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A Comprehensive Review: Emerging Nanotechnology in Cancer Drug Delivery

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Abstract

Nanotechnology has become a groundbreaking strategy in cancer therapy, especially in drug delivery systems, offering improved treatment effectiveness while minimizing the adverse effects associated with traditional methods. This review presents an in-depth analysis of recent progress in nanotechnology for cancer drug delivery, emphasizing the design, mechanisms, and practical applications of nanoparticle-based systems. Nanoparticles, such as liposomes, dendrimers, and gold nanoparticles, offer unique advantages, including improved drug solubility, targeted delivery to tumor cells, and controlled release of therapeutic agents. These systems can be designed to target cancerous tissues specifically, reducing harm to healthy cells and substantially enhancing the therapeutic index. The review also highlights varioufis strategies for achieving targeted drug delivery, such as passive targeting via the enhanced permeability and retention effect, and active targeting using surface modifications like antibodies or ligands that bind specifically to cancer cell receptors. Moreover, incorporating imaging functionalities into nanoparticles enables real-time tracking of treatment progress and evaluation of tumor response. The potential of multifunctional nanoparticles, which can combine drug delivery, imaging, and treatment monitoring, is also explored. Despite the promising benefits, challenges related to nanoparticle stability, scaling up production, and regulatory hurdles remain. This review concludes by discussing future directions for research and development in cancer nanomedicine, emphasizing the need for personalized treatment strategies and the continued evolution of nanotechnology to improve patient outcomes.

Keywords: Nanotechnology, anti-tumor drug delivery, nanoparticles, controlled release, personalized medicine

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INTRODUCTION

Cancer, the world's leading cause of mortality, requires rapid identification and effective antineoplastic therapy. Nanotechnology plays a crucial role in this context to precisely deliver drugs to target cancer cells, thus minimizing unwanted side effects. This offers distinct advantages in terms of cancer therapy. Theragnostics is a radioactive approach based on personalized medicine and nuclear medicine that uses a single radioactive drug to identify the tumor and a second drug to treat the tumor. One of the initial uses of theragnostics was the application of iodine-131 isotope for diagnosing and treating thyroid cancer in the field of nuclear medicine [1].

Nuclear medicine uses different chemicals for diagnostic imaging and targeted treatment, individually or in combination. Some of these chemicals, such as iodine, enter the target for metabolic processes, while others, such as receptor ligands, are already present in the target tissue. Theragnostics uses these processes to activate localization of diseased tissues with imaging and targeted removal of these tissues from radiation. Nanoparticle research represents a fascinating field of science, offering diverse and far-reaching applications. Its development, yielding groundbreaking results in modern studies, is not confined to synthetic materials alone. Nanotechnology is an emerging field that leverages current and future scientific and technological advancements using nanoparticles (NPs) that are 100 nm or smaller, which exhibit entirely new and enhanced properties that set them apart from larger particles. These NPs are typically engineered with specific characteristics, including size, shape, distribution, and surface structure. Cancer remains a major global health challenge, ranking among the leading causes of morbidity and mortality. Traditional cancer therapies, including chemotherapy, radiation, and surgery, often lack specificity in targeting cancer cells, leading to substantial side effects caused by systemic toxicity [2].

Nanotechnology, which involves the use of nanoscale materials (ranging from 1 to 100 nm), has shown considerable promise to overcome these limitations to improve drug delivery, improve therapeutic efficacy and reduce adverse effects. This comprehensive review presents the latest advances in nanotechnology-based cancer drug delivery systems, examining the types of nanomaterials, drug delivery mechanisms, and their clinical applications (Figure 1).

TYPES OF CANCER

Cancer is a term that encompasses a wide range of diseases marked by abnormal cell growth and the ability of these cells to spread to different areas of the body.

There are more than 100 types of cancer, each categorized based on the type of cell or tissue from which it originates. Listed below are the primary types of cancer, classified based on the organ or tissue in which they commonly originate:

Carcinomas

Carcinomas, the most prevalent type of cancer, arise from epithelial cells that form the lining of the body's internal and external surfaces. They can occur in a wide range of organs and tissues.

1. *Lung Cancer:* It begins in the lungs and is commonly associated with smoking, although it can also develop in nonsmokers.
2. *Breast Cancer:* It originates in the breast tissue, primarily in the milk ducts or lobules. While it is one of the most common cancers in women, it can also affect men.
3. *Liver Cancer:* It begins in the liver and may develop as a result of chronic liver conditions, such as hepatitis or cirrhosis.
4. *Skin Cancer:* This category includes several types, such as basal cell carcinoma, squamous cell carcinoma, and melanoma, with melanoma being the most aggressive form.

Sarcomas

These cancers arise in the body's connective tissues, including muscles, bones, cartilage, and fat.

1. *Osteosarcoma:* It is a type of bone cancer that primarily affects children and young adults.
2. *Liposarcoma:* It originates in fat cells and can develop in any part of the body.
3. *Rhabdomyosarcoma:* A cancer of muscle tissue, more common in children [3].

Leukemias

Leukemia is cancer of the blood or bone marrow. It causes the uncontrolled production of white blood cells.

1. *Acute Lymphoblastic Leukemia:* Primarily affects lymphoid cells and is most common in children.
2. *Acute Myeloid Leukemia:* It targets myeloid cells and is more commonly diagnosed in adults.
3. *Chronic Lymphocytic Leukemia:* A slower-progressing leukemia that predominantly affects older adults [4].

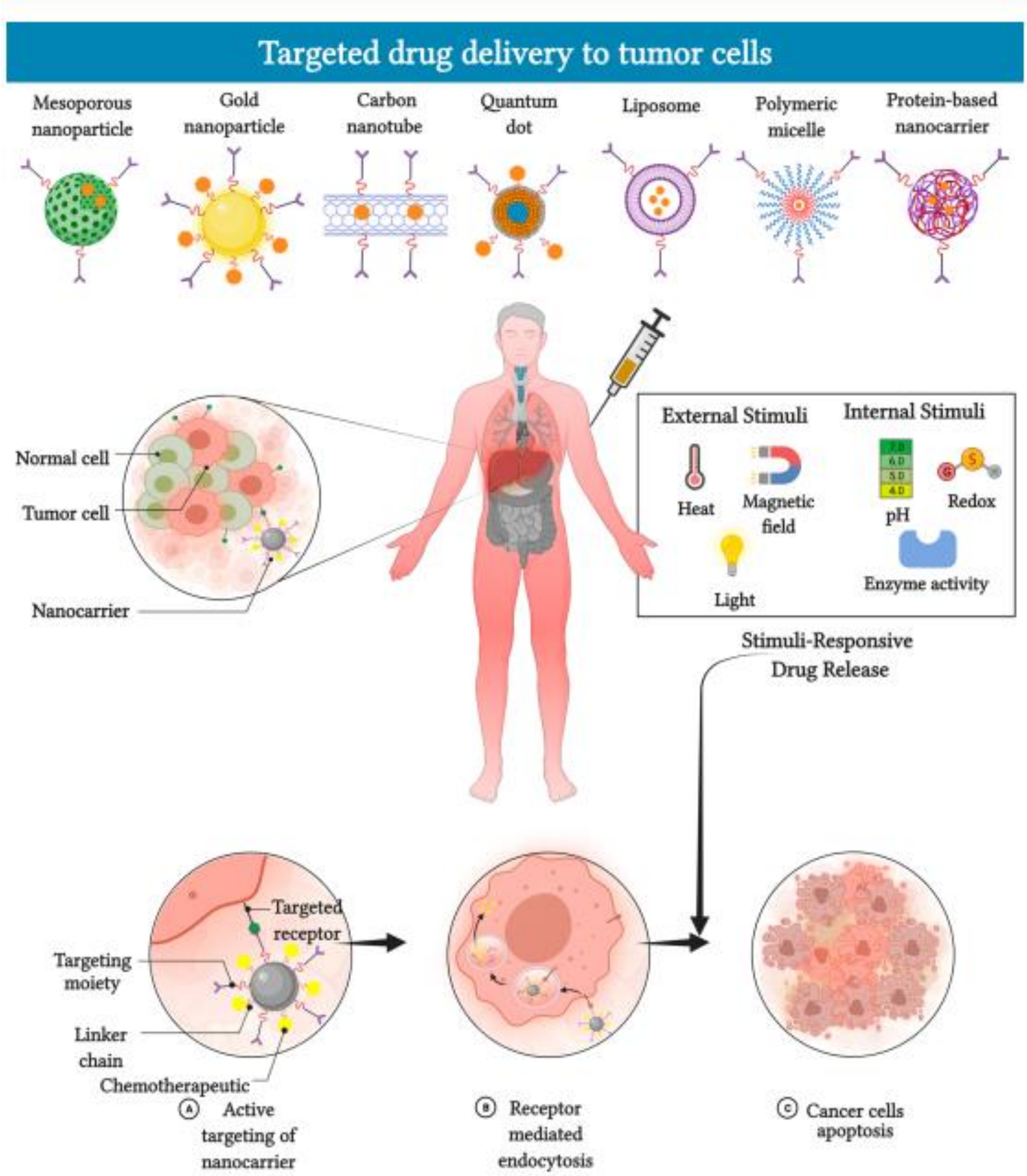

Figure 1. Targeted Drug Delivery to Tumor Cells.

Lymphomas

Lymphomas are cancers that originate in the lymphatic system, a key component of the body's immune system. They typically impact the lymph nodes and spleen.

1. *Hodgkin's Lymphoma:* is characterized by the presence of Reed-Sternberg cells and typically affects younger individuals.
2. *Non-Hodgkin Lymphoma:* A broad category of lymphomas with varying degrees of severity, and it is more common than Hodgkin's lymphoma [5].

Myeloma

Multiple myeloma is a cancer of plasma cells, a type of white blood cell found in the bone marrow. It results in the overproduction of abnormal antibodies.

Central Nervous System Cancers

Cancers that affect the brain and spinal cord are classified based on the type of cell from which they originate.

1. *Gliomas:* These tumors originate from glial cells, the supportive cells of the brain, and include glioblastomas, which are particularly aggressive.
2. *Meningiomas:* These tumors originate in the meninges, the protective membranes that surround the brain and spinal cord.
3. *Medulloblastomas:* These tumors are more common in children and usually develop in the cerebellum.

Other Rare Cancers

- *Esophageal Cancer:* This cancer occurs in the esophagus and is commonly linked to smoking, alcohol consumption, and gastroesophageal reflux disease.
- *Kidney Cancer:* Renal cell carcinoma is a cancer that affects the kidneys and may be detected by the presence of blood in the urine.
- *Bladder Cancer:* It originates in the bladder lining and is commonly associated with smoking and exposure to certain chemicals.
- *Bile Duct Cancer:* Also known as cholangiocarcinoma, this cancer affects the bile ducts within the liver.
- *Throat Cancer:* Involves the larynx (voice box) and is often related to smoking and alcohol use [6].

Oral Cancer

It begins in the mouth or throat and is often related to tobacco and alcohol use.

NANOTECHNOLOGY IN CANCER DRUG DELIVERY

Nanotechnology-based drug delivery systems have been designed to improve the bioavailability, stability, and targeting of cancer drugs. Using NPs, nanocarriers and nanosystems, these technologies can enable site-specific delivery, controlled release and enhanced drug penetration into tumors. The main advantages of using nanotechnology in the treatment of cancer are, for example, Doxil, ambisome, abraxane, nanotaxel.

ENHANCED PERMEABILITY AND RETENTION (EPR) EFFECT

Tumor blood vessels are often permeable and disorganized, allowing NPs to accumulate in tumor tissue more efficiently than in healthy tissue [7].

Example: Liposomal doxorubicin, paclitaxel – loaded NPs, antibody-drug conjugates, etc.

Improved Bioavailability

NPs can increase the solubility and stability of poorly water-soluble anticancer drugs, thereby improving their pharmacokinetics.

Targeted Drug Delivery

NPs can be designed to specifically target cancer cells, reducing the exposure of healthy cells to the toxic effects of chemotherapy. This is achieved through:

Examples: Liposomes, dendrimers, and gold NPs [8, 9].

Passive Targeting

This approach utilizes the EPR effect, where NPs accumulate more in tumor tissues due to the typically leaky blood vessels found in tumors.

Active Targeting

This involves modifying the surface of NPs with antibodies, ligands, or peptides that specifically bind to receptors that are overexpressed of cancer cells [10].

CONTROLLED RELEASE

NPs can be designed to release drugs in a regulated manner, triggered by specific environmental factors (such as pH, temperature, or enzymes) or over an extended period. This approach helps maintain consistent therapeutic drug levels while reducing toxic peaks.
Examples: Polyethylene glycol, Genexol-PM, and Doxil.

INCREASED BIOAVAILABILITY

NPs can enhance the solubility and stability of drugs that are poorly soluble in water, thus improving their bioavailability.

This is particularly important for many chemotherapeutic agents that have only limited solubility in the blood [11].

SIDE EFFECTS ARE REDUCED

By delivering drugs more specifically to cancer cells and tissues, NPs can reduce the systemic side effects typically associated with conventional chemotherapy, such as damage to healthy cells, nausea, and immune suppression.

COMBINED THERAPY

Nanotechnology can be used to deliver multiple drugs (chemotherapeutic agents, targeted therapies, or immunotherapy) in a single nanoparticle, thereby enhancing therapeutic effects and potentially overcoming drug resistance [12].

MULTIFUNCTIONALITY

NPs can be engineered to carry out multiple functions simultaneously, such as drug delivery, imaging (using NPs different from imaging technologies like MRI or PET), and tracking treatment progress. This enables real-time monitoring of both drug delivery and tumor response [13].

TYPES OF NANOMATERIAL USED IN CANCER DRUG DELIVERY

Liposomes are lipid-based NPs capable of encapsulating both water-soluble and fat-soluble drugs. Due to their biocompatibility, liposomes are widely used in cancer treatment.

Example: Doxil®, a liposomal formulation of doxorubicin, is a prominent example that has demonstrated improved therapeutic outcomes.

Polymeric NPs

These are constructed from biodegradable polymers like poly lactic-co-glycolic acid (PLGA), which can hold a diverse range of drugs.

They offer excellent control over the release rate of the drug and can be easily modified to improve drug loading and targeting efficiency [14].

Dendrimers

Dendrimers are highly branched, tree-like macromolecules that can carry a high payload of drugs. Their distinctive structure enables precise control over both size and surface characteristics, allowing for customization aimed at targeted delivery.

Inorganic NPs

Metal-based NPs, such as gold NPs, silica NPs, and iron oxide NPs, have been studied for their ability to enhance drug delivery. For instance, gold NPs can be modified with ligands that target tumors and loaded with chemotherapy drugs [15, 16].

Carbon Nanotubes (CNTs) and Graphene Oxide

CNTs have excellent mechanical and electrical properties and can be functionalized to carry drugs and target cancer cells. Graphene oxide, another carbon-based nanomaterial, has shown promise in drug delivery due to its large surface area for drug loading and the potential for targeted therapy.

Gold NPs

They possess distinctive characteristics that make them suitable for both drug delivery and imaging.

Gold NPs have become a promising therapeutic tool. Gnostics because of their versatility and many potential biological applications. Their high surface-to-volume ratio and unique optical characteristics make them valuable for nonmetallic imaging.

These NPs can be loaded with a multitude of chemicals, including targeting or imaging parties and therapeutic drugs. Gold NPs integrate targeting, diagnosis, treatment, and monitoring, overcoming the limitations associated with traditional diagnostic and therapeutic techniques. This allows the simultaneous delivery of images and therapeutic molecules to the same site, while simultaneously monitoring their effects in real time [17, 18].

MECHANISMS OF DRUG DELIVERY AND TARGETING

Passive Target (EPR Effect)

The EPR effect is a characteristic mechanism of nanoparticulate drug delivery. It happens because:

The tumor vasculature is permeable and disorganized compared to normal tissue, which allows NPs to extravasate more easily into the interstitial space of the tumor.

Poor lymphatic drainage in tumors prevents the rapid elimination of NPs, leading to their accumulation in the tumor.

The combination of these factors allows for passive targeting, where NPs accumulate more in tumor tissue than in healthy tissue, thus increasing local drug concentration at the tumor site while minimizing systemic exposure.

Active Targeting

Active targeting involves functionalizing the surface of NPs with specific ligands that bind to receptors overexpressed on cancer cells, facilitating their selective uptake [19].

THE MAIN MECHANISMS OF ACTIVE TARGETING INCLUDE

Receptor-mediated Endocytosis (RME)

Tumor cells often overexpress specific receptors, such as folate receptors (for folate targeted NPs) or epidermal growth factor receptors (EGFR), which can be exploited to enhance cellular uptake of NPs.

Antibody-Conjugated NPs

Specific targeting antibodies or antibody fragments are used to decorate the surface of NPs, ensuring that they selectively bind to antigens present on the surface of tumor cells, such as HER2 or CD44, leading to selective internalization [20].

Stimuli Response of Drug Delivery

One of the most promising developments in nanoparticulate drug delivery is the creation of stimulus-responsive systems, where the release of the drug is activated by external or internal triggers [21].

These systems can provide controlled and precise drug release in the tumor environment.

SOME OF THE KEY DRIVERS INCLUDE

pH-Sensitive NPs

Tumor tissues have an acidic extracellular pH (about 6.5–7.0), which is lower than normal tissue pH of about 7.4. NPs can be designed with pH-sensitive polymers or coatings (eg, poly(lactic-co-glycolic acid) [PLGA], poly(ethylamine)) that release the encapsulated drug when exposed to the acidic conditions of the tumor microenvironment [22].

Temperature-Sensitive NPs

Tumor tissue often has higher temperatures than normal tissue. NPs can be engineered to release their cargo after exposure to hyperthermic conditions, either with materials that undergo a phase transition or by using thermo-responsive hydrogels or liposomes [23].

NPs Enzyme-Sensitive

Many tumors show the expression of specific enzymes (e.g., matrix metalloproteinases, cathepsins). NPs can be designed with linkers that are cleaved by these enzymes, which cause drug release at the tumor site.

NANOPARTICLE INTERNALIZATION AND CELLULAR UPTAKE

Once NPs arrive at the tumor site, they need to be absorbed by the cancer cells for the drug to work. This absorption typically occurs via endocytosis, a process in which the cell membrane surrounds and engulfs material from outside the cell.

THERE ARE SEVERAL WAYS FOR NPs TO ENTER

Clathrin-Mediated Endocytosis

This is the most common mechanism, where NPs are incorporated into clathrin-coated vesicles, which then fuse with endosomes. Caveolae-mediated endocytosis: Some types of NPs can be taken up via caveolae, small indentations in the cell membrane that facilitate nanoparticle uptake.

Macropinocytosis

This is a form of endocytosis that can occur when cells take up the extracellular fluid with the NPs it contains. This mechanism is generally used by cells that actively participate in the absorption of nutrients [24].

After uptake, the NPs are sent to the endosomal/lysosomal compartment, where the drug is released by degradable nanoparticle systems or by activation of endosomal escape. This safety mechanism is essential to ensure that the drug reaches its intended target (e.g., cytoplasm or nucleus).

Clinical Applications of Nanotechnology in Cancer Treatment

Several nanoparticle-based drug delivery systems have advanced clinical trials, showing both better effects and challenges in cancer treatment.

Doxil (Liposomal Doxorubicin)

One of the most popular clinical applications of nanotechnology is the use of liposomal doxorubicin, marketed under the name Doxil. This formulation improves the pharmacokinetics of doxorubicin, reducing cardiotoxicity and increasing its therapeutic efficacy in cancers, such as ovarian cancer, Kaposi’s sarcoma and breast cancer.

Abraxane (Nanoparticle Albumin-bound Paclitaxel)

Abraxane is a nanoparticulate form of albumin-bound paclitaxel. It is used in the treatment of breast cancer, non-small cell lung cancer, and pancreatic cancer. Nanoparticle formulation increases the solubility of paclitaxel, improves its bioavailability, and reduces side effects, such as hypersensitivity reactions.

ONIVYDE (Liposomal Irinotecan Injection)

ONIVYDE is a liposomal formulation of irinotecan, a chemotherapy drug used in metastatic pancreatic cancer. The liposomal formulation prolongs the circulation time of irinotecan, thereby improving its therapeutic effect and reducing gastrointestinal side effects.

NPs for Gene Therapy

NPs are also used to deliver nucleic acids (DNA, RNA) to cancer cells for gene therapy. These include plasmid DNA-encoding therapeutic proteins, RNA interference (RNAi) molecules, and CRISPR-Cas9-based gene editing tools. Clinical trials are underway to assess the safety and efficacy of gene delivery using NPs in cancers, such as lungs, liver and melanoma [25].

Immunotherapy Based on NPs

NPs are used to deliver immunotherapeutic agents, such as checkpoint inhibitors, cancer vaccines and cytokines. These nanocarriers can enhance the antitumor immune response by directly targeting immune cells or improving the pharmacokinetics of immune agents [26].

Nanotechnology Challenges for Cancer Drug Delivery

Although nanotechnology holds great promise for improving cancer treatment, several challenges remain:

1. *Toxicity and biocompatibility:* The long-term toxicity of NPs remains a major concern. The body's immune system can recognize NPs as foreign bodies, leading to their rapid clearance, reducing the effectiveness of treatment. The biocompatibility of nanomaterials needs to be further evaluated to ensure their safety in clinical settings.
2. *Nanoparticle stability:* Ensuring the physical and chemical stability of NPs in the bloodstream and under storage conditions is essential to maintain their functionality and efficacy.
3. NPs can aggregate or undergo degradation, which affects their drug delivery capabilities.
4. *Scalability and reproducibility:* Manufacturing NPs at scale while maintaining consistent quality and drug loading is a significant challenge. Variations in size, shape, or surface charge can affect the pharmacokinetics and pharmacodynamics of NPs, making large-scale production difficult.
5. *Efficient drug loading and release:* Although NPs can deliver drugs in a controlled manner, it is difficult to achieve an optimal loading capacity and a consistent release profile. Overloading can lead to premature release, while underloading can lead to insufficient drug concentration at the tumor site.
6. *Heterogeneity of tumors:* Tumors show significant heterogeneity in their size, microenvironment and molecular characteristics, which can influence the effectiveness of nanoparticle-based therapies. Tumors may develop mechanisms to avoid the accumulation or uptake of NPs, thereby reducing the efficiency of the drug delivery system [27].

LIMITATIONS OF NANOTECHNOLOGY IN CANCER DRUG DELIVERY

1. *Limited tumor penetration:* While the EPR effect facilitates the accumulation of NPs in tumors, NPs often fail to penetrate deeply into tumor tissue. This limitation may reduce the overall effectiveness of therapy, particularly in well-placed or dense solid tumors.
2. *Penetration of the blood-brain barrier (BBB):* For cancers located in the brain, crossing the blood-brain barrier is a major obstacle. NPs designed for drug delivery to the brain must be able to cross the BBB without causing toxicity or immune reactions.
3. *Immunogenicity and elimination:* Since NPs are foreign objects, the immune system can recognize them as invaders and trigger an immune response. This can lead to the rapid elimination of NPs from circulation and decrease the therapeutic effect.
4. *Cost and regulatory issues:* Manufacturing and commercializing nanoparticle-based drug delivery systems require significant financial investment. In addition, regulatory hurdles related to safety and efficacy testing can delay the introduction of new treatments into clinical practice.

Future Directions of Nanotechnology for Anticancer Drug Delivery

Several exciting avenues are emerging that could shape the future of nanomedicine in cancer treatment:

1. *Personalized nanomedicine:* As we learn more about the molecular profiles of tumors, personalized nanomedicines tailored to specific genetic mutations and biomarker profiles may become the norm.
2. *Smart NPs:* Future developments may include NPs that respond to specific environmental signals in the tumor, such as changes in pH or temperature, for precise and controlled drug release.
3. *Combination therapies:* NPs can be used to deliver combinations of therapeutic agents, including chemotherapy, immunotherapy and gene therapy, to fight cancer on multiple fronts.
4. *Imaging and in vivo monitoring:* Advanced nanomaterials can enable real-time monitoring of drug delivery and therapeutic responses, thus enabling adaptive treatment strategies.
5. *Artificial intelligence in nanomedicine:* The integration of AI and machine learning in the design, synthesis and delivery of NPs could revolutionize the way nanomedicine is developed, improving its efficacy and safety profiles.
6. *Clinical trials and translation:* As more clinical trials investigate the use of NPs for drug delivery, the successful translation of these technologies into clinical practice is expected to increase, leading to better outcomes for cancer patients [28].

CONCLUSIONS

The comprehensive examination of nanotechnology in cancer diagnostics indicates a potential area for customized treatment. NPs offer distinct benefits in targeted drug delivery, advanced imaging tools, and novel treatment approaches, such as – photothermal therapy and controlled drug release. Their capacity to selectively target cancer cells while reducing adverse effects marks a paradigm leap in cancer treatment. However, challenges, such as - biocompatibility, toxicity, and integration with existing medicines remain, necessitating further research and development. Prospects lead to predictive oncology, where nanotechnology might play a critical role in early detection, precision therapy, and improved cancer outcomes. Nano-theranostics has the potential to transform cancer therapy by linking diagnostics and treatments, enabling more effective, less invasive, and highly tailored methods. Cancer, a life-threatening disease, can be effectively treated with new nano-technological approaches in the future, which will have a major clinical impact that will ultimately improve public health.

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