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NANOPARTICLE MEDIATED DRUG DELIVERY SYSTEMS FOR CANCER TREATMENT

Chapter 8: Metallic and Magnetic Nanoparticle in Oncology

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Abstract

The highly interesting physicochemical properties of metallic and magnetic nanoparticles and their multifunctional application have propelled them into the modern oncology arena as promising diagnostic and therapeutic agents. However, the nanomaterials, such as gold, silver, iron oxide, and other metal-based nanoparticles, have proven to be very useful in the field of diagnosis, imaging, delivery and therapy of cancer. Their small size, large surface area and ease of surface modification means that therapeutic agents can be targeted to tumour tissues, limiting the systemic toxicity and enhancing the efficacy of the treatment. Magnetic nanoparticles, specifically super paramagnetic particles of iron oxide (SPIONs), have been highlighted for their magnetic resonance imaging (MRI) uses, magnetic targeting, and the hyperthermia treatment of cancer. Gold nanoparticles are commonly studied for Photothermal therapy, radio sensitization and bio sensing purposes. In addition, nanoparticle systems can optimize anticancer drug bioavailability and may provide for slow or sustained release. Moreover, the recent developments in nanotechnology have allowed the development of multifunctional platforms to integrate diagnostic and therapeutic activities into a single nanostructure called theranostic platforms. In spite of all these developments, issues concerning the long-term toxicity, biocompatibility, bio-distribution, and clinical approval are relevant considerations for Clinical Translations. On-going research and innovations are necessary to get more and new applications, the best design of nanoparticles, and progress to make them safe in applications for personalized cancer therapy. In conclusion, metallic and magnetic nanoparticles are a revolutionary solution in the field of oncology, with the potential to revolutionize cancer diagnosis and treatment.

Keywords: Metallic nanoparticles, Magnetic nanoparticles, Oncology, Gold nanoparticles, Nanomedicine.





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1. Introduction

1.1 Nanotechnology in Medicine

Nanotechnology is an interdisciplinary subject with applications, design, synthesis, characterization and application of materials and devices ranging in size from 1 to 100 nanometres (nm). The physical, chemical, optical and magnetic properties of materials are very different at this scale as compared to those of bulk materials. The special properties have led to the development of new applications in a variety of biomedical areas including diagnosis, imaging, drug delivery, tissue engineering and treatment of disease. The merging of nanotechnology and healthcare has resulted in the birth of a new field called nanomedicine, which seeks to harness the power of nanotechnology to create novel tools and materials for prevention, diagnosis and treatment. Nanomedicine has numerous benefits compared to traditional treatment methods, including increased drug solubility, increased bioavailability, ability to control drug release rate, ability to target drug delivery and decreased systemic toxicity. The advantages of nanotechnology have opened up the possibility of using the technology to solve intricate medical problems, such as cancer treatment [1, 2].

1.2 Role of Nanoparticles in Oncology

Tremendous progress has been made in diagnosis and therapy of cancer but it remains a leading cause of death in the world today. The use of traditional cancer treatment methods like surgery, chemotherapy, and radiotherapy has disadvantages, such as the nonspecific targeting of cancer cells, toxicity to healthy tissues, resistance, and low efficacy. In this context, nanoparticles have been identified as promising instruments to tackle these challenges and enhance the treatment results in cancer. Nanoparticles can be targeted to tumour tissue with a greater quantity of therapeutic agents (passive or active) than normal tissue. They exhibit a large surface area and their surfaces are modifiable for the binding of drugs, antibodies, peptides, nucleic acids or imaging agents that makes them versatile platforms for diagnosis and therapy. Nanoparticles are used in oncology for tumor imaging, early cancer detection, targeted drug delivery, photo thermal therapy, magnetic hyperthermia, gene therapy, immunotherapy and theranostic applications. They have facilitated the combination function in one system approach for the development of personalized/precision treatment of cancer [3,4].

1.3 Types of Metallic and Magnetic Nanoparticles

Metallic and magnetic nanoparticles represent two important classes of nanomaterials extensively investigated for oncological applications [5,6,7].

Table 1 Classification of Metallic and Magnetic Nanoparticles

Category	Nanoparticle Type	Key Properties	Applications in Cancer Research and Therapy
Metallic Nanoparticles	Gold Nanoparticles (AuNPs)	Excellent optical properties, high biocompatibility, easy	Used in medical imaging, targeted drug delivery, photothermal therapy,





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		surface functionalization, strong light absorption	biosensing, and radiosensitization to enhance radiotherapy effectiveness.
	Silver Nanoparticles (AgNPs)	Strong antimicrobial activity, high surface reactivity, ability to generate reactive oxygen species (ROS)	Applied in anticancer therapy through induction of oxidative stress, apoptosis, and inhibition of tumor cell proliferation.
	Platinum Nanoparticles (PtNPs)	High catalytic activity, antioxidant and redox properties, enhanced cellular interactions	Investigated for improving chemotherapy effectiveness, inducing cancer cell death, and enhancing therapeutic responses.
	Palladium Nanoparticles (PdNPs)	Excellent photothermal conversion efficiency, catalytic properties	Utilized in photothermal therapy, drug delivery systems, and tumor-targeted treatments.
	Copper Nanoparticles (CuNPs)	Cost-effective, catalytic and antimicrobial properties	Explored for anticancer therapy, drug delivery, and generation of reactive oxygen species to destroy tumor cells.
	Titanium Dioxide Nanoparticles (TiO₂ NPs)	Photocatalytic activity, chemical stability, UV light responsiveness	Used in photodynamic therapy, cancer imaging, and targeted therapeutic applications.
	Zinc Oxide Nanoparticles (ZnO NPs)	Selective toxicity toward cancer cells, ROS generation, biocompatibility	Applied in cancer diagnosis, drug delivery, and induction of apoptosis in tumor cells.
Magnetic Nanoparticles	Superparamagnetic Iron Oxide Nanoparticles (SPIONs)	Strong magnetic responsiveness, superparamagnetic behavior, excellent biocompatibility	Widely used in MRI contrast enhancement, targeted drug delivery, magnetic hyperthermia, and cancer diagnosis.





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	Cobalt-Based Nanoparticles	High magnetic strength, strong magnetic anisotropy	Investigated for magnetic drug targeting, imaging applications, and hyperthermia treatment; require surface modification to improve biocompatibility.
	Nickel-Based Nanoparticles	Strong magnetic properties and catalytic activity	Studied for specialized biomedical applications, targeted therapy, and diagnostic imaging; toxicity concerns limit widespread use.
	Hybrid Magnetic Nanoparticles	Combination of magnetic cores with metallic, polymeric, or biological coatings	Provide multifunctional capabilities including targeted drug delivery, MRI imaging, theranostic, bio sensing, and magnetic hyperthermia.

2. Fundamentals of Nanoparticles

2.1 Definition

Nanoparticles are very small particles that are between 1 and 100 nanometres (nm) in diameter. The small size leads to the unique physical, chemical, optical, electrical and magnetic properties of nanoparticles that are different from bulk materials. Nanoparticles are used in oncology for diagnosis, imaging, drug delivery and therapy. The optical properties of metallic nanoparticles, including gold nanoparticles, silver nanoparticles, and platinum nanoparticles, are extremely interesting, as are the magnetic properties of magnetic nanoparticles, especially super paramagnetic iron oxide nanoparticles (SPIONs). These properties can be used to target a tumour precisely, to improve the imaging properties and to increase the effectiveness of treatment. There are some key properties of nanoparticles which are:

- High surface-area-to-volume ratio
- Improved reactivity and functionalization ability
- Adaptable size and shape
- Therapeutic and diagnostic agent carrying ability.
- Better penetration into tumour tissues
- Controlled and targeted drug delivery ability.





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Such properties make the metallic and magnetic nanoparticles very promising tools for cancer nanomedicine [8-11].

2.2 Physicochemical Properties

Biological effects of nanoparticles are heavily dependent on their physicochemical characteristics. They interact with biological systems based on a number of parameters including their size, shape, composition, surface charge and magnetic properties.

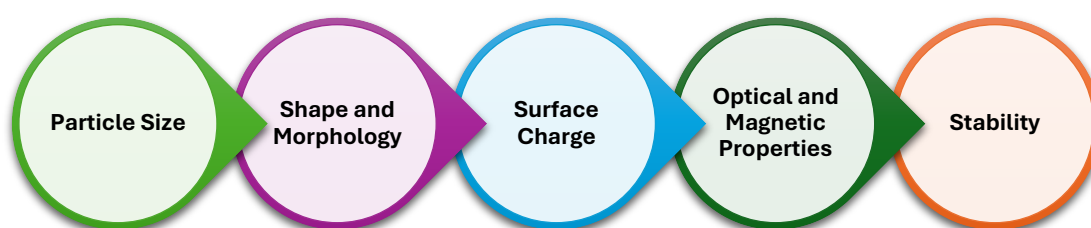


Fig.1. Physicochemical Properties of Nanoparticles

a. Particle Size: Cellular Uptake, Circulation Time and Tumor Accumulation are influenced by the size of the nanoparticles. Particles in the range of 10–100 nm are generally regarded as optimal for cancer applications since they are known to take advantage of the Enhanced Permeability and Retention (EPR) effect, which results in selective accumulation in the tumor tissue.

b. Shape and Morphology: Nanoparticles can be synthesized in different shapes such as spheres, rods, cubes, stars and shells. Shape affects the behavior of the circulation, internalization of cells, and therapy. For instance, gold nanorods have a higher photothermal conversion efficiency than spherical nanoparticles.

c. Surface charge: Surface charge has an impact on the stability of nanoparticles and their interaction with cell membranes. As the cell membranes have a negative charge, positively charged nanoparticles tend to have better cellular uptake as a result of electrostatic attraction. Too much positive charge can lead to greater toxicity and faster clearance, though.

d. Optical and Magnetic Properties: Metallic nanoparticles have interesting magnetic and optical properties like surface Plasmon resonance, which is significant in imaging and Photothermal therapy. Magnetic nanoparticles have super paramagnetic properties, which makes them controllable with the help of magnets and allows their use in targeted drug delivery and magnetic resonance imaging (MRI).





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e. Stability: It's critical to maintain the stability of the nanoparticles during storage and circulation to ensure their functionality. The stable nanoparticles do not aggregate and have a stable physicochemical property under physiological conditions [12,13].

2.3 Surface Modification and Targeting

A key approach to improve the efficacy of metallic/magnetic nanoparticles in cancer diagnosis and therapy is to modify the surface. Nanoparticles exhibit physicochemical characteristics that are distinct from those of their bulk counterparts, which make them applicable in biomedical fields, however, direct delivery of the nanoparticles into the body may result in rapid clearance by immune system, a low level of tumour accumulation and toxicity. These limitations are overcome by functionalization of the surfaces of the metallic nanoparticles (gold, silver) and magnetic nanoparticles (super paramagnetic iron oxide nanoparticles (SPIONs) and others) with the help of biocompatible materials, polymers, antibodies, peptides, and targeting ligands. Surface engineering increases the stability of nanoparticles, extends the blood circulation time, increases the tumor targeting, decreases the immune recognition and increases the therapeutic efficacy. These changes allow nanoparticles to be utilized as a powerful drug delivery system, imaging agent and therapeutic molecule, and thus play a significant role in today's oncology.

Polyethylene Glycol (PEG) Coating

One of the most widely used surface modification methods for metallic and magnetic nanoparticles is the coating with polyethylene glycol (PEG) commonly referred to as PEGylation. PEG is a hydrophilic polymer to coat the surface of nanoparticles and prevent aggregation and interaction with plasma proteins. The protective coating helps to avoid recognition by the mononuclear phagocyte system (MPS), which would lead to rapid clearance. With gold nanoparticles and magnetic iron oxide nanoparticles, PEGylation extends blood circulation, which is long enough to make the nanoparticles accumulate in tumor areas via the Enhanced Permeability and Retention (EPR) effect. Oncology is an example of a field where nanoparticles with PEG coatings have shown to have greater efficiency in drug delivery, better imaging capabilities and lower toxicity. Besides, PEGylation makes nanoparticles more biocompatible and more stable under physiological conditions, making it a popular approach in cancer nanomedicine.

Active Targeting

Active targeting is a novel strategy that boosts the selectivity of the targeting of the nanoparticles to the cancer cells. This approach is based on the attachment of certain targeting ligands on the surface of the NP that can recognize and bind to receptors that are over-expressed on tumor cells. After binding, the nanoparticles could be internalized into the cancer cells via receptor-mediated endocytosis, which leads to increased penetration of drugs into the cell.

Monoclonal Antibodies

To obtain a highly specific targeting to cancer cells, monoclonal antibodies are often attached to metallic nanoparticles and magnetic particles. Gold nanoparticles and SPIONs can target





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tumour-associated antigens and carry therapeutic agents directly to the tumour site. These methods help increase the specificity of treatment, and reduce the damage to normal cells.

Peptides

Peptides are short amino acid chains which bind selectively to receptors expressed on cancer cells. The small size of peptide-modified nanoparticles along with their superior tissue penetration ability allow for superior tumor targeting and cellular uptake. Tumor-targeting peptides have been functionalized for gold nanoparticles, which have demonstrated great potential in cancer imaging and targeted therapy.

Aptamers

Aptamers are synthetic nucleic acid molecules with high affinity to cell-specific targets. The combination of aptamers with metallic and magnetic nanoparticles has excellent targeting ability with low immunogenicity. Increasingly these systems are being explored for precision drug delivery and cancer diagnostics.

Folic Acid

Folic acid is one of the most incisive targeting ligands used in oncology in view of the known high expression of Folate receptors on multiple cancer cells. Selective targeting of tumors occurs for folic acid-functionalized gold nanoparticles and magnetic nanoparticles, increasing the efficiency of drug delivery and minimizing effects on the rest of the body.

Transferrin

The iron needed for cancer cell growth and proliferation is often high, which results in the overexpression of transferrin receptors. This property can be utilized to target and deliver therapeutic agents to tumor tissues by using transferrin as a coating agent for the nanoparticles [14, 15].

2.4 Biocompatibility and Bio distribution

Biocompatibility is the capacity of nanoparticles to interact with biological systems without causing a significant toxicity or adverse immune response. Safety is an important research priority as nanoparticles are to be used in clinical applications. Factors Influencing Biocompatibility The biocompatibility of a nanoparticle depends on several factors:

- Chemical composition
- Particle size and shape
- Surface charge
- Coating materials

The route of exposure, along with the dosage and duration of exposure. Gold nanoparticles are generally considered to be very biocompatible and chemically inert, while the nanoparticles of silver can produce oxidative stress at higher concentrations. Iron oxide nanoparticles are considered safe as iron can be metabolized by the normal physiological pathways.

Bio distribution





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Bio distribution refers to the pathway of nanoparticles in the body following their introduction into the body. After systemic injection, nanoparticles can be delivered to organs like tumour tissues, spleen, lungs, kidneys and liver.

The Bio distribution is influenced by several factors:

- Nanoparticle size
- Surface chemistry
- Blood circulation time
- Route of administration
- Tumor vascularization

The Enhanced Permeability and Retention (EPR) effect permits nanoparticles to selectively target tumors, which have more leaky blood vessels and fewer lymphatics.

Clearance Mechanisms

Nanoparticles are excreted by the body via the mononuclear phagocyte system (MPS), hepatic metabolism or renal excretion. To minimize potential long-term toxicity and clinical safety, it is important to understand these clearance routes. In general, the physicochemical properties, surface modifications, biocompatibility and biodistribution of the metallic/ magnetic nanoparticles are critical in the determination of their efficacy as diagnostic and therapeutic agents in oncology [9,16,17].

3. Metallic Nanoparticles in Oncology

Gold Nanoparticles (AuNPs): They are nanosized particles of gold, usually 1-100nm in diameter. They have unique physicochemical properties which are different from those of the bulk gold, and they are used in scientific and technological applications.

Properties of Gold Nanoparticles (AuNPs)

1. Unique Optical Properties: Gold nanoparticles have some properties of localized surface plasmon resonance (LSPR) that allow them to absorb and scatter light strongly. This property is very useful for cancer imaging, biosensing and Photothermal Therapy in oncology.

2. High Surface Area-to-Volume Ratio: AuNPs have a high surface area to volume ratio, which means that they can be coated with anticancer drugs, antibodies, peptides and targeting ligands. This enhances selective delivery of therapeutic agents to tumor cells.

3. Chemical Stability: Gold nanoparticles are also stable against oxidation and corrosion, which is important for maintaining their stability in biological systems and for applications involving cancer.

4. Biocompatibility and Low Toxicity: AuNPs are highly biocompatible and have relatively low toxicity, allowing them to be safely used as diagnostic, imaging, and therapeutic agents in cancer treatments without harming normal tissues.





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5. Tunable Size and Shape: Gold nanoparticles can be synthesized as nanospheres, nanorods, nanoshells or nanostars. They can be tailored to be smaller and more targeted to the tumor, enabling more cellular uptake and therapeutic efficacy.

6. Easy Surface Functionalization: AuNPs surface can be easily functionalized with antibodies, tumor-specific ligands, DNA and polymers, and thus actively targeted to cancer cells and personalized cancer therapy [18,19].

3.1 Applications of Gold Nanoparticles (AuNPs) in Oncology

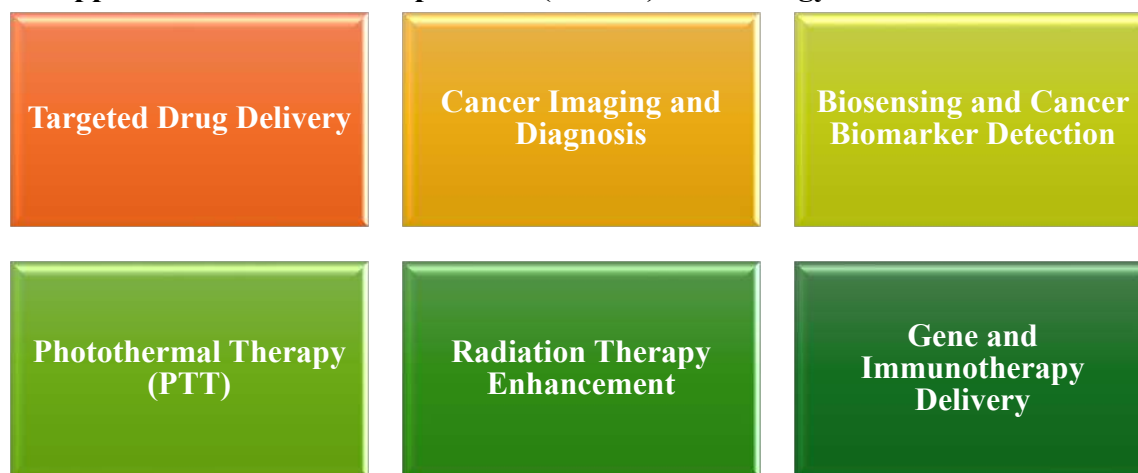


Fig. 2 Applications of Gold Nanoparticles (AuNPs) in Oncology

1. Targeted Drug Delivery: Gold nanoparticles are widely used as nanocarriers for anticancer drugs. They have the capability to accumulate specifically in tumors, which helps to increase the amount of a substance in the tumor area and decrease the systemic toxicity and side effects.

2. Cancer Imaging and Diagnosis: AuNPs are used as "contrast agents" in computed tomography (CT) imaging, optical imaging, and photoacoustic imaging for cancer diagnostics. They allow earlier detection and correct diagnosis of tumors.

3. Bio sensing and Cancer Biomarker Detection: Gold nanoparticle-based biosensors can be used to detect cancer biomarkers, circulating tumor cells and genetic mutations with high sensitivity and rapid speed, aiding in early diagnosis and monitoring of disease.

4. Photo thermal Therapy (PTT): One of the most significant oncological applications of AuNPs is known as Photo thermal Therapy (PTT). When AuNPs are exposed to near-infrared (NIR) light, the energy of light is transformed into heat, and can selectively destroy cancer cells without harming neighboring healthy cells. Gold nanoparticles' high atomic number allows radiation absorption enhancement in tumors

5. Radiation Therapy Enhancement: his enhances the effects of radiotherapy and makes cancer cells more vulnerable to radiotherapy.





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6. Gene and Immunotherapy Delivery: Gold nanoparticles are being studied as vehicles for genes and siRNA and immunotherapeutic agents. They enhance delivery and effectiveness of advanced cancer treatment options [19,20,21].

3.2 Silver Nanoparticles (AgNPs): Anticancer Activity

The reactivity of silver nanoparticles (AgNPs) with the production of reactive oxygen species (ROS) is the main cancer inhibitory property of AgNPs. These ROS cause oxidative stress resulting in DNA damage, mitochondrial dysfunction, cell cycle arrest and apoptosis to cancer cells. AgNPs have been found to have efficacy against a number of cancers, such as breast, lung, liver, prostate, and colorectal cancers. Furthermore, chemotherapeutic drugs can be made more effective by using silver nanoparticles. With some toxicity concerns and possible adverse effects on normal tissues, however, careful optimization of particle size, dosage and surface modification is needed prior to clinical use. Nanoparticles of metallic elements other than Iron and Cobalt. Other metallic nanoparticles e.g. Platinum.

3.3 Platinum and Other Metallic Nanoparticles

Platinum nanoparticles (PtNPs) have been found to be promising nano-carriers for cancer therapy, which exhibit both catalytic activity and improved drug transportation capabilities along with low systemic toxicity. They promote the accumulation of drugs in the tumour tissues and boost the effectiveness of chemotherapy. Besides platinum, several other metallic nanoparticles are being explored for oncological applications. Palladium nanoparticles have very good characteristics to use in cancer photothermal therapy due to their high photothermal properties and thermal stability. Copper nanoparticles are also used for drug delivery and thermal therapies, and are replacing gold nanoparticles at lower cost. Titanium dioxide nanoparticles have been used in photodynamic therapy due to their capacity to produce ROS upon activation by light, and zinc oxide nanoparticles have selectively killed cancer cells by oxidative stress mechanisms [17,22,23].

3.4 Role of Metallic Nanoparticles in Diagnosis and Therapy

The use of metallic nanoparticles is of paramount importance for cancer diagnosis and treatment. Their use in diagnostics enhances the sensitivity and accuracy of imaging techniques like computed tomography (CT), optical imaging and biosensor-based detection systems. They help in early detection of cancer biomarkers and monitoring the disease. From a therapeutic perspective, metallic nanoparticles can serve as efficient drug delivery vehicles for targeted delivery of anti-cancer agents leading to controlled and sustained drug release. They are also used in photo thermal therapy, photodynamic therapy, radiotherapy enhancement and chemotherapy. Additionally, metallic nanoparticles enable the creation of theranostic systems that integrate the diagnostic and therapeutic functions in a single platform, enabling real-time tracking of therapeutic efficacy. Metallic nanoparticles have multifunctional properties that are useful in the development of precision oncology and clinical applications [19,20,24].





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4. Magnetic Nanoparticles in Oncology

4.1 Iron Oxide Nanoparticles (SPIONs)

Super paramagnetic nanoparticles of iron oxide (SPIONs) are the most popular magnetic nanoparticles in oncology because of their good biocompatibility and biodegradability, and magnetic responsiveness. Usually, these nanoparticles are constructed with a magnetic core material, such as magnetite (Fe_3O_4) or maghemite ($\gamma\text{-Fe}_2\text{O}_3$), and exhibit superparamagnetic properties, which means that they are magnetized only when a magnetic field is applied, but lose any magnetism when the magnetic field is removed. SPIONs are widely used as contrast agents for magnetic resonance imaging (MRI), providing better imaging of tumors and metastatic lesions. Moreover they can also be used as efficient drug transporters, into which targeted drugs are loaded and directed to the desired tumor location by the application of external magnetic fields. SPIONs are also used in magnetic hyperthermia therapy, which involves using a magnetic field to induce localized heating that can be used to target cancer cells without harming surrounding healthy tissue. These have become valuable parts of the modern day cancer nanomedicine and have been found to possess both diagnostic and therapeutic properties.

4.2 Other Magnetic Nanomaterials

Besides iron oxide nanoparticles, various other magnetic nanomaterials have been explored for cancer diagnosis and therapeutic applications. The magnetic properties and magnetic saturation of cobalt-based nanoparticles are quite strong; thus they can be used for imaging and therapeutic applications. Their biomedical applications are, however, limited by their potential toxicity, requiring protective surface coatings. Nickel-based nanoparticles also are known to possess high magnetic properties and have been investigated for targeted drug delivery and bio sensing applications, but biocompatibility issues have arisen. The hybrid magnetic nanoparticles (MNP) are composed of magnetic cores coated with metallic, polymeric or silica shells, which have enhanced stability, low toxicity and multifunctionalities. Such hybrid system can be used simultaneously for imaging, drug delivery and therapeutic functions, and are promising candidates for advanced cancer treatment strategies. The magnetic properties of the materials and their applications in biomedical sector.

4.3 Magnetic Properties and Biomedical Applications

The unique magnetic properties of magnetic nanoparticles play a crucial role in their biomedical applications. The ability to respond to external magnetic fields gives them control over their movement and localization in the body. Magnetic nanoparticles can be targeted to tumor tissue using magnetic targeting, thereby delivering a higher amount of the drug to the tumor site and therefore minimizing the side effects from the drug in the body. They enhance contrast in diagnostic imaging, such as MRI, to ensure precise detection and monitoring of tumors. In therapeutic purposes, magnetic nanoparticles are employed in magnetic hyperthermia, which generates heat in the alternating magnetic field and causes the death of





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cancerous cells. Moreover, magnetic nanoparticles are increasingly used in the areas of biosensors, cell separation methods, gene delivery systems and theranostics, combining diagnosis and treatment. The versatile properties of magnetic nanoparticles open the door to magnetic nanoparticle applications that are important to the advancement of personalized and precision oncology [8,16,25].

5. Mechanisms of Action in Oncology

5.1 Passive and Active Targeting

Selective accumulation of metallic and magnetic nanoparticles in tumor tissues via passive and active targeting is the key of their effectiveness in oncology. Passive targeting is mainly based on the Enhanced Permeability and Retention (EPR) effect resulting from the disordered blood vessel architecture of tumors. Typically, tumors have leaky vasculature with large fenestrations and poor lymphatic drainage, and it is this that enables nanoparticles with a size appropriate to the interstitium (often 10–200 nm) to accumulate. Passive accumulation involves building up of the drug in the local area without the need of specific molecular recognition. In contrast, active targeting is through surface modification of the nanoparticles with specific ligands like antibodies, peptides, aptamers, or low molecular weight molecules that have a high affinity for overexpressed receptors on cancer cells. Typical targets are: Folate receptors, transferrin receptors, and epidermal growth factor receptors (EGFR). Upon binding to these receptors, the nanoparticles are then internalized via receptor-mediated endocytosis, increasing cellular uptake and therapeutic specificity. The magnetic nanoparticles can also be directed by the application of an external magnetic field, leading to an increased efficacy in targeted delivery.

5.2 Cellular Uptake Mechanisms

Nanoparticles enter into the tumor cell by several endocytic routes once at the tumor site. The most frequent mechanism is by endocytosis, which involves the Cathrin mediated, caveolae mediated, and micropinocytosis pathways. Uptake varies, depending on the size, shape, surface charge and surface coating of the nanoparticles. For example, smaller nanoparticles are taken up more effectively by Cathrin mediated endocytosis, larger or surface modified nanoparticles by micropinocytosis. Once internalized, the nanoparticles are usually contained in endosomes and can be transported to lysosomes, where the acid environment might induce the release of the drug from the surface of the nanoparticles. In certain instances, nanoparticles will be able to leave endosomal compartments and deliver their therapeutic agents directly into the cytoplasm, making them more effective. Changing the surface properties with PEGylation or ligand conjugation can have a profound effect on cellular uptake efficiency and intracellular trafficking behaviour.

5.3 Interaction with the Tumour Microenvironment

The tumour microenvironment (TME) is a key factor in nanoparticle distribution, activity and response to therapy. The TME is a complex system consisting of cancer cells, stromal cells, immune cells, extracellular matrix (ECM), blood vessels and signalling molecules. It is





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hypoxic, acidic, has elevated interstitial fluid pressure, and abnormal vascular structure, which all affect the behavior of nanoparticles. The tumor microenvironment is affected by nanoparticles in several manners. Their small size enables them to enter tumor tissues and surface modifications can help with retention and stability inside the TME. It is possible to release drugs only at the tumor site by using acid pH-responsive nanoparticles, and thereby enhance the selectivity of the treatment. Moreover, nanoparticles can alter the function of immune cells in the TME, which can either be pro- or anti-tumoral. Magnetic nanoparticles can also be steered externally to reduce high interstitial pressure to enhance tumor penetration. In addition, nanoparticles can modulate the functions of tumor-associated macrophages, fibroblasts and angiogenic pathways, and thus modulate the pathways of the tumor progression. Nanoplatfroms that help to normalize tumor vasculature or change the extracellular matrix to allow for better penetration of drugs and increased efficacy have been developed. Overall, interactions with the tumor microenvironment can greatly improve the efficacy of nanoparticle-based cancer therapeutics, and are likely to be an increasingly important part of precision oncology [4,9,13,14,26].

6. Diagnostic Applications

1.	MRI and CT Imaging
2.	Optical Imaging Techniques
3.	Biosensors and Early Cancer Detection

Fig. 3 Diagnostic Applications of Nanoparticles

6.1 MRI and CT Imaging

Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) imaging are two of the most important diagnosis tools used in modern medicine. MRI involves powerful magnets and radio waves to produce very detailed images of the soft tissues, organs, muscles and nervous system. Non-invasive imaging, without the need for patients to be exposed to the effects of X-rays or other forms of radiation, can be used to provide clear images of the body, including high-resolution images of the brain, spinal cord, joints, and cardiovascular system, which are useful for diagnosing various diseases. X-rays and a computer are used in CT imaging to create cross-sectional views of the body. CT scans are very useful for identifying fractures, bleeding, tumors, lung disease, or abnormalities in the organs. The treatment of advanced medical conditions requires the use of nanoparticles or contrast agents to increase the clarity of images and to make parts of the body or diseases more visible. Physicians can use these imaging techniques to learn more about early disease detection, disease monitoring and disease treatment planning.





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6.2 Optical Imaging Techniques

Optical imaging techniques involve the use of light, including visible, UV and near-infrared, to image biological tissues and cellular structures. These techniques are commonly applied in medical diagnostics due to their real-time, non-invasive and highly sensitive imaging capabilities. Typical optical imaging techniques include fluorescent imaging, optical coherence tomography (OCT), confocal microscopy and photo acoustic imaging. Fluorescence imaging is a technique that involves the use of fluorescent dyes or nanoparticles that specifically bind to cells or markers, allowing the detection of diseases at the molecular level, such as cancer. In ophthalmology, OCT is often employed to inspect the retina, and to diagnose eye diseases like macular degeneration and glaucoma. Optical imaging has several benefits such as high spatial resolution, low damage to tissue and real-time observation of biological processes. Improvements in optical imaging have been made recently with the help of nanotechnology that has increased the image contrast, sensitivity and ability to detect diseased tissues.

6.3 Biosensors and Early Cancer Detection

A biosensor is an analytical device comprised of a biological recognition component and a transducer to detect specific biological molecules, pathogens, or chemicals. They are essential in diagnostics and disease surveillance for fast, accurate and economical detection of biomarkers. Biosensors can detect cancer at its earliest stages by identifying extremely low concentration of cancer related biomarkers in blood, saliva, urine, or tissue samples, which is important in cancer diagnostics. The use of nanomaterials like gold nanoparticles, carbon nanotubes, quantum dots and graphene has greatly enhanced the sensitivity and specificity of biosensors based on nanotechnology. The sophisticated biosensors can identify molecular changes that occur in the body before there are any signs of a cancer, providing early intervention for better treatment outcomes. Also, biosensors enable point-of-care testing, which minimizes elaborate laboratory procedures and speeds up clinical decision-making. With the on-going development of research, biosensors are anticipated to play a greater role in personalized medicine and early disease diagnosis in the future [9,23-26].

7. Therapeutic Applications

7.1 Targeted Drug Delivery

Targeted drug delivery is an innovative therapeutic method that allows the precise delivery of a drug to a particular diseased tissue or cells, with minimal exposure of healthy tissue. The traditional approach to drug administration involves distributing the drug throughout the body, which can result in side effects and inefficiency in the treatment. Nanotechnology-based drug delivery systems include nanoparticles, liposomes, dendrimers and polymeric carriers, which selectively carry therapeutic agents to the target site. They can be designed to target particular biomarkers or receptors that are over-expressed on diseased cells, especially cancer cells. This results in increased levels of the drug being delivered to the affected area, enhancing the effectiveness of treatment, while minimizing the toxicity and adverse effects. One of the most





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promising applications of modern nanomedicine is targeted drug delivery, which has a great potential for the treatment of cancer, cardiovascular diseases, neurological diseases and infectious diseases.

7.2 Photothermal Therapy

Photothermal therapy (PTT) is one of the minimally invasive treatment methods, which involves the use of light-absorbing materials, usually nanoparticles, to heat and eliminate diseased cells. This involves targeting nanoparticles like gold nanorods or nanoshells or carbon-based nanomaterials to the tumor tissue by delivering them into the body. These nanoparticles absorb the near-infrared (NIR) light and convert the light into heat when exposed to it. Localized heat increases the temperature and damages or destroys cancer cells, but does not harm or destroy surrounding healthy tissue. Photothermal therapy has many merits such as high precision, less side effects, and the capability to treat the tumors that are not easy to access in surgery. Combination treatments with chemotherapy and immunotherapy are also being investigated in conjunction with the photothermal therapy to improve overall therapy.

7.3 Magnetic Hyperthermia

Magnetic hyperthermia is a novel technique in cancer therapy, where magnetic nanoparticles are used to heat the cancer cells. The first method involves infusion of magnetic nanoparticles typically iron oxide into the tumor. These nano-particles generate heat under application of alternating magnetic field due to magnetic energy conversion. The resulting rise in temperature, usually in the range of 42°C – 46°C, can cause damage to or destroy cancerous cells and increase their sensitivity to other forms of treatment, like chemotherapy or radiotherapy. The heat is produced inside the tumour making healthy tissues less damaged. The concept of magnetic hyperthermia has attracted a great deal of interest as a localised and less invasive therapeutic approach, especially for solid tumour and recurrent cancer therapy.

7.4 Radiotherapy Enhancement

Radiotherapy is a common treatment for cancer, which uses ionizing radiation to kill cancer cells. One of the biggest problems of radiotherapy is however, to ensure that the tumor receives enough radiation, while at the same time reducing the radiation dose to healthy tissues. The answer lies in nanotechnology, by using nano-sized particles that are able to sensitize the tumor, such as gold nanoparticles, hafnium oxide nanoparticles, and other high atomic number materials. These Nano-particles enter the tumour's and increase the uptake of the radiation, leading to generation of more reactive oxygen species, and hence to more damage to DNA in cancerous cells. As a result, the destruction of tumors is enhanced with minimal radiation exposure of nearby normal tissues. Nanotechnology can improve the efficacy of radiotherapy, decrease side effects and improve the survival of patients.





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7.5 Gene and Immunotherapy Delivery

Gene therapy and Immunotherapy are two new and advanced treatments for genetic disorders, cancers and a range of chronic diseases. One big hurdle in these therapies is the delivery of genetic material or immune modulatory agents in a safe and efficient manner to target cells. The protection of therapeutic molecules from degradation and delivery into targeted cells by nanotechnology-based systems are effective solutions. Nanoparticles may be used to deliver DNA, RNA, small interfering RNA (siRNA), messenger RNA (mRNA) or gene editing tools like CRISPR-Cas9 straight to target tissues. Immunotherapy involves the use of nanoparticles to carry antigens, vaccines, cytokines or immune checkpoint inhibitors to boost the body's immune response against cancer and infectious diseases. These sophisticated delivery systems boost the effectiveness of therapy, minimize side effects, and pave the way for customized treatment plans. The success of mRNA vaccine technology has also clearly shown the great potential of nanotechnology in the field of gene and immunotherapy [27-30].

8. Theranostic Applications

8.1 Combined Diagnosis and Treatment

Theranostics is the new and developing field in nanomedicine which unites diagnosis and therapy in the same platform. Theranostics refers to the combination of therapeutics and diagnostics of the word, as it is used to detect the disease and to provide treatment at the same time. Typical medical treatment uses distinct treatment and diagnosis methods, which may be time consuming and less effective. Theranostic systems however can allow healthcare practitioners to detect the location, size and progression of a disease, and provide targeted treatment, on site, as it happens. Nanoparticles are especially important for theranostic applications since they can be designed to include imaging agents as well as therapeutic drugs. A single nanoparticle could carry an anticancer agent and a contrast agent for Magnetic Resonance Imaging (MRI) or for fluorescence imaging. Once inside, the nanoparticle localizes at the disease site to enable the doctors to see the affected tissue with imaging and then deliver the treatment directly to the target cells. The result is more accurate treatment, decreased healthy tissue damage and decreased side effects in the body. In addition, theranostic systems provide real-time data on therapeutic response, enabling clinicians to adapt their therapeutic approach. These features are especially beneficial in the field of cancer care, where timely diagnosis, accurate drug administration, and monitoring treatments can lead to better patient outcomes.

8.2 Multifunctional Nanoparticle Platforms

Multifunctional nanoparticle platforms are advanced nanomaterials with the ability to carry out multiple biomedical tasks in a single platform. These nanoparticles combine multiple elements such as targeting ligands, imaging agents, therapeutic agents, and protective coatings to improve diagnostic and therapeutic efficacy. Multifunctional nanoparticles can specifically recognize diseased cells, provide detailed imaging information, deliver therapeutic agent and





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monitor the effectiveness of treatment, depending on the design. The most prevalent multifunctional nanoparticles are liposomes, polymeric nanoparticles, dendrimers, gold nanoparticles, magnetic nanoparticles, quantum dots, and hybrid nanoparticles. They can be designed to have surface molecules that are selectively bound to disease-specific biomarkers, for targeted delivery to diseased tissue. Techniques like MRI, CT, positron emission tomography (PET) and optical imaging allow imaging components like fluorescent dyes, magnetic materials, or radioactive tracers to be seen. At the same time, therapeutic agents like chemotherapeutic drugs, genes, proteins or photosensitizers can be delivered on the same nanoparticle platform. One of the most important benefits of the multifunctional nanoparticles is their capacity to offer customized and precision medicine. These nanoparticles combine the diagnosis and the targeted therapy with the monitoring of the treatment in a single device, thus improving the effectiveness of the treatment and its reduction of adverse effects. For example, multifunctional nanoparticles have been used in cancer treatment to detect tumour's, to target and release anticancer drugs directly to the tumor cells, to produce heat for Photothermal therapy, and to image the treatment outcome. These platforms hold potential for future advancements in advanced healthcare and personalized medicine, with on-going research focused on enhancing their safety, biocompatibility, and clinical performance [31-33].

9. Toxicity and Safety Considerations

The growing nanotechnology advancements in the field of medicine have provided great potential for diagnosis, treatment, and monitoring of diseases. The characteristics of nanomaterials, however, are also unique physical, chemical, and biological attributes that raise important issues of safety and potential toxicity. The very small size and enormous surface area to volume ratio of nanoparticles can allow them to have a different interaction with biological systems compared to traditional materials. Hence, prior to their extensive use in the clinic there is a need for a complete knowledge of their toxicity, biodistribution, metabolism, and long-term effects. The careful consideration of these safety aspects will help to make sure nanomedicine products offer therapeutic benefits without causing adverse effects in the patient.

9.1 Cytotoxicity and Biocompatibility

Cytotoxicity means to cause the death of living cells; biocompatibility means that a substance is able to exist in the body without causing any undesirable biological reaction. They are some of the most important parameters for evaluating the risk of nanomaterials for medical use. Several factors have to do with the cytotoxicity of nanoparticles, such as size, shape, surface charge, chemical composition, concentration of exposure, and length of time exposed. Certain nanoparticles can cause oxidative stress by producing ROS that can damage cells, cause inflammation or mutations in DNA, or trigger programmed cell death (apoptosis). Biocompatibility is essential as nanoparticles can be directly exposed to blood, tissues and organs. Any nanoparticle that is biocompatible should not provoke too strong an immune response, allergic reactions, or toxicity to the tissue. In order to make the nanoparticles more





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compatible with the biological system, the surface of the nanoparticles is often modified with biocompatible polymers, such as polyethylene glycol (PEG) or natural biomolecules. These surface modifications not only minimize adverse reactions; they also increase circulation time in the blood stream and reduce immune recognition. To make nanoparticles suitable for clinical applications, they need to be subjected to extensive in vitro and in vivo studies and shown to be biocompatible and non-toxic. Maintaining a successful therapeutic efficacy and biological safety is still a major goal in nanomedicine research.

9.2 Biodistribution and Clearance

Biodistribution is the distribution of nanoparticles in the body after administration and clearance is the mechanisms by which nanoparticles are removed from the body. An understanding of these processes is important for determining the efficacy of therapy and possible toxic effects. Once within the body, the particles could travel through the bloodstream and deposit in other organs, such as liver, spleen, kidneys, lungs or bone marrow. They are affected by particle size, shape, surface properties and the route of administration. Foreign particles are recognized and removed by a body structure called the reticuloendothelial system (RES), or mononuclear phagocyte system. This means that large proportions of the nanoparticles are quickly cleared by macrophages in the liver and spleen and therefore may not reach the target tissue. Scientists have tried to overcome this limitation by creating surface modifications that allow nanoparticles to avoid being targeted by the immune system and stay in circulation for longer. The mechanisms of clearance are usually renal elimination or biliary elimination or metabolic degradation. The very small sized nanoparticles can be filtered by kidneys and excreted in urine, while larger particles are processed by liver and excreted via bile. Efficient clearance is significant as it is possible that the long-term accumulation of nanoparticles within organs can raise the risks of toxicity and damage to the tissues. Thus, one of the most important challenges in the field of Nanomedicine is designing nanoparticles that can be predicted to have a desired biodistribution, while maintaining predetermined safe elimination.

9.3 Long-Term Safety Concerns

A number of nanomaterials have been shown to be effective for certain short-term therapies, but their long-term safety is being investigated. Some nanoparticles may be able to remain in tissues and organs for long periods of time because they degrade slowly or are not well eliminated. The long-term retention is a concern for chronic toxicity, inflammation, organ dysfunction and potential carcinogenic effects. The fear is that nanoparticles might be slowly concentrated in particular organs like the brain, lungs, spleen, and liver. This accumulation can over time disrupt the normal cellular functioning and cause damage. Some nanoparticles can also penetrate biological barriers, like the blood–brain barrier and placental barrier, which could lead to neurological effects and potential fetal development risks. Furthermore, chronic





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effects for some nanomaterials might lead to prolonged immune response, chronic inflammation, oxidative stress or genetic changes which could promote disease development. Another consideration is exposure to nanoparticles in the environment and workplace. There is the possibility of exposure to nanomaterials by researchers and healthcare workers during manufacturing, handling and disposal. Therefore, the regulatory framework, safety testing and long-term monitoring studies must be very strict in order to assess the potential health and environmental effects of nanotechnology products. With the ongoing progress of nanomedicine, there is a need for extensive toxicological research and standardized safety assessment procedures to guarantee that nanotechnology-based treatments are effective and safe for long-term clinical applications. The ability to evaluate and mitigate this toxicity and safety issues will be important for the effective clinical translation of nanotechnology from the lab to the bedside [34-36].

10. Clinical Translation and Future Perspectives

Over the last few decades, nanomedicine has made incredible progress, presenting novel approaches to disease diagnosis, therapy and prevention. Many nano-based systems have been seen to be very successful in laboratory and preclinical research, including cancer therapy, drug delivery, imaging and regenerative medicine. But the application of these technologies from the research laboratory to everyday clinical care is a complicated journey. The safety, efficacy, manufacturing quality and regulatory compliance are all extensively assessed for clinical translation. However, on-going technological innovations and a better understanding of science are helping to drive development of next-generation nanomedicine platforms. The potential applications of nanomedicine in the field of personalized healthcare, precision medicine and patient outcomes are limitless.

10.1 Clinical Applications and Regulatory Challenges

Nanomedicine has already made great leaps in the clinic, with a number of approved nano-based therapeutics and diagnostic agents developed. There are several types of nanoformulations including liposomal drug, polymeric nanoparticles, iron oxide nanoparticles, and lipid-based delivery systems, which are currently being used in cancer, infectious diseases, and other medical areas. One recent and salient example is messenger RNA (mRNA) vaccines, which relied on lipid nanoparticles to prove the clinical utility of nanomaterials in contemporary medicine. The delivery of therapeutic agents using nanoparticles has enhanced the solubility, circulation time, reduced toxicity, and targeted delivery to diseased tissues, in order to improve therapeutic effectiveness. These accomplishments are not without challenges, however, as there are a number of regulatory hurdles to this field's broad clinical application. Conventional pharmaceutical assessment procedures may be inappropriate for the unique physicochemical properties in the case of nanoparticles. The safety and efficacy of a product should be evaluated by the regulatory agencies, with regard to particle size, shape, surface chemistry, stability, biodistribution, and toxicity and degradation behaviour. Furthermore,





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different approaches to nanoparticle manufacturing can cause the quality and performance of the products to vary, which can pose difficulties in standardization and quality control. Another important regulatory issue is long-term safety: certain nanomaterials may be toxic after a period of time or be bio accumulated in tissues. Full preclinical studies, clinical trials and post-marketing surveillance are therefore needed to guarantee patient safety. Moreover, the lack of internationally agreed upon guidelines for nanomedicine makes product approval and commercialization in different countries more challenging. Standardized testing protocols and international collaboration are vital to help speed clinical translation of nanotechnology-based therapeutics while addressing some of these regulatory issues.

10.2 Recent Advances in Nanomedicine

Over the last few years, there has been significant progress in the field of nanomedicine, particularly in the areas of materials science, biotechnology, molecular biology, and artificial intelligence. The delivery of mRNA-based therapeutics and vaccines using lipid nanoparticles (LNPs) is one of the most promising advances. It has proved that nanocarriers are capable of packaging delicate genetic materials and efficiently transporting them into cells of interest, paving the way for new applications in gene therapy and personalized medicine. There have also been tremendous advances in the development of multifunctional nanoparticles that have the ability to carry both diagnostic and therapeutic payloads within a single platform. These theranostic nanoparticles can detect the disease, give treatment (targeted), and monitor the therapeutic response. These systems are especially beneficial in the field of cancer treatment, where accurate diagnosis and immediate assessment of treatment effects are essential. Targeted drug delivery technologies have led to the creation of nanoparticles which are capable of recognising certain receptors on cells and disease marker and directing them to them. Such systems provide for greater treatment accuracy and reduce the impact on normal tissues. Moreover, new technologies concerning nanomaterials, related to gold nanoparticles, quantum dots, carbon nanotubes, graphene-based materials, dendrimers and magnetic nanoparticles, have extended the biomedical applications. Nanotechnology has also made a huge contribution to the field of medical imaging in the form of better contrast agents for MRI, CT, PET and optical imaging techniques. One of the other significant developments is the use of nanotechnology and immunotherapy. Means for delivery of antigens, cytokines, and immune-modulating agents to nanoparticles are being developed to augment immune responses against cancer or infectious diseases. The progress made in these areas exemplifies the potential of nanomedicine to move beyond drug delivery into a platform for innovative therapeutic treatments.

10.3 Emerging Trends and Future Opportunities

This domain will focus on the latest trends and opportunities for the future. Several new technologies and interdisciplinary innovations have the potential to influence the future of nanomedicine. A key upcoming development is the development of precision and personalized





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medicine. New nanotechnology-based systems will be created for each patient, depending on his or her individual genetic makeup, nature of the disease, and treatment needs. These tailor-made methods will help to achieve more efficient treatments, with fewer side effects, and better clinical results. It is anticipated that the use of artificial intelligence (AI) and machine learning will further become a vital part of the development of nanomedicine. The technologies can help researchers to design optimized nanoparticles, to predict biological interactions, to determine potential toxicity, and to shorten the drug discovery process. This integration of AI and nanotechnology could significantly cut down on the time and expense of clinical translation. Another area of great promise for the use of nanomedicine in the future is gene-editing technologies, including the CRISPR-Cas system. Nanoparticles could also be used to transport parts of the gene-editing process to treat genetic diseases at the molecular level. Likewise, innovations in RNA therapeutics, such as mRNA and small interfering RNA (siRNA) therapeutics are providing the possibility to improve the treatment of intractable diseases. The development of Nano robotics and smart Nano devices is also a promising field of research. These miniaturised systems could be used to navigate inside the human body, find disease sites, deliver therapeutic agents with great precision and have the ability to monitor treatment responses in real time. Moreover, an advanced approach of designing stimuli-responsive nanoparticles that release drugs upon reception of certain bio-signals such as pH, temperature, enzymes and magnetic field would significantly improve the effectiveness of treatment. Nanotechnology can be used in regenerative medicine for the creation of advanced tissue-engineering scaffolds, artificial organs and stem-cell therapies. Nanomaterials can be used to create a structure similar to the biological one, which encourages the repair and regeneration of tissues. Moreover, the development of nanotechnology-based biosensors and wearable diagnostic devices could enable ongoing health monitoring and early detection of diseases, further driving the rise of preventive healthcare. The potential for nanomedicine is very bright in general. Evolving materials technology, biotechnology, artificial intelligence and molecular medicine will likely address current challenges and broaden the potential uses of nanotechnology in clinical medicine. Nanomedicine can offer safer, more effective and highly personalized ways to diagnose and treat a myriad of disease processes in the future, as research continues and standards are developed [37-41].





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