

Nanotechnology: A Promising Approach for Cancer Diagnosis, Therapeutics and Theragnosis

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Abstract: Cancer remains the most devastating disease and the major cause of mortality worldwide. Although early diagnosis and treatment are the key approach in fighting against cancer, the available conventional diagnostic and therapeutic methods are not efficient. Besides, ineffective cancer cell selectivity and toxicity of traditional chemotherapy remain the most significant challenge. These limitations entail the need for the development of both safe and effective cancer diagnosis and treatment options. Due to its robust application, nanotechnology could be a promising method for in-vivo imaging and detection of cancer cells and cancer biomarkers. Nanotechnology could provide a quick, safe, cost-effective, and efficient method for cancer management. It also provides simultaneous diagnosis and treatment of cancer using nano-theragnostic particles that facilitate early detection and selective destruction of cancer cells. Updated and recent discussions are important for selecting the best cancer diagnosis, treatment, and management options, and new insights on designing effective protocols are utmost important. This review discusses the application of nanotechnology in cancer diagnosis, therapeutics, and theragnosis and provides future perspectives in the field.

Keywords: cancer, nanotechnology, diagnosis, treatment, theragnostics

Introduction

Cancer is a very complex disease that develops through a multistep process which includes resistance to cell death (apoptosis), uncontrolled cell growth, alterations in cellular signaling, tissue invasion, metastasis, and angiogenesis.¹ Cancer generally begins as a localized tumor and can spread (metastasize) to distant sites in the body, making the management difficult. Cancer morbidity and mortality are on the rise across the world. According to global cancer incidence, mortality and prevalence (GLOBOCAN) 2018 data, the number of new cancer cases was expected to exceed 18.1 million, with 9.6 million cancer-related deaths.² The World Health Organization (WHO) estimated more than 19.3 million new cases and 10 million deaths from cancer in 2020.³ It is projected that 30 million people will die of cancer each year after 2030.⁴

Factors that enhance the emergence of cancer include rising pollution, radiation, sedentary life, unbalanced diet, infection with oncogenic microorganisms, and other variables (eg, heredity) which are also becoming common in developing countries. Any of these variables can cause a damage in host cells' deoxyribose nucleic acid (DNA) genes known as oncogenes that lead to cancer. Individual cells that have achieved immortality and are capable of replicating at incredible rates surpass all healthy functional cells resulting in death.⁵⁻⁹

Nanotechnology is the field that deals with atomic, molecular, and supramolecular levels of molecules (1–100 nm) to understand the properties that can be exploited for human well-being. Nanotechnology uses nanoscale principles and methods to know biosystems, and it is being emerged with modern biology and medicine to generate more nanoscale materials that can be used in biological systems.^{10,11}

Nanoparticles are used in medical applications because of their unique properties such as quantum properties, a surface-to-mass ratio much larger than that of other particles, and an adsorption capacity to transport other compounds such as probes, proteins, and drugs. The composition of nanoparticles can be varied, just as starting materials can be biological lipids, dextran, lactic acid, phospholipids, chitosan, or chemicals such as silica, carbon, metals, and different polymers.¹²⁻¹⁶

Imaging techniques and morphological study of tissues (histopathology) or cells (cytology) are currently used to aid in the early detection of cancer. Imaging technologies enable to see tissue alterations for the detection of cancer cells. However, due to the time demanding nature of these methods, cancer cells can have time to replicate and invade tissue. Furthermore, existing imaging technologies are unable to discriminate between benign and malignant tumors.¹⁷ Besides, cytology and histopathology cannot be used to diagnose cancer at an early stage in a reliable and independent manner. As a result, developing reliable methods that can detect cancer at an early stage is necessary.^{18–21}

Nanotechnology-based diagnostic technologies are being developed as promising tools for cancer diagnosis that are real-time, convenient, and cost-effective.²² Nanoparticles are being used to capture cancer biomarkers such as exosomes, circulating tumor cells, circulating tumor DNA, and cancer associated proteins for effective cancer diagnosis.^{20,23,24} The high surface area-to-volume ratio of nanoparticles in comparison to bulk materials is a key benefit for using them for cancer diagnosis.^{20,24–28} This characteristic allows for the dense coating of nanoparticle surfaces with antibodies, small molecules, peptides, aptamers, and other moieties to detect specific cancer molecules.^{28–31} Multivalent effects can also be achieved by exposing cancer cells to a variety of binding ligands, which can increase an assay's specificity and sensitivity.^{32–34}

Currently, chemotherapy, surgery, radiation, and a combination of these treatments are the most common methods of cancer treatment. However, these methods have significant drawbacks including, but not limited to, non-specificity and toxicity.^{35–38} The goal of modern medication is to optimize the pharmacological efficacy of drugs and minimize possible side effects. To avoid any unwanted responses, the drug's local concentration at cancer sites must be high, while its concentration in other tissues must be low.³⁹ The application of nanotechnology in cancer treatment holds the potential to overcome the constraints of the conventional methods. Using nanotechnology, the amount of drug required to provide a therapeutic impact can be considerably lowered, and the drug concentration on the cancer site can be boosted without having any negative effects on healthy cells.^{40–43}

Several nanoparticle-based drug delivery systems such as nano-discs, high-density lipoprotein (HDL) nanostructures, gold nanoparticles, and viral nanoparticles have demonstrated promising outcomes in cancer therapy. Auspicious progress has been achieved in understanding the biological characteristics of cancer to improve the usage of nanoparticles by overcoming biological barriers and distinguishing between malignant and healthy tissues. Nano-drugs offer a lot of potential in cancer therapy because of their unique qualities such as limiting damage to healthy cells, overcoming multidrug resistance (MDR), and improving anti-cancer drug solubility.¹⁹

Nanoparticles are used in medical applications because of their unique properties and due to their adsorption capacity to transport other compounds such as probes, proteins, and drugs.⁴⁴ The composition of nanoparticles can be varied, just as starting materials can be biological lipids,⁴⁵ dextran,⁴⁶ lactic acid,⁴⁷ phospholipids,⁴⁸ chitosan,⁴⁹ or chemicals such as silica,⁵⁰ carbon,⁵¹ metals,⁵² and different polymers.¹² Updating the available literature, summarizing new discussions, and adding new insights are very crucial to select the best options for cancer diagnosis and treatment. The main goal of this review is to summarize current advances in nanotechnology-based cancer diagnosis, therapeutics, and theragnostics. Further, current challenges and future perspectives are also discussed which could contribute to future studies working in the field.

Application of Nanotechnology for Cancer Diagnosis and Treatment

The unique features of nanoparticles led to their adoption in a variety of applications. Nanoparticles have a variety of shapes, sizes, and structures.⁵³ Nanoparticles have several auspicious advantages that they are multifunctional, they can deliver hydrophobic compounds, they can target disease cells actively and passively, they have the capacity to prolong the drug's circulation time, they can boost the entrance and accumulation of drugs in tumor sites, they overcome drug resistance, they promote the safety and tolerability of drugs, and they assist the improvement of other technologies.^{54,55}

Nanotechnology for Cancer Diagnosis

Although nanotechnology has yet to be used in clinical cancer detection, it is already applied in a range of medical tests and screens, such as gold nanoparticles in home pregnancy tests.⁵⁶ Nanoparticles are being used to capture cancer biomarkers including cancer-associated proteins,^{57,58} circulating tumor DNA (ctDNA),^{59,60} circulating tumor cells (CTC), and exosomes.^{61,62} Antibodies, small molecules, peptides, aptamers, and other compounds can be thickly coated on nanoparticle

surfaces because of this high surface area-to-volume ratio. Multivalent effects can be obtained by presenting multiple binding ligands to cancer cells, which can improve the specificity and sensitivity of diagnosis.²⁹

Nanotechnology for the Detection of Cancer Biomarkers

A cancer biomarker is a detectable biological molecule present in the blood, various tissues, and body fluids including saliva and urine that indicates the presence of cancer cells in the body.¹⁹ Proteins (released proteins or cell surface proteins),⁶³ carbohydrates,⁶⁴ or nucleic acids (ct DNA, micro-RNA, etc.)⁶⁵ are all examples of cancer biomarkers that are secreted by the body or cancer cells during carcinogenesis.⁶⁶ Measurement of cancer biomarker levels aids in the early detection of cancer or tumor recurrence as well as the monitoring of therapeutic efficacy.

Nanotechnology provides excellent selectivity and sensitivity, as well as the capacity to assess numerous targets at the same time. Nanoparticles/nanomaterials can be used to improve biosensors and offer more precise targeting.⁶⁷ Furthermore, the introduction of nanoparticles increases the surface-to-volume ratio of biosensors, making them more sensitive to the demands of certain biomolecular diagnostics.⁶⁸ The three most frequent nanoparticle probes employed in cancer diagnosis are quantum dots (QDs), gold nanoparticles (AuNPs), and polymer dots (PDs).⁶⁹ Different cancer markers can be used in nanotechnology. The following markers are among the examples.

Protein Detection

CEA for colorectal cancer,⁷⁰ AFP for liver cancer,⁷¹ PSA for prostate cancer,^{72,73} and CA-125 for ovarian cancer⁷⁴ are among the protein markers that have received approval for cancer detection. The identification of these traits can be aided by specific interactions with antibodies, antibody fragments, or aptamers.⁷⁵ After then, the interaction event will be turned into a measurable signal.⁷⁶ QDs have unique features such as high quantum yield and molar extinction coefficient, wide absorption, excellent photobleaching resistance, and outstanding degradation resistance.^{77,78} QD-based biosensors have been utilized to detect cancer biomarkers in recent investigations.⁷⁹ QDs conjugated with aptamers were applied to detect CA-125 biomarker for ovarian cancer⁷⁴ while QD-embedded silica nanoparticles were used to detect PSA antigens with lateral flow technique.⁸⁰ QDs were also used to detect CEA^{81–83} and AFP antigens.^{84,85} Generally, a sandwich-type test, which includes a biomarker, a capture antibody, a second capture antibody, and a secondary antibody that binds to the capture antibody, is a typical approach for detecting protein biomarkers.¹⁸ Various approaches, like staining and fluorescence, can be used to visualize the secondary antibody.⁸⁶ Aptamers, which are single-stranded DNA (ssDNA) or RNA sequences that can be extracted via ligand systematic evolution and exponential enrichment (SELEX), can also be attached to nanoparticles. Aptamers can attach to their targets such as ions, bacteria, peptides, viruses, phospholipids, and even complete cells) with high affinity and strong binding specificity.⁸⁷

Circulating Tumor DNA Detection

Tumor-derived DNA fragments (about 100–200 base pairs long) circulate in the bloodstream as circulating tumor DNA (ctDNA). Cancer-specific genetic abnormalities can be detected using ctDNA, which can be secreted from primary tumors or circulating tumor cells (CTCs).^{19,88,89} The detection of genetic abnormalities in ctDNA can aid in the detection of cancer even before any symptoms appear.⁹⁰ To detect cancer-related genetic abnormalities, highly specific hybridization with nucleic acid probes having complementary sequences can be utilized. For the detection of a single exon in the BRCA1 gene in breast cancer, a DNA silver nanocluster (NC) fluorescent probe was designed. This probe significantly raised the limit of detection (LOD) under optimal conditions. Large deletion mutations in BRCA1 were discovered using nanocluster fluorescence produced by recognition hybridization.⁹¹

MicroRNA Detection

Micro-RNAs (miRNAs) are naturally occurring ssRNAs with 20–22 nucleotide sequences long and have the capacity to bind with mRNA and repress its translation. A single miRNA can regulate many gene expressions, and a single mRNA can be targeted with many miRNAs.⁹² These genetically encoded regulatory molecules support gene expression that controls cell proliferation, growth, and apoptosis. The normal cellular function will be compromised as the synthesis of miRNAs is dysregulated, which finally leads to cancer. Oncogenic viruses cause cancer by affecting the regulation of

miRNAs in different ways including upregulating the miRNA of the host to activate the proliferation of virally infected cells, encoding viral miRNAs that target the host cell mRNA, and minimizing the host miRNA that has a role in tumor suppression.⁹² Detection of miRNA has a good advantage in that circulating miRNAs are more stable. Moreover, a simple blood sample can be used because RNase enzyme activity does not affect these miRNAs.⁹³ Different tissue or organ-specific miRNA markers can be used for early diagnosis, prognosis, and therapy monitoring.⁹⁴

DNA Methylation Detection

The genome methylation landscape (Methylscape) has recently been identified as a common feature of most types of malignancies, suggesting that it could be used as a cancer biomarker. In a study, the authors used DNA-gold affinity and DNA solvation to find differences between cancer and normal genomes, and then, they could develop simple, rapid, selective, and sensitive electrochemical or colorimetric one-step assays to diagnose cancer.⁹⁵

Extracellular Vesicle Detection

Extracellular vesicles (EVs) are circulating vesicles (30nm–1µm in size) that package molecular information from mother cells, such as miRNA, DNA, protein, and mRNA, and allow the detection of tumor cells at molecular state that are usually difficult to access. Scientists created a unique magnetic nanopore capture approach to isolate specific subsets of EVs from plasma in a recent work.¹⁹

Nanotechnology for Detection of Cancer Cells

Detection of Circulating Tumor Cells

Metastasis is responsible for approximately 90% of solid tumor mortality. During metastatic dissemination, a cancer cell from the primary tumor first invades the surrounding tissue, then enters the blood and lymph systems' microvasculature (intravasation), followed by survival and translocation through the bloodstream to micro-vessels in distant tissues. Finally, these cells exit the bloodstream (extravasation) and survive in the distant microenvironment, which provides a suitable foreign microenvironment for the development of secondary tumors. The early diagnosis of metastatic cancer cells in the bloodstream, CTCs, can have a significant impact on cancer prognosis and diagnosis.⁹⁶

CTCs have been examined extensively as part of a liquid biopsy due to their potential applications. CTC detection is a minimally invasive method for understanding the molecular organization of tumors. Despite this, CTCs have a low abundance and variability, posing technological obstacles for CTC isolation and characterization. Researchers have focused on the use of nanotechnologies for sensitive detection of CTCs in recent years; these technologies can help characterize cells and molecules, resulting in a wide range of clinical applications, such as disease detection at an early stage and evaluation of treatment response and disease progression.¹⁹

Nanomaterials have an important advantage for CTC detection in that they have a large surface-to-volume ratio, which allows for the adsorption of high-efficiency targeting ligands that can recognize specific molecules on cancer cells. As a result, CTC isolation has high specificity and recovery, and the sensitivity of detection is improved.¹⁹

Different types of nanomaterials have been described for CTC detection, including magnetic nanoparticles (MNPs), AuNPs, QDs, nanowires, nanopillars, silicon nanopillars, carbon nanotubes, dendrimers, graphene oxide, and polymers. These nanomaterials have been shown to improve the sensitivity and specificity of CTC collection devices, with the potential to aid cancer detection and prognosis⁹⁷ (Table 1).

Detection of Cell Surface Proteins

Binding of nanoparticle probes coupled with moieties (proteins, short peptides, antibodies, oligonucleotide aptamers) to surface markers on cancer cells and those entering cells and detecting genetic content is the major method for detecting cancer cells. The first and most crucial step in detecting cancer cells, such as CTCs, is to capture or isolate them. Although physical features of cells such as size, deformability, and density are sometimes exploited, cell capture is primarily dependent on the affinity of cell surface chemicals for CTCs as measured by antibodies or aptamers. The major targets are CTCs' unique surface proteins (eg, EpCAM). EpCAM can be employed as a cell surface biomarker because it

Table 1 Nanotechnology for Detection of Cancer Cells

Nanoparticle	Type of Probe	Specific Ligand	Type of Cancer	Reference
Magnetic nanoparticle	Antibody	EpCAM	Colon/liver/lung/breast	[149]
Quantum dots	Aptamer	PTK7	Leukemia	[150]
Polymer dots	Antibody	EpCAM	Breast	[151]
Gold nanoparticle	Aptamer	Her2	Breast	[152]
	Antibody	Cd2/Cd3	Leukemia	[153]
Carbon nanotubes	Antibody	EpCAM	Liver	[154]
Upconversion NPs	Antibody	Her2	Breast	[155]
Nanorod arrays	DNA aptamers	EpCAM	Breast	[156]
NP-coated silicon bead	Antibody	EpCAM/CD146	Breast, colorectal	[97]
Nanofibers	Antibody	EpCAM	Breast	[22]

has been shown in numerous studies to be significantly expressed on CTCs from a variety of human cancers. As a result, anti-EpCAM compounds are frequently used in CTC screening.¹⁹

mRNA-Based Detection

Nanoparticles have also been produced to detect intracellular nucleic acids in addition to external nucleic acids. Seferos et al⁹⁸ showed that transfection agents and cellular “nanoflares” can be used to detect mRNA in living cells using novel gold nanoparticle probes modified by oligonucleotides hybridized to complements tagged with a fluorophore. Nanoflares overcome many obstacles in the development of effective and sensitive intracellular probes. Nanoflares are effective for detecting intracellular mRNA because they have a high orientation, dense oligonucleotide coating, and they may penetrate cells without a harmful transfection agent.⁹⁸ Figure 1 describes the application of nanoparticles in cancer diagnosis.

Nanotechnology for Cancer Therapy

Due to their unique properties and suitable features, nanoparticles are ideal means of delivering treatment. For drug delivery, the size of the nanoparticles should be less than 0.1 μm . The composition of nanoparticles can be varied, just as starting materials can be biological lipids, dextran, lactic acid, phospholipids, chitosan, or chemicals such as silica, carbon, metals, and different polymers. The interactions of biological components of nanoparticles are different from those of non-biological components. Biodegradable nanoparticles are needed in drug delivery to transport the drug and release it at the target site.¹²

Surgery, chemotherapy, and radiation are currently available and frequently used cancer therapy methods. However, they all not only kill cancer cells but also normal cells, and this is the main and foremost drawback of current cancer therapy. Nanoparticles are non-toxic, chemically stable, and biocompatible materials in nature, and this nature enables them to be selected as an efficient drug delivery tool.³⁹

Recently, nanotechnology and nanoparticles have attracted great interest in cancer therapeutics as they can provide improved and targeted drug delivery systems to overcome the drawbacks of conventional chemotherapy.⁹⁹ Limitations of chemotherapy include inefficient drug delivery at the target site due to physical and biochemical barriers and drug resistance at the tumor level because of cellular and non-cellular mechanisms that limit drug action resulting in recurrence and high mortality.

Poorly developed vascularized tumor regions and tumor microenvironment are the main mechanisms that impede drug access to tumor tissue and reduce drug efficiency. Similarly, increased interstitial pressure and decreased microvascular pressure may also delay the extravasation of drug molecules.¹⁰⁰ To overcome these limitations, the development of nanoscale delivery vehicles for anticancer drugs with nanoparticles could address the pharmacokinetic disadvantages of traditional chemotherapy.⁹⁹

The main goals of nanotechnology in drug delivery include specification of drug delivery, reducing toxicity along with maintaining therapeutic effects, safety, biocompatibility, and improving the production of new facial drugs. The fundamental knowledge required before selecting suitable carriers as a drug delivery system includes drug uptake and release, stability and shelf life of drug and carrier, biocompatibility, bio-distribution of the drug and carrier, and mode of action of the drug.¹²

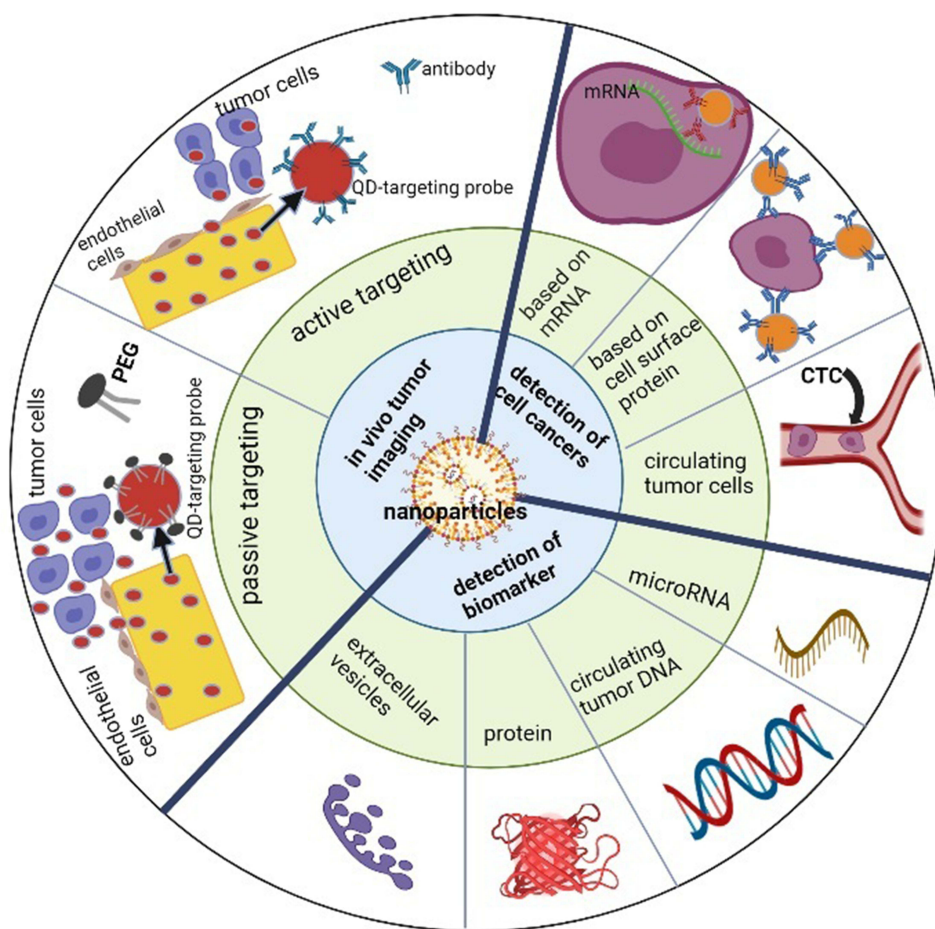


Figure 1 Schematic illustration of nanotechnology applications in cancer diagnosis. Nanotechnology-based diagnostic technologies are being developed as promising tools for cancer diagnosis and detection that are real-time, convenient, and cost-effective. Adapted from Zhang Y, Li M, Gao X, Chen Y, Liu T. Nanotechnology in cancer diagnosis: progress, challenges and opportunities. *Journal of Hematology & Oncology*. 2019;12(1):137. <https://creativecommons.org/licenses/by/4.0/>.¹⁴⁶

Viral nanoparticles are naturally biocompatible and encode their building instructions using the host cell's resources. Their packaging abilities are promising when it comes to delivering chemotherapy to tumors. PEGylation, in turn, can be applied to enhance viral survival from the immune system, and its natural host specificity can be exploited in fighting tumors.³⁹

Virus-like particles (VLPs) are constructs that can be engineered for just such purposes without concern for the actual viral infection of the whole organism.¹⁰¹ The cowpea mosaic virus has recently become of interest because it does not contain nucleic acid material. It is empty, which means that its use should not have any harmful effects like the virus strain does, and therefore it can be safely introduced into a living organism.

It has been found that injection or inhalation of this VLP into a tumor microenvironment can induce an immune response that releases large amounts of neutrophils. These recruit cytokines and T lymphocytes to invade and attack metastatic cancer cells. This yields a result ranging from delayed metastasis to the complete elimination of cancer cells. This method does not require the insertion of an anti-cancer drug. Rather, it simply uses our natural defense mechanisms against cancer cells. Prospects are high and under-development, although the extensive study has not yet been conducted.³⁹

Nano-diamonds are microscopic carbon-based agents that have numerous biological applications because of their extremely high biocompatibility as compared to other nanoparticles similar in size. They can be used as biomarkers and tracers that mark cancer or loaded with doxorubicin and deliver it to metastatic tumor cells. Chan and his research group¹⁰² have used nano-diamonds to not only target cancer cells but also to deliver doxorubicin directly into the mitochondria once inside. This kills the cell by eliminating its energy source, consequent inhibition of growth, reproduction, and normal cell function. Cancer cells that are typically resistant to doxorubicin (eg, MCF-7) can still be targeted by nano-diamonds by specifically targeting the mitochondria rather than the whole cell in general.¹⁰²

Nanotechnology has paved a new insight into cancer immunotherapy. The multifunctional nature of nanoparticles enables an improved way to deliver different antigens, nucleic acids, and antibodies.¹⁰³ Nanotechnology has been used to load synthetic or natural molecules that have a crucial role in restoring the immune system's anti-tumor function. Small molecular inhibitors, antibodies, and proteins that target programmed cell death protein 1 (PD 1)¹⁰⁴ and cytotoxic T-lymphocyte associated protein 4 (CTLA 4)¹⁰⁵ have shown promising results in recent years.¹⁰⁶ Nanoparticles can be used as vehicles for these immunotherapeutic agents such as cancer vaccines, cytokines, and adoptive cellular therapies to fight cancer.

DNA and RNA-based cancer treatment with gene therapy becomes a promising tool in recent days. However, challenges such as solubility, permeability, lack of target specificity, and stability faced this technique. Moreover, nucleic acid is an extremely negatively charged and hydrophilic structure that makes it be easily digested with enzymes and cleared with renal elimination. Nanotechnology has become a good tool to address these challenges.^{107,108} Organic nanoparticles including lipid-based nanoparticles, prodrug-based nanoparticles, and lipid-polymer hybrid nanocarriers and inorganic nanoparticles like QDs, AuNPs, and silica-based nanoparticles have been used to deliver siRNAs.^{100,109} Combination therapy (chemotherapy combined with wild-type p53) encapsulated with nanoparticles also showed a better result.¹¹⁰ CRISPR/Cas9 gene-editing system delivered with nanoparticles has also shown promising advancement in cancer therapy in recent years.¹¹¹

Drug Targeting Mechanism in Cancer Nanotechnology

There are two models of drug targeting mechanisms: passive targeting and active targeting. In passive targeting, the reason behind enhanced permeability and retention (EPR) based drug targeting is the rapidly growing leaky vascularization and defective lymphatic drainage that contributes to the retention of nanoparticles and submicron particles in tumors. Nanoscale drug carriers, which include liposomes, dendrimers, polymeric micelles, polymer-drug conjugates, and inorganic nanoparticles, are being extensively studied in drug delivery for this specific approach in cancer chemotherapy.¹¹² These nanoparticles pass through hyper-permeable blood vessels and, due to their small size (typically between 1 nm and 200 nm), preferentially accumulate at the tumor site through their EPR effect.¹¹³

The basis of the active targeting strategy involves the interaction of a ligand-loaded drug carrier with surface-exposed receptors on the target cells, which aids in their accumulation in a tumor and also aids in their intracellular accumulation through receptor-mediated endocytosis.¹¹⁴ Tumor cells are normally overexpressed with one or more types of specific receptors that can act as target sites for active targeting by ligand-functionalized nanoparticles. Due to this reason, an active targeting approach uses cellular targets to recognize the tumor and endothelial cells,^{115,116} as illustrated in Figure 2.

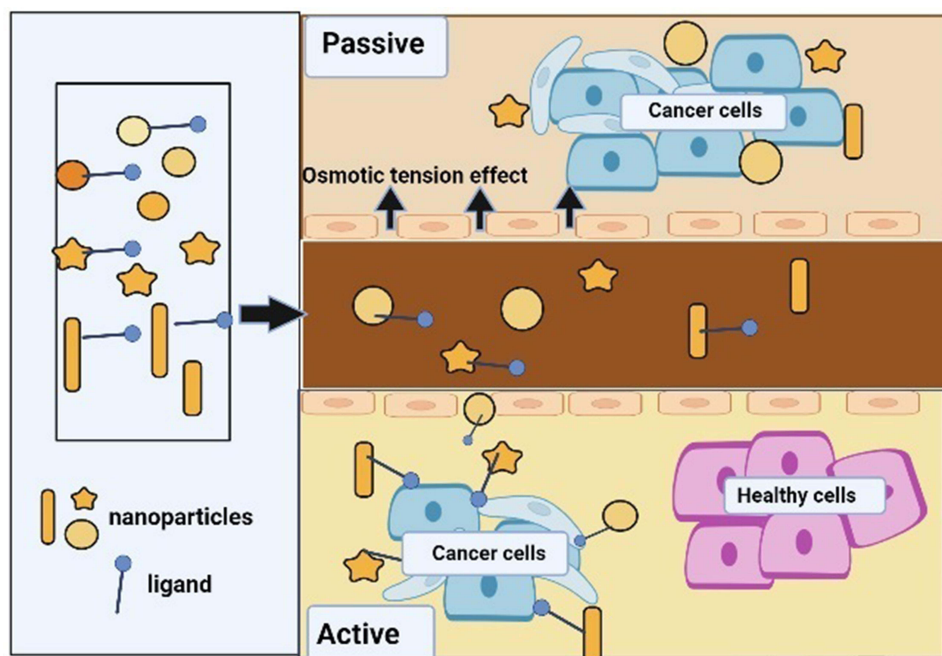


Figure 2 Passive and active drug targeting mechanism. Adapted from Jin C, Wang K, Oppong-Gyebi A, Hu J. Application of Nanotechnology in Cancer Diagnosis and Therapy - A Mini-Review. International Journal of Medical Sciences. 2020;17:2964–2973. <https://creativecommons.org/licenses/by/4.0/>.¹⁴⁷

The Concept of Theragnosis

The term “theragnosis” refers to the integration of imaging/diagnostic and therapeutic capabilities on a single platform, with the imaging/diagnostic agent and therapeutic agent being delivered in a single dose with an integrated system to diagnose, treat, and monitor therapeutic response at the same time.^{117,118} Theragnostic nanoparticles are multifunctional nano-systems that combine diagnostic and therapeutic properties into a single biocompatible and biodegradable nanoparticle. They are well designed for more specific disease management.¹¹⁹ Theragnostic nanoparticles need to be safe for human beings and have the following capabilities: (1) accumulate in target(s) sites selectively and rapidly; (2) indicate morphological and biochemical features of the disease; (3) effectively deliver an appropriate amount of drug(s) required with no harmful effect on healthy organs; and (4) eliminated from the body within hours or biodegraded into non-toxic by-products.¹¹⁹

The diagnostic and therapeutic abilities of nanoparticles can be combined in a single system for theragnosis (illustrated in Figure 3). These multifunctional nanoparticles are expected to propel medication research to new heights while minimizing risks and costs. Nanoparticles with hydrophilic and hydrophobic surfaces can now be manufactured using new polymerization and emulsifying processes, allowing them to be loaded with a variety of active compounds (ie, a contrasting agent of hydrophobic nature while a therapeutic agent of hydrophilic nature and vice versa).¹¹⁵

Cancer theragnosis is a new concept in cancer nanotechnology that is proving to be very useful for both clinicians and patients. Nanotechnology’s main goal is to enable nanoparticle-based agents to deliver payload (radioisotopes, medicines, genes, etc.) efficiently and selectively while avoiding systemic toxicity, and to accurately monitor non-invasively delivered therapeutic efficacy over time.¹²⁰

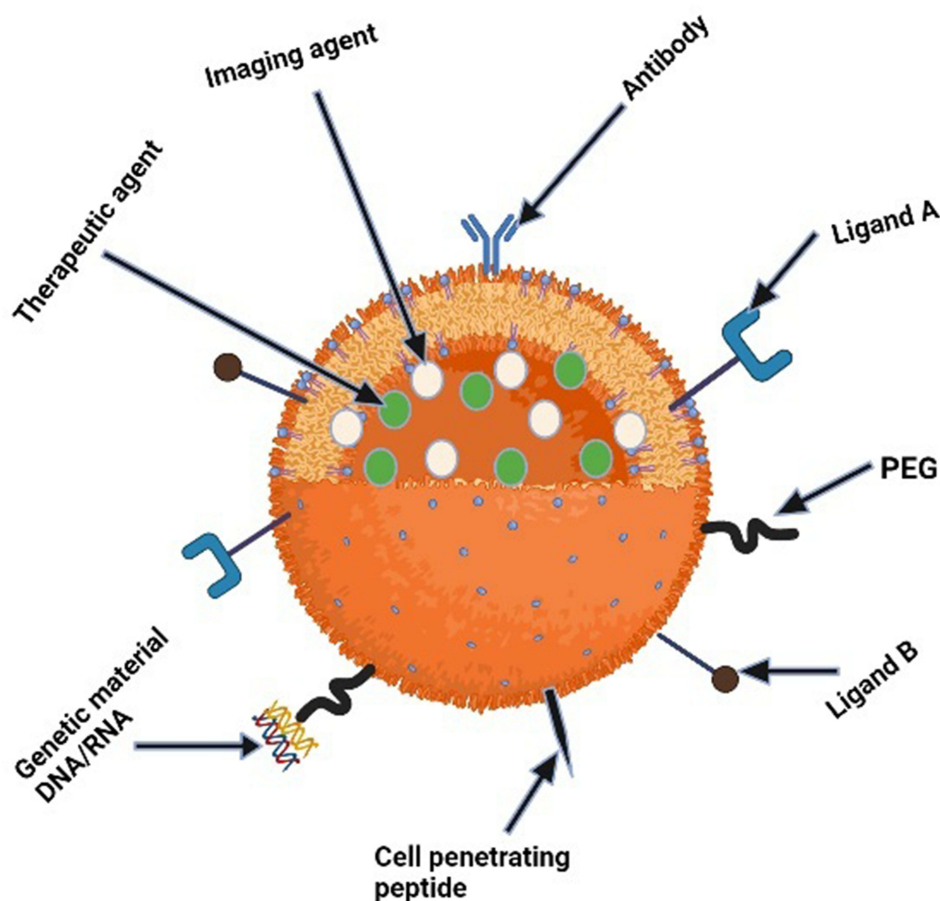


Figure 3 A schematic representation of theragnostic nanoparticles (diagnostic and therapeutic agents in a single NP). Adapted from Alshehri S, Imam SS, Rizwanullah M, Akhter S, Mahdi W, Kazi M, et al. Progress of cancer nanotechnology as diagnostics, therapeutics, and theranostics nanomedicine: preclinical promise and translational challenges. *Pharmaceutics*. 2020;13(1):24. <https://creativecommons.org/licenses/by/4.0/>.¹⁴⁸

Nanotechnology has established itself as a possible aid in cancer treatment due to its wide range of applications. Gold nanoparticles, QDs, carbon nanoparticles, silver nanoparticles, and Chitosan-based nanoparticles (CNPs) have all been created into multimodal theragnostic nanoparticles with targeting, imaging, and therapeutic characteristics. Theragnostic nanoparticles (similar to nanoparticles), are administered to tumor sites through active and passive targeting.¹²¹

Theragnostic nanoparticles conjugated with a specific ligand of cancer cells can be targeted actively, whereas theragnostic nanoparticles are passively targeted by extravasation of nanoparticles from a leakier tumor blood artery and accumulating at the tumor location via the EPR effect. Cancer theragnostic nanoparticles can be generated by encapsulating anti-cancer drugs with nanoparticles that are labeled with noninvasive imaging modalities such as MRI, CT, and PET.¹²¹

Non-invasive imaging methods in cancer diagnosis aid in early detection, targeted drug delivery, and cancer therapy monitoring. Chemotherapy, photo thermal therapy, and siRNA/miRNA therapy are a few examples of cancer therapies being extensively studied with theragnostic nanoparticles.^{122–128}

Furthermore, theragnostic nanoparticles could aid in the assessment of a patient's optimal anti-cancer treatment dosage and tumor growth monitoring.¹²⁹ A rush of research activity in the creation of theragnosis nanoparticles has led to the use of novel optical imaging modalities such as fluorescence resonance energy transfer (FRET) to monitor the drug release behavior of nanoparticles at selected tumor sites. As a result, continued progress in the development of cancer theragnostic nanoparticles will pave the way for a new era in cancer diagnosis and treatment.¹²⁷

The designed theragnostic nanocarriers have the possibility to be targeted, non-targeted, or stimuli based. A targeting ligand is added to the targeted theragnostic carriers, which can bind to overexpressed receptors in tumor cells. Antibodies can also be used to target cancer cells although their immunogenicity and big size make them difficult to penetrate into tumor cells.¹³⁰ Because of their smaller size and lesser immunogenicity, peptides are useful as theragnostic carriers. The enhanced permeability effect is the main principle of non-targeted theragnostic carriers. The tumor microenvironment, which includes hypoxia and low extracellular pH, are the main advantages of stimuli-based theragnostic nanocarriers.¹³¹

Discussion and Future Perspective

Nanotechnology is the best approach to deal with the diagnosis and treatment of cancer. Besides, theragnosis has become an emerging novel approach for the safe and efficient diagnosis and treatment of malignancies.¹³² It offers a number of benefits, including improved detection, targeted drug delivery to tumor cells, and lessened fatal effects on healthy tissues.¹³³ These theragnostic methods combine targeted drug delivery with diagnostic imaging techniques. Additionally, by utilizing specialized probes, imaging approaches can assess the efficacy of drugs during the drug development process, maximizing the choice of imaging tools and agents in addition to choosing the best combination for various therapeutic applications.^{134,135} Nanotechnology has shown a devastating improvement in aiding conventional therapy such as photothermal therapy.^{121,136} Although significant progress has been seen in nanotechnology-based cancer diagnostics and treatment, only a few cases have progressed to clinical trials.^{137,138} To apply nanotechnology in cancer diagnosis and therapeutic practice, many hurdles must be overcome.

Reliability is the primary difficulty in nanotechnology-based cancer diagnosis. To apply nano-based technologies in diagnostic centers, it is mandatory to obtain a consistent result. NP-based detection signals can be influenced by a variety of circumstances such as nonspecific NP probe binding, aggregation, and unsuitable detection.¹³⁹ Reliability and reproducibility of assays must be considered and thoroughly examined with big clinical sample pools in clinical trial application. In this regard, continuous effort is necessary to overcome these hurdles.

The second difficulty is to produce nanoprobe in large amounts that are highly sensitive, repeatable, and have long-term storage stability at an affordable price. Most of the today's nanoprobe are made in labs under highly optimized settings; yet, producing these probes in batches remains a significant difficulty. The detection efficiencies vary substantially due to the composition, size, shape, charge, and surface coating of nanoprobe. The synthesis procedures and nanoprobe functionalization must be simplified to reduce batch-to-batch variations. Furthermore, nanoprobe tend to aggregate during storage. It is also necessary to evaluate the cost-effectiveness of developing a nanotechnology-based platform.¹⁴⁰

The third difficulty is to create NP-based devices that are very sensitive, easy to handle and use, and cost-effective. Although many NP-based tests were developed in academic laboratories, many of them are unsuitable for clinical use.

The successful development of nanoparticle-based point-of-care devices will substantially simplify the clinical application of nanotechnology in cancer diagnostics.¹⁹

The fourth challenge is the potential for nanoparticle toxicity due to systemic administration. This problem is largely about in-vivo NP-based imaging. The potential toxicity of new nanoparticle probes should be examined before they are used in-vivo imaging. The toxicity of nanoparticles is influenced by their shape, size, charge, surface chemistry, targeted ligands, and composition. The biodistribution, biodegradability, and pharmacokinetic features of nanoparticles should also be taken into account.¹⁹

Cancer biomarkers can be used for the diagnosis of cancer at early time. Nonetheless, various obstacles have hampered the use of biomarkers, including low biomarker concentrations in body fluids, variation in biomarker abundance and timing within patients, and the difficulty of conducting prospective research.¹⁴¹

Nanotechnology has been used extensively in a wide range of cancer diagnosis and therapeutic investigations, and it may provide a good alternative to cancer diagnosis and treatment soon.^{142,143} Although much research has been done in the field of cancer nanotechnology to date, there is still a remaining scrutiny to fully understand the scenario. Despite the difficulties, the promise of nanomaterials in cancer diagnosis and therapy is undeniable, and continued progress in the field of nanomaterials would give a significant cancer detection and treatment method. Furthermore, the synthesis of a successful multimodal nanoparticle must be highlighted, as this might provide cancer with a double punch in terms of rapid diagnosis and effective therapy.¹⁴³

The future of nanotechnology depends on the development of multi-functional nanoplatforms that combine therapeutic capabilities with multimodal imaging capabilities. To overcome the challenges of cancer heterogeneity and adaptation, such coordination of detection capability with therapeutic interventions is required.¹⁴⁴ The nanocarriers' small size is a significant benefit since they can quickly permeate the tumor vasculature and be kept due to the EPR effect.¹⁴⁵ Cancer nanotechnology will undoubtedly deliver a robust, effective, reliable, and safe cancer detection and treatment solution soon.

Although nanotechnology is a promising approach for tackling cancer through effective drug delivery and early diagnosis, there are still several hurdles to deal with. More controlled and longitudinal studies are quite helpful to tackle the limitations of nanotechnology-based cancer diagnosis and treatment. Efforts making reliable application of nanotechnology are utmost important; thus, multidisciplinary and comprehensive studies are required. Nanotechnology-based applications in cancer management should also be affordable and accessible to developing countries.

Concluding Remarks

Many efforts have been in place in the last decade to create nanotechnology-based cancer diagnosis and treatment. Compared to currently existing cancer diagnostics in the clinical settings, several NP-based assays improved selectivity and sensitivity or provided whole new capabilities that could not be attained by the traditional methods. Nanotechnology, with its high sensitivity, specificity, and multiplexed measuring capabilities, has tremendous potential for improving cancer detection and therapy, resulting in a higher cancer patient survival rate. One of the greatest advantages is the combined application of diagnosis and treatment in a single platform (theragnosis). Overall, nano-oncology has opened an unlimited number of possibilities for finding and designing drugs and drug delivery systems for cancer treatment. In contrast to the outstanding advantages of nanotechnology in cancer management, the technology has its own drawbacks, mainly possible toxicity, resource intensiveness, unproved reliability and applicability. Therefore, continuous effort is required to improve these limitations to apply the platform in clinical decision-making.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that there are no conflicts of interest.

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