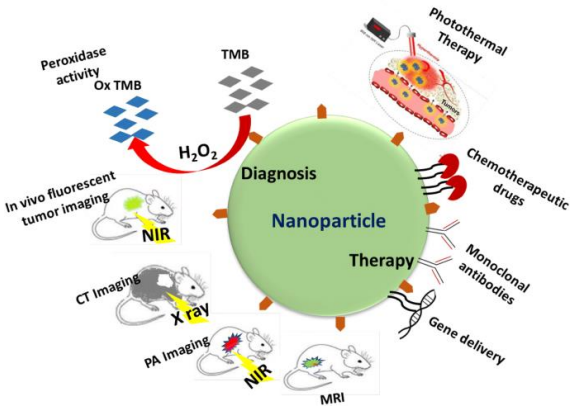

Figure 4: Diagnosis of cancer using different nanotechnologies

NANOMATERIALS FOR CANCER IMMUNOTHERAPY

Nanomaterials show considerable promise in enhancing the effectiveness of cancer immunotherapy, which comprises two main components: cancer vaccines and tumor microenvironment (TME) modulation. Cancer vaccines aim to present cancer antigens to dendritic cells (DCs), stimulating a robust effector T-cell response, while TME modulation focuses on improving the ability of cytotoxic T cells to target and eliminate cancer cells [88-90]. Additionally, nanomaterials can be preloaded with targeting ligands to enable selective uptake by specific cells. For example, recent research has demonstrated that a D-enantiomeric supermolecule nanoparticle was designed to exhibit p53-dependent antiproliferative activity, thereby enhancing antitumor immunity. The delivery of tumor antigens through nanomaterials can significantly improve immunotherapy, as these materials can also modulate immune responses due to their unique characteristics [91-93]. Notably, PC7A nanoparticles have been shown to activate the

stimulator of interferon genes pathway, contributing to a robust anti-tumor immune response [94].

SIGNIFICANT CHALLENGES IN THE CLINICAL APPLICATION OF NANOPARTICLES

As nanotechnology advances, the research and knowledge surrounding nanoparticles have significantly expanded. However, only a limited number of these formulations move on to clinical trials, with many remaining in the in vivo and in vitro stages. Each nanoparticle formulation faces unique challenges for clinical translation, but several common obstacles can be categorized into biological, technological, and study-design-related issues.

Biological challenges include limited routes of administration, difficulties in achieving the desired biodistribution, and the ability of nanoparticles to cross biological barriers. Concerns about degradation and potential toxicity are also prominent. Typically, nanoparticles are administered via intravenous injections, which can lead to rapid clearance from the bloodstream, making it difficult for them to effectively interact with target sites. This often necessitates high drug concentrations, which may not always result in the desired therapeutic effects [95]. Magnetic nanoparticles offer a potential solution, as studies indicate that 3D magnetic fields can be utilized to control the movement of nanoparticles against blood flow [96]. However, further research is needed to understand the effects of magnetic fields on the human body and how they interact with various types of nanoparticles.

Controlling the biological fate of nanoparticles (NPs) presents significant challenges and requires careful consideration. Even when made from biocompatible materials and modified to improve retention time and half-life, there remains a risk of damage to the lungs, liver, and kidneys. Key factors influencing toxicity include surface area, particle size and shape, solubility, and the tendency to agglomerate. Research has indicated that NPs can accumulate in the lungs, leading to inflammatory responses, oxidative stress, and cytotoxic effects. Additionally, free radicals generated by NPs may adversely affect healthy cells [97]. To mitigate these concerns, one strategy is to use more biocompatible substances, such as chitosan, in NP fabrication [98]. Moreover, incorporating materials that can disintegrate upon exposure to near-infrared light could enhance safety while maintaining therapeutic efficacy [99].

Another significant challenge in nanoparticle (NP) delivery is evading the "mononuclear phagocytic system" (MPS). In biological fluids, NPs tend to adsorb proteins, resulting in the formation of a protein corona (PC) that facilitates their uptake by the MPS. Various coatings have been developed to prevent protein corona formation; however, these approaches have not yielded substantial improvements. One potential strategy to address this issue involves designing NPs that specifically target macrophages, effectively utilizing them as drug delivery vehicles. Current strategies to navigate the challenges posed by tumor-associated macrophages (TAMs) include preventing macrophage recruitment, depleting these cells, reprogramming TAMs, and obstructing the “CD47-SIRPα pathway.” These approaches aim to enhance the therapeutic efficacy of NPs while minimizing their clearance by the immune system [100].

Technological challenges related to nanoparticles (NPs) encompass issues like scale-up synthesis, uniform optimization, and performance predictions, all of which are critical for ensuring their clinical success. Most NPs used in in vivo and in vitro studies are produced in small batches, making it difficult to scale up for larger quantities due to limitations in instrumentation and other factors. Additionally, lead clinical candidates that demonstrate promise in animal models often lack systematic design and optimization. To tackle these challenges, methods can be utilized to evaluate various nanoparticle formulations, allowing for selective iterations to identify a single optimized version. However, these formulations should not be directly introduced into human testing without comprehensive validation. Predicting the efficacy and performance of nanoparticles is complex, and replicating in vivo results in human trials presents significant difficulties [101-103]. Utilizing computational or theoretical modeling alongside experimental results can help simulate physiological conditions and environments. For example, "organs-on-chips" technology is actively being researched and may enhance predictions regarding the efficacy and performance of NPs.

Study-design challenges in clinical research on nanoparticles (NPs) significantly influence outcomes. Many studies rely on cell and animal models, which

may not accurately reflect human responses. This reliance makes it difficult to generalize results, as a single model cannot replicate the complex interactions occurring in the human body. Furthermore, there is a pressing need for research on cancer metastasis models, given that metastasis is a crucial aspect of cancer progression. Personalized medicine approaches, such as N=1 clinical studies, will be essential to account for individual factors like genetics, environmental influences, and medical history. This personalized approach requires careful consideration and design to ensure effective and meaningful therapeutic outcomes [104,105].

Another significant challenge in the clinical application of nanoparticles (NPs) is that they are rarely used as first-line therapies. Even when nanoformulations receive approval, they are often reserved for later stages of treatment, typically after patients have undergone multiple lines of therapy or developed drug resistance. This practice can skew clinical trial results, as the patient populations may already be compromised, reducing the likelihood of observing the full therapeutic potential of NPs. Consequently, this limits opportunities for NPs to benefit patients who might still respond positively to treatment at earlier stages of their disease.

FUTURE PERSPECTIVES

Despite the promising potential of nanotechnology, no nanoparticle-based cancer treatment has yet reached blockbuster status like Revlimid®, Opdivo®, Imbruvica®, Keytruda®, Tecentriq®, or Perjeta®. The unique features of nanoparticles, such as their small size, high reactivity, and specialized properties, raise important health and safety concerns. For example, the toxicity of carbon nanotubes (CNTs) seen in animal studies is not fully understood in living systems. However, advancements in the development and production of nanoparticles, combined with rigorous safety evaluations, suggest that new nanotechnology products may be safe for clinical use. Key characteristics for any new nanotechnology agent include reliability, reproducibility, high sensitivity and specificity, structural stability, ease of handling, and cost-effectiveness. Despite these advancements, current strategies - such as advanced immunotherapy, gene therapy, and integrative approaches involving nanobubbles and nutraceuticals - face significant challenges. Many of these challenges stem from the limitations of existing animal model systems and the research and development methodologies used in the field [106].

Most tested and approved cancer therapies typically extend patient survival by only 1 to 18 months or help alleviate some side effects of chemotherapy, radiation, or surgery. There is a pressing need for synergistic, multimodal therapies that incorporate nanomedicine, particularly through the promising concept of theragnostics. Precision medicine and personalized approaches are vital due to the significant heterogeneity and uniqueness of tumors. Our ability to detect the small number of cancer cells that survive treatment remains limited. The National Institutes of Health Cancer Genome Atlas has characterized over 20,000 primary cancers across 33 types, integrating genomics with epigenomics, transcriptomics, proteomics, and increasingly, single-cell spatially resolved multi-omics. The remarkable ability of cancer cells to mutate and adapt against therapies presents a significant challenge. To enhance our therapeutic strategies, "out of the box" thinking is essential. We have only begun to tackle the complexities of cancer stem cells and resistant metastatic tumors. Researchers face a long road ahead in developing a diverse range of safe nanoparticle-based therapeutic systems for effective cancer treatment.

CONCLUSION

Nanotechnology offers a promising approach to cancer treatment, enabling the targeted delivery of small molecules for detection, diagnosis, and therapy. Drug delivery systems (DDS) based on nanoparticles (NPs) are increasingly used in clinical applications across various cancer types, thanks to their improved pharmacokinetics, biocompatibility, tumor targeting, and stability compared to traditional therapies.

Research has extensively investigated the use of nanomaterials in cancer treatment. These materials can be modified in numerous ways, allowing for the incorporation of anti-tumor drugs into nanocarriers. The efficacy, targeting ability, and biocompatibility of these systems are heavily influenced by the specific modifications applied to the nanomaterials. They enable both targeted and non-targeted delivery of a range of agents, including drugs, peptides, and small molecules. This mini-review discusses the properties of common nanomaterials and their evolving roles in cancer therapy.

We categorize the various types of nanomaterials employed in cancer treatment and describe different therapeutic strategies that utilize these technologies. Additionally, nanoplatforms can be engineered to specifically address the tumor microenvironment (TME). As research continues to deepen our understanding of cancer pathophysiology and the mechanisms underlying multi-drug resistance, further exploration of nanomaterial-based therapies is expected. Despite notable progress, only a few nanomaterial-based treatments are currently in clinical use, highlighting the necessity for ongoing research. Ultimately, advancements in nanobiotechnology have the potential to enhance clinical translation and improve outcomes for cancer patients.

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